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PCA3 Screening Test for Prostate Cancer

APPENDIX – Statistical Analysis

Here an attempt will be made to clarify how the numbers we have been using to judge screening tests arise from the experimental data. In Table 1 are given the results derived from a graph in the FDA report of the percent positive biopsies in each PCA3 Score quartile along with the number of subjects for each quartile. From these numbers Table 1 follows since for each quartile the percentage of biopsies negative for PC is simply 100 – percentage of positive biopsies. One can then calculate both the actual subject numbers and the total number of subjects with positive and negative biopsies for each quartile of the PCA3 score. The upper limit of the quartile range becomes a cut-off Score and allows one to group the total study cohort into positive and negative groups for three different values of the cut-off.

Table 1. Clinical results from study cited by the FDA (approximate numbers derived from graphical presentation of % biopsies positive for each quartile of the study population)[1]

	Q1	Q2	Q3	Q4	Total
PCA3 Score	<12	12-<24	25-<47	≥48	
Number in each Q	114	117	116	119	466
% biopsies + for PC*	9%	11%	29%	37%	
Number with PC*	10	13	34	44	101
% biopsies – for PC*	91%	89%	71%	63%	
Number without PC*	104	104	82	75	365

**** In each quartile***

Table 2 illustrates the nature of the entries into the standard 2X2 table used for calculations. Positive (P) and negative (N) refer to the results of the PCA3 test. True (T) and false (F) refer to the biopsy results of either finding or not finding PC. The double use of the terms positive and negative for biopsy results and urine test results can cause confusion. This further serves to define these terms and their role in describing the study results.

Table 2. A 2X2 table illustrating true positives, true negatives, false positives and false negatives

PCA3 Test Results

Biopsy Outcome	Positive	Negative
PC present	TP	FN
PC absent	FP	TN

The numbers in Table 1 can then be used to construct the 2X2 Tables 3, 4 and 5. In Table 3, for example, the cut-off is a score of 12, so TP is 13 + 34 + 44 = 91. Since there were 101 with PC (Table 1), the FN is 101 – 91 = 10, which is also the number of subjects given in Table 1 with PC but with a negative test score, in this case < 12. Likewise, there were 104 (Q1) with no PC and a PCA3 score of < 12, making them true negatives. Since there were 365 total without PC (Table 1), the false positives were 365 – 104 = 261, which is also the sum of the number in Q2 through Q4 without PC who had a positive PCA3 score, i.e. ≥ 12. Thus Table 3 can be formed.

Table 3. A 2X2 table giving the number of patients for each outcome according To the PCA3 test results. Test positive for PCA3 Score ≥ 12

PCA3 Test Results

Biopsy Outcome	Positive	Negative	Totals
PC present	91	10	101
PC absent	261	104	365
Totals	352	114	466

Tables for cut-off values of the PCA3 test of 25 and 47 are obtained in the same way.

Table 4. A 2X2 table giving the number of patients for each outcome according To the PCA3 test results. Test positive for PCA3 Score ≥ 25

PCA3 Test Results

Biopsy Outcome	Positive	Negative	Totals
PC present	78	23	101
PC absent	157	280	365
Totals	235	231	466

Table 5. A 2X2 table giving the number of patients for each outcome according To the PCA3 test results. Test positive for PCA3 Score ≥ 48

PCA3 Test Results

Biopsy Outcome	Positive	Negative	Totals
PC present	44	57	101
PC absent	75	290	365
Totals	119	347	466

From these tables, using Table 2 to identify TP, FP, FN and TN, and the following relationships, one can calculate the common statistical parameter discussed in the text.

Sensitivity: SEN = TP = TP/(TP + FN) **Specificity: SP = TN/(TN + FP)**

Positive Predictive Value: PPV = TP/(TP + FP) **Negative predictive value: NPV = TN/(TN + FN)**

Table 6. Calculated statistical parameters for three cut-offs of the PCA3 score

Cut-off	SEN	SP	PPV	NPV
≥12	90	28	26	91
≥25	77	57	33	90
≥48	44	79	37	84

If any PCA3 score from zero to the maximum present in the study group is taken as a positive test result, then TP = 104, FP = 0, FN = 361 and TN = 0. This yields a sensitivity of 1.0 and a specificity of zero. If on the other hand, the score cut off is set so high that there are no subjects who qualify as positive, the sensitivity becomes zero and the specificity 1.0, the other limiting case.

In screening studies, one collects two pieces of information on each participant, the biopsy result and the PCA3 score. The cut-off to be used in decision-making and recommendations is clearly arbitrary but guided by an attempt to optimize the sensitivity and specificity. In the FDA table in the report, the results were presented for a cut-off of PCA3 score of 25, the value that will probably be used in practice. It is noteworthy that lowering the cut-off to 12 strongly increases the sensitivity, results in a very poor specificity, but has little impact on the negative predictive value while the positive predictive values remain poor.

It will be noted that as the cut-off is increased the sensitivity decreases and the specificity increases. The reason for the reciprocal behavior of sensitivity and specificity can be seen from Tables 3, 4 and 5. As the cut-off increases, the true positives decrease while the total group with positive biopsies remains the same at 101. The reverse happens with specificity because the true negatives increase but the total without PC remains constant at 365. This is the trade-off and dilemma of trying to pick out those that really do or do not have a disorder with a screening test. One cannot really win and the approach is imperfect. The problem is that the risk of having the disorder simply increases with the value of a marker, in this case rising rather steeply, but there are those who have the disorder who have a value of the marker below a cut-off, and those who do not have the disorder who have the disorder who are above the cut-offs. Put another way, as is illustrated in many textbooks, there are overlapping distributions of those with and without the disease when plotted as a function of the PCA3 score. As the cut-off changes, the proportion of false positives to false negatives in the overlap region changes. The ideal diagnostic tool has a marker where everyone who is positive down to the detection limits of the marker has the disorder. An X-ray looking for a leg fracture has this feature. The cancer cell specific enzyme CYP1B1 and its metabolites may be another.[2]

Reference List

(1) FDA. Summary of safety and effectiveness data (PCA3 Assay). *www accessdata fda gov/cdrh_docs/pdf10/P100033b pdf* 2012.

(2) Ware WR. Nutrition and the prevention and treatment of cancer: association of cytochrome P450 CYP1B1 with the role of fruit and fruit extracts. *Integr Cancer Ther* 2009 March;8(1):22-8.

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