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Use of Likelihood Ratios in Evidence-based Clinical Decision Making

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Abstract : During the clinical decision making practitioners are often faced with performing diagnostic tests to solve the presenting problems seen in the patients. The diagnostic utility of a test has traditionally been described by technical terms such as sensitivity, specificity, and positive (PPV) and negative predictive value (NPV). Although well known, clinicians are frequently unclear about the concept and application of these terms in everyday evidence-based clinical decision making. Sensitivity and specificity, which are intrinsic properties of diagnostic tests, summarizes the characteristics of the test over a population. The PPV and NPV are greatly dependent on the population prevalence of disease, and thus they do not transferable to different patients or clinical settings. Besides, considering the fact that clinicians more often interested in knowing the extent to which a test result could confirm or exclude of a condition under consideration (posttest probability), these measures do not provide answers on this question. The likelihood ratios (LR) using the information contained in sensitivity and specificity are becoming increasingly popular for reporting the usefulness of diagnostic tests because this term provide an indication of posttest probability as a function of the pretest probability. In this article, clinical applications of LR are illustrated with some practical examples. Discussion is also included of the inherent limitations regarding diagnostic test characteristics.

Key words **:** likelihood ratio, diagnostic test, heartworm, evidence-based medicine (EBM)

Introduction

During the clinical decision making clinicians perform diagnostic tests after taking a history and examining the patient, and the choice of the test is largely based on the patient's symptoms and signs and clinician's personal experience. Performing a diagnostic test is to testing their presumptive diagnoses under consideration and consequently this allows rule in or rule out the diagnosis given a test result. The prompt and accurate diagnosis of a disease is clinically and economically important for both patients and their owners. However, the majority of the screening tests and even confirmatory tests are rarely 100% accurate, and all are capable of giving false-negative and false-positive test results (27). In this situation, understanding of posttest probability from a diagnostic point of view is an essential when interpreting test results (17,19,28).

The usefulness of diagnostic tests that is to detect a patient with disease or exclude a patient without disease has long assessed by technical terms such as sensitivity (Se), specificity (Sp) and predictive value for positive (PPV) and negative (NPV), but misunderstanding is still common among practitioners (32). The Se and Sp do not reflect characteristics of individual patients and provide the probability that a patient has a disease with a given test results. It is well known that PPV and NPV vary with the prevalence of the disease in the population though these values may be used to estimate probability of disease (5,15-18). Clinicians more often interested in knowing the posttest probability, the extent to which a positive or negative test result could confirm or exclude of a condition. To meet this ends and as an alternative tool, likelihood ratios are increasingly being used in the medical literatures (8,9,14,16). Because clinical and laboratory findings can sometimes be ambiguous and somewhat subjective, it is even more important to approach from an evidence-based point of view. It is clear from a review of the literatures that evidence-based approach in veterinary medical treatment is ever increasing (2,15,20,29). The aim of this paper is to draw clinician's attention to and increase the understanding of likelihood ratio and to guide the ways of estimating a patient's probability of having disease given positive or negative test results in clinical settings.

Practical illustration

Data search

For illustrative purposes, prevalence data of heartworm (*Dirofilaria immitis*) in domestic dog populations was used. To identify Korean- and English-language studies published from January 1996 to December 2007 on the prevalence of canine heartworm disease in Korea, the authors initially performed a computer-aided search of MEDLINE and the Korean Studies Information Service System (KISS). In addi-

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tion, we carried out a manual search of the references included in the articles retrieved in the electronic search, to identify studies that were not identified initially, from the following peer-reviewed journals: Korean Journal of Veterinary Research, Journal of Veterinary Clinics, Korea Journal of Public Health, and Korean Journal of Veterinary Service.

Statistical analysis

Total number of dogs examined and number of test positives reported by each study was extracted to calculate prevalence of microfilaria and ELISA for adult worms, and their 95% confidence interval (CI) was computed using the binomial distributions. The PPV and NPV were also calculated using the Bayes' theorem (17, 28): PPV = (Sexp)/[Sexp + (1-Sp)x(1-p)] and NPV = [Spx(1-p)]/[Spx(1-p) + (1-Se)xp]. The LR(+) and LR(-) were calculated using the following formulae: LR(+) = Se/(1-Sp) and LR(-) = (1-Se)/Sp. The confidence interval of LR(+) was calculated through a logarithmic transformation of each cell in contingency tables. Posttest probability was calculated using the Bayes' theorem: the posttest odds were obtained by multiplying the pretest odds by the LR of a test. Odds were calculated from probabilities by the formula: odds = probability/(1-probability). The odds were then converted back to probabilities by using the relationship, probability = odds/(1 + odds).

Results

Overall prevalence for microfilaria and ELISA for adult worm was 11.9% (186/1,563; 95% CI, 10.4-13.6%) and 16.3% (376/2,302; 95% CI, 14.9-17.9%), respectively (Table 1). The prevalence varied depending on the region studied, with a high of 23.2% in Daegu and a low of 4.0% in Jeonnam. The relationships between pretest probability and posttest probability of being infected with heartworm disease according to the predefined various LRs are shown in Fig. 1. This graph tells clinicians to evaluate the posttest probability

Table 1. Selected studies reporting to the prevalence (P) of *Dirofilaria immitis* in dogs using by either microscopic microfilarial test or ELISA for adult worms

City or province	Microfilaria		Adult worm		Ref.
	No. tested	P (%)	No. tested	P (%)	
Seoul	Not tested		363	2.2	31
Gyunggi	Not tested		122	50.8	31
Jeonnam	200	4.0	200	2.5	7
Incheon	Not tested		150	2.7	23
Chuncheon	175	13.7	175	25.7	34
Kangwon	22	9.1	73	30.1	30
Kyunggi	92	22.8	92	66.3	30
Chungnam	100	11.0	100	19.0	26
Daegu	220	23.2	220	23.6	26
Daejeon	Not tested		206	12.1	21
Jeonju	307	10.1	307	14.0	25
Pusan	294	6.5	294	10.2	4
Kwangju	153	12.4	Not tested		22
Total	1,563	11.9	2,302	16.3	
95% CI		10.4-13.6	14.9-17.9		

CI, 95% confidence interval.

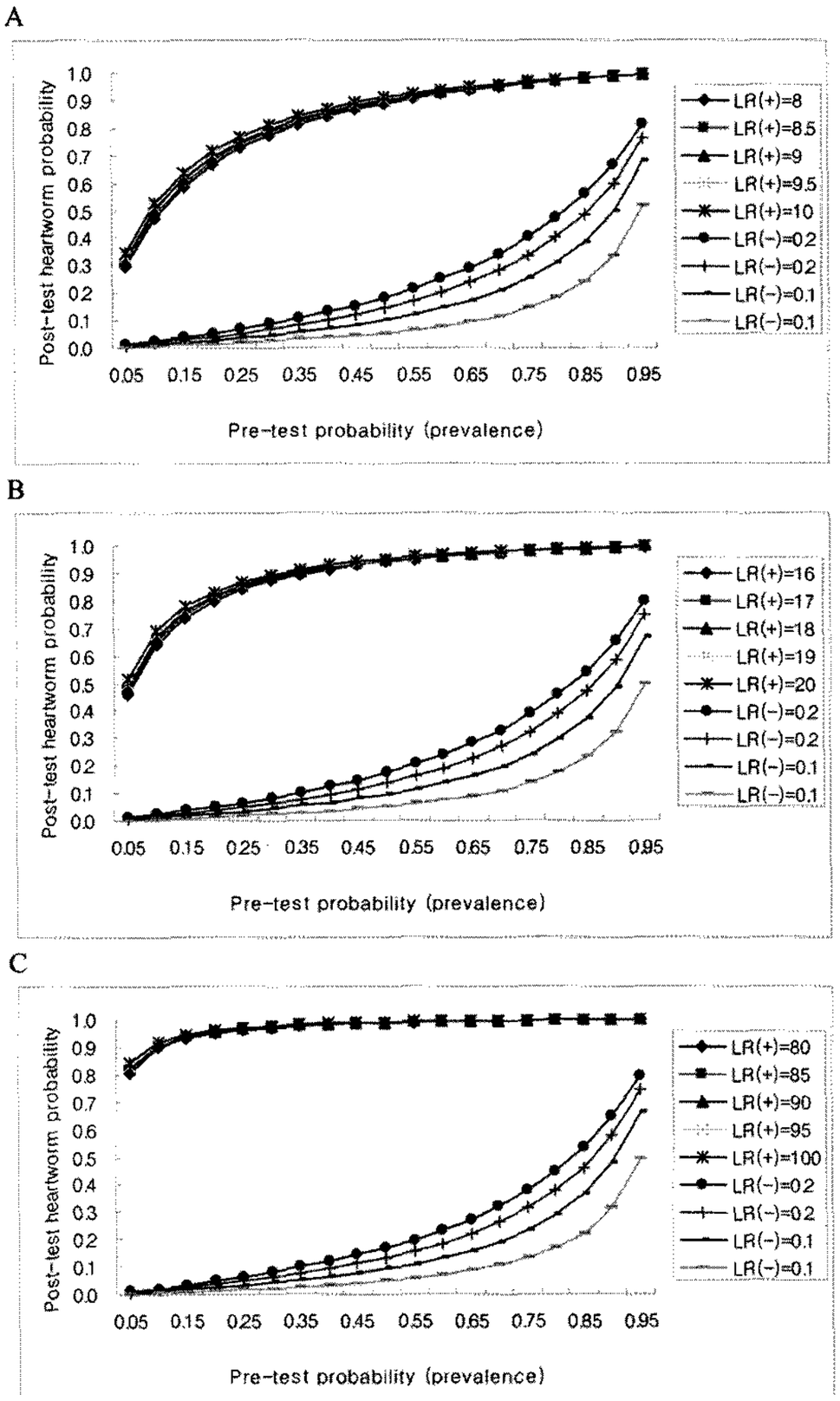

Fig 1. Relationship between pretest probability and posttest probability of being infected with disease according to various likelihood ratios (LR). Assumptions: (panel A) LR(+) = 8.0 & LR(-) = 0.2 for Se = 0.8 & Sp = 0.9; LR(+) = 8.5 & LR(-) = 0.2 for Se = 0.85 & Sp = 0.9; LR(+) = 9.0 & LR(-) = 0.1 for Se = 0.9 & Sp = 0.9; LR(+) = 9.5 & LR(-) = 0.1 for Se = 0.95 & Sp = 0.9; LR(+) = 10 & LR(-) = 0.0 for Se = 1.0 & Sp = 0.9. (panel B) LR(+) = 8.0 & LR(-) = 0.2 for Se = 0.8 & Sp = 0.95; LR(+) = 8.5 & LR(-) = 0.2 for Se = 0.85 & Sp = 0.95; LR(+) = 9.0 & LR(-) = 0.1 for Se = 0.9 & Sp = 0.95; LR(+) = 9.5 & LR(-) = 0.1 for Se = 0.95 & Sp = 0.95; LR(+) = 10 & LR(-) = 0.0 for Se = 1.0 & Sp = 0.95. (panel C) LR(+) = 8.0 & LR(-) = 0.2 for Se = 0.8 & Sp = 0.99; LR(+) = 8.5 & LR(-) = 0.2 for Se = 0.85 & Sp = 0.99; LR(+) = 9.0 & LR(-) = 0.1 for Se = 0.9 & Sp = 0.99; LR(+) = 9.5 & LR(-) = 0.1 for Se = 0.95 & Sp = 0.99; LR(+) = 10 & LR(-) = 0.0 for Se = 1.0 & Sp = 0.99.

Table 2. Sensitivity (Se) and specificity (Sp) of some selected test kit for heartworm disease and example calculation of post-test probabilities using likelihood ratio (LR) for positive [LR(+)] and negative [LR(-)]

Kit*	Sensitivity (%)	Specificity (%)	LR(+)	LR(-)
DiroCHEK	85.6[a]	96.6	25.2	0.15
			(95% CI, 8.9-71.4)	
	76.5[b]	84.6	5.0	0.28
			(95% CI, 3.2-7.8)	
SNAP	90.0[c]	90.0	9.0	0.11
			(95% CI, 5.0-16.2)	
	84.0[d]	96.9	27.1	0.17
			(95% CI, 9.1-80.8)	
	65.7[e]	97.5	26.3	0.35
			(95% CI, 7.8-88.9)	
Solo Step	79.0[d]	96.9	25.5	0.22
			(95% CI, 8.5-76.0)	

[Interpretation for DiroCHEK assuming pretest probability of 15%]
LR(+): The likelihood of a dog having heartworm disease is increased by about 25-fold given the positive test result. That is, this dog has a 96.2% probability of having the disease given the ELISA test positive. Combining 15% of pretest probability with 25.2 the posttest probability is estimated to be 82%, indicating that this dog is 4 times more likely to be infected with heartworm disease.
LR(-): The negative LR of 0.15 means that the dog has a 13.2% probability of having the disease given the ELISA test negative. Combining 15% of pretest probability with 0.15 the posttest probability is estimated to be 3%, indicating that after a negative test this dog has only a 3% probability having a heartworm disease.

CI, 95% confidence interval.
*DiroCHEK (Synbiotics, USA), SNAP (IDEXX, USA), Solo Step (Heska, Switzerland).
[a]Courtney *et al.* (10).
[b]Brunner *et al.* (3).
[c]Fan *et al.* (13).
[d]Atkins (1).
[e]Wang (33).

of the disease by combining the pretest probability of disease with the information that the test is positive or negative. Posttest probability increases with increasing prevalence but the changes are minimal at higher levels of prevalence. Also, as LR(+) increases the posttest probability increases, but the impact of disease prevalence on posttest probability is not remarkable when LR(+) <10 compared to LR(+) ≥10. The computation of LR(+) and LR(-) and their interpretation is shown in Table 2. As the prevalence of heartworm disease increases the PPV of ELISA test increases, but the NPV decreases (Fig 2). The upward changes of PPV were greater at low level of prevalence. A posttest probability for a positive or negative test result can be quickly estimated using the LR nomogram (Fig 3).

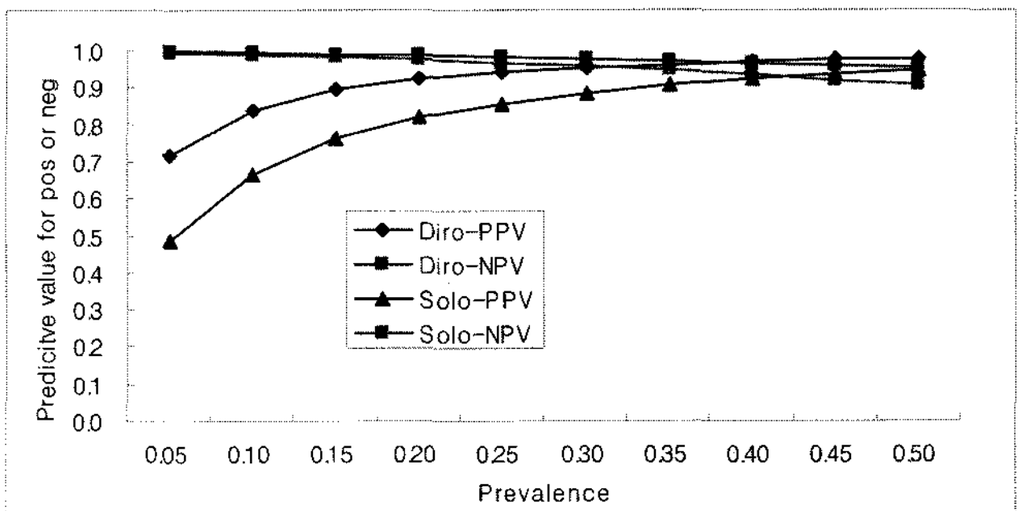

Fig 2. Relationship between predictive values for positive (PPV) and negative (NPV) and disease prevalence, assuming that sensitivity and specificity were 0.856 and 0.966 for DiroCHEK (Diro), respectively and 0.79 and 0.969 for Solo Step (Solo), respectively.

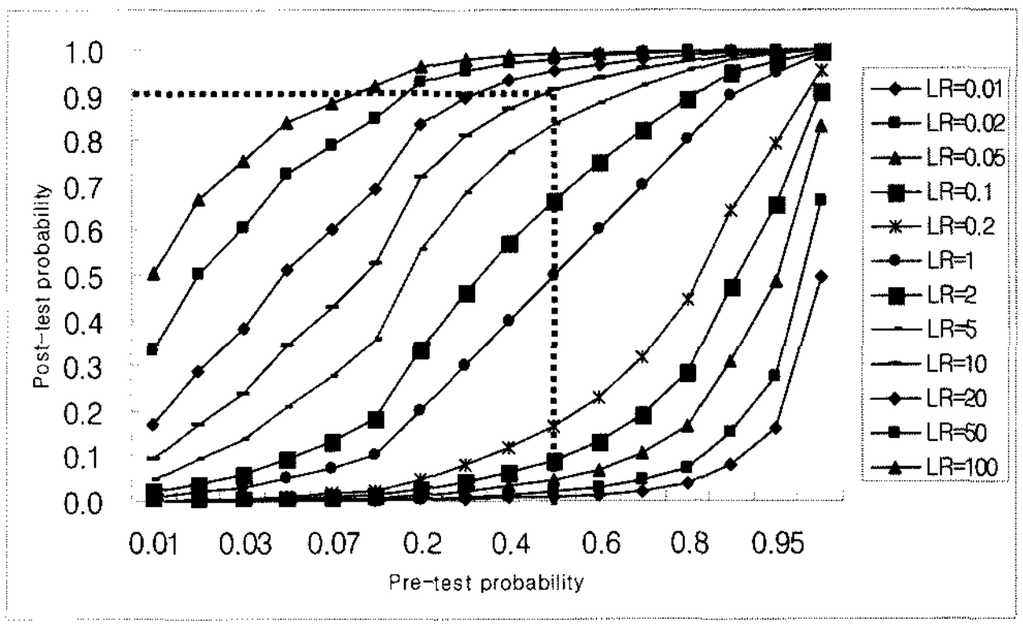

Fig. 3. Use of nomogram. For a patient with a pretest probability of heartworm of 50%, obtaining results of a diagnostic test with likelihood ratio (LR) of 10 results in a posttest probability of about 90% (dotted line).

Discussion

The Se of a test is defined as the proportion of those with disease who test positive. As a sensitive test has few false negatives, a test with a high Se is useful for ruling out a disease if test result is negative (17-18,28). The Sp of a test is the proportion of those without disease who test negative. As a specific test has few false positives, a test with a high Sp is useful for ruling in a disease if test result is positive. Both indices can be obtained from individuals or groups whose infection status has already known. However, clinicians usually do not know whether or not a patient truly has the condition. In addition, the Se and Sp of a test do not provide information on the probability of disease. Predictive values describe a patient's probability of having disease given a positive or negative test result. These probabilities are termed PPV and 1-NPV, respectively. The PPV of a test is defined as the proportion of those with positive test results who truly have the disease (17-18,28). Similarly the NPV of a test is defined as the proportion of those with negative test results

who truly do not have the disease. However, these measures are critically dependent on the population with different prevalence of disease. As the prevalence of disease decreases, the PPV decreases and the NPV increases (Fig 1). This means that both indices are not transferable from one clinical setting to another or from one patient to another. This is just the case for the prevalence of heartworm disease in this study with great variations by regions. Also a test with a constant Se and Sp may have different predictive values when performed among different demographic groups (6).

Pretest probability, varying from 0 and 100%, is a probability estimate of having disease in a patient before doing the test, and this can be obtained from either published data or the clinician's subjective impression on patient examination or personal experience (6,11). Pretest probabilities have some level of uncertainty and might be different between clinical settings and even in geographic locations (15). Based on this information, clinicians may derive a temporary conclusion that it is likely or unlikely a particular disorder is present. As a result of any diagnostic tests such as hematology, serology, and radiography the likelihood of disease then can be modified.

The LR(+) and LR(-) represents how many more times likely a given test result is from an infected animal compared to one that is uninfected, using the information contained in both Se and Sp. Interpreting the LR is straightforward. The higher the positive LR the more certain clinician can be that a positive test indicates the patient has the condition. The lower the negative LR, the more certain clinician can be that a negative test indicates the patient does not have the condition. In particular, test results with LR >10 or <0.1 are useful because of substantial changes in posttest probability, and thus they provide relatively strong evidence about the presence of absence of a disease. LRs between 5 and10 or between 0.1 and 0.2 produce moderate changes in this probability (15,17,28). If the LR is close to 1, then the test result will not provide much information to decide on the likelihood of a patient has, or does not have, a condition (18). For example, the LR of 20 for a dog does not mean that this dog is 20 times more likely to be infected with specific disease. It really means that 20 times more dogs within that test result are infected. To calculate how many more times it is likely that a dog is infected information regarding the pretest probability would be necessary. If we assume pretest probability of 1%, then Bayes' theorem can be used to compare the dog's probability of being infected (probability = 0.69) to not being infected (probability = 0.31) giving a ratio of 2.2. A pretest probability of 0.4 would make this ratio about 13 (probability infected = 0.93 and not infected = 0.07). A 50% prevalence of infection produce posttest probability to be equal to the LR, and higher pretest probability produce much higher ratios (Fig 2).

Let us take an example of a dog with positive heartworm ELISA test with Se of 90% and Sp of 95%. The PPV of 18 indicates that the probability of this dog having heartworm disease has increased by 18-fold given the positive test result. Here, suppose that the dog has a 30% chance of having the disease (pretest probability) from a clinician's assessment. Then consult with Fig 2, yielding a 90% probability of having heartworm disease given the positive test result. Practically, this means that we can consider false negative for a dog with ELISA negative test result. Likewise, suppose that a dog has a 20% of pretest probability of being infected with heartworm disease for ELISA with Se of 80% and Sp of 90%. The NPV of 0.22 indicates that the probability of a truly infected dog giving a negative test result is reduced to 0.22 times the probability of a truly non-infected dog giving a negative test result. Combining 20% with 0.22 a posttest probability is approximately 5%. This represents that after a negative test the dog has a 5% probability of having heartworm disease. Accordingly, we might consider false positive for a dog with positive test result.

Let us take another example. Assume that a clinician have opted for anything from 20% to 40% as pretest probability and a dog tests positive with heartworm ELISA test with Se of 85% and Sp of 95%. The resultant LR(+) is 17, and posttest probability at 20% and 40% pretest probability is 81% and 92%, respectively. In both cases, increasing the pretest to posttest probability from 20% and 40% to 81% and 92% makes the test useful, but about 11% of increase may not clinically important. This result attributed by high value of LR(+). If the LR(+) decreases to low level, for example, less than 5, a test may not increase the pretest to posttest probability significantly no matter how accurate is that test, as is indicated in Fig 1. This means that pretest probability is already high (say, 90%), further tests will not significantly improve the posttest probability. An accurate test is most useful when the pretest probability is approximately between 20% and 60% (28). Similarly, if the LR is infinite, the posttest probability is 1, regardless of the magnitude of the pretest probability (15).

The LR has several advantages. They can be used directly for any individual patient level and do not vary in different populations or clinical settings. Furthermore, they enable clinicians to quantify the probability of disease as a single value, and unlike predictive values are independent of disease prevalence (15,17). If we know the pretest probability of a disease, LRs allow for direct calculation of posttest probabilities based on Bayes' theorem (12). A major limitation to using LRs in routine practice is to compile information on the prevalence of all the conditions in that population of animals. Few authors in veterinary medicine have reported this information so far. Even experiences clinicians have difficulty estimating those values, and the majority of clinicians thus tend to rely instead on personal experiences on what is likely, resulting in biased estimates.

In conclusion, Se and Sp of a test do not provide to estimate how much a test result affects the probability of disease. Both PPV and NPV can provide estimates this information but depend greatly on disease prevalence, which

may not be available. Also, published predictive values should not be applied to populations whose prevalence is different from the population where the cited values were drawn. The LR, a valuable tool to estimate probability of having a disease, is independent of disease prevalence and is predominantly used in evidence-based diagnosis based on the results of diagnostic tests.

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