Biostatistics

林　建　甫
C.F. Jeff Lin, MD. PhD.

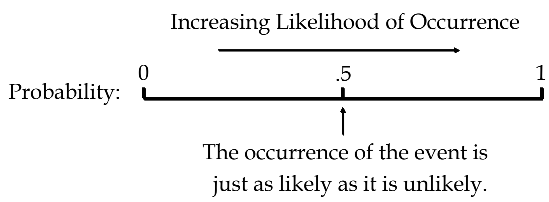
台北大學統計系助理教授
台北榮民總醫院生物統計顧問
美國密西根大學生物統計博士

Review Probability

Probability

- Probability is a numerical measure of the likelihood that an event will occur.
- Probability values are always assigned on a scale from 0 to 1.
- A probability near 0 indicates an event is very unlikely to occur.
- A probability near 1 indicates an event is almost certain to occur.
- A probability of 0.5 indicates the occurrence of the event is just as likely as it is unlikely.

Probability as a Numerical Measure of the Likelihood of Occurrence



An Experiment

- An experiment is any process that generates well-defined outcomes.
- **隨機實驗的意義**
- 隨機實驗是一種過程(process)，是一種不能確定預知會發生何種結果的實驗方式。在實驗前已知所有可能出現的結果，而實驗後的結果為所有可能的結果之一，但實驗前並未能正確的、肯定的預知它是何種結果。隨機實驗可重複進行，而經過長期重複實驗，出現的結果會遵循某一些統計規則。

Types of Probability

- Classical
- Relative Frequency
- Subjective (Personal)
- Mathematical (Axiomatic, Objective) Probability

Assigning Probabilities

- Classical Method
  Assigning probabilities based on the assumption of equally likely outcomes.
- Relative Frequency Method
  Assigning probabilities based on experimentation or historical data.
- Subjective Method
  Assigning probabilities based on the assignor's judgment.
- Mathematical Method
  Based on set theory and mathematical functions

Classical Probability

- Based on gambling ideas
- Fundamental assumption:
  - the game is fair
  - All possible outcomes have the same probability.
- The concept of throwing a "fair" die or a "fair" coin and observing the outcome are examples.

Classical Probability

- **Mutually exclusive** events:
  - The occurrence of any one of event precludes the occurrence of another
  - Tossing a coin once yields two events--either heads or tails occurs--never both.
- **Equal likely** events:
  - Means equal probable events
  - Tossing a ``fair" coin means the chance of occurrence of head is the same as the chance of the occurrence of tail.

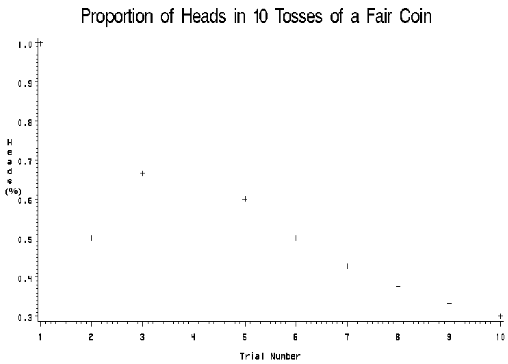
Classical Probability

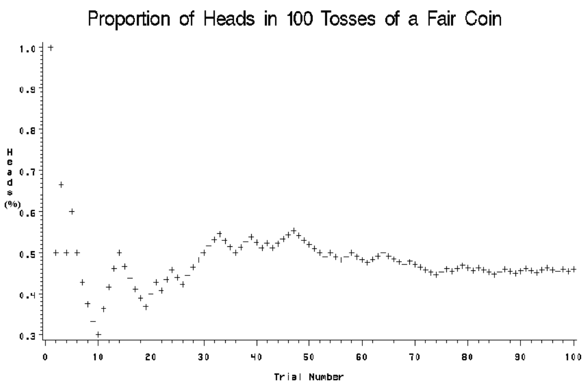
If an experiment has n possible outcomes, this method would assign a probability of $1/n$ to each outcome.

- Example
  Experiment: Rolling a die
  All possible outcomes: $S = \{1, 2, 3, 4, 5, 6\}$
  Probabilities:
  Each point has a 1/6 chance of occurring.

Relative Frequency Probability

- When an experiment can be repeated, then the **relative frequency** of an outcome is the **proportion** of the event occurs in the long run.
- If some process is repeated a large number of times, n, and if some resulting event with the characteristic of A occurs n(A) times, the relative frequency of occurrence of A, n(A)/n, will be approximately equal to the **probability** of A: P(A)=n(A)/n

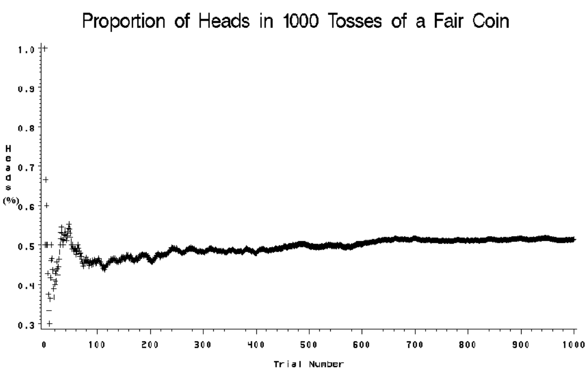




Relative Frequency Probability

What have we said?

- **The probability of an event is the relative frequency that an event occurs in a very large number of "trials" (times it could have occurred).**
- **The relative frequency gets nearer to the true probability as the number of "trials" increases.**



Relative Frequency Probability

- A **stable experiment** is one in which the relative frequency of a particular outcomes converge to a particular number upon replication of the experiment.
- The **relative frequency probability** of an outcome is the **long-term number**, or **fraction**, of times that the particular outcome results from replication of a stable experiment.
- The probability determined by the classical definition are called a **posteriori**.

Relative Frequency Probability

$f_A = n(A)/n \qquad P(A) = \lim_{n\to\infty} f_A$

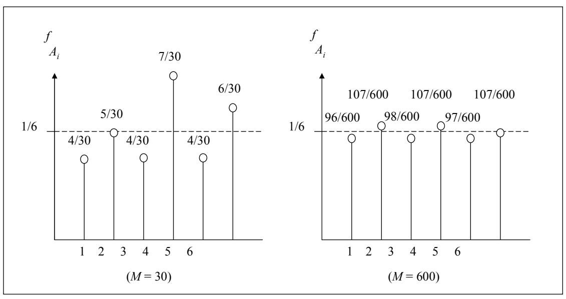


Figure 1.1

Relative Frequency Probability

- The throw of a die is an experiment.
- In reality, no die is exactly "fair".
- Conceptually, we could throw the same die again and again, the throw of a die is a repeatable experiment.
- A stable experiment?
- In fact, with repeated throwing of the die, the corners may wear down and the relative frequency of a particular outcomes, a "1", say may change over time.

Relative Frequency Probability

- Generally, the **concept of a stable repeatable experiment** is an **idealized abstraction** that is often difficult to attain in the practice of science.
- For another example, **drawing a random sample** from a **fixed population** and computing the **sample average** is a **repeatable stable experiment**.

Subjective (Personal) Probability

- Most of life's events are not repeatable.
- Subjective (personal) probability is an **individual's personal assessment** of an outcome's likelihood.

Subjective (Personal) Probability

- Note that the frequency concept does not apply to experiments that cannot be repeated.
- Thus, before the last election, the **winner** may have had a **subjective probability** with value less than 1.0 that he would win the election.
- After success, that subjective probability changed to 1 for that election.
- After success, the experiment could not be repeated, so the probability of success in a subsequent experiment was no longer relevant.

Mathematical Probability (Axiomatic, Objective)

- Based upon a conceptual **experiment** for which each outcome has a prescribed probability of occurrence.
- The concept of throwing a "fair" die or a "fair" coin and observing the outcome are examples.
- An **objectivist** uses either the **classic** or **frequency** definition of probability.
- A **subjectivist** or **Bayesian** applies formal laws of chance to his own, or yours, personal probabilities.

Set theory

- Sample Space
- Subset
- Event
- Empty Set, Equivalent Set
- Union and Intersection
- Complementation
- Difference
- Disjoint

Random Experiment

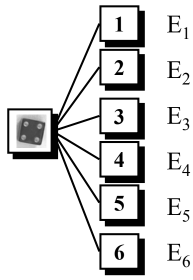
- **Random experiment** is the process of observation of the result, governed by chance, from any collection of all possible results.
- **Elementary outcomes** are all possible results of the random experiment.

Sample Space and Events

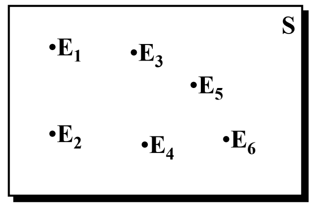
- **Sample space** is the set or collection of all elementary outcomes resulting from a random experiment.
- **Event** is a subset of the sample space. Event can be any collection of possible outcomes of an experiment.
- **Simple event** (or **elementary event**) is an a single observation or a single member of the sample space.
- An experiment will result in one, and only one simple event.
- Simple event is a particular type of event.
- **Probability** measure the likelihood of an event.

Example

- **The die toss:**
- Simple events: Sample space:



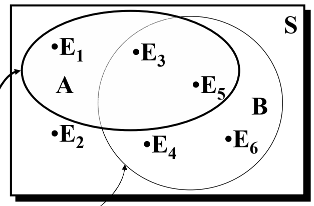
S ={E_1, E_2, E_3, E_4, E_5, E_6}



Example

- An **event** is a collection of one or more **simple events.**

•**The die toss:**
- A: an odd number
- B: a number > 2



A ={E_1, E_3, E_5}

B ={E_3, E_4, E_5, E_6}

Sample Space

- Countable (**discrete**, finite or countable infinite)
- Uncountable (**continuous**)

Example:

- Discrete: A coin is tossed repeatedly until a head occurs, S = {H, TH, TTH, …}, S^* = {0, 1, 2, …}
- Continuous: Place light bulb in service, measure time until it burns out

$$S = \{t \mid 0 \le t < \infty\}$$

Set Theory

- **Subset**: If every element of a set, A, is also an element of a set S, then A is defined to a **subset** of S, and we shall write $A \subseteq S$ or $S \supseteq A$; read "A is contained in S" or "S contain A".
- An **event** is any collection of possible outcomes of an experiment, that is, any subset of S (including S itself)
- **Probability** is a numerical measure of the likelihood that an event will occur.

Set Theory

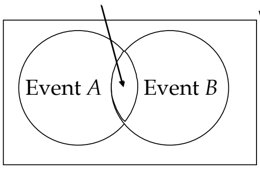
- **Empty set:**
  - If a set S contains no points, it will be called the **null set**, or **empty set**, (denoted as $\varnothing$).
  - Empty set is a subset of any set.
- **Equivalent sets:**
  - Two sets A and B are defined to be equivalent, or equal, if $A \subseteq B$ and $B \supseteq A$.
  - This will be indicated by writing A = B.

Intersection of Two Events

- The **intersection** of events A and B is the set of all sample points that are in both A and B.
- The intersection is denoted by $A \cap B$.
- The intersection of A and B is the area of overlap in the illustration below.

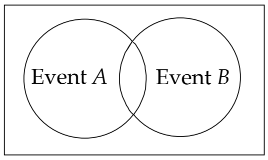
Sample Space ***S***

Intersection



Union of Two Events

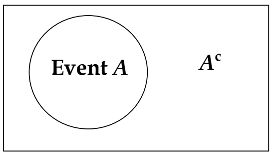
- The **union** of events A and B is the event containing all sample points that are in A or B or both.
- The union is denoted by $A \cup B$.
- The union of A and B is illustrated below.



Sample Space *S*

Complement of an Event

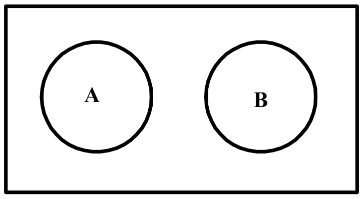
- The complement of event A is defined to be the event consisting of all sample points that are not in A.
- The complement of A is denoted by A^c.
- The Venn diagram below illustrates the concept of a complement.



Sample Space *S*

Disjoint Events

- Two events A and B are disjoint (or mutually exclusive) if $A \cap B = \varnothing$.
- Pairwise disjoint



Function

- A **function**, say $f(\cdot)$, is a rule (law, formula, recipe) that associates each point in one set of points with one and only one point in another set points.
- $f(a)=b$
  - $a \in A$ = Domain, Preimage
  - $B \in B$ = Counterdomain, Image

Probability Set Function

- A **set function** that associates a real value **P (A)** with each event A is called a **probability set function.**
- A sample space ***S*** with a collection of subsets, ***B,*** a **probability is a function, P,** with domain ***B,*** and couterdomain [0, 1].
- P: $\boldsymbol{B} \rightarrow [0, 1]$.

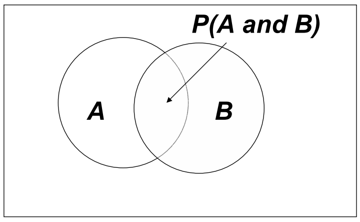
Axiomatic Foundations

Let $S = \{E_1, E_2, \ldots\}$, E_i denote simple event and and event A, then

1. $0 \le P(A) \le 1$
2. $P(S) = \Sigma P(E_1) + P(E_2) + \ldots = 1$
3. $P(A) = \Sigma_{i \mid E_i \in A} P(E_i)$

Union and Intersection Notation

- P(A or B) = P(A $\cup$ B) probability of A union B.
- P(A and B) = P(A $\cap$ B) joint probabilities - probability of A intersect B.

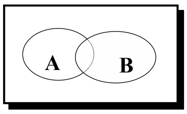


Venn Diagram

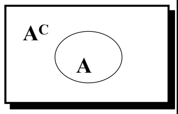
Calculating Probabilities for Unions and Complements

- There are special rules that will allow you to calculate probabilities for composite events.
- **<u>The Additive Rule for Unions:</u>**
- For any two events, **A** and **B**, the probability of their union, **$P(A \cup B)$**, is

$$\boxed{P(A \cup B) = P(A) + P(B) - P(A \cap B)}$$



Calculating Probabilities for Complements



- We know that for any event **A:**
  - **$P(A \cap A^C) = 0$**
- Since either **A** or **A^C** must occur,
  $P(A \cup A^C) = 1$
- so that **$P(A \cup A^C) = P(A) + P(A^C) = 1$**

$$\boxed{\mathbf{P(A^C) = 1 - P(A)}}$$

Mutually Exclusive Events

- Addition Law for Mutually Exclusive Events

$$P(A \cup B) = P(A) + P(B)$$

Event Probability Using Contingency Table

	Event		
Event	**B_1**	**B_2**	**Total**
A_1	**$P(A_1 \cap B_1)$**	**$P(A_1 \cap B_2)$**	**$P(A_1)$**
A_2	**$P(A_2 \cap B_1)$**	**$P(A_2 \cap B_2)$**	**$P(A_2)$**
Total	**$P(B_1)$**	**$P(B_2)$**	**1**

Joint Probability

Marginal (Simple) Probability

Conditional Probability

- The probability of an event given that another event has occurred is called a conditional probability.
- The conditional probability of *A* given *B* is denoted by P(*A*|*B*).
- A conditional probability is computed as follows:

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

Multiplication Law of Probability

P(A and B) = P(A|B) x P(B)

and

P(A and B) = P(B|A) x P(A)

Independent Events

- Events *A* and *B* are independent if

  P(*A*|*B*) = P(*A*).

Bayes′ Theorem

Bayes′ Theorem

- Often we begin probability analysis with initial or prior probabilities.
- Then, from a sample, special report, or a product test we obtain some additional information.
- Given this information, we calculate revised or posterior probabilities.
- Bayes′ theorem provides the means for revising the prior probabilities.

Prior Probabilities → New Information → Application of Bayes′ Theorem → Posterior Probabilities

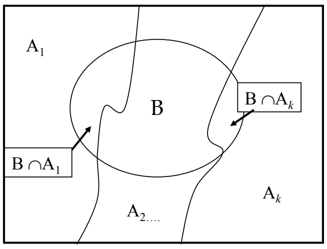
Bayes' rule

- P (A and B) = P (B and A); so
- P (A |B) P (B) = P (B|A) P (A)

  -- just using the definition of prob (X|Y));
- Hence

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

The Law of Total Probability



P(B) = P(B ∩ A$_1$) + P(B ∩ A$_2$) + … + P(B ∩ A$_k$)

= P(A$_1$)P(B|A$_1$) + P(A$_2$)P(B|A$_2$) + … + P(A$_k$)P(B|A$_k$)

Bayes' Rule

- Let A$_1$, A$_2$, A$_3$,..., A$_k$ be mutually exclusive and exhaustive events with prior probabilities P(A$_1$), P(A$_2$),…,P(A$_k$). If an event B occurs, the posterior probability of A$_i$, given that B occurred is

$$P(A_i \mid B) = \frac{P(A_i)P(B \mid A_i)}{\sum P(A_i)P(B \mid A_i)} \text{ for } i \;=\; 1,\, 2,...k$$

Counting Rule for Permutations

- When *n* objects are to be selected from a set of *N* objects where the order of selection is important.
- Number of permutations of *N* objects taken *n* at a time

$$P_n^N = n!\binom{N}{n} = \frac{N!}{(N-n)!}$$

where $N! = N(N-1)(N-2)\ldots(2)(1)$

$n! = n(n-1)(n-2)\ldots(2)(1)$

$0! = 1$

Counting Rule for Combinations

Another useful counting rule enables us to count the number of experimental outcomes when *n* objects are to be selected from a set of *N* objects.

- Number of combinations of *N* objects taken *n* at a time

$$C_n^N = \binom{N}{n} = \frac{N!}{n!(N-n)!}$$

Screening and Diagnostic Test

- **prevalence =** probability of disease in the entire population at any point in time (i.e. 2% the U.S. population has diabetes mellitus)
- **incidence** = probability that a patient without disease develops the disease during an interval (the incidence of diabetes mellitus is 0.2% per year, referring only to new cases)
- **sensitivity** = probability of a positive test among patients with disease
- **specificity** = probability of a negative test among patients without disease

Screening

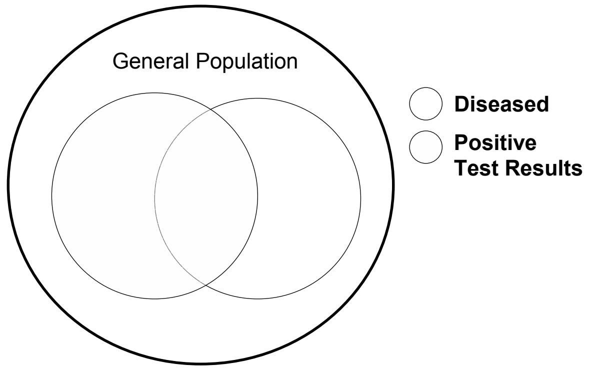
Definition:

Application of a test or procedure to asymptomatic, apparently well individuals, in order to separate those with a relatively high probability of having a given disease from those with a relatively low probability of having the disease.

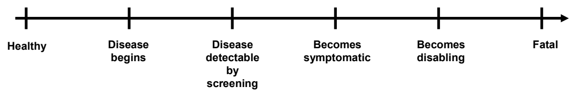
Diagnostic Tests

- Application of a test or procedure to a symptomatic, apparently ill individuals, in order to separate those with a relatively high probability of having a given disease from those with a relatively low probability of having the disease

Screening Tests and Diagnostic Tests



Model of Disease Natural History



What characteristics of a disease make it appropriate for screening for?

1. Important public health problem – frequent or serious
2. Reasonably long, recognizable pre-symptomatic stage
3. Effective treatment exists and is available, or effective ways of preventing spread
4. Treatment (or measures take to prevent spread) should be more effective if initiated in the pre-symptomatic stage than when initiated in symptomatic patients

What characteristics of a disease make it appropriate for screening for?

5. A suitable screening test or procedure should be available and be:
    1. Reliable
    2. Sensitive and specific
    3. Acceptable to the population screened
    4. Reasonably inexpensive and safe

Predictive Value

- A person's *true* disease status is often unknown when a test is applied to detect it
- The probability of *truly* having the disease when the test detects it is called the **predictive value**

Predictive Value

	Gold Standard	
Test Result	+	–
+	*a*	*b*
–	*c*	*d*
Total	*a* + *c*	*b* + *d*

$$a = number\ of\ true\ positives$$
$$b = number\ of\ false\ positives$$
$$c = number\ of\ false\ negatives$$
$$d = number\ of\ true\ negatives$$

Definitions

- Sensitivity - The probability of a positive test given that the person has disease
  - P(T+ | D+)
- Specificity - The probability of a negative test given that the person does not have disease
  - P(T− | D −)

Definitions
Fundamental Assumption

- It is possible to define what is meant by a "positive test" and a "negative test".

Two-by-Two Table
Sensitivity and Specificity

Test Result		Disease	No Disease
	Positive	True Positive	False Positive
	Negative	False Negative	True Negative

Sensitivity = True Positives

Specificity = True Negatives

The Two-by-Two Table
Estimation Sensitivity and Specificity

Test Result		Disease	No Disease	
	Positive	A	B	A + B
	Negative	C	D	C + D
		A + C	B + D	N

Sensitivity = A/A+C Specificity = D/B+D

Sensitivity and Specificity

- Sensitivity – How often does a test detect the disease if it is truly present?

$$Sensitivity = \frac{a}{a+c} = \Pr\left(T_+ \mid \mathrm{D}_+\right)$$

- Specificity – How often does a test give a negative result if the disease is truly absent?

$$Specificity = \frac{d}{b+d} = \Pr\left(T_- \mid \mathrm{D}_-\right)$$

Example: New Diagnostic Test

		Disease	No Disease	
Test Result	Positive	75	20	95
	Negative	25	180	205
		100	200	300

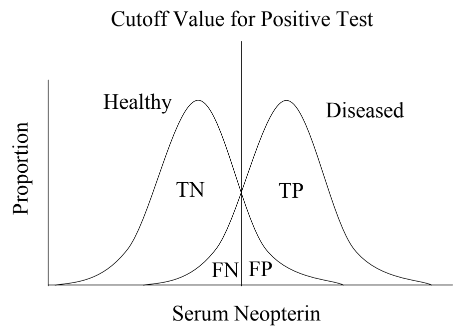
Sensitivity = 75/100 = 75%

Specificity = 180/200 = 90%

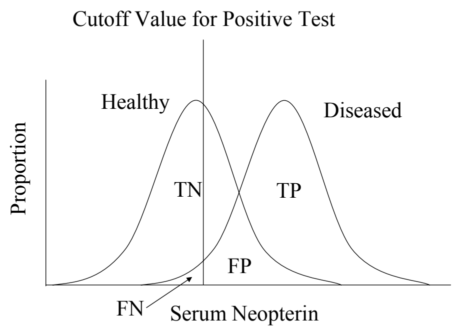
False Negative and False Positive

- False Negative: the conditional probability that a person had a negative test result given they have the disease.
  False negative = 1 – sensitivity.
- False Positive: the conditional probability that a person has a positive test result given they do not have the disease.
  False positive = 1 – specificity.

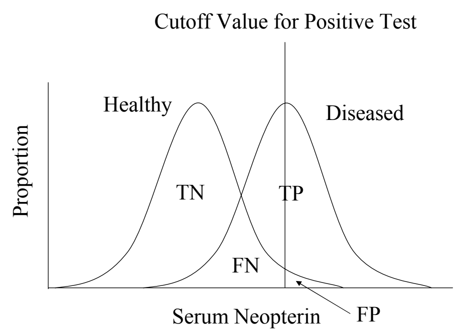
Continuous Measurements



Continuous Measurements



Continuous Measurements



Effect of Setting Cut-Off Point

- One way of addressing the trade off between sensitivity and specificity is to use the results of several screening tests together either in parallel or in series
  - MSAFP, serum estriol, serum HCG in Down Syndrome screening
  - RPR followed by FTA-Abs in syphilis screening

Sensitivity and Specificity

- How useful is it to express misclassification in terms of sensitivity and specificity?
  - Does it answer the question you are really interested in?

Sensitivity and Specificity

- Sensitivity indicates the proportion of patients with disease who have a positive test.
- But you are interested in knowing what the likelihood of disease in people with a positive test.

Sensitivity and Specificity

- Specificity tells you what proportion of healthy people have a negative, or normal, test
- You are interested in knowing what is the likelihood of disease in a person with a negative, or normal, test

Definitions

- Predictive Value Positive Test (PV+)
  - The proportion of people with a positive test who have disease
  - PV+ = P(D+ | T+)
- Predictive Value Negative Test (PV −)
  - The proportion of people with a negative test who are healthy
  - PV − = P(D− | T −)

Predictive Value

		Disease	No Disease	
Test Result	Positive	A	B	A + B
	Negative	C	D	C + D
		A + C	B + D	N

Predictive value - Positive test = A/A+B
Predictive value - Negative test = D/C+D

Predictive Value

- Predictive value of a positive test (PV_+):

$$= \frac{a}{a+b}$$

$$= \frac{True\ Positives}{True\ Positives + False\ Positives}$$

- Predictive value of a negative test (PV_-)

$$= \frac{d}{c+d}$$

$$= \frac{True\ Negatives}{False\ Negatives + True\ Negatives}$$

Predictive Value

		Disease	No Disease	
Test Result	Positive	75	20	95
	Negative	25	180	205
		100	200	300

Predictive value - positive test = 75/95 = 79%
Predictive value - negative test = 180/205 = 88%

Effect of Disease Prevalence

Low Prevalence: 10%

		Disease	No Disease	
Test Result	Positive	990	90	1,080
	Negative	10	8,910	8,920
		1,000	9,000	10,000

Sensitivity = 99%
Specificity = 99%

Predictive value - positive test = 990/1080 = 92%

Effect of Disease Prevalence

High Prevalence: 60%

		Disease	No Disease	
Test Result	Positive	5,940	40	5,980
	Negative	60	3,960	4,020
		6,000	4,000	10,000

Sensitivity = 99%
Specificity = 99%

Predictive value - positive test = 5,940/5,980 = 99%

Predictive Value

- Depends on…
  - Sensitivity
  - Specificity
  - Prevalence of the underlying condition in the population to whom the test is applied

Using Conditional Probabilities through Bayes' Theorem:

- Sensitivity = $\Pr(T_+|D_+)$

  Specificity = $\Pr(T_-|D_-)$

  Positive predictive value = $\Pr(D_+|T_+)$

  Negative predictive value = $\Pr(D_-|T_-)$

  Prevalence of the underlying disease condition = $\Pr(D_+)$

Bayes' Theorem

$$p(B|A) = \frac{p(B)\left[p(A|B)\right]}{p(B)\left[p(A|B)\right] + \left[(1-p(B))(1-p(\overline{A}|\overline{B})\right]}$$

$$p(D+|T+) = \frac{p(D+)\left[p(T+|D+)\right]}{p(D+)\left[p(T+|D+)\right] + \left[1-p(D+)\right]\left[1-p(T-|D-)\right]}$$

Bayes' Theorem

$$p(D+|T+) = \frac{\overbrace{p(D+)}^{\text{Prevalence}}\overbrace{\left[p(T+|D+)\right]}^{\text{Sensitivity}}}{p(D+)\left[p(T+|D+)\right]+\left[1-p(D+)\right]\underbrace{\left[1-p(T-|D-)\right]}_{\text{Specificity}}}$$

According to Bayes' Theorem:

Predictive Value Positive

$$= \text{PV+}$$

$$= \frac{Pr(\text{D+})\cdot Pr(T+\mid \text{D+})}{Pr(\text{D+})\cdot Pr(T+\mid \text{D+}) + \left[1-Pr(\text{D+})\right]\cdot\left[1-Pr(T+\mid \text{D+})\right]}$$

$$= \frac{\text{Prevalence}\times\text{Sensitivity}}{\text{Prevalence}\times\text{Sensitivity}+(1-\text{Prevalence})\times(1-\text{Specificity})}$$

According to Bayes' Theorem:

Predictive Value Negative

$$= \text{PV}-$$

$$= \frac{Pr(D-)\cdot Pr(T-\mid D-)}{Pr(D-)\cdot Pr(T-\mid D-)+Pr(D+)\left[1-Pr(T+\mid D+)\right]}$$

$$= \frac{\text{(1-Prevalence)}\times\text{Specificity}}{(1-\text{Prevalence})\times\text{Specificity}+\text{Prevalence}\times(1-\text{Sensitivity})}$$

What are the Results?

Likelihood Ratios

Simply stated, the Likelihood Ratio is how much more likely someone is to get a positive test result if they have the disease, compared to someone who doesn't.

In fact, the LR is how much more likely someone is to get any particular test result (positive, negative, "intermediate probability, etc) if they have disease, compared to someone who doesn't.

Likelihood Ratios

- Likelihood ratios tell us how much we should shift our suspicion for a particular test result.
- Because tests can be positive or negative, there are at least two likelihood ratios for each test.
- The "positive likelihood ratio" (LR+) tells us how much to increase the probability of disease if the test is positive.
- While the "negative likelihood ratio" (LR-) tells us how much to decrease it if the test is negative.

Application of likelihood Ratios

The likelihood ratio is:

$$\textit{Likelihood Ratio} = \frac{\textit{probability of an individual with the condition having the test result}}{\textit{probability of an individual without the condition having the test result}}$$

or

$$LR_+ = \frac{\textit{probability of an individual with the condition having a positive result}}{\textit{probability of an individual without the condition having a positive result}}$$

$$LR_- = \frac{\textit{probability of an individual with the condition having a negative result}}{\textit{probability of an individual without the condition having a negative result}}$$

or

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

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

What are the Results?

From example:
The LR is (90/100) / (90/900) = 9.0

This is the LR for a (+) result. Someone with disease is 9 times as likely to test positive than someone without it.

	Dz (+)	Dz (-)
Test(+)	90	90
Test(-)	10	810
	100	900

Note also that :
LR = SENS / 1 - SPEC

What are the Results?

The LR for a negative test is:
(10/100) / (810/900) = 0.11

Someone with disease is 0.11 times as likely (1/9) to test negative than someone without it.

	Dz (+)	Dz (-)
Test(+)	90	90
Test(-)	10	810
	100	900

What are the Results?

What do all the numbers mean?

The Likelihood Ratio tells you by how much a given diagnostic test result will raise or lower the probability of having the disorder.

Pretest Probability: the chance that the pt has disease, prior to ordering any tests. This is often an estimation based on clinical experience

Posttest Probability: the chance that the pt has disease, given the results of the test

Application of Likelihood Ratio

- Bayes' Theorem can be used to derive a simple formula involving the likelihood ratio based on the odds of having the underlying condition, before and after a certain test result is obtained.
- Note that:

$$Pretest\ Odds = \frac{Pr(D+)}{Pr(D-)} = \frac{Prevalence}{1 - Prevalence}$$

Application of likelihood ratio

And if the test result is X, then:

$$Posttest\ Odds = \frac{Pr(D+ \mid T = X)}{Pr(D- \mid T = X)}$$

Application of likelihood Ratios

Remember that the likelihood ratio is:

$$Likelihood\ Ratio = \frac{probability\ of\ an\ individual\ with\ the\ condition\ having\ the\ test\ result}{probability\ of\ an\ individual\ without\ the\ condition\ having\ the\ test\ result}$$

or

$$LR_+ = \frac{probability\ of\ an\ individual\ with\ the\ condition\ having\ a\ positive\ result}{probability\ of\ an\ individual\ without\ the\ condition\ having\ a\ positive\ result}$$

$$LR_- = \frac{probability\ of\ an\ individual\ with\ the\ condition\ having\ a\ negative\ result}{probability\ of\ an\ individual\ without\ the\ condition\ having\ a\ negative\ result}$$

or

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

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

Application of Likelihood Ratio

And if the test result is X, then:

$$Posttest\ Odds = \frac{Pr(D+ \mid T = X)}{Pr(D- \mid T = X)}$$

With some algebra, we can show that

$$Posttest\ Odds = Pretest\ Odds \cdot LR_x$$

This relation makes it easy to determine how the odds of having the condition changes if one applies the test and obtains the result X.

What are the Results?

What do all the numbers mean?

A LR of 1.0 means the posttest probability is exactly the same as the pretest probability.

A LR >1.0 increases the probability of having the disorder.

A LR<1.0 decreases the probability of having the disorder.

What are the Results?

Likelihood ratios >10 or <0.1 generate large changes from pre- to posttest probability and are generally considered significant.

Likelihood ratios of 5-10 and 0.1-0.2 generate moderate changes in probability

Likelihood ratios of 2-5 and 0.2-0.5 generate small changes

Likelihood ratios 0.5-2 usually have little effect

Likelihood Ratio Interpretation

LR	Interpretation
> 10	Large and often conclusive increase in the likelihood of disease
5 - 10	Moderate increase in the likelihood of disease
2 - 5	Small increase in the likelihood of disease
1 - 2	Minimal increase in the likelihood of disease
1	No change in the likelihood of disease
0.5 - 1.0	Minimal decrease in the likelihood of disease
0.2 - 0.5	Small decrease in the likelihood of disease
0.1 - 0.2	Moderate decrease in the likelihood of disease
< 0.1	Large and often conclusive decrease in the likelihood of disease

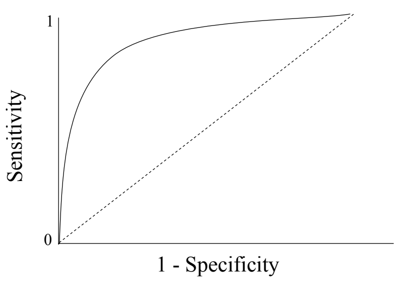
Application of Likelihood Ratio

- The LR+ corresponds to the clinical concept of "ruling-in disease"
- The LR- corresponds to the clinical concept of "ruling-out disease"
- The LR+ and LR- don't change as the underlying probability of disease changes (predictive values do change, as you just learned)
- LR's using multiple "levels" of positive (i.e. not just a simple yes/no or positive/negative result) provide much richer, more useful information to you as a clinician.

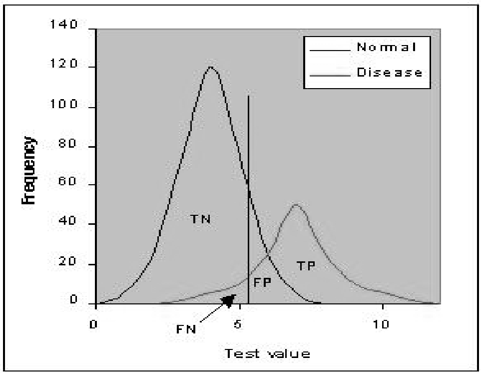
ROC Curve: Rock and Roll

- Time to ROC'n'roll...
- Receiver-operating characteristic curves, for obvious reasons called ROC (pronounced rock) curves, are an excellent way to compare diagnostic tests. Remember that when a test becomes more sensitive, it becomes less specific, and vice versa.

Receiver Operator Characteristic Curves



Different Cut-off Points



Consider the data for serum ferritin as a test for iron deficiency anemia:

Serum ferritin (mmol/l)	# with IDA (% of total)	# without IDA (% of total)
< 15	474	20
15-34	175	79
35-64	82	171
65-94	30	168
> 94	48	1332

ROC Curve

- Consider the data for serum ferritin as a test for iron deficiency anemia:

Serum ferritin (mmol/l)	# with IDA (% of total)	# without IDA (% of total)
< 15	474	20
15-34	175	79
35-64	82	171
65-94	30	168
> 94	48	1332

ROC Curve

- If we just want to calculate sensitivity and specificity for this test, we have to choose a "cutpoint" which separates 'normal' from 'abnormal'. If we choose <= 34 as an abnormal ferritin, we can "collapse" some rows and get the following table:

Serum ferritin (mmol/l)	# with IDA (% of total)	# without IDA (% of total)
<= 34	474 + 175	20 + 79
> 34	82 + 30 + 48	171 + 168 + 1332

ROC Curve

- Doing the math, we know have a familiar 2 x 2 table:

Serum ferritin (mmol/l)	# with IDA (% of total)	# without IDA (% of total)
<= 34	649	99
> 34	160	1671

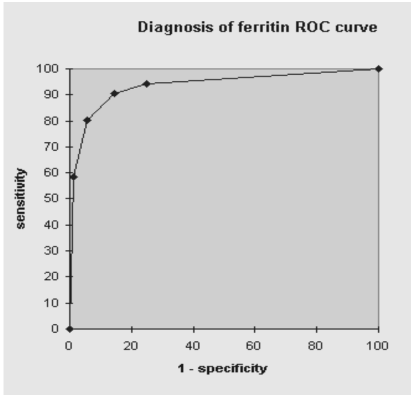
- Finally, we can calculate sensitivity and specificity for this cutpoint of 34:
- Sensitivity = 649 / (649 + 160) = 649 / 809 = 80.2%
- Specificity = 1671 / (1671 + 99) = 1671 / 1770 = 94.4%

ROC Curve

- Remember, though, that the sensitivity and specificity depend on where we make the cutpoint. I have done the math, and calculated the sensitivity and specificity for each of 4 different cutpoints in the table below:

Cutpoint abnormally low serum ferritin	Sensitivity	Specificity
< 15	58.5%	98.9%
<= 34	80.2%	94.4%
<= 64	90.4%	84.7%
<= 94	94.1%	75.3%

ROC Curve



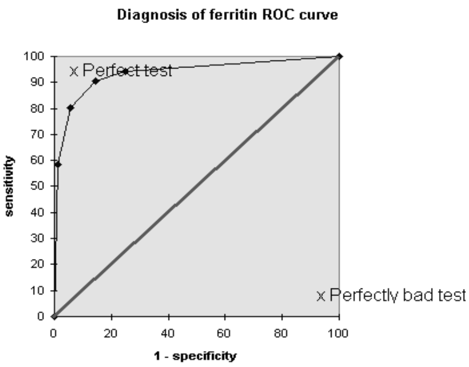
ROC Curve

- The area under the ROC curve (AUROCC) or (Area Under Curve AUC) is a reflection of how good the test is at distinguishing (or "discriminating") between patients with and without iron deficiency anemia. The greater the area, the better the test.

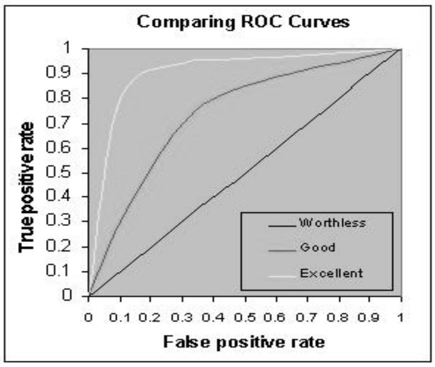
ROC Curve

- Let's look at another graph, which shows where a really good test (that has a high sensitivity and specificity)
- A perfectly bad test (which classifies diseased patients as healthy, and vice versa) would fall on the ROC curve.

ROC Curve



ROC Curve



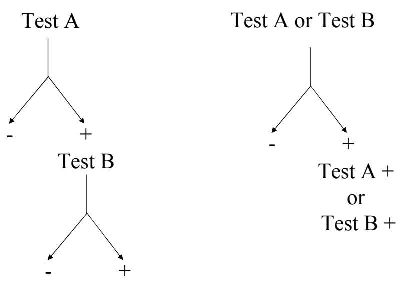
Sensitivity and Specificity: Considerations

- A highly sensitive test is best used if there is a significant penalty for missing the disease. (STDs, Tuberculosis, Hodgkin's Lymphoma, Malignant Melanoma…)
- A highly specific test is best used if there are other physical findings suggesting the presence of disease and the disease cannot be treated effectively or cured. (Multiple Sclerosis, Alzheimer's Disease…)

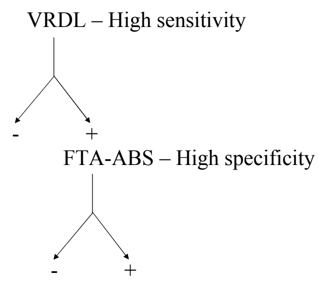
Combination Testing

- Series Testing
  - A test is first applied to a group. All those with a positive result are retested.
  - E.g., Serological testing for syphilis
- Parallel Testing
  - Two tests are applied together. All those with either or bother tests are considered to be positive.

Combination Testing



Combination Testing
Syphilis



High specificity testing strategy

Serial Testing

Test A
Sensitivity = 95%
Specificity = 90%

		D	$\bar{D}$	
Test Result	+	950	9,900	10,850
	-	50	89,100	
		1000	99,000	

Test B
Sensitivity = 80%
Specificity = 95%

		D	$\bar{D}$	
Test Result	+	760	495	1,255
	-	190	9,405	
		950	9,900	10,850

Predictive value of a positive test = 760/1,255 = 60.6%

Serial Testing

Test B
Sensitivity = 80%
Specificity = 95%

		D	$\bar{D}$	
Test Result	+	800	4,950	5,750
	-	200	94,050	
		1000	99,000	

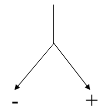
Test A
Sensitivity = 95%
Specificity = 90%

		D	$\bar{D}$	
Test Result	+	760	495	1,255
	-	40	4,455	
		950	4,495	5,750

Predictive value of a positive test = 760/1,255 = 60.6%
Overall Sensitivity = 760/1000 = 76%
Overall Specificity = 94,050 + 4,450/99,000 = 99.5%

Combination Testing
Myocardial Infarction

EKG and Cardiac Enzymes



EKG +
or
Cardiac Enzymes +

High sensitivity testing strategy

Parallel Testing

Positive Test - Either test A or test B are positive
Negative Test - Both test A and test B are negative

		Disease	No Disease	
Test Result	Positive	990	14,750	15,740
	Negative	10	84,250	84,260
		1,000	99,000	100,000

Predictive value of a positive test = 990/15,740 = 6.3%
Sensitivity = 990/1,000 = 99%

Combination Testing

- Serial Testing
  - Determine optimal approach by evaluating the predictive value of a positive test.
- Parallel Testing
  - Sensitivity improved
  - Specificity worse, more false positives

Characteristics of an Appropriate Screening Test

- Remember that screening tests are applied to apparently *well* individuals therefore there are ethical obligations to be fulfilled
- WHO (Wilson & Junger, 1968)
  1. The condition being screened for should be an important health condition
  2. The natural history should be well understood
  3. There should be a detectable early stage
  4. Treatment at an early stage should be of more benefit than at a later stage
  5. There should be a suitable test for the early stage

Characteristics of an Appropriate Screening Test

6. The test should be acceptable
7. Intervals for repeating the screening test should be determined
8. There should be adequate health service provision for the extra clinical workload resulting from the screen
9. The risks, both physical and psychological, should be less than the benefits
10. The costs should be balanced against the benefits

Thanks !