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Case Report

Pretest Probability in Laboratory Medicine: An Educational Review

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Abstract

Pretest probability is the likelihood of a screened patient having the disease and is estimated before the test result is known. This estimation is a critical skill for physicians and requires an understanding of biostatistics such as sensitivity, specificity, and positive predictive value. One of our key educational objectives is to convince the reader that most positive test results will be false positives when there is a low prevalence of the disease in the patient population to which the patient belongs. This is because a lab test's sensitivity and specificity come from data that are specific to a particular study population, and a particular patient may or may not have similarities to those in the study population. A judicious use of lab tests can help the physician diagnose the patient's condition, while a misguided use of lab tests can mislead the physician and potentially lead to unnecessary and/or harmful interventions.

Introduction

Clinicians must often judge what the pretest probability is for a clinical diagnosis before the use of a diagnostic test. This probability is defined as the chance a patient has the disease before the test result is known.[1] Estimation of this value is helpful for diagnostic purposes and is a critical skill for physicians to have. Clinically, diagnostic tests are often unnecessary when the pretest probability is either high or low, as it may not provide useful and accurate information that the physician does not already know.

A high enough pretest probability can guarantee initiation of a treatment, while a low pretest probability can exclude the presence of the disease without need for further testing. A diagnostic test is often only useful when there is diagnostic uncertainty as it can provide clues into honing down the differential diagnosis. Thus, when the pretest probability is not at either extreme, one or more diagnostic tools may be required for confirmation.

Our goal of this educational review is to evaluate the impact of differing pretest probabilities on the positive and negative predictive value of the test using two fictional case examples. We hope these case examples will exemplify the utility and pitfalls of using pretest probability in clinical scenarios by illustrating statistical extremes of population prevalence that may be seen. When used correctly, pretest probability can

be helpful in evaluating clinical diagnoses, developing screening tools, and elaborating on treatment protocols. Caution must be taken to avoid its misinterpretation.

Case Example 1

A 20-year-old male patient presents with fever, chills, muscle aches, rash, fatigue, sore throat, mouth ulcers, and swollen lymph nodes. He states these debilitating symptoms have progressively gotten worse over the past month. The patient notes he has been sexually active with 10+ partners in the last 6 months and never uses condoms. He also reports he engages in intravenous drug use about 3 times a week and routinely shares needles.

The patient tests positive for HIV using a novel test. This lab test was performed on 10,000 high-risk men, and the results from that population study are shown in Table 1.

	No. of high-risk men with HIV	No. of high-risk men without HIV	Total
Number of high-risk men with positive HIV test	7149 (TP)	190 (FP)	7339
Number of high-risk men with negative HIV test	176 (FN)	2485 (TN)	2661
Total	7325	2675	10,000

Table 1: Data Relevant to High-Risk Patient

Sensitivity is the percentage of individuals with disease who have a positive test result. Mathematically, Sensitivity = True positives / (True positives + False negatives).[1] Using the data in Table 1, the sensitivity is:

TP / (TP + FN) = 7149 / (7149 + 176) = 7149/7325 = 0.976 = 97.6%

Specificity is the percentage of individuals without disease who have a negative test result.[1] Mathematically, Specificity = True negatives / (True negatives + False positives). Using the data in Table 1, the specificity is:

TN / (TN + FP) = 2485 / (2485 + 190) = 2485/2675 = 0.929 = 92.9%

Prevalence is the number of people in the sample with the characteristic (disease) of interest, divided by the total number of people in the sample.[1] Mathematically, Prevalence = TP / total study population. Using the data in Table 1, the prevalence is:

TP / (total study population) = 7325/10,000 = .733 = 73%

Positive Predictive Value (PPV) is the percentage of individuals with a positive test result who truly have the disease.[1] Mathematically, PPV = True positives / (True positives + False positives). Using the data in Table 1, the PPV is:

PPV = TP / (TP + FP) = 7149 / (7149 + 190) = 7149/7339 = 0.974 = 97.4%

This patient has a high pretest probability because he belongs to a patient population with a high prevalence. In other words, he has a high chance of having the disease even before the test result is known due to his abundance of risk factors as well as his signs and symptoms. A high prevalence of disease within this patient's sample population leads to a high positive predictive value for this patient. This means that positive tests will tend to be true positives when the test is applied to patients who have high pretest probabilities.

The estimation of a patient's pretest probability is a critical skill for physicians. With this skill, tests can be employed with efficiency and prudence. Without this skill, tests may mislead the physician and potentially lead to unnecessary procedures and treatments.[2] In sum, a clinical judgment often plays a larger role in the diagnosis than a test does.[3]

Case Example 2

At the same time, a 55-year-old female presents to a blood donor center to donate blood. She states she feels well and she also answers no to every question in the donor health questionnaire that asks about medical conditions, high risk behaviors, and exposures. The same novel HIV test is required as part of donation. The test is positive. Data for the relevant study population is shown in Table 2.

	No. of low-risk women with HIV	No. of low-risk women without HIV	Total
Number of low-risk women with positive HIV test	8 (TP)	98 (FP)	106
Number of low-risk women with negative HIV test	1 (FN)	9893 (TN)	9894
Total	9	9991	10,000

Table 2: Data Relevant to Low-Risk Blood Donor

When we repeat the same calculations, we obtain these values.

Sensitivity = TP / (TP + FN) = 8 / (8 + 1) = 8/9 = 0.889 = 88.9%

Specificity = TN / (TN + FP) = 9893 / (9893 + 98) = 9893 / 9991= .990 = 99.0%

Prevalence = 9/10,000 = .0009 = .09%

Positive Predictive Value = TP / (TP + FP) = 8 / (8+ 98) = 8/106 = .0755 = 7.55%

The donor center physician defers her from donating blood and counsels her. Further diagnostic and clinical workup confirm that the patient indeed had a false positive.

This is an extremely low positive predictive value. This indicates a low number of true disease cases are identified out of all positive test results. Because the donor had a low pre-test probability of having the disease, there is a very high chance of a false positive. The low PPV can make it appear as if a good laboratory test is relatively ineffective.[1] If the test is used selectively on a population of individuals likely to have a disease, then the same test will have an excellent PPV (as seen in Case Example 1).[1] In short, when the prevalence of disease is very low in certain population, the positive predictive value will also be very low when it is applied to an individual who belongs to that population. This is true even for a test with a high sensitivity and specificity.

Two other helpful ways to think about this are the following. One, when the prevalence in the population to which your patient belongs is markedly lower than the false positive rate, then most positives will be false positives. For the blood donor, the prevalence was about 2 orders of magnitude lower than the false positive rate (~0.1% vs ~10%). Secondly, a lab test's sensitivity and specificity are calculated from data that are specific to a particular study population. A given patient may or may not have similarities to the study population that was used to calculate the sensitivity and specificity of that lab test. In sum, a test's sensitivity and specificity are not merely specific to a disease but specific to a disease that was observed in a particular patient population.

Thus, when a test is used on people with very low pretest probabilities, a large proportion of people with positive tests will inevitably be found not to have the disease upon further investigation. In the case of the blood donor, she had a very low pretest probability of having HIV. In other words, the patient population to which she belongs had a low prevalence of HIV, and the prevalence is a key determinant of the PPV.[4]

A liberal use of laboratory tests in low-risk patients tends to increase the risk of unnecessary interventions with the attendant risks, costs, and psychological stress.[5] In addition to physical harms than can occur with invasive interventions, the less physical harms are often overlooked.[5,6] A mindful use of labs and other tests tends to lead to an accurate diagnosis while minimizing those tradeoffs. These examples illustrate how low or high pretest probability alone can often guide decisions.[7] While the incentives and temptations to over-test are great in number and magnitude, tests are often best used in cases of diagnostic uncertainty and when committed to act on the result.[8,9,10]

Conclusion

Pretest probability is the chance that the patient has the disease and is estimated before the test result is known. This estimation is a critical skill for physicians. Most positive test results will be false positives when the false positive rate of the test is significantly higher than the prevalence of the disease in the population to which the patient belongs. This nuance of laboratory testing is not widely appreciated.11 One key reason is that a lab test's sensitivity and specificity come from data that are specific to a particular study population, and a given patient may or may not have similarities to those in the study population.12,13 The assessment of an individual patient's similarity to a study population is the fundamental task of every physician.

In sum, a judicious use of lab tests can help the physician diagnose the patient's condition, while a misguided use of lab tests can mislead the physician and potentially lead to unnecessary and/or harmful interventions. Diagnostic tests are often unnecessary when the pretest probability is either very high or very low, while they are often useful when there is diagnostic uncertainty. A lab test result cannot be interpreted in isolation and out of context; it must be integrated with all the other relevant data. The caveat, "Clinical correlation is recommended," sounds glib on the surface but contains much wisdom.

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