

Testing strategies for antibodies against nuclear antigens in lupus nephritis

Serological markers can be helpful in determining the need for renal biopsy in patients with systemic lupus erythematosus (SLE). Elsewhere in this issue (pp. 259–265), Dr. Clough and co-workers evaluate a number of these markers and their usefulness in predicting lupus nephritis. The predictive value model¹ is applied by these investigators to come up with their recommended use of these tests: “The presence of the combination of anti-nDNA, anti-Sm, and anti-RNP . . . should encourage greater vigilance in monitoring disease activity, and liberal use of renal biopsy in evaluation of such patients seems justified.”²

While it is quite simple to apply the predictive value model to the evaluation of a single test, it can similarly be used to evaluate more than one test. In general there are two basic strategies for applying two or more tests in a screening or diagnostic situation. These are called series and parallel testing strategies. For two tests A and B, these strategies are as follows: In series testing test A is applied first, and all those with a positive result are retested with test B. Patients must be positive on both tests to be considered positive. Of course, the tests can be run at the same time. The interpretation, however, requires that all tests in the group must be positive to consider the outcome of testing positive. In parallel testing, tests A and B are used together, and all those with positive results for one or more tests are considered to be positive. Which approach or strategy is better? This depends on the testing situation and the sensitivity and specificity of the individual tests and their combinations. With parallel testing, the combined sensitivity is greater than the individual sensitivities of the contributing tests. Parallel testing results in the highest

sensitivity, but the lowest specificity, whereas series testing results in the lowest sensitivity but the highest specificity.

For tests run in parallel (A and B determined simultaneously), but considered positive if either component is positive and negative only if both are negative, the sensitivity is higher and the specificity is lower than in comparable series testing. The sensitivity is increased because some patients with disease are positive on one test, but not on the other. Similarly, there are more false-positive results in patients without disease.

The advent of microcomputers has made it possible for investigators to share data bases with one another and Dr. Clough has been kind enough to provide me with the data base from his investigation. The above relationships can be demonstrated with his test results (*Tables 1 and 2*). *Table 1* shows the analysis of the combination test rule when interpreted in a series fashion; *Table 2* shows the same tests applied in a parallel fashion. The overall effect of the series approach is that more cases will be missed, but there will be a higher predictive value of the positive result (fewer false-positive results). This is frequently the desired outcome of the testing strategy, as is the case here.

The authors reported that the combined presence of anti-native DNA, anti-Sm, and anti-RNP (series testing) had a positive predictive value of 50% for class IV nephritis. This is indeed correct (*Table 1*), but readers must bear in mind the effect of prevalence on the predictive value of any test. *Table 3* demonstrates how this testing strategy would function under conditions where the frequency of nephritis were more, as well as less, common than in the authors' study. As the frequency of this complication of SLE becomes less likely, the tests similarly become less useful.

Lastly we have developed a computer program

Table 1. Predicting lupus nephritis with antinuclear antibodies: Series testing*

	Test +	Test -	Total
Nephritis +	5	11	16
Nephritis -	5	73	78
Total	10	84	94

* Series rule: A positive test consists of the combined presence of anti-native DNA, anti-Sm, and anti-RNP antibodies.

Prevalence	17%
Sensitivity	31.3%
Specificity	93.6%
Predictive value (+)	50%
Predictive value (-)	86.9%
Efficiency	83%

Table 2. Predicting lupus nephritis with antinuclear antibodies: Parallel testing*

	Test +	Test -	Total
Nephritis +	15	1	16
Nephritis -	55	23	78
Total	70	24	94

* Parallel rule: A positive test consists of the presence of any one of the following antibodies: anti-native DNA, anti-Sm, or anti-RNP.

Prevalence	17%
Sensitivity	93.8%
Specificity	29.5%
Predictive value (+)	21.4%
Predictive value (-)	95.8%
Efficiency	40.4%

called the PVC[®] Optimizer, which automatically analyzes a data base and selects the best test or test combination for a particular diagnostic problem. We evaluated the authors' data using PVC[®] and the computer program was unable to find a test combination that had a higher predictive value than reported by the authors. The program

Table 3. Effect of prevalence of lupus nephritis on usefulness of antinuclear antibody tests in predicting its occurrence*

Prevalence	Predictive Value (+)	Predictive Value (-)	Efficiency
1	4.5	99.3	93
2	8.7	98.5	92.3
5	20.8	96.3	90.5
10	34.8	92.4	87.3
15	46.5	88.5	84.3
20	55.3	84.5	81.2
25	61.9	80.3	78
50	83	57.6	62.4

* Based on series testing illustrated in Table 1. A positive test consists of the combined presence of anti-native DNA, anti-Sm, and anti-RNP antibodies.

was, however, able to produce the same results as the three tests shown in Table 1 using only two tests: positive anti-nDNA and positive anti-other. Anti-other antibodies were antinuclear antibodies of undetermined specificity. What the computer didn't know was that anti-other was not a test. There still seems to be some value in having people involved in data analysis after all!

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References

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2. Clough JD, Couri J, Youssoufian H, Gephardt GN, Tubbs R. Antibodies against nuclear antigens: Association with lupus nephritis. *Cleve Clin Q* 1986; 53:259-265.