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.

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?

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?

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.

| | B+ | B- |
|---|---|---|
| **T+** | | 113.5 |
| **T-** | | |
| Total | | |

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

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.

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?

REFERENCE

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