4.4 Liver Biopsy

According to Mehta et al [1], biomarkers have not been accurate enough to use as non-invasive alternatives to biopsy for staging of liver disease caused by Hepatitis C virus (HCV). The staging is important because it can affect treatment decisions such as whether to treat with anti-HCV drugs. But the problem may not be with the markers but with the reference standard liver biopsy. In this problem, we will explore the effect of an imperfect gold standard (aka copper standard) on the apparent sensitivity and specificity of an index test that is actually better than the copper standard biopsy at identifying liver cirrhosis (scarring), the true disease state of interest.

Assume that the copper standard liver biopsy (B) has sensitivity 75% and specificity 95% for true cirrhosis (D). The prevalence of "true" disease D+ is 0.40. The table below illustrates this with a hypothetical population of 1000.

	D+	**D–**	Total
B+	300	30	330
B–	100	570	670
Total	400	600	1000

Assume that the new biomarker (index test) T is *perfect* relative to the "true" disease state D+/D-. So, all 100 false negatives on the biopsy will be T+ and none of the 570 true negatives on the biopsy will be T+, as shown below.

	D+	**D-**	
B+T+			
B+T–			
B–T+	100	0	100
B–T–			
	400	600	1000

a) Fill in the other 3 rows of the table above.

Begin Answer: Because the new test is perfect, an easy way to do this is just to fill in zeroes for false positives and false negatives in the table below. Then fill in the rest of the true positives in appropriate cells.

	D+	***D-***	
B+T+	***300***	***0***	***300***
B+T-	***0***	***30***	***30***
B-T+	***100***	***0***	***100***
B-T-	***0***	***570***	***570***
	400	***600***	***1000***

End Answer

The true disease status D+/D- is never observed, so the table used to calculate the sensitivity and specificity of the test T will be the following.

	B+	B-
T+		100
T-		

b) Fill in the other 3 cells of the table above. How does it compare with the first table in this problem that showed the sensitivity and specificity of the biopsy relative to the true disease status?

Begin Answer:
It's just the first table on its side, because we swapped the index test with the gold standard, as in Figure 4.3. We can't quite just roll it on its side like in Figure 4.3 if we want to keep B+ on the left, so we can just swap the columns after doing that.

(Roll the original table on its side and move T+ and T- labels to the left)		
	B-	***B+***
T+	***100***	***300***
T-	***570***	***30***
	670	***330***
(Swap B+ and B– rows)		
	B+	***B-***
T+	***300***	***100***
T-	***30***	***570***
	330	***670***

End Answer.

c) Calculate the apparent sensitivity and specificity of T relative to the liver biopsy B. How do these compare to the "true" PPV and NPV of the biopsy?

Sensitivity = 300/330 = 0.91
Specificity = 570/670 = 0.85

They are the same as the PPV and NPV from the table at the top since all we have done is turned that table on its side.

Now, repeat the process, but assume that T is 85% sensitive and 95% specific (compared with the true gold standard). You may assume that the sensitivity and specificity of T are independent of the biopsy result. For example, 85% of the 100 false negatives on B (0.85*100=85) will be positive on T and 5% of the 570 true negatives on B will be false positive on T.

	D+	D-	
B+T+			
B+T-			
B-T+	85	28.5	**113.5**
B-T-			
	400	**600**	**1000**

d) Fill in the other 3 rows of the table above.

Begin Answer:
The easiest way to do this is start with the table you made in part A. The 2 cells at the upper left of the table were 300 and 0 when the new test was perfect, now they will be 300 ×0. 85 = 255 (true positives) and 300 × 0.15 =45 (false negatives). You do the same thing with the cells in the lower left. For the cells in the upper right, which were 30 and 0 you now replace 30 with 30 × 0.95 = 28.5 (true negatives) and 0 with 30 × 0.05 = 1.5 (false positives).

	D+	*D-*	
B+T+	***255***	***1.5***	***256.5***
B+T-	***45***	***28.5***	***73.5***
B-T+	***85***	***28.5***	***113.5***
B-T-	***15***	***541.5***	***556.5***
	400	***600***	***1000***

End Answer

	B+	B-
T+		113.5
T-		
Total		

e) Fill in the other 4 cells of the table above.

Begin Answer:

Because we are now combining B+ and B−, we just put the row totals from part d in the appropriate cells:

	B+	***B-***
T+	***256.5***	***113.5***
T-	***73.5***	***556.5***
Total	***330***	***670***

End Answer

f) Calculate the apparent sensitivity and specificity of T relative to the liver biopsy B. Compare these to the true sensitivity and specificity of T.

Sensitivity = 256.5/330 = 0.78
Specificity = 113.5/670 = 0.83

The true sensitivity and specificity were 0.85 and 0.95. The index text is actually an improvement over the biopsy, but it looks worse when its sensitivity and specificity are calculated by comparing with the imperfect (copper standard) biopsy.

g) (Extra credit) If you were a scientist developing a marker you believed to be superior to liver biopsy for Hepatitis C staging, what data could you collect to make a case for your new marker even if (as seems likely) the errors between the two tests (biopsy and marker) were not independent?

The reason why staging is used to select patients for treatment is because it is predictive of prognosis – those at highest risk have the greatest urgency for treatment. So one approach would be to compare the ability of liver biopsy and the new marker to predict prognosis in patients with HCV. (We'll discuss prognostic tests in Chapter 6.) Even better would be to obtain values of these markers at baseline from a randomized trial of a treatment for hepatitis C, and show that they predict need for or response to treatment better than a liver biopsy (if patients with a range of liver biopsy results were included). This study design would be similar to the design of studies that showed that the Onco-Type Dx test mentioned in Scenario #4 from Chapter 1 was better than axillary node dissection at guiding treatment for breast cancer.

REFERENCE

1. Mehta SH, Lau B, Afdhal NH, Thomas DL. Exceeding the limits of liver histology markers. J Hepatol. 2009;50(1):36-41.