

# POPULATION MEDICINE NEWS

Epidemiology, Preventive Medicine, Public Health  
Production Medicine, Computer Applications in Vet Med

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## FOREKNOWLEDGE

### Its central role in interpreting clinical tests

*Can the same test result have opposite meanings depending on one's foreknowledge? Not only is this so, but an extension of the underlying principle is at the core of modern diagnostic theory.*

NORMAL	10
ABNORMAL	31

### Quiz: Last week on Oprah...

you saw a lady with some mysterious genetic disease; they said it only occurs in one out of 1 million people. Being a hypochondriac, you were sure that you had it. You certainly had one of the symptoms: waking up in a cold sweat at 3 AM dreaming of epidemiology and predictive values (a hint). So you marched right down to the hospital and had a test run for the disease. Sure enough, yours came back positive.

You had some free time on the way to the lawyer's to make out your will, so you stopped in at the library to look up some articles on your malady. One interesting piece of data you found was that the test is 99.5% specific and 98.9% sensitive. Assuming that there is no reason to believe that you should have been at any higher risk than the general population, what is the probability that you really have the disease?

1.
  - A. < 5% probability
  - B. 6-25% probability
  - C. 26-50% probability
  - D. 51-75% probability
  - E. 76-95% probability
  - F. > 95% probability
  - G. none of the above

As you continue your reading, you discover that this disease is known to have a simple Mendelian inheritance and is manifested only in homozygous recessives (ie, only bb's are affected, not BB's or Bb's). Another point, important to consider for those of us deficient in X-chromosomes, is that the disease is autosomal and, thus, not sex linked. Likewise, the correct answer to the next question is not sex linked.

When you stopped by to drop a copy of

the will off at your Mom's, she tearfully informed you that both she and Pop are carriers (Bb). Repeat your calculation with this new knowledge and put the letter of your choice here: 2. \_\_\_\_\_.

After performing these calculations, you fetch your Epidemiology notes in an attempt to understand how the meaning of the same test result leads to entirely different conclusions based on foreknowledge. 3. Explain this to yourself before proceeding.

### THE ANSWERS

If you answered "A" for the first question and "F" for the second, and if you really believed that "A" and "F" were the right answers rather than just choosing them in a vain attempt to avoid looking like a bonehead, then count yourself among the exceptional and brilliant few to whom predictive values are intuitive. The other 99.99% of us will need to consider the following discussion.

### DISCUSSION

However high or low they may be, sensitivity and specificity are not directly useful to practitioners. Consider their definitions.

**Sensitivity:** given a known positive individual, the probability that it will test positive.

**Specificity:** given a known negative individual, the probability that it will test negative.

The obvious trouble with these definitions from a practitioner's perspective is that we are never given a known negative or known positive individual. Why would we be doing further tests on a known negative or known positive? The probabilities in which a practitioner is interested are those associated with positive and negative test results. Given a positive test result, what is the chance that the individual truly has the condition

in question? Given a negative test result, what is the chance that the individual is truly free of the condition in question? These probabilities, called predictive values, are not the same as sensitivity and specificity.

Let us now determine the predictive value of your positive test PRIOR to your finding out about Mom's little secret. We could plug-in a complicated formula for computing predictive value, but let's take an intuitive route in hopes of gaining true intellectual enlightenment. Now, 99.5% specificity sounds pretty good, but you have to admit that there will be false positives—0.5% of the true negatives tested will give false positive results. A measly 1/2% doesn't sound like much until you test a million people; then you'll have 5000 falsely branded citizens on your hands. The benefit derived from causing all this trouble is the detection of the single true positive you fully expect to correctly identify since the test sensitivity is 98.9%.

Now, here's the where the brain work comes in. You've tested yourself a million people and found how many positives? Well, that would be, let's see, 5000 false positives + 1 true positive equals... mmm ...5001 total positives. And what percent of those truly have the disease? You divide 1 true positive by 5001 total positives and your trusty calculator says 0.0002 or 0.02%. If your calculations are correct, far, far less than 1% of test positive people are expected to really have the disease; this in spite of the seemingly superb specificity and sensitivity. We call this computation the predictive value of a positive test.

Why would you ever want to use such a test? There are at least 2 reasons, one of which is illustrated in question 2 of the Oprah scenario (the other in ref 1). Suppose you test people for this recessive, genetic disease only AFTER you have

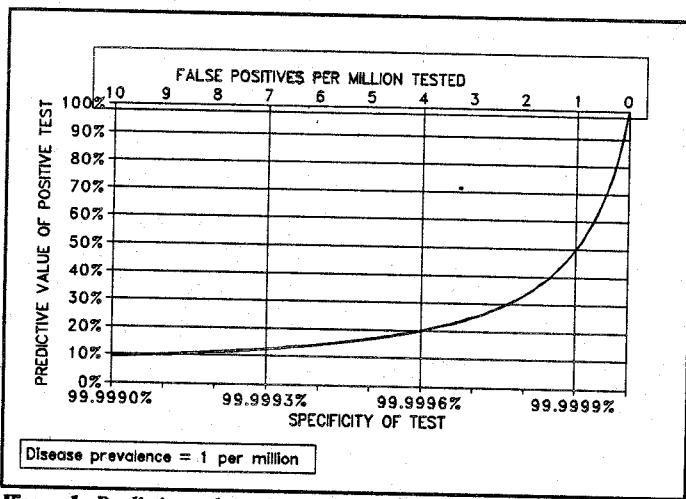


Figure 1. Predictive value of a positive test in a population with a 1 per million prevalence.

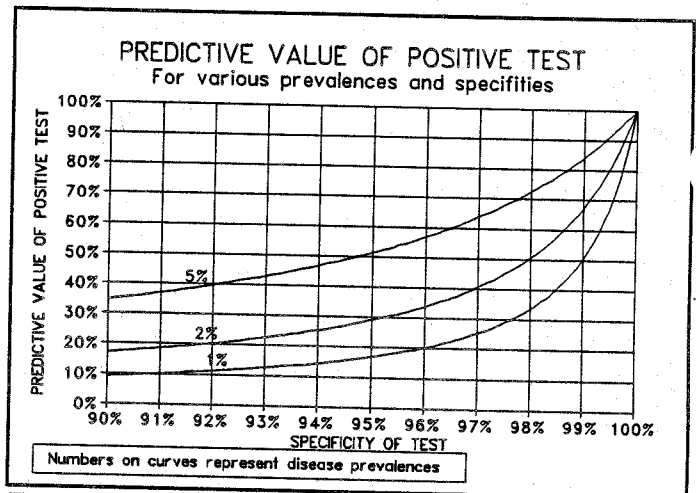


Figure 2. Predictive values of positive tests are low for many of the diseases veterinarians deal with even though test specificities are high.

identified both their parents as carriers. What is the probability of disease in this small subgroup of the entire population? As you remember from Genetics class, the probability is 25%. If you test, say, 100 people who have 2 carrier parents, what would you expect to find? You anticipate 25 true positives and expect to detect 98.9% of them. Your calculator reads "24.725". Since you are dealing with probabilities here and could have chosen expectations based on more than 100 people, you wisely elect to carry all your digits. How many false positives do you expect? That would be  $75 * 0.005 = .375$ . And computing the predictive value of a positive test, we obtain

$$24.725 / (24.725 + 0.375) = 98.5\%$$

That is, if we perform the test on people AFTER they have discovered their parents are both carriers, the predictive value of a positive test is 98.5%; whereas, had we performed the same test without knowing parental status, the predictive value of any positive tests we obtained would have been a mere 0.02%.

Ergo, we make opposite interpretations from the same test, potentially on the same people, depending on one factor and one factor alone: FOREKNOWLEDGE. Those with a mathematical background will recognize these goings-on as an application of Bayes' theorem.

Quibblers will argue that we wouldn't have gotten ourselves into this trouble if we'd used a better test. Not so. Consider Fig 1 which shows the predictive values for a 1/1,000,000 prevalence disease over the entire range of test specificities from 99.999% to 100%. We note that 99.999% is substantially better

than that in the Oprah scenario, yet the predictive value of a positive test is still less than 10%. Even at 99.9999% specificity, we would expect an equal number of false and true positives (ie,  $PV+ = 50\%$ ). And, and on a practical note, you cannot validate a test at anywhere close to 99.9999% specificity (problem #1 is funding).

Our final conclusion is that a clinician would be unwise to perform this test on someone without an expectation that the person was at a higher risk for the disease in question than the general population. Probably, the test would only be useful for those persons whose families have a history of the disease.

You may wonder how common such circumstances are in practice. Though, we seldom deal with diseases as rare as 1 per million, we also seldom have test specificities of 99.5%. What if we were using a test with a 90 or 95% specificity? (Fig 2). Joseph Romatowski has discussed low predictive values with regard to feline leukemia screening in cats and heartworm testing in dogs. (2,3). The same reasoning applies to any disease condition for which the test being applied is not 100% specific and for which we are testing in a low prevalence population.

Beyond interpretation of a single test result, predictive values represent quantitatively what we (should) do qualitatively in the diagnostic process. We begin with a broad history and physical exam in an attempt to place the individual into defined groups with higher prevalences of several suspected diseases. Only then should we use (selected) clinical tests. In the second stage of diagnosis, we may use certain tests (eg,

cheaper ones) in a screening mode for more expensive tests. Thus, we converge on a diagnosis by steadily increasing the probability of a particular disease.

The problem with the intuitive approach is that we sometimes don't do it very well. Research employing scenarios such as the one above has shown the human mind to be rather feeble when it comes to intuitively estimating predictive values (you are not alone). This has led to interest in developing tools for obtaining quantitative estimates or, at least, better intuitive ones. Each monthly release of Medline/CDROM contains 8 to 12 "hits" on Bayes' theorem and dozens on predictive values, many dealing directly with clinical decision making. (e.g., 4,5)

Interpreting clinical tests goes beyond merely reading O.D.'s or color changes or comparisons to published "normal ranges". It involves the use of quantitative tools such as predictive values.

References: 1. Pop Med News, Brucellosis Ring Test, Mar 27, 1989. 2. Romatowski J; Interpreting feline leukemia test result; JAVMA 195:928, 1989. 3. Romatowski J; Effect of disease prevalence on a test's predictive value, JAVMA 197:1263, 1990. 4. Cimino; Evaluation of patients with HIV-related disorders and brain mass lesions; Arch Int Med 151:1381, 1991. 5. Kerna; Highly specific prediction of antineoplastic drug resistance... J Nat Cancer Inst. 82:582, 1990.

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