

Exercise - diagnostic tests

Medical checkups

A simple and inexpensive screening method has been developed to identify individuals with a specific disease at medical check-ups. To study the sensitivity and specificity the method was tested on 200 persons who underwent a simultaneous thorough clinical examination that was considered to give an accurate diagnosis. The results are shown in the following table:

	Disease +	Disease -	Total
Test +	60	40	100
Test -	20	80	100
Total	80	120	200

Calculate the sensitivity and the specificity of the screening method.

The screening test has a sensitivity of $60 \div 80 = 0.75$ and a specificity of $80 \div 120 = 0.67$.

Deep vein thrombosis

In a diagnostic study for deep vein thrombosis (DVT) a clinician targets only patients with a specific symptom (for example, 'acute swelling of the leg') and then applies a diagnostic test (an ultrasound examination) and the gold standard procedure (an x-ray venogram). Results are shown in the following 2×2 table:

	Disease +	Disease -	Total
Test +	48	14	62
Test -	12	126	138
Total	60	140	200

1. Calculate the sensitivity and the specificity of the above test.
2. What is the [true] prevalence of DVT, based on these data?
3. What is the positive predictive value of the DVT test?
4. Based on the data provided, what is the estimate of the average patient's probability of not having DVT prior to testing?
5. What is the likelihood ratio of a positive test result? What is the likelihood ratio of a negative test result?
6. What is the probability of DVT in a patient with a negative ultrasound result?

1. The test has a sensitivity of $48 \div 60 = 0.80$. The test has a specificity of $126 \div 140 = 0.90$.
2. The true prevalence of disease is $60 \div 200 = 0.30$. In this population, 30% of individuals had DVT.
3. The positive predictive value of the DVT test is $48 \div 62 = 0.77$. Of those that return a positive test result, 77% are expected to be truly diseased.
4. The estimate of the average patient's probability of not having DVT prior to testing is 1 minus the prevalence, $1 - 0.30 = 0.70$.
5. Likelihood ratios. Given $Se = 0.80$ and $Sp = 0.90$:

$$LR(+) = 0.80 \div (1 - 0.90) = 8.0$$
$$LR(-) = (1 - 0.80) \div 0.90 = 0.22$$

6. What is the probability of DVT in those patients with a negative ultrasound result?

The pre-test probability of DVT: 0.30
The pre-test odds of DVT: $(0.30:0.70) = 0.43$
The post-test odds of DVT (given a negative test result): $0.43 \times 0.22 = 0.09$
The post-test probability of DVT: $0.09 \div (1 + 0.09) = 0.08$

The probability of DVT in patients with a negative ultrasound result is 0.08 (8%).

Anaemia

Suppose you are working up a patient with anaemia and you think that the probability that the patient has iron deficiency anaemia is 50%. A blood sample that you have tested yields a serum ferritin level of 60 mmol/L, which is considered to be indicative of iron deficiency anaemia. You read an article by Guyatt et al. (1992) where the following data are presented:

	Fe defic +	Fe defic -	Total
Ferritin +	731	270	1001
Ferritin -	78	1500	1578
Total	809	1770	2579

What is the post-test probability that this patient has iron deficiency anaemia?

On the basis of the data presented in the 2 × 2 table the serum ferritin test has the following characteristics:

$$\text{Se} = 731 \div 809$$
$$\text{Se} = 0.90$$

$$\text{Sp} = 1500 \div 1770$$
$$\text{Sp} = 0.85$$

$$\text{LR}(+) = \text{Se} \div (1 - \text{Sp})$$
$$\text{LR}(+) = 0.90 \div (1 - 0.85)$$
$$\text{LR}(+) = 6$$

$$\text{LR}(-) = (1 - \text{Se}) \div \text{Sp}$$
$$\text{LR}(-) = (1 - 0.90) \div 0.85$$
$$\text{LR}(-) = 0.12$$

We have an even bet on the probability that this patient is iron deficient. The pre-test probability of iron deficiency is 0.50. The pre-test odds of iron deficiency anaemia is $0.50 \div (1 - 0.50) = 1$.

The post-test probability of iron deficiency anaemia given a positive test result:

$$\text{Post-test odds of disease} = \text{pre-test odds} \times \text{LR}+$$
$$\text{Post-test odds of disease} = 1 \times 6$$
$$\text{Post-test odds of disease} = 6$$
$$\text{Post-test probability of disease} = \text{post-test odds} \div (1 + \text{post-test odds})$$
$$\text{Post-test probability of disease} = 6 \div (1 + 6)$$
$$\text{Post-test probability of disease} = 0.86$$

As a result of testing, we are 86% certain that this patient has iron deficiency anaemia.

Reference: Guyatt GH, Oxman AD, Ali M, Willan A, Malloy W, and Patterson C. Laboratory diagnosis of iron-deficiency anaemia: an overview. *Journal of General Internal Medicine* (1992) 7: 145 - 153.

Johne's disease

Faecal culture methods for *Johnes* disease typically allow an 8 week period of growth before declaring a sample test negative. It has been suggested that increasing the culture period to 12 weeks might increase the sensitivity of the test significantly. In the following table the number of culture positive and culture negative samples at the two time points are given.

	Culture 12w +	Culture 12w -	Total
Culture 8w +	159	0	159
Culture 8w -	154	1519	1673
Total	313	1519	1832

- What is the diagnostic sensitivity for the 8-week method relative to the 12-week method?

- What is the diagnostic specificity of the 8-week method relative to the 12-week method?

The sensitivity of faecal culture using an 8-week incubation period, relative to a 12-week incubation period:

$$Se_{8\text{-week}:12\text{-week}} = 159 \div 313 = 0.51.$$

The specificity of faecal culture using an 8-week incubation period, relative to a 12-week incubation period:

$$Sp_{8\text{-week}:12\text{-week}} = 1519 \div 1519 = 1.00.$$

Cushing's syndrome

Interest lies in using the presence of osteoporosis as an indicator for Cushing's Syndrome in dogs. Veterinarians have referred dogs with suspected Cushing's syndrome to a university teaching hospital. On examination at the referral centre it was found that 25% of referred dogs did not have Cushing's syndrome. Among the 25%, 3% had osteoporosis while 65% of dogs with Cushing's syndrome also had osteoporosis.

1. Show these data in a 2 × 2 table format.
2. What is the sensitivity and specificity of osteoporosis as a test for Cushing's syndrome in the given circumstances?
3. What proportion of the referred dogs with osteoporosis had Cushing's syndrome?
4. What is the epidemiological term for this proportion?
5. Would another evaluation of the sensitivity and specificity be required, if osteoporosis should be used as a screening test for Cushing's syndrome in the general dog population?

1. Show these data in a 2 × 2 table format:

	Cushings +	Cushings -	Total
Osteoporosis +	49	1	50
Osteoporosis -	26	24	50
Total	75	25	100

2. The sensitivity of osteoporosis as a test for Cushing's syndrome is $49 \div 75 = 0.65$. The specificity of osteoporosis as a test for Cushing's syndrome is $24 \div 25 = 0.96$.
3. The proportion of osteoporosis positive dogs with Cushing's syndrome is $49 \div 50 = 0.98$.
4. This proportion is termed the positive predictive value.
5. Another evaluation of sensitivity and specificity would not be required if osteoporosis was to be used as a screening test for Cushing's syndrome in the general dog population.

Tuberculosis

A simple and inexpensive screening method has been developed to identify individuals with tuberculosis of the lungs at medical check-ups. To study the sensitivity and specificity the method was tested on 200 persons who underwent a simultaneous and thorough clinical examination that was considered to give an accurate diagnosis. The results are shown in the following table:

	Test +	Test -	Total
TB +	70	20	90
TB -	10	100	110
Total	80	120	200

1. Calculate the sensitivity and specificity of this test. Compute the positive and negative predictive values for the test.
2. An ELISA-antigen test for Mycobacterium tuberculosis has a sensitivity of 0.92 and a specificity of 0.57. For the same tuberculosis prevalence as above, calculate the positive and negative predictive values for this ELISA

test.

- If your primary concern is that the disease can kill a person, which test would you prefer and why? If your primary concern is that unnecessary treatment has possible side effects and is stressful for the patient, which test would you use and why? Comment on the usefulness of each test.
- The true prevalence in the population is likely much lower than in this experimental setting. What effect will this have on the usefulness of these tests in the medical practice situation? Explain quantitatively using reasonable estimates of prevalence. Hint: (1) there are approximately 4 million people living in New Zealand, (2) in 2002 a total of 380 cases of tuberculosis were diagnosed throughout the country.

- Re-arrange the data:

	TB +	TB -	Total
Screen +	70	10	80
Screen -	20	100	120
Total	90	110	200

The sensitivity of the test is $70 \div 90 = 0.78$. The specificity of the test is $100 \div 110 = 0.91$. The positive predictive value is $70 \div 80 = 0.88$. The negative predictive value is $100 \div 120 = 0.83$.

- Calculate cell values on the basis of the sensitivity and specificity of the ELISA-antigen test:

	TB +	TB -	Total
ELISA +	$0.921 \times 90 = 83$	$110 - 63 = 47$	$83 + 47 = 130$
ELISA -	$90 - 83 = 7$	$0.571 \times 110 = 63$	$7 + 63 = 70$
Total	90	110	200

The sensitivity of the test is 0.92. The specificity of the test is 0.57. The positive predictive value of the new test is $83 \div 130 = 0.64$. The negative predictive value is $63 \div 70 = 0.90$.

- If your primary concern is that the disease can kill a person, you need a test that will identify the highest proportion of disease positive individuals, that is a highly sensitive test (in this case the antigen-ELISA test). If your primary concern is that unnecessary treatment has side effects and is stressful for the patient, you need a test that will identify the highest proportion of disease negative individuals, that is a highly specific test (in this case the inexpensive screening test).
- The true prevalence in the population is likely much lower than in this experimental setting. What effect will this have on the usefulness of these tests in the medical practice situation? Explain quantitatively using reasonable estimates of prevalence.

Three hundred and eighty cases in a population of 4 million gives an incidence risk of 10 cases per 100,000. We compute positive and negative predictive values for each test on this basis:

	TB +	TB -	Total
Screen +	8	8999	9007
Screen -	2	90991	90993
Total	10	99990	100000

When the incidence risk is 10 cases per 100,000 the positive predictive value of the screening test is 0.0009. The negative predictive value is 0.999.

	TB +	TB -	Total
ELISA +	9	42996	43005
ELISA -	1	56994	56995
Total	10	99990	100000

When the incidence risk is 10 cases per 100,000 the positive predictive value of the screening test is less than 0.0002. The negative predictive value is 0.999.

When the prevalence of disease is low both tests have low positive predictive values and high negative

predictive values.

Screening test

A screening test for a disease gives a positive result in 50% of non-infected animals and a negative result in 20% of infected animals.

1. For this test, what is the sensitivity, specificity, positive predictive value and negative value?
2. If the true prevalence is 10%, what will be the apparent prevalence and the positive and negative predictive values?

1. Construct a 2 x 2 table and enter cell values on the basis of the information provided:

	Disease +	Disease -	Total
Test +	800	500	1300
Test -	200	500	700
Total	1000	1000	2000

$$Se = 800 \div 1000$$
$$Se = 0.80$$

$$Sp = 500 \div 1000$$
$$Sp = 0.50$$

$$PPV = 800 \div 1300$$
$$PPV = 0.61$$

$$NPV = 500 \div 700$$
$$NPV = 0.71$$

2. True prevalence set to 10%:

	Disease +	Disease -	Total
Test +	160	900	1060
Test -	40	900	940
Total	200	1800	2000

$$\text{Apparent prevalence} = 1060 \div 2000$$
$$\text{Apparent prevalence} = 0.11$$

$$PPV = 160 \div 1060$$
$$PPV = 0.15$$

$$NPV = 900 \div 940$$
$$NPV = 0.96$$

The window cleaner

Your window cleaner tells you that lately he has been feeling run down and thirsty. He asked his general practitioner to be tested for diabetes, which runs in his family. The nurse in his general practitioner's surgery asked him to provide a urine specimen. The nurse dipped used a dipstick test to check for the presence of glucose in his urine. Because the dipstick stayed green the nurse told him that he did not have diabetes. Because you are a good epidemiologist, you recall the following details for the dipstick urine test for diabetes: sensitivity 0.22; specificity 0.99; positive predictive value 0.46; negative predictive value 0.98; likelihood ratio of a positive test 32; likelihood ratio of a negative test 0.78. How would you respond to your window cleaner?

Reference: Andersson DK, Lundblad E, Svardsudd K. A model for early diagnosis of type 2 diabetes mellitus. *Diabetes Medicine* (1993) 10: 167 - 173.

A positive urine test is only 22% sensitive, which means that the dipstick test misses around 80% of true diabetics. In the presence of the classic symptoms and a family history, the window cleaner's baseline odds (i.e. the pre-test likelihood) of having the condition are high, and they are only reduced by four-fifths of this (the likelihood ratio of a negative test is 0.78) after a single negative urine test. In view of his symptoms, this man needs to undergo a more definitive test for diabetes.

Elective surgery

Alanine aminotransferase (ALT) values from the 38 diseased dogs and 115 clinically healthy dogs were categorised into 3 groups of test results, and likelihood ratios calculated on an interval-specific basis. Their data are shown below. The number of categories was limited to 3 because of the small sample size and the minimal overlap of ALT values for the 2 groups of dogs. An upper threshold of 80 U/L was selected because it was approximately the upper limit of the reported ALT reference interval, and 50 U/L as the lower threshold because it corresponded with the 75th percentile of the reference interval.

ALT (U/L)	n diseased	n healthy	Likelihood ratio
>80	30	1	$30/38 \div 1/115 = 91$
50 -- 80	4	22	$4/38 \div 22/115 = 0.55$
<50	4	93	$4/38 \div 93/115 = 0.13$
Total	38	116	

Suppose that a dog of a high-risk breed for hepatic disease, but with no clinical signs of disease, is being considered for elective surgery under general anaesthesia. A standard biochemical profile is done as part of preoperative management. Assume a pre-test probability of potential complications resulting from premedication and anaesthesia of 1% (equivalent to an odds of 1:99) and an ALT value of 70 U/L, which has a corresponding likelihood ratio of 0.55. What is the post-test probability of complications?

The post-test odds of complications given an ALT of 30 U/L:

Post-test odds of complications = pre-test odds \times LR+
 Post-test odds of complications = 0.01×0.55
 Post-test odds of complications = 0.005

The post-test probability of complications given an ALT of 70 U/L:

Post-test probability of complications = post-test odds \div (1 + post-test odds)
 Post-test probability of complications = $0.005 \div (1 + 0.005)$
 Post-test probability of complications = 0.005

The post-test probability of complications is 0.5%. This value might be low enough to consider this dog as a better candidate for elective surgery than what the initial (pretest) anaesthetic risk evaluation would have indicated.

The likelihood ratio of 0.55 for this category should be interpreted cautiously because the study was of limited size. It is also possible that the ALT values of diseased and non-diseased dogs in the study were not representative of values in the source populations (these limitations could apply to any cell in the table above). Hence, an assumption that non-diseased (diseased) animals will never present with very high (low) test results is likely to be incorrect, and proper statistical inference should account for the uncertainty in estimates by calculation of a confidence interval for the likelihood ratio estimates. On the basis of the data presented above, use the `epiR` package to estimate a confidence interval around the likelihood ratio estimate for the 50 -- 80 U/L category:

```
library(epiR)
epi.tests(a = 4, b = 22, c = 34, d = 94, conf.level = 0.95, verbose = FALSE)
```

The likelihood ratio of disease for the 50 -- 80 U/L category is 0.55 (95% CI 0.20 -- 1.51). Use the upper bound of the confidence interval to re-calculate the post-test probability of complications:

Post-test odds of complications = pre-test odds \times LR+
 Post-test odds of complications = 0.01×1.51
 Post-test odds of complications = 0.015

The post-test probability of complications given an ALT of 50 -- 80 U/L:

Post-test probability of complications = post-test odds ÷ (1 + post-test odds)

Post-test probability of complications = $0.015 \div (1 + 0.015)$

Post-test probability of complications = 0.015

Using the upper bound of the confidence interval of our likelihood ratio the post-test probability of complications is approximately 1.5% (a 3-fold difference).

If the dog had an ALT of 200 U/L what would be the post-test probability of complications?

The post-test odds of complications given an ALT of 200 U/L:

Post-test odds of complications = pre-test odds × LR+

Post-test odds of complications = 0.01×91

Post-test odds of complications = 0.91

The post-test probability of complications given an ALT of 200 U/L:

Post-test probability of complications = post-test odds ÷ (1 + post-test odds)

Post-test probability of complications = $0.91 \div (1 + 0.91)$

Post-test probability of complications = 0.48

The post-test probability of complications is 48%. Postpone anaesthesia until you evaluate this dog further.