

S1 Supporting information: Example of reference bias

The presence of systemic infection (sepsis) is sometimes inferred through a combination of measurements of inflammation-related biomarkers [1-5]. However, conditions besides sepsis can cause inflammation, so diagnostic tests for sepsis that are based on inflammatory markers may give false positives due to other inflammatory conditions.

Suppose, for the sake of argument, that a comparator (reference test) for sepsis is defined in terms of such inflammation markers. If both the comparator and a new diagnostic test produce positive results in response to inflammation, then there will be a high correlation between the results of the comparator and the new test, even in cases where both are wrong. This leads to an inflation of the measured performance of the test relative to the comparator. This situation is shown in Fig. S1.1.

It is not difficult to imagine the converse situation, in which reference bias could lead to under-estimation of performance. This would occur if there was an anticorrelation in the response of the comparator and test under evaluation.

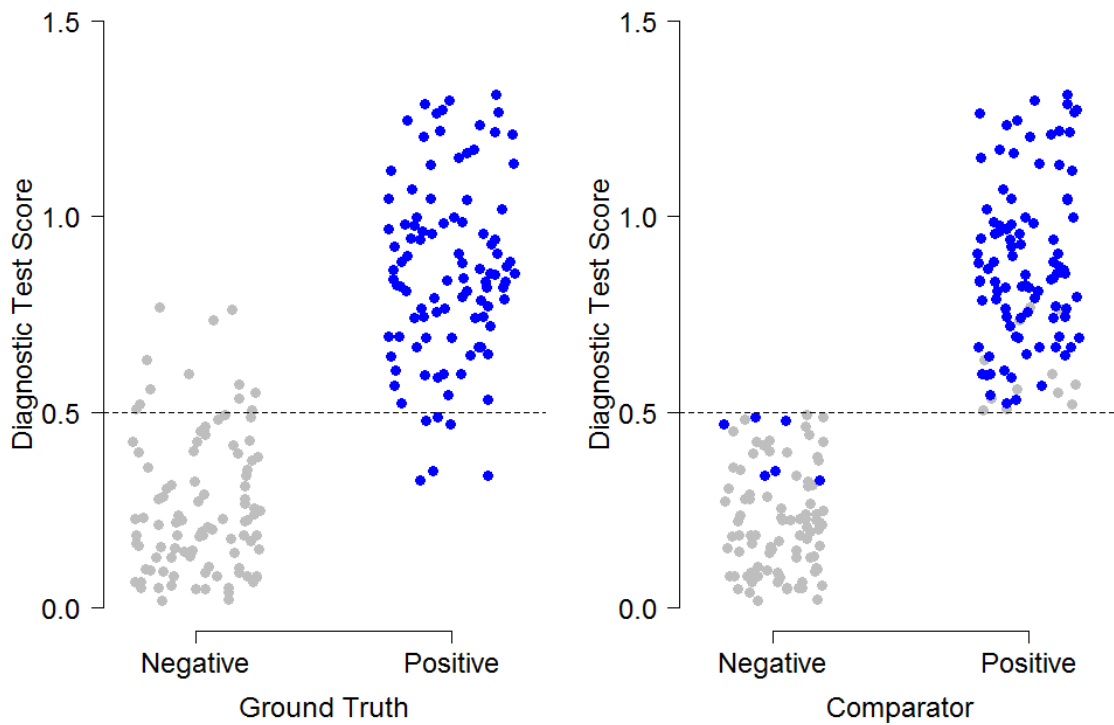


Fig. S1.1 Example of reference bias resulting in over-estimation of test performance. (A) Diagnostic test score (y-axis) compared to the Ground Truth, showing the true test performance. Grey points: 100 True Negatives at the level of Ground Truth. Blue Points: 100 True Positives at the level of Ground Truth. The test has AUC 0.976 using the Ground Truth as reference. (B) An example of where the comparator deviates from the Ground Truth in the same direction as the test, resulting in over-estimation of test performance. The test has AUC 1.00 using the biased comparator as reference.

References

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