Statistical Evaluation for Medical Screening & Diagnostic Tests

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  - True positive (TP), False positive (FP), True negative (TN), False negative (FN)
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  - Sensitivity & Specificity
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- Bayes' theorem
  - The theorem
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Learning objectives

- Understand the events and measures for evaluating a screening/diagnostic test
- Know how to estimates the measures for evaluating a screening/diagnostic test
- Understand Bayes’ theorem
- Know how to calculate the predictive values of a screening/diagnostic test using Bayes’ theorem

Events related to evaluation of a diagnostic test

- Notation
  - A randomly selected subject
  - Disease status
    - D = diseased
    - $\bar{D}$ = non-diseased
  - Test result
    - T = positive
    - $\bar{T}$ = negative

Table 1 Classification of test results by disease status

Test Result	Disease Status	
	Diseased (D)	Nondiseased $(\bar{D})$
Positive (T)	True Positive (TP)	False Positive (FP)
Negative (T)	False Negative (FN)	True Negative (TN)

- Joint Events

True Positive $= T \cap D$, False Positive $= T \cap \bar{D}$,
False Negative $= T \cap D$, True Negative $= T \cap \bar{D}$.

- In the case to evaluate association of the disease and certain symptom
  - T = positive (presence of symptom)
  - $\bar{T}$ = negative (absence of symptom)

Questions of interests in biomedical field

1. Given that a subject has the disease, what is the probability of a positive test result (or the presence of a symptom), *i.e.*, $P\{T|D\} =?$
2. Given that a subject does not have the disease, what is the probability of a negative test result (or the absence of a symptom), *i.e.*, $P\{\bar{T}|\bar{D}\} =?$

3. Given a positive screening test (or the presence of a symptom), what is the probability that the subject has the disease, *i.e.*, $P\{D|T\} =?$
4. Given a negative screening test (or the absence of a symptom), what is the probability that the subject does not have the disease, *i.e.*, $P\{\bar{D}|\bar{T}\} =?$

Sensitivity and Specificity of a diagnostic test

Table 2 Statistical measures for evaluating a diagnostic test (I)

Test Result	Disease Status	
	Diseased (D)	Nondiseased ($\bar{D}$)
Positive (T)	True positive fraction (TPF) $P\{T \mid D\}$	False positive fraction (FPF) $P\{T \mid \bar{D}\}$
Negative ($\bar{T}$)	False negative fraction (FNF) $P\{\bar{T} \mid D\}$	True negative fraction (TNF) $P\{\bar{T} \mid \bar{D}\}$
Sum	1	1

- Only two fractions are needed
  - $TPF + FNF = 1, FPF + TNF = 1.$
- Option 1. Use
  - $TPF = P\{T|D\}$ and $FPF = P\{T|\bar{D}\}$
- Option 2. Use
  - $TPF = P\{T|D\}$ = Sensitivity
  - $TNF = P\{\bar{T}|\bar{D}\}$ = Specificity

Estimations of Sensitivity and Specificity of a diagnostic test

Table 3 Diseased samples classified according to test result

Test Result	Samples		
	Diseased (D)	Nondiseased ($\bar{D}$)	Total
Positive (T)	a	b	$a + b$
Negative ($\bar{T}$)	c	d	$c + d$
Total	$a + c$	$b + d$	n

- Relative Frequency Probability
  - If a random experiment is repeated a large number of times, n, and if a resulting event E occurs m times, then

$$P(E) \approx m / n$$

- Estimations

$$\hat{TPF} = a/(a+c) \text{ (Sensitivity)},$$

$$\hat{FNF} = c/(a+c),$$

$$\hat{FPF} = b/(b+d),$$

$$\hat{TNF} = d/(b+d) \text{ (Specificity)}.$$

Estimations of Sensitivity and Specificity of a diagnostic test

- Example 1 (EXAMPLE 3.5.1 on page 81, 10^{th} Ed)
  - A medical research team wished to evaluate a proposed screening test for Alzheimer's disease. The test was given to a random sample of 450 patients with Alzheimer's disease and an independent random sample of 500 patients without symptoms of the disease. The two samples were drawn from populations of subjects who were 65 years of age or older. The results are as follows:

Table 4 Sample Classifications and Estimation for evaluation measures

Test Result	Samples (Diseased or not)			Estimations	
	Yes (D)	No ($\bar{D}$)	Total	diseased (D)	nondiseased ($\bar{D}$)
Positive (T)	436	5	441	$\hat{TPF} = 436/450$	$\hat{FPF} = 5/495$
Negative ($\bar{T}$)	14	495	509	$\hat{FNF} = 14/450$	$\hat{TNF} = 495/500$
Total	450	500	950	1	1

- Sensitivity = $\widehat{TPF} = 436/450 \approx 0.9689$
- Specificity = $\widehat{TNF} = 495/500 \approx 0.99$

Predictive values of a diagnostic test

Table 5 Statistical measures for evaluating a diagnostic test (II)

	Disease Status		Sum
	Diseased (D)	Nondiseased ($\overline{D}$)	
Positive (T)	Positive predictive value = $P\{D \mid T\}$	$P\{\overline{D} \mid T\}$	1
Negative ($\overline{T}$)	$P\{D \mid \overline{T}\}$	Negative predictive value = $P\{\overline{D} \mid \overline{T}\}$	1

- In the text book
  - Positive predictive value = Predictive value positive
  - Negative predictive value = Predictive value negative
- Notes on Estimation
  - Data from Table 3 cannot be directly used to estimate predictive values
  - If the disease prevalence, $P\{D\}$, is known, then the predictive values can be calculated from the sensitivity and specificity using Bayes' theorem

Bayes' Theorem

$$P\{D \mid T\} = \frac{P\{T \mid D\}P\{D\}}{P\{T \mid D\}P\{D\} + P\{T \mid \overline{D}\}P\{\overline{D}\}}$$

Sensitivity

Prevalence

1 − Prevalence

FPF = 1 −Specificity

$$P\{\overline{D} \mid \overline{T}\} = \frac{P\{\overline{T} \mid \overline{D}\}P\{\overline{D}\}}{P\{\overline{T} \mid \overline{D}\}P\{\overline{D}\} + P\{\overline{T} \mid D\}P\{D\}}$$

Specificity

1 − Prevalence

Prevalence

FNF = 1 −sensitivity

Bayes' Theorem

$$P\{D \mid T\} = \frac{P\{T \mid D\}P\{D\}}{P\{T \mid D\}P\{D\} + P\{T \mid \overline{D}\}P\{\overline{D}\}}$$

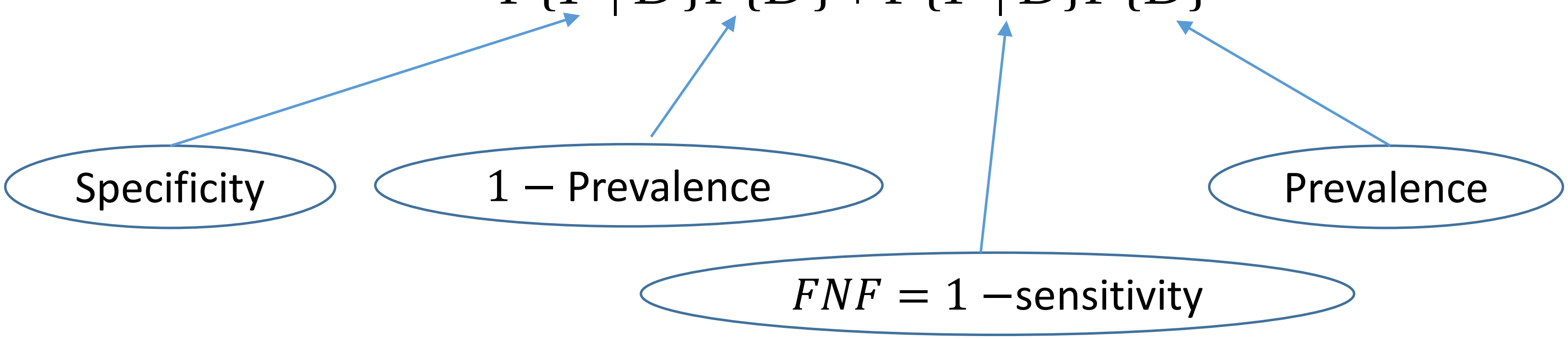
- Sensitivity → $P\{T \mid D\}$
- Prevalence → $P\{D\}$
- $FPF = 1 -$Specificity → $P\{T \mid \overline{D}\}$
- 1 − Prevalence → $P\{\overline{D}\}$

- Example 1 (continued)
  - Sensitivity = $P\{T|D\} \approx 0.9689$, Specificity = $P\{\bar{T}|\bar{D}\} \approx 0.99$
  - Assume disease prevalence is $P\{D\} = 0.113$ (age 65 or older)
  - Find the positive predictive value of the screening test

$$P\{D \mid T\} = \frac{0.9686 \times 0.113}{0.9686 \times 0.113 + (1 - 0.99) \times (1 - 0.113)} = 0.925$$

Bayes' Theorem

$$P\{\overline{D} \mid \overline{T}\} = \frac{P\{\overline{T} \mid \overline{D}\}P\{\overline{D}\}}{P\{\overline{T} \mid \overline{D}\}P\{\overline{D}\} + P\{\overline{T} \mid D\}P\{D\}}$$



- Example 1 (continued)
  - Sensitivity = $P\{T|D\} \approx 0.9689$, Specificity = $P\{\bar{T}|\bar{D}\} \approx 0.99$
  - Assume disease prevalence is $P\{D\} = 0.113$ (age 65 or older)
  - Find the negative predictive value of the screening test

$$P\{\overline{D} \mid \overline{T}\} = \frac{0.99 \times (1 - 0.113)}{0.99 \times (1 - 0.113) + (1 - 0.9689) \times 0.113} = 0.996$$

Bayes' Theorem

- Example 2
  - Alpha-fetoprotein Blood (AFP) Test is widely used in diagnosis of liver cancer. A study indicates that the sensitivity and specificity of AFP are 0.95 and 0.90. It was reported that the prevalence of liver cancer in a population is 0.0004. What are the predictive values of the test?
- Solution
  - $P\{T|D\} = 0.95, P\{\bar{T}|\bar{D}\} = 0.90, P\{D\} = 0.0004$
  - Positive predictive value:

$$P\{D \mid T\} = \frac{P\{T \mid D\}P\{D\}}{P\{T \mid D\}P\{D\} + P\{T \mid \bar{D}\}P\{\bar{D}\}}$$

$$P\{D \mid T\} = \frac{0.95 \times 0.0004}{0.95 \times 0.0004 + (1 - 0.90) \times (1 - 0.0004)} = 0.00379$$

  - Negative predictive value:

$$P\{\bar{D} \mid \bar{T}\} = \frac{P\{\bar{T} \mid \bar{D}\}P\{\bar{D}\}}{P\{\bar{T} \mid \bar{D}\}P\{\bar{D}\} + P\{\bar{T} \mid D\}P\{D\}}$$

$$P\{\bar{D} \mid \bar{T}\} = \frac{0.90 \times (1 - 0.0004)}{0.90 \times (1 - 0.0004) + (1 - 0.95) \times 0.0004} = 0.99998$$

Derivation of Bayes' Theorem

$$P\{D \mid T\} = \frac{P\{T \mid D\}P\{D\}}{P\{T \mid D\}P\{D\} + P\{T \mid \overline{D}\}P\{\overline{D}\}}$$

- $P\{D|T\} = \frac{P\{D \cap T\}}{P\{T\}}$ (Definition of conditional probability)
- $P\{D \cap T\} = P\{T|D\}P\{D\}$ (Multiplication rule)
- $P\{T\} = P\{T \cap D\} + P\{T \cap \overline{D}\}$ (Low of total probability)

$P\{T|D\}P\{D\}$ $\quad$ $P\{T|\overline{D}\}P\{\overline{D}\}$ $\quad$ (Multiplication rule)

General form of Bayes' Theorem

- Suppose that $A_1, A_2, \ldots, A_n$ are n mutually exclusive and exhaustive events, then

$$P\{A_i \mid B\} = \frac{P\{A_i\}P\{B \mid A_i\}}{P\{A_1\}P\{B \mid A_1\} + P\{A_2\}P\{B \mid A_2\} + \cdots + P\{A_n\}P\{B \mid A_n\}}$$

$$(i = 1, 2, \cdots, n)$$

- Sometimes we call
  - $P\{A_1\}, P\{A_2\}, \cdots, P\{A_n\}$ as prior probabilities.
  - $P\{A_1|B\}, P\{A_2|B\}, \cdots, P\{A_n|B\}$ as posterior prob abilities

- Bayesian Statistics (Methods)
  - Prior probability of an event – a probability based on prior knowledge, prior experience, or results derived from prior data collection activity
  - Posterior probability of an event – a probability obtained by using new in formation to update or revise a prior probability

Summary

- What we have learned
  - Events related to a diagnostic test
    - TP, FP, FN, TN
  - Measures for evaluating a diagnostics test
    - Sensitivity (*TPF*) and specificity (*TNF*)
    - Positive and negative predictive values
  - Bayes’ theorem
  - Given disease prevalence, how to calculate the predictive values from sensitivity and specificity
- Focuses
  - Understanding the concepts, relationship of the predictive values with sensitivity and specificity.
  - Application to clinical and translational researches

Homework (due Aug 3)

- Exercises 3.5.1 and 3.5.2 on page 83 (10^{th} Ed)
- Review exercises 9 (page 88) and 22 (page 90)