

## Explanation:

[See Figure 1]

One of the objectives for the national Healthy People 2020 initiative is to reduce the prevalence of tobacco smoking in adults from 20% in 2008 to less than 12% by 2020. Tobacco use, especially smoking, is the single most preventable cause of death and disease in the United States. In addition to its numerous direct adverse effects, tobacco smoking also substantially increases the risk for macrovascular (eg, myocardial infarction [MI], stroke) and microvascular (eg, retinopathy, nephropathy) complications of diabetes mellitus. These complications significantly increase mortality, primarily by increasing the risk of MI. The risk of MI-associated mortality begins to decrease immediately upon smoking cessation. However, it takes several tobacco-free years before the risk returns to baseline, especially in patients with a long history of smoking. In addition, smokers with diabetes have a higher likelihood of developing hypercholesterolemia, poor glycemic control, and end-stage renal disease. It appears that smoking not only worsens the complications of diabetes but also increases the likelihood of developing diabetes in the first place, thus highlighting the importance of prevention and early cessation.

**(Choice A)** Fecal occult blood testing screens for colorectal cancer and improves mortality through earlier detection. Even so, the mortality benefit is much lower than that achieved by smoking cessation.

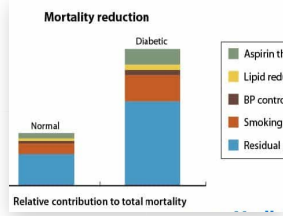
**(Choice B)** Prostate-specific antigen is increased in some patients with prostate cancer. However, annual prostate-specific antigen testing has not been shown to improve mortality from prostate cancer.

**(Choice C)** Aspirin use significantly reduces the risk of death from coronary heart disease in diabetic patients, at levels similar to smoking cessation. However, when all-cause mortality is compared, smoking cessation has a greater effect on reducing mortality than daily aspirin therapy.

**(Choices D, E, and G)** Dietary modification and exercise reduce the risk of cardiovascular disease (to a lesser extent than smoking cessation) and help improve glycemic control in diabetic individuals. Although tight glycemic control has been shown to reduce the risk of microvascular complications from diabetes, it does not significantly improve cardiovascular or all-cause mortality.

### **Educational objective:**

Smoking cessation is by far the most effective preventive intervention in almost all patients, and this is especially true in those with diabetes.



**Figure 1**

## Question 2 of 121

A new biomarker has been identified that allows for the early detection of invasive gastric carcinoma. It has a sensitivity of 89% and a specificity of 85% when compared to endoscopy with multiple biopsies. The test is used in 2 groups: a population in the United States, where 5 out of 100,000 people have gastric cancer, and a population in China, where 100 out of 100,000 people have been diagnosed with the disease. Which of the following is the most accurate statement concerning this new test?

- A Negative predictive value of the test is lower in the American population
- B Positive predictive value of the test is higher in the Chinese population**
- C Sensitivity of the test is higher in the American population
- D Specificity of the test is higher in the Chinese population
- E The test is not reliable in the American population

### Explanation:

**Positive condition    Negative condition**

<b>Positive test result</b>	TP	FP	PPV = TP / (TP + FP)
<b>Negative test result</b>	FN	TN	NPV = TN / (TN + FN)
	Sensitivity = TP / (TP + FN)	Specificity = TN / (TN + FP)	

**FN** = false negative; **FP** = false positive; **NPV** = negative predictive value; **PPV** = positive predictive value; **TN** = true negative; **TP** = true positive.

The **positive predictive value** (PPV) is defined as the proportion of individuals with positive test results who actually have the disease. This concept can be understood in terms of probability: given that a patient has a positive test result, what is the likelihood that he or she actually has the disease? PPV depends not only on the sensitivity and specificity of a test, but also on the **prevalence** of the disease in the population being tested. The more common the disease in the population, the more likely it is that a patient with a positive test result actually has the disease.

If the disease is relatively common (eg, gastric cancer in China), there is a higher probability that a patient who tests positive actually has the disease (ie, more likely to be a true positive). However, if the disease is relatively uncommon (eg, gastric cancer in the United States), a patient who tests positive will have a lower probability of actually having the disease (ie, more likely to be a false positive).

**(Choice A)** Like PPV, the negative predictive value (NPV) depends on disease prevalence. However, NPV is inversely associated with the prevalence: NPV increases as the disease prevalence decreases. This is because the probability of a true negative result is higher in a population with low disease prevalence (eg, gastric cancer in the United States).

**(Choices C and D)** Sensitivity and specificity are intrinsic test parameters that do not depend on the prevalence of disease in the tested population.

**(Choice E)** Reliability is a measure of the consistency (reproducibility) of a diagnostic test result (ie, if the test is taken multiple times, will the results be the same?). No information is provided to suggest that the gastric cancer biomarker is unreliable.

**Educational objective:**

Positive and negative predictive values depend on disease prevalence in the tested population. The sensitivity and specificity of a diagnostic test are not affected by disease prevalence.

### Question 3 of 121

A new biomarker has been shown to allow for the early detection of non-small cell lung carcinoma. A preliminary analysis on a cohort study of this new test demonstrates that its use prolongs survival of lung cancer patients by 3 months when compared to the survival of patients diagnosed by conventional methods. A secondary analysis reveals no difference in 6-month mortality rates between the 2 groups. Which of the following factors most likely explains the study results?

A Confounding

B Lead-time bias

C Length-time bias

D Measurement bias

E Observer bias

F Rare disease assumption

#### Explanation:

[See Figure 1]

**Lead-time bias** should always be considered when evaluating any screening test.

Lead-time bias is an **apparent increase in survival time** among patients undergoing screening when they actually have an **unchanged prognosis**.

Patients screened with more sensitive tests may appear to live longer only because the disease was detected earlier than had it been diagnosed clinically. The overall length of time from disease onset to death actually remains the same with or

without the earlier screening. To determine the actual effectiveness of the screening program, it is necessary to follow up patients for periods that are **longer** than the apparent increase in survival time, and then to estimate and compare mortality rates among patients who have undergone the additional screening and those who have not.

In this case, patients screened by the new test appeared to have increased their survival time by 3 months when compared to those diagnosed by conventional methods. However, there was **no difference in 6-month mortality** rate between the 2 groups, which indicates that there is no actual benefit to the screening program.

**(Choice A)** Confounding distorts the relationship between risk factors and the disease of interest, and can wholly or partially account for the observed effect. Although the results of this study could be potentially confounded, there is no information on how potential confounders were treated during the design or analysis stage of the study.

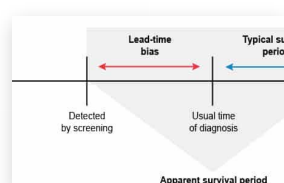
**(Choice C)** Length-time bias occurs when subjects with a rapidly progressive form of disease are less likely to be detected by screening compared to those with slowly progressive disease. This bias tends to overstate the beneficial effects of screening on length of survival and mortality. In this case, there is no indication that the patients identified by the new test have more benign forms of lung cancer.

**(Choices D and E)** Measurement bias and observer bias refer to the misclassification of outcome and/or exposure (eg, labeling diseased as non-diseased and vice versa) and are related to poor study design. The scenario described does not mention how the study was conducted.

**(Choice F)** Rare disease assumption refers to the practice of approximating the odds ratio and relative risk when conducting a case-control study for rare diseases. According to the assumption, the odds ratio approximates relative risk when disease incidence is low (eg, <10%).

### **Educational objective:**

Lead-time bias occurs when a new test diagnoses a condition earlier than conventional studies, causing an apparent increase in survival time despite no improvement in overall mortality. Long-term mortality rates, not survival times, should be considered for measuring the effect of early screening and treatment.



**Figure 1**

## Question 4 of 121

A 73-year-old man comes to the office for follow-up. He was diagnosed with chronic lymphocytic leukemia (CLL) 3 years ago when routine laboratory testing revealed a markedly elevated leukocyte count. He feels well. On examination, he has stable lymphadenopathy. He has been reading about management options should his CLL progress and inquires about an experimental drug that selectively binds malignant lymphocytes. The drug has been shown to significantly prolong survival in patients with stage 3 and 4 CLL, without curing the malignancy. If this new drug were widely used, what changes would be expected in the number of incident and prevalent cases of CLL?

- A The number of incident cases will decrease, the number of prevalent cases will decrease
- B The number of incident cases will increase, the number of prevalent cases will not change
- C The number of incident cases will decrease, the number of prevalent cases will increase
- D The number of incident cases will not change, the number of prevalent cases will increase**
- E The number of incident cases will not change, the number of prevalent cases will not change

### Explanation:

**Incident cases** represent **new cases** diagnosed in a given period of time.

**Prevalent cases** are the **total number of cases** (both old and new) at a particular

point in time. For a non-transmissible condition such as chronic lymphocytic leukemia (CLL), the number of incident cases will **not** be changed by any kind of treatment because the disease has already developed when the treatment is started (and treatment of existing patients will not prevent new patients from developing CLL). Any treatment that prolongs survival but does not cure the disease will **increase** the number of prevalent cases due to an increase in the number of afflicted (but still living) individuals over time.

Differences in terminology may lead to confusion. Incident cases and prevalent cases are often referred to as simply "incidence" and "prevalence." Incidence can also represent the number of new cases divided by the population at risk over a period of time and can be converted into a rate (eg, annual incidence per 10,000 population). Prevalence typically refers to point prevalence (total number of cases at a particular point in time) as opposed to period prevalence (over a period of time). The specific meaning is often clear from the context.

**Educational objective:**

Incident cases represent new cases diagnosed in a given period of time. Prevalent cases are the total number of cases (both old and new) at a particular point in time. Any treatment that prolongs survival but does not cure the disease will increase prevalence due to an increase in the number of afflicted (but still living) individuals over time.

## Question 5 of 121

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A large study of serum folate levels in a sample of women age 16-45 reveals that this parameter is normally distributed with a mean of 5.0 ng/mL and a standard deviation of 0.5 ng/mL. According to the study results, 95% of serum folate observations in these patients will lie approximately between which of the following limits?

**A** 3.5 and 6.0 ng/mL

**B** 3.5 and 6.5 ng/mL

**C** 4.0 and 6.0 ng/mL

**D** 4.0 and 5.5 ng/mL

**E** 4.5 and 5.5 ng/mL

### Explanation:

[See Figure 1]

A **normal (Gaussian) distribution** is defined as a symmetrical, bell-shaped distribution curve. One of the most important attributes of the normal distribution is the "**68/95/99 rule**," which states that 68% of all observations lie within 1 standard deviation (SD) of the mean, 95% within 2 SDs of the mean, and 99.7% within 3 SDs of the mean. The SD is a measure of dispersion or variance (how far the measurements are from one another). In this example, the mean folate level is 5.0 ng/mL with a SD of 0.5 ng/mL. Therefore:

- 4.5-5.5 ng/mL is the range within +/- 1 SD of 5.0 ng/mL (given that  $5.0 - 1 \times 0.5 = 4.5$  ng/mL and  $5.0 + 1 \times 0.5 = 5.5$  ng/mL);
- 4.0-6.0 ng/mL is the range within +/- 2 SDs of 5.0 ng/mL (given that  $5.0 - 2 \times 0.5 = 4.0$  ng/mL and  $5.0 + 2 \times 0.5 = 6.0$  ng/mL)
- 3.5-6.5 ng/mL is the range within +/- 3 SDs of 5.0 ng/mL (given that  $5.0 - 3 \times 0.5 = 3.5$  ng/mL and  $5.0 + 3 \times 0.5 = 6.5$  ng/mL)

Based on the 68/95/99 rule, approximately 95% of observations lie within 2 SDs of the mean, so between 4.0 and 6.0 ng/mL in this case. These are helpful approximations; to be more precise, 95% of the observations lie within 1.96 SDs of the mean and 95.45% of the observations lie within 2 SDs of the mean.

Note that SD is used to describe individual observations in a dataset. A closely related measure called standard error (SE) is used to show how closely sample means are related to population means;  $SE = SD / \sqrt{n}$ , where n is the sample size. In this example, if SE had been given instead of SD, investigators would be 95% confident that the true mean folate level in the underlying population lies within the mean +/- 2 SE (which is also the range that would include 95% of sample means calculated from repeated samples of the same size taken from that population).

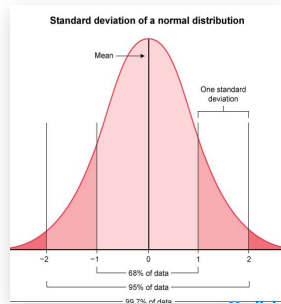
**(Choices A and D)** These limits are asymmetric and are therefore inconsistent with a normal distribution curve around the mean.

**(Choice B)** Approximately 99.7% of all observations lie within 3 SDs of the mean (3.5-6.5 ng/mL).

**(Choice E)** Approximately 68% of all observations lie within 1 SD of the mean (4.5-5.5 ng/mL).

**Educational objective:**

In a normal (bell-shaped) distribution curve, 68% of observations lie within 1 standard deviation (SD) of the mean, 95% of observations lie within 2 SDs of the mean, and 99.7% of observations lie within 3 SDs of the mean.



**Figure 1**

## Question 6 of 121

Researchers conduct a prospective study that demonstrates an association between alcohol consumption and transitional bladder carcinoma, with a relative risk (RR) of 1.81 and a p-value of 0.03. They then divide the study subjects into 2 groups, smokers and non-smokers, and again examine the association between alcohol consumption and bladder cancer:

	RR	P-value
Smokers	0.95	0.87
Non-smokers	1.03	0.96

The discrepancy between the overall results and the stratified results is best explained by which of the following?

**A** Confounding

**B** Effect modification