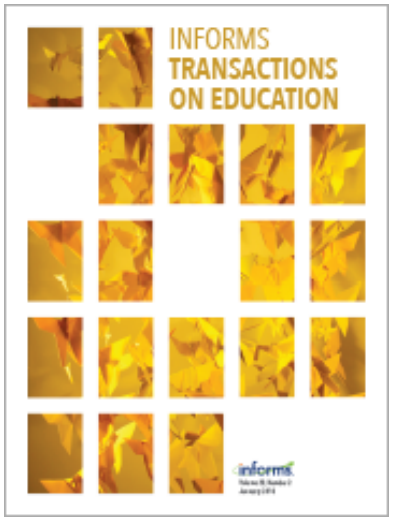
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Case

Vermillion OVA1 Test, Part A

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Introduction

In March 2010, *The Wall Street Journal* (WSJ) published an article about OVA1, a triage test for ovarian cancer (Johannes 2010). Vermillion, Inc., the company that developed the test, received U.S. Food and Drug Administration (FDA) approval for its use and planned to charge $650 per test. One of the obstacles to the adoption of OVA1 was its low specificity (the rate of true negatives).

This two-part case is based on the WSJ article. This case is organized as follows. Part A provides information about the disease and its treatment gathered from the WSJ article and academic medical articles. In this part, we discuss diagnostic tests in medicine; define sensitivity (true positive rate), and specificity (true negative rate), positive and negative predictive values; and explore how the sensitivity and specificity of a test combined with the incidence of a disease in a population may affect patients, physicians, and insurance companies. In Part B, we discuss classifier tests, receiver operating characteristic (ROC) curves, the selection of a cutoff value for a classifier test, and the economic value of the new test as a supplement to the existing diagnostic tests.

Background on Ovarian Cancer Diagnosis and Surgical Treatment

According to the American Cancer Society (ACS 2011), close to 22,000 women are diagnosed with ovarian cancer every year in the United States. For those diagnosed early, the 5-year survival rate is 93%. Unfortunately, ovarian cancer is difficult to diagnose and early diagnoses are rare. More than 80% of patients are diagnosed at advanced stages and the probability of 5-year survival at that point is much lower.

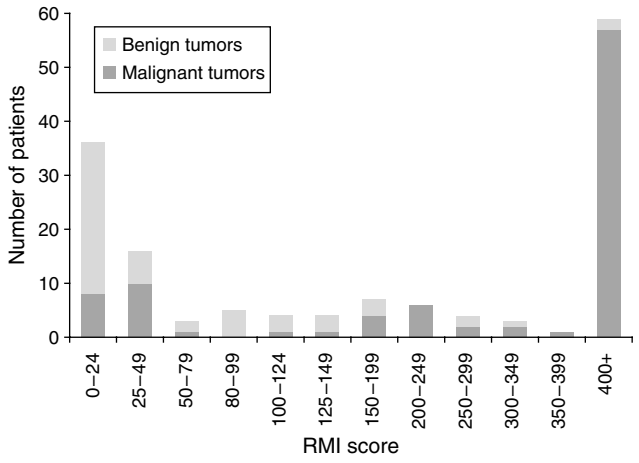
An ovarian tumor can be detected during a physical exam or via an imaging study such as an ultrasound examination. The majority of ovarian tumors are benign (not cancerous), but a definitive diagnosis requires surgery and a direct examination of tumor tissue.

Often an ovarian tumor is detected in an exam performed by an ob/gyn physician (who is normally trained in surgery). An ob/gyn physician who thinks a tumor is benign but should still be removed can surgically remove the tumor and send tissue samples to a pathologist for definitive diagnosis. Patients whose tumors are thought to be cancerous are referred to a gynecologic oncologist. Gynecologic oncologists are specialist surgeons who have three to four years of additional training for cancer surgery, chemotherapy, and/or radiation therapy. Clinical studies show that cancer patients' median survival times are six to nine months longer when their surgery is performed by a gynecologic oncologist rather than a surgeon without this specialization (Vernooij et al. 2007). An oncologist would also have a pathologist examine the tissue. Using a technique called frozen section, the pathologist can perform a rapid analysis of the tissue during surgery. If the frozen section examination confirms cancer, the oncologist can perform the additional surgical procedures needed during surgery.

The ability to predict the nature of a tumor prior to surgery can help direct patients to an appropriate physician. A general ob/gyn physician could be sensitive about referring a patient to an oncologist because such a referral is usually distressing for a patient. There could also be unnecessary costs and inconvenience for patients from remote areas. A benign tumor

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Figure 1 **Histogram of RMI Scores for Patients in the Manjunath et al. (2001) Study**



could be removed effectively at a local hospital. However, if an examination of the tumor tissue reveals cancer, having a second surgery by an oncologist would involve not only additional expense but also a longer recovery and additional risks.

In 1990, Jacobs et al. proposed to triage patients with suspicious tumors based on the calculation of a risk of malignancy index (RMI). RMI combines three factors: the blood serum level of cancer antigen 125 (CA125) along with the patient's ultrasound and age scores. Higher RMI is associated with a higher risk of malignancy (cancer). Jacobs et al. (1990) showed that the index was a better indicator of risk than any of the three factors separately. Subsequently, multiple researchers replicated the study with similar conclusions. For example, Manjunath et al. (2001) reviewed the charts of 148 patients who underwent ovarian tumor surgery in a hospital in India, 93 of these patients had malignant tumors. Figures 1 and 2 illustrate the association between the patients' RMI scores and whether they had cancer. Figure 1 shows how many cases of malignant and nonmalignant tumors fell within each score bin. Figure 2 shows the same

Figure 2 **RMI Scores for Patients in the Manjunath et al. (2001) Study**

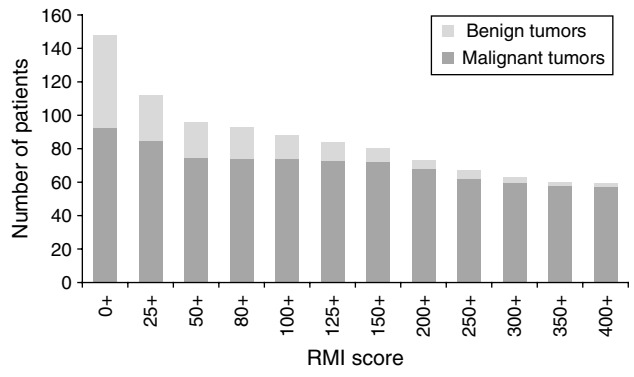


Table 1 **Example to Illustrate the Concepts of Sensitivity, Specificity, and Positive and Negative Predictive Values**

	Patient positive (malignant tumor)	Patient negative (benign tumor)	Total
Test positive (predicts malignancy)	30	6	36
Test negative (predicts benign tumor)	10	54	64
Total	40	60	

data cumulatively: The first bar contains information about all the patients in the study, the second bar only shows the patients whose RMI index was 25 or above, etc. Looking at the data in this way makes it easier to see that the likelihood of malignancy increases with the RMI score.

The performance of a medical diagnostic test is described in terms of *sensitivity*, *specificity*, *positive predictive value*, *negative predictive value*, and *accuracy*. These terms refer to different conditional probabilities.

Consider a population of 100 patients with ovarian tumors and suppose a pathologist finds that 40 cases are malignant. A test that predicts malignancy for 30 out of the 40 patients with the malignancy has a true positive rate (or sensitivity) of $30/40 = 75\%$. If the same test predicts that 54 of the 60 benign tumors are benign, then the test has a $54/60 = 90\%$ true negative rate (or specificity). This example is shown in Table 1.

Sensitivity and specificity are inherent characteristics of the test. Positive predictive value, negative predictive value, and accuracy depend on the incidence of the disease in the patient population. In the example, the incidence of malignancy is 40% because 40 of the 100 patients have malignant tumors. Positive predictive value is the probability that a patient who tests positive really has the disease. In the example, the test predicted malignancy in 36 patients of which 30 were true positives; thus, positive predictive value is $30/36 \approx 83.3\%$. Negative predictive value is the probability that a patient who tests negative does not have the disease. In our example, 64 tumors were predicted to be benign and 54 of them really were, which means that the negative predictive value is $54/64 \approx 84.4\%$. Accuracy is the percentage of cases in which the results of the test and the true diagnosis are the same. For our example, accuracy is $(30 + 54)/100 = 84\%$.

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