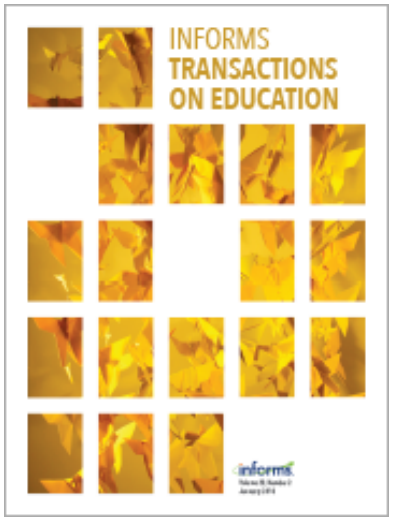

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Case

Vermillion OVA1 Test, Part B

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Valuing a Medical Diagnostics Test

Jacobs et al. (1990) recommend using risk of malignancy indey (RMI) cutoff value of 200 in referring ovarian tumor patients to oncologists. One way in which physicians arrive at recommendations for cutoff values is by plotting the test's *sensitivity* (true positive rate) against the false negative rate, calculated as 1-*specificity*. A plot of a test's *sensitivity* versus 1-*specificity* is called a receiver operating characteristic (ROC) plot.[1]

An RMI cutoff value can be thought of as a *classifier* test because it classifies patients into two groups: those whose tumors are likely malignant and those whose tumors are likely benign. A perfect classifier has 100% true positive rate and 0% false negative rate. One way to determine that one test might be better than the other is to compare which test is closer to the (0%, 100%) point in the ROC space. Figure 3 shows an ROC plot for different cutoff values from Figure 2 in Part A.

Different studies of RMI's usefulness have reported different sensitivities and specificities for the same RMI cutoff value of 200. A small selection of published studies is presented in Table 2. Part of the difference comes from sampling. However, a significant part of the variation has been attributed to differences in scoring ultrasound images. Differences in equipment and in operator experience imply that the same patient could be assigned different scores depending on the operator and on the ultrasound equipment. An image can also be scored differently by different physicians.[2] It is thus valuable to have a more reliable diagnostic test.

Experts consider early detection of cancer to be the best hope for improved outcomes. A number of biotech companies are exploring clinical laboratory tests to enable early detection. Early detection has yet to materialize, but in 2009, Vermillion, Inc. received U.S. Food and Drug Administration (FDA) approval for OVA1, a laboratory triage test based on proteomic analyses of blood samples. According to an FDA statement (Long 2009) and the article in *The Wall Street Journal* (WSJ) mentioned in Part A, OVA1 estimates the levels of five proteins that change because of ovarian cancer. The five protein level measurements combine into a single score to indicate the likelihood that the tumor is cancerous.

To evaluate OVA1, Vermillion, Inc., conducted a prospective clinical trial comparing physicians' presurgery designations of tumors with the results of OVA1. (Mutch and Herzog 2010). The physicians' presurgery recommendations were based on the guidelines of the American College of Obstetrics and Gynecology and their outcomes performance differed from the results in the previous RMI studies (Table 3).

The FDA statement read "OVA1 identifies some women who will benefit from referral to a gynecological oncologist for their surgery, despite negative results from other clinical and radiographic tests for ovarian cancer. If other test results suggest

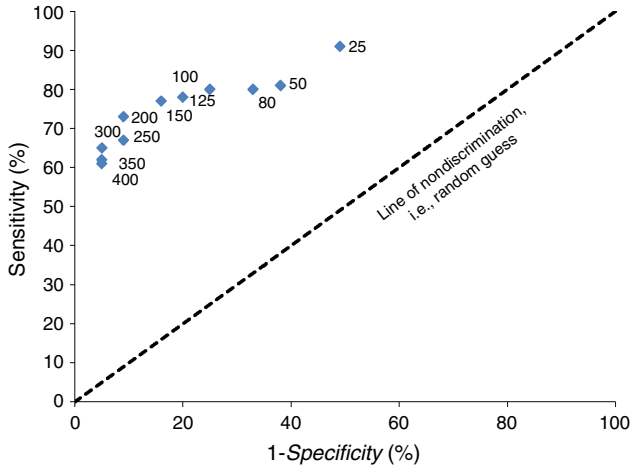
[1] According to Wikipedia, an ROC plot was first used during World War II for the analysis of radar signals.

[2] Differences between physicians in the interpretation of the same image have also been found in clinical studies of other diseases (Bialik 2011).

Table 2 Sensitivity and Specificity for RMI with Cutoff of 200 Reported by Different Researchers

Sensitivity (%)	Specificity (%)	Year	Country	Reference
85.4	96.9	1990	U.S.	(Jacobs et al. 1990)
73	91	2001	India	(Manjunath et al. 2001)
90	89	2004	Jordan	(Obeidat et al. 2004)
71.7	80.5	2007	Turkey	(Ulusoy et al. 2007)
87.4	56.8	2006	U.S.	(Bailey et al. 2006)
80	84	2009	Japan	(Yamamoto et al. 2009)

Figure 3 ROC for Various RMI Cutoff Values (Based on Data from Manjunath et al. (2001))



cancer, referral to an oncologist is appropriate even with a negative OVA1 result." The WSJ article indicated that Vermillion, Inc., planned to offer the test through Quest Diagnostics at a charge of $650 per test (Johannes 2010). Since FDA approval, physicians have debated whether or not to recommend the test to patients (Abraham 2010, Miller 2010). The implications of the low specificity of OVA1 were of particular concern.

Table 3 Data from OVA1 Trial

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Physicians (%)	77	68	52	87
OVA1 test (%)	92	43	41	93

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