Screening and Diagnostic Tests

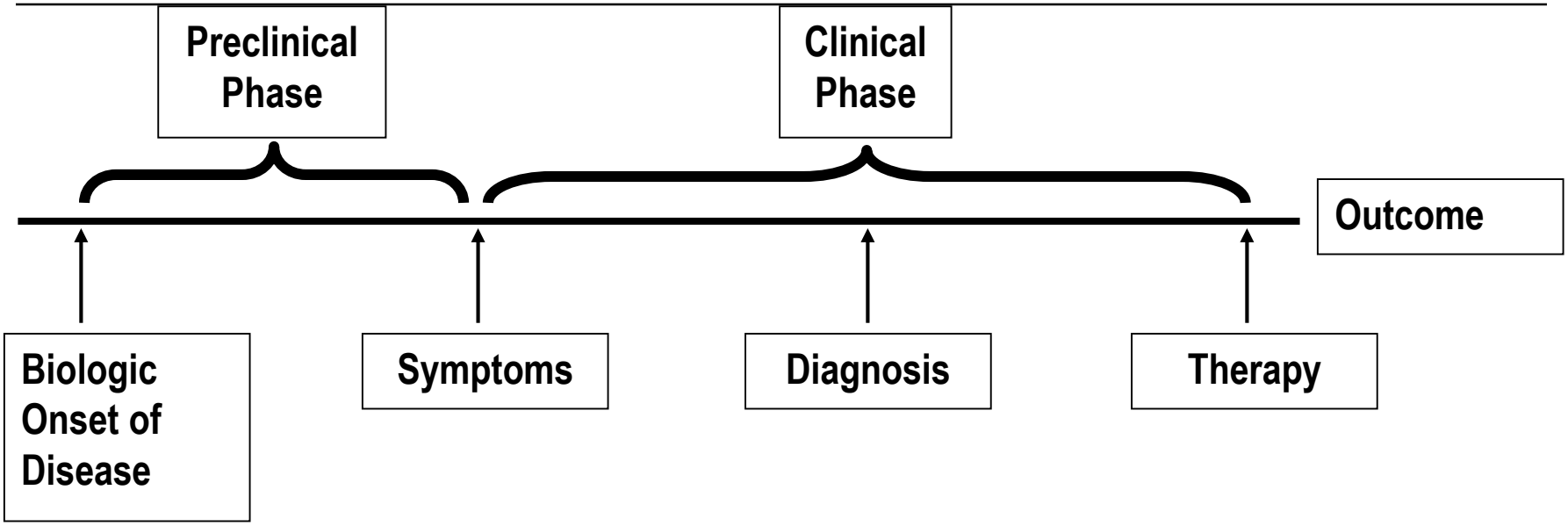
Learning Objectives

- Describe the general features of the natural history of disease
- Distinguish between primary, secondary, and tertiary prevention
- List the key characteristics of diseases appropriate for screening

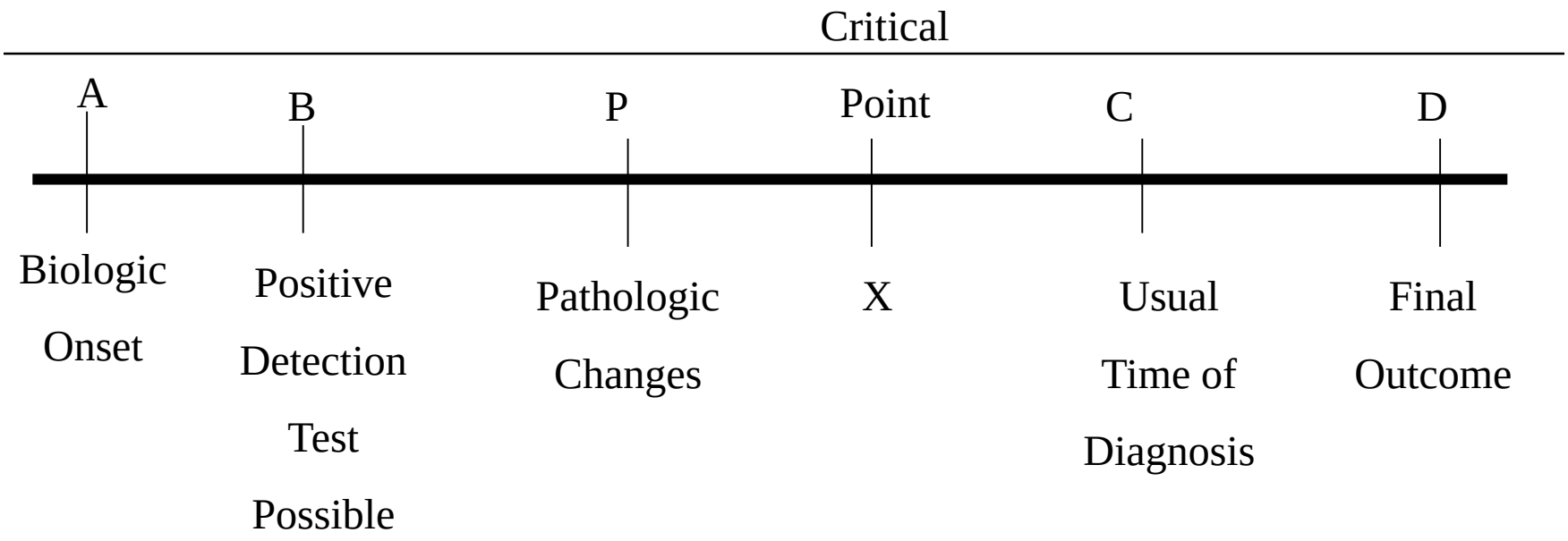
Learning Objectives (continued)

- Describe the important features of a screening test based on the hallmarks of a disease that make it appropriate for screening
- Define and calculate sensitivity, specificity, predictive value positive, and predictive value negative (performance characteristics of screening tests and programs)
- Define lead-time bias, length-bias sampling, and volunteer bias (biases in evaluating the effectiveness of screening programs)

Natural History of Disease

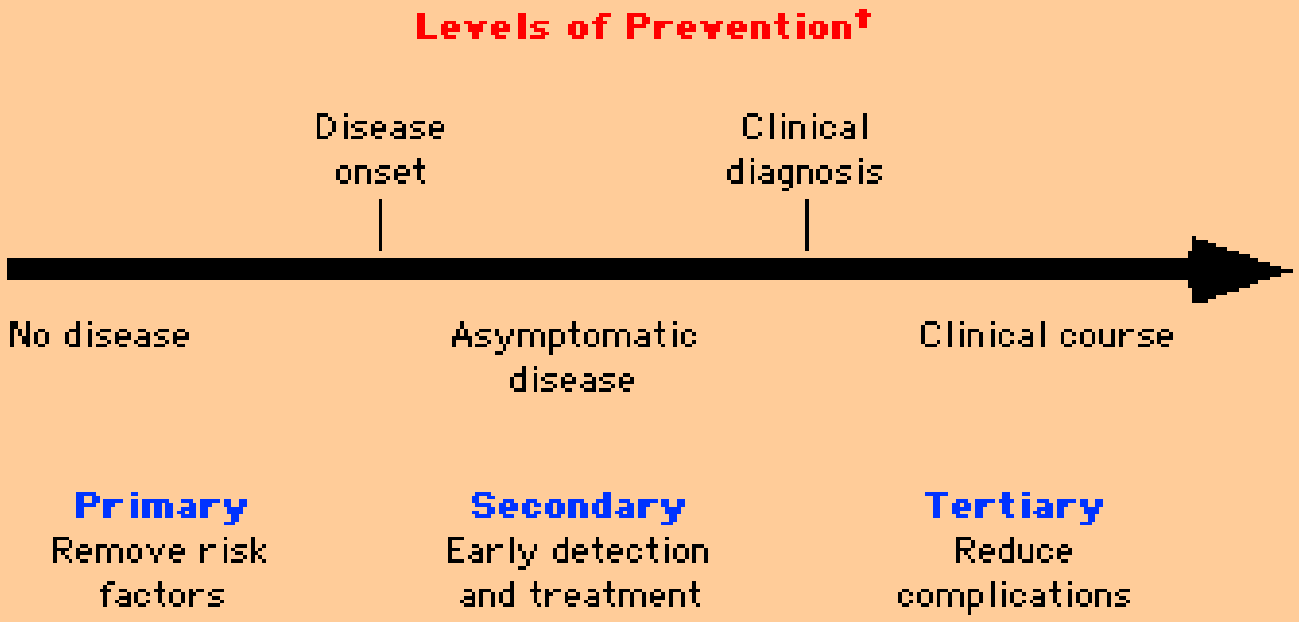


Time of Intervention



- Screening is beneficial if we can detect disease prior to time of usual clinical diagnosis and if treatment or control at this point is either more effective or easier to apply than treatment initiated later.

Prevention Types



†Adapted from Fletcher, RF, Fletcher, SW, Wagner, EH. Clinical Epidemiology: The Essentials, 3rd ed. Williams & Wilkins, Baltimore, 1996, p. 165.

Screening

- Identification of asymptomatic disease
- Typically employed as secondary prevention (Delays onset and duration of clinical disease with the goal to improve survival)
- Determine the presence of disease among apparently healthy patients

The presumptive identification of an unrecognized disease or defect by the application of tests, examinations or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment.

SCREENING

A Dictionary of Epidemiology 2001

Basic Principles of Screening

- Disease reasonably **prevalent** in the population screened and of reasonable severity to justify a screening program
- Effective **treatment available** for detected disease
- Preclinical stage is **detectable**
- Early detection **improves outcome** with acceptable morbidity

Examples of Diseases Appropriate for Screening

Cancer of the cervix

Diabetes

Breast cancer

Hypertension

Tuberculosis

Glaucoma

HIV

HIV meets all criteria

- Severe disease with very dire consequences: Case-fatality rate 56% (1981-2004)
- Disease is prevalent in the target population (e.g., intravenous drug users)
- Disease has a detectable preclinical phase (the seroprevalence of HIV among intravenous drug users have been reported to be 45%)
- Treatment at early stage is effective at reducing the disease sequelae

https://www.youtube.com/watch?v=R61QBvTBY68

Characteristics of a Screening Test

- Economical
- Convenient
- Relatively free of risk or discomfort
- Acceptable to a large number of individuals
- Highly valid and reliable

Examples

- Serology tests for markers for HIV
- Serology tests for markers for hepatitis B
- Serology tests for markers for TB
- Mammograms for the detection of breast cancer
- Pap smears for cervical cancer
- Blood pressure monitoring and cholesterol screening for heart disease
- Stool guaiac tests for colorectal cancer
- Visions tests for glaucoma

Validity

- Is the ability of a screening test to successfully separate those who have preclinical disease from those who do not have it

Sensitivity

- Is the probability that a test correctly classifies as positive individuals who have preclinical disease

Specificity

- Is the probability that a test correctly classifies individuals without preclinical disease as negative

Sensitivity vs. Specificity

$$\text{specificity} = \frac{\text{number of true negatives}}{\text{number of true negatives} + \text{number of false positives}}$$

$$= \frac{\text{number of true negatives}}{\text{total number of well individuals in population}}$$

$$= \text{probability of a negative test given that the patient is well}$$

$$\text{sensitivity} = \frac{\text{number of true positives}}{\text{number of true positives} + \text{number of false negatives}}$$

$$= \frac{\text{number of true positives}}{\text{total number of sick individuals in population}}$$

$$= \text{probability of a positive test, given that the patient is ill}$$

Disease presence and test results

- The true state of disease status as ascertained by gold standard
  - Present or absent

- What a test determines the disease status to be
  - Present (positive) or absent (negative)

- Possibilities after cross-classification then include
  - True positive: Disease present and test is positive
  - True negative: Disease absent and test is negative
  - False positive: Disease absent and test is positive
  - False negative: Disease present and test is negative

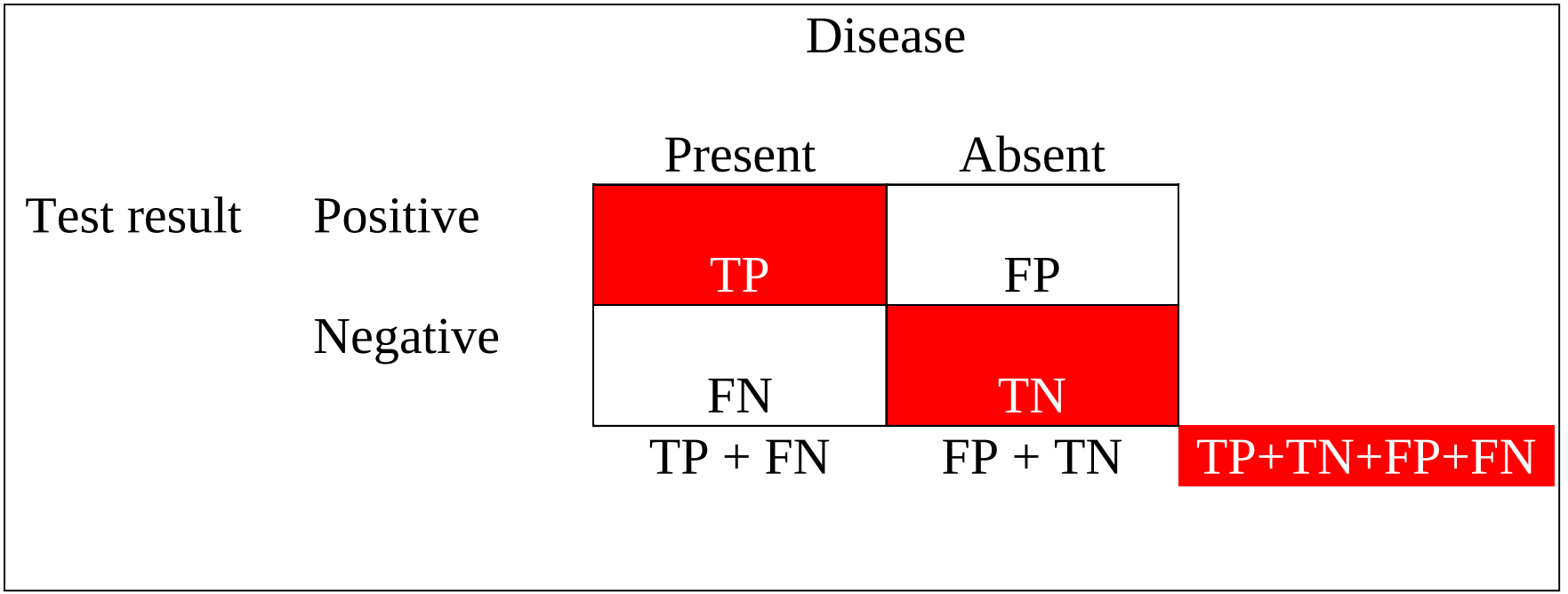
Comparison 2x2 table

		Disease, as ascertained by the gold standard: Present	Absent
Test result	Positive	TP	FP
	Negative	FN	TN
		TP + FN	FP + TN

TP = True positive
TN = True negative
FP = False positive
FN = False negative

Accuracy

- The proportion of test results that are correct



Accuracy = (TP+TN) / (TP+TN+FP+FN)

Sensitivity

- Proportion of those with disease who have a positive test result

		Disease	
		Present	Absent
Test result	Positive	100 TP	0 FP
	Negative	0 FN	100 TN
		TP + FN	FP + TN

Sensitivity (Se) = TP / (TP+FN)

Sensitivity application

- A sensitive test will rarely miss people with disease
- Use when it is important not to miss disease

Specificity

- Proportion of those without disease with a negative test result

		Disease	
		Present	Absent
Test result	Positive	100 TP	0 FP
	Negative	0 FN	100 TN
		TP + FN	FP + TN

Specificity (Sp) = TN / (FP + TN)

Specificity application

- Specific tests are useful for confirming diagnoses

Example of Sensitivity and Specificity

		Disease: Present	Disease: Absent	
Test result	Positive	34		Total Positive results =49
	Negative		282	Total Negative results=292

Sensitivity =?

Specificity =?

	Disease		Total
	Present	Absent	
Positive	34 TP	15 FP	49
Negative	10 FN	282 TN	292

Accuracy = (TP+TN) / (TP+TN+FP+FN) = (34+282) / (34+282+15+10) = 0.92

Sensitivity (Se) = TP / (TP+FN) = 34 / (34+10) = 0.77

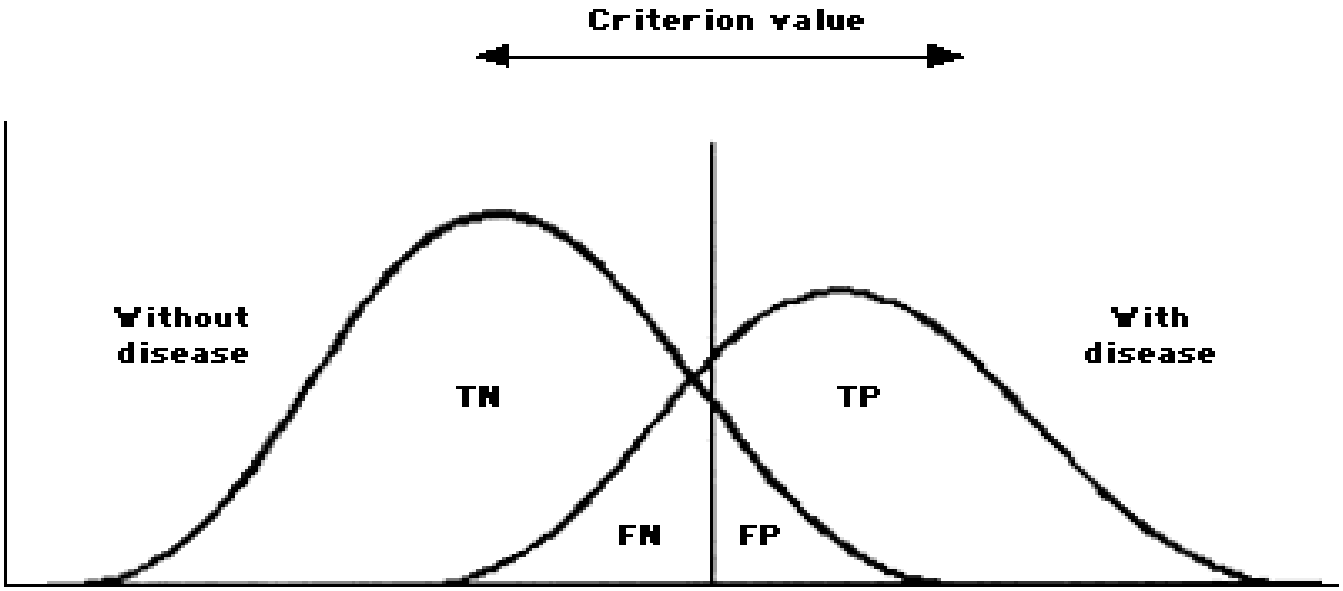
Specificity (Sp) = TN / (FP+TN) = 282 / (15+282) = 0.94

Sensitivity vs. Specificity

- Sensitivity and specificity can be improved at the expense of the other

- This can be considered when making cut-offs based on a test with a continuous measurement

Sensitivity & Specificity



Importance of cut-off value on test performance As the cut-off value is moved to the left, sensitivity (the true positive rate) increases, but specificity decreases. TN = true negatives, TP = true positives; FN = false negatives; FP = false positive.

Results of Breast Cancer Screening Program

	Breast Cancer		
Test	Yes	No	Total
Positive	190	796	986
Negative	10	39,004	39,014
Total	200	39,800	40,000

Sensitivity ?
Specificity ?

	Breast Cancer		
Test	Yes	No	Total
Positive	190 TP	796 FP	986
Negative	10 FN	39,004 TN	39,014
Total	200	39,800	40,000

Sensitivity (Se) = TP / (TP+FN) = 190 / (190+10) = 0.95

Specificity (Sp) = TN / (FP+TN) = 39,004 / (796+39,004) = 39,004 / 39800 = 0.98

Predictive value

- The probability of disease given the results of a test
- There are two types:
  - *Positive* predictive value (PPV)
  - *Negative* predictive value (NPV)
- The PPV is the proportion of individuals with a positive test who have preclinical disease
- The NPV is the proportion of individuals without preclinical disease who test negative

Positive predictive value (PPV)

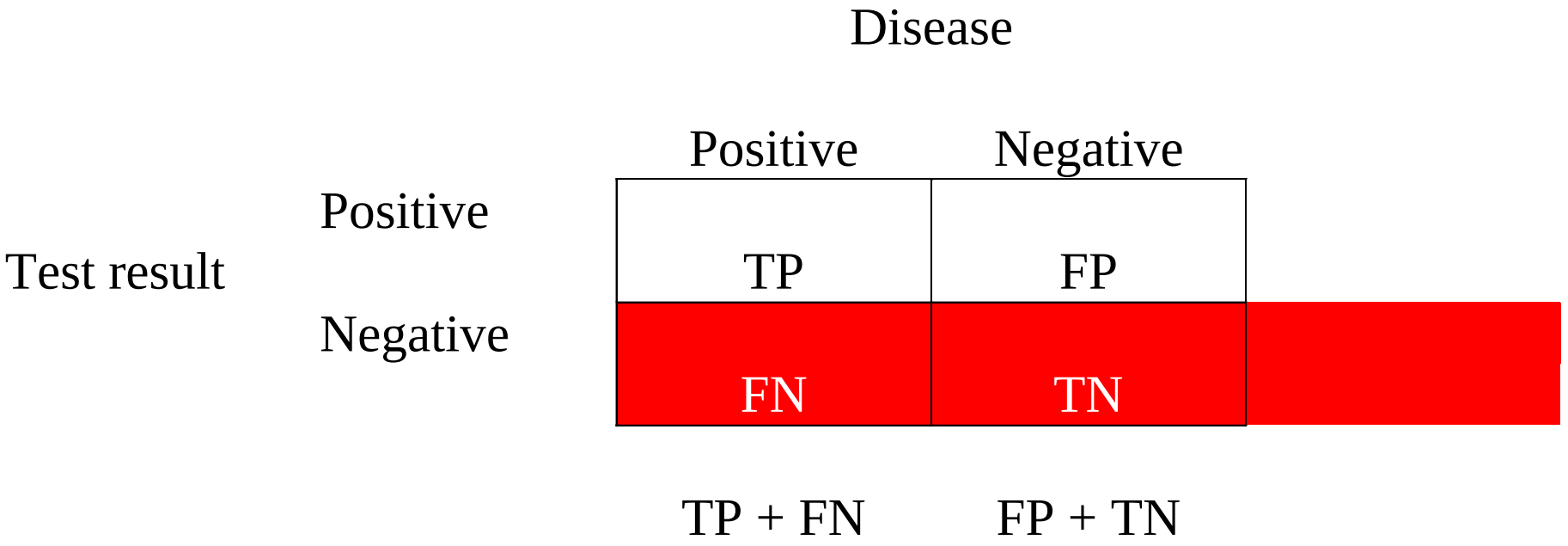
- Proportion of those with a positive test result who have disease

		Disease: Present	Disease: Absent
Test result	Positive	TP	FP
	Negative	FN	TN
		TP + FN	FP + TN

Positive predictive value (PPV) = TP / (TP+FP)

Negative predictive value (NPV)

- Proportion of those with a negative test result who do not have disease



Negative predictive value (NPV) = TN / (TN+FN)

$$\text{PPV} = \frac{\text{number of true positives}}{\text{number of true positives} + \text{number of false positives}} = \frac{\text{number of true positives}}{\text{number of positive calls}}$$

$$\text{NPV} = \frac{\text{number of true negatives}}{\text{number of true negatives} + \text{number of false negatives}} = \frac{\text{number of true negatives}}{\text{number of negative calls}}$$

	Breast Cancer		
Test	Yes	No	Total
Positive	190 TP	796 FP	986
Negative	10 FN	39,004 TN	39,014
Total	200	39,800	40,000

PPV = ?

NPV = ?

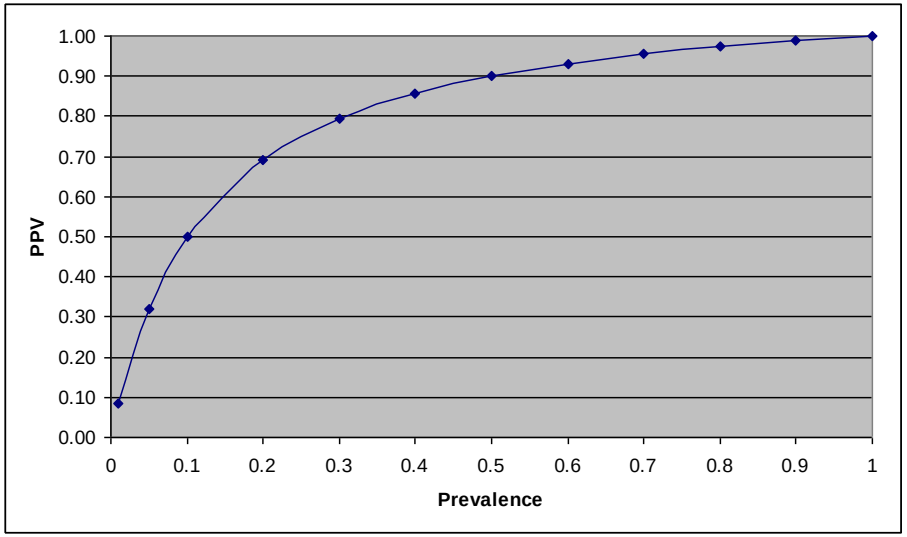
	Breast Cancer		
Test	Yes	No	Total
Positive	190 TP	796 FP	986
Negative	10 FN	39,004 TN	39,014
Total	200	39,800	40,000

PPV = TP / (TP+FP) = 190 / (190+796) = 190 / 986 = 0.19

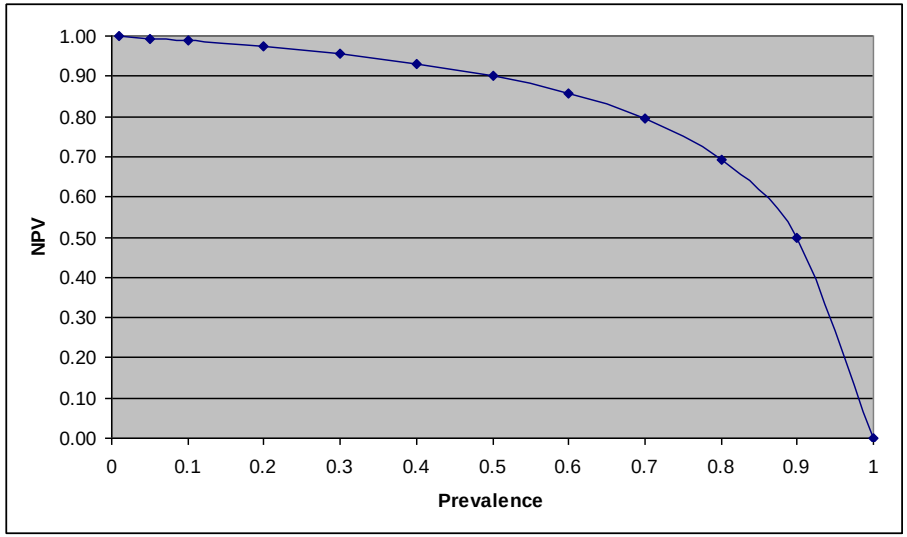
NPV = TN / (TN+FN) = 39,004 / 39,014 = 0.99

Effect of prevalence

- Prevalence of disease will affect the PPV and NPV
- Consider if there was:
  - An extremely small prevalence of disease
  - An extremely high prevalence of disease



PPV



NPV

The effect of prevalence on predicted values

Test result	Disease: Present	Disease: Absent
Positive	TP 34	FP 30
Negative	FN 4	TN 282

PPV = 53%
NPV = 99%
Prev = 11%

PPV=**TP**/(TP+FP)
NPV=TN/(TN+**FN**)

Test result	Positive	Negative
Positive	TP 93	FP 24
Negative	FN 12	TN 221

PPV = 79%
NPV = 95%
Prev = 30%

https://www.youtube.com/watch?v=qA52zndm9Hg

Likelihood ratios (LR)

- Another method of describing the performance of a test
- Summarize the same information as Se and Sp
- They can be used to calculate probability of disease status

"The probability of a test result among those with disease divided by the probability of a test result among those without disease"

- Express how many more times likely or unlikely a test result is found among diseased compared to non-diseased

Likelihood Ratio (+)

- The ratio of the proportion of diseased people with a *positive* test result (Se) to the proportion of non-diseased people with a *positive* test result (1-Sp)

		Disease	
		Present	Absent
Test result	Positive	TP	FP
	Negative	FN	TN

$$\frac{\text{Se}}{\text{1-Sp}} = \frac{\text{TP} / (\text{TP} + \text{FN})}{\text{FP} / (\text{FP} + \text{TN})}$$

Likelihood Ratio (-)

- The ratio of the proportion of diseased people with a *negative* test result (1-Se) to the proportion of non-diseased people with a *negative* test result (Sp)

		Disease: Present	Disease: Absent
Test result	Positive	TP	FP
	Negative	FN	TN

$$\frac{1\text{-Se}}{\text{Sp}} = \frac{\text{FN} / (\text{TP} + \text{FN})}{\text{TN} / (\text{TN} + \text{FP})}$$

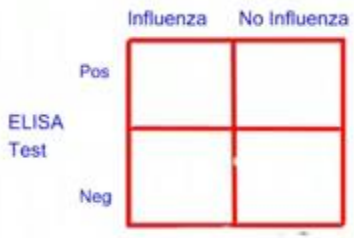
Likelihood ratios

- Likelihood ratio *positive*: sensitivity/(1-specificity)
  - 1-5 poor
  - 5-10 fair
  - >10 good

- Likelihood ratio *negative*: (1-sensitivity)/specificity
  - 0.5-1.0 poor
  - 0.1-0.5 fair
  - <0.1 good

200 patients are enrolled in a study to evaluate the accuracy of a new ELISA-based test for the diagnosis of influenza. 100 patients were diagnosed with influenza by the reference standard culture of respiratory secretions. 80 of the patients with influenza had a positive ELISA-based test as did 5 of the patients without influenza.

What is the postive likelihood ratio of the ELISA-based test?

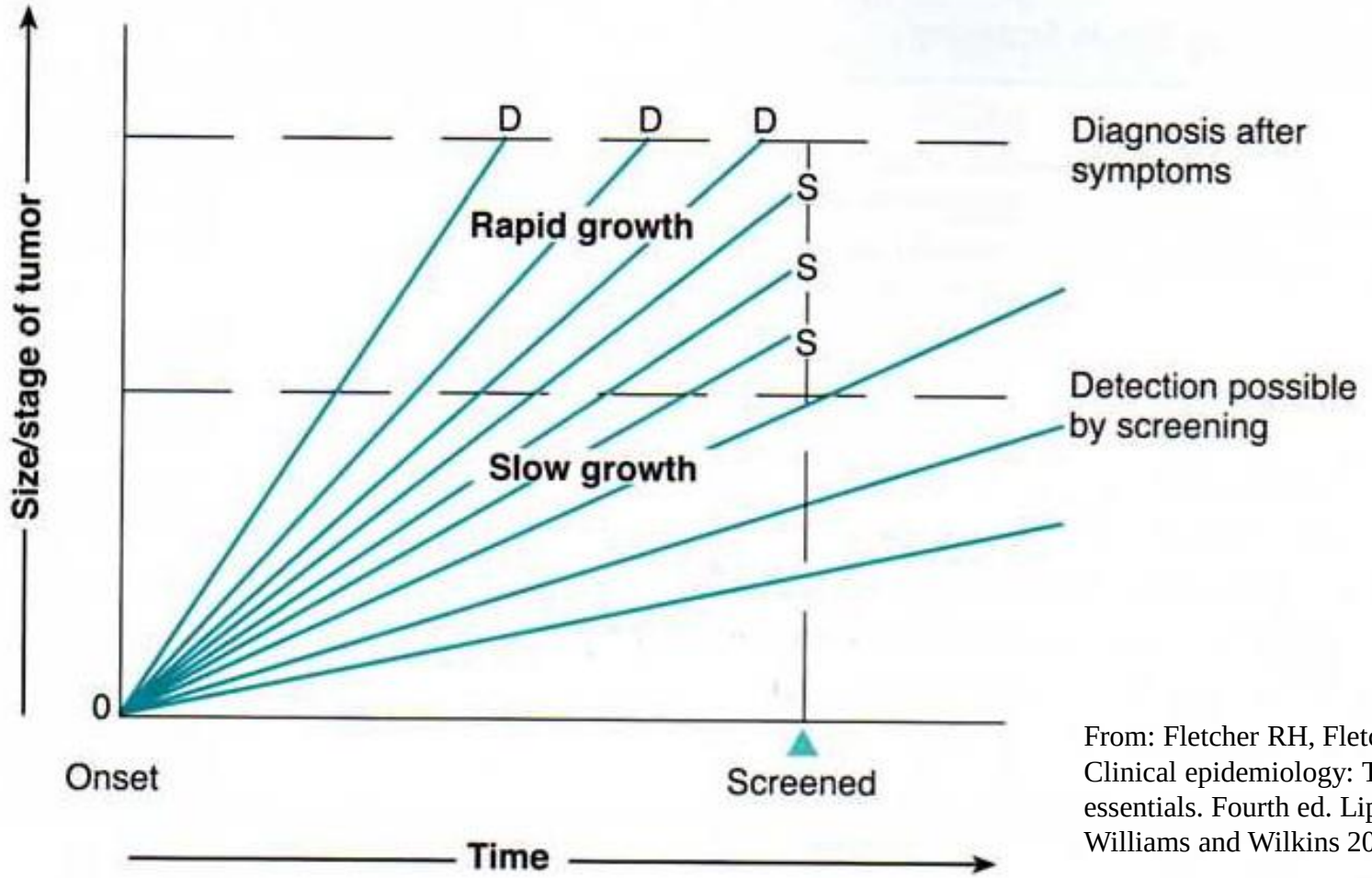


Bias in Screening

Length-time Bias

- **Length-time**: Time from onset of disease to development of symptoms resulting in diagnosis
- Depends on rate of progression of disease
- Screening works better for slow progressing conditions where slow growing conditions are more easily screened for than fast growing conditions
- Screening will tend to find conditions with better prognosis

Length-time Bias



From: Fletcher RH, Fletcher SW. Clinical epidemiology: The essentials. Fourth ed. Lipincott Williams and Wilkins 2005

Lead-time Bias

- **Lead-time**: the period between detection of a condition from screening to when it normally would be detected
- Depends on the rate of progression and how early a screening test can detect disease
- Effectiveness of intervention can depend on lead time
- A bias occurs when there appears to be an increase in survival but this is due to earlier detection even if early treatment is not effective

Lead-time Bias

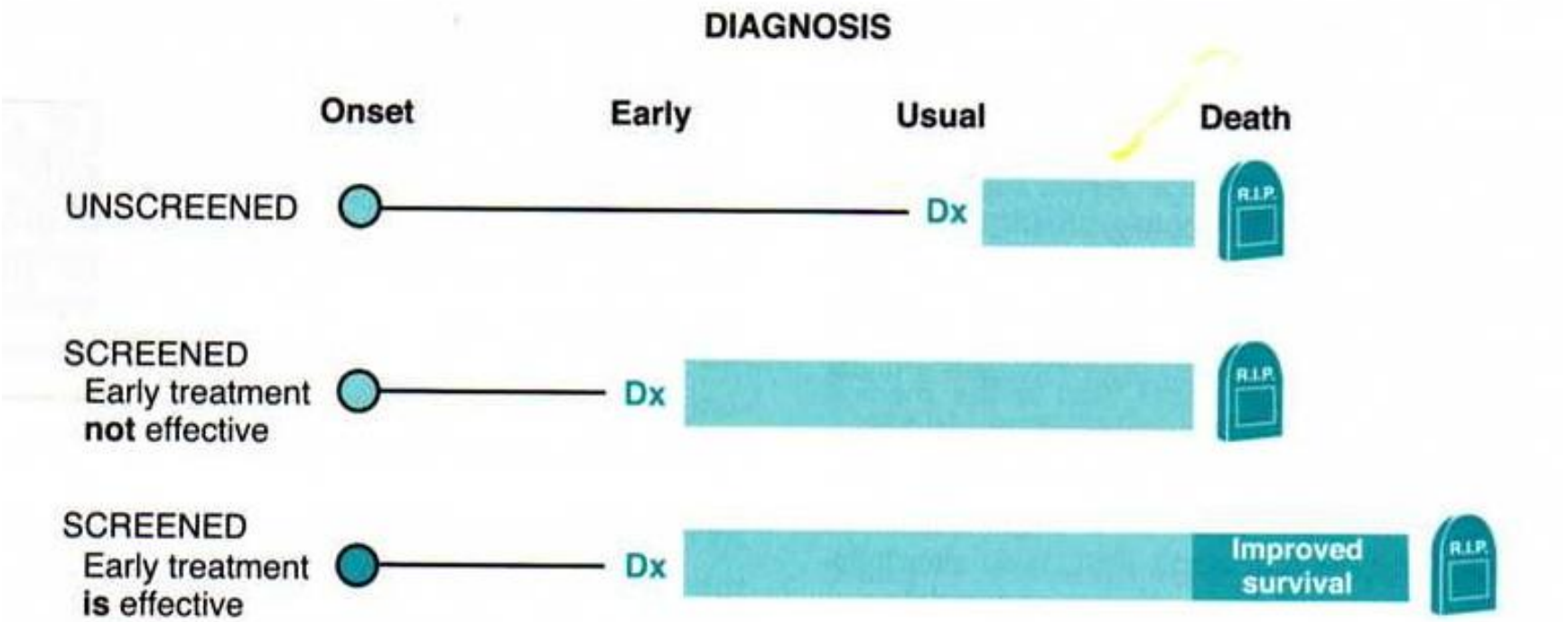


FIGURE 9.3 ■ How lead time affects survival time after screening; O = onset of disease. Shaded areas indicate length of survival after diagnosis (Dx).

From: Fletcher RH, Fletcher SW. Clinical epidemiology: The essentials. Fourth ed. Lipincott Williams and Wilkins 2005

Compliance Bias

- Results from the extent to which patients follow medical advice
- Compliant patients have better prognoses regardless of screening

Summary of Screening

- Objective is to come to a conclusion regarding the presence or absence of disease at an earlier stage in asymptomatic individuals
- Screening is part of prevention activities (primary, secondary, tertiary)
- Screening test: low cost, minimal risk, convenient, reliable, valid
- Describe the validity of the test
  - Se: The proportion of those with disease who test positive
  - Sp: The proportion of those without a disease who test negative
- Describe the use in a clinical setting and assess feasibility
  - PPV: The proportion of those with a (+) test who have the disease
  - NPV: The proportion of those with a (-) test who do not have disease
  - Affected by the prevalence of disease
- Consider three sources of bias: Lead-time bias, length-biased sampling, and volunteer bias

Accuracy	Ability of a test to correctly detect the **presence or absence** of a lesion
Sensitivity	Ability of a test to correctly detect the **presence** of a lesion
Specificity	Ability of a test to correctly detect the **absence** of a lesion
PPV	Frequency of **positive** initial diagnosis confirmed postoperatively
NPV	Frequency of **negative** initial diagnosis confirmed postoperatively

References

- Fletcher RH, Fletcher SW. Clinical epidemiology: The essentials. Fourth ed. Lipincott Williams and Wilkins 2005.
- Greenberg RS, Daniels SR, Flanders WD, Eley JW, Boring JR. Medical epidemiology. Fourth ed. Lange Medical Books/McGraw Hill 2001.
- Aschengrau A, Seage GR III. Essentials of epidemiology in public health. 2nd ed. Jones and Bartlett Publishers 2008.