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Editorial

Why we Need Evidence-Based Breast Cancer Biomarker Testing?

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EDITORIAL

The field of biomarker and molecular pathology research is booming. As a result hundreds of antibodies and molecular diagnostic tests are now available on the market. The implementation of new biomarkers into diagnostic histopathology often lacks an evidence-based approach, and this results in unknown diagnostic accuracy of new tests. High quality systematic reviews of diagnostic testing accuracy are urgently needed, as stated by Cochrane initiative [1]. To date, only 2-3 biomarkers routinely used in breast surgical pathology (steroid hormone receptors and Her2) are supported by high quality research evidence (i.e. randomized clinical trials or well designed cross-sectional studies), while similar quality evidence is lacking for the others. Still, sufficient and rigorous scientific data on sensitivity, specificity, reproducibility and expected positive and negative predictive values of ER, PR and Her2 remains difficult to obtain and is not explicit in pathology literature. The diagnostic accuracy of ER staining has been recently exposed and has resulted in liability issues in various countries, leading to a proliferation of quality control programs. These, in turn, use various designs and methods and are not directly comparable to each other.

On the other hand, molecular pathology is offering replacement tests (RT-PCR based; new generating sequencing; etc) to routinely used immunohistochemical tests. The validation of genomic signatures is evolving and requires a clear and robust assessment strategy and solid proof of reproducibility prior to any implementation [2]. The biomarker driven-clinical trial should provide high level evidence data which strategy is superior and economically sensible in directing therapeutic decisions leading to improved patient outcomes in patients with breast cancer.

In order to obtain a realistic picture of diagnostic accuracy in histopathology, the fundamental methodology questions will have to be answered through reviews of all scientific evidence prior to wide implementation of the tests. The Center of Evidence-Based Medicine in Oxford proposed a system for grading of quality of evidence for diagnostic and prognostic studies, which, along with STARD initiative (standard of reporting of diagnostic accuracy studies) sets a new high standard for biomarker research [3-5]. The following questions must be answered: - what is the analytic validity of the new test (sensitivity/specificity)?

- what is the reference standard?
- is the test free from avoidable bias (partial validation, incorporation bias, work-up bias, lack of blinding, non-independent reference, non-representative spectrum of disease)
- what is test reproducibility (intra- and inter-observer variation)?
- what is clinical validity of the test, i.e. what's the role of the test in the clinical pathway, i.e. does it lead to improved therapeutic strategies and better outcomes for the patients?
- what is the economic impact of the test for the healthcare system?

Definitions necessary for evaluation of diagnostic accuracy (organized into classic 2 x 2 table, see Table 1):

- True positive: test result matching positive reference standard
- True negative: test result matching negative reference standard
- False positive: positive test result, while reference standard is negative.
- False negative: negative test result, while reference standard is positive.
- Sensitivity, Sn (proportion of the true positive tests against positive reference standard
- Specificity, Sp (proportion of the true negative tests against negative reference standard
- Positive predictive value, PPV: post-positive test probability of a correct positive result)
- Negative predictive value, NPV: post-negative test probability of a correct negative result)
- Prevalence: proportion of target positive (true positive) cases in a testing population.

Example

A lab is requested to re-test its all ER negative results over a period of time (of total 1000 ER tests) by the reference laboratory, assuming that the ER test is at least 90% sensitive and 90% specific. The literature states that about 80% of breast cancers are ER positive. What's the most likely error rate one can

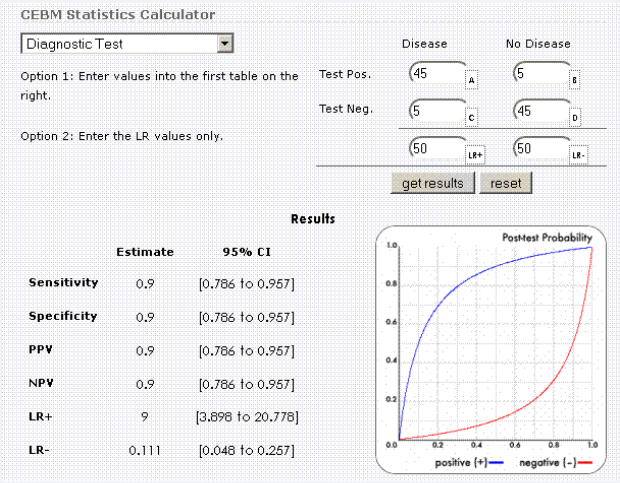

Figure 1 ER test optimization, based on 50 positive and 50 negative cases.

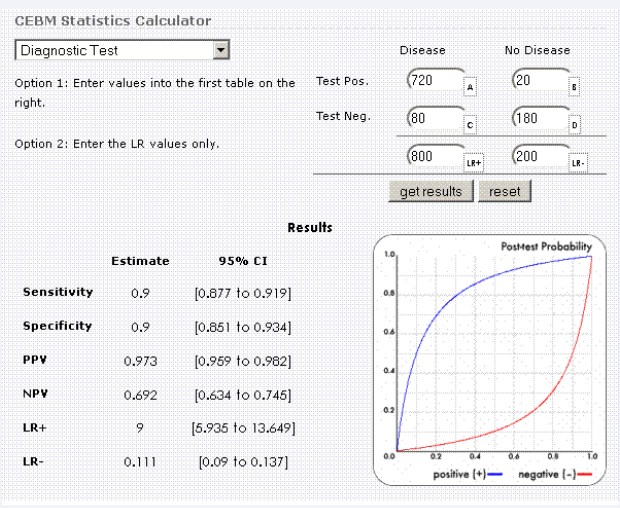

Figure 2 ER: imaginable re-test of 1000 cases.

expect on such re-testing? Select one best answer:

a. 1%
b. 5%
c. 10%
d. 15%
e. 30%.

Explanation

Surprisingly, the correct answer is "e". You've been asked to calculate NPV of the ER test.

Using the formulas and the approach described above one can determine the most likely diagnostic accuracy of ER testing in real clinical settings, providing that the laboratory properly optimized its ER immunostaining by testing 50 positive and 50 negative samples and reached minimal 90% concordance through participation in external quality assurance program (i.e. ER test is at least 90% sensitive and 90% specific against the reference laboratory). One can make calculations by hand using the formulas (Table 1) or by using online calculators [6].

Table 1: Review of Basic Statistics of Diagnostic Test Accuracy.

	Reference"+"	Reference"-"	
Test"+"	a.True Positive	c. False Positive	PPv=a/(a+c)
Test"-"	b. False negative	d. True Negative	NPv=b/(b+d)
	Prevalence=(a+b)/N Sn=a/(a+b)	Sp=d(c+d)	N (Total tests)= a+b+c=d

Figure 1 shows test validation result (50 positive and 50 negative cases) using diagnostic test accuracy online calculator [6]. Here, the "Disease positive" column means "Reference ER positive" and "Disease negative" means "Reference ER negative". All parameters show at least 90% accuracy.

Figure 2 shows the expected results for 1000 samples from that laboratory, but taking into account ER+ prevalence in clinical practice (around 80%). When compared with Figure 1 the sensitivity and specificity remains the same, yet the negative predictive value (proportion of true negative results of all tested negative) decreases significantly, making each third negative test result produced by the laboratory false negative. Therefore, the correct answer is e.

This is a predictable result, based NOT on poor performance, but on prevalence effect: the technical test parameters remained the same, while the negative result accuracy (i.e. NPV) decreased significantly due to a prevalence effect. Note that the optimization of the test was performed with the prevalence of reference positive result of 50%, while in clinical practice the prevalence of ER is 80%. This caused the change in NPV from 90% to below 70% in logarithmic fashion, based on Baysian theorem. Therefore, any judgement on diagnostic test performance should consider this effect [5].

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