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# Prevalence-based Interpretation of Predictive Values of Diagnostic Tests: An Example for Detection of Canine Heartworm Infection

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**Abstract :** The use of screening tests as part of a diagnostic work-up is common in domestic canine practice, but understanding of the diagnostic test characteristics and factors affecting diagnostic accuracy is not clear among clinicians. This article was aimed to provide clinicians with a better understanding on the selection of test kits and with a proper interpretation of test results using an example from heartworm (*Dirofilaria immitis*) studies. From the literatures, diagnostic accuracy varied depending on the kits: percent average sensitivity and specificity of ELISA antigen-detecting kits were DiroChek (Synbiotics, USA) 78.1 and 95.2, SNAP (IDEXX, USA) 66.3 and 98.1, and Solo Step (Heska, Switzerland) 69.5 and 97.5, respectively, while the values for three hematological methods (Modified Knott's, direct smear and capillary tube) ranged from 38.4 to 81.8% and from 96.9 to 100%, respectively. Furthermore, it was also reported that the prevalence of heartworm disease in domestic dog populations varied depending on the regions studied: 2.5-22.8% for microfilarial test and 2.2-66.3% by ELISA. The values of predictive values for positive (PPV) and negative (NPV) provide useful information to clinicians on the probability of heartworm infection, but the PPV and NPV are greatly dependent on the heartworm prevalence. This suggests that PPV or NPV values of a test should be interpreted carefully in different clinical settings. Practical methods on the interpretation taking into account heartworm prevalence were discussed.

***Key words* :** heartworm, predictive value, prevalence, dog.

## Introduction

Clinicians are frequently faced with making important decisions on the basis of diagnostic tests that often yield dichotomous results. Conducting such a test represents that they would make modify pretest probability (prevalence) of suspected disorders given a positive or negative result (13). To achieve this primary purpose successfully, perfect diagnostic test (also known as gold test, definitive test, or reference test) that provides true disease status of a patient must be available in any circumstances. A gold test is a test or combination of tests that is absolutely accurate and without misdiagnoses. In reality, however, such tests with perfect sensitivity (Se) and specificity (Sp) are not available for many animal diseases (15). In other cases, these are not practical to use in the clinic because they usually are expensive for a client to perform, labor-intensive, or are even risky to the patients (16). Thus, an imperfect test which inevitably capable of giving false positive (FP) or negative (FN) results is often used as a compromise (8). Accordingly, this indicates that a positive or negative test does not always rule in or rule out disease.

The use of commercial test kits for diagnosing animal disease is common because of ease of use, cost, rapidity of use, or accuracy. Among these and other considerations, the single most important factor to be considered when selecting a test is the accuracy of a test. On the other hand, predictive value for positive (PPV) and negative (NPV) together with likelihood ratio is more important when interpreting test result and making a diagnosis in clinical settings because the posttest probability of a patient having a specific disorder could be drawn from those estimates (7). The concepts and clinical utility of these terms have been described elsewhere (8-10,14,15-20,25). Clinicians more often interested in knowing the extent to which a positive or negative test result could confirm or exclude of a condition. In this regard, if the prevalence of a disease of interest varies depending on the regions studied and test kits employed, the results of a test may have different clinical implications. Understanding on the relationship between predictive values and prevalence in the population is essential to correct interpretation of test results. This is of particular importance for canine heartworm disease because the prevalence was reported greatly different by geographic regions in the country. The objective of this paper is to provide clinicians practical methods of interpreting heartworm test result as a function of the disease prevalence that affecting the interpretation of an individual result.

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## Materials and Methods

### Data and statistical analysis

The relationships between PPV, NPV and heartworm prevalence were analyzed using the data from a previously published study (22). For brevity, estimates of the prevalence (P) of heartworm (*Dirofilaria immitis*) infection in domestic dog populations was identified using the meta-analytic approach by use of a computer-aided search of published literatures. Studies on military populations or whether a gold test for detection of heartworm was used was not considered in the inclusion criteria of articles for further review. Three ELISA kits DiroChek (Synbiotics, USA), SNAP (IDEXX, USA), and Solo Step (Heska, Switzerland) and three hematological methods (Modified Knott's, direct smear and capillary tube) were included. 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. From those studies, the Se and Sp were also extracted. For dichotomous test results, the posttest probabilities of disease (PPV and NPV) were calculated using the Bayes' theorem (17,25) :

$$PPV = (Se \times P)/[Se \times P + (1-Sp) \times (1-P)] \text{ and}$$
$$NPV = [Sp \times (1-P)]/[Sp \times (1-P) + (1-Se) \times P].$$

## Results

From the literatures, the prevalence was reported to be varied depending on the regions studied, ranging 2.5-22.8% by microscopic microfilarial test and 2.2-66.3% by ELISA test for adult worms (Table 1). The Se and Sp of selected heartworm antigen tests and hematological methods are summarized in Table 2. Percent average Se and Sp of antigen-detecting kits were DiroChek 78.1 and 95.2, SNAP 66.3 and 98.1, and Solo Step 69.5 and 97.5, respectively. For three hematological methods, the Se and Sp ranged from 38.4 to 81.8% and from 96.9 to 100%, respectively. The relationships between PPV, NPV of diagnostic tests and prevalence are shown in Fig 1 and 2. The probability of heartworm infection given a positive or negative test result is shown in Fig 3.

**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 in Korea

| Test kit | City or province | Microfilaria | | ELISA | |
|---|---|---|---|---|---|
| | | No. tested | P (%) | No. tested | P (%) |
| SNAP | Seoul | Not tested | | 363 | 2.2 |
| | Gyunggi | Not tested | | 122 | 50.8 |
| | Pusan | 294 | 6.5 | 294 | 10.2 |
| DiroChek | Jeonnam | 200 | 2.5 | 200 | 4.0 |
| | Gangwon | 22 | 9.1 | 73 | 30.1 |
| | Incheon | 92 | 22.8 | 92 | 66.3 |
| Solo Step | Jeonju | 307 | 10.1 | 307 | 14.0 |

**Table 2.** The sensitivity and specificity of selected ELISA kits for adult worms

| Test kit | Sensitivity (%) | Specificity (%) | Reference |
|---|---|---|---|
| DiroChek | 73.1 | 95.9 | 2 |
| DiroChek | 76.5 | 84.6 | 5 |
| DiroChek | 85.6 | 96.6 | 10 |
| DiroChek | 77.4 | 100.0 | 11 |
| DiroChek | 84.9 | 100.0 | 21 |
| DiroChek | 71.0 | 94.0 | 12 |
| SNAP | 48.5 | 100.0 | 21 |
| SNAP | 65.7 | 97.5 | 28 |
| SNAP | 67.0 | 98.0 | 12 |
| SNAP | 84.0 | 96.9 | 1 |
| Solo Step | 79.0 | 96.9 | 1 |
| Solo Step | 60.0 | 98.0 | 12 |
| Modified Knott's | 81.8 | 100.0 | 21 |
| Modified Knott's | 44.3 | 100.0 | 11 |
| Modified Knott's | 38.4 | 100.0 | 28 |
| Direct smear | 64.5 | 96.9 | 23 |
| Capillary tube | 60.0 | 96.9 | 23 |

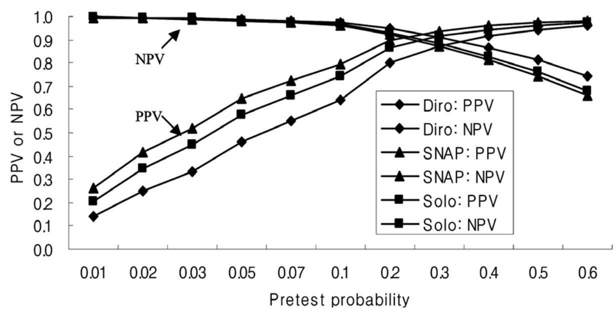


**Fig 1.** Predictive values for positive (PPV) and negative (NPV) of 3 ELISA kits for detection of canine heartworm infection as a function of prevalence of the disease. The sensitivity (%) and specificity (%) were assumed DiroChek 78.1 and 95.2, SNAP 66.3 and 98.1, and Solo Step 69.5 and 97.5, respectively.

## Discussion

It has been well documented that diagnostic accuracy of a test is useful for ruling in or ruling out a disease given a test result (15,24,27). For clinicians, to proper interpret the test results of heartworm disease, information on the pretest probability of infection in the dog as well as diagnostic accuracy need to be combined to obtain PPV and NPV. The estimate of the pretest probability of infection can be derived from prevalence estimates in their respective clinical settings. The way of deriving pretest probability was described previously

(22). The Se and Sp estimates might be available on test kit inserts or from the manufacturers. To becoming an evidence-based practitioner consultation with the scientific publications as the most reliable sources is essential (3,26). Besides, they need to be able to evaluate the quality of those estimates (18,25).

The PPV and NPV are strongly dependent on the pretest probability (Fig 1, 2). As the pretest probability increase above 60%, the PPV increases toward 100% with an associated decrease in NPV. Similarly, as specificity increases at a fixed pretest probability, PPV increases. For all antigen tests assessed in this study, a negative test result will effectively rule out heartworm infection at less than 30% of pretest probability (Fig 1), indicating that clinicians are at least 90% certain that the dog is truly not infected. In contrast, a positive test is a poor predictor of infection at the same level of pretest probability, except when the probability is greater than 40%. These figures can be used to estimate the posttest probability of heartworm infection in any individual patient with a positive or negative test result. In addition, the implications of these relationships represent that different interpretation on a positive test result should be made depending on the pretest probability. For example, given that the pretest probability of heartworm infection in a clinic practiced in region A is 23.2%, clinician is 76.8% certain that the dog is not infected before the test is done. If DiroChek test kit is chosen as an in-clinic test and the dog is test positive, assuming the Se and Sp value shown in Table 2, the resultant PPV is 83%. With the same kit and pretest probability of 4% in a clinic in region B, the PPV is estimated to be only 40.3%; 1 in every 3 positive test results is likely to be a true positive. The resultant gain in probability in region A and B is 59.8% and 36.3%, respectively. Thus, the clinical value of the DiroChek in region B would be less than in region A, which has more diagnostic uncertainty. That is, a positive test in region B might not change the clinician's initial judgment of the infection status even after the test result is obtained. Similar reasoning can be applied any diseases with different prevalence rates by geographical regions. Depending on the circumstances, the results of Fig 3 can be applied in situations to decide whether a clinician should initiate treatment or further test need to be performed (6,25). If a clinician's threshold probability for initiation of heartworm treatment were 0.9, then pretest probability greater than 0.35 and a positive test result in DiroChek with Se of 78% and Sp of 95% would be adequate to the predefined threshold, while for a hypothetical test with Se of 95% and Sp of 99% and a positive test result, about 1% of pretest probability would be sufficient to exceed the threshold. If posttest probability belongs to the values between exclusion and treatment threshold, the possible diagnosis of heartworm infection must be pursued further by conducting additional diagnostic tests.

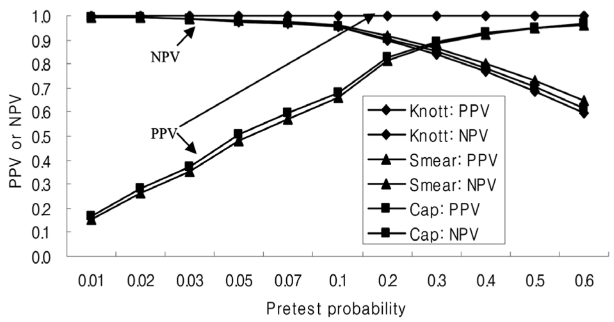


**Fig 2.** Predictive values for positive (PPV) and negative (NPV) of 3 hematological methods for detection of canine heartworm infection as a function of prevalence of the disease. The sensitivity (%) and specificity (%) were assumed Modified Knott's 54.8 and 100, direct smear 64.5 and 96.9, and capillary tube 60.0 and 96.9, respectively.

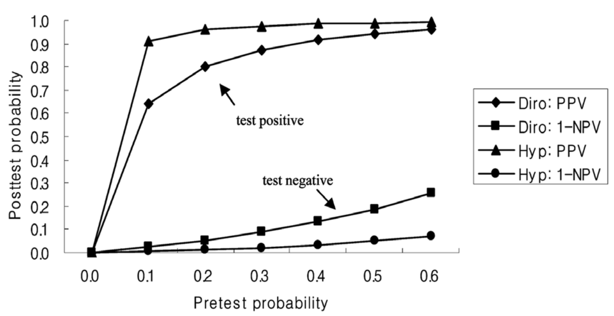


**Fig 3.** Relationship between pretest and posttest probabilities of canine heartworm infection based on two antigen tests. Sensitivity (%) and specificity (%) were assumed 0.78 and 0.95 for DiroChek and 0.95 and 0.99 for a hypothetical test (Hyp in legend).

In conclusion, the PPV and 1-NPV provide valuable information on the probability of disease which is more concern for the majority of clinicians. As these measures, however, are strongly dependent on the prevalence of heartworm disease alternative interpretation in different clinical settings should be considered given a positive or negative test result.

## Acknowledgement

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# 진단키트 검사결과에 대한 유병율 위주 해석: 개 심장사상충의 예

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**요 약** : 검사키트의 신속성과 간편성이 보편화되면서 진단목적으로 키트를 사용하는 빈도가 증가하고 있다. 그러나 대부분의 검사키트는 민감도와 특이도가 100% 완벽하지 못하기 때문에 진단검사의 특성과 이러한 특성에 영향을 미치는 요인을 이해하지 못할 경우 검사결과를 해석하는데 오류를 범하게 된다. 임상의는 검사결과 양성 혹은 음성일 때 환자가 실제로 질병에 감염되어 있을 확률이 어느 정도인지에 관심을 두기 때문에 본 연구에서는 예측도를 이용하여 유병율에 따른 결과 해석방법을 개 심장사상충 진단키트를 예로 들어 설명하였다. 문헌고찰 결과 심장사상충 진단용 키트검사의 평균 민감도와 특이도는 DiroChek 78.1-95.2%, SNAP 66.3-98.1%, Solo Step 69.5-97.5%를 보였다. 혈액학적 검사법 (Modified Knott's, direct smear, capillary tube)의 민감도와 특이도는 각각 38.4-81.8%, 96.9-100%의 범위를 보여 검사법에 따라 상당한 차이를 보였다. 또한 국내 개 심장상충의 자충과 항원 유병율은 지역별로 차이가 있으며 키트검사의 예측도는 유병율에 매우 민감하다는 점을 고려하면 개 심장사상충에 대한 검사결과에 근거하여 감염확률을 추정할 때 유병율이 상이한 임상환경에서는 양성 혹은 음성결과에 대하여 신중하게 해석할 필요가 있다.

**주요어** : 심장사상충, 예측도, 유병율, 개.