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COST AND ACCURACY COMPARISONS IN MEDICAL TESTING USING SEQUENTIAL TESTING STRATEGIES

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Virginia Commonwealth University
School of Medicine

This is to certify that the dissertation prepared by Anwar Elsiddig Ahmed entitled "Cost and Accuracy Comparisons in Medical Testing Using Sequential Testing Strategies" has been approved by his committee as satisfactory completion of the dissertation requirement for the degree of Doctor of Philosophy

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COST AND ACCURACY COMPARISONS IN MEDICAL TESTING USING SEQUENTIAL TESTING STRATEGIES

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

by

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ANWAR ELSIDDIG AHMED, M.Sc.

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

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The practice of sequential testing is followed by the evaluation of accuracy, but often not by the evaluation of cost. This research described and compared three sequential testing strategies: believe the negative (BN), believe the positive (BP) and believe the extreme (BE), the latter being a less-examined strategy. All three strategies were used to combine results of two medical tests to diagnose a disease or medical condition. Descriptions of these strategies were provided in terms of accuracy (using the maximum receiver operating curve or MROC) and cost of testing (defined as the proportion of subjects who need 2 tests to diagnose disease), with the goal to minimize the number of tests needed for each subject while maintaining test accuracy. It was shown that the cost of the test sequence could be

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reduced without sacrificing accuracy beyond an acceptable range by setting an acceptable tolerance (*q*) on maximum test sensitivity. This research introduced a newly-developed ROC curve reflecting this reduced sensitivity and cost of testing called the Minimum Cost Maximum Receiver Operating Characteristic (MCMROC) curve. Within these strategies, four different parameters that could influence the performance of the combined tests were examined: the area under the curve (AUC) of each individual test, the ratio of standard deviations (*b*) from assumed underlying disease and non-disease populations, correlation (*rho*) between underlying disease populations, and disease prevalence. The following patterns were noted: Under all parameter settings, the MROC curve of the BE strategy never performed worse than the BN and BP strategies, and it most frequently had the lowest cost. The parameters tended to have less of an effect on the MROC and MCMROC curves than they had on the cost curves, which were affected greatly. The AUC values and the ratio of standard deviations both had a greater effect on cost curves, MROC curves, and MCMROC curves than prevalence and correlation. The use of BMI and plasma glucose concentration to diagnose diabetes in Pima Indians was presented as an example of a real-world application of these strategies. It was found that the BN and BE strategies were the most consistently accurate and least expensive choice.

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Chapter 1: Introduction

1.1 Definition of Problem

In response to the current economic slowdown and increasing healthcare costs in the United States, patients, health insurance companies, healthcare professionals, and government agencies are interested in reducing health care spending. Therefore, economic assessment is important in the field of healthcare.

In clinical practice, multiple tests are often used in diagnosing a patient. Performing several diagnostic tests on an individual provides multiple measures with additional information that can be combined in order to improve the overall accuracy of the diagnostic process, compared to that of a single test. However, multiple testing could be more costly than using a single test strategy. The consequence of this is that significant cost is added to healthcare. Consequently, medical tests should be evaluated individually and in combination to assure appropriate accuracy while limiting healthcare costs.

There are several techniques available to combine multiple tests in order to classify subjects into one of two groups (diseased or non-diseased) and these techniques will depend on the type of testing. In clinical settings, two types of testing are considered: non-sequential and sequential testing. Non-sequential testing is the method of performing all tests simultaneously on all subjects or performing all tests prior to deciding on the diagnosis. Techniques to combine test results in order to make a diagnosis, in non-sequential testing include logistic regression, which uses likelihood ratios and linear

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combinations of variables, as well as classification trees. Sequential testing is the method of performing a secondary test based on the results of the previous test.

The research here concentrates on sequential testing, in which decisions on whether or not to order subsequent tests are based on the results of a previous test. In sequential testing, the most popular technique to combine multiple sequences of tests is to use combinations of logic rules (Ruczinski, Kooperberg, LeBlanc, 2003). An example of some of these logic rules are believe the positive (BP), and believe the negative (BN), which will be described in detail in Chapter 2. Logic rules can be used to construct predictors that are logical combinations of the original predictors. This research focused on three forms of these logic rules: believe the positive (BP), believe the negative (BN), and believe the extreme (BE). These will be described and compared, in the coming chapters, in terms of accuracy and cost of testing.

Since cost is the main issue in this research, it must be given a narrow definition from the beginning. Cost can be thought of from many different perspectives: the patient could worry about the financial cost or physical burden of each individual test, while governments and health insurance companies may think about cost economically. In this research, cost will primarily be thought of in terms of the cost of the sequenced tests, called hereafter the cost of testing (no non-sequential testing strategies were considered). Since the goal here is to reduce the numbers of tests administered to each patient, 'low cost' could be defined as a reduction in the number of tests performed.

To evaluate the sequence of tests, several traditional measures of diagnostic accuracy can be employed. The most popular measures are the test's sensitivity and

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specificity. Sensitivity is the probability that the test or testing strategy correctly identifies the subject with disease as having the disease. This is estimated by computing the proportion of subjects with the disease that the test or testing strategy correctly identifies as having disease. Specificity is the probability that the test or testing strategy correctly identifies the subject without disease as not having the disease. This is estimated by computing the proportion of subjects without the disease that the test or strategy correctly identifies as non-disease.

In this study, tests using continuous measures will be considered. Thus, thresholds for each measure are used to dichotomize the test results into diseased and non-diseased. The measures of sensitivity and specificity are estimated using these thresholds. Because the disease detectability of these thresholds varies, clinicians will want to know what thresholds to use to diagnose new patients as having disease or not. The combination of thresholds that produce the best trade-off in sensitivity and specificity is considered the optimal operating point (OOP).

In later chapters, another cost will be considered when calculating the optimal operating point. This is the cost of misclassification. Misclassification could be defined as declaring a test result as positive erroneously for a patient who is actually negative for a disease, or declaring a test result as negative for a patient who actually has disease. Each test has four possible outcomes for diagnosis: False Positive (FP), in which the patient is falsely classified as positive, False Negative (FN), in which the patient is falsely classified as negative, True Positive (TP), in which the patient is correctly classified as positive, and finally, True Negative (TN), in which the patient is correctly classified as negative. The

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risks in falsely classified tests are many. A patient, falsely believing to be positive, may undergo harmful, unnecessary treatments to combat a disease they do not have. Conversely, a patient, falsely believing to be negative for disease, could avoid treatments that may be necessary for recovery. The total cost of misclassification could be either the total proportion of these misclassified subjects or a function of the misclassification errors.

A ROC curve demonstrates the characteristics of a diagnostic test by graphing the false-positive rate (1-specificity) on the horizontal axis and the true-positive rate (sensitivity) on the vertical axis for various cutoff values. As the false-positive rate increases, so does the true-positive rate. The diagonal line connecting the points (0, 0) and (1, 1), i.e. the chance line, is used to divide the plot into two spaces (bad or good). Points falling above the chance line indicate test performance better than chance and points falling below the chance line indicate performance worse than chance. Perfect classification occurs at the (0, 1) point which corresponds to a specificity and sensitivity of 1.0. The closer the ROC curve is to this point, the more accurate the test is.

Single tests defining a binary outcome such as disease/non-disease, typically use a single threshold, thus resulting in a single (1-Specificity, Sensitivity) pair on the ROC curve. However, the use of logic rules in a sequence of tests may be associated with more than one threshold (at least one from each test) which may produce more than one sensitivity value corresponding to a fixed specificity.

Thompson (2003) and Shen (2008) refer to the plot of maximum value of sensitivity for each false-positive rate as the maximum ROC (MROC) curve, but cost of testing was not considered from their analysis. This research extends previous research by

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evaluating the three sequential strategies mentioned above by comparing the accuracy and cost of testing of combined tests. It also considers thresholds that produce the same or slightly lower sensitivity than the maximum sensitivity.

1.2 Motivation and Goals

Considering two tests given sequentially, it is possible that the second test could be uninformative or might add too little information to the diagnostic process. Although the practice of sequential testing is followed by the evaluation of accuracy, it is often not by the evaluation of cost of testing. Consequently, much work remains to be done to evaluate sequences of tests using both accuracy and cost of testing.

The motivation here is to consider a sequential strategy to reduce cost of testing, as defined in section 1.1. Performing multiple tests can be expensive. Some tests may not provide relevant information and conducting many tests does not ensure accuracy. Instead, multiple tests could be difficult to interpret, risky or painful. Government agencies will benefit from this research because reducing the number of tests for all patients could reduce the cost of testing. The innovative approach of not performing all tests on every patient, as well as improving the accuracy of diagnosis, can make an important contribution in reducing the number of tests, thus limiting health care costs.

Further, the goal is to give a general direction on the choice of an optimal operating point (OOP); this is the point that produces the best set of sensitivity and specificity considering restriction on the cost of testing. In this research, the benefits of lowering the number of tests were considered. Increasing the number of tests makes healthcare costs rise, thus causing financial problems for those who have no health insurance, and possibly

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increasing the insurance premiums for those who are well-insured. In summary, the goal of this research is to offer solutions for medical testing to be accurate while lowering the cost of testing.

1.3 Prospectus

This research is organized as follows: Chapter 2 begins with a review of the strategies to consider for sequential testing. Early work regarding sequential testing and a special ROC curve adapted to such testing (called MROC curves) will be considered as well. Chapter 3 demonstrates how to obtain an MROC curve, the newly developed Minimum Cost Maximum ROC (MCMROC) and cost curves. Formulas are derived for sensitivity, specificity, false-positive rate and cost of testing for each of the strategies, and a technique to find optimal operating points is provided. Chapters 4 and 5 are devoted to describing and comparing the strategies in terms of cost of testing, and accuracy. Chapter 6 applies these techniques to real data, obtaining MROC, MCMROC and cost curves. Chapter 7 concentrates on discussion and directions for future research.

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Chapter 2: Review of Relevant Statistical Topics

2.1 Review of sequential testing and literature

In sequential settings, a diagnostic decision is made based on earlier test results as to whether to continue testing another subject. The research described here concentrates on combining two medical tests administered in a sequence. The first test, Test 1, is measured on all subjects. Sometimes a diagnosis can be made with Test 1 only. If a diagnosis cannot be made by Test 1, then Test 2 is administered. A sequence is used in order to avoid administering Test 2 to all subjects, because of the cost of testing. Therefore, it can be understood that the reason for using sequential testing is to reduce cost of testing and burden by decreasing the number of subjects taking all tests.

This study considered three logic rules that allow combining multiple sequences of tests. The following sequential testing strategies (logic rules) were considered: believe the negative (BN), believe the positive (BP) and believe the extreme (BE). In the scenario of two tests (Test 1 and Test 2), these strategies could be written as follows:

- Assuming that Test 1 and Test 2 are a sequence of tests, the BN strategy will classify the subject as non-diseased if the result of Test 1 is negative. If the result is not negative, the subject will take the second test. If the result for Test 2 is negative, the subject will be classified as non-diseased. Otherwise, the subject will be classified as diseased. Thus, in the BN strategy, Test 1 is administered to each subject, while Test 2 is administered only for those whose test values are positive for disease in order to confirm if disease is really present.

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- Assuming that Test 1 and Test 2 are a sequence of tests, the BP strategy will classify the subject as diseased if the result of Test 1 is positive. If the result is not positive, the subject will take the second test. If the result for Test 2 is positive, the subject will be classified as diseased. Otherwise, the subject will be classified as non-diseased. Thus, in the BP strategy, Test 1 is administered to each subject, while Test 2 is administered only for those whose test values are negative for disease in order to confirm if disease is really absent.

- Assuming that Test 1 and Test 2 are a sequence of tests, the BE strategy will classify a subject as diseased if 1) the results of Test 1 say the subject is diseased, or 2) the results of Test 1 are in an intermediate range and the results of Test 2 say the subject is diseased. If not, the subject is classified as non-diseased. Thus, for the BE strategy, Test 1 is administered to each subject, but Test 2 is administered only for those whose test values fall in an intermediate unfixed range.

The BE strategy has only rarely been mentioned in the literature. Etzioni (2003) utilized the BE strategy for screening of prostate cancer, but did not call it by that name. The research considered here will examine BE as an alternative strategy to BN and BP. Marshall, writing about sequential strategies BN and BP, notes, **"**These rules do not necessarily have better predictive values than a single test**"** (1989). Etzioni (2003) proposed sequencing tests to improve overall accuracy over the single test.

The decision rules presented above are used to combine sequences of tests using Boolean logic rules of "OR" and "AND" combinations to predict a binary outcome. BN

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and BP are well known in clinical settings and currently are the most popular techniques for combining sequential tests; they were discussed and utilized in research by Marshall (1989), Zhou, Obuchowski, and McClish (2002), Pepe (2003), Thompson (2003), and Shen (2008).

Thompson (2003) focused on BP and BN strategies to combine two diagnostic tests, the ratio of free to total Prostate-Specific Antigen (RPSA) and total Prostate-Specific Antigen (TPSA). The BP strategy increased sensitivity but decreased specificity to be lower than either individual test. Conversely, the BN strategy increased specificity but decreased the sensitivity to be lower than either individual test. Marshall (1989), Geisser and Johnson (1992), Macaskill et al. (2002), Pepe (2003), Man-Lai Tang (2004), and Kelly et al. (2006) focused their work primarily on combining multiple binary or discrete tests using BN and BP. Binary tests will not be considered here; this research focuses on combining multiple continuous sequences of tests.

When considering continuous tests, the use of BP, BN and BE strategies are associated with more than one threshold and as such, may produce more than one sensitivity value corresponding to each fixed false positive rate (FPR). FPR is the probability that the test incorrectly identifies a subject without disease as having the disease (e.g, 1-specificity). The graph of every pair of FPR and sensitivity values for the ROC curve appears as a cloud of points, as mentioned by Baker (2000). This cloud is made up of an infinite number of ROC curves. Consequently, a special point of concern is

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how one can maximize sensitivity for each at each specificity level. Several authors have addressed this question.

Baker (2000, 2003), who focused primarily on evaluating the performance of early detection tests, was the first to mention the cloud of points. Baker proposed a nonparametric approach and used logic rules to combine diagnostic tests and introduced a utility function to "to identify the point on the ROC curve with the highest utility" (2000). This utility function maximized the product of sensitivity and benefit to determine the acceptable FPRs that were clinically relevant. For this research, the parametric approach, assuming a binormal model, e.g., tests are normally distributed for diseased and non-diseased populations, is used. Also, rather than looking at a portion of the ROC curve, this research examines the ROC curve in its entirety.

Etzioni (2003) used logic rules to combine diagnostic tests by minimizing an objective function called weighted misclassification error which could be given by the equation $L(\alpha) = \alpha FP + FN$ where a higher value of α led to lower FPR and vice versa. Here, FP referred to the false positive result; FN, the false negative result. Etzioni created optimal logic rules by varying α while minimizing the weighted misclassification error. The $ROC(\alpha)$ curve represented the sensitivity produced by the thresholds that minimized the weighted misclassification error function.

Thompson (2003) used a more general approach to evaluate accuracy of a sequence of tests, focusing primarily on BP. Her choice of threshold for each test was set at specific percentile values in the non-diseased distribution. Thompson let future thresholds depend on the results from previous tests. She also developed the MaxROC curve that maximized

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the overall sensitivity at a fixed specificity. This allowed the researcher to choose a threshold for a non-diseased population and apply it to the diseased; however she did not address which threshold should be used in implementation of a test sequence. Such choices will depend on issues such as disease prevalence as well as the costs of false positives and false negatives, and the costs of the tests themselves. Rather than following the Thompson percentile approach, this research tries to maximize the sensitivity with the lowest cost.

Finally, Shen (2008) examined the BP and BN strategies, using the maximum of sensitivity values and plotting it against each FPR (MROC). Shen compared the BP and BN strategies by finding the maximum sensitivity across both strategies. Shen considered identical-negative correlation, identical-positive correlation, and different sign correlation for diseased and non-diseased population. She saw that one strategy (BP or BN) was always better than the other when the correlation was of a different sign. When the correlation sign was the same, she found the BP strategy inferior to the BN strategy at the low FPR region; the opposite occurred at the low specificity region. The research detailed in this paper will also include the cost of testing as to evaluate the combined tests that MROC and ROC curves do not provide. Also, it introduces BE as an alternative to BN and BP.

2.2 Discussion of cost in the literature

This research incorporates the cost of testing to evaluate testing strategies. Cost is defined in this research as the proportion of subjects who need 2 tests to diagnose disease. The goal here is to look at cost in terms of a sequence of tests, and compare strategies for the same sequence of tests, not different tests. Some of the literature, for example (Pepe,

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2003), considered cost, as it is defined here, in terms of performing a single test, not of a sequence of tests. Very little research has dealt with the cost of sequenced testing. However, Geisser and Johnson (1992) used two binary tests in a sequence to develop a Bayesian approach to estimating posterior distributions for the prevalence and the accuracy of the tests. Also, they considered calculating the cost of testing. Gardner et al. (2004) mentioned that sequential testing strategies are often applied in order to reduce the cost of testing.

The reader must be careful to recognize 'cost of testing' and 'misclassification cost' as different terms. 'Cost,' for some researchers, has primarily been misclassification cost, or the cost of making a wrong decision. While this research focuses on a different aspect of cost (here, called cost of testing), misclassification cost is still important to consider in deriving the optimal operating point, as shown in Section 2.2. Zweig and Campbell (1993) defined an optimal operating point that minimized the average overall cost, including both the cost of performing the test as well as misclassification costs. Their definition of cost used Metz' formula (1995), and was defined as the ratio of the net costs for a test subject without the disease to a test subject with the disease. Metz et al. (1995) used the expected utilities and costs associated with the true positive and false-positive rates to determine the location of the optimal operating point of the ROC curve.

From the literature presented above, the issue of cost of testing remains little addressed. The motivation behind sequential testing is that it allows for reduced costs by reducing the number of subjects that need Test 2.

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2.3 Review of optimal operating point and the Youden's Index

In clinical practice, a threshold is required to classify subjects as to diseased or non-diseased from a given test. Therefore, many thresholds can be compared for this classification. However, the efficiency of these thresholds varies. While high specificity and sensitivity have been preferred in the past, it could be valuable to choose the thresholds that will reduce the costs of error and cost of testing as well. Such a point is known as an optimal operating point. Optimal operating points have an important purpose to improve the classification condition; it helps clinicians decide at which point to choose to "operate" the test, that is, what threshold to use to diagnose new patients as having disease or not. The search for optimal operating points should include either maximizing a function of the number of correctly classified subjects or minimizing a function of the number of misclassified subjects. This results in a small misclassification error rate.

Youden's index (Youden, 1950) for selecting the optimal operating point is used to choose a point with the largest sum of sensitivity and specificity, which relates to maximizing the probability of being correctly classified. A higher Youden's index corresponds to higher probabilities of correct classification and the ROC points associated with these probabilities can be used to identify the thresholds that produce this level of classification. There are two versions of the Youden's index. The first version does not consider misclassification costs or prevalence of disease. This version of the Youden's index can be defined a $\max_{\theta}\{TPR(\underset{\sim}{\theta})+TNR(\underset{\sim}{\theta})-1)\}$ which is equivalent to $\max_{\theta}$ $\{TPR(\underset{\sim}{\theta})- FPR(\underset{\sim}{\theta})\}$ over all thresholds. Here, TPR is the true positive rate (sensitivity),

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TNR is the true negative rate (specificity), θ represents the threshold. This version of the Youden's index chooses the point furthest from the ROC chance line as the optimal operating point.

The second version of Youden's index determines the optimal operating point that minimizes the average cost. Zweig and Campbell (1993) defined optimal operating point as $\max_{\theta}\{TPR(\theta)-m^{*}(1-TNR(\theta))\}$ which is equivalent to $\max_{\theta}\{TPR(\theta)-m^{*}(FPR(\theta))\}$ over all thresholds, where $m=\left[(1-p)/p\right]\times\left[\left(C_{FP}-C_{TN}\right)/\left(C_{FN}-C_{TP}\right)\right]$, as defined in work by Metz (1978) is the slope of the combined diagnostic tests' ROC curve (a straight line that passes through the ROC curve in the small FPR region, in a point called the optimal point), p is the prevalence of disease, $\left[(C_{FP}-C_{TN})/(C_{FN}-C_{TP})\right]$ is the cost/benefit ratio of false-positive compared to false-negative results, C_{FP} is the cost associated with a false positive, C_{TN} is the cost associated with a true negative, C_{FN} is the cost associated with a false negative, and C_{TP} is the cost associated with a true positive. When $m=1$, this version of the Youden's index yields the original Youden's index (which implies that the product of the cost/benefit ratio and the prevalence is 1). However, Zweig and Campbell's criterion would not assess the cost of the number of tests. What this research adds for consideration is the cost of testing as a constraint on finding the optimal operating point.

Different values of cost/benefit ratio have been used in various applications. Cantor et al. (1999) looked at previous studies to search for cost/benefit ratios that were used in determining the optimal operating point, finding cost/benefit ratios ranging between 0.0025 and 2.70. Metz et al., writing about the slope, *m*, mentioned that varying the values

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of the slope from 0.1 to 3.0, could produce an OOP that could be considered clinically relevant (1996).

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Chapter 3: Methods

3.1 Sequential testing strategies

This research offers a method to examine the cost of testing by introducing a new technique which accounts for cost called the Minimum Cost Maximum Receiver Operating Characteristic (MCMROC) curve. Here, think of cost in terms of the number of tests not in terms of dollars. This research will describe three sequential testing strategies in terms of the MCMROC: "believe the positive" (BP), "believe the negative" (BN), and "believe the extreme" (BE). The first two are known in the literature as techniques for combining two continuous tests, e.g. repeated screening tests, (Thompson, 2003) and non-sequential combination of tests (Shen, 2008). The less examined strategy, called BE, has been used for prostate cancer screening (Etzioni, 2003). The BP strategy classifies a subject as positive for disease if either of two tests are positive. The BN strategy classifies a subject as positive for disease if both of the tests are positive. The BE strategy classifies a subject as positive for disease if the first test is positive, or if the result for the first test is neither positive or negative (ambiguous) and the second test is positive for disease. BP and BN strategies have two thresholds with which to dichotomize subjects as diseased or not diseased, one threshold for each test. The BE strategy has two thresholds for the first test (separating the disease positive, disease negative and ambiguous regions) and one threshold for the second test.

Comparison between these strategies will provide indications that one strategy may be less costly or more accurate than the others. This information may be used to suggest which strategy should be used in clinical practice. Figure 3.1 shows a tree diagram for the

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application of Test1 and Test 2, where $(\theta_1, \theta_2,$ and $\theta_3)$ represent threshold values or decision levels from which to classify subjects as disease positive or negative. In the figures, the +/- symbols indicate a positive or negative test result.

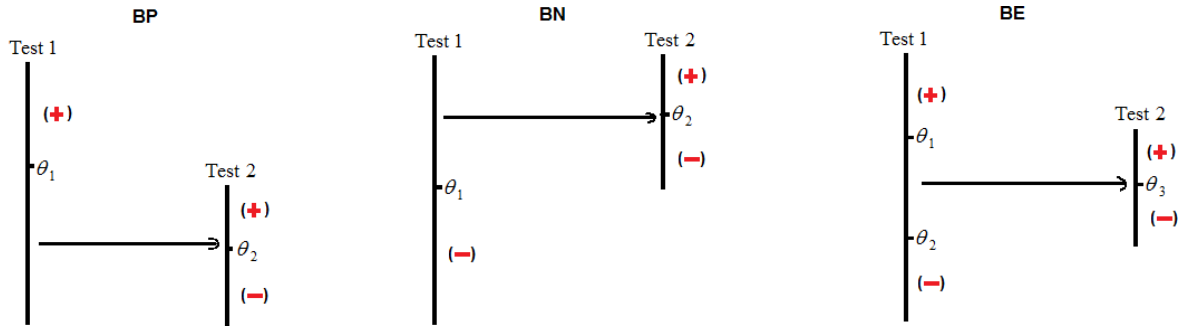

Figure 3.1 Tree diagram of the structure for three sequential testing strategies

3.2 Developing the Maximum ROC (MROC) curve

This section deals with the MROC curve, mentioned in Chapters 1 and 2. The BP, BN and BE testing strategies are each associated with more than one threshold value. As such, this may produce multiple sensitivity values for some or all FPRs. These points can be thought of as an infinite number of ROC curves, whose projection onto the FPR-true positive rate (TPR) plane appears as a cloud of points, as mentioned by Baker (2000). A graph of such a cloud (for the BP strategy) is given in Figure 3.2. The light blue represents the infinite number of ROC curves projected onto the FPR-TPR plane that is produced by all possible combinations of the thresholds.

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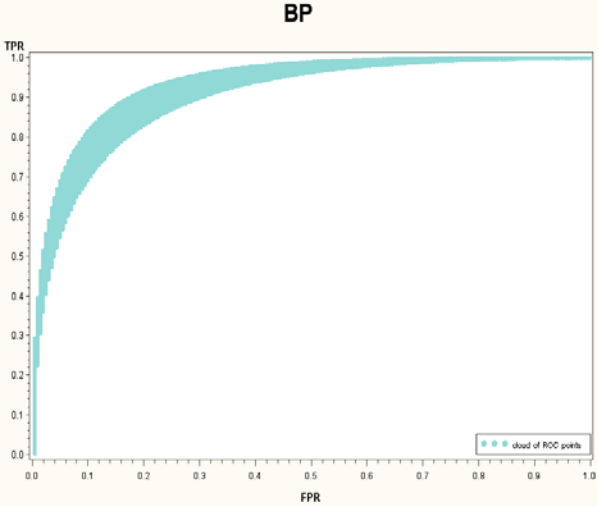

Figure 3.2: Projections of the ROC surface producing a cloud of false and true positive pairs

The ROC "function" for the graph in Figure 3.3 can be written as the set of ordered pairs:

$$\text{ROC} = \{(FPR(\underset{\sim}{\theta}), TPR(\underset{\sim}{\theta})), \underset{\sim}{\theta} \in \mathbb{R}^n\} \tag{3.1}$$

where ROC is the entire set of all possible TPR and FPR values, and $\underset{\sim}{\theta}$ represents the set of all possible thresholds. Note that the word "function" is written in quotes because equation (3.1) is not a true function as multiple TPR values are associated with a single FPR value (thus violating the definition of a function).

In order to create a single ROC curve with which to describe each sequential strategy, the MROC curve (Thompson, 2003) will be used. The MROC curve is created from the collection of points that correspond to the maximum sensitivity for each, fixed FPR. There are two approaches considered here which may be used to define the MROC function:

$$\text{MROC} = \left\{\left(\left(t, \max_{FPR(\underset{\sim}{\theta}) \le t} (TPR(\underset{\sim}{\theta}))\right) : 0 < t < 1, \underset{\sim}{\theta} \in \mathbb{R}^n\right)\right\} \tag{3.2}$$

$$\text{MROC} = \left\{\left(\left(t, \max_{FPR(\underset{\sim}{\theta}) = t} (TPR(\underset{\sim}{\theta}))\right) : 0 < t < 1, \underset{\sim}{\theta} \in \mathbb{R}^n\right)\right\} \tag{3.3}$$

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The difference between these two expressions is in how the maximum TPR is chosen. Equation 3.2 choose the maximum TPR for all FPR value less than or equal to a fixed value (t), whereas equation 3.3 choose the maximum TPR for a FPR value equal to t. Unlike equation 3.3, the first expression in equation 3.2 assures that the MROC curve is non-decreasing. For this reason, this research used equation 3.2. This can be formulated as a nonlinear optimization problem to find the thresholds that give the maximum TPR for each $FPR \le t$. Using equation 3.2, the MROC curve for the cloud of ROC points from Figure 3.2 was generated and is plotted in Figure 3.3 where the cloud of ROC points is shown in "light blue" and the MROC curve is shown in "black."

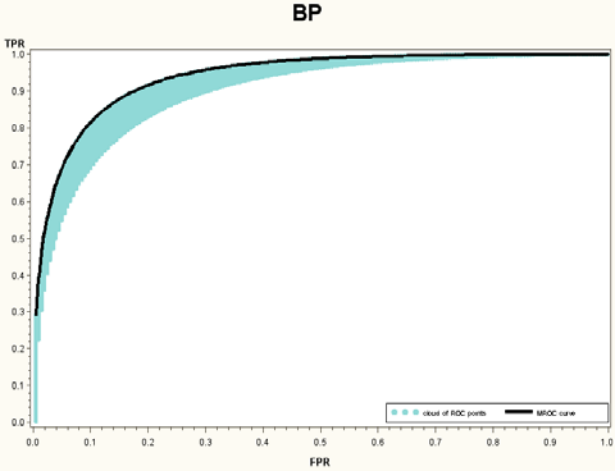

Figure 3.3: MROC curves for an example of the BP strategy

3.3 Expected cost of testing

The cost of the testing will be defined as the expected number of the 2nd tests that need to be performed to arrive at a diagnostic decision out of the total number of patients. The cost of performing tests for sample of size n, for a particular strategy would be:

$$n \times \{C_1 + C_2 \times P[\text{perform the second test}]\}$$

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where C_1 is the actual cost of performing Test 1 and C_2 is the actual cost of performing Test 2, P[perform the second test] is the proportion of subjects undergoing both tests. Here, the goal is not trying to compare the strategies based on cost in terms of dollars, but instead to compare these three strategies based on the proportion of subjects who must undergo both tests. The cost formula can be written as:

$C(\theta)$ = P [perform the 2nd test].

$C(\theta)$ is the proportion of subjects undergoing both tests. Note that this does not consider either the actual cost of performing each test or the sample size. The sample size, n, is assumed to be a fixed value; for purposes of comparing a specific sequence of tests between strategies only, n=1 is assumed and the economic cost of the individual tests can be ignored.

Formulas for the cost for each sequencing test strategy, BP, BN and BE are in next sections. From the equations below, conclusions about the nature of cost calculation can be drawn. In particular, it can be seen that cost calculation is dependent on sensitivity and specificity of the first test, and the disease prevalence. Though it appears that the second test is not involved, the cost calculation indirectly incorporates the effect of the second test because the choice of operating point will involve constraints on the cost of testing.

3.3.1 Cost of testing computation for the BP strategy

This section derives the cost of testing for the BP strategy. Recall that Test 1 is measured on all subjects. For the BP strategy, Test 2 is only administered to those whose test results from Test 1 are negative for disease. Then the cost of testing for BP strategy is given in the following theorem:

Theorem 3.1 Cost of testing for the Believe the Positive (BP) strategy

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Let X_{1D} and X_{2D} represent the test results of the diseased (D) population for tests 1 and 2, respectively. Let X_{1N} and X_{2N} represent the test results of non-diseased (N) population for tests 1 and 2 respectively. Let $F_{X_{1D}}, F_{X_{2D}}$, $F_{X_{1N}}$ and $F_{X_{2N}}$ denote the CDF functions of test results for those with (D) and without (N) disease and P(D) represent disease prevalence. Then the cost of testing for the BP strategy, denoted by $C^{BP}(\theta_1)$, is given by:

$$C^{BP}(\theta_1) = \left(F_{X_{1D}}(\theta_1)\times P(D)\right)+\left(F_{X_{1N}}(\theta_1)\times(1-P(D)\right). \quad (3.4)$$

Proof:

$$C^{BP}(\theta_1) = P(X_1 \le \theta_1)$$

$$= P\left(X_1 \le \theta_1 \text{ and } (D \text{ or } N)\right)$$

$$= \left(P(X_1 \le \theta_1 \text{ and } D) \text{ or } P(X_1 \le \theta_1 \text{ and } N)\right)$$

$$= P(X_1 \le \theta_1 \text{ and } D) + P(X_1 \le \theta_1 \text{ and } N)$$

$$= \left(P(X_1 \le \theta_1 \mid D)\times P(D)\right)+\left(P(X_1 \le \theta_1 \mid N)\times P(N)\right)$$

$$= \left(P(X_1 \le \theta_1 \mid D)\times P(D)\right)+\left(P(X_1 \le \theta_1 \mid N)\times (1-P(D))\right)$$

This can be rewritten in terms of cumulative distribution functions as

$$= \left(F_{X_{1D}}(\theta_1)\times P(D)\right)+\left(F_{X_{1N}}(\theta_1)\times(1-P(D)\right)$$

3.3.2 Cost of testing computation for the BN strategy

This section derives the cost of testing for the BN strategy. Recall that Test 1 is measured on all subjects. For the BN strategy, Test 2 is administered only to those whose test values

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are positive for disease. Then the cost of testing for BN strategy is given in the following theorem:

Theorem 3.2 Cost of testing for the Believe the Negative (BN) strategy

Let X_{1D} *and* X_{2D} *represent the test results of the diseased (D) population for tests 1 and 2, respectively. Let* X_{1N} *and* X_{2N} *represent the test results of non-diseased (N) population for tests 1 and 2, respectively. Let* $F_{X_{1D}}, F_{X_{2D}}$, $F_{X_{1N}}$ *and* $F_{X_{2N}}$ *denote the CDF functions of test results for those with (D) and without (N) disease and P(D) represent disease prevalence. Then the cost of testing for the BN strategy, denoted by* $C^{BN}(\theta_1)$, is given by:

$$C^{BN}(\theta_1) = \left((1-F_{X_{1D}}(\theta_1)) \times P(D)\right) + \left(\left(1-F_{X_{1N}}(\theta_1)\right) \times \left(1-P(D)\right)\right) \tag{3.5}$$

Proof:

$$C^{BN}(\theta_1) = P(X_1 \geq \theta_1)$$

$$= P\left(X_1 \geq \theta_1 \text{ and } (D \text{ or } N)\right)$$

$$= P(X_1 \geq \theta_1 \text{ and } D) + P(X_1 \geq \theta_1 \text{ and } N)$$

$$= \left(P(X_1 \geq \theta_1 \mid D) \times P(D)\right) + \left(P(X_1 \geq \theta_1 \mid N) \times P(N)\right)$$

$$= \left(P(X_1 \geq \theta_1 \mid D) \times P(D)\right) + \left(P(X_1 \geq \theta_1 \mid N) \times \left(1-P(D)\right)\right)$$

Using cumulative distribution functions, this can be rewritten as

$$= \left((1-F_{X_{1D}}(\theta_1)) \times P(D)\right) + \left(\left(1-F_{X_{1N}}(\theta_1)\right) \times \left(1-P(D)\right)\right)$$

3.3.3 Cost of testing computation for the BE strategy

This section shows how cost of testing can be derived for the BE strategy. Recall that Test 1 is measured on all subjects. For the BE strategy, Test 2 is administered only for those

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whose test values fall in an intermediate unfixed range. The cost of testing for BE strategy is given in the following theorem:

Theorem 3.3 Cost of testing for the Believe the Extreme (BE) strategy

Let X_{1D} and X_{2D} represent the test results of the diseased (D) population for tests 1 and 2, respectively. Let X_{1N} and X_{2N} represent the test results of non-diseased (N) population for tests 1 and 2 respectively. Let $F_{X_{1D}}, F_{X_{2D}}$, $F_{X_{1N}}$ and $F_{X_{2N}}$ denote the CDF functions of test results for those with (D) and without (N) disease and P(D) represent disease prevalence. Then the cost of testing of the BE strategy, denoted by $C^{BE}(\theta_1,\theta_2)$, is given by:

$$C^{BE}(\theta_1,\theta_2) = \left(\left(F_{X_{1D}}(\theta_1) - F_{X_{1D}}(\theta_2)\right)\times P(D)\right) + \left(\left(F_{X_{1N}}(\theta_1) - F_{X_{1N}}(\theta_2)\right)\times (1-P(D))\right) \quad (3.6)$$

Proof:

$$C^{BE}(\theta_1,\theta_2) = P(\theta_2 \le X_1 \le \theta_1)$$

$$= P\left(\theta_2 \le X_1 \le \theta_1 \text{ and } (D \text{ or } N)\right)$$

$$= P\left((\theta_2 \le X_1 \le \theta_1 \text{ and } D) \text{ or } (\theta_2 \le X_1 \le \theta_1 \text{ and } N)\right)$$

$$= P\left(\theta_2 \le X_1 \le \theta_1 \text{ and } D\right) + P\left(\theta_2 \le X_1 \le \theta_1 \text{ and } N\right)$$

$$= \left(P(\theta_2 \le X_1 \le \theta_1 \mid D)\times P(D)\right) + \left(P(\theta_2 \le X_1 \le \theta_1 \mid N)\times P(N)\right)$$

$$= \left(P(\theta_2 \le X_1 \le \theta_1 \mid D)\times P(D)\right) + \left(P(\theta_2 \le X_1 \le \theta_1 \mid N)\times (1-P(D))\right)$$

$$= \left(\left(P(X_1 \le \theta_1 \mid D) - P(X_1 \le \theta_2 \mid D)\right)\times P(D)\right) + \left(\left(P(X_1 \le \theta_1 \mid N) - P(X_1 \le \theta_2 \mid N)\right)\times (1-P(D))\right)$$

Using cumulative distribution functions, this can be rewritten as

$$C^{BE}(\theta_1,\theta_2) = \left(\left(F_{X_{1D}}(\theta_1) - F_{X_{1D}}(\theta_2)\right)\times P(D)\right) + \left(\left(F_{X_{1N}}(\theta_1) - F_{X_{1N}}(\theta_2)\right)\times (1-P(D))\right)$$

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3.4 Cost Curves

A limitation of the MROC curve is that it does not directly incorporate the effect of cost of testing. Therefore, since the primary focus of this study is the cost of testing, it is important to consider cost, particularly because sometimes the MROC curves do now show clear differences between strategies. Cost curves demonstrate the characteristics of a testing strategy by graphing the false-positive rate (1-specificity) on the horizontal axis and the cost of testing (cost) on the vertical axis. For example, Figure 3.4 shows the MROC curves and cost curves for the three strategies. From this graph, it can be seen that the BE strategy has equal or lower cost of testing as compared to BP and BN over the entire range of FPRs. The MROC curve, however, shows little difference between the three strategies. For this reason, cost curves add another factor to consider in describing and evaluating the BN, BP, and BE strategies.

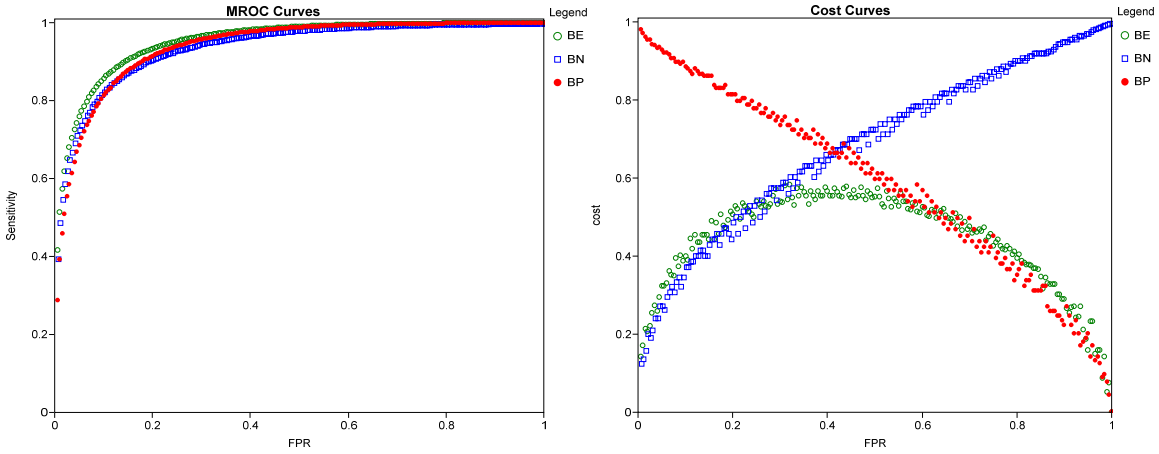

Figure 3.4: Example of MROC and Cost curves for the BE, BN, and BP strategies

3.5 Acceptable accuracy (q)

Typically, for a fixed false positive rate, the set of thresholds that produce the maximum sensitivity are considered best. However, there may be a set of thresholds that produces sensitivity that are essentially equivalent or slightly lower than maximum sensitivity yet

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lowers the cost of a sequence of tests by reducing the number of subjects that need the second test to reach a diagnosis. One can define a set of sensitivities that are "close enough" that is, are within an acceptable tolerance. Two approaches that could be considered to determine a minimal acceptable tolerance are an additive or multiplicative approach. The additive approach subtracts a fixed constant (epsilon or ε) from the maximum sensitivity at each FPR.

For each fixed FPR, this can be written as:

$$\text{maxTPR}_{\varepsilon} = \max[\text{TPR}(\underset{\sim}{\theta})] - \varepsilon \qquad (3.7)$$

where $\text{maxTPR}_{\varepsilon}$ represent the minimal acceptable value for TPR, $\varepsilon \in [0,1]$

The second approach is multiplicative and involves multiplying maximum sensitivity by the percent of the accuracy that clinicians are willing to accept (q).

For each FPR, this can be written as:

$$\text{qmaxTPR} = \text{q} \times \max[\text{TPR}(\underset{\sim}{\theta})] \qquad (3.8)$$

where qmaxTPR represents minimal acceptable value of sensitivity, q represents the percent of the accuracy (tolerance) that clinicians are willing to accept, $q \in [0,1]$. The first approach subtracts a constant value from the maximum TPR. This approach produces a consistent difference across all TPRs. The latter approach has a tolerance that varies, in fact increasing as the TPR increases. This research will explore the effects of using $\text{q} \times \max[\text{TPR}(\underset{\sim}{\theta})]$ to set an acceptable tolerance on sensitivity. Figure 3.5 shows the minimal acceptable tolerance on sensitivity in 'green' for a q value of 0.95, for the same distribution as above. By multiplying the maximum sensitivity by the q=0.95 the minimal acceptable tolerance stretches outside of the cloud of points at higher FPRs. This is because there are no thresholds which give sensitivity values that different from the

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maximum sensitivity. Represented in light blue, as before, is the cloud of points. The black line represents the MROC curve.

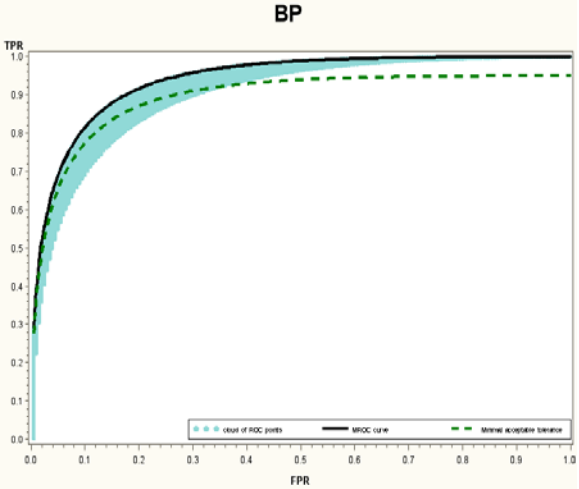

Figure 3.5: Minimal acceptable sensitivity when a tolerance is set, for an example of the BP strategy

3.5.1 The Minimum Cost Maximum ROC (MCMROC) curve

The Minimum Cost Maximum Receiver Operating Characteristic (MCMROC) curve is developed to show, graphically, the sensitivity (within an acceptable tolerance q of the maximum sensitivity) that is associated with the lowest cost.

Considering only values of sensitivity within the acceptable tolerance allows the researcher to consider more points in the cloud in addition to those lying on the MROC. The purpose of this is to examine thresholds associated with the lowest cost as long as the corresponding sensitivity is above the minimal acceptable sensitivity. This can be written as a set of ordered pairs:

$$f_q = \left\{ \left(\left(\mathrm{FPR}(\underset{\sim}{\theta}), TPR(\underset{\sim}{\theta}) \right) : TPR(\underset{\sim}{\theta}) \geq \mathrm{qmaxTPR},\ \mathrm{FPR}(\underset{\sim}{\theta}) \leq \mathrm{t}, \underset{\sim}{\theta} \in \mathbb{R}^n \right) \right\} \qquad (3.9)$$

f_q is a subset of the entire set of all possible TPR and FPR values, constrained to the values within the minimal acceptable tolerance and including the constraint on the FPR. From

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these pairs, the ones with the lowest cost for a fixed FPR will be used to define the MCMROC. Calculating the cost of testing for every threshold set in Equation 3.9, the MCMROC can be defined as:

$$\text{MCMROC} = \left\{ \left(\left(\text{t}, \max_{\min(C(\underset{\sim}{\theta}))} (TPR(\underset{\sim}{\theta})) \right) : TPR(\underset{\sim}{\theta}) \geq \text{qmaxTPR}, \text{FPR}(\underset{\sim}{\theta}) \leq \text{t}, \underset{\sim}{\theta} \in \mathbb{R}^n \right) \right\} \quad (3.10)$$

where, for every pair of FPR and TPR within the minimal acceptable tolerance, the highest true positive rate with the lowest cost for each fixed $\text{FPR} \leq \text{t}$, will be chosen. Because cost of testing could be varied for each $FPR \leq t$, the lowest cost is preferred. However, because there are two or more thresholds, there may be more than one sensitivity value with identical costs corresponding to a false positive rate. Thus the maximum sensitivity at each $\text{FPR} \leq t$ with the lowest cost will be the sensitivity value associated with the MCMROC curve. This can be formulated as a nonlinear optimization problem to find the thresholds that maximize TPR with lowest cost, subject to multiple constraints that need to be satisfied: $\underset{\sim}{\theta} \in \mathbb{R}^n$, $TPR(\underset{\sim}{\theta}) \geq \text{qmaxTPR}$, and $FPR \leq t$.

Defining the MCMROC function depends on the way one defines the MROC curve. For example, if one defines the MROC curve by using $\text{FPR}(\underset{\sim}{\theta}) = t$, then $\text{FPR}(\underset{\sim}{\theta}) = t$ will be substituted for $\text{FPR}(\underset{\sim}{\theta}) \leq t$ in the above equations. The MCMROC curve for the graphs from Figure 3.5 are plotted in Figure 3.6. In this figure, the MCMROC curve is shown in "red" for BP strategy, the cloud of ROC points is shown in "light blue", the MROC curve is shown in "black", and the minimal acceptable tolerance on sensitivity is shown in "green".

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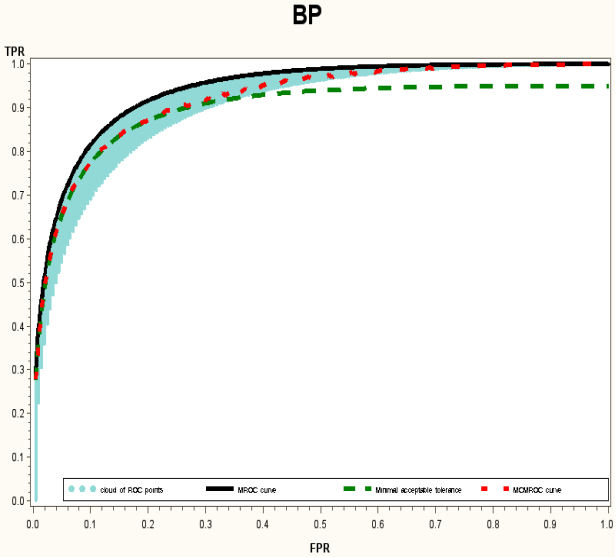

Figure 3.6: MCMROC curve for an example of the BP strategy

3.6 Computing sensitivity and specificity for the three strategies

The formulas for computing sensitivity and FPR (FPR=1-specificity), for each strategy are introduced in the next sections.

3.6.1 Believe the positive (BP)

The BP strategy uses a combination of "AND" and "OR" statements to define test overall positive or negative. The key rules of testing for this strategy may be expressed as follows:

Test positive if $X_1 > \theta_1$ *or* $(X_2 > \theta_2$ *and* $X_1 \le \theta_1)$ (3.11)

Negative result if $X_1 \le \theta_1$ *and* $X_2 \le \theta_2$ (3.12)

Theorem 3.4 FPR of the Believe the Positive (BP) strategy

Let X_{1D} *and* X_{2D} *represent the test results of the diseased (D) population for tests 1 and 2, respectively. Let* X_{1N} *and* X_{2N} *represent the test results of non-diseased (N) population for tests 1 and 2 respectively. Let* θ_1 *represent the threshold associated with test 1, and* θ_2 *is the threshold associated with test 2. Let* $F_{X_{1D}}, F_{X_{2D}}$, $F_{X_{1N}}$ *and* $F_{X_{2N}}$ *denote the CDF functions*

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of test results for those with (D) and without (N) disease. Let $F_{X_{1D},X_{2D}}, F_{X_{1N},X_{2N}}$ *denote the joint distribution functions of test results for those with (D) and without (N) disease between tests 1 and 2.*

Assuming some level of non-zero correlation (dependency) between the two tests for the non-diseased population, the formula for FPR of the BP strategy, denoted by $FPR^{BP}(\underset{\sim}{\theta})$, is given by

$$FPR^{BP}(\underset{\sim}{\theta}) = 1 - F_{X_{1N},X_{2N}}(\theta_1,\theta_2) \tag{3.13}$$

Proof:

$$\text{Specificity} = P(X_{1N} \le \theta_1 \text{ and } X_{2N} \le \theta_2)$$

This can be rewritten in terms of cumulative distribution functions as

$$= F_{X_{1N},X_{2N}}(\theta_1,\theta_2)$$

$$FPR^{BP}(\underset{\sim}{\theta}) = 1 - \text{Specificity}$$

$$FPR^{BP}(\underset{\sim}{\theta}) = 1 - F_{X_{1N},X_{2N}}(\theta_1,\theta_2)$$

Corollary *If the two tests are independent for the non-diseased population, then*

$$FPR^{BP}(\underset{\sim}{\theta}) = 1 - F_{X_{1N}}(\theta_1) \times F_{X_{2N}}(\theta_2)$$

Proof:

Since the two tests for the non-diseased population are independent, then

$$F_{X_{1N},X_{2N}}(\theta_1,\theta_2) = F_{X_{1N}}(\theta_1) \times F_{X_{2N}}(\theta_2)$$

and $FPR^{BP}(\underset{\sim}{\theta}) = 1 - F_{X_{1N},X_{2N}}(\theta_1,\theta_2) = 1 - F_{X_{1N}}(\theta_1) \times F_{X_{2N}}(\theta_2)$

Theorem 3.5 TPR of the Believe the Positive (BP) strategy

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Let X_{1D} and X_{2D} represent the test results of the diseased (D) population for tests 1 and 2, respectively. Let X_{1N} and X_{2N} represent the test results of non-diseased (N) population for tests 1 and 2 respectively. Let θ_1 represent the threshold associated with test 1, and θ_2 is the threshold associated with test 2. Let $F_{X_{1D}}, F_{X_{2D}}$, $F_{X_{1N}}$ and $F_{X_{2N}}$ denote the CDF functions of test results for those with (D) and without (N) disease. Let $F_{X_{1D},X_{2D}}, F_{X_{1N},X_{2N}}$ denote the joint distribution functions of test results for those with (D) and without (N) disease between tests 1 and 2.

Assuming some level of non-zero correlation (dependency) between the two tests for the diseased population, the formula for TPR of the BP strategy, denoted by $TPR^{BP}(\underset{\sim}{\theta})$, is given by

$$TPR^{BP}(\underset{\sim}{\theta}) = 1 - F_{X_{1D},X_{2D}}(\theta_1,\theta_2) \tag{3.14}$$

Proof:

$$\begin{aligned}\text{Sensitivity} &= P\left(X_1 > \theta_1 \text{ or } (X_2 > \theta_2 \text{ and } X_1 \le \theta_1)\right)\\ &= P\left((X_{1D} > \theta_1) \cup \left((X_{2D} > \theta_2) \cap (X_{1D} \le \theta_1)\right)\right)\\ &= P\left(\left((X_{1D} > \theta_1) \cup (X_{2D} > \theta_2)\right) \cap \left((X_{1D} > \theta_1) \cup (X_{1D} \le \theta_1)\right)\right)\\ &= P\left((X_{1D} > \theta_1) \cup (X_{2D} > \theta_2)\right)\\ &= 1 - P\left((X_{1D} \le \theta_1) \cap (X_{2D} \le \theta_2)\right)\end{aligned}$$

This can be rewritten in terms of cumulative distribution functions as

$$TPR^{BP}(\underset{\sim}{\theta}) = 1 - F_{X_{1D},X_{2D}}(\theta_1,\theta_2)$$

Corollary *If the two tests are independent for the diseased population, then*

$$F_{X_{1D},X_{2D}}(\theta_1,\theta_2) = F_{X_{1D}}(\theta_1) \times F_{X_{2D}}(\theta_2) \tag{3.15}$$

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Proof:

Since the two tests for the diseased population are independent, then

$$F_{X_{1D},X_{2D}}(\theta_1,\theta_2) = F_{X_{1D}}(\theta_1)\times F_{X_{2D}}(\theta_2)$$

and $$FPR^{BP}(\underset{\sim}{\theta}) = 1 - F_{X_{1D},X_{2D}}(\theta_1,\theta_2)$$
$$= 1 - F_{X_{1D}}(\theta_1)F_{X_{2D}}(\theta_2)$$

3.6.2 Believe the negative (BN)

The BN strategy uses combinations of "AND" and "OR" statements to define test overall positive or negative. The key rules of testing for this strategy were the following:

Positive result if ($X_2 > \theta_2$) and ($X_1 > \theta_1$) (3.16)

Negative result if ($X_1 \le \theta_1$) or ($X_2 \le \theta_2$ and $X_1 > \theta_1$) (3.17)

Theorem 3.6 FPR of the Believe the Negative (BN) strategy

Let X_{1D} and X_{2D} represent the test results of the diseased (D) population for tests 1 and 2 respectively. Let X_{1N} and X_{2N} represent the test results of non-diseased (N) population for tests 1 and 2 respectively. Let θ_1 represents the threshold associated with test 1, and θ_2 is the threshold associated with test 2. Let $F_{X_{1D}}, F_{X_{2D}}$, $F_{X_{1N}}$ and $F_{X_{2N}}$ denote the CDF functions of test results for those with (D) and without (N) disease. Let $F_{X_{1D},X_{2D}}, F_{X_{1N},X_{2N}}$ denote the joint distribution functions of test results for those with (D) and without (N) disease between tests 1 and 2.

Assuming some level of non-zero correlation (dependency) between the two tests for the non-diseased population, the formula for FPR of the BN strategy, denoted by $FPR^{BN}(\underset{\sim}{\theta})$, is given by

$$FPR^{BN}(\underset{\sim}{\theta}) = 1 - F_{X_{1N}}(\theta_1) - F_{X_{2N}}(\theta_2) + F_{X_{1N},X_{2N}}(\theta_1,\theta_2) \quad (3.18)$$

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Proof:

Specificity = $P\left(X_{1N} \le \theta_1 \text{ or } (X_{2N} \le \theta_2 \text{ and } X_{1N} > \theta_1)\right)$

$$= P\left((X_{1N} \le \theta_1) \cup \left((X_{2N} \le \theta_2) \cap (X_{1N} > \theta_1)\right)\right)$$

$$= P\left(\left((X_{1N} \le \theta_1) \cup (X_{2N} \le \theta_2)\right) \cap \left((X_{1N} \le \theta_1) \cup (X_{1N} > \theta_1)\right)\right)$$

$$= P\left((X_{1N} \le \theta_1) \cup (X_{2N} \le \theta_2)\right)$$

$$= P(X_{1N} \le \theta_1) + P(X_{2N} \le \theta_2) - P\left((X_{1N} \le \theta_1) \cap (X_{2N} \le \theta_2)\right)$$

This can be rewritten in terms of cumulative distribution functions as

$$= F_{X_{1N}}(\theta_1) + F_{X_{2N}}(\theta_2) - F_{X_{1N},X_{2N}}(\theta_1, \theta_2)$$

$FPR^{BN}(\underset{\sim}{\theta})$ =1- Specificity

$$FPR^{BN}(\underset{\sim}{\theta}) = 1 - F_{X_{1N}}(\theta_1) - F_{X_{2N}}(\theta_2) + F_{X_{1N},X_{2N}}(\theta_1, \theta_2)$$

Corollary *If the correlation between the two tests is zero (independent tests) for the non-diseased population, then*

$$FPR^{BN}(\underset{\sim}{\theta}) = 1 - F_{X_{1N}}(\theta_1) - F_{X_{2N}}(\theta_2) + F_{X_{1N}}(\theta_1) \times F_{X_{2N}}(\theta_2) \qquad (3.19)$$

Proof:

Since the two tests for the non-diseased population are independent, then

$$F_{X_{1N},X_{2N}}(\theta_1, \theta_2) = F_{X_{1N}}(\theta_1) \times F_{X_{2N}}(\theta_2)$$

and $FPR^{BN}(\underset{\sim}{\theta}) = 1 - F_{X_{1N}}(\theta_1) - F_{X_{2N}}(\theta_2) + F_{X_{1N},X_{2N}}(\theta_1, \theta_2)$

$$= 1 - F_{X_{1N}}(\theta_1) - F_{X_{2N}}(\theta_2) + F_{X_{1N}}(\theta_1) \times F_{X_{2N}}(\theta_2)$$

Theorem 3.7 TPR of the Believe the Positive (BN) strategy

Let X_{1D} and X_{2D} represent the test results of the diseased (D) population for tests 1 and 2, respectively. Let X_{1N} and X_{2N} represent the test results of non-diseased (N) population for

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tests 1 and 2 respectively. Let θ_1 *represent the threshold associated with test 1, and* θ_2 *is the threshold associated with test 2. Let* $F_{X_{1D}}, F_{X_{2D}}$, $F_{X_{1N}}$ *and* $F_{X_{2N}}$ *denote the CDF functions of test results for those with (D) and without (N) disease. Let* $F_{X_{1D},X_{2D}}, F_{X_{1N},X_{2N}}$ *denote the joint distribution functions of test results for those with (D) and without (N) disease between tests 1 and 2.*

Assuming some level of non-zero correlation (dependency) between the two tests for the diseased population, the formula for TPR of the BN strategy, denoted by $TPR^{BN}(\underset{\sim}{\theta})$, is given by

$$TPR^{BN}(\underset{\sim}{\theta}) = 1 - F_{X_{1D}}(\theta_1) - F_{X_{2D}}(\theta_2) + F_{X_{1D},X_{2D}}(\theta_1,\theta_2) \tag{3.20}$$

Proof:

$$TPR^{BN}(\underset{\sim}{\theta}) = P\left(X_{2D} > \theta_2 \text{ and } X_{1D} > \theta_1\right)$$

$$= P\left((X_{2D} > \theta_2) \cap (X_{1D} > \theta_1)\right)$$

$$= 1 - \left(\left(P(X_{2D} \le \theta_2) + P(X_{1D} \le \theta_1)\right) - P\left((X_{2D} \le \theta_2) \cap (X_{1D} \le \theta_1)\right)\right)$$

$$= 1 - P(X_{2D} \le \theta_2) - P(X_{1D} \le \theta_1) + P\left((X_{2D} \le \theta_2) \cap (X_{1D} \le \theta_1)\right)$$

$$= 1 - F_{X_{1D}}(\theta_1) - F_{X_{2D}}(\theta_2) + F_{X_{1D},X_{2D}}(\theta_1,\theta_2)$$

Corollary *If the correlation between the two tests is zero (independent tests) for the non-diseased population, then*

$$TPR^{BN}(\underset{\sim}{\theta}) = 1 - F_{X_{1D}}(\theta_1) - F_{X_{2D}}(\theta_2) + F_{X_{1D}}(\theta_1) \times F_{X_{2D}}(\theta_2) \tag{3.21}$$

Proof:

Since the two tests for the diseased population are independent, then

$$F_{X_{1D},X_{2D}}(\theta_1,\theta_2) = F_{X_{1D}}(\theta_1) \times F_{X_{2D}}(\theta_2)$$

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and $TPR^{BN}(\underset{\sim}{\theta}) = 1 - F_{X_{1D}}(\theta_1) - F_{X_{2D}}(\theta_2) + F_{X_{1D},X_{2D}}(\theta_1,\theta_2)$

$= 1 - F_{X_{1D}}(\theta_1) - F_{X_{2D}}(\theta_2) + F_{X_{1D}}(\theta_1) \times F_{X_{2D}}(\theta_2)$

3.6.3 Believe the negative (BE)

The BE strategy also uses combinations of "AND" and "OR" statements to define overall disease positive or negative test results. The key rules of testing for this strategy were the following:

Positive result if $X_1 > \theta_1$ or ($X_2 > \theta_3$ and $\theta_2 \le X_1 \le \theta_1$) (3.22)

Negative result if $X_1 < \theta_2$ or ($X_2 \le \theta_3$ and $\theta_2 \le X_1 \le \theta_1$), where $\theta_2 \le \theta_1$ (3.23)

Theorem 3.8 FPR of the Believe the Extreme (BE) strategy

Let X_{1D} and X_{2D} represent the test results of the diseased (D) population for tests 1 and 2 respectively. Let X_{1N} and X_{2N} represent the test results of non-diseased (N) population for tests 1 and 2 respectively. Let θ_1 and θ_2 represent the threshold associated with test 1, and θ_3 is the threshold associated with test 2. Let $F_{X_{1D}}, F_{X_{2D}}$, $F_{X_{1N}}$ and $F_{X_{2N}}$ denote the CDF functions of test results for those with (D) and without (N) disease. Let $F_{X_{1D},X_{2D}}, F_{X_{1N},X_{2N}}$ denote the joint distribution functions of test results for those with (D) and without (N) disease between tests 1 and 2.

Assuming some level of non-zero correlation (dependency) between the two tests for the non-diseased population, the formula for FPR of the BE strategy, denoted by $FPR^{BE}(\underset{\sim}{\theta})$, is given by

$$FPR^{BE}(\underset{\sim}{\theta}), = 1 - F_{X_{1N}}(\theta_2) + F_{X_{1N},X_{2N}}(\theta_2,\theta_3) - F_{X_{1N},X_{2N}}(\theta_1,\theta_3) \quad (3.24)$$

Proof:

$$\text{Specificity} = P\left(X_{1N} < \theta_2 \text{ or } (X_{2N} \le \theta_3 \text{ and } \theta_2 \le X_{1N} \le \theta_1)\right)$$

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$$= P\left((X_{1N} < \theta_2) \cup \left((X_{2N} < \theta_3) \cap (\theta_2 \le X_{1N} \le \theta_1)\right)\right)$$

$$= P\left(\left((X_{1N} < \theta_2) \cup (X_{2N} < \theta_3)\right) \cap \left((X_{1N} < \theta_2) \cup (\theta_2 \le X_{1N} \le \theta_1)\right)\right)$$

$$= P\left(\left((X_{1N} < \theta_2) \cup (X_{2N} < \theta_3)\right) \cap (X_{1N} < \theta_1)\right)$$

$$= P\left(\left((X_{1N} < \theta_1) \cap (X_{1N} < \theta_2)\right) \cup \left((X_{1N} < \theta_1) \cap (X_{2N} < \theta_3)\right)\right)$$

$$= P\left((X_{1N} < \theta_2) \cup \left((X_{1N} < \theta_1) \cap (X_{2N} < \theta_3)\right)\right)$$

$$= P\left((X_{1N} < \theta_2) + \left((X_{1N} < \theta_1) \cap (X_{2N} < \theta_3)\right) - \left((X_{1N} < \theta_1) \cap (X_{1N} < \theta_2) \cap (X_{2N} < \theta_3)\right)\right)$$

$$= P(X_{1N} < \theta_2) + P\left((X_{1N} < \theta_1) \cap (X_{2N} < \theta_3)\right) - P\left((X_{1N} < \theta_2) \cap (X_{2N} < \theta_3)\right)$$

This can be rewritten in terms of cumulative distribution functions as

$$= F_{X_{1N}}(\theta_2) + F_{X_{1N},X_{2N}}(\theta_1,\theta_3) - F_{X_{1N},X_{2N}}(\theta_2,\theta_3)$$

$FPR^{BE}(\underset{\sim}{\theta})$=1- Specificity

$$FPR^{BE}(\underset{\sim}{\theta}) = 1 - F_{X_{1N}}(\theta_2) + F_{X_{1N},X_{2N}}(\theta_2,\theta_3) - F_{X_{1N},X_{2N}}(\theta_1,\theta_3)$$

Corollary *If the correlation between the two tests is zero (independent tests) for the non-diseased population, then*

$$FPR^{BE}(\underset{\sim}{\theta}) = 1 - F_{X_{1N}}(\theta_2) + F_{X_{1N}}(\theta_2) \times F_{X_{2N}}(\theta_3) - F_{X_{1N}}(\theta_1) \times F_{X_{2N}}(\theta_3) \qquad (3.25)$$

Proof:

Since the two tests for the non-diseased population are independent, then

$$F_{X_{1N},X_{2N}}(\theta_1,\theta_3) = F_{X_{1N}}(\theta_1) \times F_{X_{2N}}(\theta_3),$$

$$F_{X_{1N},X_{2N}}(\theta_2,\theta_3) = F_{X_{1N}}(\theta_2) \times F_{X_{2N}}(\theta_3),$$

and $FPR^{BE}(\underset{\sim}{\theta}) = 1 - F_{X_{1N}}(\theta_2) + F_{X_{1N},X_{2N}}(\theta_2,\theta_3) - F_{X_{1N},X_{2N}}(\theta_1,\theta_3)$

$$= 1 - F_{X_{1N}}(\theta_2) + F_{X_{1N}}(\theta_2) \times F_{X_{2N}}(\theta_3) - F_{X_{1N}}(\theta_1) \times F_{X_{2N}}(\theta_3)$$

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Theorem 3.9 TPR of the Believe the Extreme (BE) strategy

Let X_{1D} and X_{2D} represent the test results of the diseased (D) population for tests 1 and 2 respectively. Let X_{1N} and X_{2N} represent the test results of non-diseased (N) population for tests 1 and 2 respectively. Let θ_1 and θ_2 represent the threshold associated with test 1, and θ_3 is the threshold associated with test 2. Let $F_{X_{1D}}, F_{X_{2D}}$, $F_{X_{1N}}$ and $F_{X_{2N}}$ denote the CDF functions of test results for those with (D) and without (N) disease. Let $F_{X_{1D},X_{2D}}, F_{X_{1N},X_{2N}}$ denote the joint distribution functions of test results for those with (D) and without (N) disease between tests 1 and 2.

Assuming some level of non-zero correlation (dependency) between the two tests for the diseased population, the formula for TPR of the BE strategy, denoted by $TPR^{BE}(\underset{\sim}{\theta})$, is given by

$$TPR^{BE}(\underset{\sim}{\theta}) = 1 - F_{X_{1D}}(\theta_2) + F_{X_{1D},X_{2D}}(\theta_2,\theta_3) - F_{X_{1D},X_{2D}}(\theta_1,\theta_3) \tag{3.26}$$

Proof:

$$\begin{aligned}
\text{Sensitivity} &= P\left(X_{1D} > \theta_1 \text{ or } (X_{2D} > \theta_3 \text{ and } \theta_2 \le X_{1D} \le \theta_1)\right) \\
&= P\left((X_{1D} > \theta_1) \cup \left((X_{2D} > \theta_3) \cap (\theta_2 \le X_{1D} \le \theta_1)\right)\right) \\
&= P\left(\left((X_{1D} > \theta_1) \cup (X_{2D} > \theta_3)\right) \cap \left((X_{1D} > \theta_1) \cup (\theta_2 \le X_{1D} \le \theta_1)\right)\right) \\
&= P\left(\left((X_{1D} > \theta_1) \cup (X_{2D} > \theta_3)\right) \cap (X_{1D} > \theta_2)\right) \\
&= P\left(\left((X_{1D} > \theta_1) \cap (X_{1D} > \theta_2)\right) \cup \left((X_{1D} > \theta_2) \cap (X_{2D} > \theta_3)\right)\right) \\
&= P\left((X_{1D} > \theta_1) \cup \left((X_{1D} > \theta_2) \cap (X_{2D} > \theta_3)\right)\right) \\
&= P\left((X_{1D} > \theta_1) + \left((X_{1D} > \theta_2) \cap (X_{2D} > \theta_3)\right) - \left((X_{1D} > \theta_1) \cap (X_{1D} > \theta_2) \cap (X_{2D} > \theta_3)\right)\right)
\end{aligned}$$

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$$= P\left((X_{1D} > \theta_1) + \left((X_{1D} > \theta_2) \cap (X_{2D} > \theta_3)\right) - \left((X_{1D} > \theta_1) \cap (X_{2D} > \theta_3)\right)\right)$$

$$= P(X_{1D} > \theta_1) + P\left((X_{1D} > \theta_2) \cap (X_{2D} > \theta_3)\right) - P\left((X_{1D} > \theta_1) \cap (X_{2D} > \theta_3)\right)$$

$$= 1 - P(X_{1D} \le \theta_2) + 1 - P\left((X_{1D} \le \theta_1) \cap (X_{2D} \le \theta_3)\right) - 1 + P\left((X_{1D} \le \theta_2) \cap (X_{2D} \le \theta_3)\right)$$

$$= 1 - P(X_{1D} \le \theta_2) - P\left((X_{1D} \le \theta_1) \cap (X_{2D} \le \theta_3)\right) + P\left((X_{1D} \le \theta_2) \cap (X_{2D} \le \theta_3)\right)$$

$$= 1 - P(X_{1D} \le \theta_2) + P\left((X_{1D} \le \theta_2) \cap (X_{2D} \le \theta_3)\right) - P\left((X_{1D} \le \theta_1) \cap (X_{2D} \le \theta_3)\right)$$

This can be rewritten in terms of cumulative distribution functions as

$$TPR^{BE}(\underset{\sim}{\theta}) = 1 - F_{X_{1D}}(\theta_2) + F_{X_{1D},X_{2D}}(\theta_2,\theta_3) - F_{X_{1D},X_{2D}}(\theta_1,\theta_3)$$

Corollary *if the correlation between the two tests is zero (independent tests) for the diseased population, then*

$$TPR^{BE}(\underset{\sim}{\theta}) = 1 - F_{X_{1D}}(\theta_2) + F_{X_{1D}}(\theta_2) \times F_{X_{2D}}(\theta_3) - F_{X_{1D}}(\theta_1) \times F_{X_{2D}}(\theta_3) \qquad (3.27)$$

Proof:

Since the two tests for the diseased population are independent, then

$$F_{X_{1D},X_{2D}}(\theta_1,\theta_3) = F_{X_{1D}}(\theta_1) \times F_{X_{2D}}(\theta_3),$$

$$F_{X_{1D},X_{2D}}(\theta_2,\theta_3) = F_{X_{1D}}(\theta_2) \times F_{X_{2D}}(\theta_3),$$

and $$TPR^{BE}(\underset{\sim}{\theta}) = 1 - F_{X_{1D}}(\theta_2) + F_{X_{1D},X_{2D}}(\theta_2,\theta_3) - F_{X_{1D},X_{2D}}(\theta_1,\theta_3)$$
$$= 1 - F_{X_{1D}}(\theta_2) + F_{X_{1D}}(\theta_2) \times F_{X_{2D}}(\theta_3) - F_{X_{1D}}(\theta_1) \times F_{X_{2D}}(\theta_3)$$

3.7 Special relationships between the BP, BN and BE strategies

It can be shown through asymptotic properties of the thresholds from the first test of the BE strategy, i.e. as the thresholds approach $+\infty$ or $-\infty$, that the MROC curves for the BP and BN strategies cannot be better than the MROC curve for the BE strategy. Specifically, it can be shown that a set of thresholds for the BE strategy gives a particular FPR, and TPR that will be at least as good as the FPR and TPR of the BP or BN strategy.

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Theorem 10: For any (FPR, TPR) pair found in the BP strategy, a set of thresholds can be found (in the limit) in the BE strategy with equivalent FPR and TPR values.

Let θ_1^{BE} *and* θ_2^{BE} *represent the BE strategy's threshold associated with test 1 and* θ_3^{BE} *represent the BE strategy's threshold associated with test 2. Let* θ_1^{BP} *and* θ_2^{BP} *represent the BP strategy's threshold associated with test 1 and test 2. Then values of* $\underset{\sim}{\theta}^{BE} = (\theta_1^{BE}, \theta_2^{BE}, \theta_3^{BE})$ *can be found such that, in the limit, formulas for TPR and FPR of the BE strategy, denoted by* $TPR^{BE}(\underset{\sim}{\theta}^{BE})$ *and* $FPR^{BE}(\underset{\sim}{\theta}^{BE})$ *are given by*

I. $\lim_{\theta_2 \to -\infty} TPR^{BE}(\underset{\sim}{\theta}^{BE}) = TPR^{BP}(\theta_1^{BP}, \theta_2^{BP})$

II. $\lim_{\theta_2 \to -\infty} FPR^{BE}(\underset{\sim}{\theta}^{BE}) = FPR^{BP}(\theta_1^{BP}, \theta_2^{BP})$

Proof I:

From theorem 3.9, it has been shown that:

$$TPR^{BE}(\underset{\sim}{\theta}^{BE}) = 1 - F_{X_{1D}}(\theta_2^{BE}) + F_{X_{1D},X_{2D}}(\theta_2^{BE}, \theta_3^{BE}) - F_{X_{1D},X_{2D}}(\theta_1^{BE}, \theta_3^{BE})$$

Assume that $\theta_1^{BE} = \theta_1^{BP}$, $\theta_3^{BE} = \theta_2^{BP}$. As θ_2^{BE} approaches $-\infty$, then

$$\lim_{\theta_2^{BE} \to -\infty} TPR^{BE}(\underset{\sim}{\theta}^{BE}) = 1 - \lim_{\theta_2^{BE} \to -\infty} F_{X_{1D}}(\theta_2^{BE}) + \lim_{\theta_2^{BE} \to -\infty} F_{X_{1D},X_{2D}}(\theta_2^{BE}, \theta_3^{BE}) - F_{X_{1D},X_{2D}}(\theta_1^{BE}, \theta_3^{BE})$$

$$= 1 - 0 + 0 - F_{X_{1D},X_{2D}}(\theta_1^{BE}, \theta_3^{BE})$$

$$= 1 - F_{X_{1D},X_{2D}}(\theta_1^{BE}, \theta_3^{BE})$$

$$= 1 - F_{X_{1D},X_{2D}}(\theta_1^{BP}, \theta_2^{BP})$$

This has been shown, by Theorem 3.5 to be equal to $TPR^{BP}(\theta_1^{BP}, \theta_2^{BP})$

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Proof II:

From theorem 3.8, it has been shown that:

$$FPR^{BE}(\underset{\sim}{\theta}^{BE}) = 1 - F_{X_{1N}}(\theta_2^{BE}) + F_{X_{1N},X_{2N}}(\theta_2^{BE},\theta_3^{BE}) - F_{X_{1N},X_{2N}}(\theta_1^{BE},\theta_3^{BE})$$

Assume that $\theta_1^{BE} = \theta_1^{BP}$, $\theta_3^{BE} = \theta_2^{BP}$. As θ_2^{BE} approaches $-\infty$, then

$$\lim_{\theta_2^{BE} \to -\infty} FPR^{BE}(\underset{\sim}{\theta}^{BE}) = 1 - \lim_{\theta_2^{BE} \to -\infty} F_{X_{1N}}(\theta_2^{BE}) + \lim_{\theta_2^{BE} \to -\infty} F_{X_{1N},X_{2N}}(\theta_2^{BE},\theta_3^{BE}) - F_{X_{1N},X_{2N}}(\theta_1^{BE},\theta_3^{BE})$$

$$= 1 - 0 + 0 - F_{X_{1N},X_{2N}}(\theta_1^{BE},\theta_3^{BE})$$

$$= 1 - F_{X_{1N},X_{2N}}(\theta_1^{BE},\theta_3^{BE})$$

$$= 1 - F_{X_{1N},X_{2N}}(\theta_1^{BP},\theta_2^{BP})$$

This has been shown, by Theorem 3.4 to be equal to $FPR^{BP}(\theta_1^{BP},\theta_2^{BP})$.

Theorem 11: For any (FPR, TPR) pair found in the BN strategy, a set of thresholds can be found (in the limit) in the BE strategy with equivalent FPR and TPR values.

Let θ_1^{BE} and θ_2^{BE} represent the BE strategy's threshold associated with test 1 and θ_3^{BE} represent the BE strategy's threshold associated with test 2. Let θ_1^{BN} and θ_2^{BN} represent the BN strategy's threshold associated with test 1 and test 2. Then values of $\underset{\sim}{\theta}^{BE} = (\theta_1^{BE},\theta_2^{BE},\theta_3^{BE})$ can be found such that, in the limit, formulas for TPR and FPR of the BE strategy, denoted by $TPR^{BE}(\underset{\sim}{\theta}^{BE})$ and $FPR^{BE}(\underset{\sim}{\theta}^{BE})$ are given by

I. $\lim_{\theta_1 \to +\infty} TPR^{BE}(\underset{\sim}{\theta}^{BE}) = TPR^{BN}(\theta_1^{BN},\theta_2^{BN})$

II. $\lim_{\theta_1 \to +\infty} FPR^{BE}(\underset{\sim}{\theta}^{BE}) = FPR^{BN}(\theta_1^{BN},\theta_2^{BN})$

Proof I:

From theorem 3.9, it has been shown that:

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$$TPR^{BE}(\underset{\sim}{\theta}^{BE}) = 1 - F_{X_{1D}}(\theta_2^{BE}) + F_{X_{1D},X_{2D}}(\theta_2^{BE},\theta_3^{BE}) - F_{X_{1D},X_{2D}}(\theta_1^{BE},\theta_3^{BE})$$

Assume that $\theta_2^{BE} = \theta_1^{BN}, \theta_3^{BE} = \theta_2^{BN}$. As θ_1^{BE} approaches $+\infty$, then

$$\lim_{\theta_1^{BE} \to +\infty} TPR^{BE}(\underset{\sim}{\theta}^{BE}) = 1 - F_{X_{1D}}(\theta_2^{BE}) + F_{X_{1D},X_{2D}}(\theta_2^{BE},\theta_3^{BE}) - \lim_{\theta_1^{BE} \to +\infty} F_{X_{1D},X_{2D}}(\theta_1^{BE},\theta_3^{BE})$$

$$= 1 - F_{X_{1D}}(\theta_2^{BE}) + F_{X_{1D},X_{2D}}(\theta_2^{BE},\theta_3^{BE}) - F_{X_{2D}}(\theta_3^{BE})$$

$$= 1 - F_{X_{1D}}(\theta_2^{BE}) - F_{X_{2D}}(\theta_3^{BE}) + F_{X_{1D},X_{2D}}(\theta_2^{BE},\theta_3^{BE})$$

$$= 1 - F_{X_{1D}}(\theta_2^{BN}) - F_{X_{2D}}(\theta_3^{BN}) + F_{X_{1D},X_{2D}}(\theta_2^{BN},\theta_3^{BN})$$

This has been shown, by Theorem 3.7 to be equal to $TPR^{BN}(\theta_1^{BN},\theta_2^{BN})$

Proof II:

From theorem 3.8, it has been shown that:

$$FPR^{BE}(\underset{\sim}{\theta}^{BE}) = 1 - F_{X_{1N}}(\theta_2^{BE}) + F_{X_{1N},X_{2N}}(\theta_2^{BE},\theta_3^{BE}) - F_{X_{1N},X_{2N}}(\theta_1^{BE},\theta_3^{BE})$$

Assume that $\theta_2^{BE} = \theta_1^{BP}$, $\theta_3^{BE} = \theta_2^{BP}$. As θ_1^{BE} approaches $+\infty$, then

$$\lim_{\theta_1^{BE} \to +\infty} FPR^{BE}(\underset{\sim}{\theta}^{BE}) = 1 - F_{X_{1N}}(\theta_2^{BE}) + F_{X_{1N},X_{2N}}(\theta_2^{BE},\theta_3^{BE}) - \lim_{\theta_1^{BE} \to +\infty} F_{X_{1N},X_{2N}}(\theta_1^{BE},\theta_3^{BE})$$

$$= 1 - F_{X_{1N}}(\theta_2^{BE}) + F_{X_{1N},X_{2N}}(\theta_2^{BE},\theta_3^{BE}) - F_{X_{2N}}(\theta_3^{BE})$$

$$= 1 - F_{X_{1N}}(\theta_2^{BE}) - F_{X_{2N}}(\theta_3^{BE}) + F_{X_{1N},X_{2N}}(\theta_2^{BE},\theta_3^{BE})$$

$$= 1 - F_{X_{1N}}(\theta_1^{BN}) - F_{X_{2N}}(\theta_2^{BN}) + F_{X_{1N},X_{2N}}(\theta_1^{BN},\theta_2^{BN})$$

This has been shown, by Theorem 3.6 to be equal to $FPR^{BN}(\theta_1^{BN},\theta_2^{BN})$.

The above proofs are only true if the assumptions given in each proof are satisfied

3.8 Optimal operating points

An optimal operating point corresponds to the threshold combination that produces the best accuracy used to classify subjects with respect to disease, often while considering the

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prevalence of the disease and misclassification costs. Since this work is concerned with the cost of administering a number of tests, the technique of finding the optimal operating point should take the cost of sequencing two tests under consideration in addition to misclassification costs.

3.8.1 Generalized Youden index

Recall that the Generalized Youden Index (GYI) can be given by

$$\max_{\theta} \{TPR(\underset{\sim}{\theta}) - m*(FPR(\underset{\sim}{\theta}))\} \tag{3.28}$$

where m is given by

$$m = \left[(1-p)/p\right] \times \left[(C_{FP} - C_{TN})/(C_{FN} - C_{TP})\right] \tag{3.29}$$

The cost/benefit ratio of false-positive compared to false-negative results weighs four outcomes: C_{FP} is the cost associated with a false positive, C_{TN} is the cost associated with a true negative, C_{FN} is the cost associated with a false negative, C_{TP} is the cost associated with a true positive. When $m = 1$, equation (3.28) above yields the original Youden's index which indicates product of cost/benefit ratio and prevalence ratio is 1. To incorporate testing cost into finding the optimal point, the thresholds can be limited such that the testing cost (probability of a second test) will be no larger than a give value (C_0). This can be written as an optimization problem as follows:

Objective function $\max_{\theta} \{TPR(\underset{\sim}{\theta}) - m*(FPR(\underset{\sim}{\theta}))\}$ (3.30)

Subject to $C(\underset{\sim}{\theta}) \le C_0$,

The objective function is the Generalized Youden index (GYI) that needs to be maximized, subject to constraints that need to be satisfied. $C(\underset{\sim}{\theta})$ is the cost of testing (probability of a second test) which is being limited to a maximum of some fixed value, C_0, $0 \le C_0 \le 1$. It

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will be shown in later chapters that this constraint essentially restricts the false positive rates which can be considered in the objective function.

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Chapter 4

4.1 Strategy Properties

This research aims to evaluate three sequential testing strategies for distinguishing between two medical conditions, such as diseased/non-diseased, by using two diagnostic tests measured in a sequence. In this chapter, properties of the sequential testing strategies will be described based on the following factors: MROC curve, cost curve, and test thresholds. This work introduces BE as an alternative strategy to the BN and BP strategies and seeks to describe the three strategies as well as examine whether the BE strategy is better than the BN and BP strategies.

The sensitivity and FPR formulas presented in Chapter 3 are defined in terms of general cumulative distribution functions (CDFs) of test results for those with disease (D) and without (N) disease. In this chapter, the strategies will be described and compared, assuming that the tests will follow a normal distribution. The estimation of these accuracy measures (sensitivity and FPR) were obtained by using normal distribution CDFs for those with and without disease. Together, these are referred to as the binormal model. The binormal model, derived from the normal distribution of test results, is recommended because it has a smooth ROC curve and this makes comparison between strategies easier. In addition, Swets (1986) found the binormal ROC curve of individual tests to be a good approximation to numerous empirical ROC curves. The requirement of the binormal model is that the test results or their transformed values follow a normal distribution with means and variances for diseased and non-diseased populations.

To be able to compare the strategies, the effect of four different parameters associated with the assumptions of normality of the diseased and non-diseased

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populations was examined; these parameters were the area under the ROC curve (AUC), correlation, standard deviation and prevalence. The parameters that were identified could influence the performance of the combined tests:

- The area under the ROC curve (AUC)
    - The values of AUC considered were: (0.90, 0.90), (0.70, 0.90), and (0.70, 0.70), for (Test1, Test2) respectively.

The assumption of each scenario was different; the first assumed that both tests had high accuracy. The second assumed that the first test was not as accurate as the second test, and the third assumed that both tests had only fair or moderate accuracy. The AUC value has an important effect on the shape of the ROC curve of an individual test. Also, combining two tests with identical AUC values improved diagnostic accuracy. This is shown in Figure 4.1 C.

- The ratio of the standard deviations for the diseased and non-diseased populations (b)
    - Three values of the ratio of disease and non-disease standard deviations (b) were considered: b=0.5; b =1; and b=2. Using these three values, nine possible combinations of standard deviations for test 1 (b_1) and test 2 (b_2), considered were: (b_1=1, b_2=1), (b_1=2, b_2=2), (b_1=0.5, b_2=0.5), (b_1=1, b_2=2), (b_1=1, b_2=0.5), (b_1=2, b_2=1), (b_1=1, b_2=0.5), (b_1=0.5, b_2=1), and (b_1=0.5, b_2=2).

This research looked at various values of b, because the shape of the ROC curve of an individual test depended on the ratio of the standard deviations between the diseased and

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non-diseased populations, even when the area was the same (see Figures 4.2.1a and b). The assumption of each scenario was different; b=1 assumes the distribution of test results for the diseased subjects had the same spread as that for the distribution of the non-diseased subjects ($\sigma_D = \sigma_N$) where D represented the diseased subject distribution and N represented the non-diseased subject distribution; b = 0.5 assumed that the distribution of test results for the diseased subjects was more heterogeneous than that for the non-diseased subjects; and b=2 assumed that the distribution of test results for the diseased subjects was more homogenous than that for non-diseased subjects. The b value had an important effect on the shape of the ROC curve of an individual test. This is shown in Figure 4.1 A and B.

Figures 4.1 show the effect of AUC values and b values on the shape of the ROC curves. Graphs A and B in Figure 4.2 show individual ROC curves and graph C shows the ROC curve for the combined tests. Graph A was derived using a binormal ROC curve for a single test with b=0.5, b=1 and b=2 and AUC =0.9. Graph B was derived using a binormal ROC curve for a single test with b=0.5, b=1 and b=2 and AUC =0.7. Graph C combines the two tests where AUC=0.9 and $b_1 = 0.5$ (blue dashed line) and $b_2 = 2$ (red dashed line). The combined test was represented by the color "green". In this case, it can be seen that combined tests improved diagnostic accuracy at the small FPR values of the ROC curve as compared to the individual tests. This motivated the use of the combined tests using sequential testing to improve the diagnostic accuracy. This motivated the use of the combined tests using sequential testing to improve the diagnostic accuracy.

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A B C

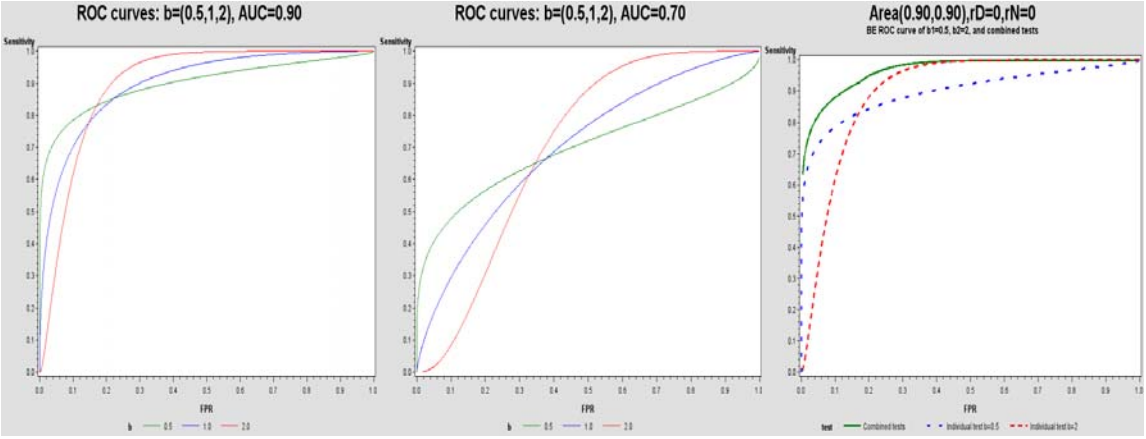

Figure 4.1: The effect of b and AUC on the shape of individual ROC curves (A, and B) and combined tests (C)

- Prevalence
    - The prevalence of disease considered was: 0.1 and 0.7.

Prevalence rates vary depending on the population under study. This research examined two different prevalence of disease (low or high). It may seem that a prevalence of 0.7 was too high to be seriously considered, however in extreme cases, like the prevalence of HIV in certain parts of Africa, the prevalence values approach or even exceed 0.6.

- Correlation between test results (ρ)
    - Five combination of correlation between the tests for both the diseased and non-diseased populations were considered: $(\rho_D = 0, \rho_N = 0)$, $(\rho_D = 0.3, \rho_N = 0.3)$, $(\rho_D = 0.3, \rho_N = 0.7)$, $(\rho_D = 0.7, \rho_N = 0.3)$, and $(\rho_D = 0.7, \rho_N = 0.7)$ where ρ_D refers to the correlation between the two tests for the diseased

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populations, and ρ_N refers to the correlation between the two tests for the non-diseased populations.

The first combination of ρ_N and ρ_D assumed independence between the diseased and non-diseased populations between the two tests. The second, $(\rho_D = 0.3, \rho_N = 0.3)$, assumed weak correlations. The third, $(\rho_D = 0.3, \rho_N = 0.7)$, assumed that the diseased populations would be less correlated than the non-diseased populations. The fourth, $(\rho_D = 0.7, \rho_N = 0.3)$, assumed that the diseased populations were more correlated than the non-diseased populations, and the fifth, $(\rho_D = 0.7, \rho_N = 0.7)$, assumed strong correlations between the diseased and non-diseased populations.

4.2 Generating MROC curve and Cost curve

Under different parameter combinations presented above, sensitivity and FPR was estimated based on normal distribution CDFs by varying the test thresholds. The BP and BN strategies had two thresholds, one for each test. For the BE strategy, two thresholds were used for the first test and one threshold for the second test. Here, the thresholds were quantities which can be varied to dichotomize the test results for subjects into diseased or non-diseased classifications. Because the binormal model assumption was made, the thresholds theoretically range between $-\infty$ and $+\infty$, however these were impractical limits to evaluate. There were several methods for determining lower and upper bounds on test thresholds (Greiner et al, 2000). Because a normal distribution has a bell-curve shape, thresholds were chosen which covered 99.7% of the distribution of test results for those with and without disease, by including all values within 3 standard deviations of the mean. The lower and upper intervals for the thresholds for non-diseased population were defined

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as $\mu_N \pm 3*\sigma_N$, where μ_N was the mean for non-diseased and where σ_N was the standard deviation for non-diseased. The lower and upper intervals for the diseased population was defined by $\mu_D \pm 3*\sigma_D$, where μ_D was the mean for diseased and where σ_D is the standard deviation for diseased. Since test thresholds had to include values from the distribution of both those with and without disease, the range of test thresholds used the minimum of lower limits of the diseased and non-diseased distributions, and the maximum of the upper limits of diseased and non-diseased distributions, given by

$$\left[\min\left(\mu_N - 3*\sigma_N, \mu_D - 3*\sigma_D\right), \max\left(\mu_N + 3*\sigma_N, \mu_D + 3*\sigma_D\right)\right] \quad (4.1)$$

For an individual test, the binormal ROC curve was defined by two components $a = (\mu_D - \mu_N)/\sigma_D$ and $b = \sigma_N/\sigma_D$, where a was the normalized difference between the diseased and non-diseased population means, b the ratio of the diseased and non-diseased population standard deviations. Without loss of generality, the ROC curves were estimated assuming a standard normal distribution for the non-diseased population, ie. $\mu_N = 0$, $\sigma_N = 1$. The parameters described above, AUC and b, were then used to calculate the parameters of the diseased population, such as σ_D, and μ_D. The standard deviation of diseased population was calculated as follows: since $b = \sigma_N/\sigma_D \Rightarrow b = 1/\sigma_D$, then $\sigma_D = 1/b$. The mean of diseased population was calculated given these components: $a = (\mu_D - 0)/\sigma_D \Rightarrow a = \mu_D/\sigma_D$, $\mu_D = a\sigma_D$, $\mu_D = a/b$. Then a was estimated from $\text{AUC} = \Phi\left(a/\sqrt{1+b^2}\right)$ so that $a = \sqrt{1+b^2} \times \Phi^{-1}(\text{AUC})$ and μ_D was written in terms of AUC and b as $\mu_D = \sqrt{1+b^2} \times \Phi^{-1}(\text{AUC})/b$.

The estimate of sensitivity and false positive rate of individual tests were:

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$$\text{TPR}(\theta) = P[Y \geq \theta \mid D] = \Phi\left(\frac{\mu_D - \theta}{\sigma_D}\right) = \Phi\left(\frac{a/b - \theta}{1/b}\right) = \Phi\left(\frac{a/b}{1/b} - \frac{\theta}{1/b}\right) = \Phi(a - \theta b) \text{ and}$$

$$\text{FPR}(\theta) = P[Y \geq \theta \mid N] = \Phi\left(\frac{\mu_N - \theta}{\sigma_N}\right) = \Phi\left(\frac{0 - \theta}{1}\right) = \Phi(-\theta) = 1 - \Phi(\theta)$$

Now, considering two tests, let X_1 and X_2 be random variables that denote the outcomes of two continuous tests with the convention that higher values indicate disease or the test results of diseased subjects were expected to be higher than those of healthy subjects, and a binary outcome variable denoting disease condition. X_{1D} and X_{2D}; X_{1N} and X_{2N} were used to denote the test results for diseased and non-diseased subjects, respectively. Assuming normality, this was written as:

$X_{1N} \sim N(\mu_{1N}, \sigma^2_{1N})$, $X_{2N} \sim N(\mu_{2N}, \sigma^2_{2N})$ and

$X_{1D} \sim N(\mu_{1D}, \sigma^2_{1D})$, $X_{2D} \sim N(\mu_{2D}, \sigma^2_{2D})$,

where the parameters of the normal distribution were determined from AUC and b as described above. These parameters are summarized in Table 4.1 through 4.3

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Table 4.1: ROC curve parameters for $AUC_1 = 0.90$, $AUC_2 = 0.90$

(AUC_1, AUC_2)	b_1, b_2	σ_{1N}, σ_{2N}	μ_{1N}, μ_{2N}	σ_{1D}, σ_{2D}	μ_{1D}, μ_{2D}	Lower and Upper bounds of thresholds(Test1);(Test2)
(0.90,0.90)	(1,1)	(1,1)	(0,0)	(1,1)	(1.81, 1.81)	(-3, 4.81);(-3, 4.81)
	(1,2)	(1,1)	(0,0)	(1,0.5)	(1.81, 1.43)	(-3, 4.81);(-3, 3)
	(1,0.5)	(1,1)	(0,0)	(1,2)	(1.81, 2.86)	(-3, 4.81);(-3.14, 8.86)
	(2,1)	(1,1)	(0,0)	(0.5,1)	(1.43, 1.81)	(-3, 3);(-3, 4.81)
	(2,2)	(1,1)	(0,0)	(0.5,0.5)	(1.43, 1.43)	(-3, 3);(-3, 3)
	(2,0.5)	(1,1)	(0,0)	(0.5,2)	(1.43, 2.86)	(-3, 3);(-3.14, 8.86)
	(0.5,1)	(1,1)	(0,0)	(2,1)	(2.86, 1.81)	(-3.14, 8.86);(-3, 4.81)
	(0.5,2)	(1,1)	(0,0)	(2,0.5)	(2.86, 1.43)	(-3.14, 8.86);(-3, 3)
	(0.5,0.5)	(1,1)	(0,0)	(2,2)	(2.86, 2.86)	(-3.14, 8.86);(-3.14, 8.86)

Table 4.2: ROC curve parameters for $AUC_1 = 0.70$, $AUC_2 = 0.90$

(AUC_1, AUC_2)	b_1, b_2	σ_{1N}, σ_{2N}	μ_{1N}, μ_{2N}	σ_{1D}, σ_{2D}	μ_{1D}, μ_{2D}	Lower and Upper bounds of thresholds(Test1);(Test2)
(0.70,0.90)	(1,1)	(1,1)	(0,0)	(1,1)	(0.74, 1.81)	(-3, 3.74);(-3, 3.74)
	(1,2)	(1,1)	(0,0)	(1,0.5)	(0.74, 1.43)	(-3, 3.74);(-3, 3)
	(1,0.5)	(1,1)	(0,0)	(1,2)	(0.74, 2.86)	(-3, 3.74);(-3.14, 8.86)
	(2,1)	(1,1)	(0,0)	(0.5,1)	(0.59, 1.81)	(-3, 3);(-3, 3.74)
	(2,2)	(1,1)	(0,0)	(0.5,0.5)	(0.59, 1.43)	(-3, 3);(-3, 3)
	(2,0.5)	(1,1)	(0,0)	(0.5,2)	(0.59, 2.86)	(-3, 3);(-3.14, 8.86)
	(0.5,1)	(1,1)	(0,0)	(2,1)	(1.17, 1.81)	(-4.83, 7.17);(-3, 3.74)
	(0.5,2)	(1,1)	(0,0)	(2,0.5)	(1.17, 1.43)	(-4.83, 7.17);(-3, 3)
	(0.5,0.5)	(1,1)	(0,0)	(2,2)	(1.17, 2.86)	(-4.83, 7.17);(-3.14, 8.86)

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Table 4.3: ROC curve parameters for $AUC_1 = 0.70$, $AUC_2 = 0.70$

(AUC_1, AUC_2)	b_1, b_2	σ_{1N}, σ_{2N}	μ_{1N}, μ_{2N}	σ_{1D}, σ_{2D}	μ_{1D}, μ_{2D}	Lower and Upper bounds of thresholds(Test1);(Test2)
(0.70,0.70)	(1,1)	(1,1)	(0,0)	(1,1)	(0.74, 0.74)	(-3, 3.74); (-3, 3.74)
	(1,2)	(1,1)	(0,0)	(1,0.5)	(0.74, 0.59)	(-3, 3.74); (-3, 3)
	(1,0.5)	(1,1)	(0,0)	(1,2)	(0.74, 1.17)	(-3, 3.74);(-4.83, 7.17)
	(2,1)	(1,1)	(0,0)	(0.5,1)	(0.59, 0.74)	(-3, 3);(-3, 3.74)
	(2,2)	(1,1)	(0,0)	(0.5,0.5)	(0.59, 0.59)	(-3, 3);(-3, 3)
	(2,0.5)	(1,1)	(0,0)	(0.5,2)	(0.59, 1.17)	(-3, 3);(-4.83, 7.17)
	(0.5,1)	(1,1)	(0,0)	(2,1)	(1.17, 0.74)	(-4.83, 7.17);(-3, 3.74)
	(0.5,2)	(1,1)	(0,0)	(2,0.5)	(1.17, 0.59)	(-4.83, 7.17);(-3, 3)
	(0.5,0.5)	(1,1)	(0,0)	(2,2)	(1.17, 1.17)	(-4.83, 7.17);(-4.83, 7.17)

Since two continuous tests were considered, the use of logic rules were sometimes associated with more than one set of thresholds which produced more than one sensitivity value corresponding to a fixed specificity level. As described in Chapter 3, in such cases, thresholds associated with maximum sensitivity were most desirable. The following are steps of how the MROC curves were constructed. Graph A in Figure 4.1 was produced by estimating sensitivity and FPR for all possible combinations of threshold values (within the above specified limits) of the test results in increments. Here, threshold increments of 0.04 were used. It is possible that two sets of thresholds may have had the same maximum sensitivity but a different cost. Since these threshold sets had the same sensitivity, it was most desirable to take the threshold set with the lowest cost. Graph B identified maximum sensitivity with lowest cost for each $FPR \leq t$, where t was 200 equally spaced values

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between 0 and 1 (increment of 0.005). The MROC curve was represented here as a black line.

A B

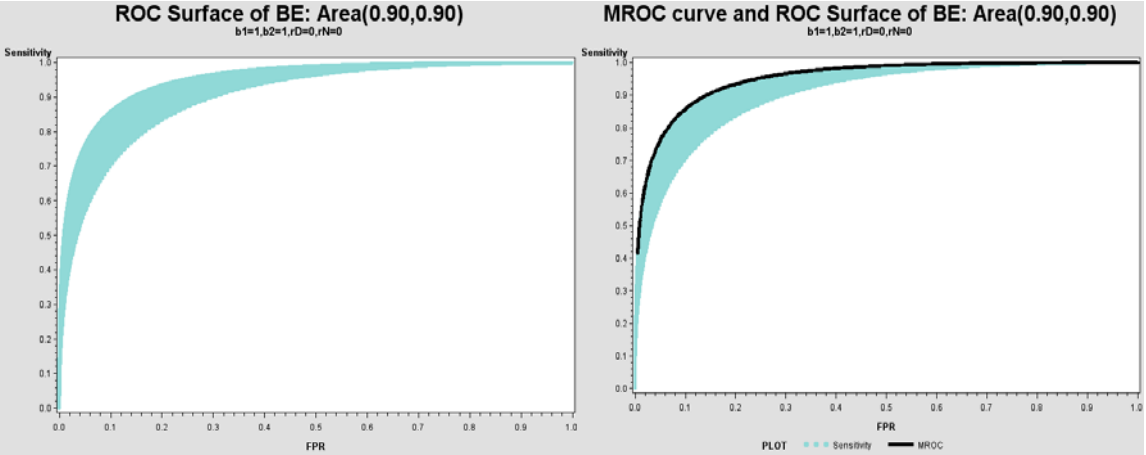

Figure 4.2: Steps in producing the MROC curve

The 'black' curve in Figure 4.2 B is identical to MROC curve, but the difference between the two curves is that the point on the MROC curve in Figure 4.2 B had the lowest cost at each $FPR \leq t$.

4.3 Description and comparison of strategies

In the previous section, four different parameters from the assumption of normality were identified that could influence the performance of the combined tests: AUC of each individual test, the ratio of the diseased and non-diseased population standard deviations (b), correlation (*rho*) between the diseased and non-diseased populations, and disease prevalence. In the remainder of this chapter the three strategies, BE, BP and BN will be compared and described using the accuracy, cost of sequential of testing, and test thresholds. Although recent articles by Etzioni (2003), Thompson (2003), and Shen (2008) presented the use of the BP and BN strategies in clinical settings to assess the overall diagnostic accuracy of a continuous sequence of tests, these articles ignored the cost of

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performing such tests. If the competing strategies have similar or the same accuracy, the MROC curve is unable to show any real difference between strategies. However, as will be seen, differences in strategies often become apparent when describing the cost curves. The following sections examine the effect of the AUC values, correlation, standard deviation, and prevalence on the MROC curves, cost curves, and test threshold.

4.3.1 The effect of area under the ROC curve (AUC)

In Section 3.7 it was proven that for a fixed FPR, the TPR of the BE strategy were at least as good as the TPR of the BP or BN strategy. On the graph series in Appendix A, the BE strategy is represented in green. The accuracy of the BE strategy does not change as much as the accuracy of the BP or BN strategy under different parameters. Regardless of the parameters, the BE strategy had similar or preferable accuracy; the BN or BP strategy consistently had the same or lower accuracy than the BE strategy, but never surpassed the accuracy of that strategy.

The MROC curve of the BE strategy often had the appearance of a combination of the MROC curves of the BN and BP strategies. There was one exception to this pattern. When identical AUC values, such as (AUC_1 = 0.90, AUC_2 = 0.90), and (AUC_1 = 0.70, AUC_2 = 0.70) with (b1=1, b2=1), the BE strategy had a slightly higher accuracy than both the BN and BP strategies combined, rather than appearing as a combination of either strategy (see Appendix A1 Figure A1.1a). This served to reinforce the idea that, in these testing situations, BE was a better strategy than the BN and BP strategies. Here the maximum sensitivity across the BN and BP strategies did not achieve the sensitivity of the BE strategy at a low FPR region.

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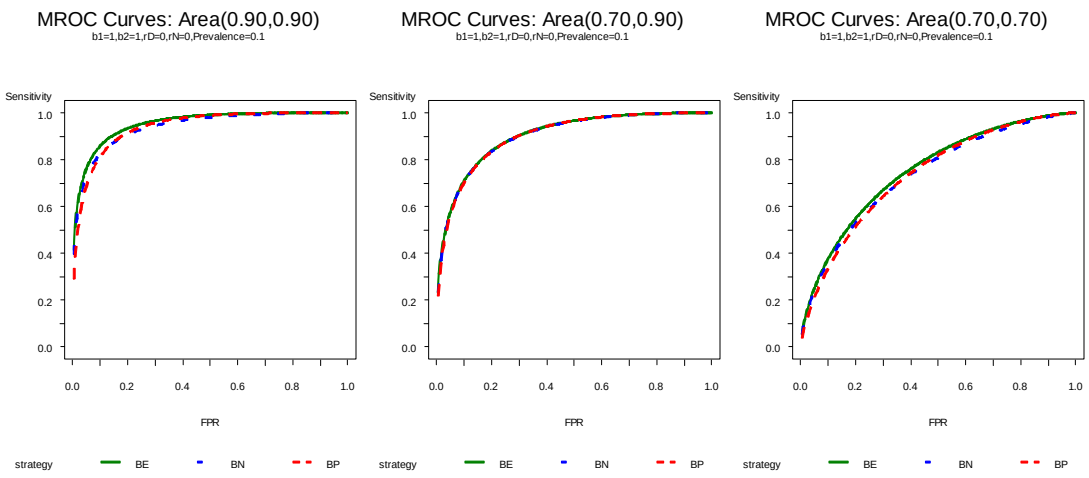
MROC curves sometimes were unable to show any real differences between the strategies (see Figure 4.3 A1, B1, and C1). However, cost curves could play a major role in differentiating between strategies. It was seen that the cost of differing AUC values, specifically when the first test had a smaller AUC than the second test, creates a higher cost compared to the cost of identical, low or high accuracy for both tests (see Figure 4.3 A2, B2, and C2). With differing AUC values (e.g., $AUC_1 = 0.70$, $AUC_2 = 0.90$), Test 1, as compared to Test 2, was not as accurate in detecting disease which is why more patients were sent to the second test and cost was higher. With identical AUC values (e.g., $AUC_1 = 0.90$, $AUC_2 = 0.90$) and similarly (e.g. $AUC_1 = 0.70$, $AUC_2 = 0.70$), Test 1 and Test 2 had similar accuracies and fewer patients went to the second test, as compared to when AUC values differed.

A1 B1 C1



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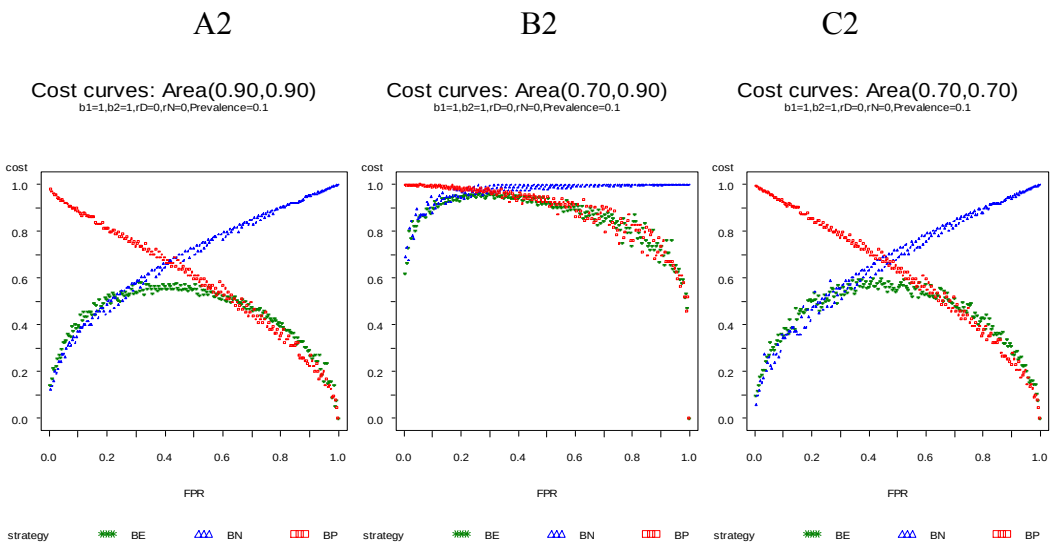

Figure 4.3: The effect of AUC values on the MROC and cost curves of competing strategies

Figure 4.3 demonstrates that cost, rather than the MROC curve, was affected by the AUC of the individual tests. For the BN strategy, as the FPR rose, the cost also roses since a high number of positive results (as demonstrated through the FPR) increased the number of individuals that must take the second test. Recall that for the BN strategy, those with a positive result must take the second test. For the BP strategy, as the FPR roses, the cost decreased since a low number of negative results (as demonstrated through the FPR) decreased the number of individuals that must take the second test. Recall that for the BP strategy, those with a negative result must take the second test.

Figure 4.4 demonstrates how the AUC had an important effect on the shape of the MROC and cost curves of each individual strategy. Certain exceptions to the pattern in effect on MROC were seen with the following parameters (here, the subscripts refer to Test 1 and Test 2): (AUC_1=0.90, AUC_2 = 0.90) and (AUC_1 = 0.70, AUC_2 = 0.90) with (b1=2, b2=2), where the MROC curves of the BP strategy were identical. (see Figure 4.4 C2 and

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B3). Overall, the varying AUC's had a major effect on the MROC curves for each strategy, because if the tests were not accurate, such as ($AUC_1 = 0.70$, $AUC_2 = 0.70$), the sensitivity was lower than ($AUC_1 = 0.70$, $AUC_2 = 0.90$) and ($AUC_1 = 0.90$, $AUC_2 = 0.90$).

One can see from the Figure 4.5 C5 and some graphs in Appendix A, that discontinuity sometimes occurred. One explanation for these was that two sets of thresholds produced the same FPR, but a slightly different sensitivity. For example, Table 4.4 contains points on the MROC curve and cost curve of the BP strategy. Table 4.5 contains points not on the MROC curve and cost curve of the BP strategy because it did not achieve the maximum sensitivity. Here, a slight difference in the two sensitivity values (0.5957142114 compared to 0.5876595627) in the threshold set (2.08, 0.52) vs. (0.52, 2.08) could have had a significant impact on cost (0.9741012430 compared to 0.6699149489). The point, then, chosen to be on the MROC curve was the point with the maximum sensitivity (FPR=0.315, maxTPR=0.5957142114), **but** a higher cost (0.9741012430). The point, not chosen to be on the MROC curve was the point with (FPR=0.315, TPR=0.5876595627), but a lower cost (0.6699149489). The choice of this slight higher point causes the discontinuity. This problem is considered further in the next chapter. See Tables 4.4 and 4.5 for the TPR, FPR and cost values where discontinuity occurs.

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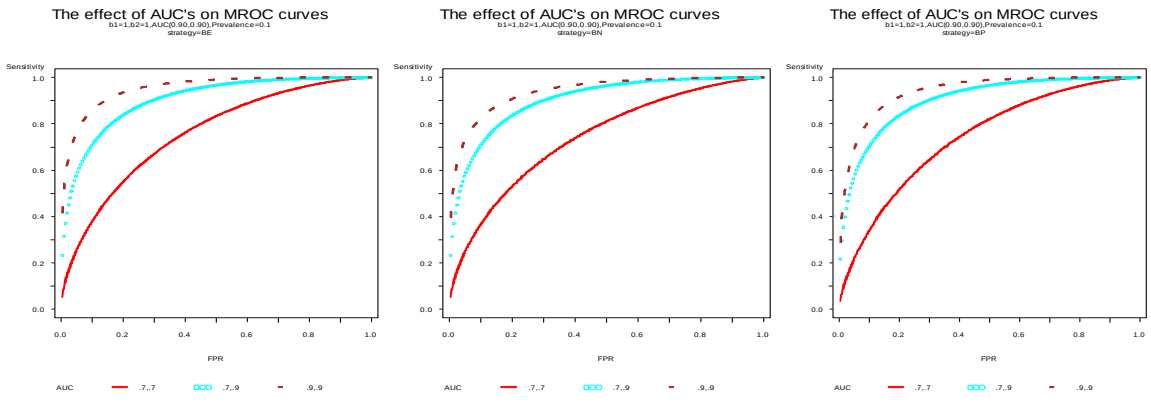
Table 4.4: The points on the discontinuity chosen to be on the MROC curve of BP strategy ($AUC_1 = 0.70$, $AUC_2 = 0.70$), and ($b_1 = 1$, $b_2 = 2$).

Cost	θ_1	θ_2	FPR	Sensitivity	strategy
0.6699149489	0.52	2.28	0.310	0.5872140825	BP
0.9741012430	2.08	0.52	0.315	0.5957142114	BP

Table 4.5: The points not chosen to be on the MROC curve of BP strategy ($AUC_1 = 0.70$, $AUC_2 = 0.70$), and ($b_1 = 1$, $b_2 = 2$).

Cost	θ_1	θ_2	FPR	Sensitivity	strategy
0.6699149489	0.52	2.08	0.315	0.5876595627	BP

A1 B1 C1



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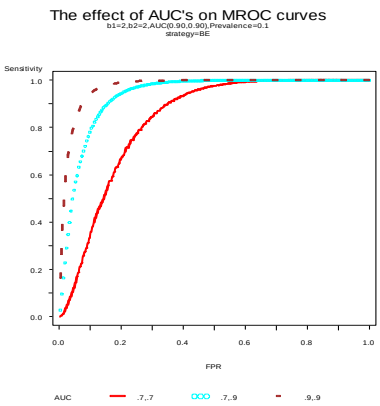
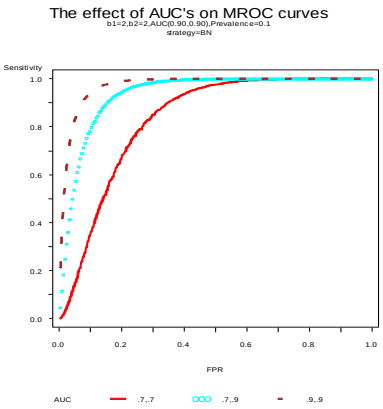
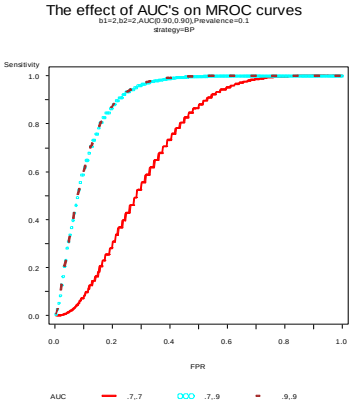
A2



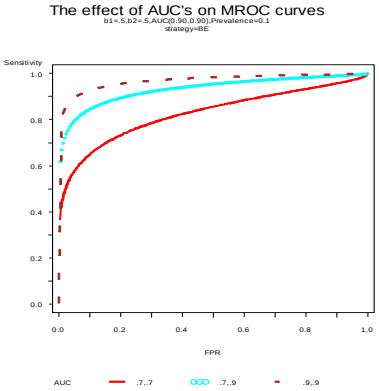
B2



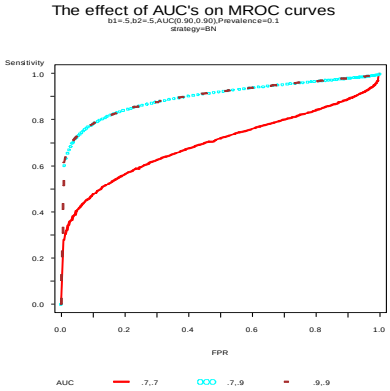
C2



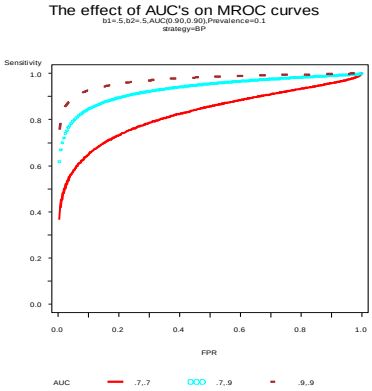
A3



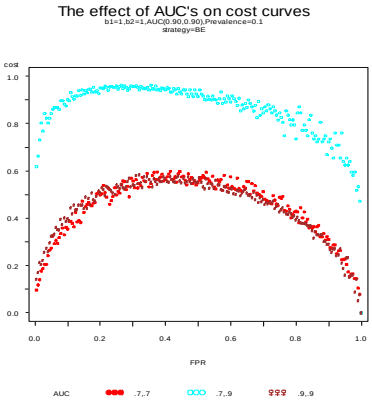
B3



C3



A4



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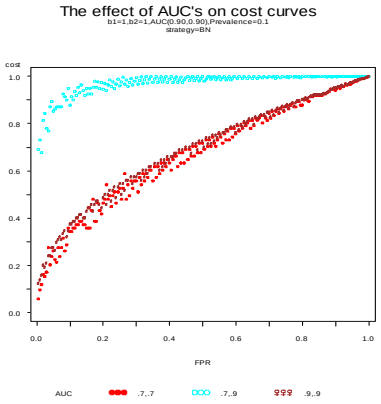

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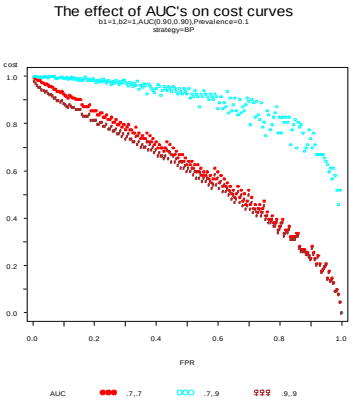

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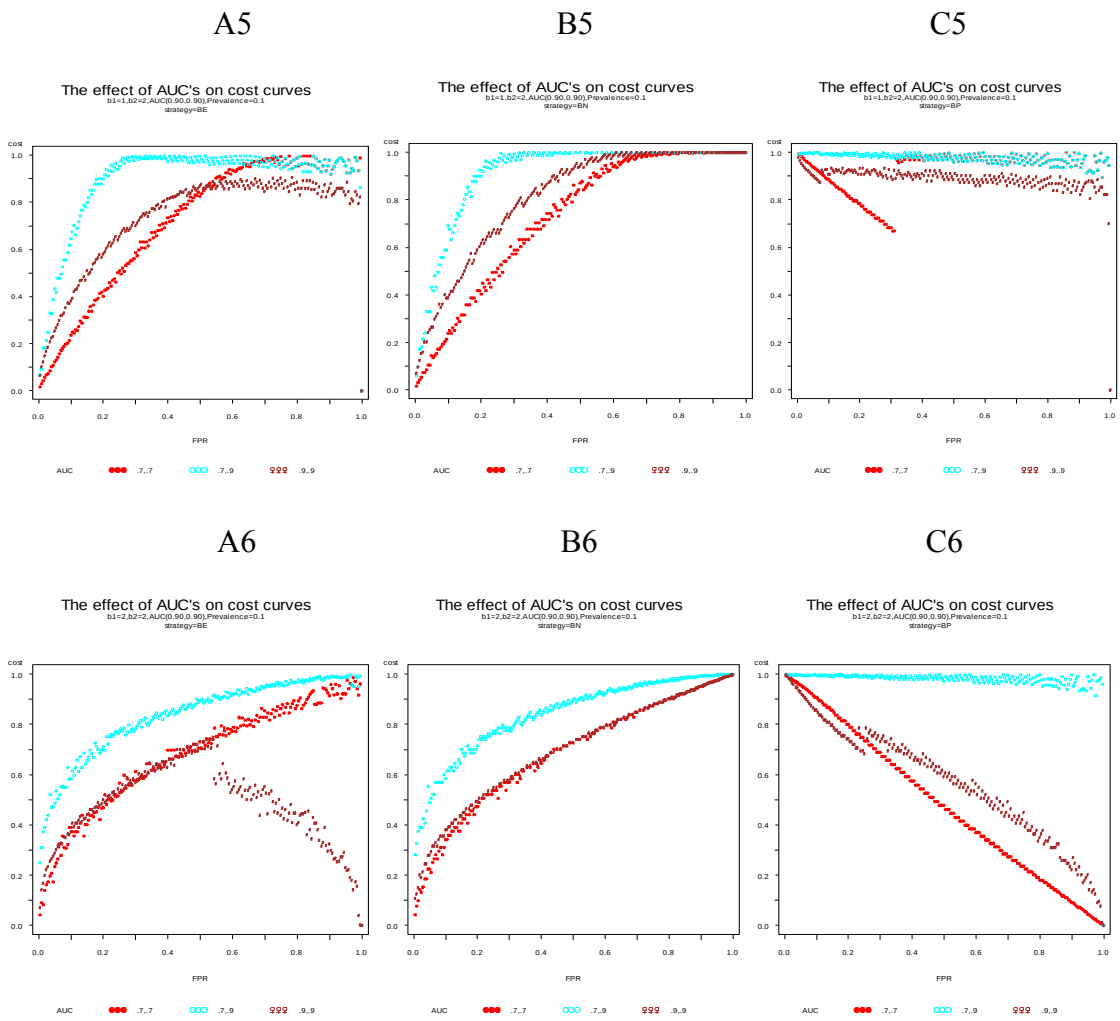

Figure 4.4: The effect of AUC values on the MROC and cost curves of individual strategies

4.3.2 The effect of standard deviation

As shown in Figure 4.5 for (AUC_1 = 0.90, AUC_2 = 0.90), in terms of accuracy, either the BN or BP strategy were, at most, as good as the BE strategy, regardless of the standard deviations of the diseased and non-diseased populations. In Appendix A, it can be seen that the performance of BP and BN depended on the parameter setting. For example, if the standard deviation was higher for the diseased population than the non-diseased population, then one strategy was better than the other and vice versa. This pattern was also seen in Shen (2008).

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In this research, one can see clearly that the accuracy of the BN and BP strategy depended on the ratio of the standard deviations. When (b_1=1, b_2=0.5), (b_1=0.5, b_2=1), or (b_1=0.5, b_2=0.5), the BE and BP strategies had the same accuracy, higher than the BN strategy, which had the worst accuracy. When (b_1=1, b_2=2), (b_1=2, b_2=1), or (b_1=2, b_2=2), the BE and BN strategies had the same accuracy, higher than the BP strategy, which had the worst accuracy. When b_1=0.5 and b_2=2 or b_1=2 and b_2=0.5, the accuracy of the BE strategy was never worse, while the accuracy of the BN and BP strategies depends on the FPR region. Here, the BP strategy had the worst accuracy at small FPRs, whereas the BN strategy had the worst accuracy at large FPRs.

In Figure 4.5 and in Appendix A, the following patterns can be noted:

1.) The BN and BE strategies were less costly than the BP strategy at lower FPRs, and the BP and BE strategies were less costly than the BN strategies at higher FPRs, when b_1=2, b_2=2 (Graphs A3, B3, and C3 in Figure 4.5).

2.) BN and BE were less costly than BP at lower FPRs, and BP and BE were less costly than BN at higher FPRs, when b_1=1, b_2=2; b_1=2, b_2=1; and b_1=2, b_2=2 (Graphs A3, B3, and C3 in Figure 4.5).

3.) BN was less costly than BP and BE at lower FPRs, and BP and BE was less costly than BN at higher FPRs (see Appendix Figure A1.1i).

4.) BE was less costly than BP and BN, when b_1=2, b_2=1 (Graph B3 in Figure 4.5).

5.) BE and BP were less costly than BN, when b_1=1, b_2=0.5 (Graph A4 in Figure 4.5).

6.) BE and BN were less costly than BP, when b_1=2, b_2=2 (Graph B4 in Figure 4.5).

Consequently, fewer subjects were required to take the second test for the BE strategy at low and high FPR values (see Appendix A).

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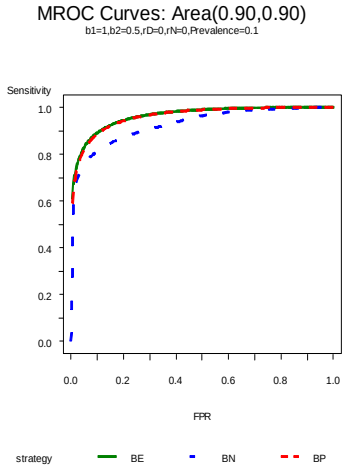
A1



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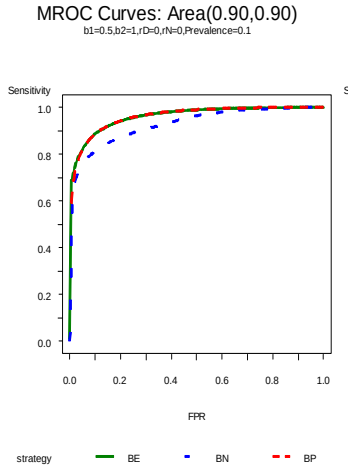

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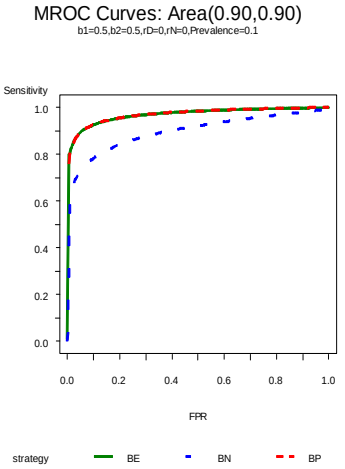

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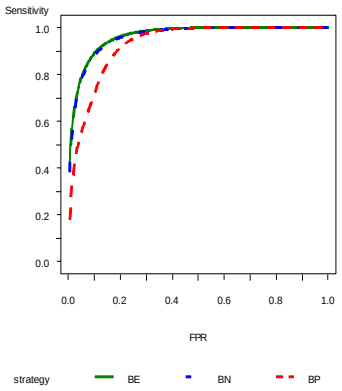

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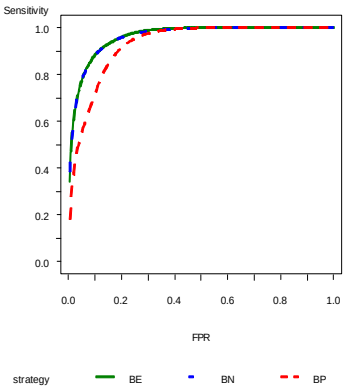

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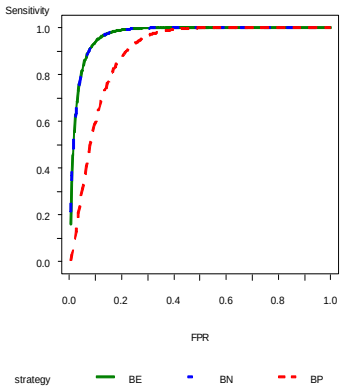

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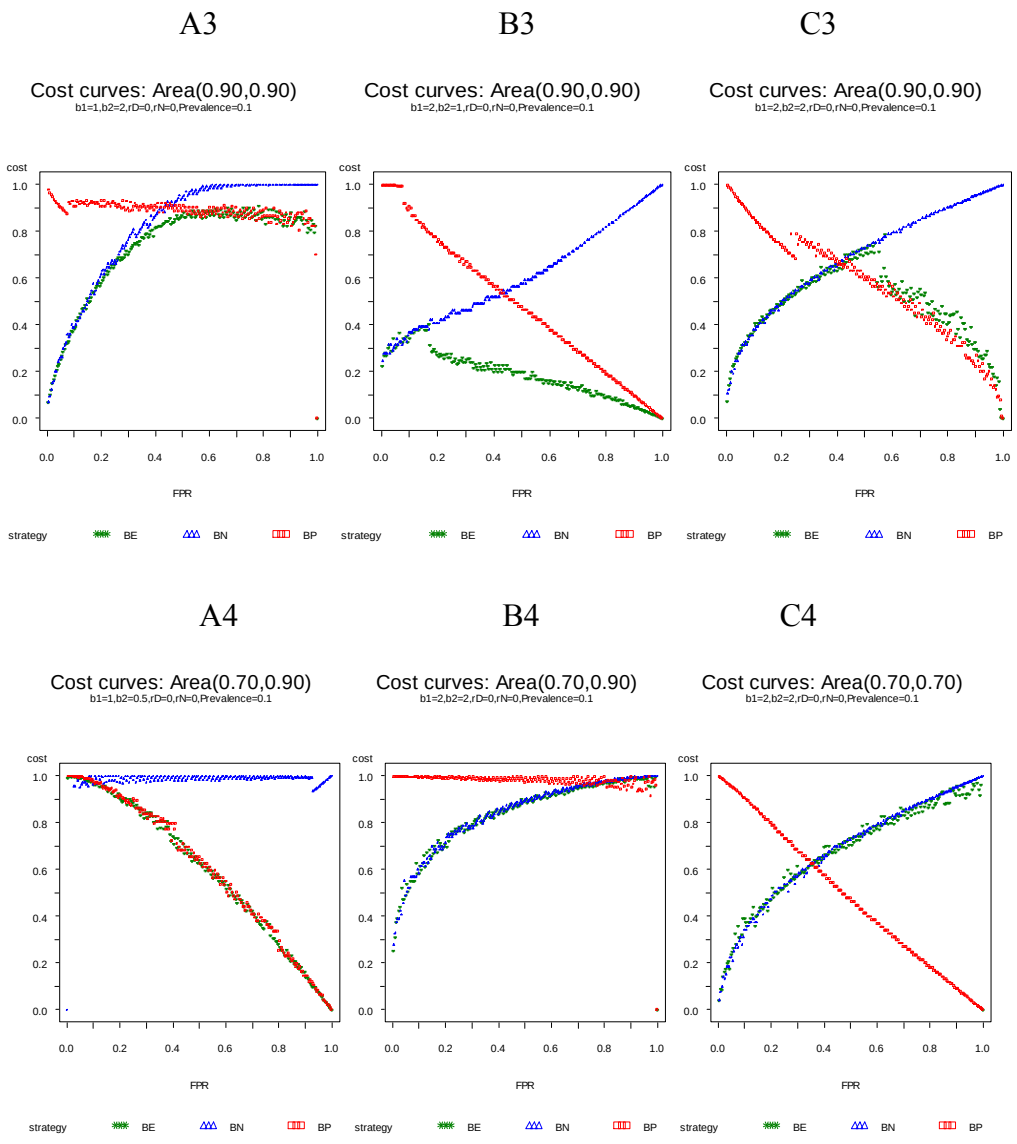

Figure 4.5: The effect of standard deviation on the MROC and cost curves of competing strategies

Figure 4.6 A1 shows that the MROC curves for varying ratios of standard deviations did not have a major effect on the BE strategy. For the BN strategy (graph B1) and the BP strategy (graph C1), however, the ratio of standard deviations did have an effect on the MROC curves, especially for extreme values of b, for which the MROC curves switched. The BN strategy's sensitivity was the best when (b_1=2, b_2=2), represented in blue, and its

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sensitivity was the worst when (b_1=0.5, b_2=0.5), represented in red. This result occurs because when (b_1=0.5, b_2=0.5), there are no thresholds which give sensitivity values that different from the maximum sensitivity. This is why the sensitivity of (b_1=2, b_2=2) is higher than the sensitivity of (b_1=0.5, b_2=0.5). In contrast, BP's sensitivity was the best when (b_1=0.5, b_2=0.5) represented in red, and worst when (b_1=2, b_2=2), represented in blue. This result occurs because when (b_1=2, b_2=2), there are no thresholds which give sensitivity values that different from the maximum sensitivity. This is why the sensitivity of (b_1=0.5, b_2=0.5) is higher than the sensitivity of (b_1=2, b_2=2). Figure 4.6 shows that the BE strategy's cost curves for the varying ratios of standard deviations spread to most portions of the graph. BN's and BP's cost curves, in contrast, were found in one diagonal portion of the graph. For BN, the curves were found in the above left diagonal, while for BP, they were found in the above right diagonal. The reader should remember that the BN strategy only classifies a patient as positive if both tests have confirmed that classification. Therefore, the BN strategy would be associated with low cost at low FPRs. Conversely, the BP strategy was associated with high cost at low FPRs, because more patients in the sample was classified as positive. For all strategies, it was seen that (b_1=0.5, b_2=1), (b_1=1, b_2=2), and (b_1=0.5, b_2=2), all have high cost.

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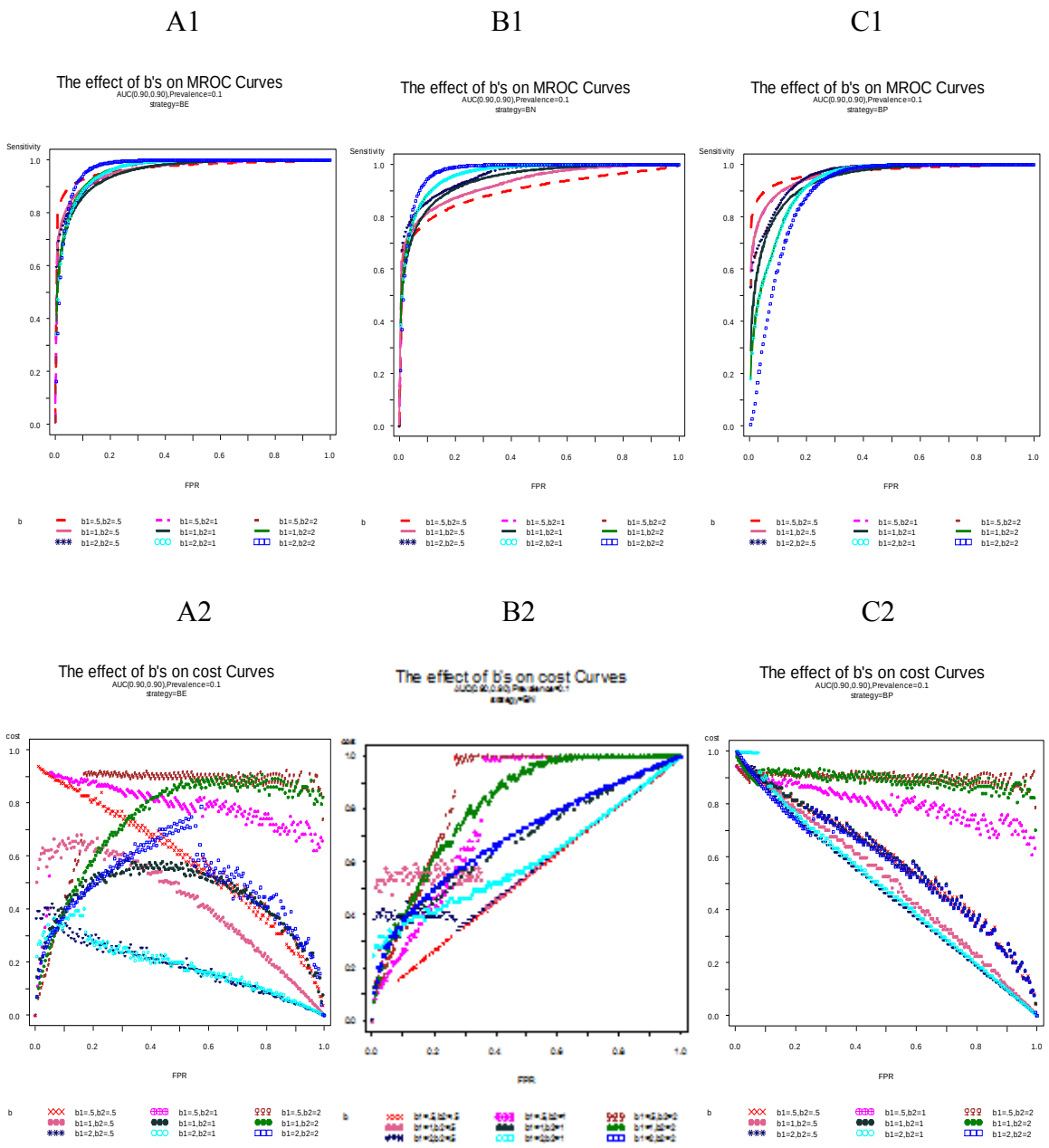

Figure 4.6: The effect of standard deviations on the MROC and cost curves of an individual strategy

4.3.3 The effect of prevalence

In general, prevalence did not have an effect on the MROC curves, but prevalence did have an effect on the cost curves for the three strategies. Figure 4.7 examines cost curves for a high (0.70) and low (0.10) prevalence. The cost associated with low prevalence shifted to

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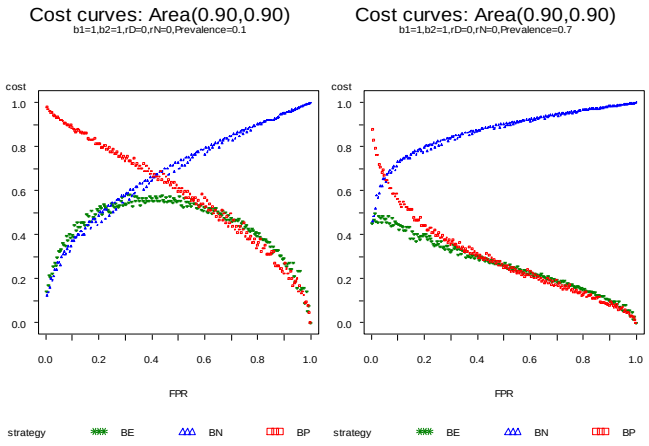
higher FPR values as compared to high prevalence. When a disease is common, or, has high prevalence, the first test will be sufficient in detecting it, because its symptoms will be more common to diagnose. When a disease is rare, having low prevalence, more subjects were likely to be sent to have the second test, because its symptoms were seen less often by clinicians. Therefore, prevalence had an effect on the cost curves. For example, in Figure 4.7, as compared to low prevalence, cost was lower for the BE strategy for higher prevalence when FPR $\geq$ 0.2. Similarly, cost was lower for the BP strategy for high prevalence and all FPR. Cost was lower for the BN strategy for low prevalence and all FPR.

A1 B1



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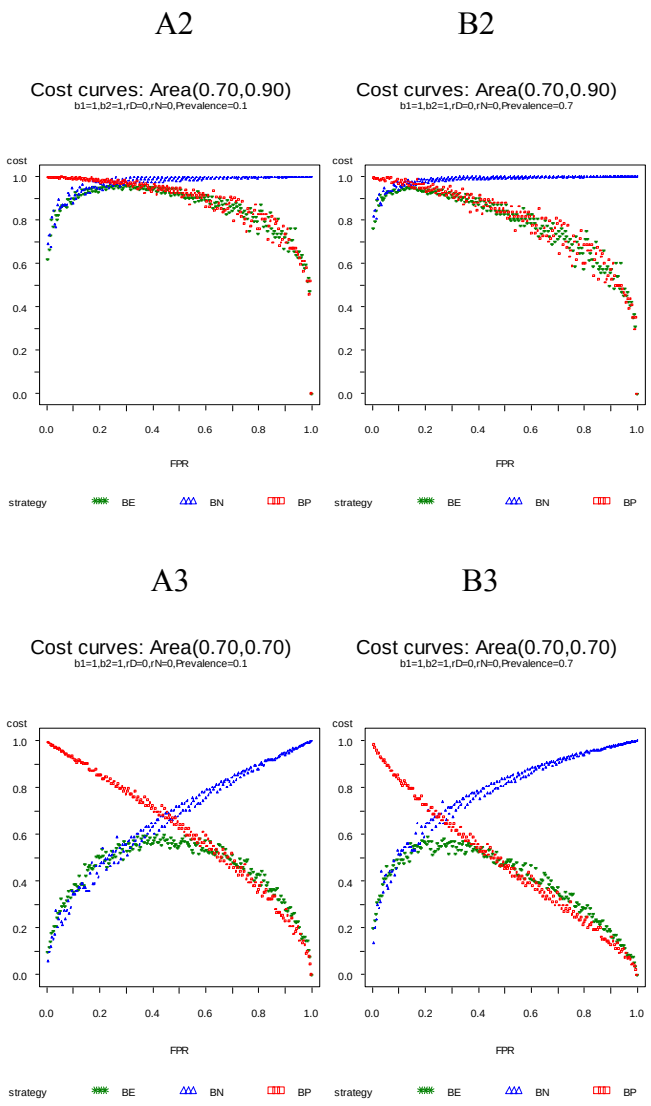

Figure 4.7: The effect of prevalence on cost curves of competing strategies

4.3.4 The effect of correlation

The presence and absence of correlation between the two tests for both the diseased and non-diseased populations was examined. It was found that correlation has an effect on the MROC curves of all three strategies. It was apparent that, in the weak (strong) correlations for the diseased and non-diseased populations, the MROC curves of the strategies became moderately (marginally) closer to each other and cost modestly (significantly) decreased with more scattered points than the uncorrelated tests. For example, in Figure 4.8, the BE

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strategy (graph A1), the BN strategy (graph B1), and the BP strategy (graph C1) show that the MROC curves were affected by varying correlations, especially for extreme values of correlation: absence of correlation and strong correlation. MROC curves seemed higher for absence of correlation than strong correlation (see Figure 4.8). Also, identical or differing correlations of the diseased and non-diseased populations affected the BP strategy and the BN strategy by switching their performances, or making their performance identical to one another, depending on the parameter settings. For example, as shown in graph B1 and C1, BN's sensitivity was the best when (ρ_D=0,ρ_N=0) and (ρ_D=0.7,ρ_N=0.3) represented in orange and red, and its sensitivity was the worst when (ρ_D=0.7,ρ_N=0.7) and (ρ_D=0.3,ρ_N=0.7) represented in blue and dark blue. In contrast, the BP strategy's sensitivity was the best when (ρ_D=0,ρ_N=0) and (ρ_D=0.3,ρ_N=0.7) represented in orange and dark blue, and its sensitivity was the worst when (ρ_D=0.7,ρ_N=0.7) and ($\rho_D = 0.7, \rho_N = 0.3$) represented in dark blue and red. Figure 4.9 demonstrates the effect of correlation on the cost curves for each individual strategy. In summary, both BN and BP were best at (ρ_D=0,ρ_N=0) and worst at (ρ_D=0.7,ρ_N=0.7). Where they differed was (ρ_D=0.3,ρ_N=0.7) and ($\rho_D = 0.7, \rho_N = 0.3$). Graphs in Figure 4.8 A4, A5, and A6 show that cost curves of all strategies remained high when correlations existed. There was little or no effect of correlations on the basic shape of the cost curves for the BN and BP strategy (see Figure 4.8 graphs B6 and C6).

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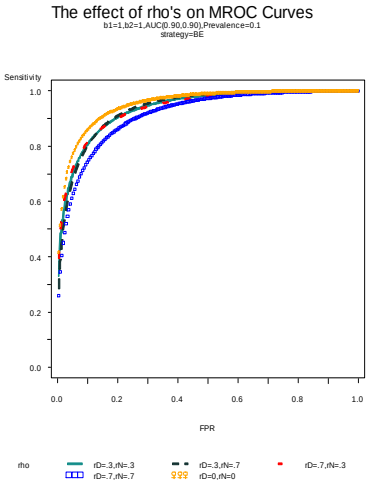
A1



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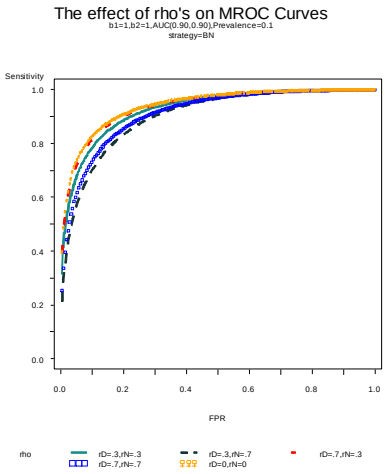

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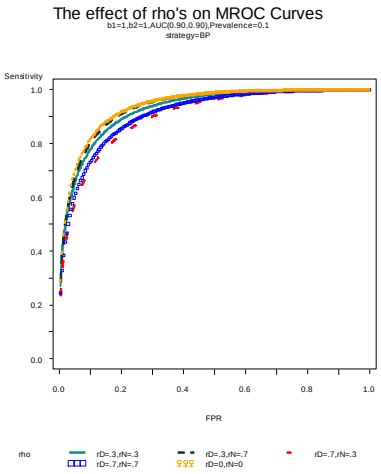

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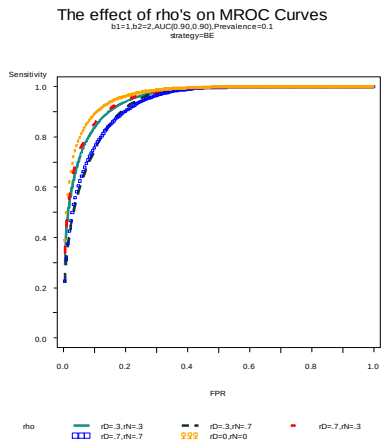

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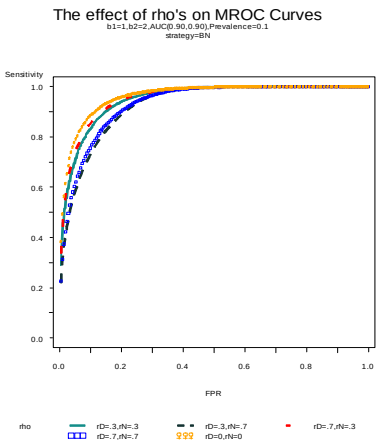

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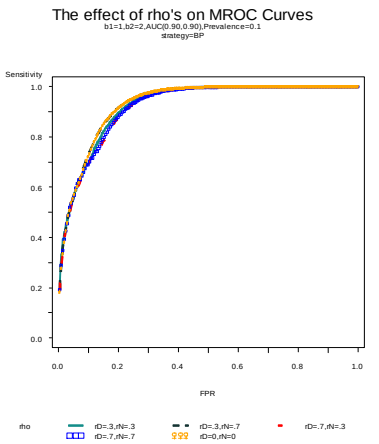

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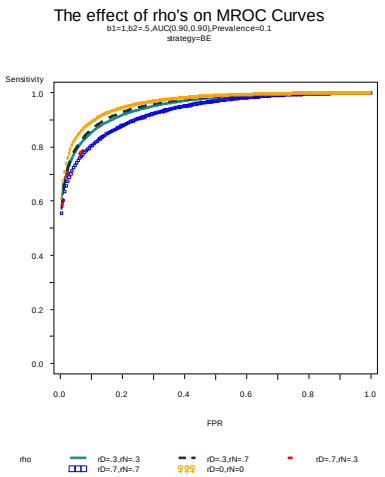

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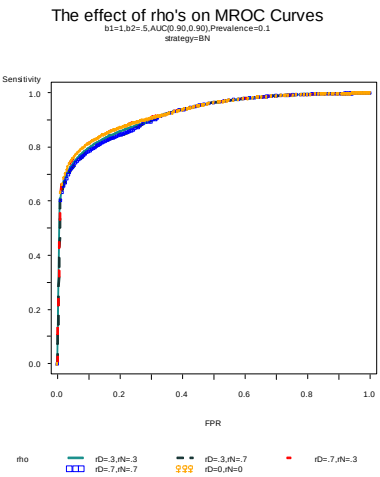

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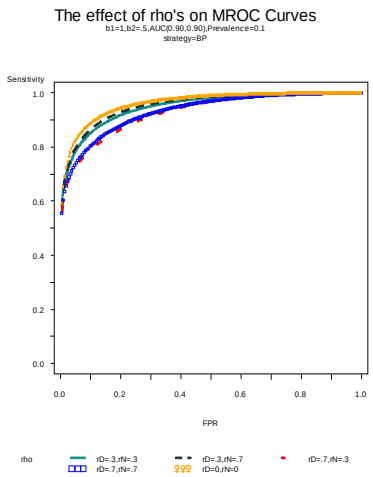

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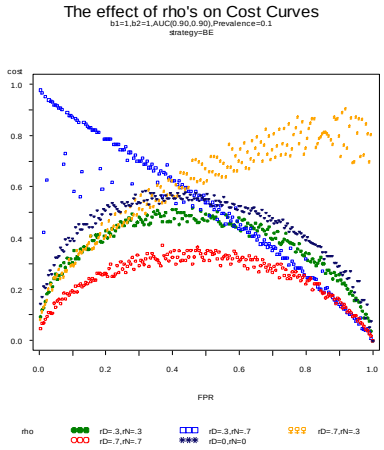
A4



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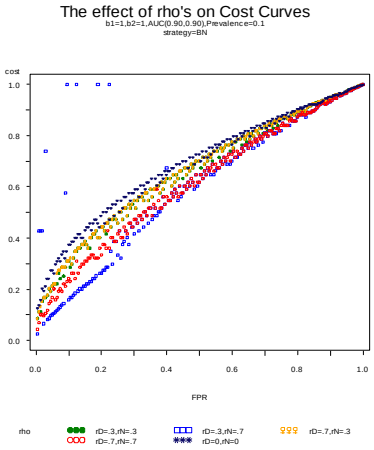

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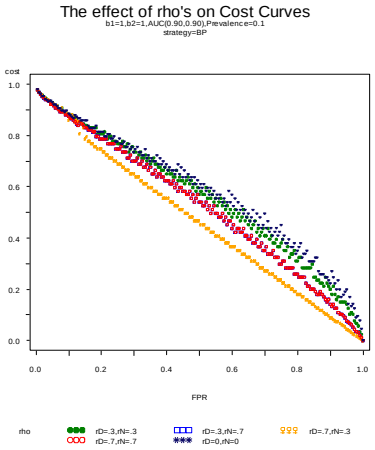

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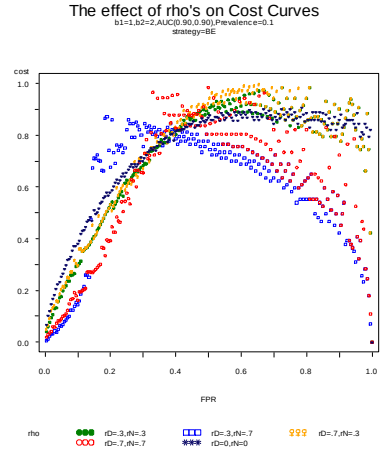

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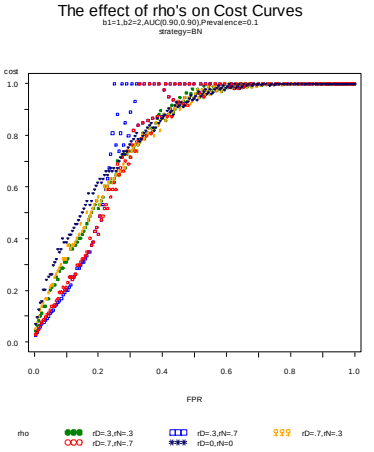

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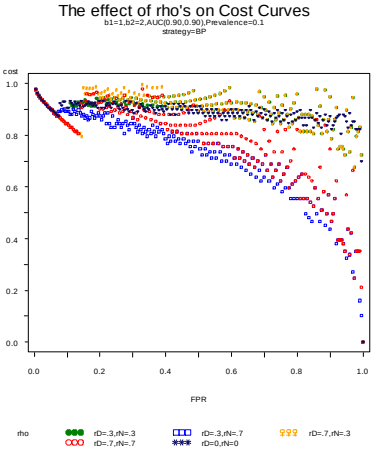

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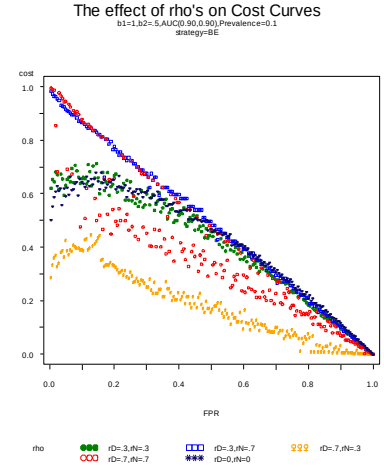

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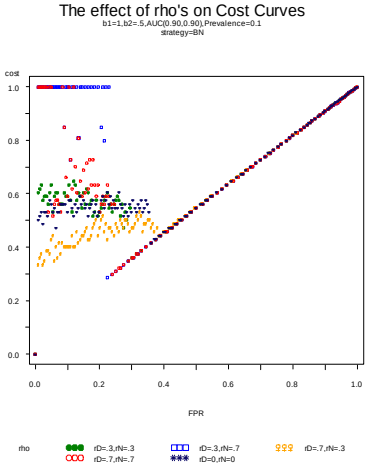

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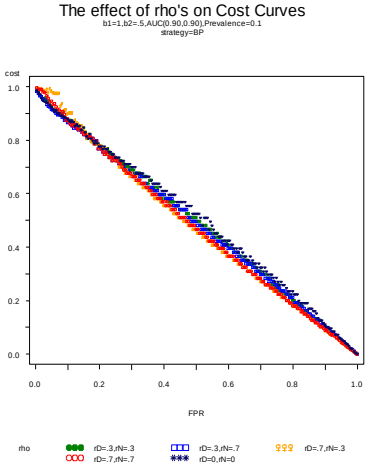

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Figure 4.8: The effect of correlation on the MROC and cost curves

4.4 Optimality criterion

The optimal operating points (OOP) were commonly defined as the thresholds corresponding to the best balance of specificity and sensitivity (this "best balance" may be defined differently depending on the criteria chosen). This research can also be used to give guidance in selecting the optimal operating points specifically when there is interest in controlling the cost of testing. Zweig and Campbell's criterion which minimizes the overall average cost was used. As described in Chapters 2 and 3, this was formulated as an optimization problem:

Objective function $\max_{\theta} \{TPR(\underset{\sim}{\theta}) - m \times (FPR(\underset{\sim}{\theta}))\}$ (4.2)

Subject to $C(\underset{\sim}{\theta}) \le C_0$,

where $m = \left[(1-p)/p\right] \times \left[\left(C_{FP} - C_{TN}\right)/\left(C_{FN} - C_{TP}\right)\right]$, as defined in work by Metz (1978) is the slope of the combined diagnostic tests' ROC curve (a straight line that passes through the ROC curve in the small FPR values, in a point called optimal point). $C(\underset{\sim}{\theta})$ was the cost of testing which satisfies up to fixed value, C_0, $0 \le C_0 \le 1$. The following values of cost of constraint were considered here: 1 and 0.75. The assumption of each scenario was different. A cost constraint of 1 means there was no constraint at all. A cost of less than 1 means not all of the subjects have the second test. The 75% constraint means that you will only consider thresholds which result in no more than 75% needing to take the 2nd test. These values helped show how much was saved at a particular optimal operating point. Table 4.6 considers the values of C/B and slopes.

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Table 4.6: C/B ratios and slope

Prevalence			
0.1		0.7	
C/B	slope	C/B	slope
0.01	0.1	0.23	0.1
0.11	1	1	0.43
0.33	3	2.33	1
1	9	7	3

The above values of slopes were suggested because they were within the range of 0.1-3.0 used in previous literature (Metz et al., 1996). Values not in this range were not considered by Metz et al. to be clinically relevant. While the slope of 9.0 may not be clinically relevant, it is it important to observe it here because the C/B ratio was 1.0, which assumed that the cost of misclassifying the non-diseased was the same as the cost of misclassifying the diseased. The C/B of 0.11 for prevalence of 0.1 and 2.33 for prevalence of 0.7 assumed that the product of C/B ratio and prevalence term ($(1-p)/p$) was 1.0 *(i.e., slope=1.0)*. This produces a formula for the optimal point which was the same as Youden's index. Here the OOP was found by measuring the maximum distance from the chance line.

This study does not intend to use the optimality criterion to choose a strategy. However, the goal was to give guidance on how the cost of sequential of testing affects the choice of optimal operating points once a strategy was chosen. One can illustrate the regions of the MROC curve which satisfied the fixed cost constraints (1 or 0.75) from which the optimal points may be chosen. Effectively, this was a graphical depiction on the MROC curve of the feasible and infeasible regions for optimal points. The optimal point from the feasible regions was found by maximizing the GYI from Equation 4.2. This section shows how the feasible region of the optimal points changes by varying the cost

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constraint. The example presented here assumed equal standard deviations for the diseased and non-diseased populations. This example was chosen because the cost curves show different cases (in particular when prevalence was 0.10, graph B) where

- The BE strategy and the BN strategy produced similar results for cost at low FPR values
- The BE strategy and the BP strategy produced similar results for cost at high FPR values
- The BE strategy and the BP strategy do not produced similar results for cost at low FPR values
- The BE strategy and the BN strategy do not produced similar results for cost at high FPR values
- Neither the BP strategy nor the BN strategy produced similar results for cost for BE at a range of FPR.

The graph in Figures 4.9 A shows the competing strategies had similar MROC curves, graphs B and C shows the cost curves for low and high prevalence, respectively, with fixed cost constraints (1 or 0.75) represented by a "black" dashed line. It was obvious that the BE strategy was not affected by cost constraints at any FPR values. In contrast, cost constraints restricted the FPRs that could be considered for the BP and BN strategies.

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A B C

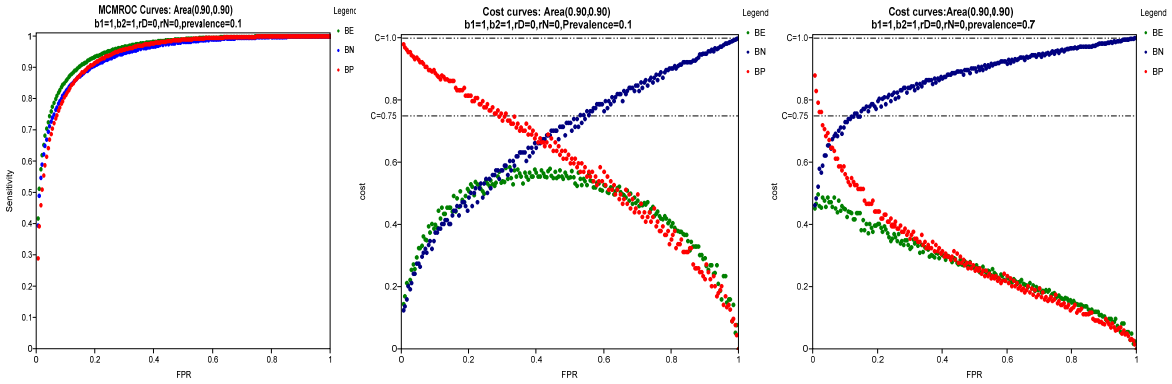

Figure 4.9: The effect of cost constraint on determining the feasible region of the MROC curve for finding optimal operating point

As shown in Table 4.7 and 4.8, when the prevalence was 0.1 and the cost constraints were 0.75 or 1, the optimal points for the BN and BE strategies were the same. This indicates that the cost of testing constraint did not affect the choice of optimal point. As shown in graph 4.10 B, the constraint didn't effect the cost curves of the BE and BN strategies in any way at a low FPR values. In contrast, the optimal points for the BP strategy did change. This was because the shape of the cost curve for BP found above the right diagonal was affected by cost constraint at a low FPR values.

Overall, the cost constraint in this example did not restrict the FPRs that could be considered for the BE strategy, but there were restrictions for the others: FPRs < 0.58 for the BN strategy and >0.25 for the BP strategy.

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Table 4.7: OOP when prevalence was 0.1 and cost of testing no larger than 75%

C/B	Slope	Strategy	GYI	θ_1	θ_2	θ_3	TPR	FPR	Cost
0.01	0.10	BE	0.947	0.72	-0.96	0.36	0.987	0.450	0.550
		BN	0.936	-0.56		-0.72	0.985	0.545	0.740
		BP	0.945	0.52		0.68	0.987	0.475	0.638
0.11	1.00	BE	0.761	1.68	0.04	0.92	0.885	0.125	0.435
		BN	0.730	0.36	.	0.32	0.863	0.135	0.416
		BP	0.667	0.88	.	1.16	0.955	0.290	0.747
0.33	3.00	BE	0.612	2.16	0.48	1.2	0.761	0.050	0.325
		BN	0.579	0.8	.	0.72	0.727	0.050	0.275
		BP	0.093	0.88	.	1.16	0.955	0.290	0.747
1.00	9.00	BE	0.439	2.8	0.96	1.44	0.574	0.015	0.214
		BN	0.412	1.28	.	1.04	0.547	0.015	0.160
		BP	-1.655	0.88	.	1.16	0.955	0.290	0.747

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Table 4.8: OOP when prevalence was 0.1 and no cost constraint

C/B	Slope	Strategy	GYI	θ_1	θ_2	θ_3	TPR	FPR	Cost
0.01	0.10	BE	0.947	0.72	-0.96	0.36	0.987	0.450	0.550
		BN	0.936	-0.6	.	-0.72	0.986	0.555	0.752
		BP	0.945	0.52	.	0.68	0.987	0.475	0.638
0.11	1.00	BE	0.761	1.68	0.04	0.92	0.885	0.125	0.435
		BN	0.730	0.36	.	0.32	0.863	0.135	0.416
		BP	0.730	1.4	.	1.4	0.884	0.155	0.861
0.33	3.00	BE	0.612	2.16	0.48	1.2	0.761	0.050	0.325
		BN	0.579	0.8	.	0.72	0.727	0.050	0.275
		BP	0.545	1.8	.	1.88	0.738	0.065	0.917
1.00	9.00	BE	0.439	2.8	0.96	1.44	0.574	0.015	0.214
		BN	0.412	1.28	.	1.04	0.547	0.015	0.160
		BP	0.331	2.24	.	2.24	0.556	0.025	0.955

For example, the plots in Figures 4.10 identify the feasible region for optimal points when prevalence was 0.1 and the C/B ratio was 0.11, so that the slope was 1.0. The points shown in "green" on the MROC curve satisfied the fixed cost constraint (identified the feasible region). The points shown in "red" on the MROC curve did not satisfy the fixed cost constraint, (the infeasible region). The point that lay in the feasible region in light blue maximized the GYI amongst all points in the feasible region, which was the best operating point that a clinician could use to classify a subject as diseased or not. It was seen that the cost constraints affected the optimal point because it restricted the feasible region. For

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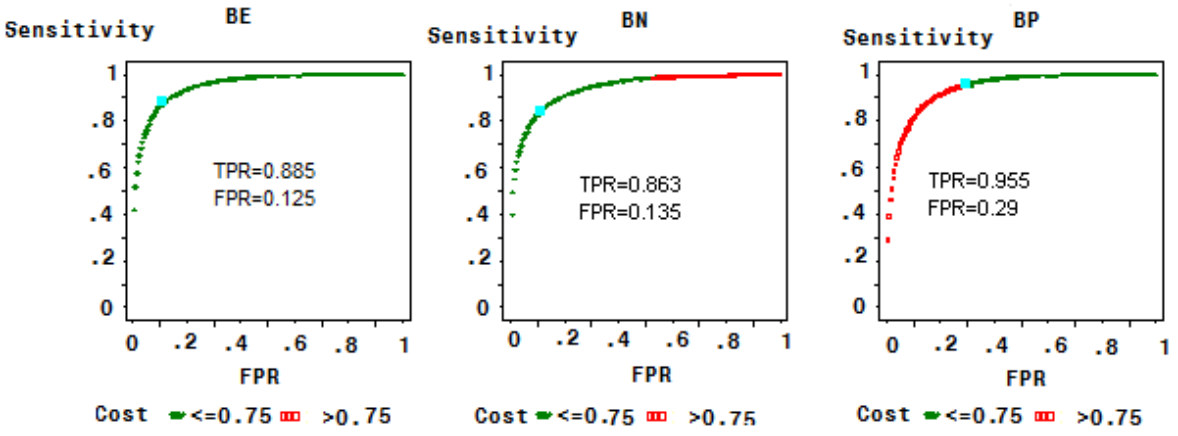
example, in Figure 4.10, a cost constraint of 0.75 provided fewer points to pick from as compared to a cost constraint of 1. Using no cost constraint allowed one to operate at the point with the maximum GYI over the whole curve. In Figure 4.10, the BE and BN strategies each found the same optimal operating point, regardless of cost constraint. This means that both the BE and BN strategies were not affected by the cost constraint. The same graph shows that the BP strategy's optimal operating point was greatly affected by the cost constraint. For other scenarios, this will be different; when a small slope of 0.01 was considered, the C/B ratio was 0.1. At this point, the FPR was less important than the sensitivity, which got very high. However, the FPR increased drastically, making this threshold unacceptable to clinicians concerned with FPR. When a large slope of 1 was considered, the C/B ratio was 1; at this point FPR and sensitivity had the same importance; when the sensitivity decreased, so did the FPR. This resulted in a very low FPR, but also a very low sensitivity, making this threshold unacceptable to clinicians concerned with sensitivity.



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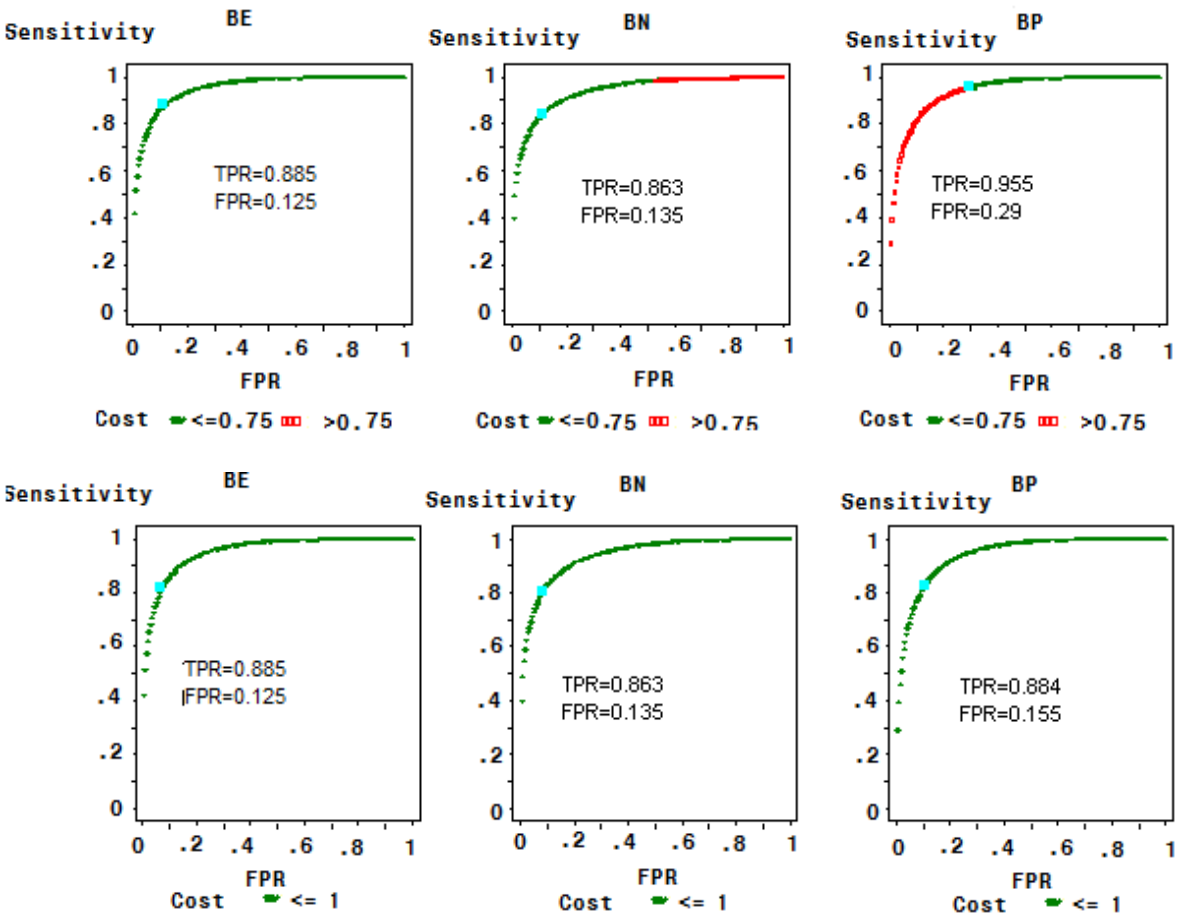

Figure 4.10: The effect of cost constraint in finding the optimal operating point for a prevalence of 0.1 and C/B ratio of 0.11

As shown in Table 4.9 and 4.10, when the prevalence is 0.7 and the cost constraints were 0.75 or 1, the optimal points found by the BP and BE strategies did not change. The BE and BP strategies were not affected by cost constraint at a high FPR because of the shape of the respective cost curves. In contrast, the optimal point found by the BN strategy changed because the shape of the cost curve was affected by cost constraint (see graph 4.11 C).

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Table 4.9: OOP when prevalence was 0.7 and cost of testing no larger than 75%

C/B	Slope	Strategy	GYI	θ_1	θ_2	θ_3	TPR	FPR	Cost
0.23	0.10	BE	0.943	0.84	-0.88	0.36	0.984	0.420	0.297
		BN	0.857	0.4		0.20	0.871	0.145	0.748
		BP	0.941	0.6		0.68	0.985	0.455	0.297
1.00	0.43	BE	0.849	1.4	-0.24	0.64	0.941	0.215	0.379
		BN	0.809	0.4		0.20	0.871	0.145	0.748
		BP	0.834	1.08		1.20	0.937	0.240	0.421
2.33	1.00	BE	0.760	1.8	0.12	0.88	0.875	0.115	0.440
		BN	0.728	0.4		0.36	0.853	0.125	0.748
		BP	0.729	1.4		1.40	0.884	0.155	0.514
7.00	3.00	BE	0.611	2.16	0.48	1.2	0.761	0.050	0.472
		BN	0.577	0.8		0.72	0.727	0.050	0.654
		BP	0.543	1.8		1.88	0.738	0.065	0.636

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Table 4.10: OOP when prevalence is 0.7 and no cost constraint

C/B	Slope	Strategy	GYI	θ_1	θ_2	θ_3	TPR	FPR	Cost
0.23	0.10	BE	0.943	0.84	-0.88	0.36	0.984	0.420	0.297
		BN	0.932	-0.56		-0.56	0.982	0.510	0.907
		BP	0.941	0.6		0.68	0.985	0.455	0.297
1.00	0.43	BE	0.849	1.4	-0.24	0.64	0.941	0.215	0.379
		BN	0.824	0.04		0.04	0.925	0.235	0.818
		BP	0.834	1.08		1.20	0.937	0.240	0.421
2.33	1.00	BE	0.760	1.8	0.12	0.88	0.875	0.115	0.440
		BN	0.729	0.36		0.32	0.863	0.135	0.756
		BP	0.729	1.4		1.40	0.884	0.155	0.514
7.00	3.00	BE	0.611	2.16	0.48	1.2	0.761	0.050	0.472
		BN	0.577	0.8		0.72	0.727	0.050	0.654
		BP	0.543	1.8		1.88	0.738	0.065	0.636

The plots in Figure 4.11 examines high prevalence (e.g 0.7), as compared to Figure 4.10 which examines low prevalence (e.g 0.1). The feasible region for optimal points increased for BP and decreased for BN. For example, in Figure 4.11, a cost constraint of 0.75 provided fewer feasible points as compared to a cost constraint of 1. In this case, BN's optimal operating point was affected by cost constraint. The formulas for BE and BP strategies individually found the optimal point for the strategies at the same place on the MROC curve, regardless of cost constraint. This means that neither were affected by the cost constraint, even with a cost constraint of 0.50 (see Table 4.11). The exception to this

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pattern occurred with a slope of 3 and a C/B ratio of 7; the BE strategy selected the same point twice, regardless of cost constraint, but BP selected two different points.

Table 4.11: OOP when prevalence was 0.7 and cost of testing was no larger than 50%

C/B	Slope	Strategy	GYI	θ_1	θ_2	θ_3	TPR	FPR	Cost
0.23	0.1	BE	0.943	0.84	-0.88	0.36	0.984	0.420	0.297
		BN	0.488	1.4		1.16	0.489	0.010	0.486
		BP	0.941	0.6		0.68	0.985	0.455	0.297
1	0.43	BE	0.849	1.4	-0.24	0.64	0.941	0.215	0.379
		BN	0.485	1.4		1.16	0.489	0.010	0.486
		BP	0.834	1.08		1.2	0.937	0.240	0.421
2.33	1	BE	0.760	1.8	0.12	0.88	0.875	0.115	0.440
		BN	0.479	1.4		1.16	0.489	0.010	0.486
		BP	0.726	1.24		1.52	0.890	0.165	0.467
7	3	BE	0.611	2.16	0.48	1.2	0.761	0.050	0.472
		BN	0.459	1.4		1.16	0.489	0.010	0.486
		BP	0.405	1.28		1.52	0.885	0.160	0.479

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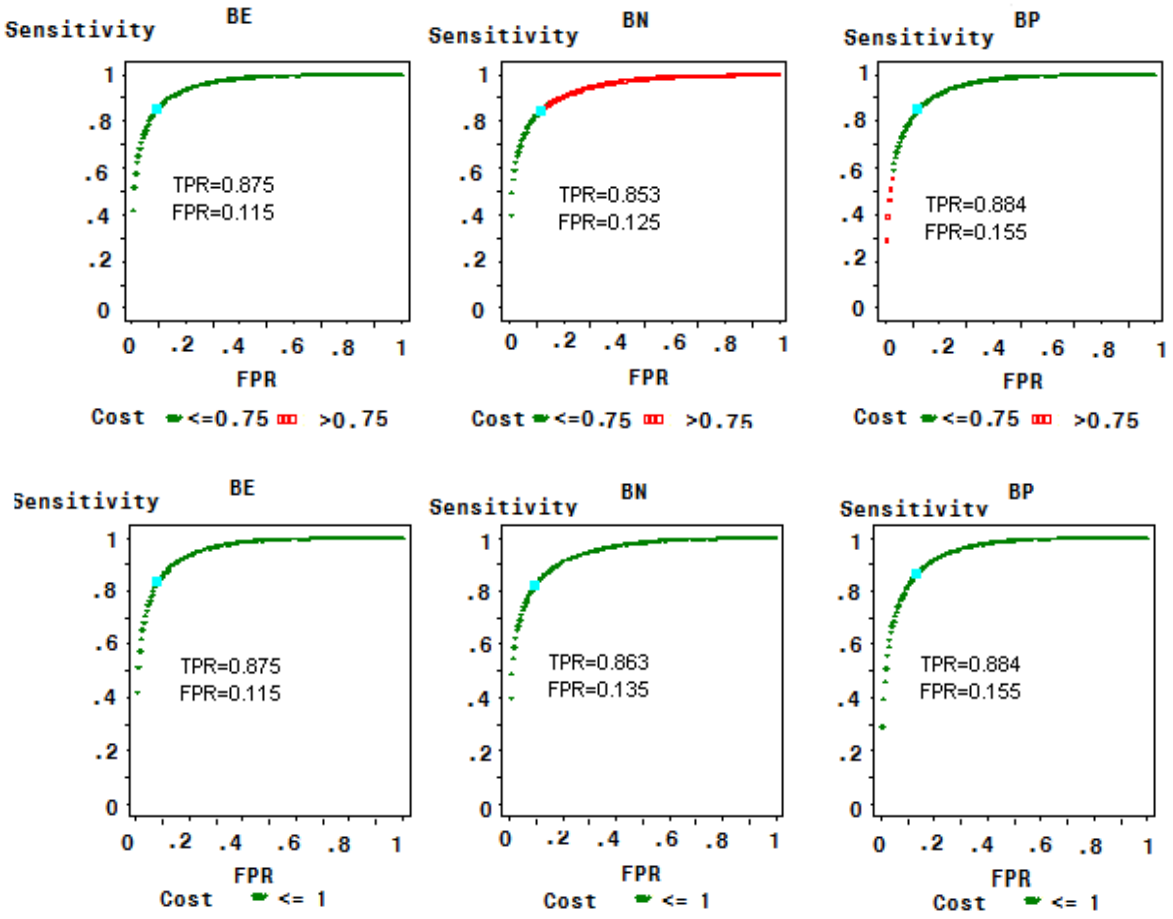

Figure 4.11: The effect of cost constraint in finding the optimal operating point for a prevalence of 0.1 and C/B ratio of 2.33

4.5 Examining the test thresholds

The BE strategy performed in three different ways as compared to the BP and BN strategy.

- The BE strategy produced results similar to the BN strategy
- The BE strategy produced results similar to the BP strategy
- The BE strategy produced results similar to the BN strategy and the BP strategy for some FPR values

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In the next sections, the characteristics of these three performance types will be explored. The following examines the instances in which the BE strategy produced similar results as the BN strategy. The section following that will examine the instances in which the BE strategy produced similar results as both the BN and BP strategy for some FPRs.

4.5.1 The BE strategy produced results similar to the BN strategy

Figure 4.12 shows the MROC and cost curves when b_1=2 and b_2=2. The BE and BN strategies had the same accuracy with MROC curves higher than the BP strategy. In terms of cost, the BE and BN strategies had the same cost, lower than the BP strategy for FPR < 0.35; and the BP strategy was less costly than the BN and BE strategies for FPR > 0.35.

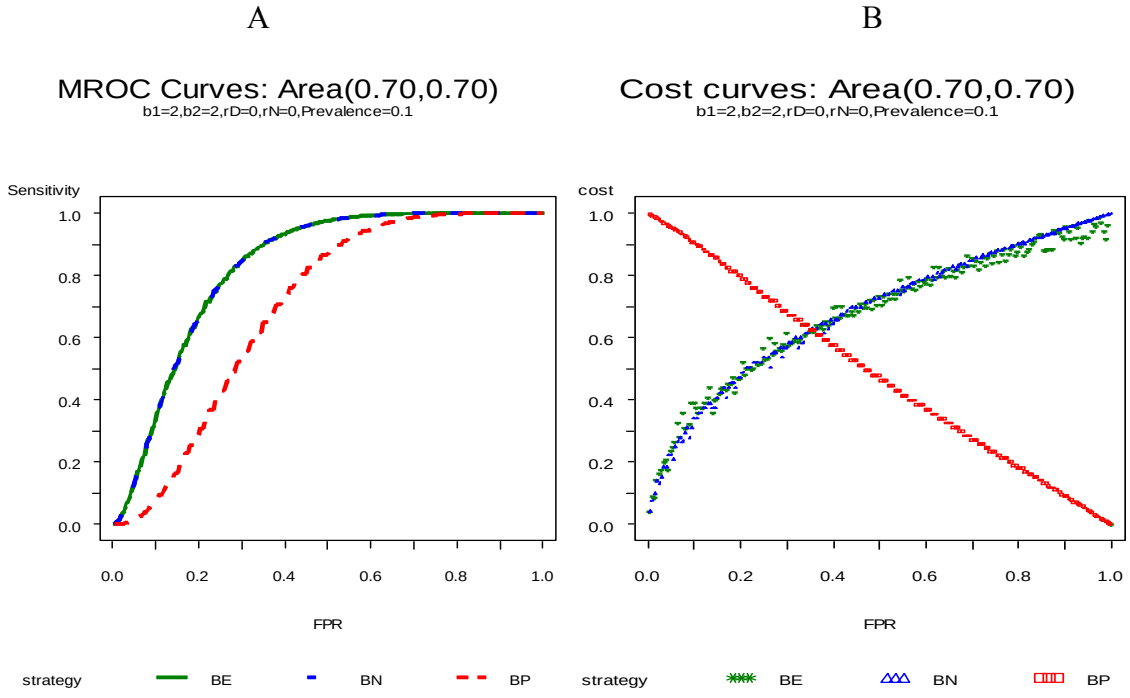

Figure 4.12: MROC curves and cost curves for (b_1=2 ,b_2=2), (AUC_1 = 0.70, AUC_2 = 0.70), (ρ_D=0,ρ_N=0), and prevalence of 0.1

Looking at this example, one might suspect that the decision rule for the BE strategy was similar to that for the BN strategy: i.e. the upper threshold for test 1 in the BE

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strategy (θ_1) was very large, and the lower threshold (θ_2) was similar to the test 1 threshold for the BN strategy. If that were the case, then the BE strategy would essentially send all subjects with a value for test 1 greater than θ_2 to a second test (similar to the BN strategy). To investigate this, the thresholds were graphed. Figure 4.13 A plots the test 1 thresholds of the BE strategy (vertical axis) vs. the threshold of the BP strategy (horizontal axis). Graph B plots the test 1 thresholds of the BE strategy (vertical axis) vs. the threshold of the BN strategy (horizontal axis). Graph C plots the test 1 thresholds of the BE strategy (vertical axis) vs. FPR (horizontal axis). The diagonal line on the first two graph connecting the two points (0, 0) and (5, 5), was used to determine if test thresholds were identical. Points falling on the diagonal line indicate test thresholds were identical. The points in Figure 4.13 A were not on the diagonal line. The threshold values for θ_1 from BE were large (approaches $+\infty$), and the thresholds θ_1 from BP and θ_2 from BE were similar for small threshold values but deviated off diagonal as the threshold increased. This indicates that both test thresholds for the BE strategy were different than the thresholds for test 1 of the BP strategy. This was as expected. Conversely, Figure 4.13B shows that the pattern that θ_2 takes was a diagonal pattern, meaning that the BE strategy's thresholds (θ_2) were equivalent to the BN strategy's thresholds (θ_1). The same graph shows θ_1 from the BE strategy approaching +3. This was equivalent to $+\infty$ because for this normal distribution, only a small percent of the distribution was larger than that 3. Taken together, this means decisions for Test 1 for the BE strategy were similar to those for the BN strategy. Graphs in Figure 4.13A and B do not show the change of Test thresholds over FPR. The graph in Figure 4.13C shows for all FPR values, the threshold θ_1 from the BE

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strategy approaches $+\infty$, meaning that the BE strategy produced similar results as the BN strategy.

A B C

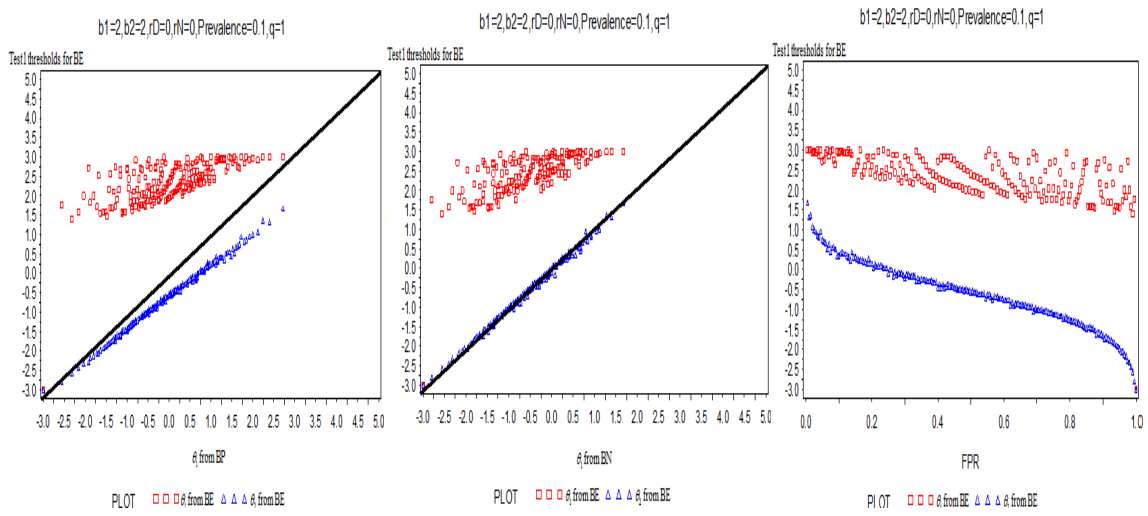

Figure 4.13: Comparison of threshold values: θ_2 from the BE strategy similar to θ_1 from the BN strategy

4.5.2. The BE strategy produced similar results as the BP strategy and the BN strategy for some FPRs

Figure 4.14 focuses on MROC curves and cost curves. When b_1=1 and b_2=1, the competing strategies have the same accuracy. In terms of cost, the BE and BN strategies have a similar cost for FPR < 0.30, lower than the BP strategy; the BE and BP strategies have a similar cost for FPR > 0.58, lower than the BN strategy; and the BE strategy was less costly for FPR between 0.30 and 0.58.

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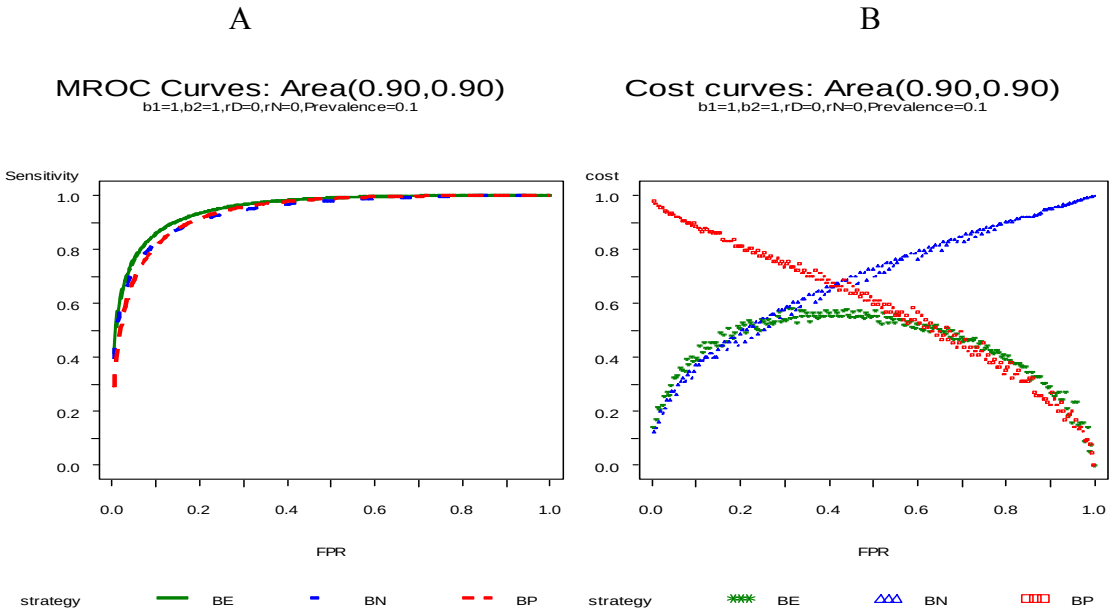

Figure 4.14: MROC curves and cost curves for (b_1=1 ,b_2=1), (AUC_1 = 0.90, AUC_2 = 0.90), (ρ_D=0,ρ_N=0), and prevalence of 0.1

Here, the cost above curves show that the BE strategy produced similar results to both the BN and BP strategies for some FPR values. It was shown graphically that the BE strategy produced similar results as the BN strategy if θ_1 from the BE strategy approaches $+\infty$ and that the BE strategy produced similar results as the BP strategy if θ_2 from the BE strategy approaches $-\infty$. It was true that, in Figure 4.14, the BE strategy produces similar results to both the BN and BP strategies for some FPR values, but it was not certain that their thresholds were equivalent until the threshold values were examined. Figure 4.15 A shows that θ_2 from the BE strategy versus θ_1 from the BP strategy do not form an equivalent diagonal but θ_1 from the BE strategy versus θ_1 from the BP strategy was close to a diagonal line, meaning that the BE strategy's thresholds θ_1 were close to the BP strategy's thresholds θ_1. Figure 4.15 B shows that θ_1 from the BE strategy versus θ_1

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from the BN strategy do not form a closer equivalent diagonal but θ_2 from the BE strategy versus θ_1 from the BN strategy was close to a diagonal line, meaning that the BE strategy's thresholds θ_2 were close to the BN strategy's thresholds θ_1. Figure 4.15 A and B do not show the change of Test thresholds over FPR values. The graph in Figure 4.15 C shows for all FPR values, the thresholds θ_1 approaches $+\infty$ at a low FPR values, and θ_2 approaches $-\infty$ at a high FPR values. This means that the BE strategy produced similar results as the BP strategy at a high FPR values and the BE strategy produced similar results as the BN strategy at a low FPR values.

A B C

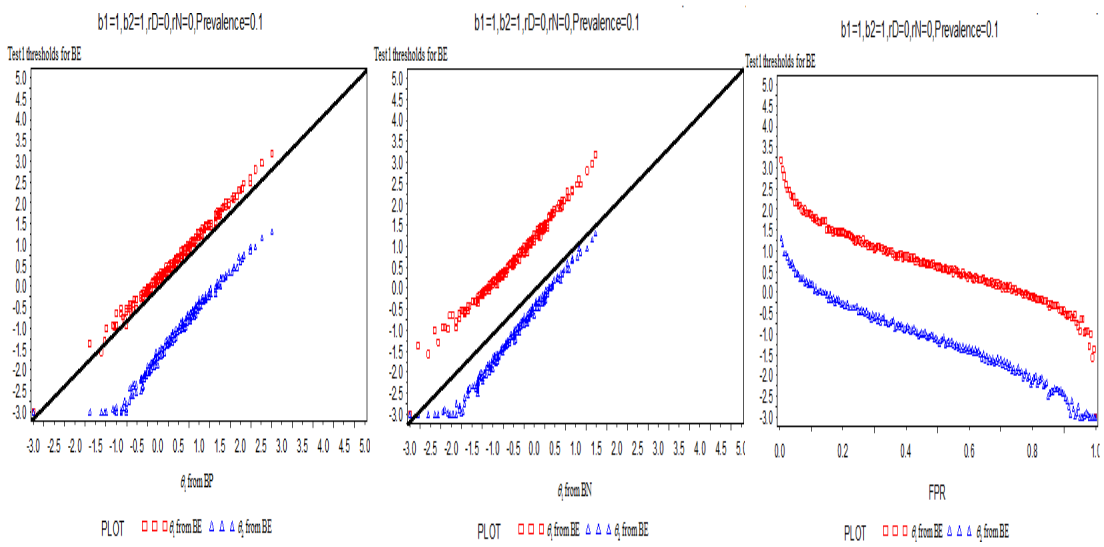

Figure 4.15: Comparison of threshold values: θ_2 from the BE strategy similar to θ_1 from the BN strategy and θ_1 from the BE strategy similar to θ_1 from the BP strategy

4.6 Final notes

This research used the increment of 0.04 for the Test thresholds because a similar pattern emerged with finer increments such as 0.03 and 0.02 and the conclusion was the same in terms of the properties of the three strategies. Figures 4.16 through 4.18 shows that the

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MROC curves were identical, regardless of the thresholds increment. For cost curves, the differences between increments were hard to see on a graph. Since the curves with finer increments take longer for a computer to process, if we get similar results from a large increment, there was no need to take time computing the finer one.

In real life data, however, a slight change in increment could affect the results; therefore, a finer increment could be considered. Chapter 6 applied the techniques developed in this research thus far to actual data, where test results might be transformed to satisfy normality. For this reason one can use finer increments to evaluate the diagnostic test.

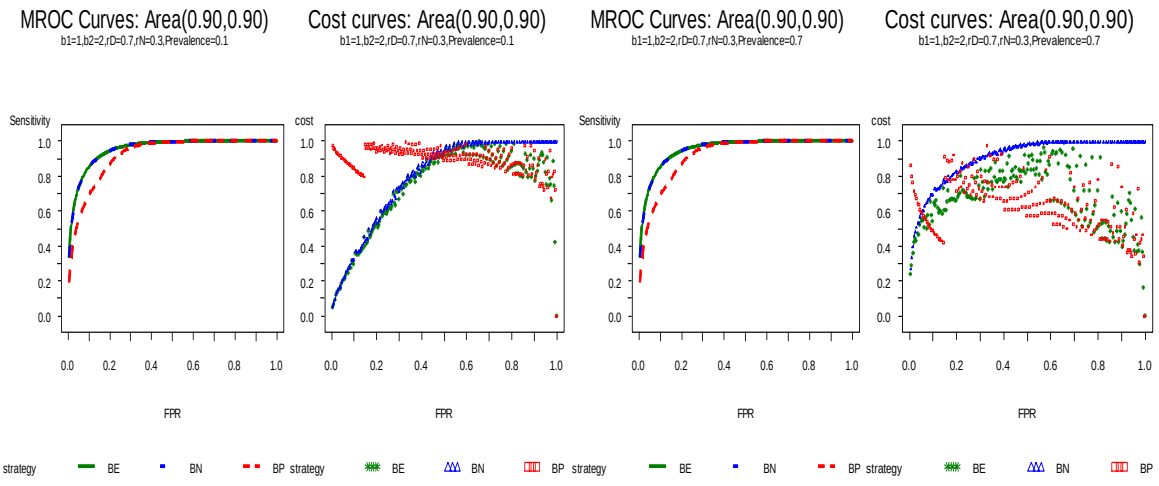

Figure 4.16: Thresholds increment 0.04

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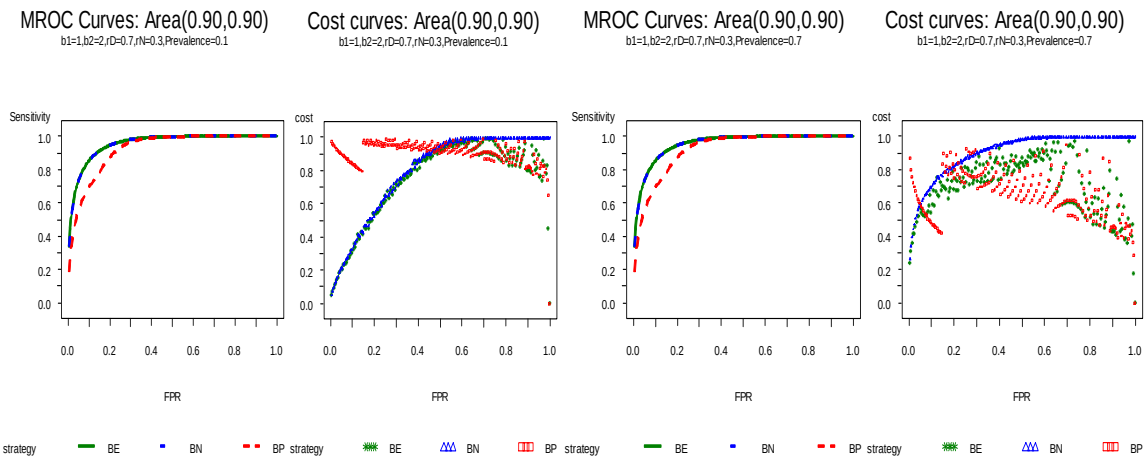

Figure 4.17: Thresholds increment 0.03

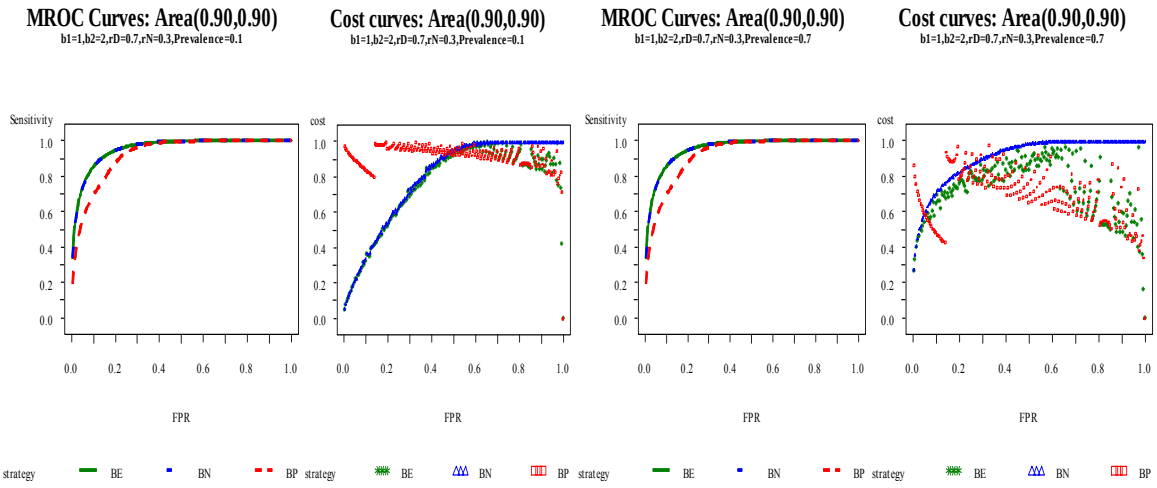

Figure 4.18 : Thresholds increment 0.02

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Chapter 5: Results II

5.1 The acceptable accuracy (q)

When evaluating two medical tests with continuous results to diagnose a disease or medical condition, the use of sequential testing will be associated with more than one threshold that produces sensitivity values that are essentially equivalent or slightly lower than the maximum sensitivity. These values may lower the cost of a sequence of tests by reducing the number of subjects that need the second test to reach a diagnosis. This is an important goal, as the second test could be costly (painful, expensive, etc.) to the patient. To achieve this, a minimal acceptable value of sensitivity must be determined ($q \times \max[TPR(\underset{\sim}{\theta})]$ is defined at the end of this section). The steps for generating the minimal acceptable tolerance will be described in section 5.2.

In past research, a variety of methods have been proposed to combine two tests in non-sequential order to increase diagnostic accuracy, for example (e.g., Pepe and Thompson, 2000; Su and Liu, 1993). There, both tests were measured on all subjects. Hence they do not consider lessening the cost of testing and burden on the patient because they cannot avoid administering Test 2. The motivation behind sequential testing is that it allows for reduced costs by reducing the number of subjects that need Test 2. Yet, little research has been done in terms of how the cost of testing is related to a sequence of tests. Chapters 3 and 4 address this issue. It was shown there that cost could remain high for all strategies. This chapter seeks to further reduce the cost of testing. Therefore, it is important to consider the minimal acceptable accuracy, as this will allow for a reduction in cost. In Chapter 3 the acceptable accuracy (q) was defined as the percent of the accuracy

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(tolerance) that clinicians are willing to accept. It used $q \times \max[TPR(\theta)]$ to set an acceptable tolerance on sensitivity. When q=1, the MROC curve from Chapter 4 was produced, which did not consider lowering sensitivity in any way. To reduce cost and still retain acceptable accuracy, a slightly lower value for q, such as that which corresponds to a 0.1% reduction in TPR (equivalent to q=0.999) or perhaps a slightly lower sensitivity, such as 5% reduction (equivalent to q=0.95) could be considered. Since the value of q=0.999 was very close to 1, the MCMROC curve of q=0.999 was virtually identical to MROC curve in Chapter 4 (equivalent to q=1), where there was no reduction in sensitivity.

The previous chapter sought to calculate the lowest cost associated with the MROC curve. Chapter 4 also made clear another issue: discontinuity occurred in some graphs in which two sets of thresholds produced the same FPR values, but slightly different TPR values with different associated costs. The effect of this was shown in Chapter 4. At times, cost remained high for some of the strategies and in some cases, the cost curves spread over the graph creating 'fuzz' and discontinuity. It will be seen in this chapter that this problem was partially solved by sacrificing a very small percentage of sensitivity, such as up to 0.1% reduction; in some situations; though, it was found that heavy discontinuity could not be solved even by sacrificing a larger percentage, such as up to 5% reduction.

5.2 Generating Minimum Cost Maximum ROC (MCMROC) Curve

This section re-introduces Minimum Cost Maximum ROC (MCMROC) Curve, which directly incorporates the effect of cost, which was first introduced in Chapter 3. The MCMROC curve showed the results of accepting a lower sensitivity within q of the maximum sensitivity, which was associated with the lowest cost. Figure 5.1 demonstrates the steps that generate the MCMROC curve. Graph A of Figure 5.1 was produced by

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estimating sensitivity and FPR for all possible combinations of threshold values. Graph B of Figure 5.1 identifies the maximum sensitivity for each $\text{FPR} \le t$, where t was 200 equally spaced values between 0 and 1 (increment of 0.005). It was represented here as a black line. Graph C of Figure 5.1 was produced by setting a minimal acceptable value of sensitivity by considering sensitivity values greater than or equal to $q \times \max[\text{TPR}(\theta)]$. Graph D of Figure 5.1 identifies sensitivity with lowest cost at each $\text{FPR} \le t$. If one observes multiple sensitivities with the same lowest cost, the maximum sensitivity at each $\text{FPR} \le t$ was found. Represented in red was the MCMROC curve for q=0.95.

A B C D

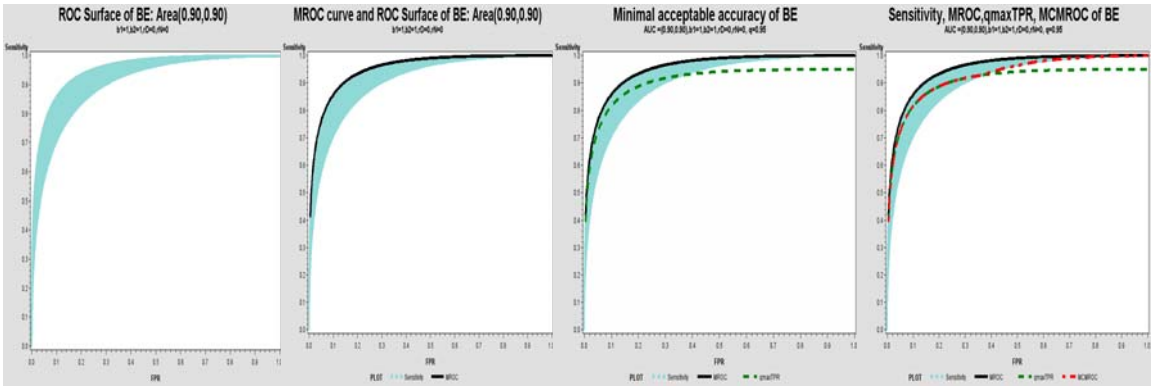

Figure 5.1: Steps in producing the MCMROC curve for q=0.95

5.3 The effect of parameter settings

Appendix C1 through C5 shows how the MCMROC and cost curves change when a slightly lower sensitivity (up to 5% reduction) was accepted. Appendix B1 through B5 shows how the MCMROC and cost curves changed when a negligible lower sensitivity (up to 0.1% reduction) was accepted. Similar to Chapter 4, it was seen that the AUC values, correlation, and standard deviation had an effect on the MCMROC and cost curves. In Chapter 3, it was proven that the BE strategy was never the worst compared to the BN and BP strategies. However, this does not apply when $q < 1.0$.

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In this chapter, a lower sensitivity ($q < 1.0$) was being allowed. The graph series in Appendix B1 through B5 shows that AUC values, standard deviation, prevalence, and correlation had an effect on cost curves for a reduction in sensitivity of 0.1%. The graph series in Appendix C1 through C5 shows that AUC values, standard deviation, prevalence, and correlation had an effect on MCMROC/cost curves for a reduction in sensitivity of 5%. This chapter will mainly focus on the effect of q, rather than the effect of other parameters on the MCMROC and cost curves, such as AUC value, standard deviation, prevalence, and correlation. The primary focus, then, was to find how q affected the MCMROC curves and cost curves and the choice of optimal point.

5.4 The effect of q on the MCMROC curves

Figure 5.2 uses the values q=1, q=0.999, and q=0.95, respectively. In graphs A1, A2 and A3, the MCMROC curve for q=0.999 was virtually identical to the MROC curve when q=1. The patterns of the three *q*'s shown in these graphs did not change the ways in which the MCMROC curves of each strategies differed from one another (the exception to this is noted in Graph C3). Only when up to 5% reduction in sensitivity was used, the MCMROC curves could be close to the minimal acceptable value of sensitivity. In graphs B1, B2 and B3, when there was 0.1% reduction, there were no clinically relevant changes to the graph. Graphs C1, C2 and C3 show that, by sacrificing up to 5% sensitivity, the MCMROC curve was lowered. Looking at graph C3, it was seen that, of our three strategies, the sensitivity of the BN strategy was the lowest, while the BP and BE strategies had a negligible difference in sensitivity. This occurred when the (b_1=0.5, b_2=0.5). See Appendix A, B, and C for situations in which this happened.

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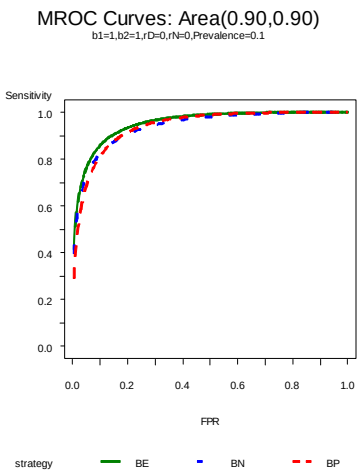
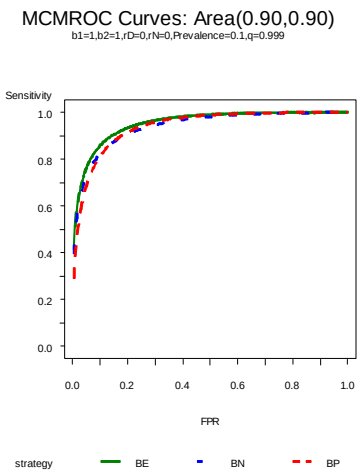
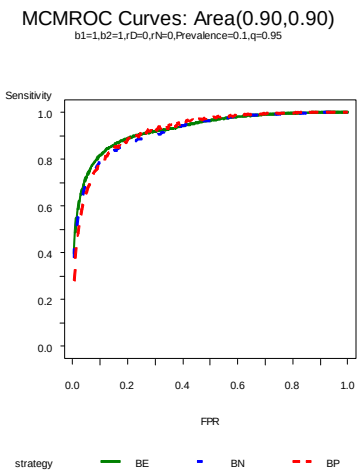
A1



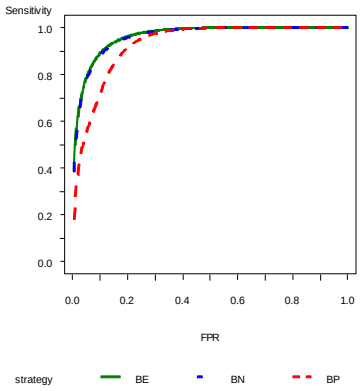
B1



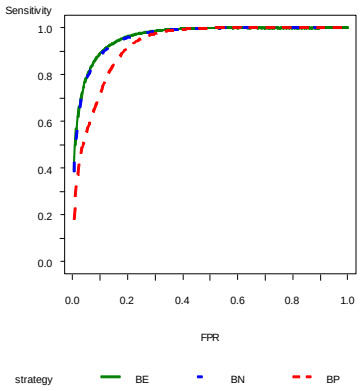
C1



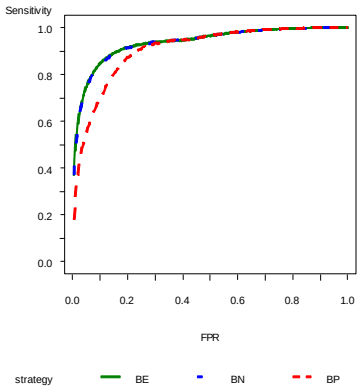
A2



B2



C2



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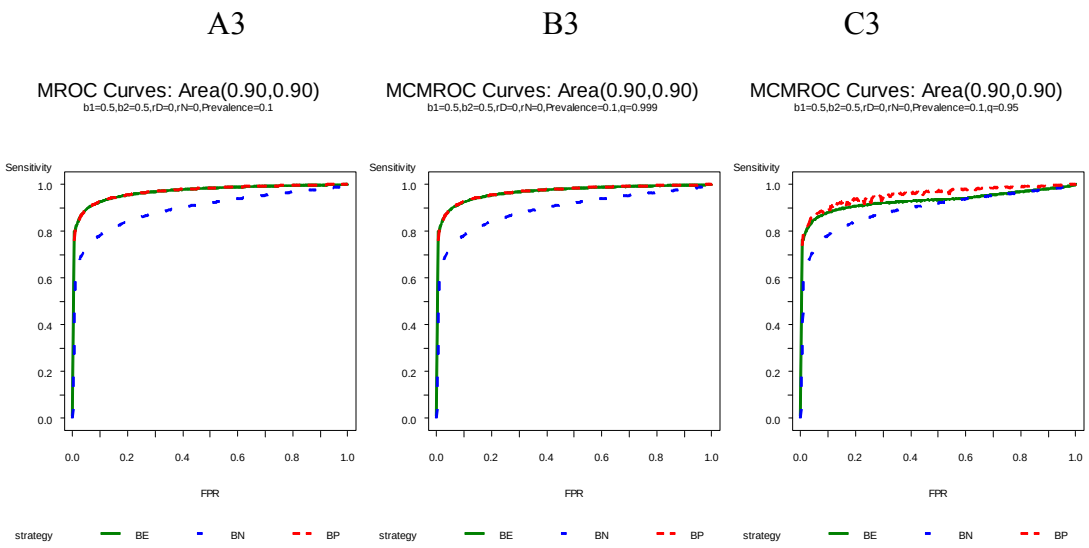

Figure 5.2: The effect of q on the MCMROC curves

5.5 The effect of q on the cost curves

Figure 5.3 uses the values q=1, q=0.999, and q=0.95, respectively. In graphs A1, A2, A3, and A4, one can see how the cost remained high when no sensitivity was sacrificed (q=1). In comparison, it can be seen that, in graphs B1, B2, B3, and B4, the cost was significantly lowered by accepting a slightly lower sensitivity (up to 0.1% reduction), thus a great reduction in cost can be achieved by sacrificing a sensitivity of 0.1%. It should be noted, though, (see B1, B2, B3, and B4) that the cost was mostly reduced for higher FPR values. Thus, there was a good reason to find a way to reduce cost at low FPR values, because clinicians may want to choose a point to "operate" the test that has small FPR values. The cost can be lowered further by allowing a larger reduction of sensitivity, as long as such a reduction was considered appropriate. Graphs C1, C2, C3, and C4 show that, by sacrificing 5% sensitivity, cost can be lowered for small FPR values. The cost of the BE strategy was severely lowered at small FPR values and then dropped to a cost of zero, eliminating the need for the second test. Also, a reduction can be seen when (AUC_1=0.7, AUC_2=0.7).

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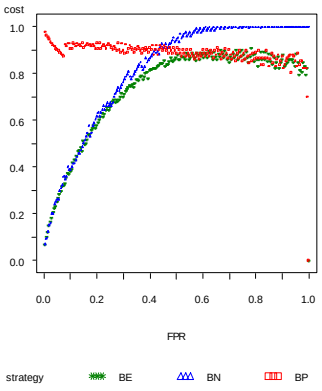
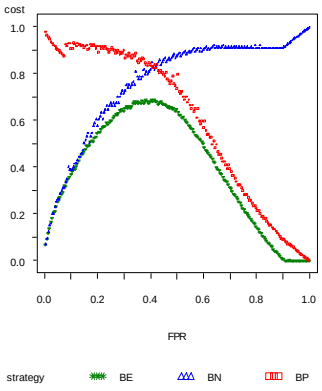
However, the same plots showed that cost can remain high for either the BN or BP strategy, though in different directions and depending on the FPR value.

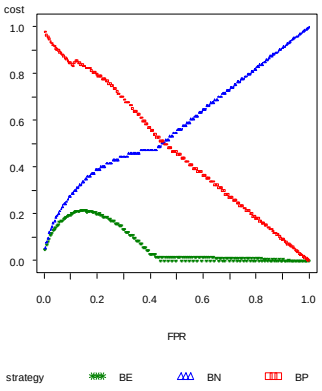
A1



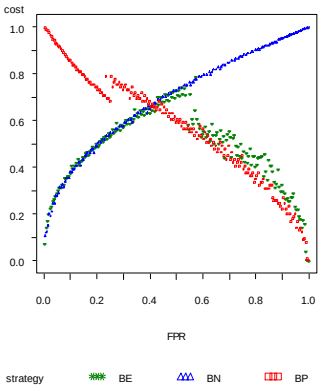
B1



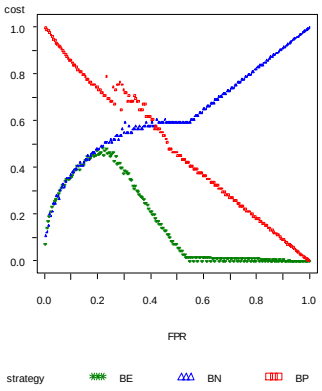
C1



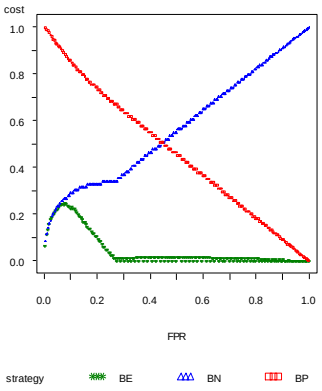
A2



B2



C2



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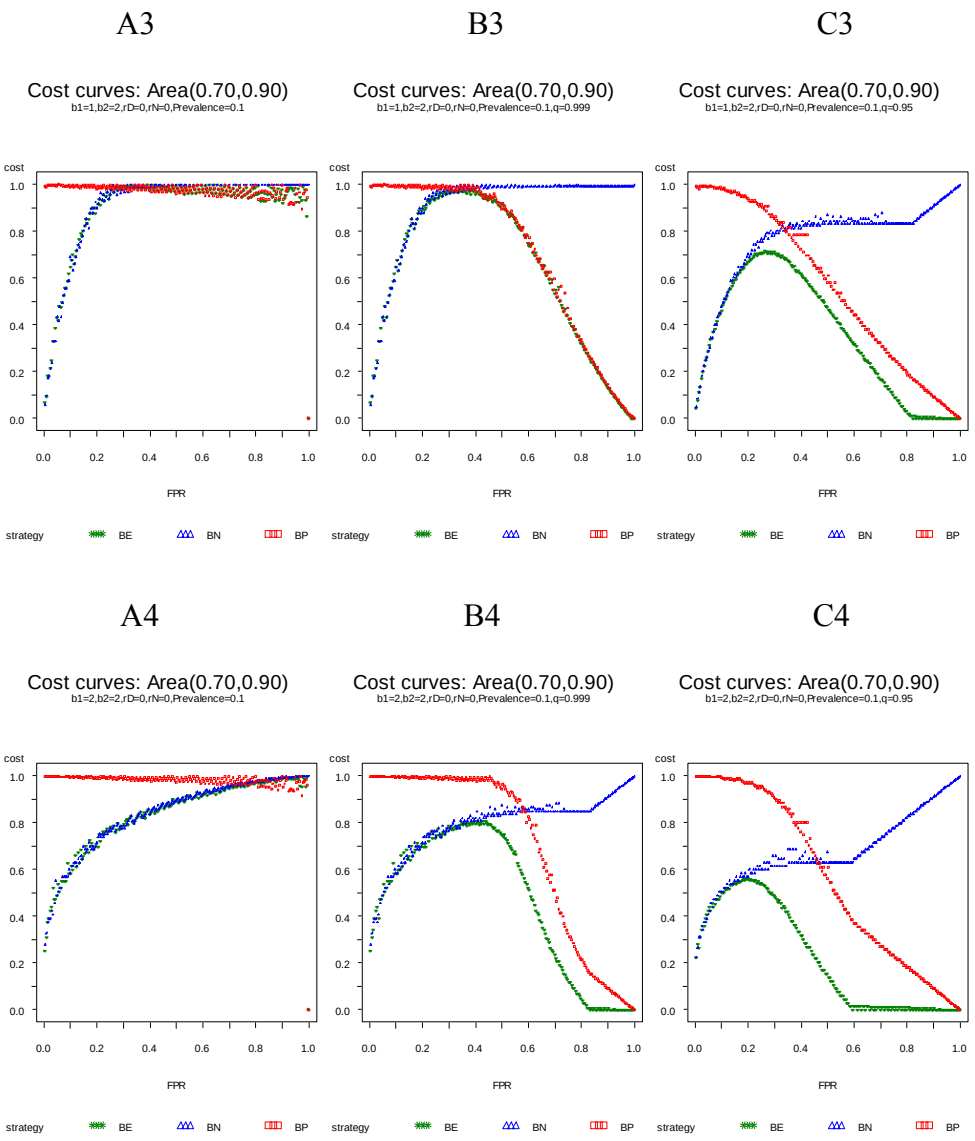

Figure 5.3: The effect of q on the cost curves of the BE, BN, and BP strategies

Reducing the percent of the accuracy (q) can lower cost in all strategies, however there were some exceptions. In Figures 5.4 A1, A2, A3, C1, C2, and C3, when b_1=0.5 and b_2=0.5 and with varying values of the AUC for test 1 and 2, the cost curves of the BP and BE strategies stayed close or the same even with up to 0.1% reduction and is reduced for a 5% reduction in sensitivity. However, for the BN strategy, in graphs B1, B2, and B3 of Figure 5.4, the cost curves stayed much the same even with up to 5% reduction.

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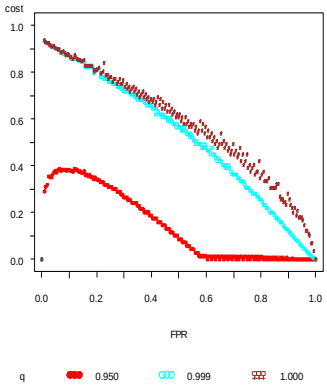
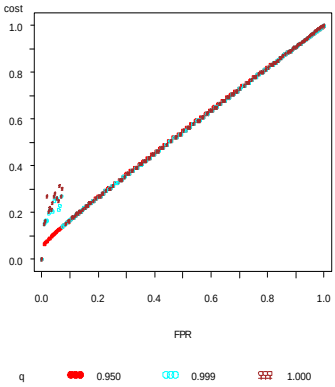
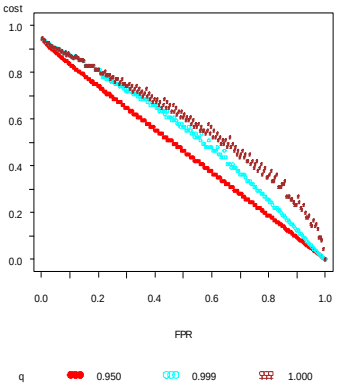
A1



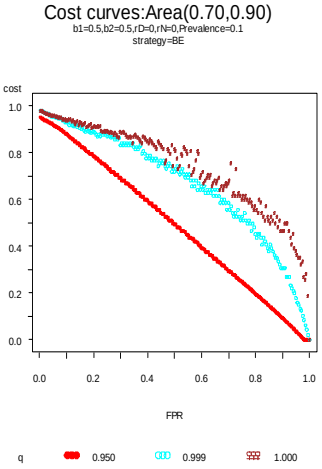
B1



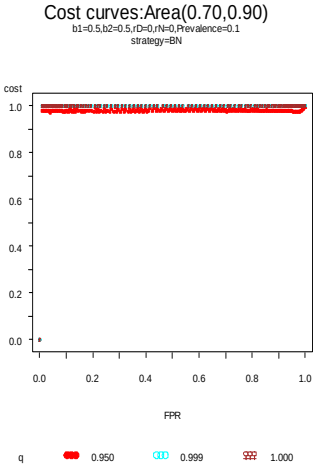
C1



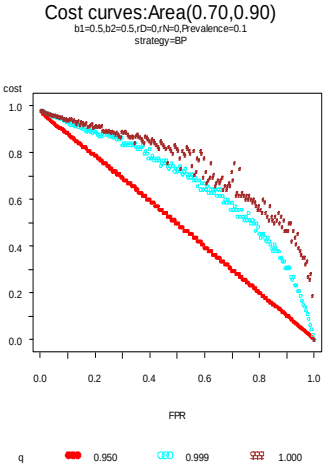
A2



B2



C2



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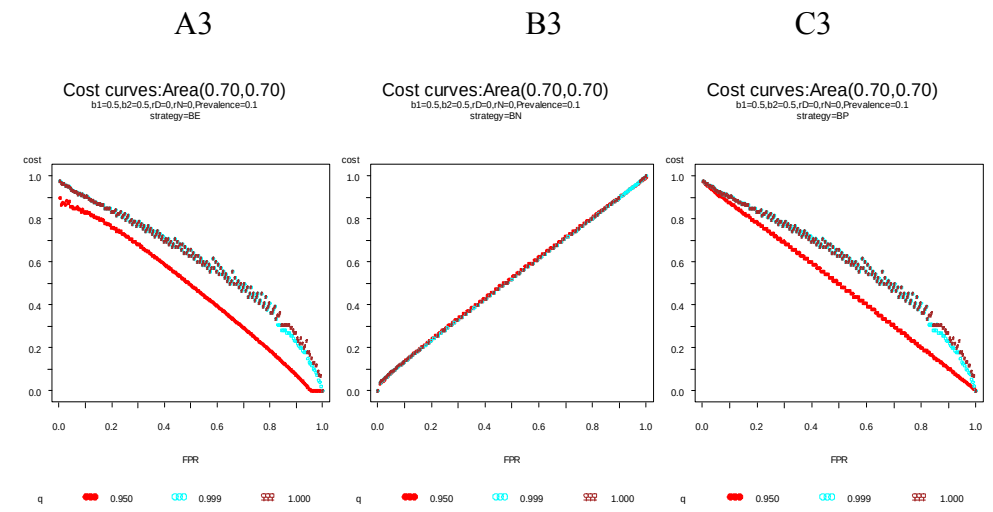
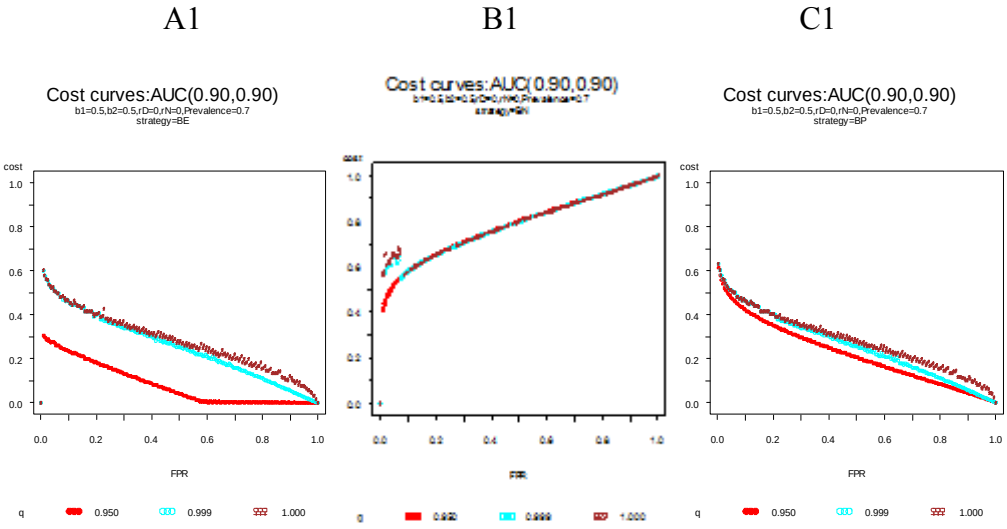


Figure 5.4 Exception to effect of q on the cost curves of each individual strategy with prevalence of 0.1

For the same parameters above, one can examine the effect of prevalence on cost curves. In comparison to the graph above with low prevalence (e.g., 0.1), cost for the BP and BE strategies decreased when prevalence was high (0.7); while in contrast, cost increased for the BN strategy. This was true for identical or differing AUC values. See Figure 5.5.



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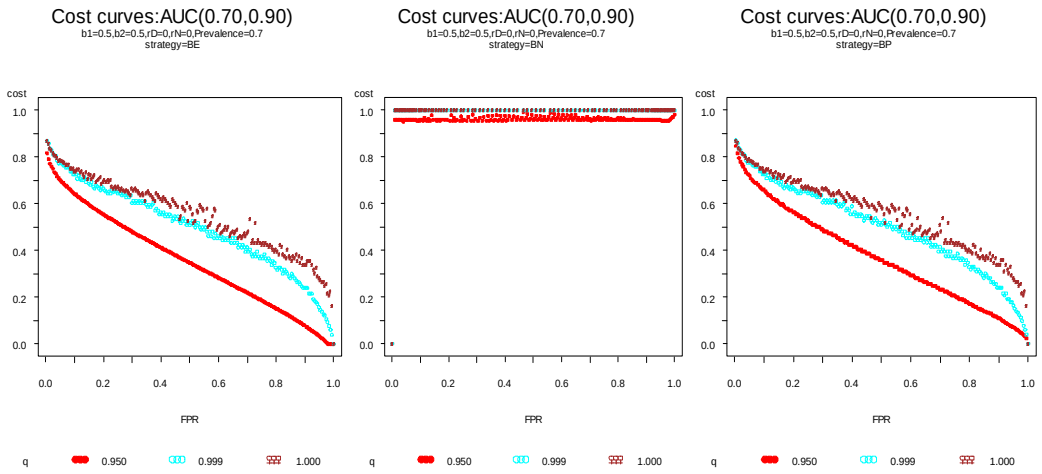
A2 B2 C2



A3 B3 C3

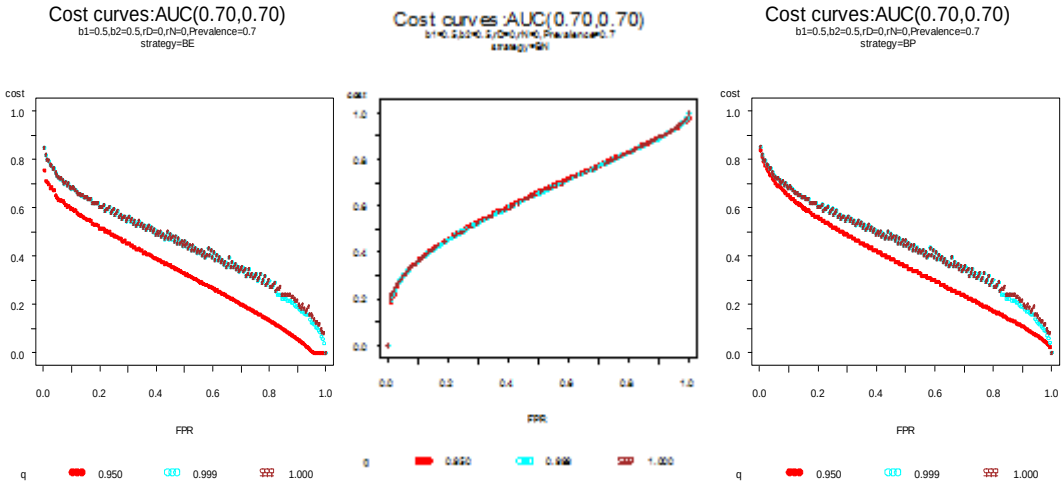


Figure 5.5 Exception to effect of q on the cost curves of each individual strategy with prevalence of 0.7.

A similar result can be observed for the corresponding MCMROC curves graphed in Figure 5.6 that were associated with the cost curves in Figure 5.4.

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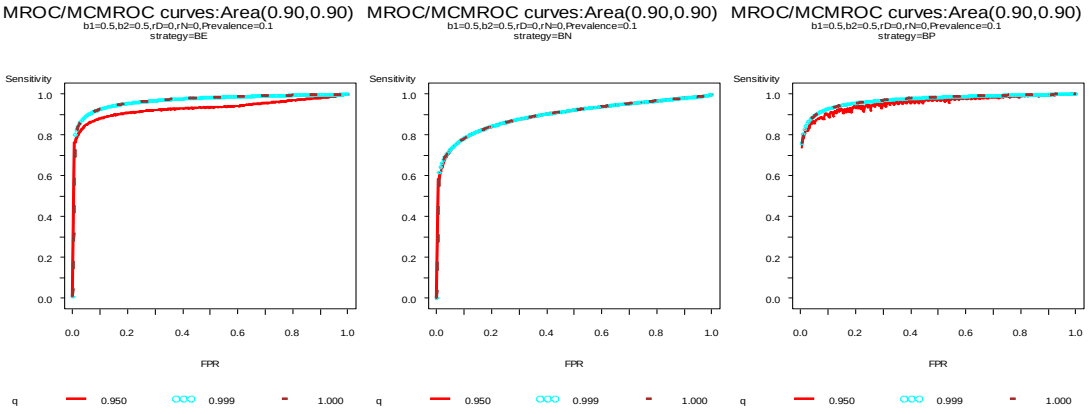
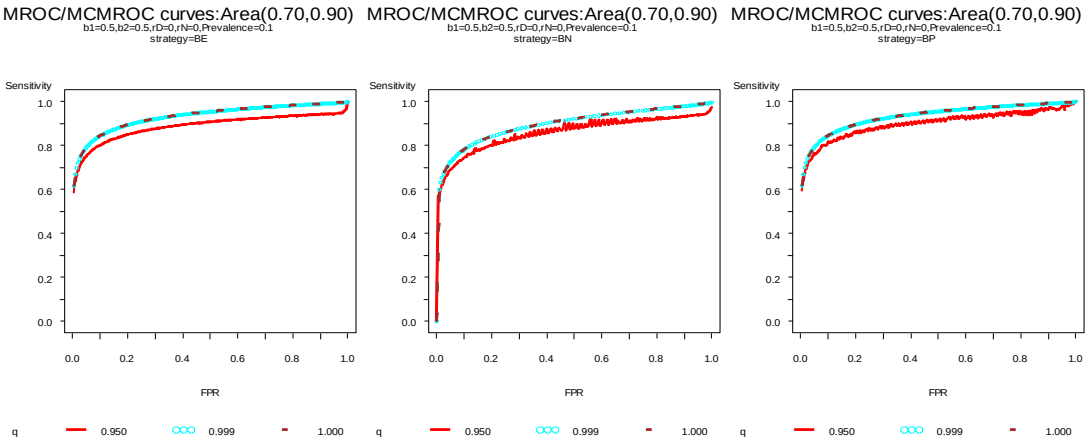
A1 B1 C1



A2 B2 C2



A3 B3 C3

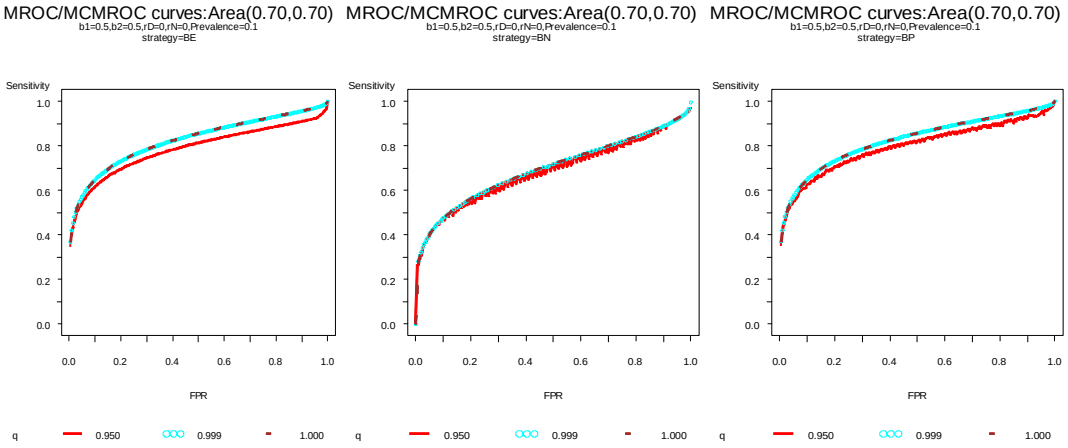


Figure 5.6 Exception to the effect of q on the MCMROC curves of each individual strategy

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It is recommended, therefore, if sensitivity is important to a researcher, to use a higher value of q rather than no reduction, such as q=0.999, as this retains the same MROC curve with the possibility of a reduced cost. If the second test is painful or expensive for the patient, q=0.95 could reduce the cost significantly.

5.6 Cost reduction

One might want to determine how much cost was saved by accepting slightly lower sensitivity. Comparing the cost associated with the MROC curve versus the MCMROC curve through calculating the percent reduction in cost can help visualize the cost-improvement created by accepting a slightly lower accuracy. The percent reduction in cost was calculated by

$$\text{Percent Reduction} = \left(\frac{(\text{CMROC} - \text{CMCMROC})}{\text{CMROC}} \right) \times 100\% \qquad (5.1)$$

where CMROC was the cost associated with MROC curve and CMCMROC was the cost associated with MCMROC curve. Figure 5.7 compared cost corresponding to 0% reduction in sensitivity against 0.1% reduction in sensitivity (i.e. q=1.0 vs q=0.999). The BE strategy had a high percent reduction in cost for FPR > 0.20, and it achieved up to a 100% reduction in cost when FPR > 0.50, eliminating the need for a second test. The BP strategy had no cost reduction at low FPRs (e.g FPR < 0.35) and the percent reduction in cost increased for FPR > 0.35 but did not achieve 100% cost reduction. There was minimal change to cost for the BN strategy.

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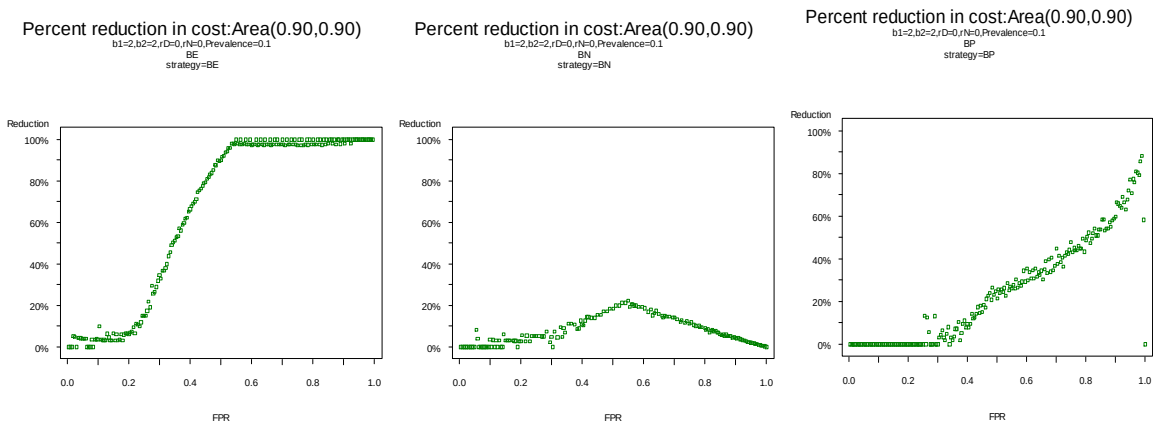

Figure 5.7: Cost reduction of 0% and 0.1% reduction in cost for the BE, BN, and BP strategies, respectively.

Figure 5.8 compared 0% reduction in cost against 5% reduction in cost. In comparison with the other strategies, the BE strategy had a greater percent reduction in cost for FPR > 0, and it achieved up to a 100% reduction in cost when FPR > 0.25, eliminating the need for a second test. The BP strategy had no cost reduction at low FPRs (e.g FPR < 0.25) and the percent reduction in cost increased for FPRs > 0.25, though it did not achieve 100% reduction. There was minimal change to cost for the BN strategy. Only the BE strategy achieved 100% cost reduction, meaning, no subjects required the second test.

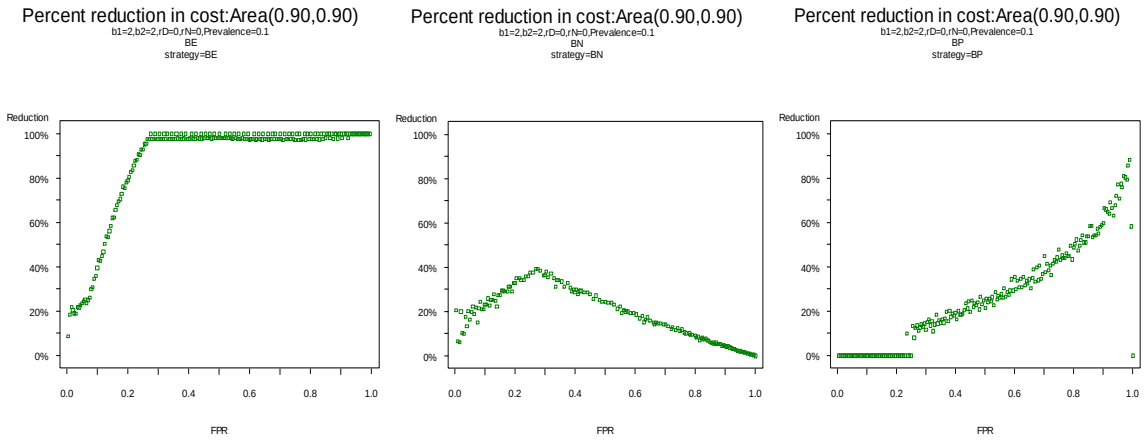

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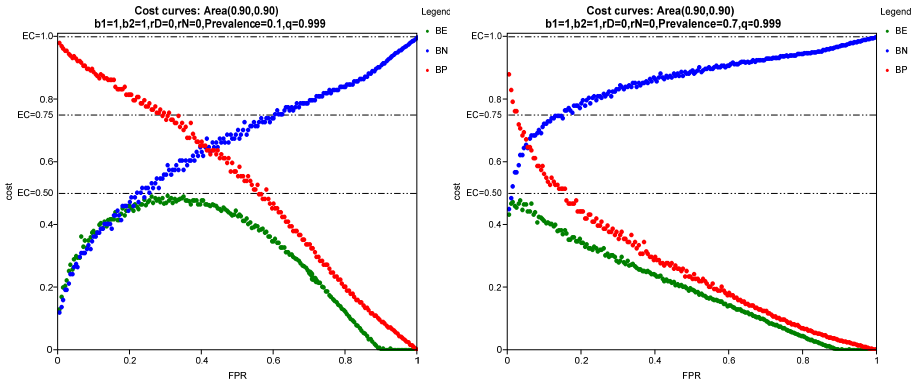
Figure 5.8: Cost reduction of 0% reduction against 5% reduction in cost for the BE, BN, and BP strategies, respectively.

5.7 The effect of q on the choice of optimal point

As demonstrated in Figure 5.9 A2 and B2 when q=5%, the need for the second test was eliminated for the BE strategy for some FPR values. The cost curves of the BN and BP strategies went in opposite directions, until they reach (0, 1) for the BP strategy and (1, 0) for the BN strategy. The cost curve for the BE strategy was lowered significantly in all FPR regions. For example, when q=0.95, all points on the MCMROC curve were considered to be in the feasible region (discussed in Chapter 4) for the BE strategy under 75% and 100% of the sample, meaning that there were more choices from which to find the optimal operating point. In comparison, the choice of optimal points for the BN and BP strategies was limited by the fixed constraint on cost of testing (see Figure A1 and A2). As the cost curve for the BN and BP strategies went up, there was more of an upward spread of points, meaning that Test 2 was required more frequently.

A1 B1



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A2 B2

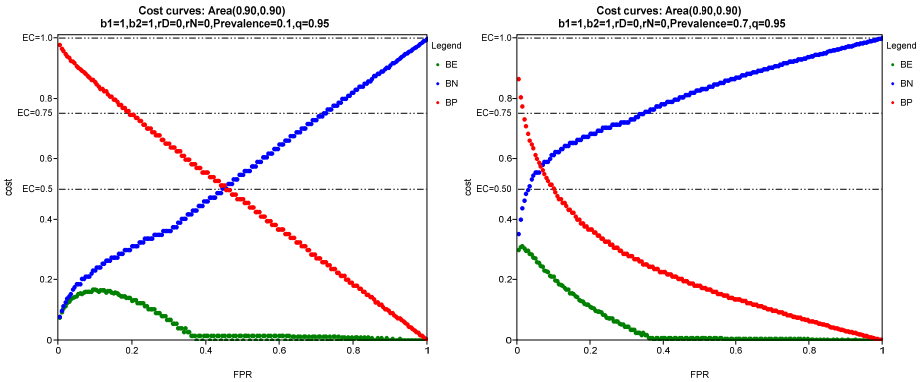

Figure 5.9: the effect of cost constraint on determining OOP, q=0.999 and q=0.95, respectively.

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Chapter 6

6.1 Outline

This chapter will apply the techniques developed in this research to collected data. The data application will be described using an introduction and data analysis section. Data analysis will provide descriptive statistics on the original distributions by group (diseased, non-diseased): N per group, means, standard deviations, minimums, maximums, and medians. Comparison between diseased and non-diseased individuals will be completed by the two-sample T-test. Normality within group will be assessed, and if necessary, transformations using the Box-Cox transformation will be used to improve normality. Using means and standard deviations of the diseased and non-diseased populations, sensitivity, FPR (1-specificity), and cost for each sequential strategy (BP, BN and BE) will be estimated. Graphical displays for the MROC, MCMROC and cost curves for each strategy will be generated and compared, including test thresholds. The optimal operating point for each strategy will be calculated using the Generalized Youden Index (GYI).

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Application: Diabetes in Pima Indians

6.2 Introduction

Type 1 (insulin-dependent) diabetes occurs when the body's immune system attacks the beta cells in the pancreas that produce insulin. Normally, insulin helps the sugar from ingested food absorb into body cells. As no insulin is produced by the pancreas in people with Type 1 diabetes, these patients need daily insulin shots in order to control their blood sugar level. This form of diabetes is generally found during the younger age or teenage years, but may occur in adults under 30. Type 2 (non-insulin-dependent) occurs when fat and muscle cells are unable to properly use the body's insulin. This is also known as insulin resistance. Some Type 2 diabetics need insulin to control their blood sugar but many can keep their blood sugar at satisfactory levels by changes in diet, food choices, diabetes pills, or regular exercise, that help the body to use insulin more efficiently. This form generally occurs in adults older than 40 years, though it can occur in teenage years. The inheritance pattern in Type 2 diabetes is further complicated, as environmental factors, genetics, and lifestyle play a major role in the overall risk (Harris M., 1999; Bener A., Zirie M., and Al-Rikabi, 2005; Romao I. and Roth J., 2008).

The Pima Indians of Arizona are known to have a high incidence of Type 2 diabetes and obesity. In this tribe, diabetes incidence has been reported to be as high as 40-50% in adults **(**Knowler et al, 1978). Data on Native American women of Pima heritage, aged 21 and over was studied by Smith *et al*, 1988, and was made publicly available through the UCI Machine Learning data depository (Keogh, Merz and Blake, 1998). These data consist of diagnostic information for 768 women; 268 with diabetes, and 500 without diabetes. The outcome investigated was whether or not the patient showed symptoms of diabetes,

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classified as showed by World Health Organization (WHO) criteria. The WHO criterion for classifying individuals as diabetic is a 2-hour postprandial plasma glucose ≥ 11.1mmol/l (WHO, 2003). This criteria considers both fasting and 2-hour blood samples, and classifies glucose tolerance as diabetes if (fasting glucose ≥7.0 or 2-h postprandial plasma glucose ≥11.1 mmol/l).

The original study collected many measurements with which to examine diabetes in this population. For the purposes of the sequential testing in the research in this dissertation, two screening tests were considered: the first test combines anthropometric measurements of height and weight to produce a single measurement, the body mass index, BMI, kg/m^2 (variable denoted by X_1). BMI is the ratio of weight (in kilograms) to the square of height (in meters). The second test was a more costly blood test, the plasma glucose concentration in mg/dl (variable denoted by X_2 and hereafter referred to as glucose in this chapter). There were no missing values in these data but there were n=16 recorded BMI or glucose with implausible results which were deleted (11 had a 0 BMI and 5 had a 0 glucose value). Deletions of these cases resulted in a sample of 752 women (264 with diabetes and 488 without diabetes) for analysis.

6.3 Data Analysis

Data were presented as mean ± SD for continuous variables (BMI and glucose) and as number and percentages (n and %) for diabetes status (Table 6.3.1). Among the 752 women, 264 (35.11%) were diagnosed with Type II diabetes (BMI =35.37± 6.63 kg/m^2 with BMI ranging between 22.9 and 67.1 kg/m^2, glucose = 142.49 ±29.64 mg/dL with glucose ranging between 78.0 and 199.0 mg/dL). There were 488 (64.89%) women diagnosed as non-diabetic (BMI = 30.88 ± 6.57 kg/m^2 with BMI ranging between 18.2 and

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57.3 kg/m^2, glucose = 110.83 ± 24.84 mg/dL with glucose ranged between 44.0 and 197.0 mg/dL).

Table 6.1: Summary of BMI and plasma glucose concentration by diabetes status

					Quartiles		
Group	n(%)	Test	SD	Mean	25%	50%	75%
Diabetes	264(35.11)	BMI	6.63	35.37	30.83	34.25	38.65
		Glucose	29.64	142.49	119	140.5	167
Non-Diabetes	488(64.89)	BMI	6.57	30.88	25.6	30.1	35.38
		Glucose	24.84	110.83	93	107.5	125

The two-sample *t*-test demonstrated significant differences in BMI and glucose levels between those with and without diabetes, (*p*-value < 0.0001 for both BMI and glucose). Further, the empirical ROC curve of each individual test suggested that the two tests had discriminating ability superior to chance (see Figure 6.1), because tests of the hypothesis, H_0: AUC=0.5, were found to be significant for each test (*p*-value <0.0001). As given in Table 6.2, the nonparametric AUC value for BMI is 0.684 (95% CI: 0.647, 0.722) and for glucose was 0.792 (95% CI: 0.759, 0.825). BMI did not appear to be as good a discriminator between those with and without diabetes as glucose because the CI around the AUC shows that BMI did not have higher AUC than glucose which can also be observed in Figure 6.1.

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Table 6.2: AUC and confidence intervals (CI) of BMI and plasma glucose concentration.

				Asymptotic 95% CI	
Test	AUC	Std. Error	Sig.	Lower Bound	Upper Bound
Glocose	0.792	0.017	<0.0001	0.759	0.825
BMI	0.684	0.019	<0.0001	0.647	0.722

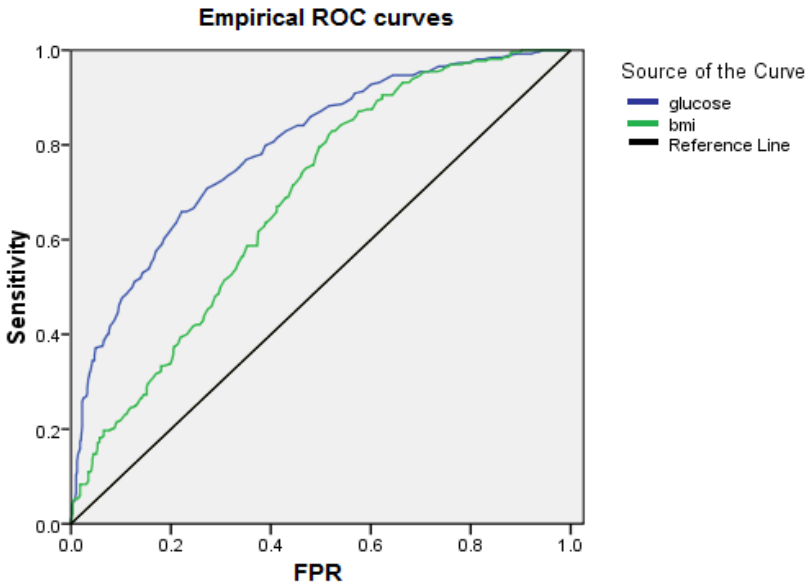

Figure 6.1: Empirical ROC curves for predicting diabetes groups from BMI and plasma glucose concentration.

The scatter plot in Figure 6.2 shows that women with diabetes had, in general, higher values of both BMI and glucose than those without diabetes. A Spearman correlation was used because the data were not normally distributed, as shown later in this section. There were weak Spearman correlations between BMI and glucose in these data, (*rho* = 0.1) for the diabetes group and (*rho* = 0.1) for the non-diabetes group. Because these points overlapped, finding perfect separation between the values for those with and without diabetes was not possible.

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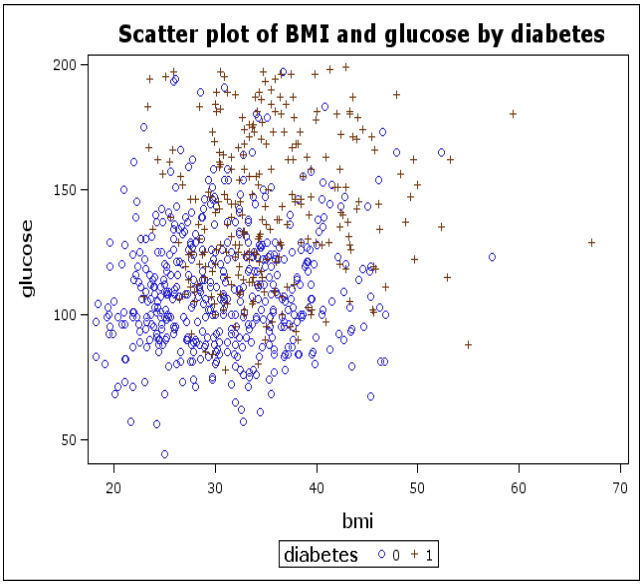

Figure 6.2: Scatter plot of plasma glucose concentration and BMI by diabetes groups.

The right panel of Figure 6.3 is the histogram of glucose by diabetes status and the left panel of Figure 6.3 is the histogram of BMI by diabetes status. These plots further demonstrated that women with diabetes tended to have higher BMI and higher glucose compared with those without diabetes. The BMI and glucose distributions in Figure 6.3 appeared to be deviated from a normal distribution. This was confirmed by the skewness of 0.65 for glucose and 0.46 for BMI, where skewness of zero indicates that the distribution was symmetric, a property of the normal distribution. Also the BMI and glucose for the diabetes group seemed a bit far from a normal distribution. This was confirmed by the skewness of 0.08 for glucose and 1.04 for BMI. One can formally test normality using Skewness/Kurtosis and Shapiro-Wilk tests (Tables 6.3 and 6.4). The *p*-value for these statistical tests was less than alpha, 0.05. This indicated the BMI and glucose were not normally distributed. The normal quantile plot, shown in Figure 6.4, suggests this. The normal quantile, shown in black, slightly deviates from the normality boundary. Therefore,

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a transformation was needed so that the distributions for BMI and glucose can follow a binormal distribution.

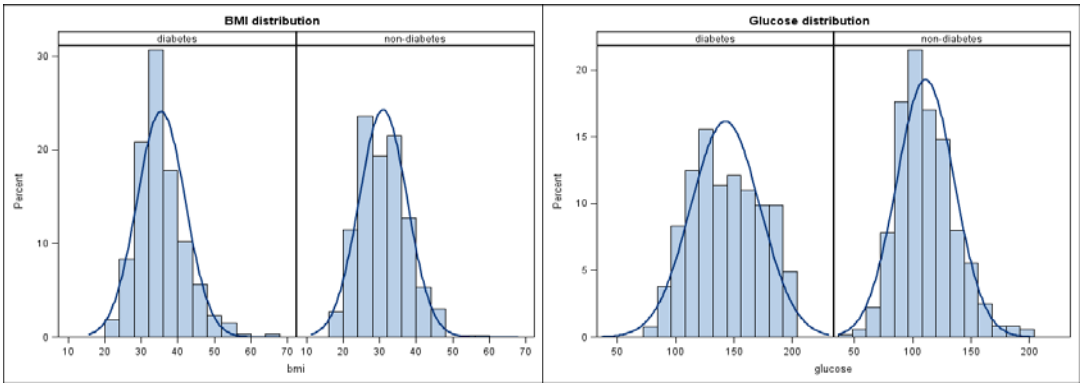

Figure 6.3: Histograms of BMI and plasma glucose concentration by diabetes groups

Non-diabetic Diabetic

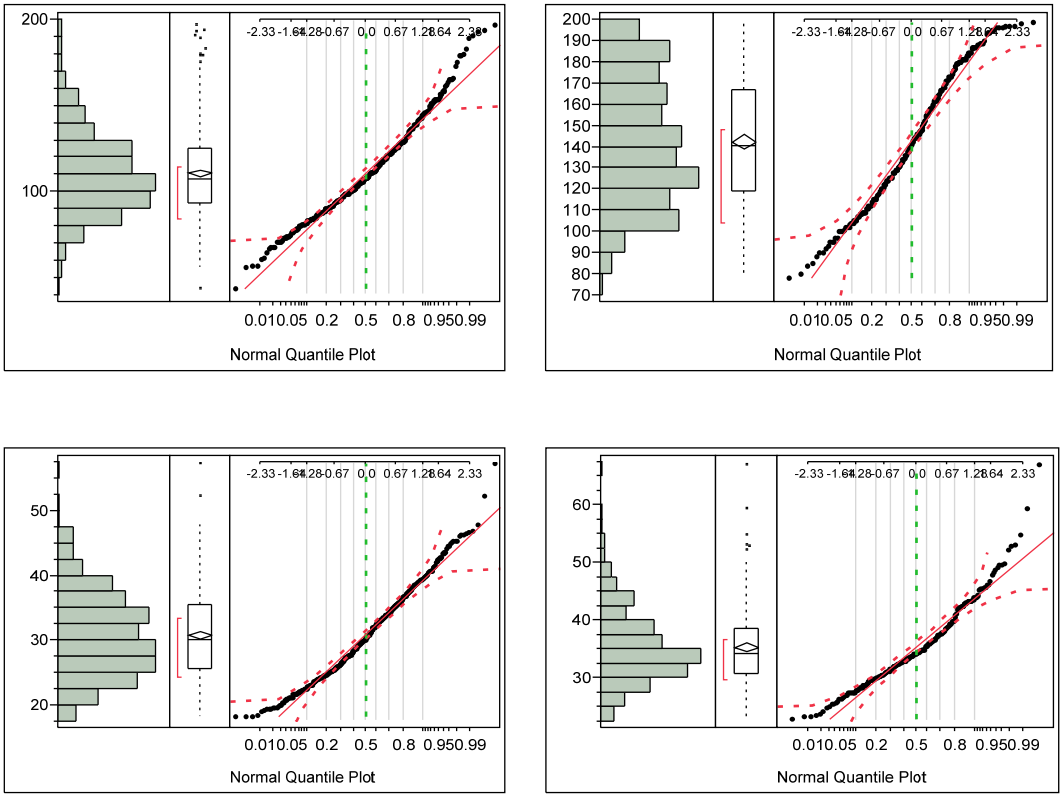

Figure 6.4: Normal Quantile plot of plasma glucose concentration and BMI by diabetes groups, respectively.

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Table 6.3: Skewness/Kurtosis tests for Normality

Group	Test	Pr(Skewness)[1]	Pr(Kurtosis)[2]	adj chi[3]	Prob>chi[4]
Non-Diabetes	Glucose	0.0000	0.0152	29.2700	0.0000
	BMI	0.0001	0.9737	14.3700	0.0008
Diabetes	Glucose	0.6005	0.0000	31.9300	0.0000
	BMI	0.0000	0.0001	39.3600	0.0000

[1] p-value to test (H_0:skewness = 0); [2] p-value to test (H_0: Kurtosis = 0) [3] adj chi is the chi-square test;

[4]p-value for combining skewness and kurtosis;

Table 6.4: Shapiro-Wilk W test for normal data

Group	Test	W[1]	V	Z[2]	Prob>z
Non-Diabetes	Glucose	0.9749	8.2730	5.0740	0.0000
	BMI	0.9804	6.4620	4.4810	0.0000
Diabetes	Glucose	0.9750	4.7660	3.6430	0.0001
	BMI	0.9478	9.9420	5.3580	0.0000

[1] Shapiro–Wilk test; [2] z statistic

Using the Box Cox transformation, the distributions were closer to normal. For the diabetes distributions, the skewness was -0.198 for glucose and 0.41 for BMI. For the non-diabetic distributions, the skewness was 0.085 for glucose and -0.005 for BMI. The

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histograms of transformed data seemed closer to the normal distribution (see Figure 6.5). The Box-Cox transformation equation that accomplished this was $X_1^{TRANS} = \left((\text{BMI})^{0.05} - 1\right) / 0.05$ for BMI and $X_2^{TRANS} = \left((\text{glucose})^{0.221} - 1\right) / 0.221$ for glucose. Since glucose and BMI values were transformed, results were not directly interpretable. Thus, after analysis, it is useful to reverse this process to interpret results in the original units. The following were the equations used to transform the data back to the original: $\text{BMI} = \left(0.05 \times X_1^{TRANS} + 1\right)^{\frac{1}{0.05}}$ and $\text{glucose} = \left(0.221 \times X_2^{TRANS} + 1\right)^{\frac{1}{0.221}}$. The ratio of disease and non-disease standard deviations (b), were estimated from the standard deviations of transformed data, for BMI $b_1 = \hat{\sigma}_N / \hat{\sigma}_D = 0.25/0.21 = 1.2$ and for glucose $b_2 = 0.63/0.63 = 1.0$. Again, there were weak Pearson correlations between BMI and glucose in these data, (*rho* = 0.1) for the diabetes group and (*rho* = 0.1) for the non-diabetes group.

Then sensitivity and FPR were estimated based on normal distribution CDFs by varying the threshold values for BMI and glucose. These were evaluated by varying BMI and glucose values in increments of 0.001. Selection of the ranges for threshold values was determined by examining data within 3 standard deviations of the diseased and non-diseased distributions. Specifically, the lower and upper intervals for the non-diseased and diseased populations were given by:

$$\left[\min\left(\mu_N - 3*\sigma_N, \mu_D - 3*\sigma_D\right), \max\left(\mu_N + 3*\sigma_N, \mu_D + 3*\sigma_D\right)\right]$$

Using the values in Table 6.5, this approach suggested a lower bound of 2.97 and an upper bound of 4.51 for BMI and a lower bound of 6.34 and an upper bound of 10.85 for glucose. Then threshold values for BMI and glucose were varied in increments of 0.001 to

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dichotomize the test results into those with or without diabetes. Sensitivity and FPR (1-specificity) were then estimated based on the formulas assuming a normal distribution CDFs.

Table 6.5: Summary of transformed data, BMI and glucose by diabetes groups

				Quartiles		
Group	Test	SD	Mean	25%	50%	75%
Diabetes	BMI	0.21	3.88	3.7	3.87	4.0
	Glucose	0.63	8.96	8.5	8.97	9.5
Non-Diabetes	BMI	0.25	3.72	3.5	3.71	3.9
	Glucose	0.63	8.23	7.8	8.20	8.6

6.4 MROC and cost curves

Figure 6.5 demonstrates the MROC and cost curves for the diabetes data using BMI as the first test in the sequence and glucose as the second test. All three sequential strategies (BP, BN, and BE) were examined. The thresholds were used to dichotomize the test results into diseased and non-diseased. Based on the normal distribution CDFs, a sensitivity and specificity was estimated using these thresholds. The MROC curve was drawn by plotting maximum sensitivity with lowest cost at each $FPR \le t$ (e.g $1-\text{specificity} \le t$). The cost curve was drawn by plotting lowest cost at each $FPR \le t$. In terms of the performance, the BE and BN strategies had identical MROC curves, and were slightly higher than the BP strategy. In terms of cost, the BE and BN strategies were less costly than the BP strategy for FPR < 0.60; and the BE and BP strategies were less costly than the BN strategy for FPR > 0.60. It was apparent that the cost curve of the BE strategy follows that of both the BN and BP strategies over specific values of the FPR. Thus, the BE strategy had lower cost

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over both low and high FPR values. If one were interested in a specific region of the MROC curve, such as FPRs < 0.60, one could choose the BE or BN strategy since the MROC curves were identical with similar cost curves for FPR< 0.60. For higher FPR values, one could choose the BE or BP strategy.

A B

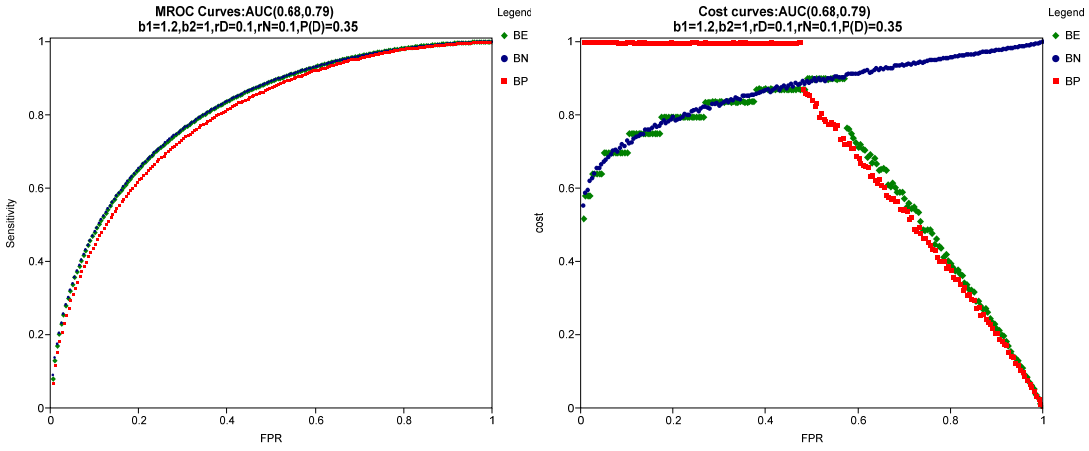

Figure 6.5: MROC curves and cost curves for the three strategies

6.5 BE produces results similar to the BN and BP strategies for some FPRs

Figure 6.5 shows MROC curves and cost curves. It appears from the cost curves that the BE strategy produced results similar to the BN strategy when FPR 0.60 and was similar to the BP strategy when FPR>0.60, but it was not known for sure that their thresholds were equivalent until the threshold values were examined. Figure 6.6 A shows that θ_2 from the BE strategy versus θ_1 from the BP strategy did not form an equivalent diagonal, but θ_1 from the BE strategy versus θ_1 from the BP strategy was close to a diagonal line. This was not true for some larger thresholds, meaning that some of the BE strategy's thresholds (θ_1) were close to the BP strategy's thresholds (θ_1). Figure 6.6 B shows that θ_1 from the BE strategy was usually not equal to θ_1 from the BN strategy but θ_2 from the BE strategy

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versus θ_1 from the BN strategy was close to a diagonal line for many of the thresholds. This was not true for smaller thresholds, meaning that the BE strategy's thresholds θ_2 were close to BN's thresholds θ_1. Graphs in Figure 6.6 A and B did not show the change of Test thresholds over FPR values. The graph in Figure 6.6C shows when FPR < 0.60, the threshold θ_1 from the BE strategy approached $+\infty$ (high values). When FPR > 0.60, the threshold θ_2 from the BE strategy approached $-\infty$ (low values). This means that the BE strategy produced results similar to the BN and BP strategies at low and high FPR values, respectively.

A B C

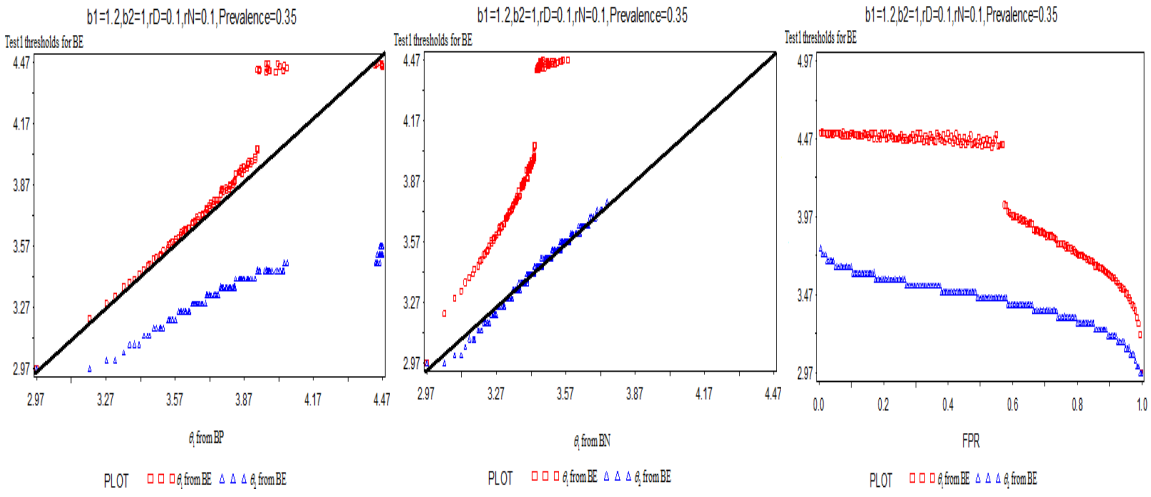

Figure 6.6: Comparison of threshold values: θ_2 from the BE strategy similar to θ_1 from the BN strategy and θ_1 from the BE strategy similar to θ_1 from the BP

6.6 The MCMROC and cost curves

This section calculates the lowest cost while a negligible lower sensitivity (0.1% reduction) was accepted, and while accepting slightly lower sensitivity (5% reduction). Figure 6.6 uses the values q=0.999, and q=0.95, respectively. In graphs A1, one can see that the

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MCMROC curves with q=0.999 were identical when no sensitivity was sacrificed (q=1.0, see section 6.3). However, cost curves were slightly lower as compared to the cost curves with no sensitivity sacrificed. In graphs A2 and B2, when there was 5% reduction (q=0.95), the MCMROC curves were a bit lowered. In terms of cost, the BE and BN strategies were less costly than the BP strategy for FPR < 0.20; and the BE strategy was less costly than the BN strategy for FPR > 0.20.

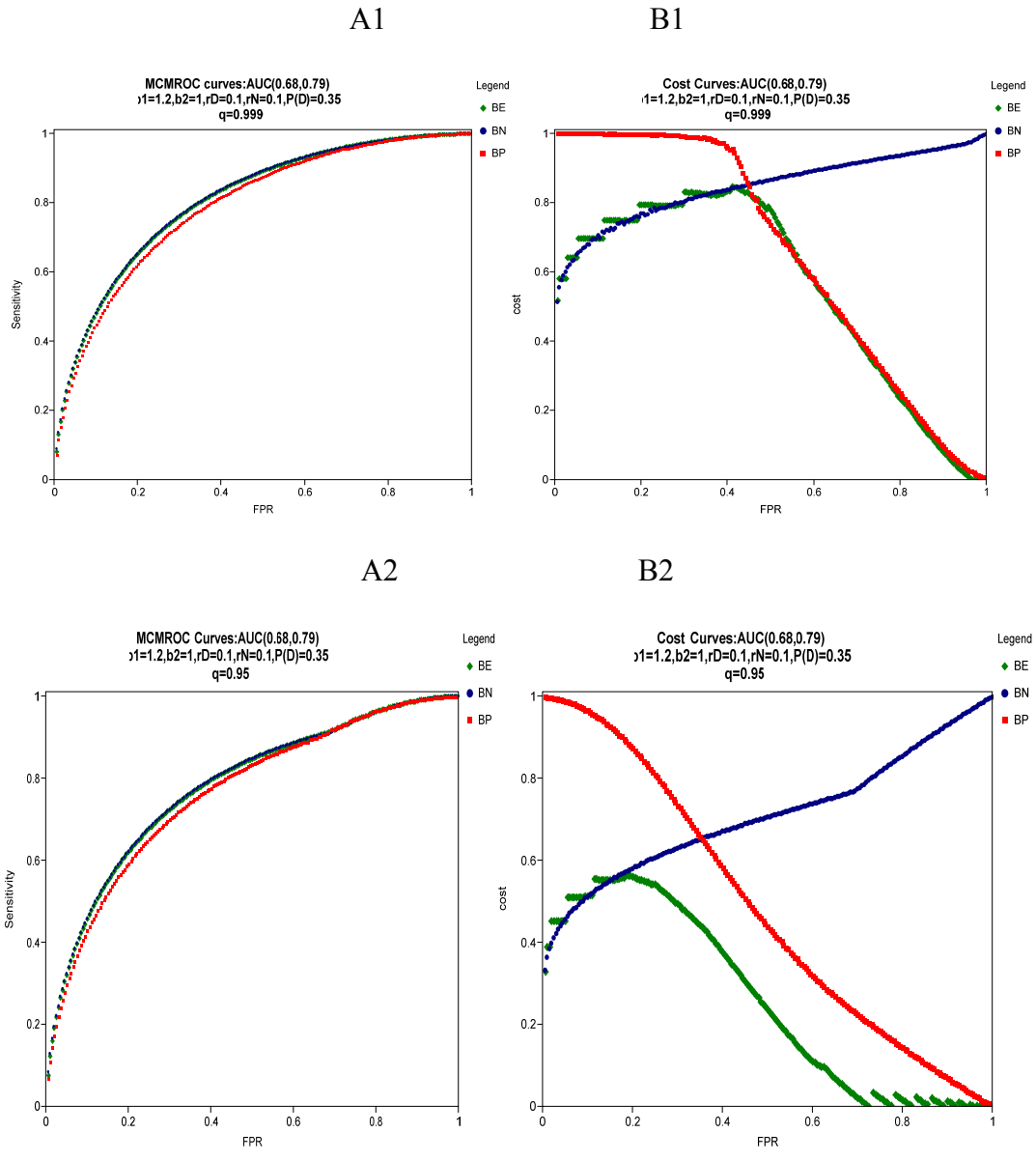

Figure 6.7: MCMROC curves and cost curves for the three strategies

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6.7 The effect of q on the MCMROC curves and cost curves

To determine the effect of q, one can plot a separate graph for each of the BE, BN and BP strategy which have either the MROC/ MCMROC curves or the cost curves for the 3 q values of interest. Here, 0% reduction (equivalent to q=1) was represented in brown, up to 0.1% reduction (equivalent to q=0.999) was represented in light blue, and up to 5% reduction (equivalent to q=0.95) was represented in red. All strategies reduced cost when allowed up to 5% reduction in sensitivity. Only the BE and BP strategies lowered the cost for large values of FPR when allowed up to 0.1% reduction in sensitivity. Figure 6.7 shows that q had an effect on the MCMROC curves cost curves of each individual strategy.

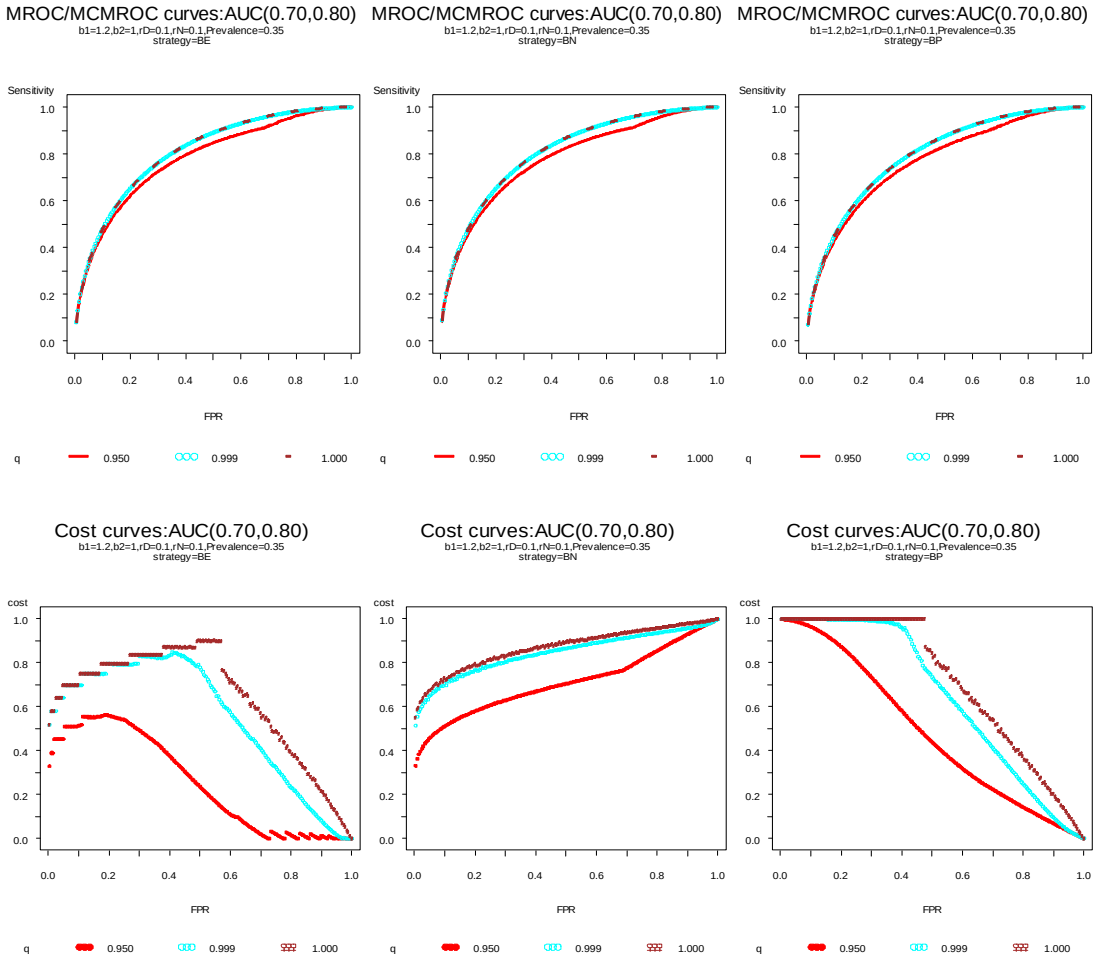

Figure 6.8: The effect of q on the MCMROC curves and cost curves of individual strategy

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6.8 Optimality criterion

From these data, clinicians would want to know what thresholds to use to diagnose new patients as having diabetes or not (the thresholds are often referred to as the "operating point" in the ROC literature). This section provides guidance in how to choose such a point that could be considered "optimal" As described in previous chapters, this optimal point will be a set of thresholds that provides a balance between specificity and sensitivity, subject to a restriction on the cost of sequential testing. It was calculated using the Generalized Youden Index (GYI).

Objective function $\max_{\theta} \{TPR(\underset{\sim}{\theta}) - m*(FPR(\underset{\sim}{\theta}))\}$

Subject to $C(\underset{\sim}{\theta}) \le C_0$,

where $m = \left[(1-p)/p\right] \times \left[\left(C_{FP} - C_{TN}\right)/\left(C_{FN} - C_{TP}\right)\right]$, as defined in work by Metz (1978), was the slope of the combined diagnostic tests' ROC curves (a straight line that passes through the ROC curves in the small FPR region, in a point called optimal point). p was the prevalence of disease, here for Pima Indian, the diabetes prevalence was 0.35, $\left[(C_{FP} - C_{TN})/(C_{FN} - C_{TP})\right]$ was the cost/benefit (C/B) ratio of false-positive compared to false-negative results. $C(\underset{\sim}{\theta})$ is the cost of testing, which satisfies as much as fixed value, C_0, $0 \le C_0 \le 1$. The following values of C_0 were considered here: 1 and 0.75. The 1 assumed that there was no cost constraint. A cost of less than 1 meant that not all of the subjects had to take the second test. The 75% constraint meant that one would only consider thresholds which result in no more than 75% needing to take the 2nd test.

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6.8.1 Determining optimal operating points to use in classifying results BMI and glucose test

The next task was to find possible thresholds to use to classify the results of the BMI and glucose test. This was done by varying the C/B ratios and the cost constraint. Table 6.6 considers three values of C/B and slopes with different assumption for each, when C/B=0.05, indicated a slope of 0.1, which gives the lowest clinically significant value, as suggested by Metz. When C/B=0.538, which indicated a slope of 1, here the GYI becomes a Youden's Index (YI). This also assumed that the cost of misclassifying non-diseased subjects was lower than the cost of misclassifying diseased subjects. The second C/B ratio considered was 1, which indicates a slope of 1.9. This ratio assumes that the cost of misclassifying non-diseased subjects was the same as the cost of misclassifying the diseased. The third C/B ratio considered was 1.538, which indicates a slope of 2.9. This ratio assumes that the cost of misclassifying the non-diseased was greater than the cost of misclassifying diseased subjects.

Table 6.6: C/B ratios and slopes

C/B	slopes
0.050	0.100
0.538	1.000
1.000	1.900
1.538	2.900

These slope values were suggested here because they were within the range of 0.1-3, used by Metz et al. in their study (1996). Figure 6.8 A shows cost curves for q=0.999 with a cost

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no larger than 75%. Using the BP strategy, in order to be able to satisfy the cost constraint, the optimal operating point must have FPRs > 0.49. Both BN and BE strategies could have an optimal operating point with FPR < 0.20; In addition, the BE strategy could also produce an optimal operating point with FPR > 0.49. Figure 6.7 B shows cost curves for q=0.95 with the cost up to 75%; For BE all points on the MCMROC curve were in the feasible region for OOP. In comparison, the choice of optimal points for the BN and BP strategies were affected by the cost of testing constraint. The optimal operation point for the BP strategy was restricted to those which produce FPRs > 0.28, while the optimal operating point for the BN strategy would have FPRs < 0.70. For cost up to 100%, all points on the MCMROC curve were considered to be in the feasible region.

A B

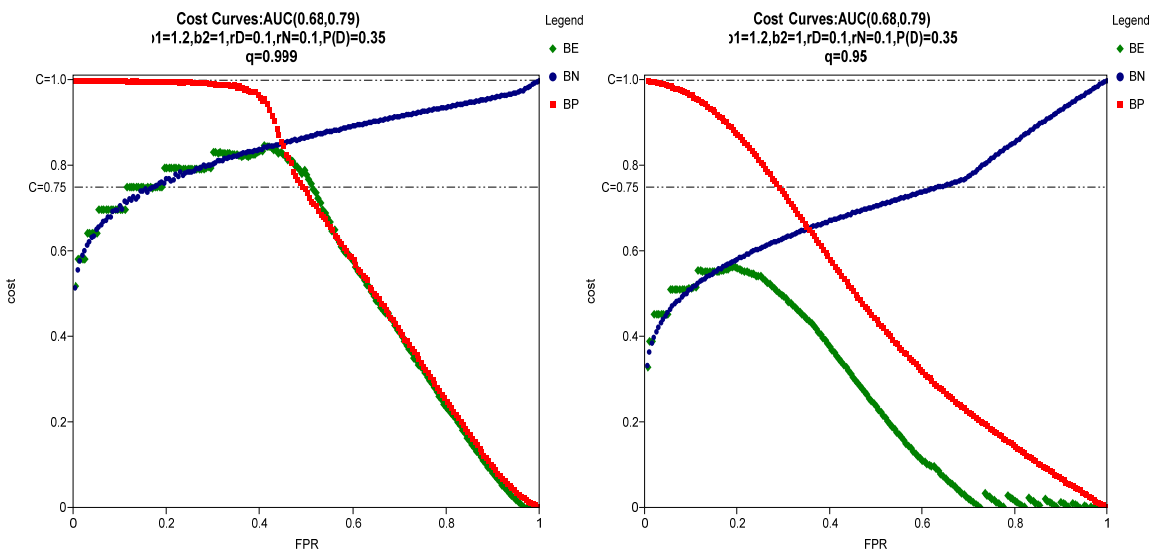

Figure 6.9: The effect of cost constraint on determining OOP, q=0.999 and q=0.95, respectively.

As a reminder, BMI ranging between 18.2 and 57.3 kg/m^2, and glucose ranged between 44.0 and 197.0 mg/dL. Table 6.7-6.10 list the optimal points found for each strategy using various C/B ratios (or slopes) for two values of q (q=0.95, 0.999), with and

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without a cost restriction. ($C_0 = 0.75,1.0$) In Table 6.7, where q=0.999 and $C_0 = 0.75$, when the slope was 1, the optimal points found by BE and BN strategy seem reasonable because the FPRs were low (19% and 17% as compared to 49.5% for the BP strategy). The thresholds associated with the optimal operating point found by the BE strategy were $\theta_1 = 56.4$ and $\theta_2 = 27.6$ for BMI, and $\theta_3 = 125$ for glucose. This means that women whose BMIs were below 27.6 kg/m2 were considered non-diabetic, women whose BMIs were over 56.4 kg/m2 were considered as diabetic, women whose BMIs were between 27.6 and 56.4 and whose glucose levels were above 125 mg/dL were considered diabetic and women whose BMIs were between 27.6 and 56.4 kg/m2 and whose glucose levels were below 125 mg/dL were considered non-diabetic. There were many values in-between θ_2 and θ_1, which means more subjects took the second test. This created high cost but did not exceed 75%. It should be noted that the upper threshold of the BE strategy, $\theta_1^{BE} = 56.4$ is so high that virtually no women will be diagnosed as diabetic based on BMI alone, Additionally, it can be seen that θ_2 from the BE strategy was similar to θ_1 from BN. This is because the curves for the BE strategy resembled those of the BN strategy for some FPR values. Similarly, this is true for the slopes of 1.9 and 2.9 with the same or slightly different optimal operating points for the BE and BN strategies. Because the optimal point for the BP strategy is restricted by the cost constraint (no larger than 75%) it does not change, for any value of slope of 1 or greater, while the optimal points found by the BN and BE strategies changed as C/B ratio or slope changes.

The set of tables below show slope of 0.1 which was the lowest value that Metz considered to be clinically relevant. It can be seen that the same optimal operating points for the BE and BN strategies remain with cost no larger than 75% and 100% for each

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q=0.95 and q=0.999. Here θ_1 and θ_2 from the BE strategy and θ_1 from the BP strategy were essentially at the lower limit of the BMI values. This means that virtually everybody will be classified as positive on BMI. This makes cost low for these two strategies. When the BN strategy has a low θ_1 value but is not at the lower limit, there were few people who will be classified as negative on the first test. This was why cost was high for the BN strategy.

Table 6.7: Optimal thresholds for each strategy when cost of testing was no larger than 75% and q=0.999

Slope	C/B	Strategy	GYI	θ_1	θ_2	θ_3	TPR	FPR	cost
0.1	0.05	BE	0.911	25.06	21.03	106	0.993	0.885	0.103
		BN	0.595	27.72		127	0.611	0.170	0.746
		BP	0.910	23.83		121	0.994	0.905	0.089
1	0.538	BE	0.449	56.40	27.60	125	0.639	0.190	0.749
		BN	0.441	27.70		127	0.611	0.170	0.746
		BP	0.379	36.60		116	0.874	0.495	0.747
1.9	1	BE	0.301	56.30	27.60	132	0.552	0.135	0.749
		BN	0.302	28.10		132	0.544	0.130	0.725
		BP	-0.046	36.60		116	0.874	0.495	0.747
2.9	1.538	BE	0.203	57.40	28.60	142	0.418	0.075	0.698
		BN	0.205	29.10	.	142	0.405	0.070	0.671
		BP	-0.540	36.60	.	116	0.874	0.495	0.747

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Table 6.8 has similar information when q=0.95 and $C_0 = 0.75$. When accepting slightly lower sensitivity (such as 5% reduction) at varying slope values, the optimal thresholds for the BE, BN, and BP strategies seemed reasonable in terms of the FPR values. In general, the BE, BN, and BP strategies all had acceptable FPR values as compared to when *q*=0.999. The optimal operating point for the BP strategy, however, remained associated with high cost, while the BN and BE strategies had, in comparison, optimal operating points associated with low cost. Since the MROC curves of the BN and BE strategies were similar, their optimal operating points were also similar. Also, because the θ_1 threshold for the BE strategy is not as high for the various slopes, compared to the θ_1 threshold for q=0.999, more women will be diagnosed as positive by BMI alone.

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Table 6.8: Optimal thresholds for each strategy when cost of testing was no larger than 75%, and q=0.95

Slope	C/B	Strategy	GYI	θ_1	θ_2	θ_3	TPR	FPR	cost
0.1	0.05	BE	0.909	20.63	20.32	147	0.998	0.965	0.004
		BN	0.838	27.65	.	74	0.898	0.640	0.750
		BP	0.909	21.15	.	175	0.997	0.955	0.030
1	0.538	BE	0.428	39.00	28.60	124	0.682	0.255	0.538
		BN	0.428	30.00	.	110	0.693	0.265	0.614
		BP	0.401	36.60	.	138	0.691	0.290	0.749
1.9	1	BE	0.275	46.70	30.60	130	0.507	0.125	0.553
		BN	0.276	31.50	.	126	0.499	0.120	0.528
		BP	0.152	36.60	.	138	0.691	0.290	0.749
2.9	1.538	BE	0.184	51.10	31.60	140	0.369	0.065	0.510
		BN	0.185	32.30	.	137	0.371	0.065	0.475
		BP	-0.137	36.60	.	138	0.691	0.290	0.749

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Table 6.9 lists the optimal points found for each strategy using various C/B ratios and sensitivity reductions when there is no cost restriction, and q=0.999. These results can be thought about in comparison to the results when the cost of testing is no larger than 75%. When the sensitivity was reduced by 0.1% with a slope greater than 1, the optimal points found by the BE and BN strategies seemed almost the same. For the BP strategy, the results varied, since there was no cost restriction. When the slope was greater than 0.1, the FPR values were lowered, but almost all patients had to have the second test. However, when the slope was 0.1, the FPR values were high for all strategies. The optimal point found by the BN and BE strategies changed but with similar optimal operating point for each slope value while the optimal point found by BP did change, as the C/B changed. This was because there were no restrictions on the cost of testing.

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Table 6.9: Optimal thresholds for each strategy when no restrictions on cost of testing and q=0.999

Slope	C/B	Strategy	GYI	θ_1	θ_2	θ_3	TPR	FPR	cost
0.1	0.05	BE	0.911	25.06	21.03	106	0.993	0.885	0.103
		BN	0.910	21.80	.	71	0.994	0.910	0.959
		BP	0.910	23.83	.	121	0.994	0.905	0.089
1	0.538	BE	0.463	52.60	26.70	118	0.733	0.270	0.792
		BN	0.464	26.80	.	118	0.733	0.270	0.791
		BP	0.437	52.20	.	123	0.722	0.285	0.994
1.9	1	BE	0.301	56.30	27.60	132	0.552	0.135	0.749
		BN	0.302	28.10	.	132	0.544	0.130	0.725
		BP	0.270	56.60	.	138	0.521	0.135	0.998
2.9	1.538	BE	0.203	57.40	28.60	142	0.418	0.075	0.698
		BN	0.205	29.10	.	142	0.405	0.070	0.671
		BP	0.174	57.50	.	150	0.374	0.070	0.999

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Table 6.10 lists the optimal points found for each strategy using various C/B ratios when q=0.95 but there is no cost restriction. When the sensitivity was reduced by 5% and a slope of 1 was used, the same θ_1, θ_2, and θ_3 for the BE holds for q=0.95 regardless of whether or not there was a cost constraint of 75% or no cost constraint. Similarly, the same θ_1 and θ_2 for the BN holds for q=0.95 regardless of the cost restriction. This was not true for the BP strategy. For the various slopes, when the optimal point for the BP strategy was not restricted by the cost constraint, the optimal point had a low FPR. The threshold θ_1 for the BP strategy was very high; few subjects were called positive on the first test (BMI), with most needing to be assessed by the second test which resulted in high cost.

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Table 6.10: Optimal thresholds for each strategy when no restrictions on cost of testing and q=0.95

Slope	C/B	Strategy	MGYI	θ_1	θ_2	θ_3	TPR	FPR	cost
0.1	0.05	BE	0.909	20.63	20.32	147	0.998	0.965	0.004
		BN	0.908	20.81	.	53	0.998	0.965	0.974
		BP	0.909	21.15	.	175	0.997	0.955	0.030
1	0.538	BE	0.428	39.00	28.60	124	0.682	0.255	0.538
		BN	0.428	30.00	.	110	0.693	0.265	0.614
		BP	0.402	37.40	.	138	0.672	0.270	0.780
1.9	1	BE	0.275	46.70	30.60	130	0.507	0.125	0.553
		BN	0.276	31.50	.	126	0.499	0.120	0.528
		BP	0.245	44.10	.	145	0.478	0.125	0.946
2.9	1.538	BE	0.184	51.10	31.60	140	0.369	0.065	0.510
		BN	0.185	32.30	.	137	0.371	0.065	0.475
		BP	0.156	48.30	.	154	0.342	0.065	0.982

Since these results are derived from samples rather than being population based, it would be appropriate to assess the level of precision of the results. The use of bootstrap confidence intervals may be appropriate, however this takes considerable time and resources (see Chapter 7).

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6.9 Summary

In Figure 6.2, the points on the scatter plot overlap so that finding perfect separation between the values for those with and without diabetes was not possible with either a single test or the combination of the two. When the testing sequence did not require subjects to undergo the second test to have a diagnosis made, that meant that the subject did not have to undergo the blood work necessary for the glucose test. Using up to 5% reduction in sensitivity greatly reduced the number of patients who were recommended to undergo the glucose test. Sequential testing, with up to 5% reduction in sensitivity, is a valid way to lower cost. It must be carefully noted though, that the sequential strategies may not result in true positive and specificities that are sufficiently high.

The risks and consequences in falsely classified tests are many. A Pima Indian woman, falsely believing herself to be positive for diabetes, may undergo harmful, unnecessary insulin injections to combat a disease she does not have. Conversely, a Pima Indian woman, falsely believing herself to be negative for disease, could avoid insulin injections that may be necessary for patient well-being. The sequalae of untreated diabetes are many and serious.

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Chapter 7

7.1 Discussion

This research demonstrated the BE strategy as an alternative strategy to the BN and BP strategies. When sensitivity was not lowered in any way (q=1), it was shown mathematically that for a fixed FPR, the BE strategy's accuracy would be at least as large as the BN strategy's or the BP strategy's accuracy, regardless of parameter settings (AUC values, standard deviations of the diseased and non-diseased populations, correlation, and prevalence). It was found that the BN and the BP strategy were greatly affected by the parameter settings. For example, when the ratio of the standard deviations of the diseased and non-diseased populations were less than 1 (meaning that the distribution for diseased subjects has twice the variability of the distribution of the non-diseased subjects), the BP strategy has as much accuracy as the BE strategy and higher than the BN strategy's accuracy. When the ratio of the standard deviations of the diseased and non-diseased populations was greater than 1 (meaning that the distribution of the non-diseased subjects has twice the variability of the distribution of the diseased subjects), the BN strategy had as much accuracy as the BE strategy and higher than the BP strategy's accuracy. Though the accuracy of the BN strategy or the BP strategy could equal that of the BE strategy, their variability based on the parameter settings makes the BE strategy the best strategy.

The main focus of this research was to incorporate cost into the evaluation of each strategy's performance. It can be seen that cost played an important role in showing real differences between the strategies. It was shown that the BN strategy could lower the cost at low FPRs and that the BP strategy could lower cost at high FPR values. The BE strategy, however, lowered cost for both low and high FPR values. Though for many situations the

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BE strategy may produce results similar to the BN or the BP strategy for some FPR values, its cost was lower overall in both portions. Though for many situations the BE strategy produces results similar to the BN strategy or the BP strategy for some FPR values, its cost was lower overall in both portions.

In Chapter 4, one may notice that cost may not be greatly reduced from 1. However, Chapter 5 showed that by allowing reduced accuracy by 5% or even 0.1%, cost was greatly reduced. With a slight sacrifice of accuracy, the BE strategy's cost was greatly decreased, as compared to the BN strategy and the BP strategy. In contrast to the cost with no reduction in sensitivity, when the sensitivity was reduced by 0.1%, the cost was reduced significantly. Some exceptions to this have already been acknowledged. Therefore, a 0.1% reduction in sensitivity was recommended, as it could reduce the cost while retaining the same sensitivity. If the second test is expensive or painful for the patient, a reduction of 5% is recommended.

When the 3 strategies were applied to real data, the BE strategy could again be described as the best strategy, in terms of accuracy and cost. The diabetes data shown in Chapter 6 provided a real world examination of the BE, BN, and BP strategies. Just as in the previous chapters, it was found that the BN and BE strategies were the most consistently accurate and least expensive choice. Also the optimal rules found by the BE and BN strategies seemed more reasonable than those found by the BP strategy because the BE and BN strategies have a lower FPRs. The findings here were recommended for the Pima Indian group only.

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7.2 Limitations

If a researcher was interested in, for example, the smaller values of FPR, they might choose the BN strategy, which may be as low in cost as the BE strategy. The BN strategy, in this case, could still be a valid choice, and this researcher does not advise against its use in certain circumstances. Another challenge in using the BE strategy was the extensive computation required to produce results. The BN and BP strategies take significantly less time than the BE strategy. If time was an issue to a researcher, they might want to avoid using the BE strategy and go with the other strategy with the lower cost. Furthermore, the approach discussed in Chapters 4-6 assumed the tests were normally distributed. In real application, diagnostic tests may not always be distributed normally. This is not an issue if the data can be transformed to normality. However, it may not always be possible to find appropriate transformations. This may appear as a limitation, but it points the way for future work.

Another limitation to be considered is that this research only examined the effect of certain parameters of AUC values and the diseased and non-diseased standard deviations. Other parameters could be considered by future researchers

The method used in sequencing the tests is another issue that could change the results of this study. The tests could be sequenced in a variety of different ways. They could be sequenced by cost, by discomfort to patient, or by accuracy (as was done in this research). In Chapter 6, the goal was to reduce the number of patients who required Test 2 (glucose), which was more painful (blood work) and expensive (processing). A different sequence of tests could be considered in future work.

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7.3 Directions for future research

The research detailed here concerned combining two continuous tests, but could be extended to more than two tests, such as three sequential tests. Research could be conducted using three tests, or more. In doing that, the strategies could be extended.

A further avenue for future research is to develop methods to use if it is not possible to find a transformation which will make the data follow a normal distribution With parametric methods, for example, the assumption that the tests are normally distributed need not be made. In this case, empirical ROC curve would be produced by using the observed data.

This research used $q \times \max[\mathrm{TPR}(\underset{\sim}{\theta})]$ to determine the acceptable accuracy, but $\max[\mathrm{TPR}(\underset{\sim}{\theta})] - \varepsilon$ could also be used in which $\max[\mathrm{TPR}(\underset{\sim}{\theta})]$, is the maximum sensitivity for $FPR \leq t$. Future researchers could explore the effects of using $\max[\mathrm{TPR}(\underset{\sim}{\theta})] - \varepsilon$.

Finally, because these techniques were applied to collected data, some estimate of precision of costs or thresholds should be made.. Assessing the precision of the optimal operating point is an issue that could be considered as future research topic by using techniques such as bootstrapping. However, this takes considerable time and resources. For example, the diabetes data used in Chapter 6 used a threshold increment of 0.001 (see Table 7.1). The BN strategy, with a threshold increment of 0.001, produced 6,951,451 thresholds that needed to be evaluated. Running two-thousand bootstrap samples of this size would require 90,000 minutes, or 62.5 days, to process bootstrapping results, not including the programming time. The other strategies also take extensive time, especially BE. It is important to note here that BE requires far more time to process than the other strategies because it has 3 rather than 2 thresholds to vary. Assuming a threshold increment

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of 0.001, BE produced 137,400,549 thresholds that needed to be evaluated. Processing these results would require the proper equipment and an ample amount of time. However, the results seen from this could be useful for future research.

Table 7.1: Estimated time needed to evaluate the three strategies

Strategy	Time[1]	Thresholds increment	Number of thresholds [2]	Number of days [3]
BN	45min	0.001	6,951,451	62.5
BP	36min	0.001	6,951,451	50
BE	137min	0.001	137,400,549	190.3

[1] Time needed to run each strategy to produce one MCMROC curve and cost curve
[2] Number of thresholds evaluated to produce one MCMROC curve and cost curve
[3] Number of days needed to run 2000 bootstrap samples to produce 2000 MCMROC curves and cost curves

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Appendices

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Appendix A

Graphs

MROC curves and cost curves

The plot in left panel shows MROC curves, and the two plots in right panel show the cost associated with MROC curves when disease prevalence is low (prevalence = 0.1) and when disease prevalence is high (prevalence = 0.7), respectively.

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A1 Independent of the tests $(\rho_D = 0, \rho_N = 0)$ **, A1.1 AUC1 = 0.90, AUC2 = 0.90**

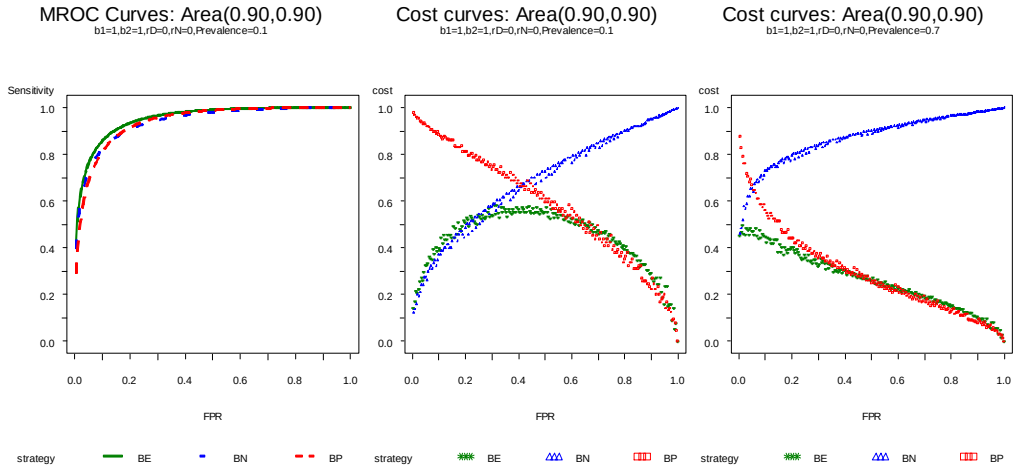

Figure A1.1a: (b1=1, b2=1)

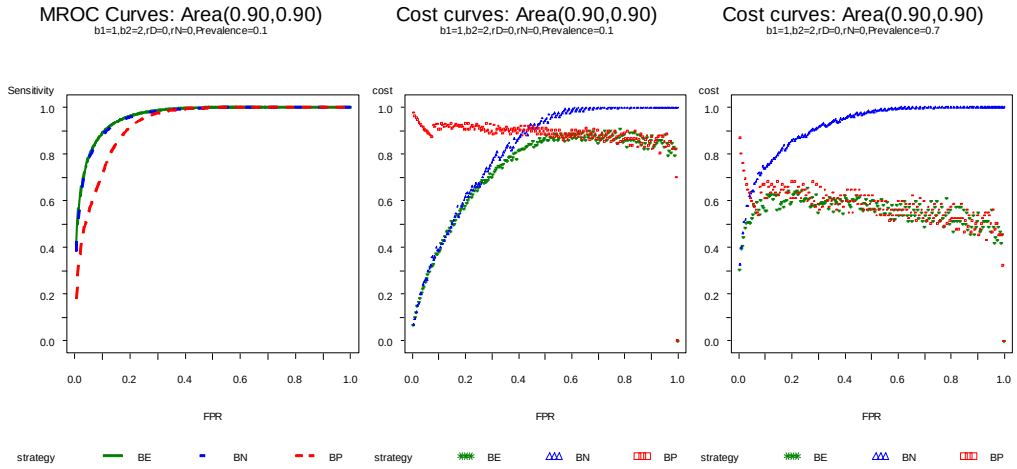

Figure A1.1b: (b1=1, b2=2)

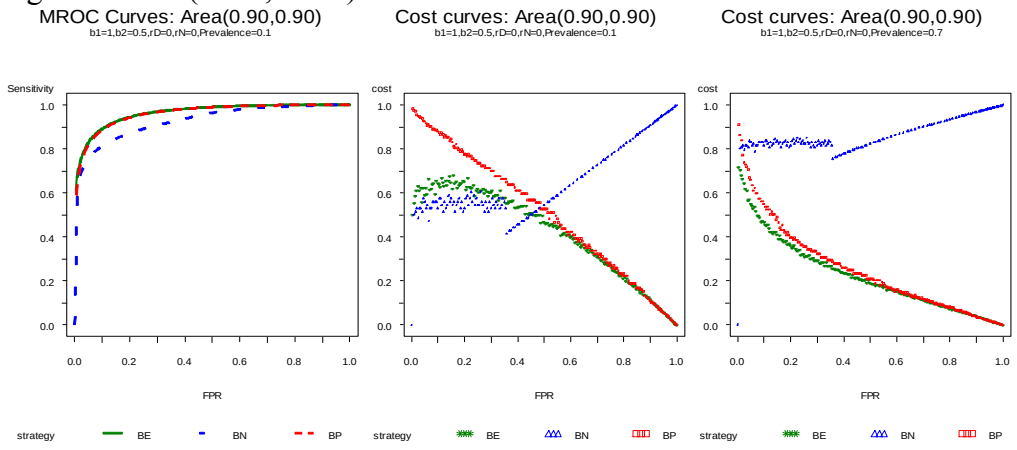

Figure A1.1c: (b1=1, b2=0.5)

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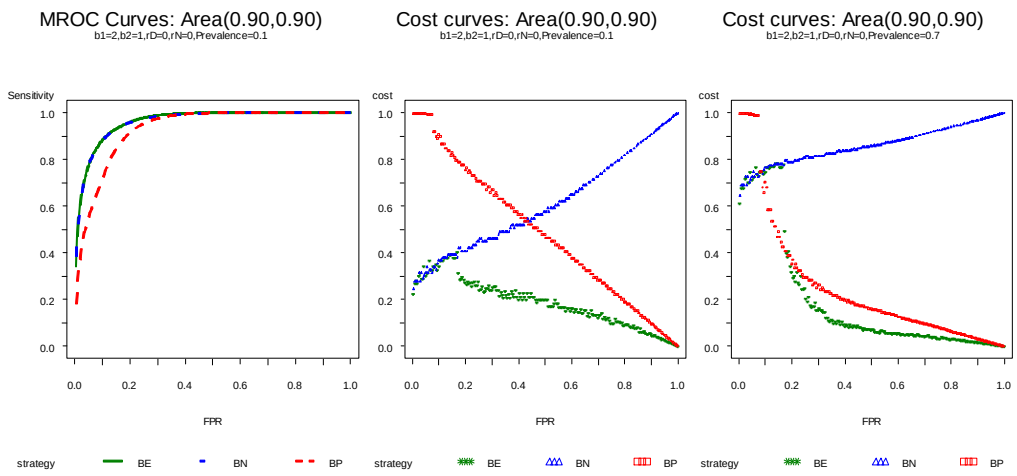

Figure A1.1d: (b1=2, b2=1)

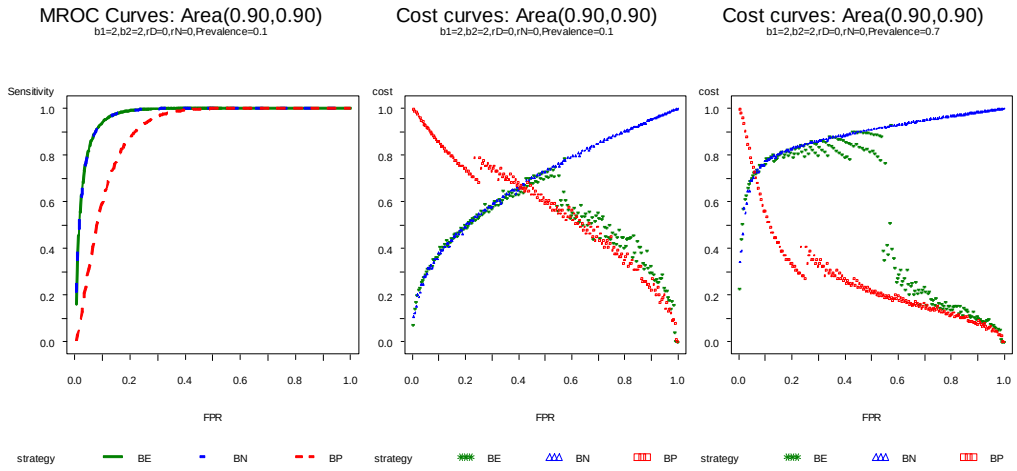

Figure A1.1e: (b1=2, b2=2)

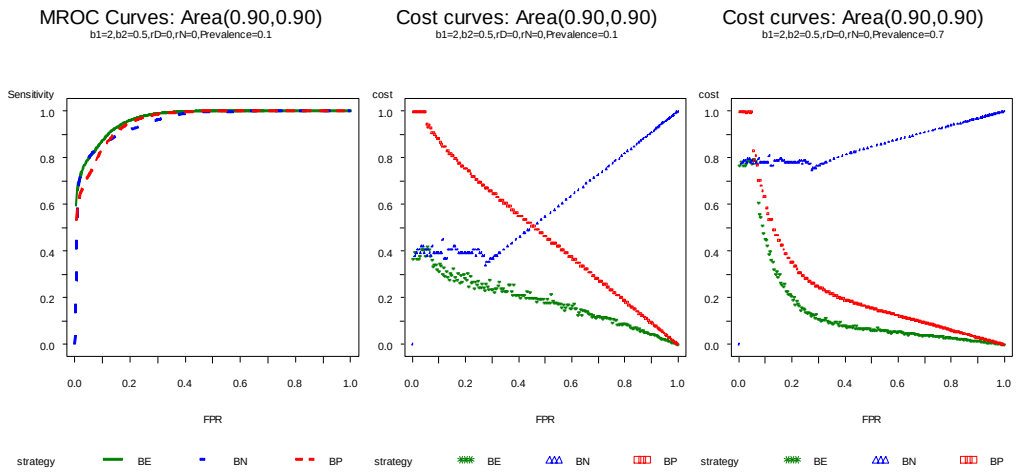

Figure A1.1f: (b1=2, b2=0.5)

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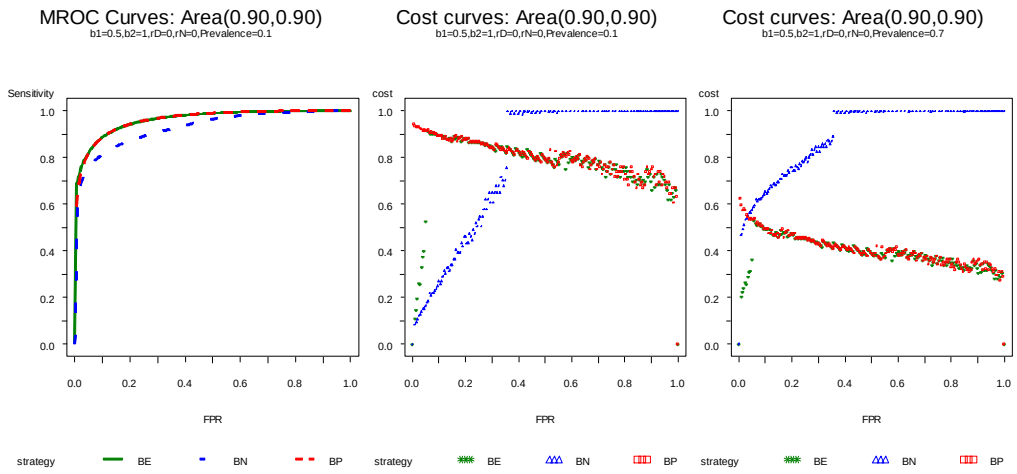

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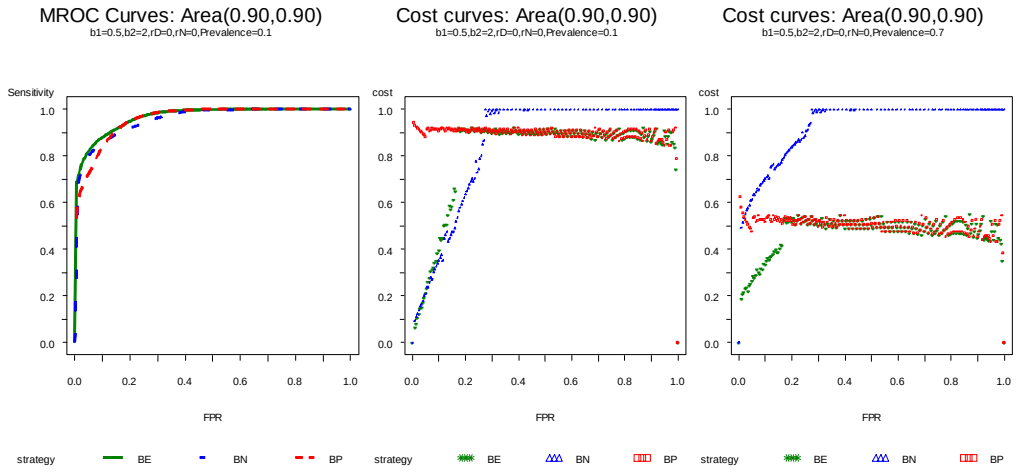

Figure A1.1h: (b1=0.5, b2=2)

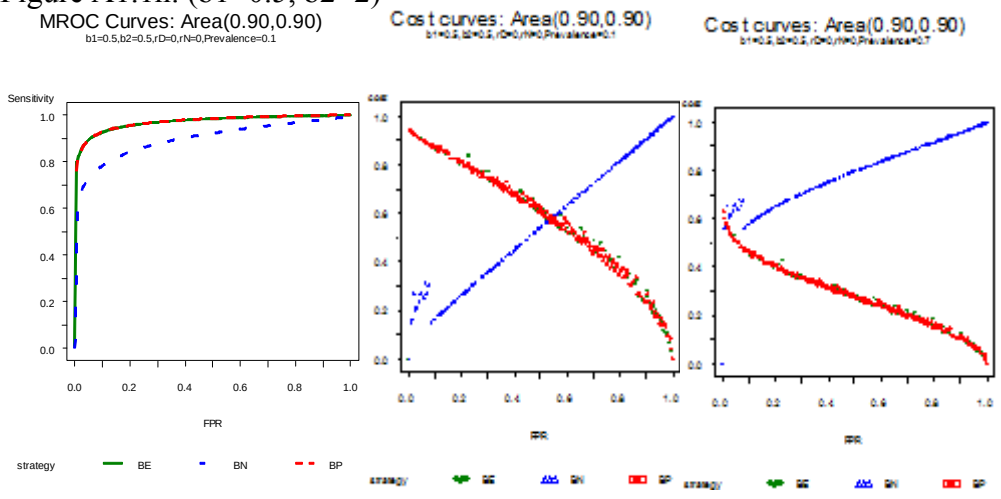

Figure A1.1i: (b1=0.5, b2=0.5)

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A1.2 **AUC1 = 0.70, AUC2 = 0.90**

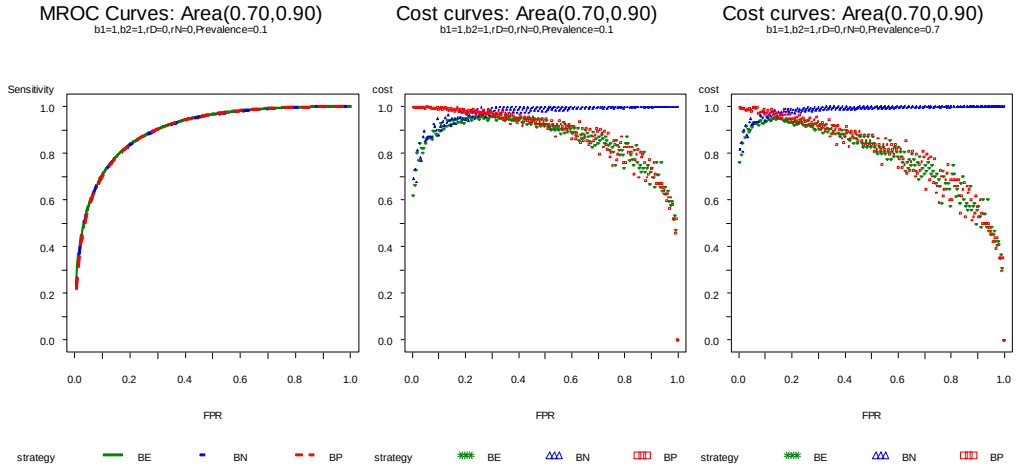

Figure A1.2a: (b1=1, b2=1)

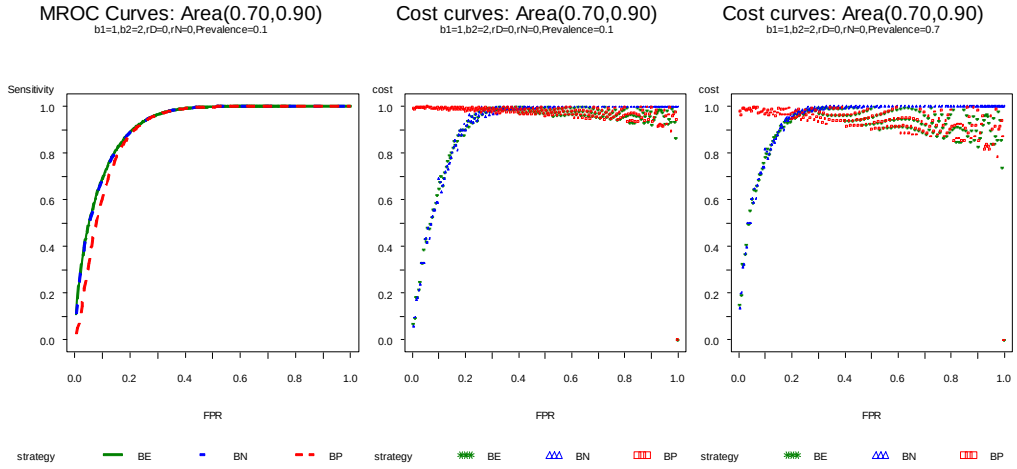

Figure A1.2b: (b1=1, b2=2)

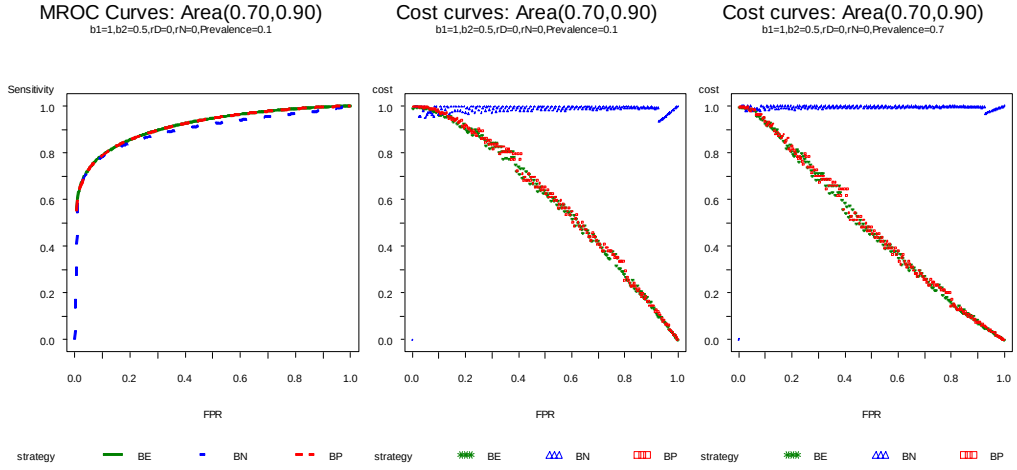

Figure A1.2c: (b1=1, b2=0.5)

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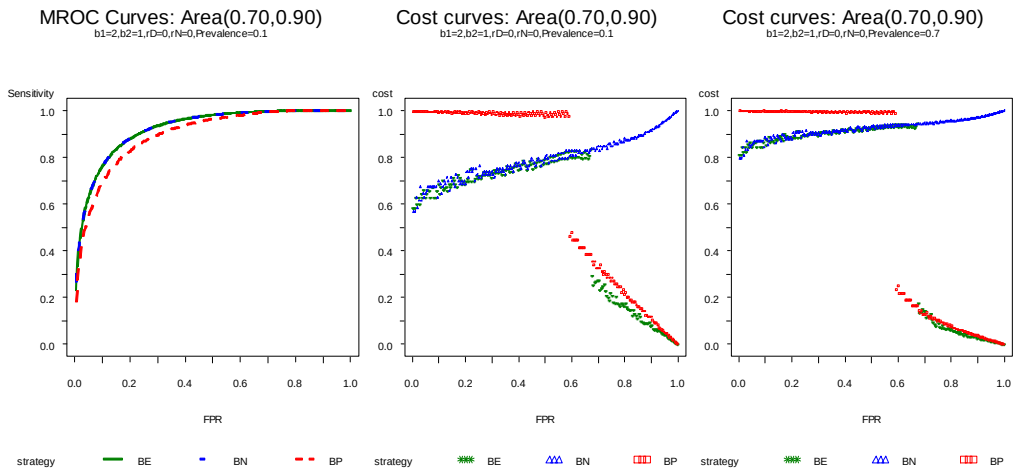

Figure A1.2d: (b1=2, b2=1)

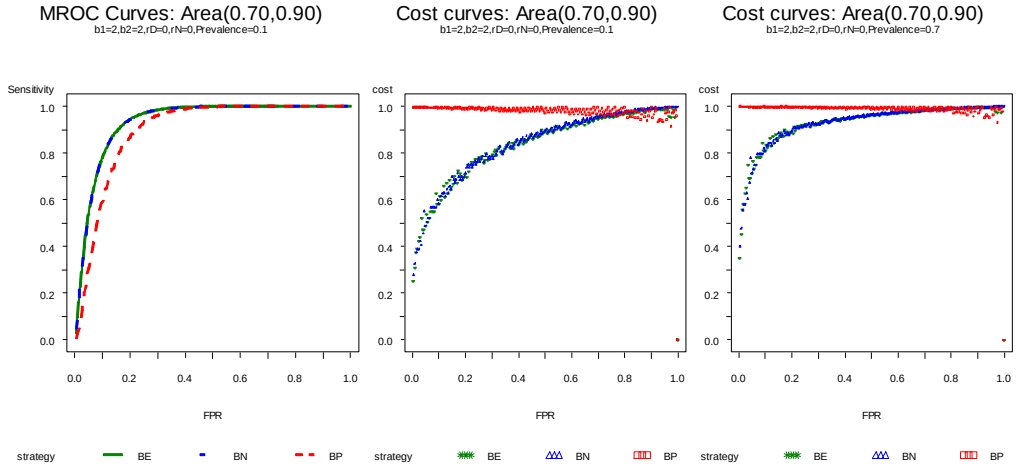

Figure A1.2e: (b1=2, b2=2)

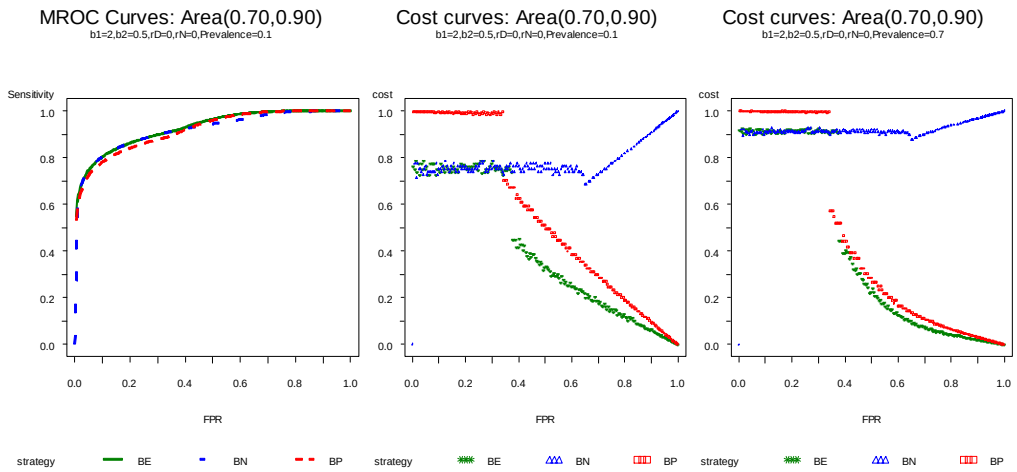

Figure A1.2f: (b1=2, b2=0.5)

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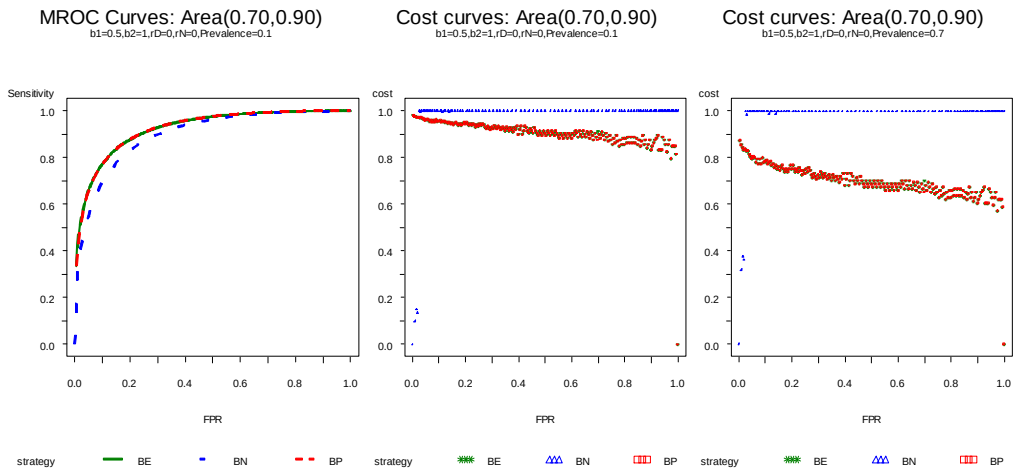

Figure A1.2g: (b1=0.5, b2=1)

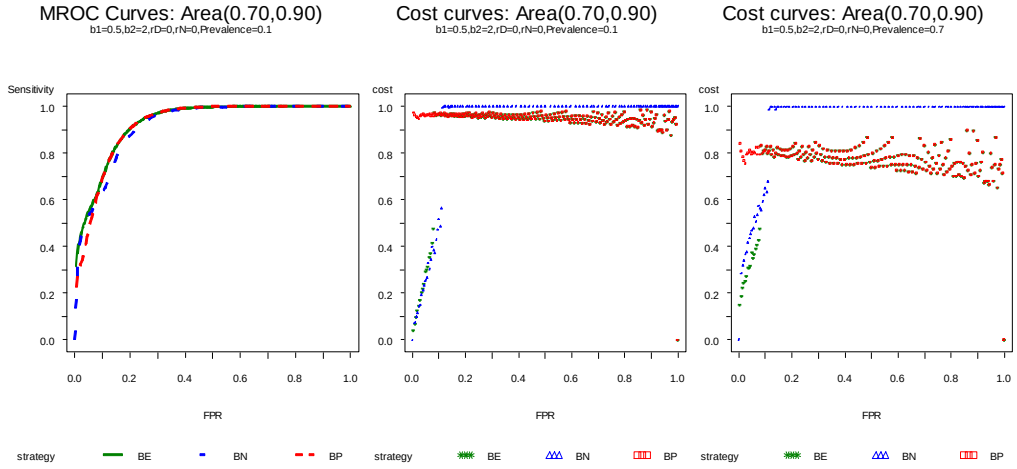

Figure A1.2h: (b1=0.5, b2=2)

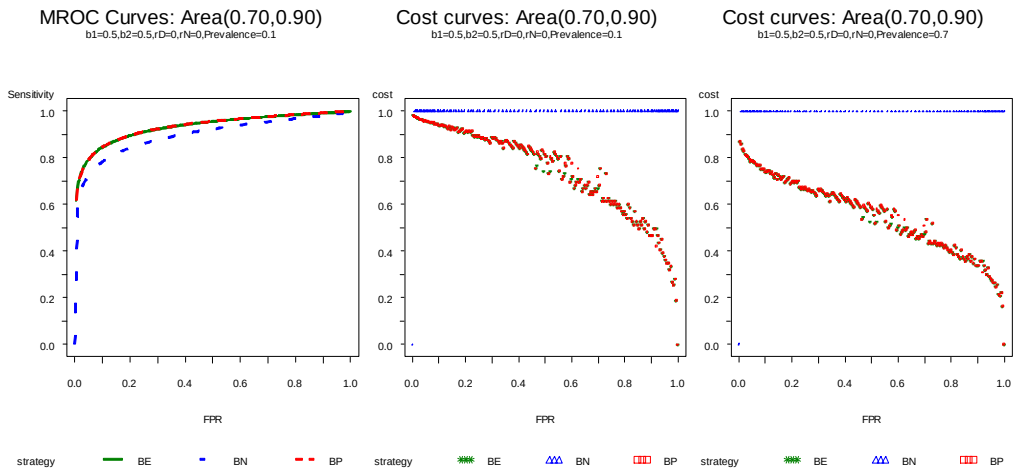

Figure A1.2i: (b1=0.5, b2=0.5)

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A1.3 AUC1 = 0.70, AUC2 = 0.70

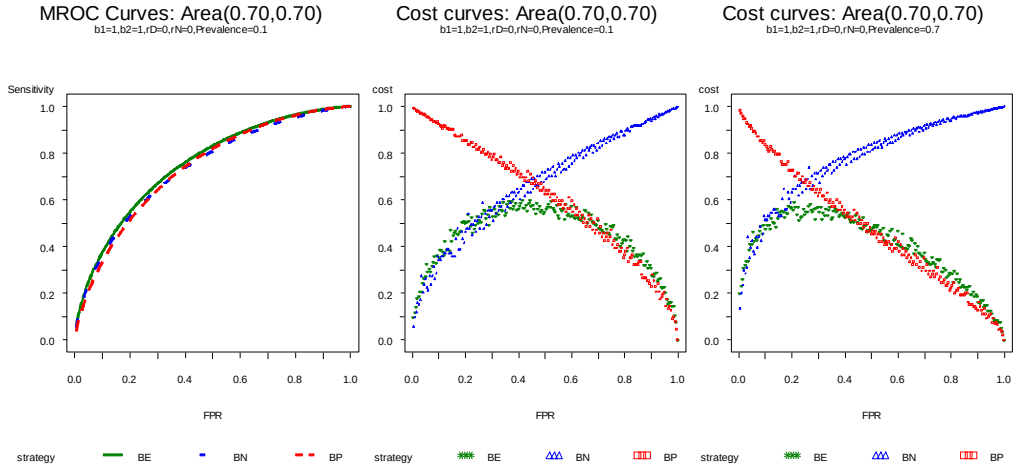

Figure A1.3a: (b1=1, b2=1)

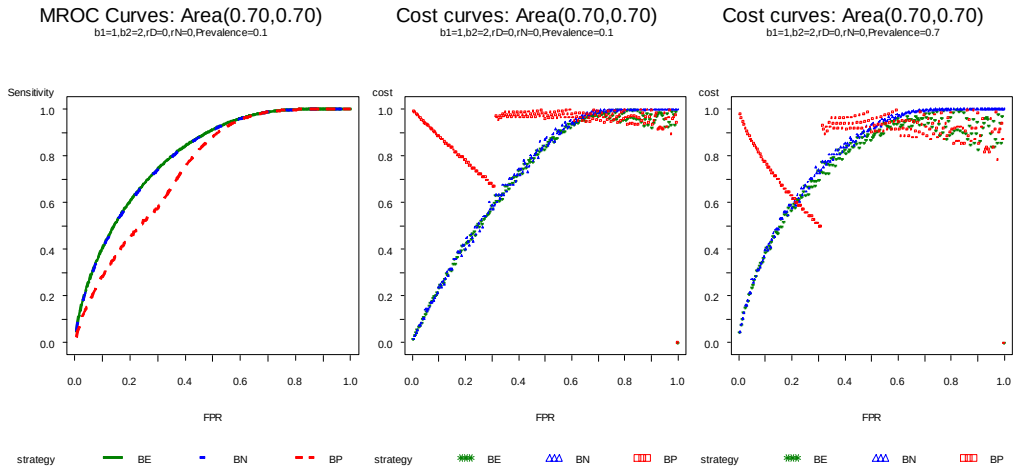

Figure A1.3b: (b1=1, b2=2)

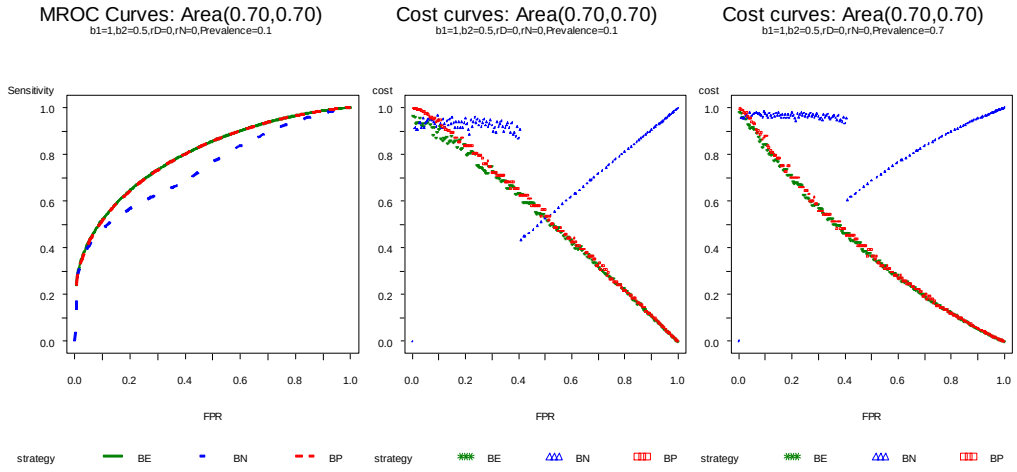

Figure A1.3c: (b1=1, b2=0.5)

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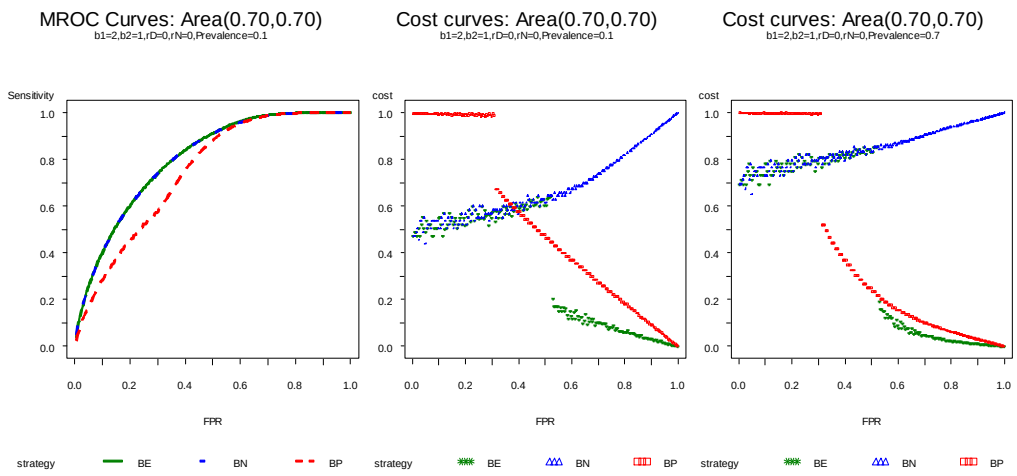

Figure A1.3d: (b1=2, b2=1)

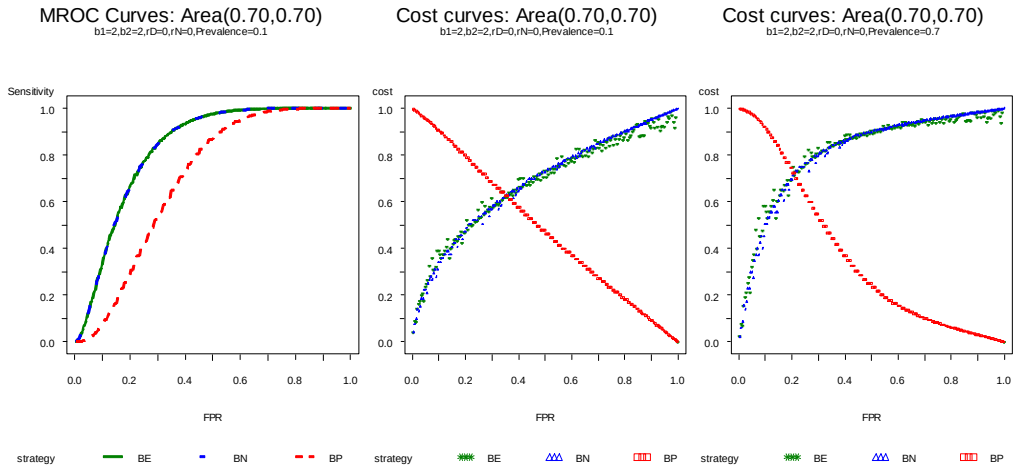

Figure A1.3e: (b1=2, b2=2)

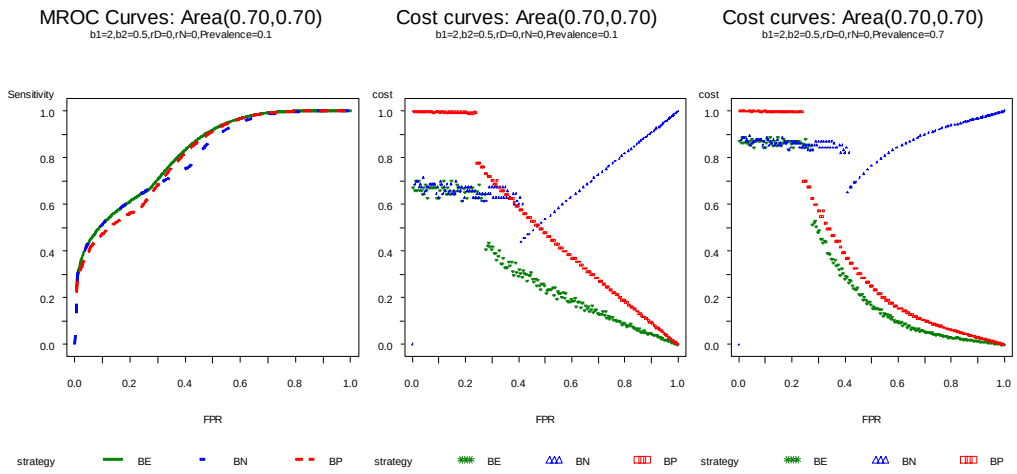

Figure A1.3f: (b1=2, b2=0.5)

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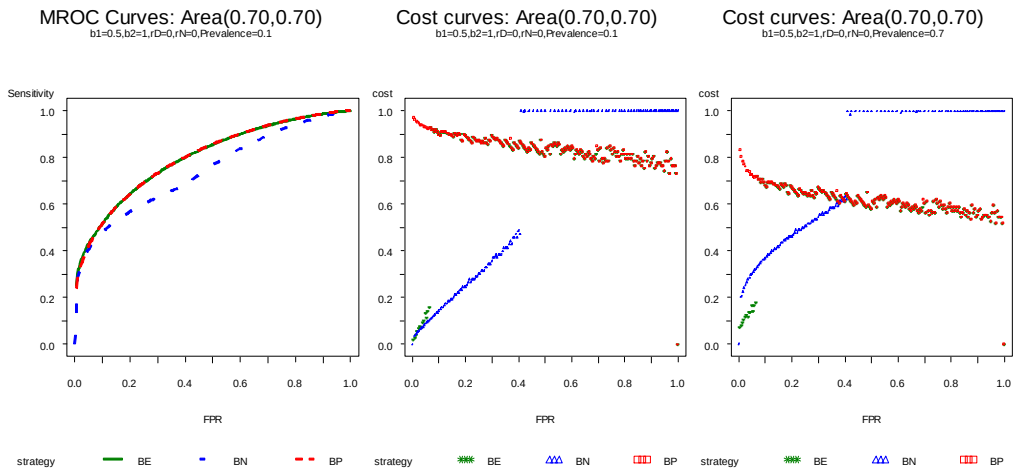

Figure A1.3g: (b1=0.5, b2=1)

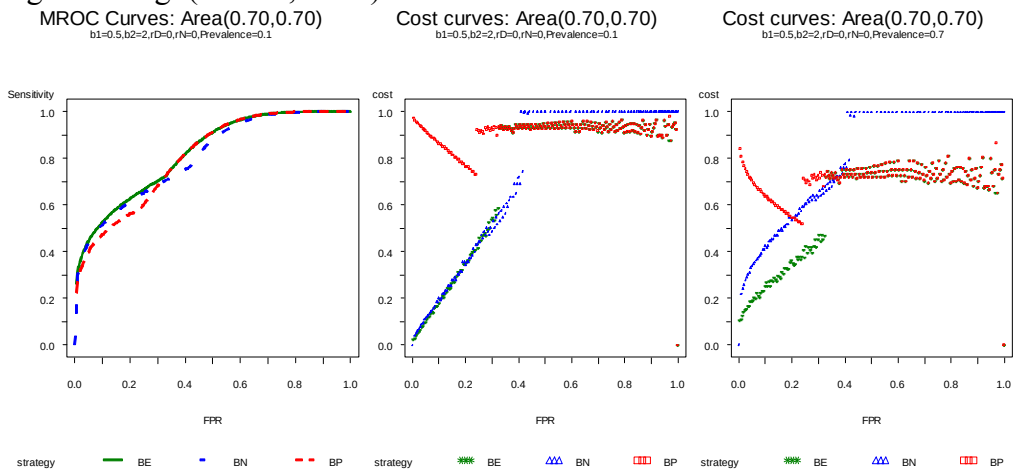

Figure A1.3h: (b1=0.5, b2=2)

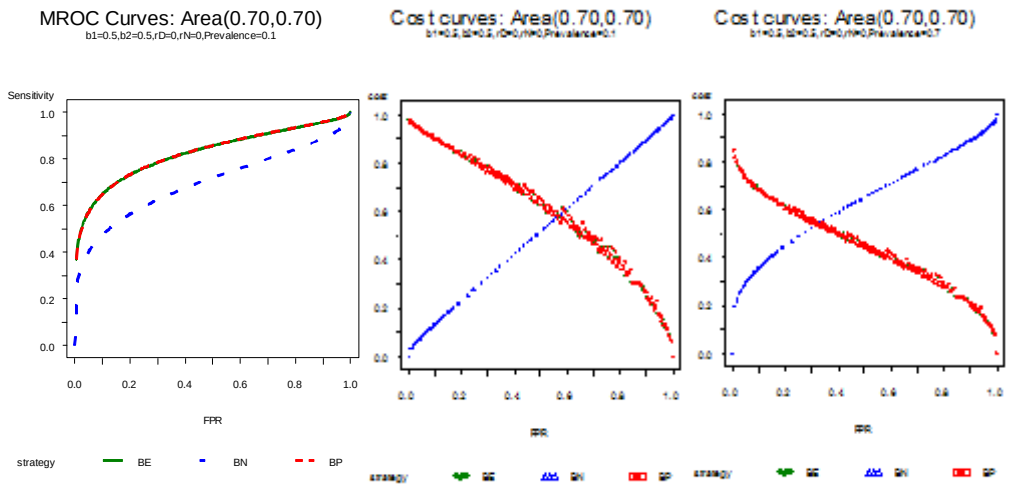

Figure A1.3i: (b1=0.5, b2=0.5)

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A2 Dependent of the tests ($\rho_D = 0.3, \rho_N = 0.3$)

A2.1 AUC1 = 0.90, AUC2 = 0.90

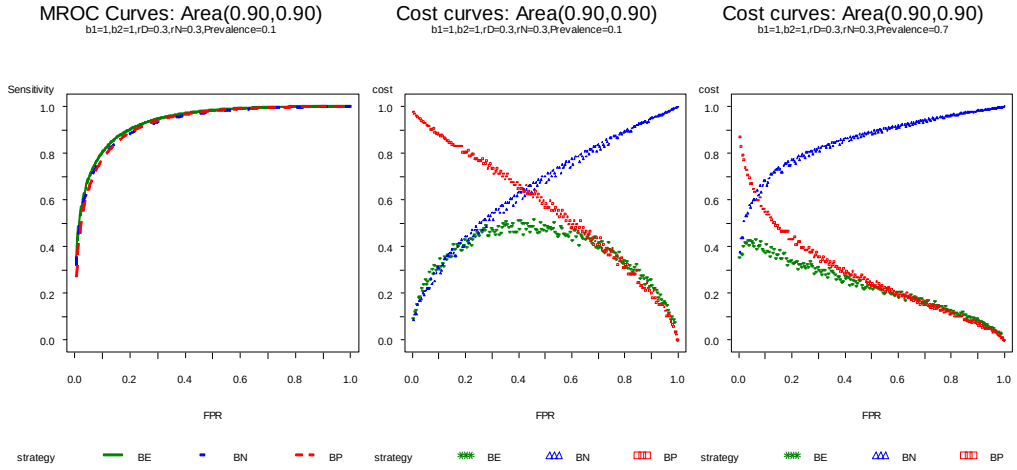

Figure A2.1a: (b1=1, b2=1)

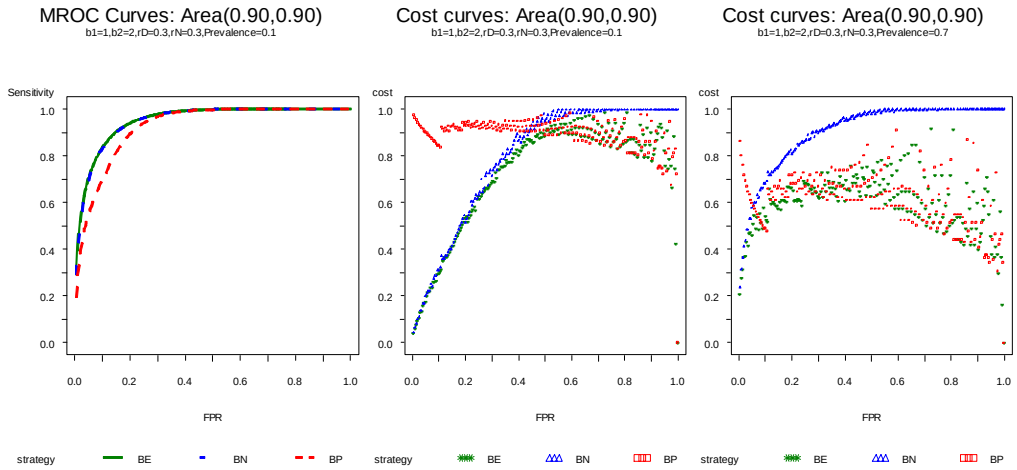

Figure A2.1b: (b1=1, b2=2)

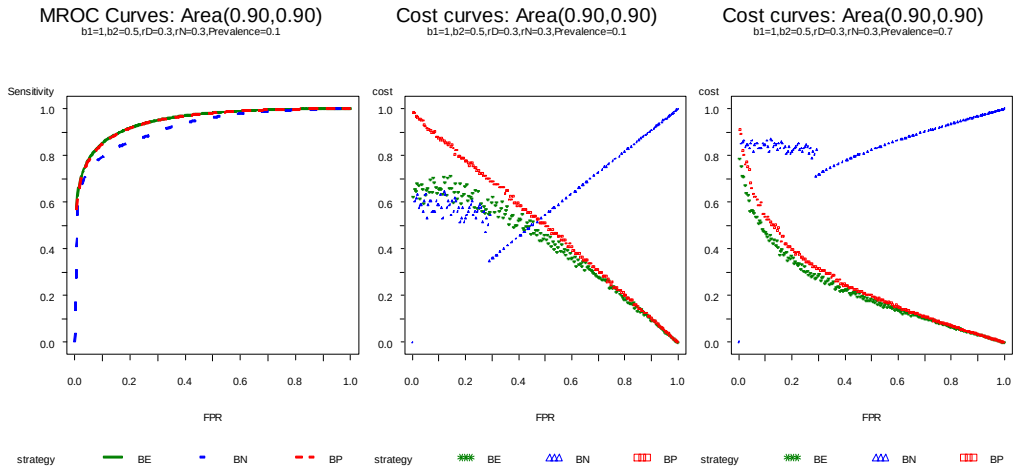

Figure A2.1c: (b1=1, b2=0.5)

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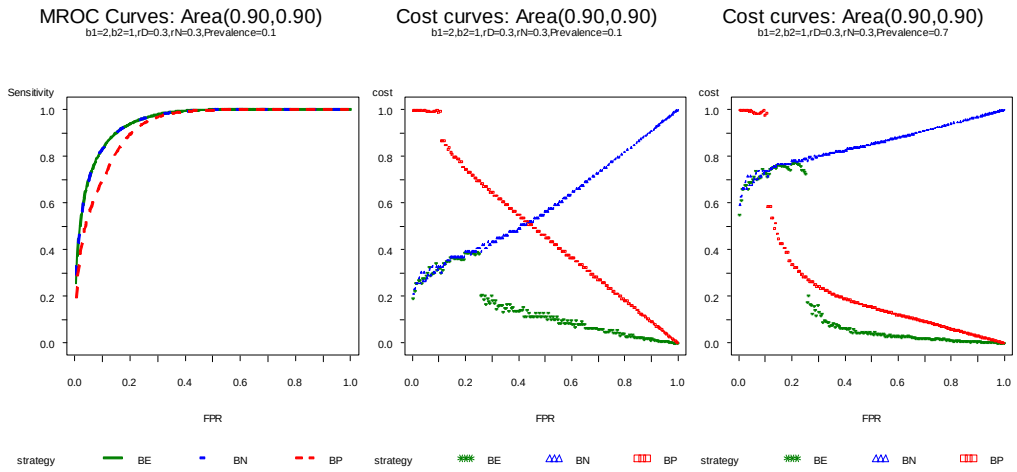

Figure A2.1d: (b1=2, b2=1)

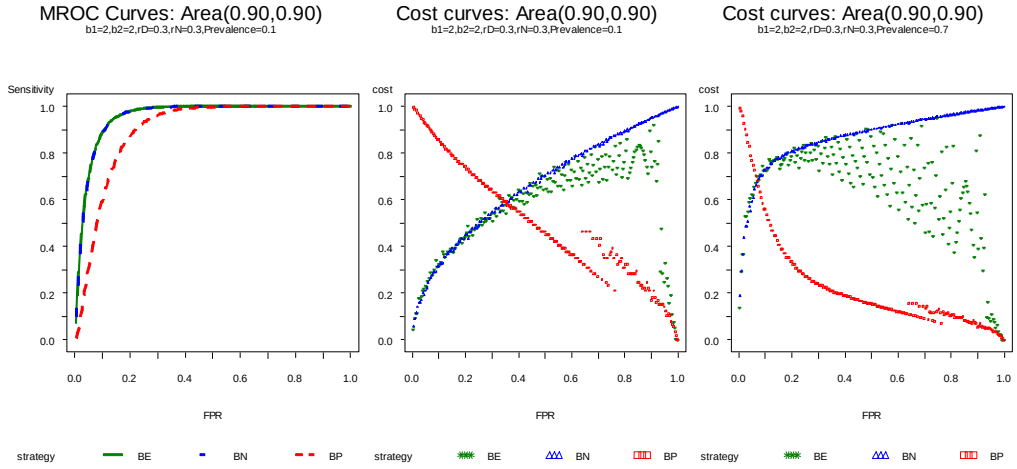

Figure A2.1e: (b1=2, b2=2)

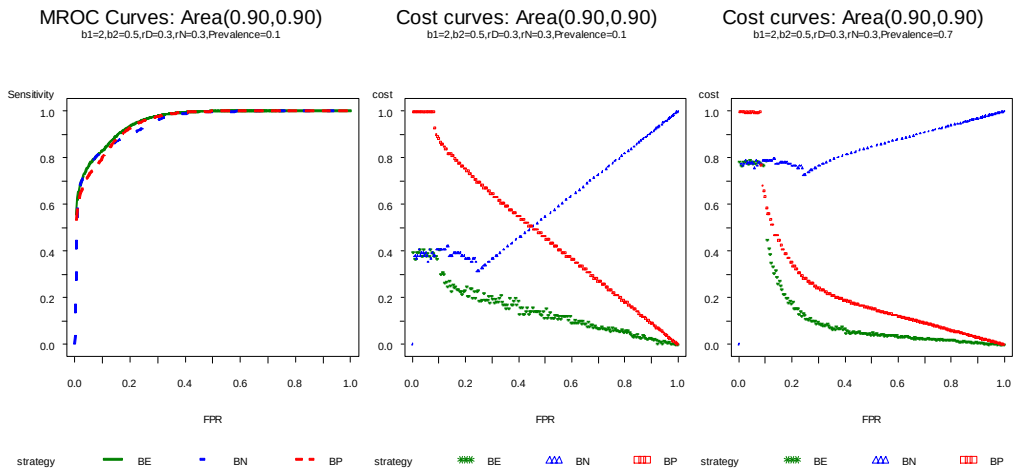

Figure A2.1f: (b1=2, b2=0.5)

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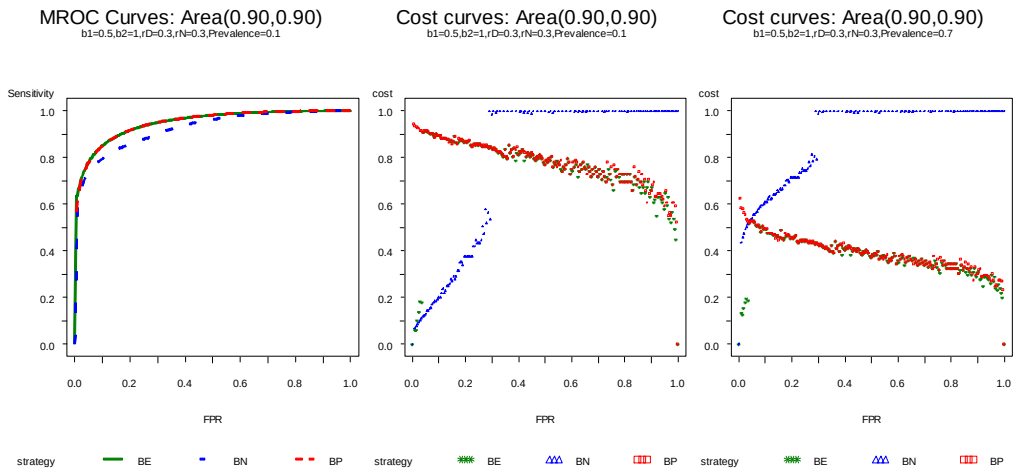

Figure A2.1g: (b1=0.5, b2=1)

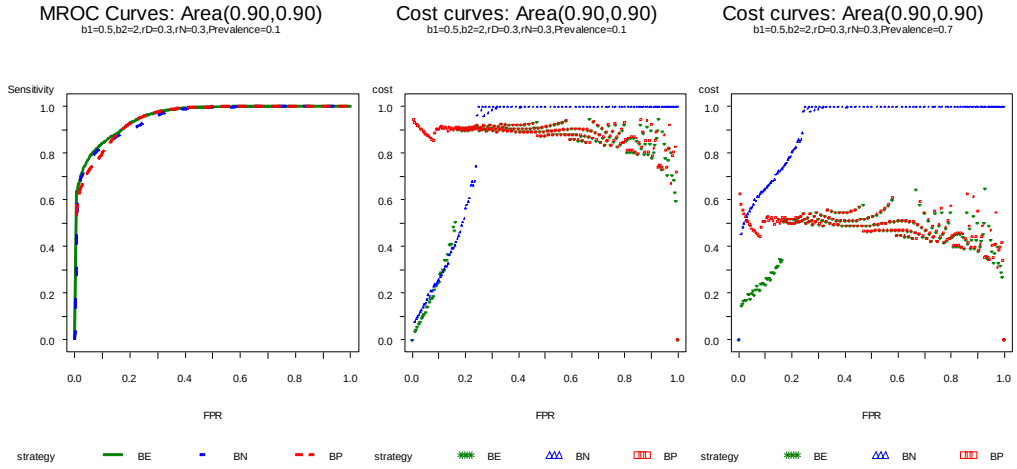

Figure A2.1h: (b1=0.5, b2=2)

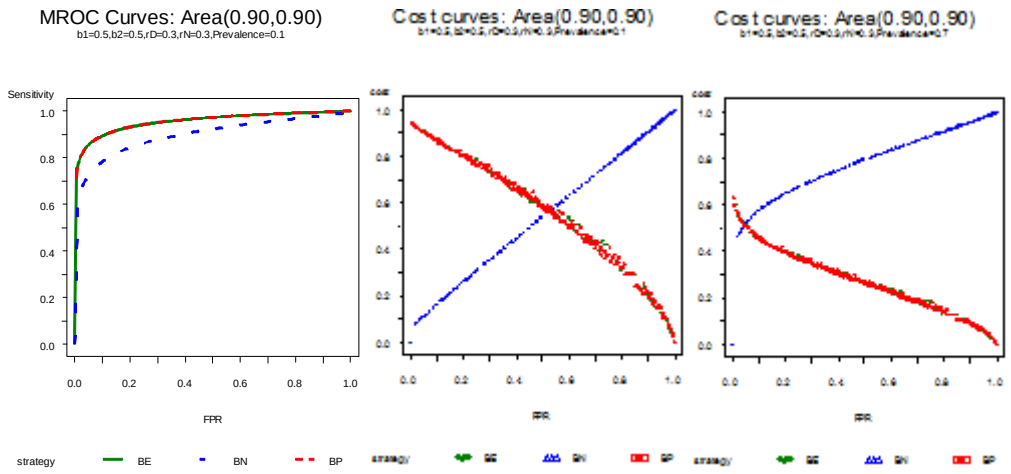

Figure A2.1i: (b1=0.5, b2=0.5)

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A2.2 AUC1 = 0.70, AUC2 = 0.90

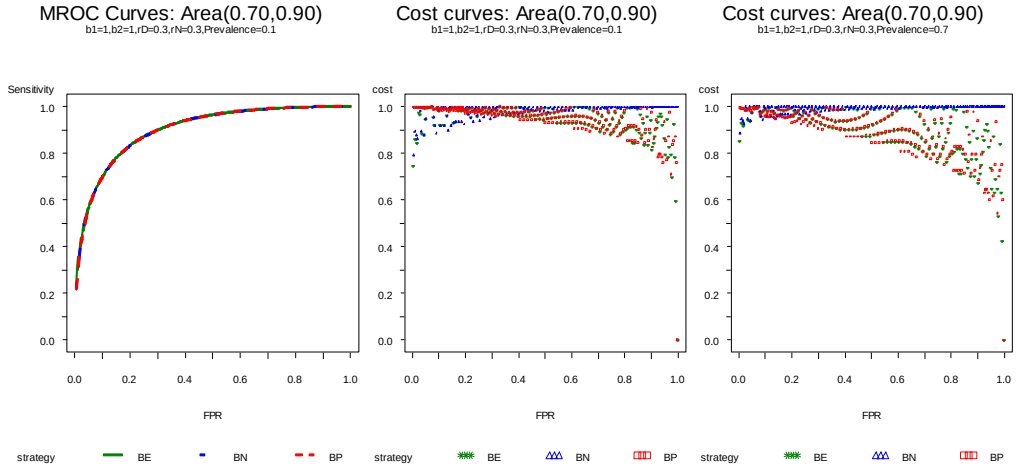

Figure A2.2a: (b1=1, b2=1)

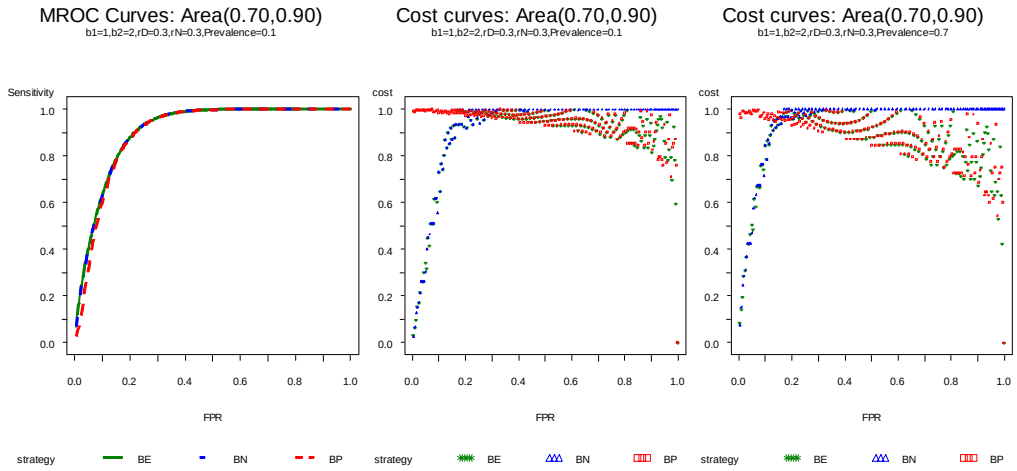

Figure A2.2b: (b1=1, b2=2)

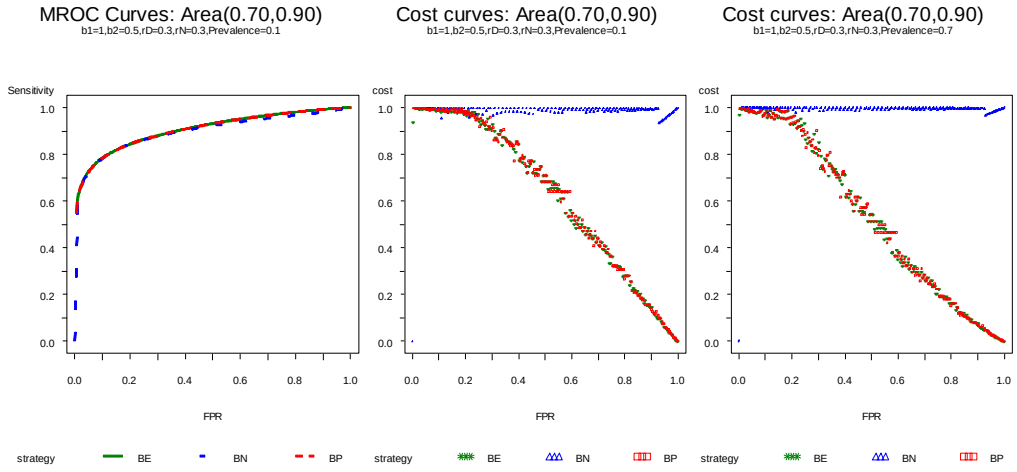

Figure A2.2c: (b1=1, b2=0.5)

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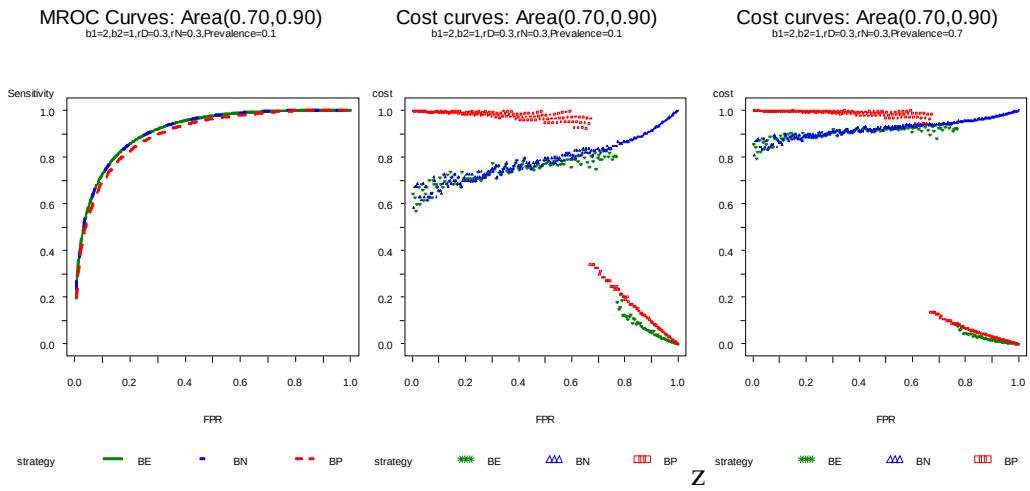

Z

Figure A2.2d: (b1=2, b2=1)

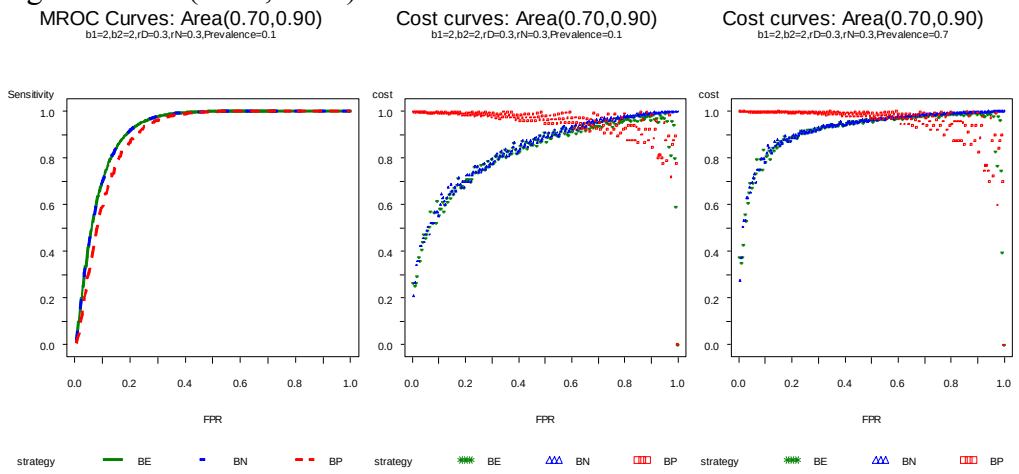

Figure A2.2e: (b1=2, b2=2)

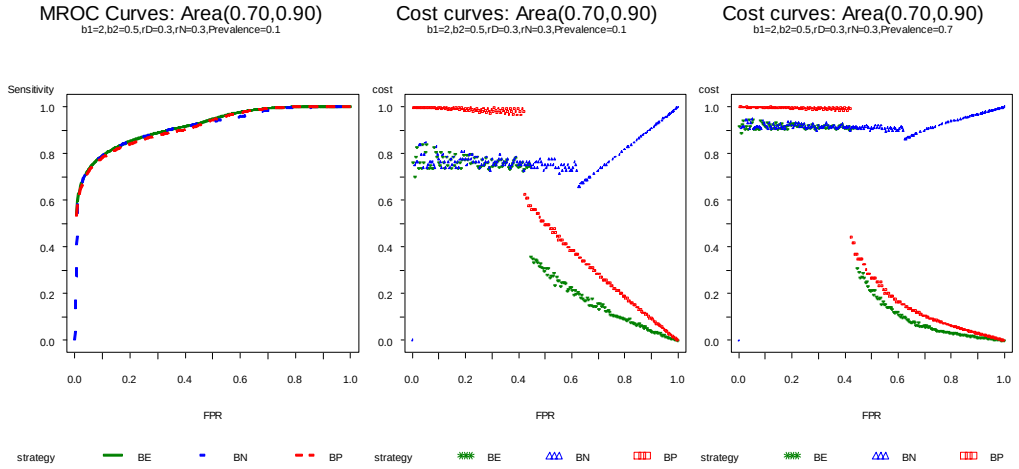

Figure A2.2f: (b1=2, b2=0.5)

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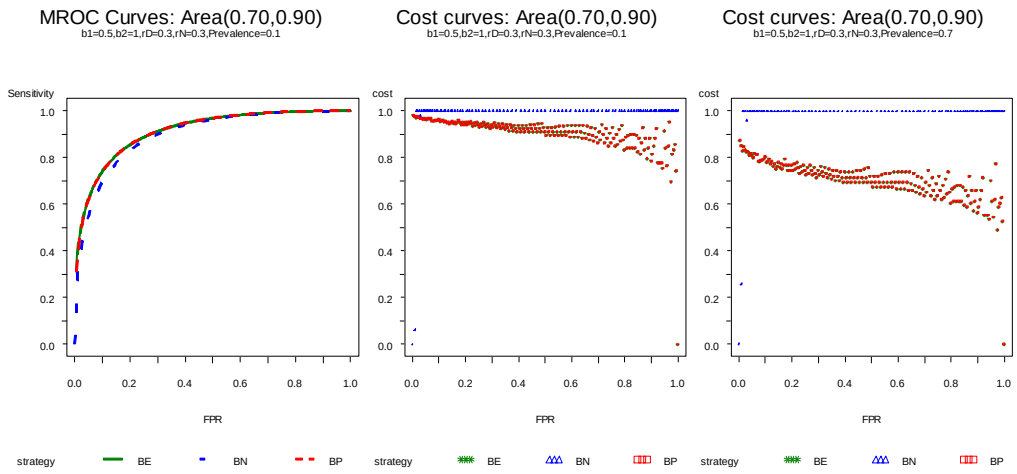

Figure A2.2g: (b1=0.5, b2=1)

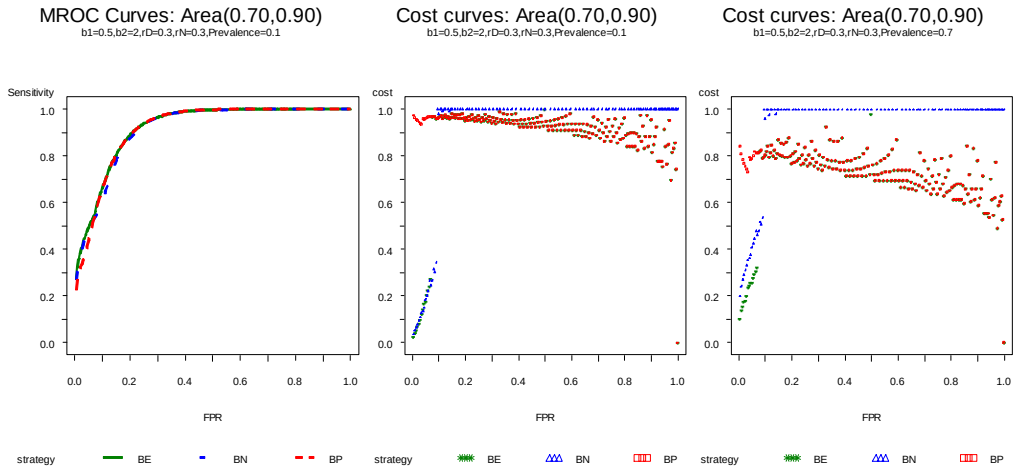

Figure A2.2h: (b1=0.5, b2=2)

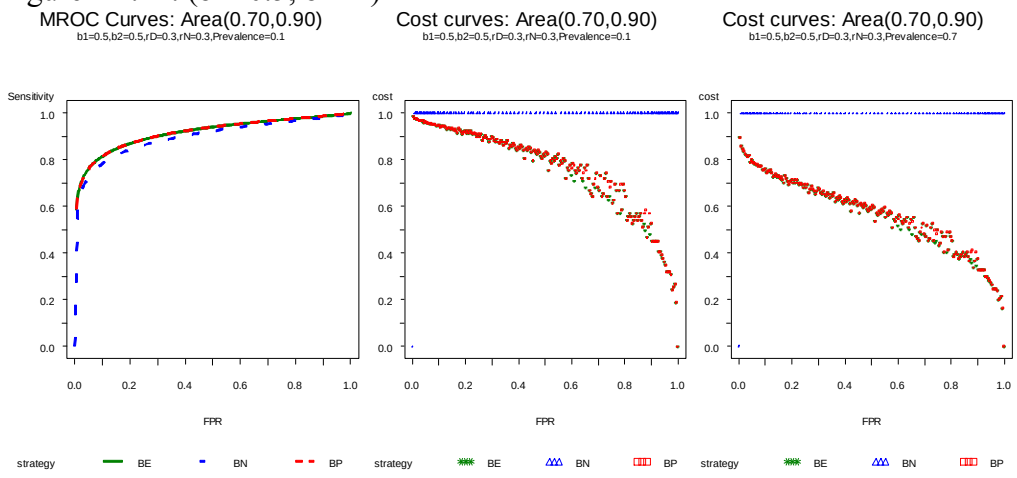

Figure A2.2i: (b1=0.5, b2=0.5)

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A2.3 AUC1 = 0.70, AUC2 = 0.70

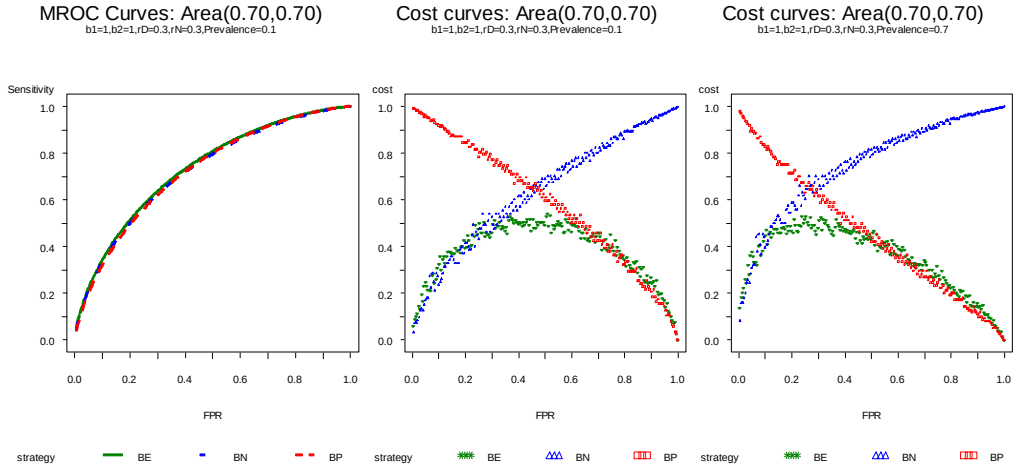

Figure A2.3a: (b1=1, b2=1)

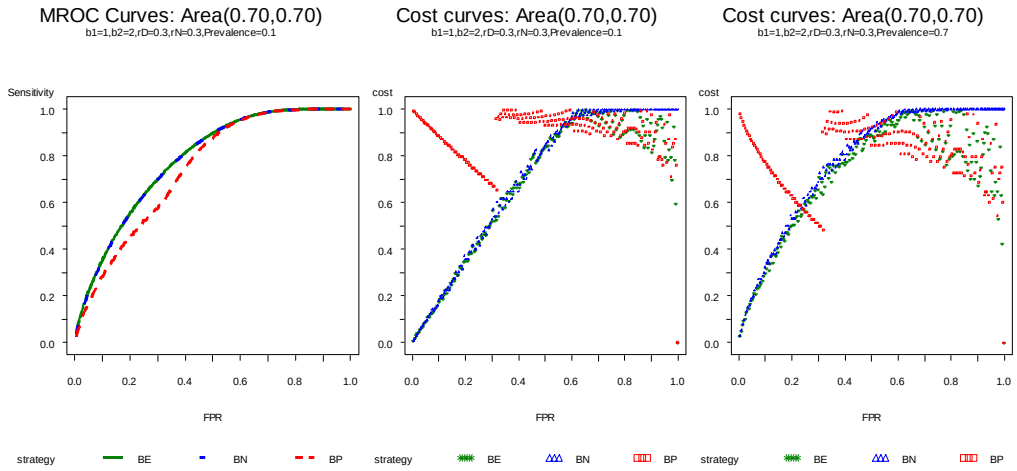

Figure A2.3b: (b1=1, b2=2)

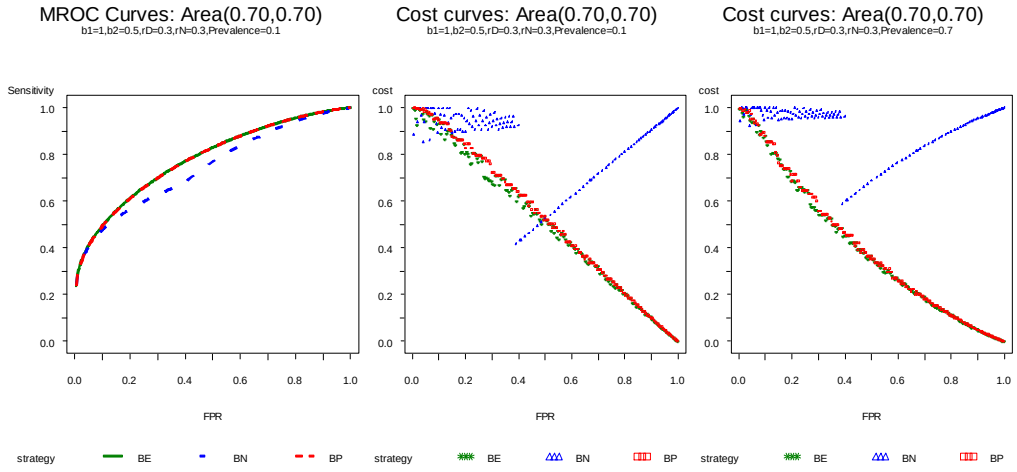

Figure A2.3c: (b1=1, b2=0.5)

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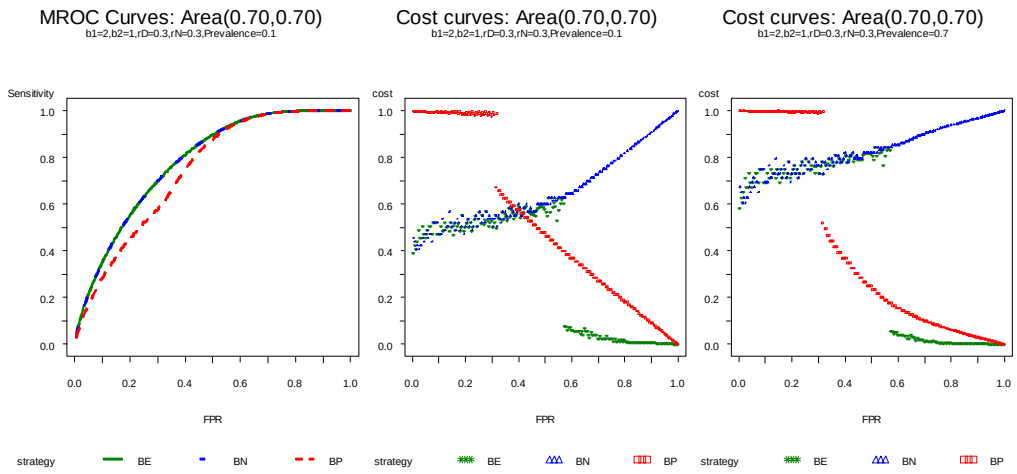

Figure A2.3d: (b1=2, b2=1)

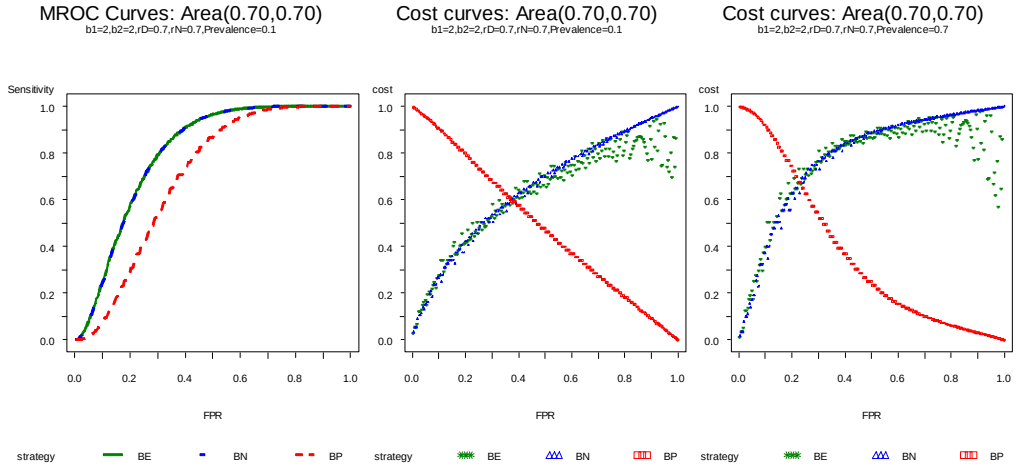

Figure A2.3e: (b1=2, b2=2)

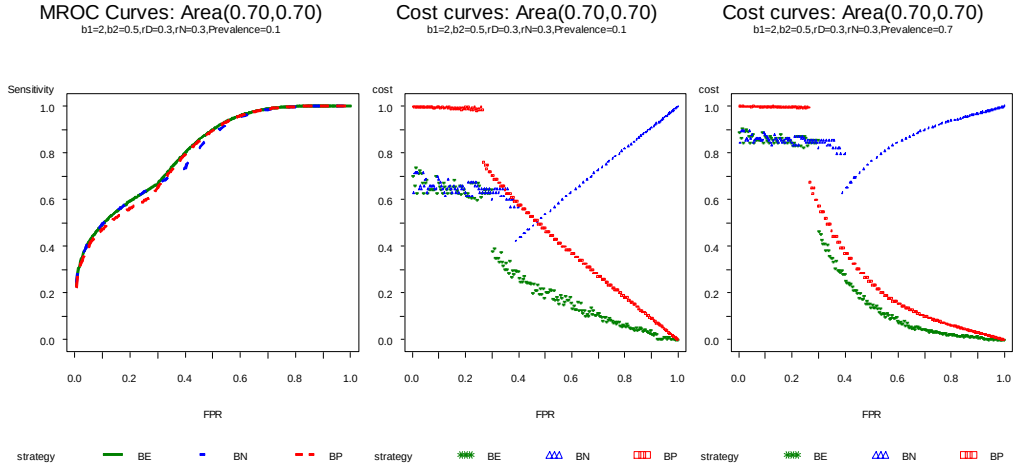

Figure A2.3f: (b1=2, b2=0.5)

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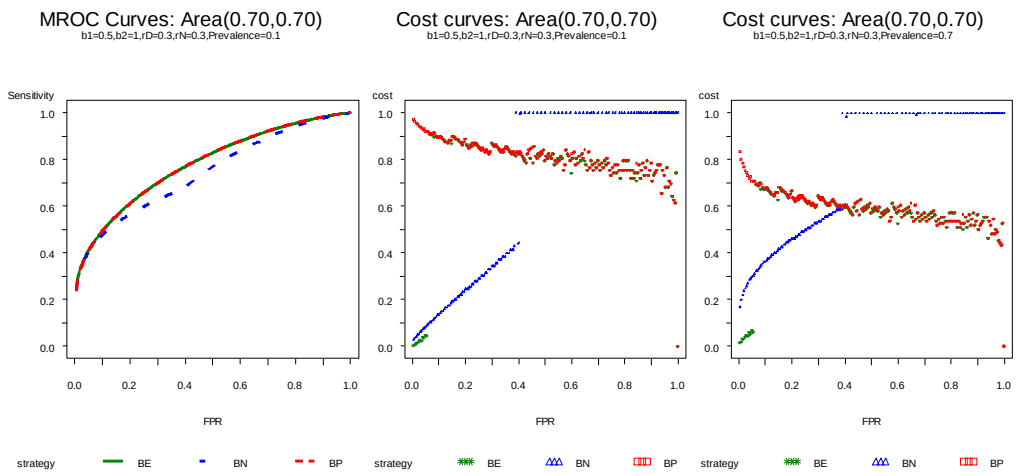

Figure A2.3g: (b1=0.5, b2=1)

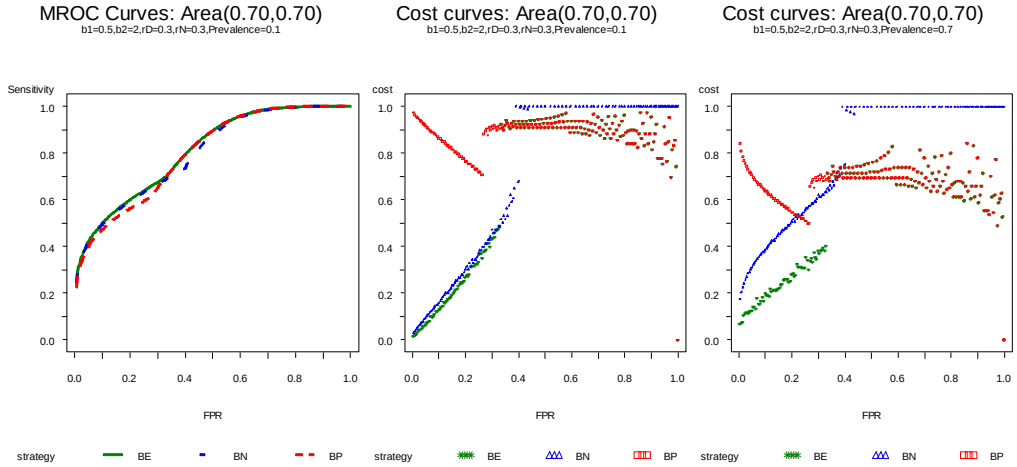

Figure A2.3h: (b1=0.5, b2=2)

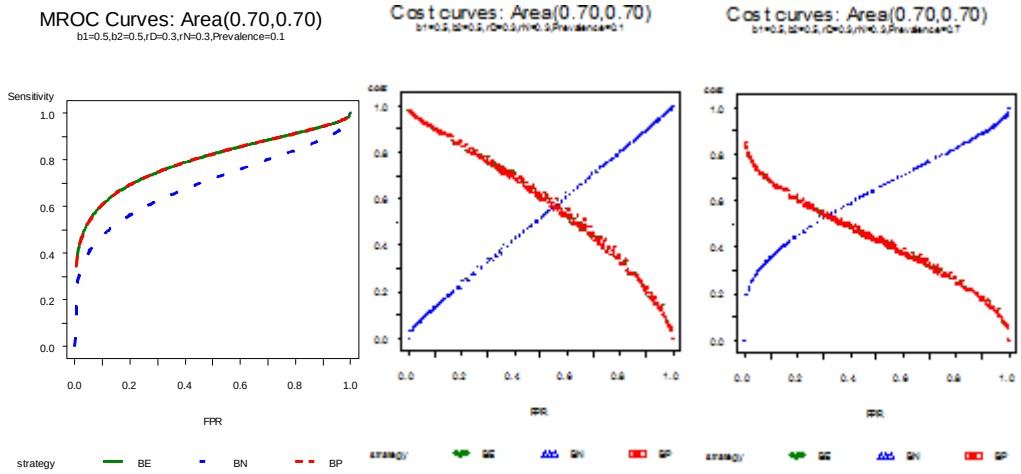

Figure A2.3i: (b1=0.5, b2=0.5)

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A3 Dependent of the tests $(\rho_D = 0.3, \rho_N = 0.7)$

A3.1 AUC1 = 0.90, AUC2 = 0.90

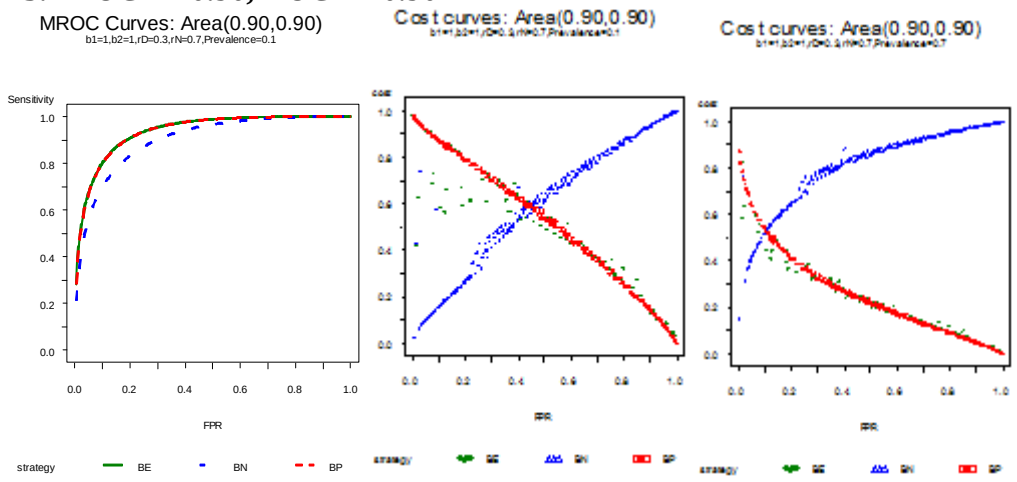

Figure A3.1a: (b1=1, b2=1)

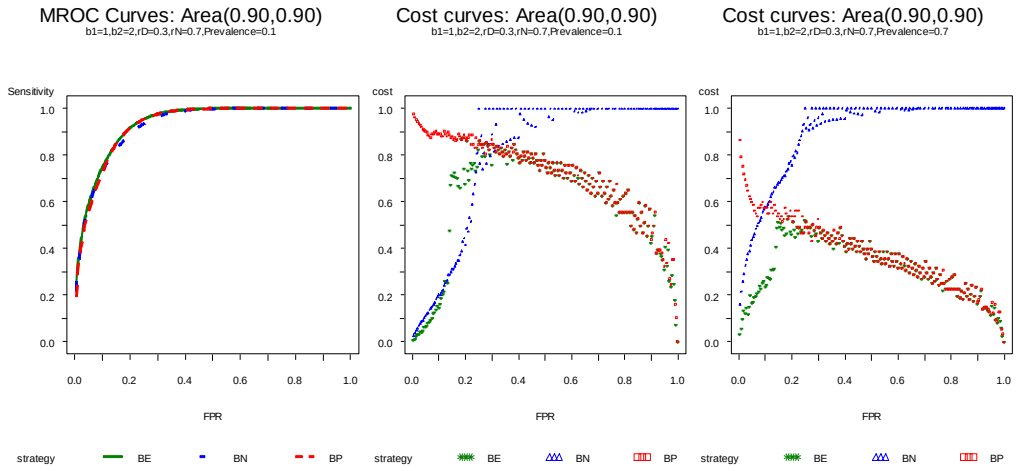

Figure A3.1b: (b1=1, b2=2)

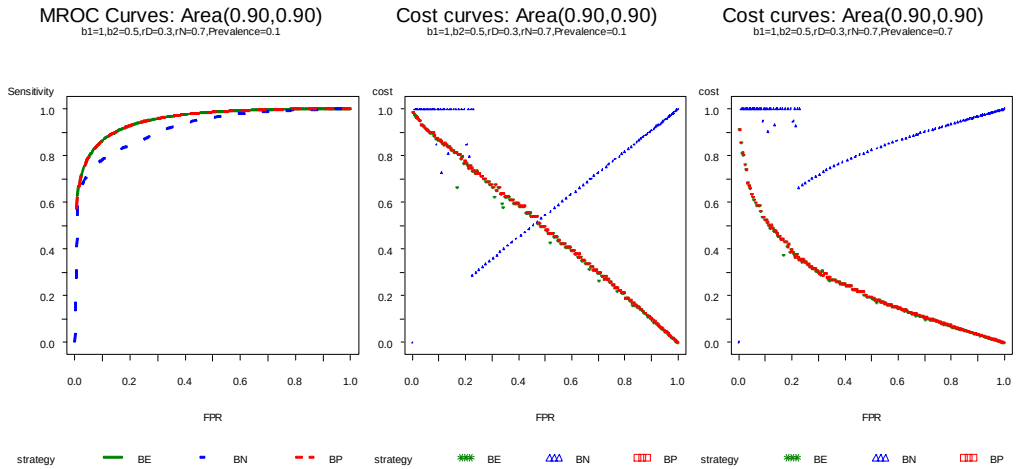

Figure A3.1c: (b1=1, b2=0.5)

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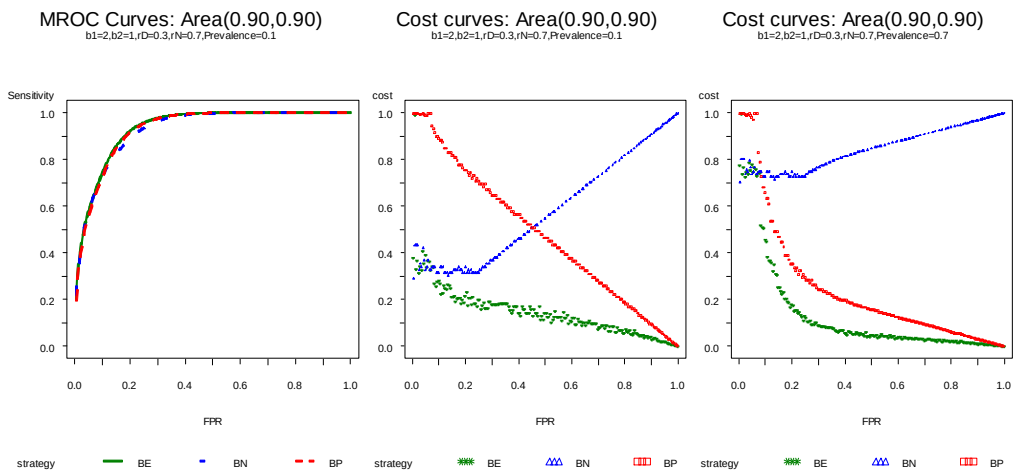

Figure A3.1d: (b1=2, b2=1)

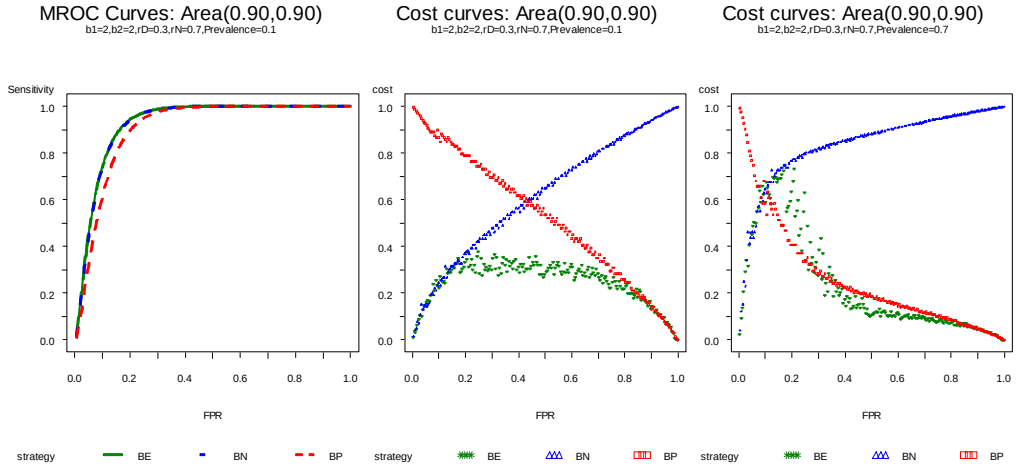

Figure A3.1e: (b1=2, b2=2)

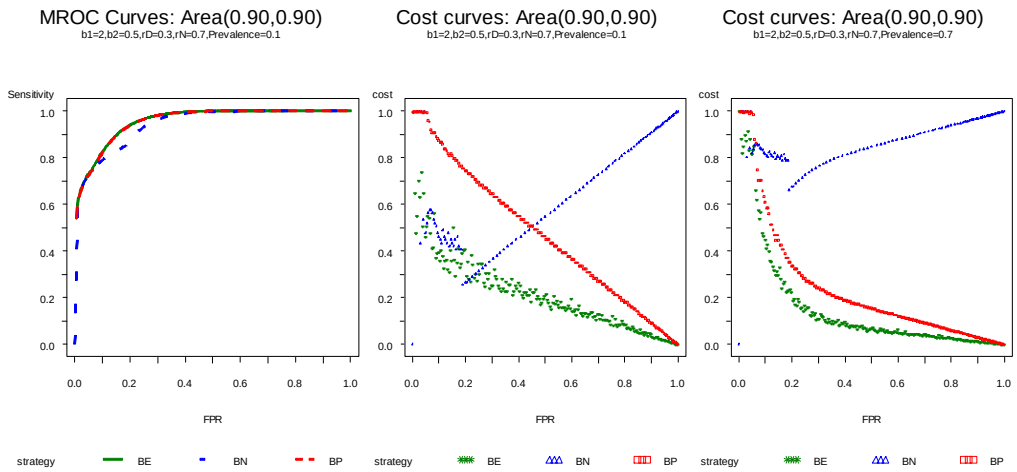

Figure A3.1f: (b1=2, b2=0.5)

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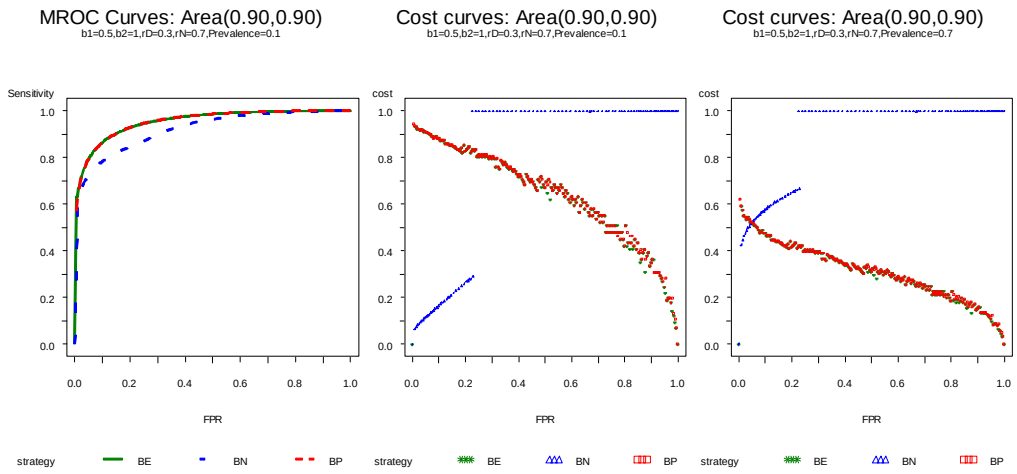

Figure A3.1g: (b1=0.5, b2=1)

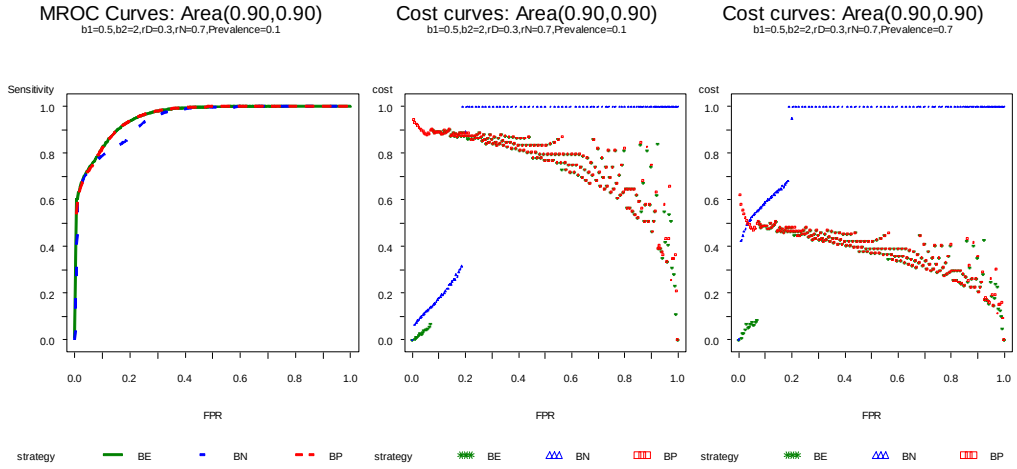

Figure A3.1h: (b1=0.5, b2=2)

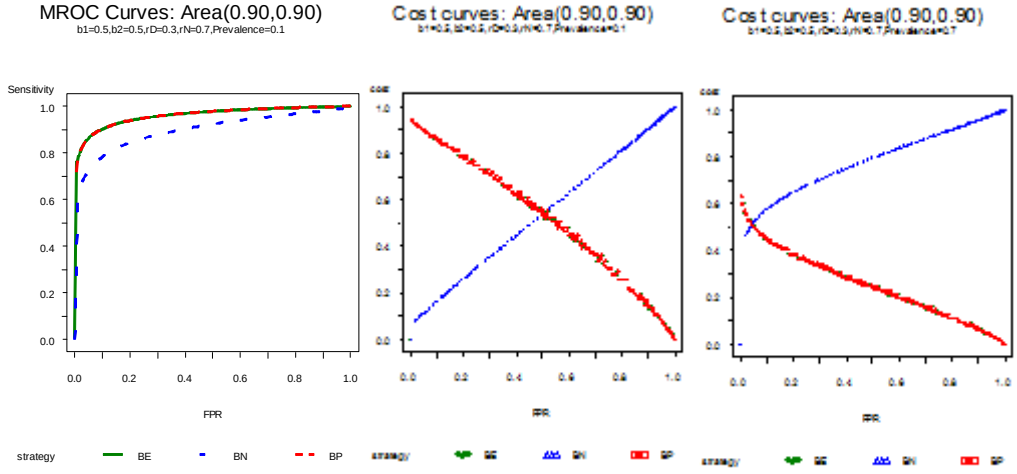

Figure A3.1i: (b1=0.5, b2=0.5)

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A3.2 AUC1 = 0.70, AUC2 = 0.90

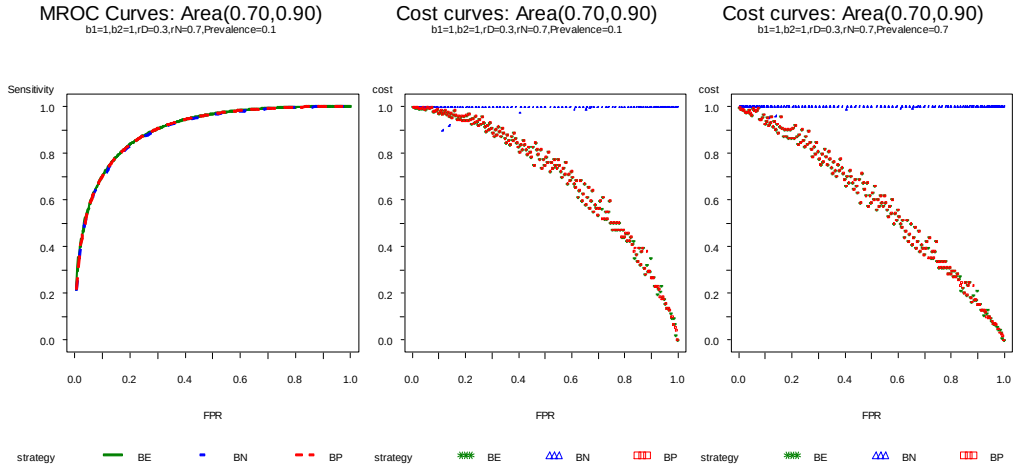

Figure A3.2a: (b1=1, b2=1)

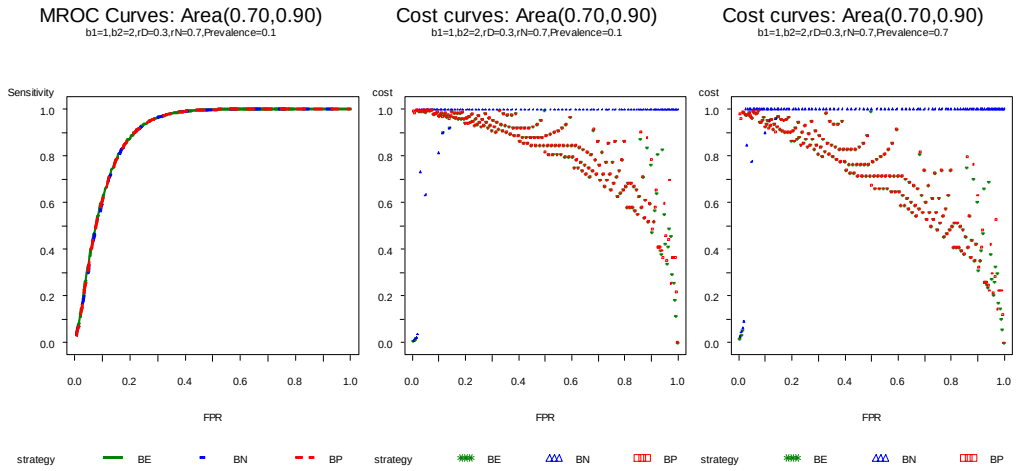

Figure A3.2b: (b1=1, b2=2)

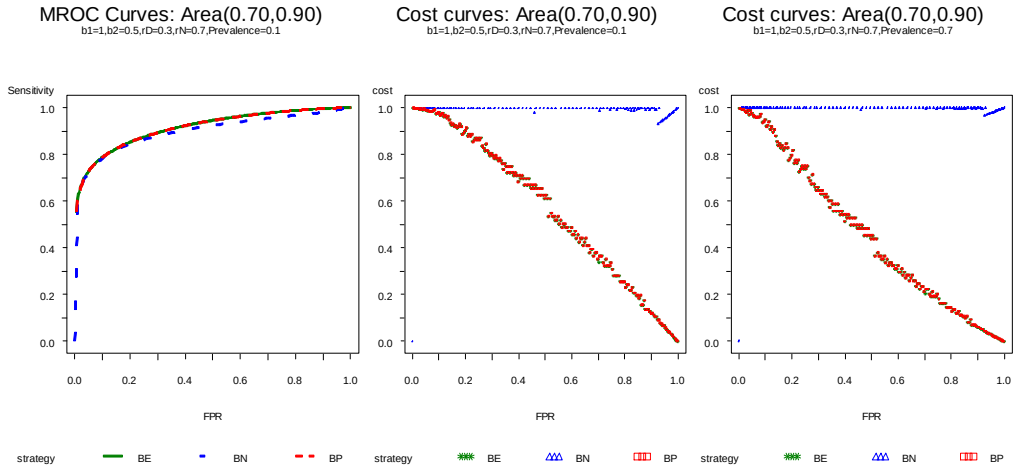

Figure A3.2c: (b1=1, b2=0.5)

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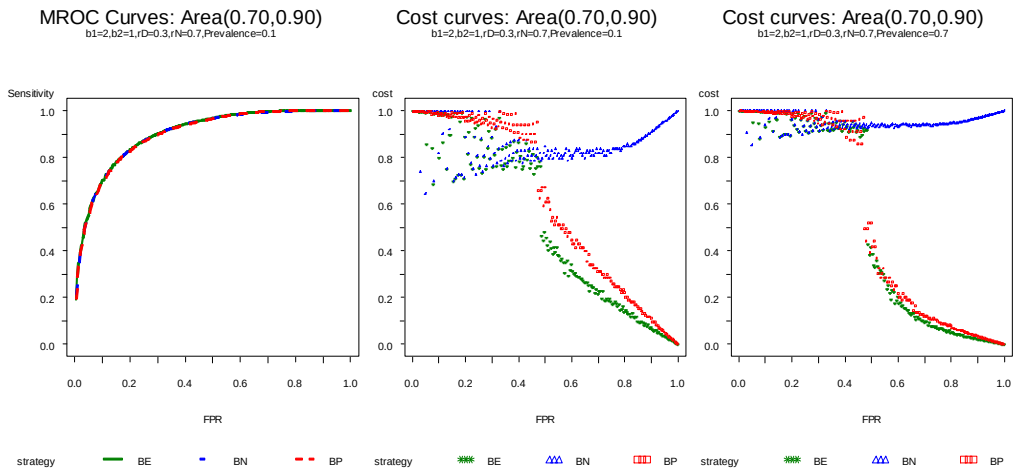

Figure A3.2d: (b1=2, b2=1)

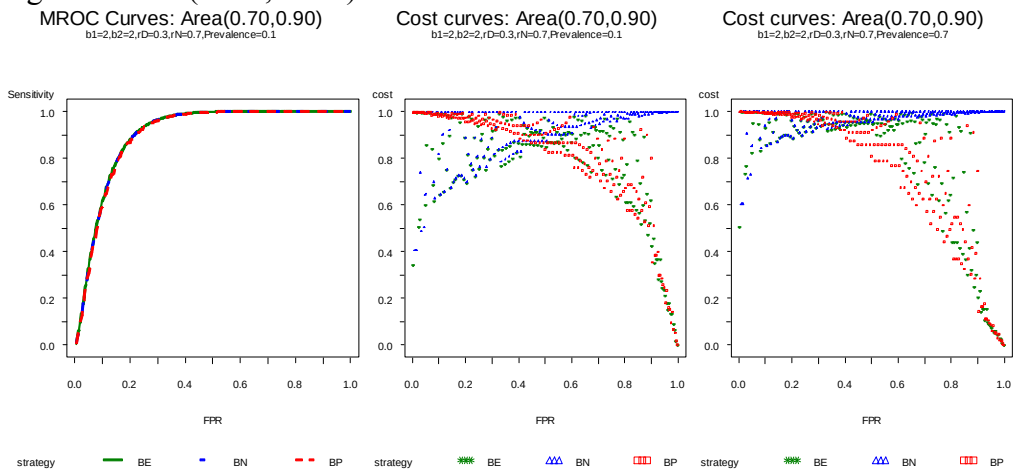

Figure A3.2e: (b1=2, b2=2)

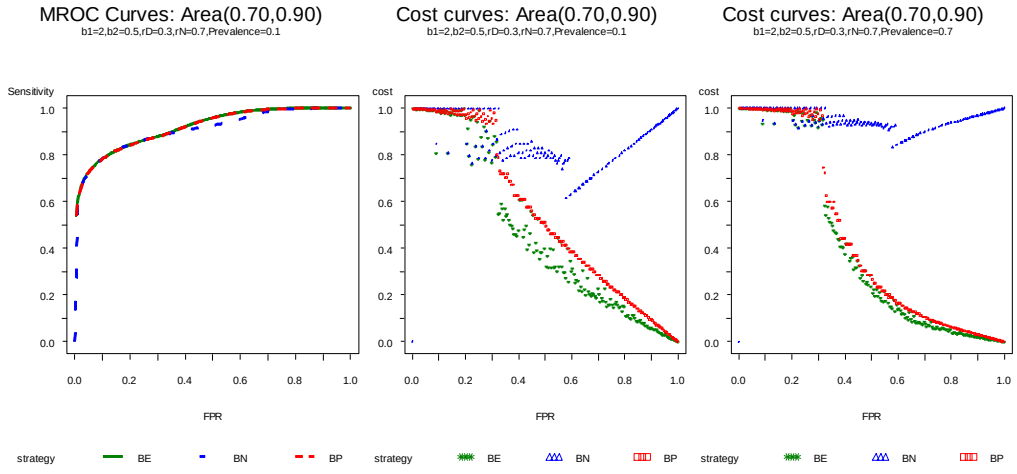

Figure A3.2f: (b1=2, b2=0.5)

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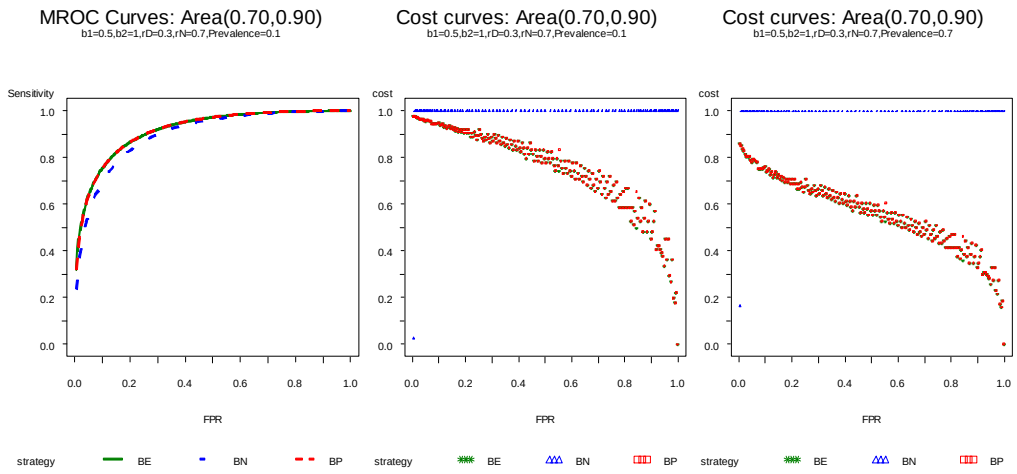

Figure A3.2g: (b1=0.5, b2=1)

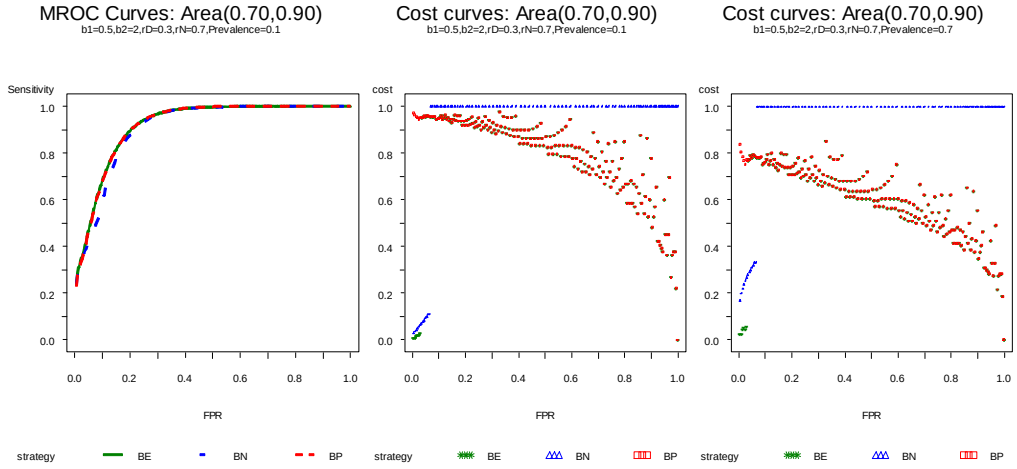

Figure A3.2h: (b1=0.5, b2=2)

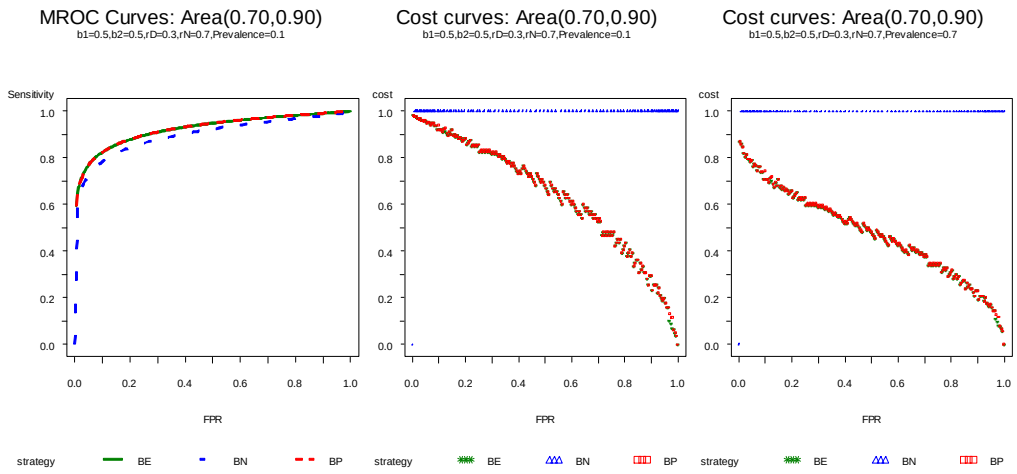

Figure A3.2i: (b1=0.5, b2=0.5)

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A3.3 AUC1 = 0.70, AUC2 = 0.70

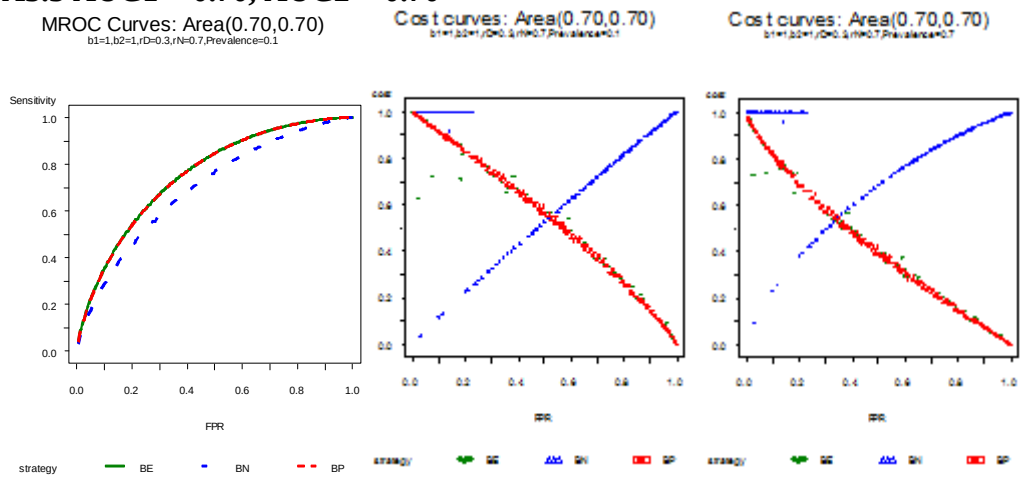

Figure A3.3a: (b1=1, b2=1)

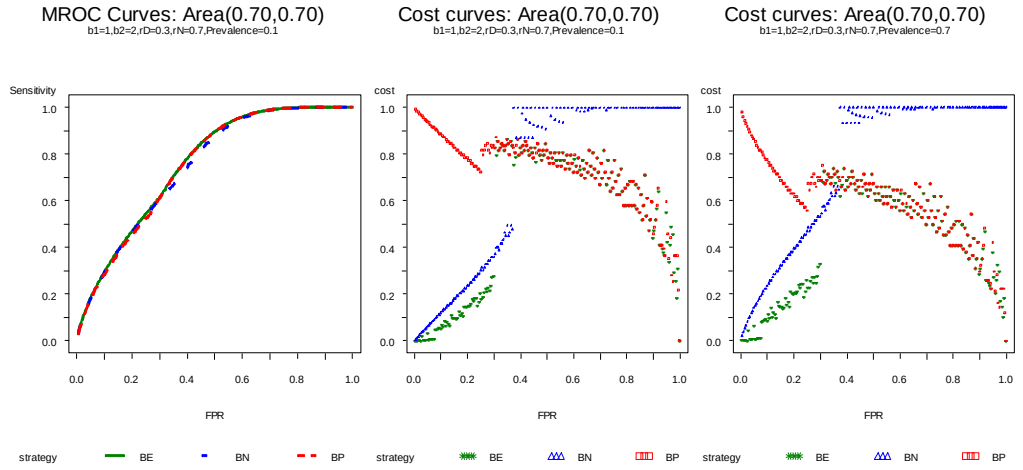

Figure A3.3b: (b1=1, b2=2)

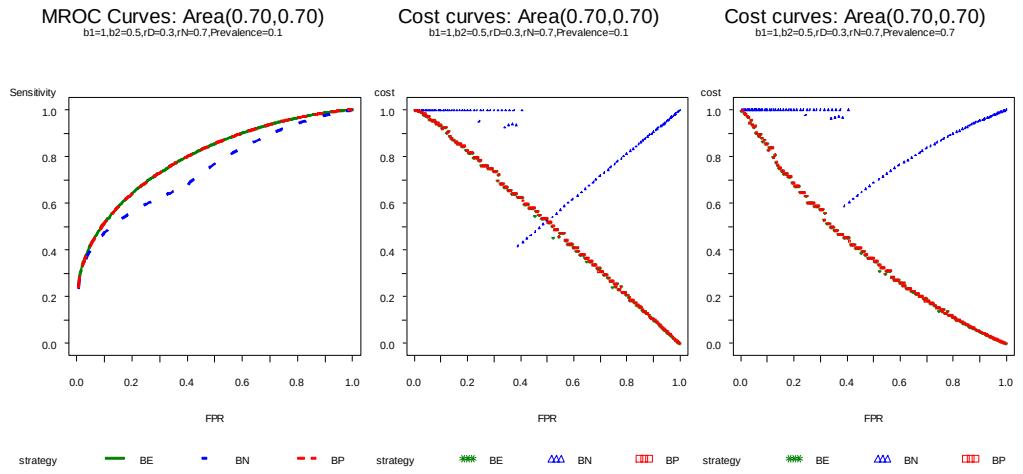

Figure A3.3c: (b1=1, b2=0.5)

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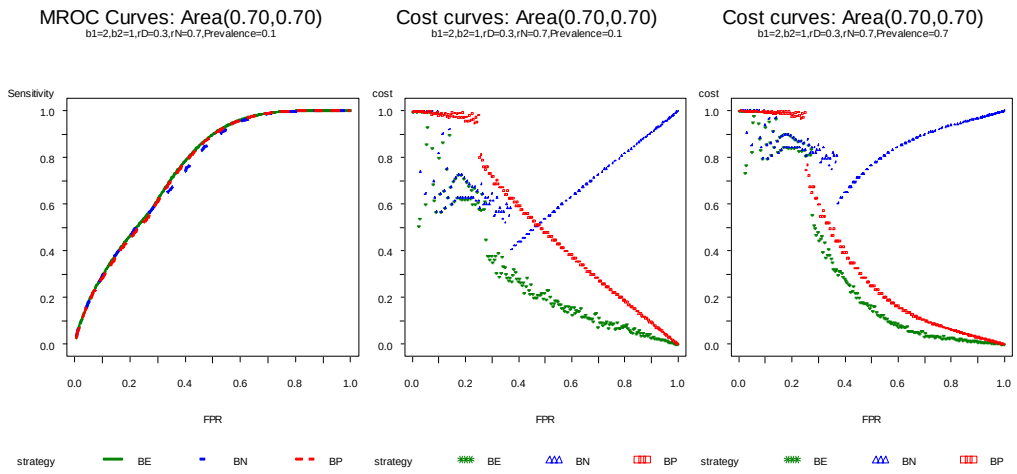

Figure A3.3d: (b1=2, b2=1)

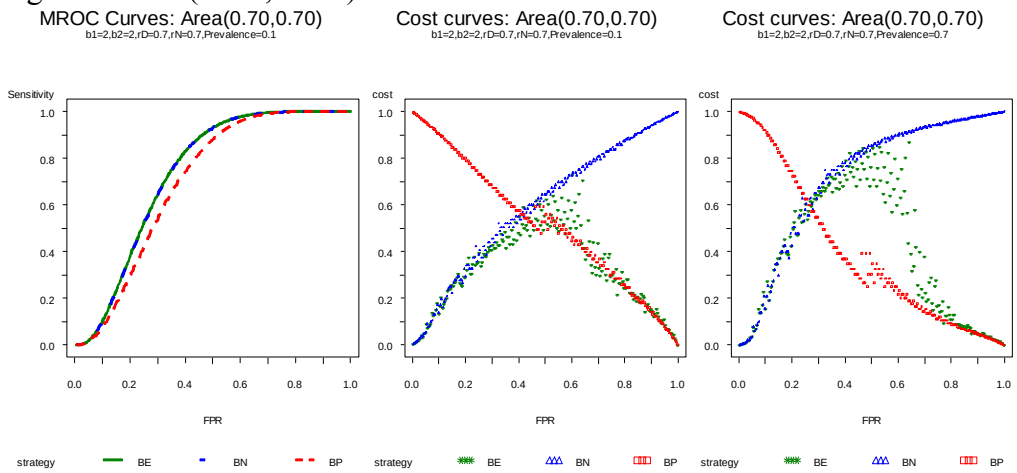

Figure A3.3e: (b1=2, b2=2)

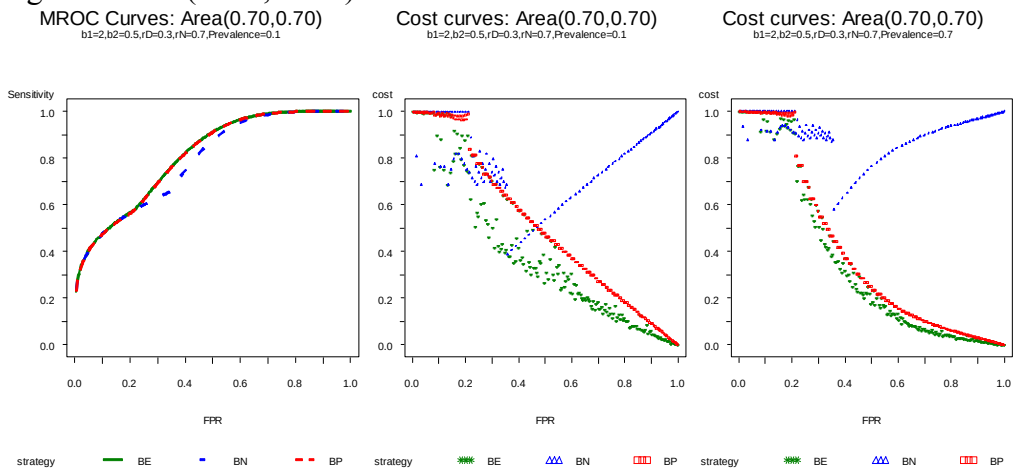

Figure A3.3f: (b1=2, b2=0.5)

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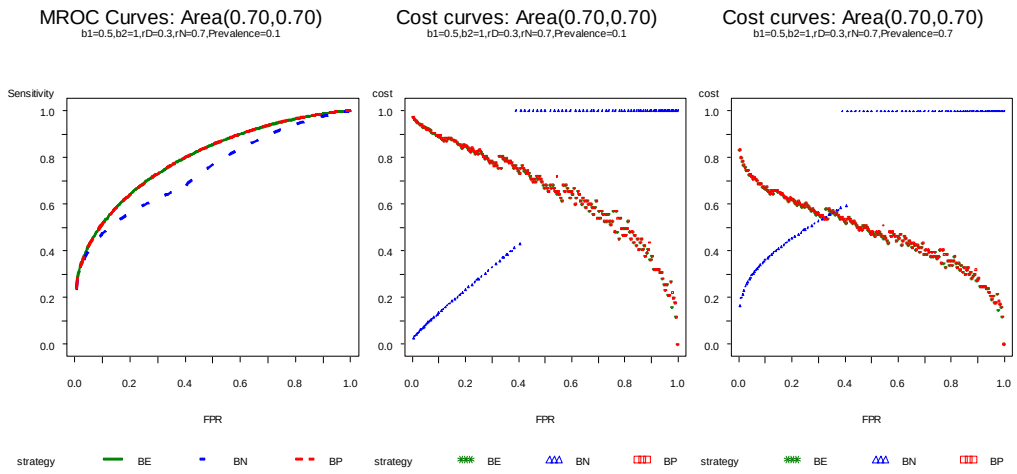

Figure A3.3g: (b1=0.5, b2=1)

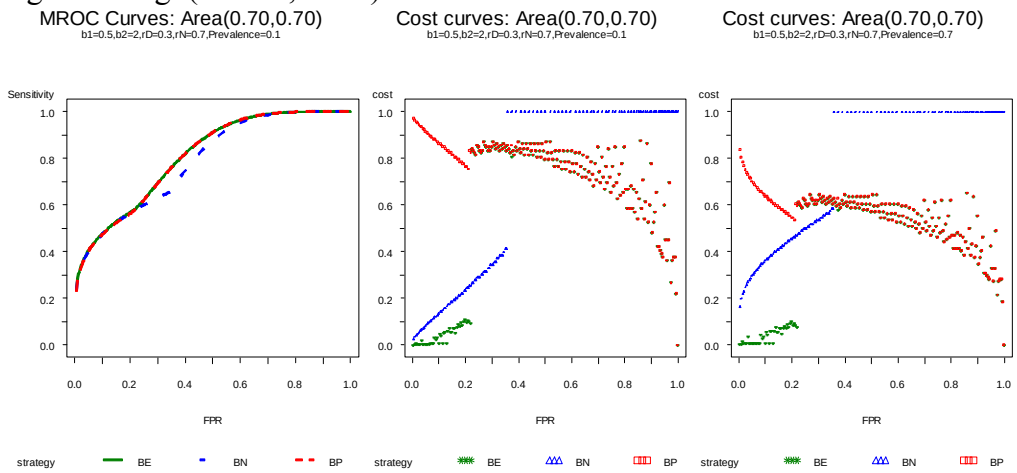

Figure A3.3h: (b1=0.5, b2=2)

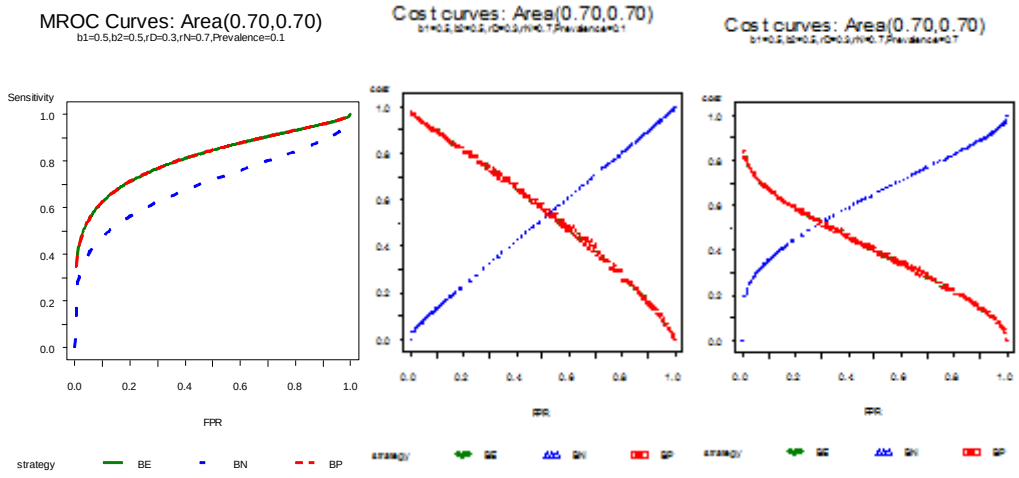

Figure A3.3i: (b1=0.5, b2=0.5)

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A4 Dependent of the tests ($\rho_D = 0.7, \rho_N = 0.3$)

A4.1 AUC1 = 0.90, AUC2 = 0.90

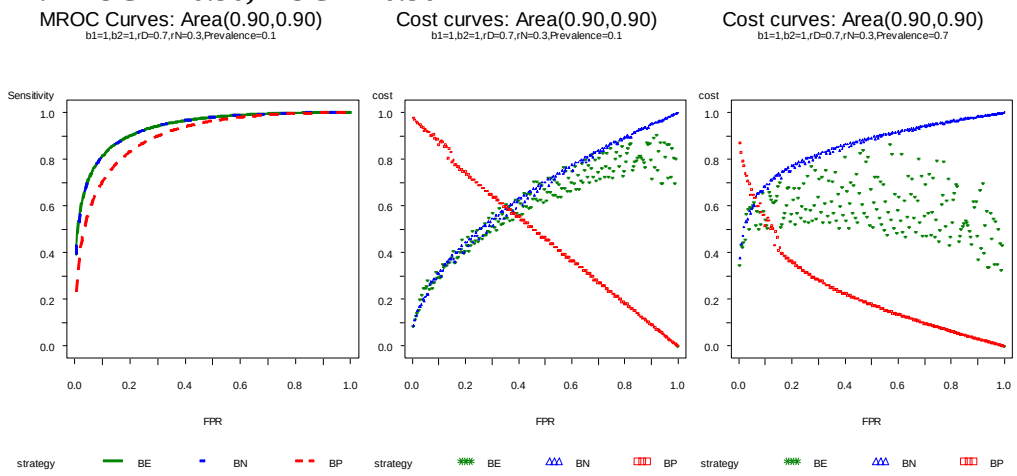

Figure A4.1a: (b1=1, b2=1)

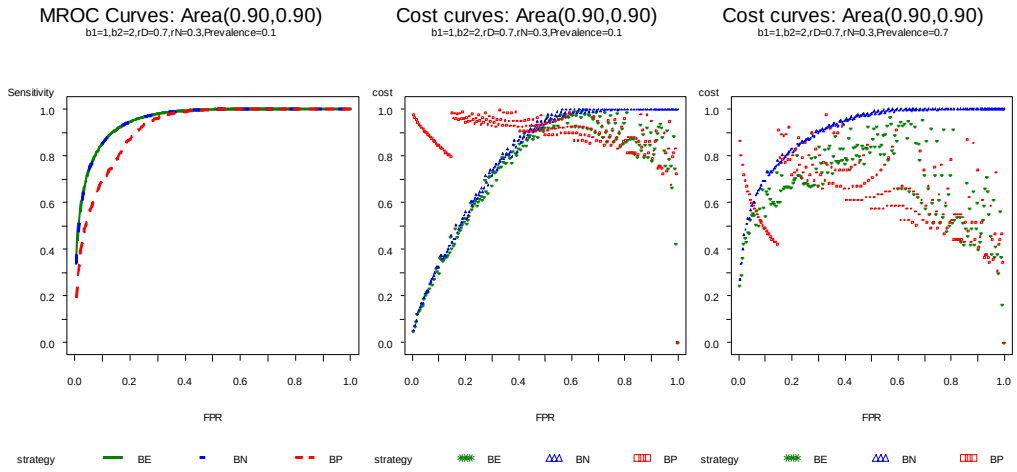

Figure A4.1b: (b1=1, b2=2)

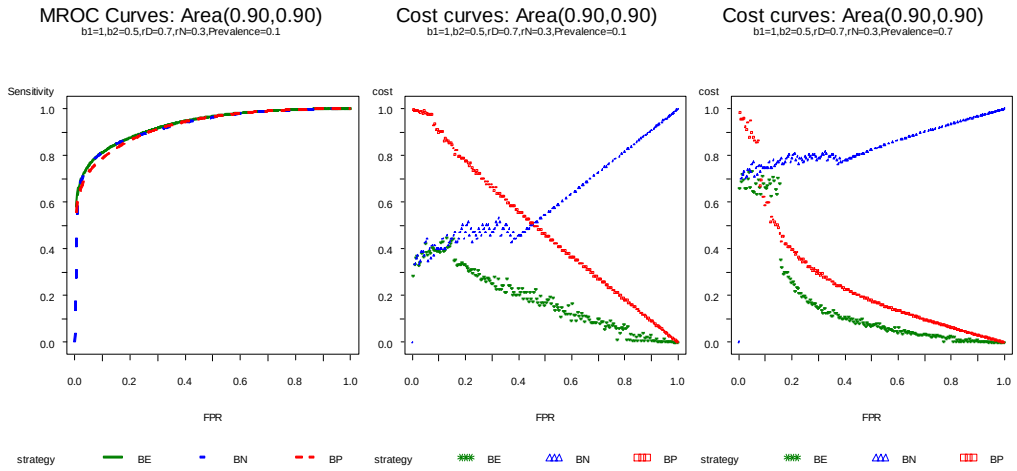

Figure A4.1c: (b1=1, b2=0.5)

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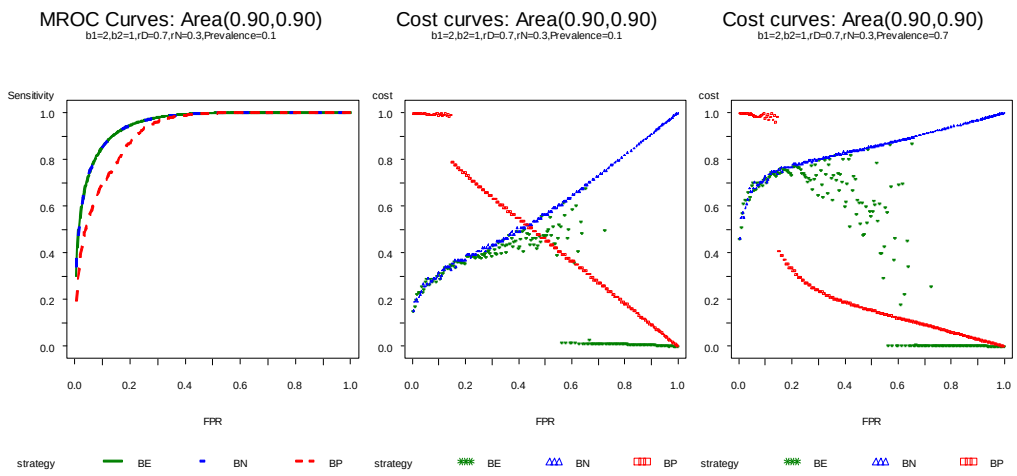

Figure A4.1d: (b1=2, b2=1)

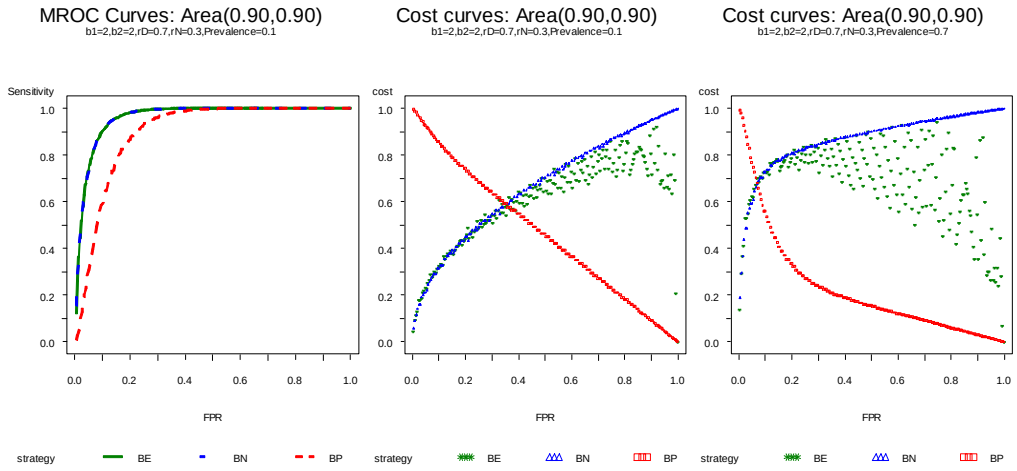

Figure A4.1e: (b1=2, b2=2)

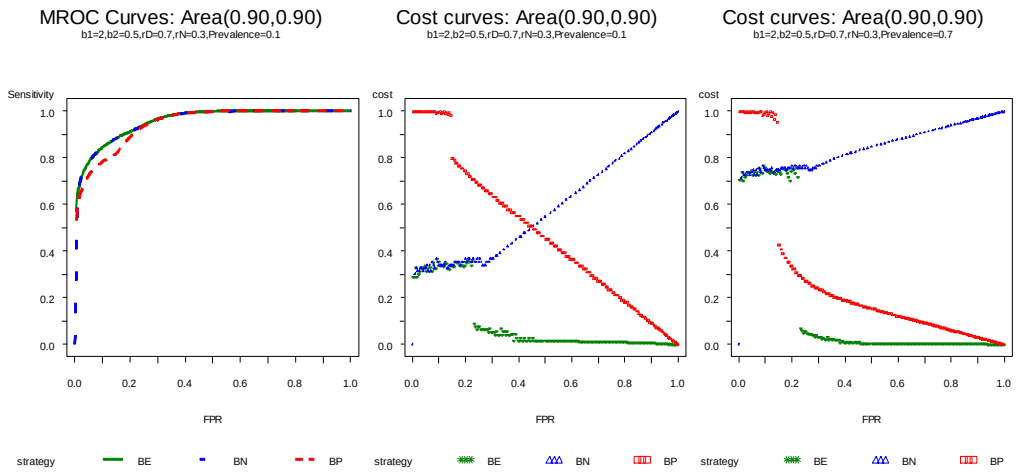

Figure A4.1f: (b1=2, b2=0.5)

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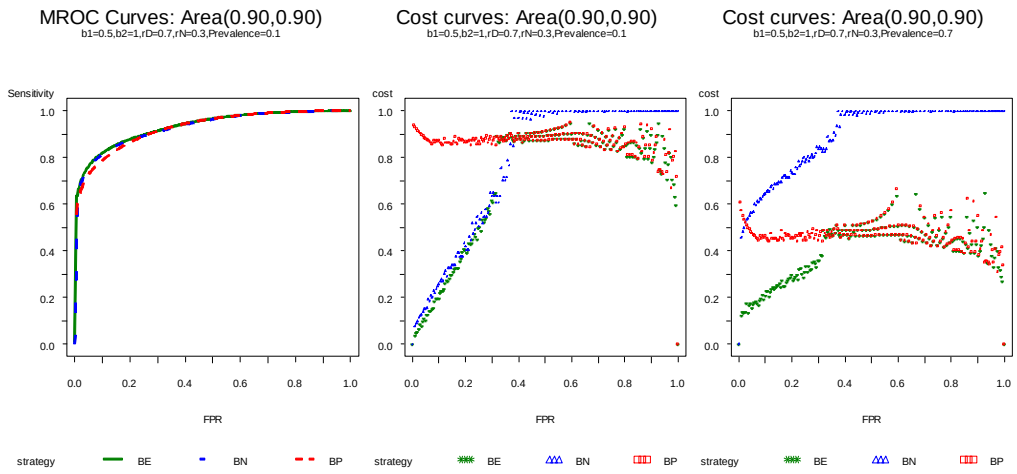

Figure A4.1g: (b1=0.5, b2=1)

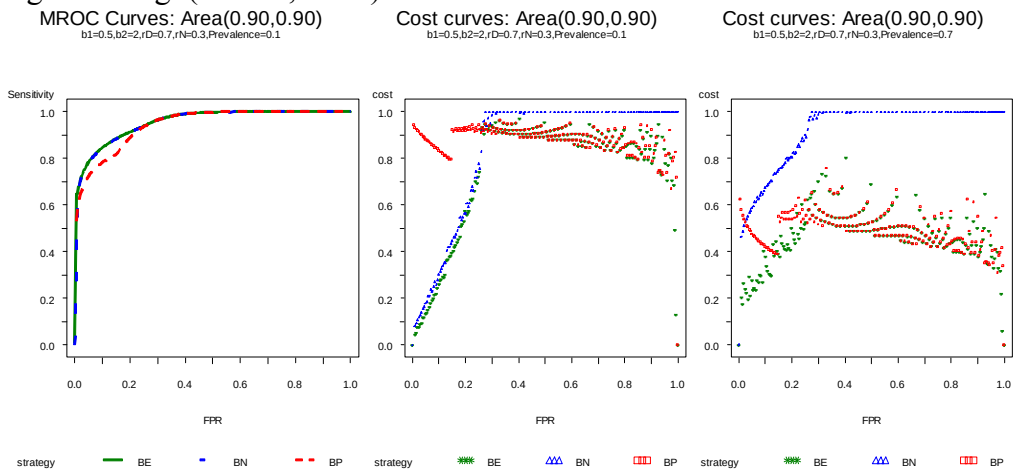

Figure A4.1h: (b1=0.5, b2=2)

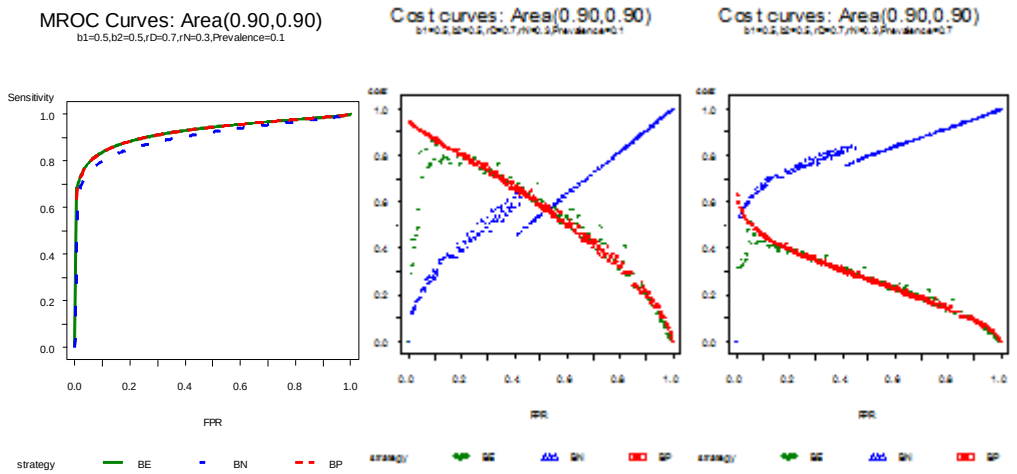

Figure A4.1i: (b1=0.5, b2=0.5)

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A4.2 AUC1 = 0.70, AUC2 = 0.90

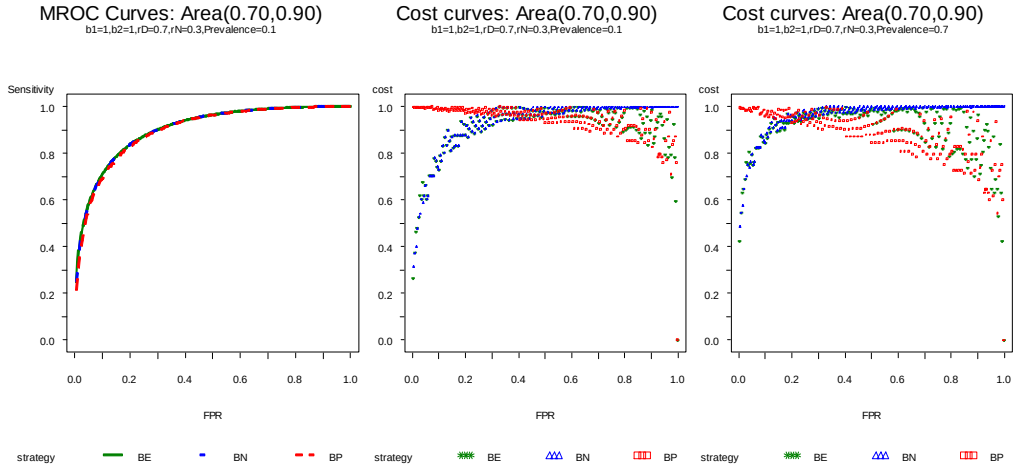

Figure A4.2a: (b1=1, b2=1)

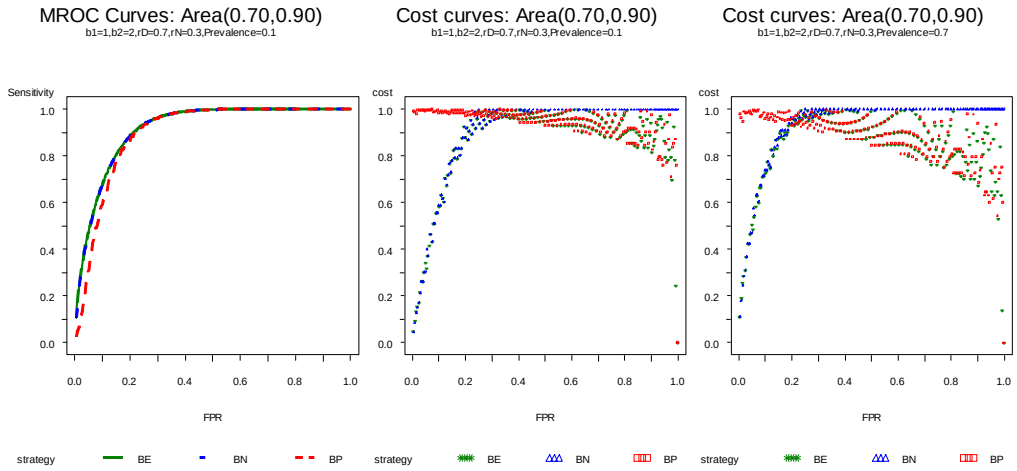

Figure A4.2b: (b1=1, b2=2)

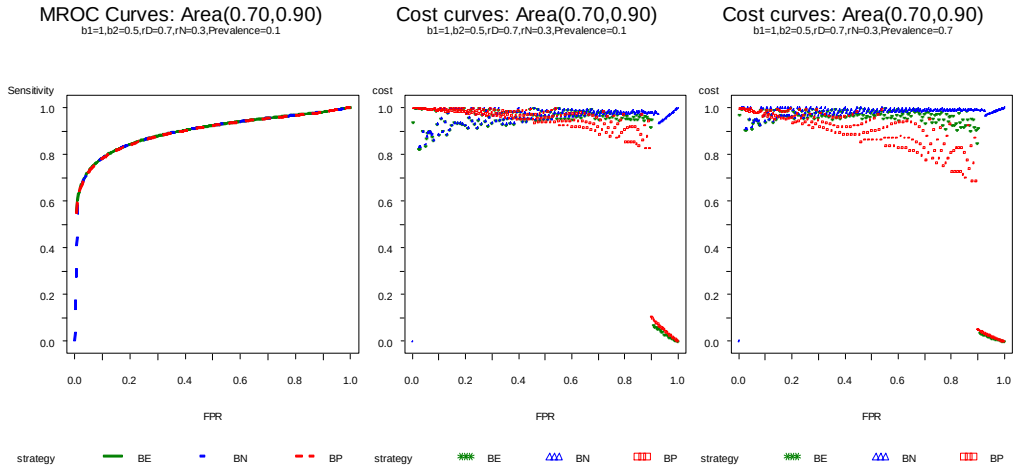

Figure A4.2c: (b1=1, b2=0.5)

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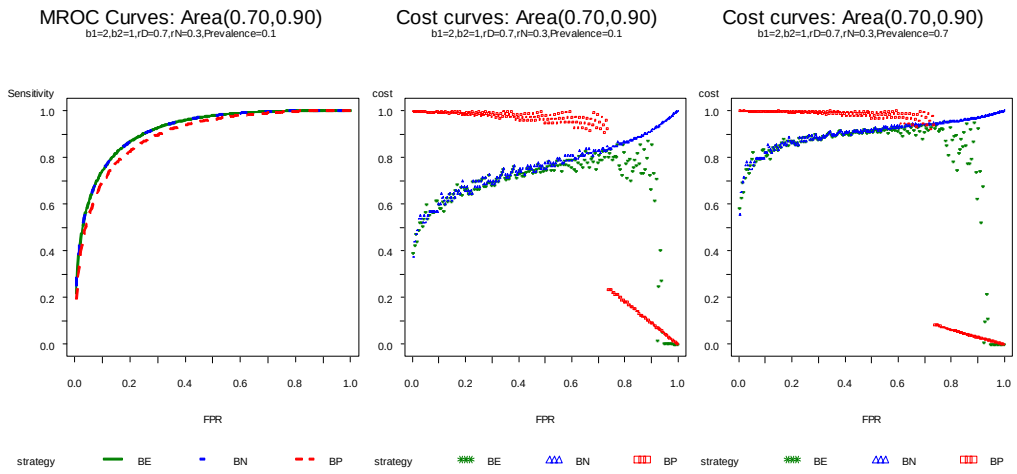

Figure A4.2d: (b1=2, b2=1)

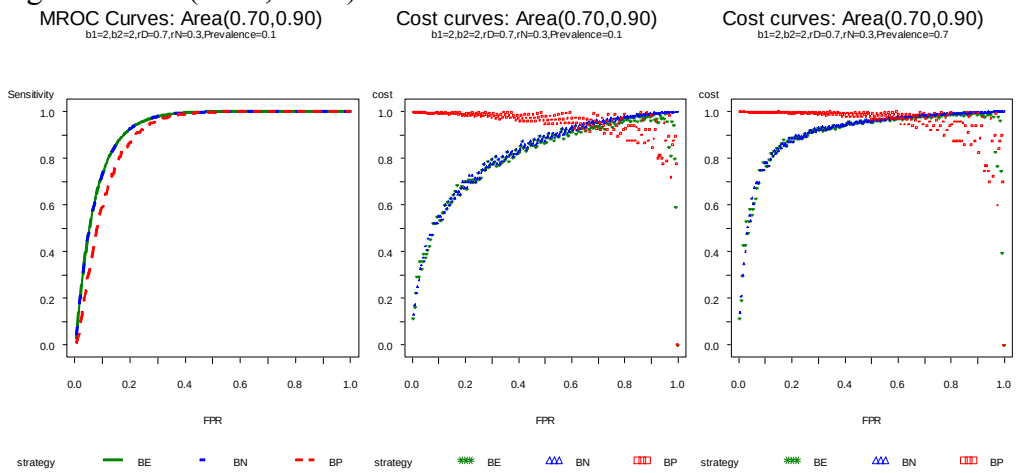

Figure A4.2e: (b1=2, b2=2)

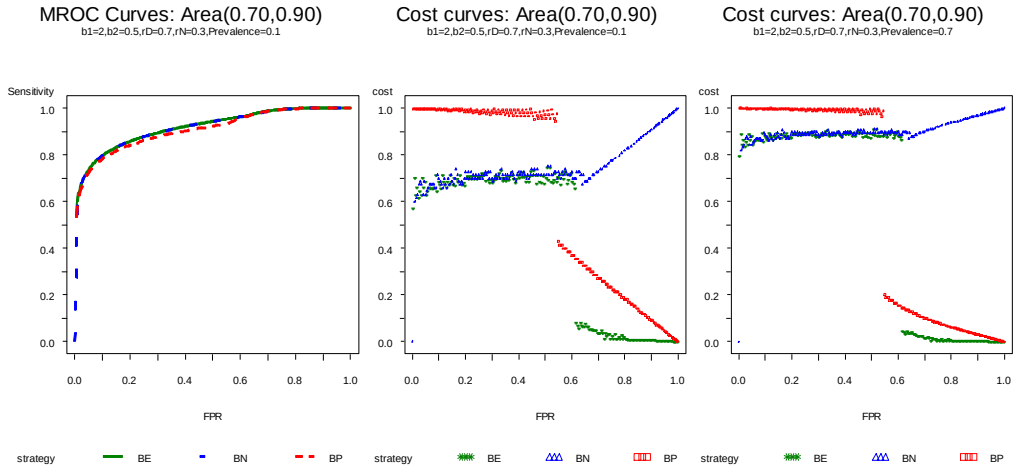

Figure A4.2f: (b1=2, b2=0.5)

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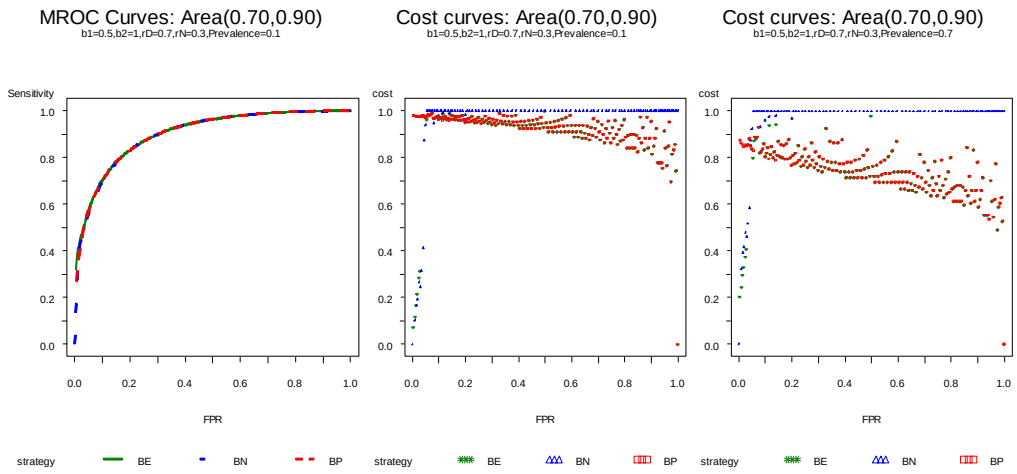

Figure A4.2g: (b1=0.5, b2=1)

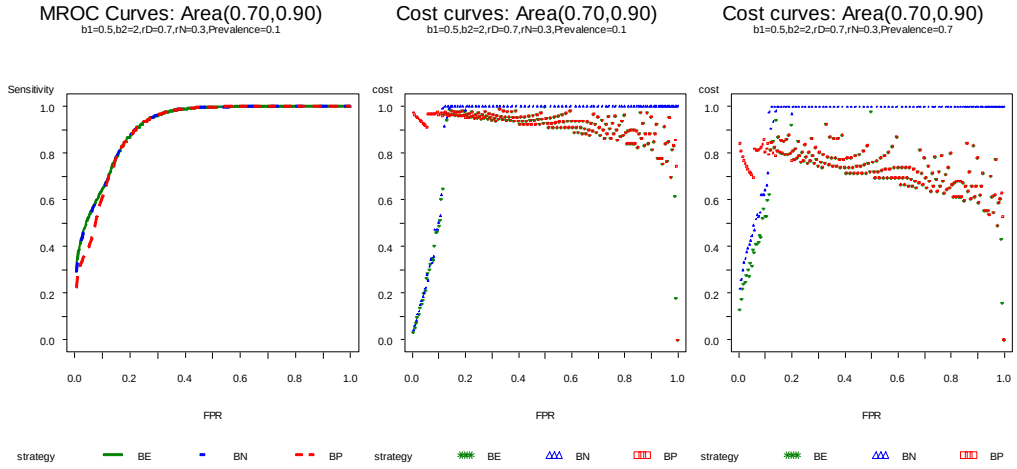

Figure A4.2h: (b1=0.5, b2=2)

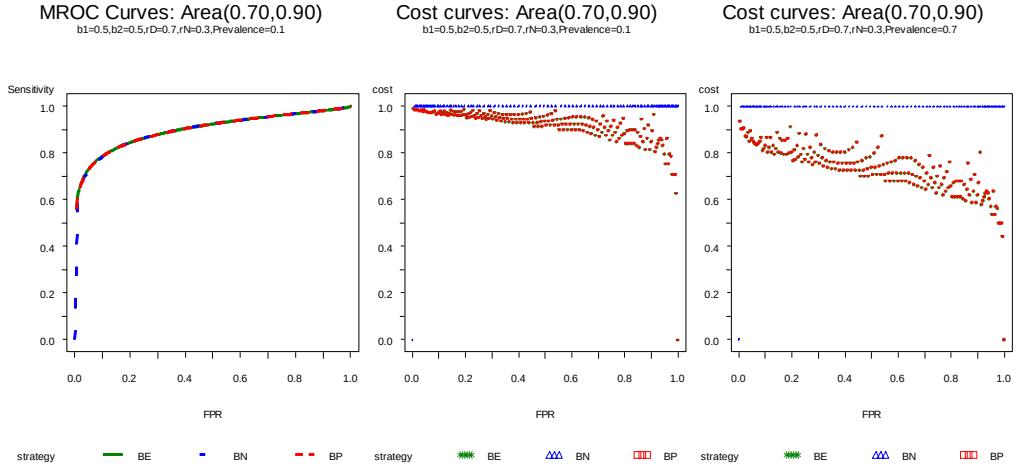

Figure A4.2i: (b1=0.5, b2=0.5)

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A4.3 AUC1 = 0.70, AUC2 = 0.70

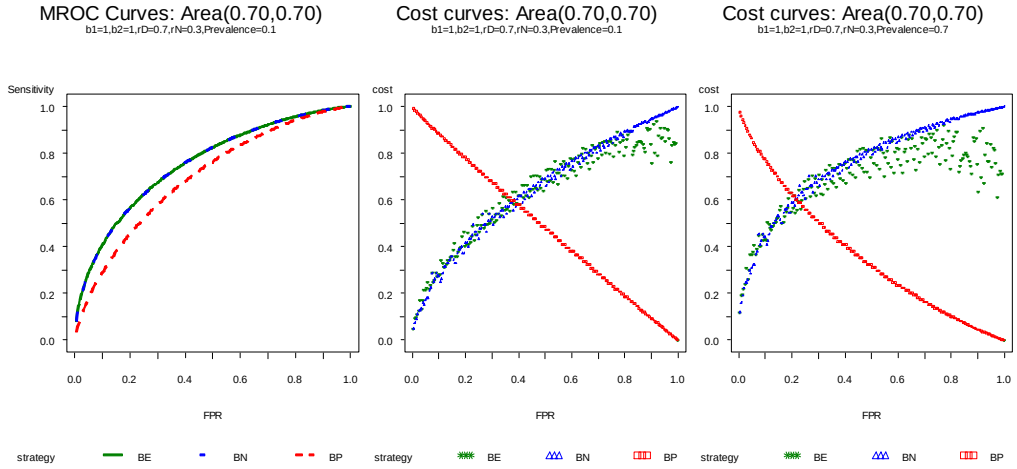

Figure A4.3a: (b1=1, b2=1)

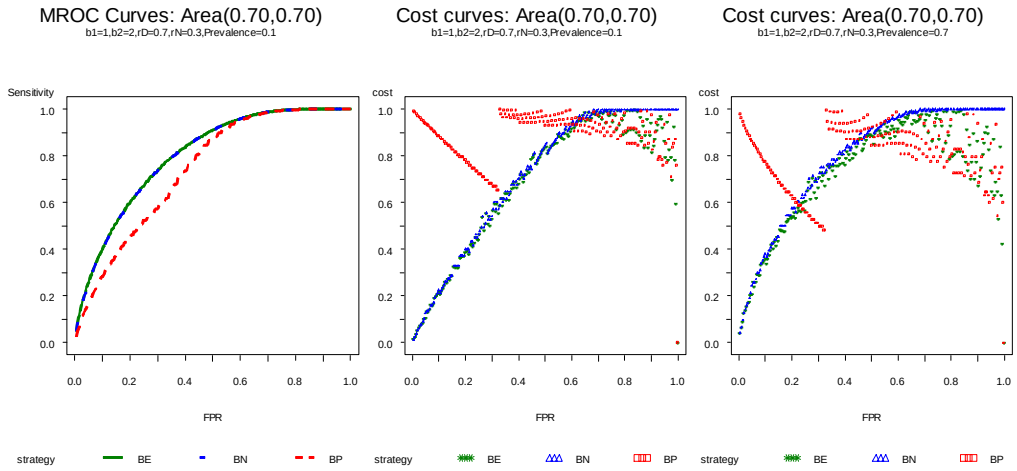

Figure A4.3b: (b1=1, b2=2)

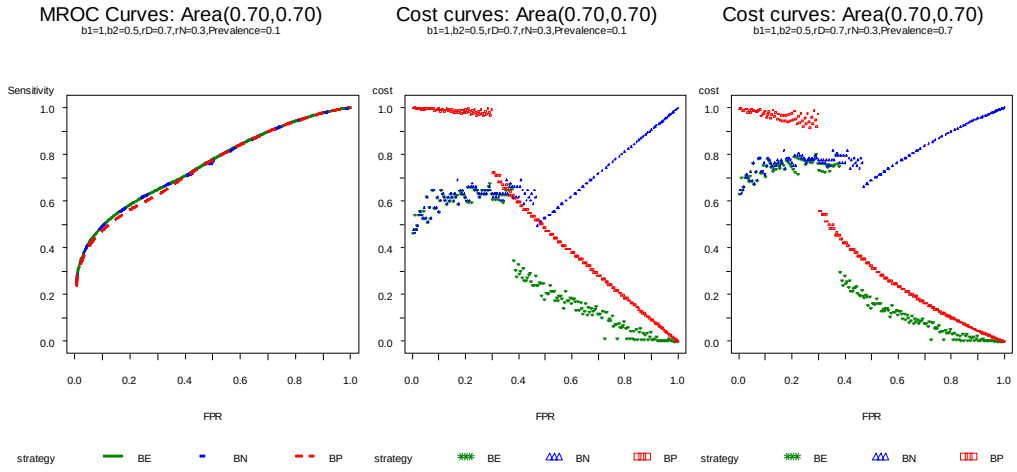

Figure A4.3c: (b1=1, b2=0.5)

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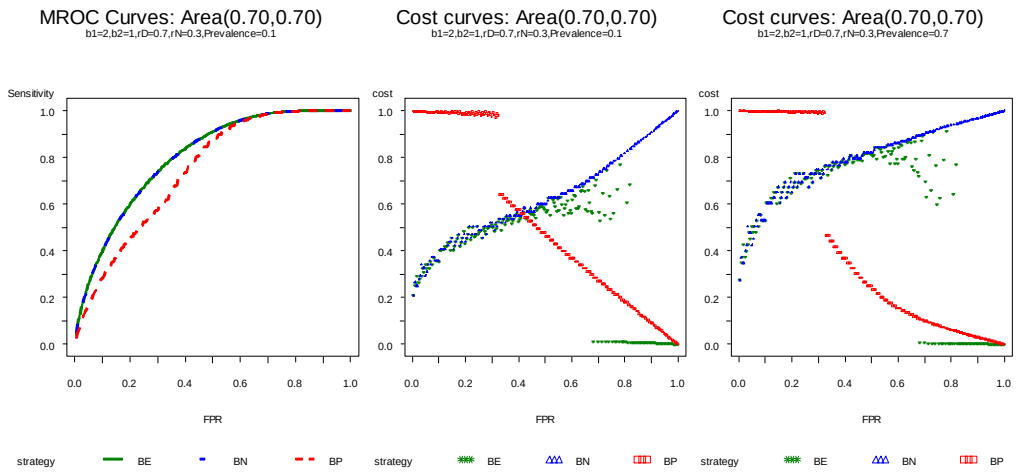

Figure A4.3d: (b1=2, b2=1)

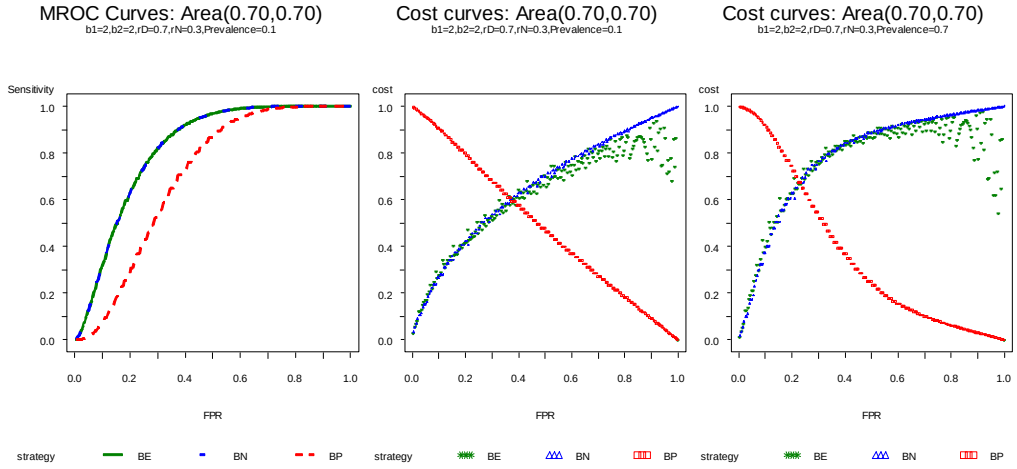

Figure A4.3e: (b1=2, b2=2)

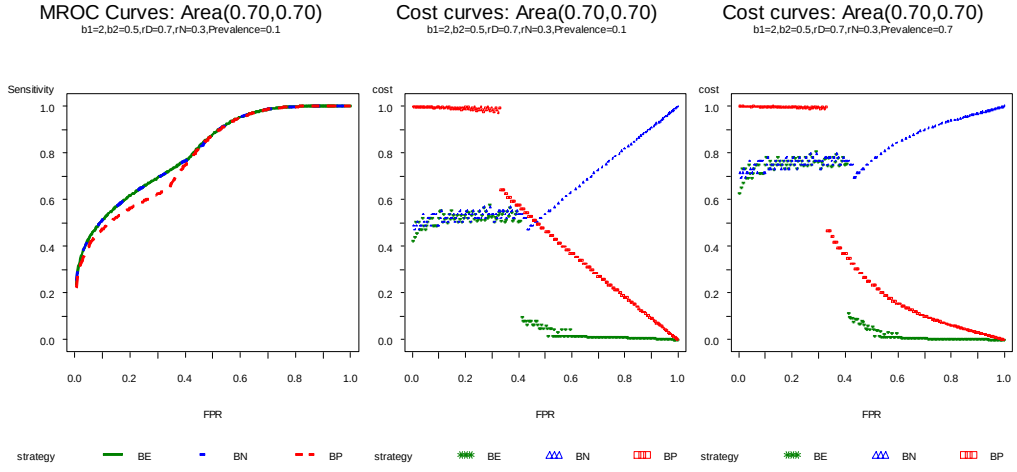

Figure A4.3f: (b1=2, b2=0.5)

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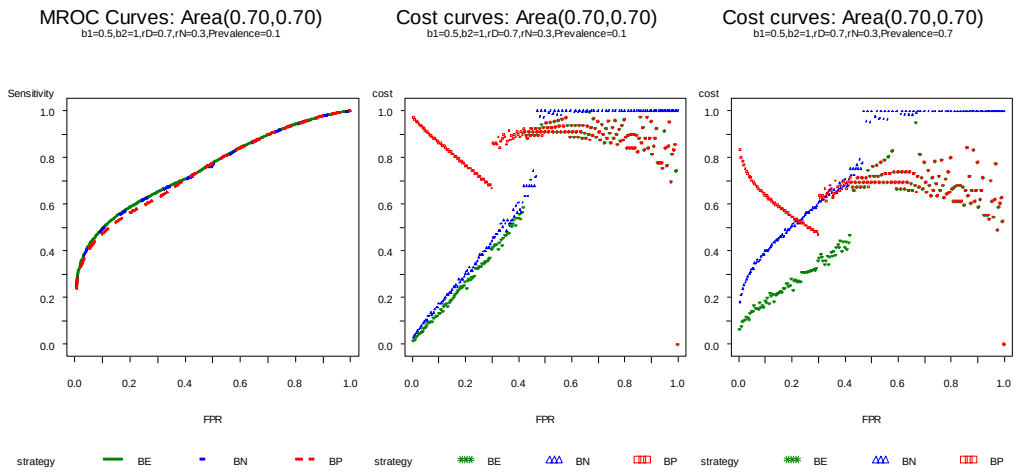

Figure A4.3g: (b1=0.5, b2=1)

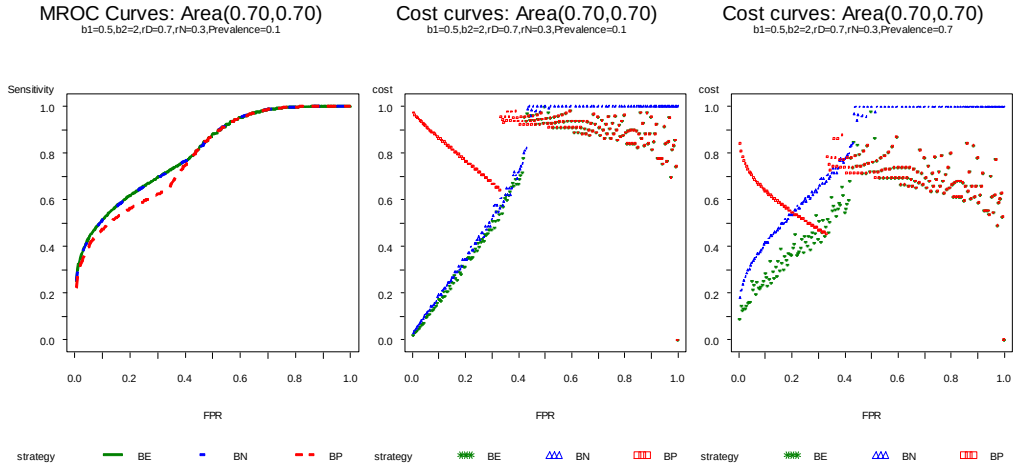

Figure A4.3h: (b1=0.5, b2=2)

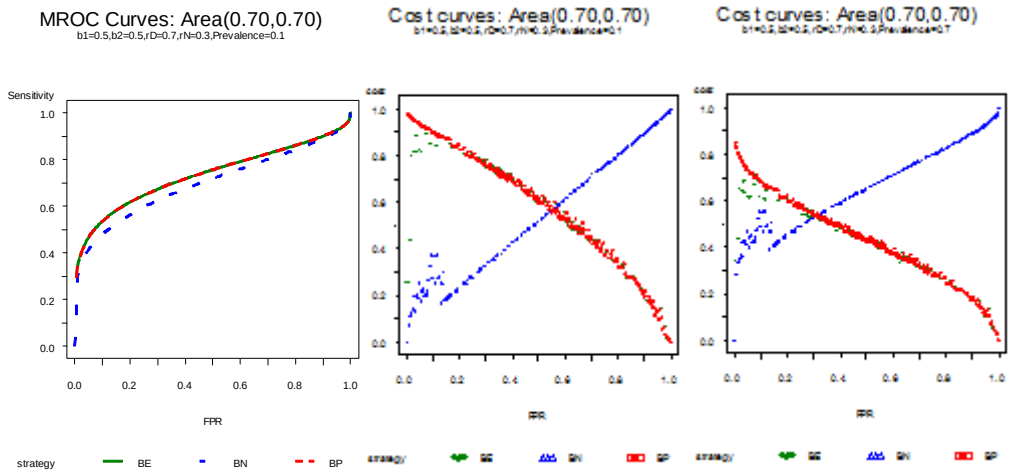

Figure A4.3i: (b1=0.5, b2=0.5)

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A5 Dependent of the tests ($\rho_D = 0.7, \rho_N = 0.7$)

A5.1 AUC1 = 0.90, AUC2 = 0.90

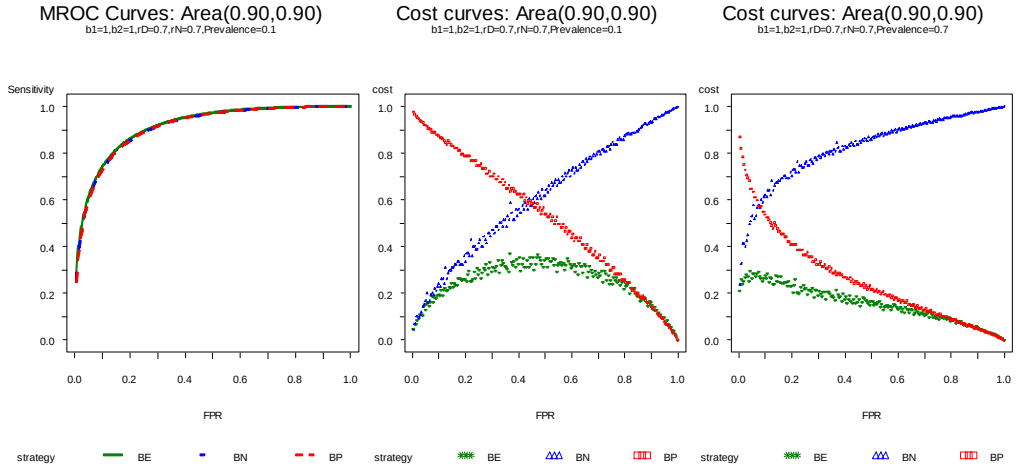

Figure A5.1a: (b1=1, b2=1)

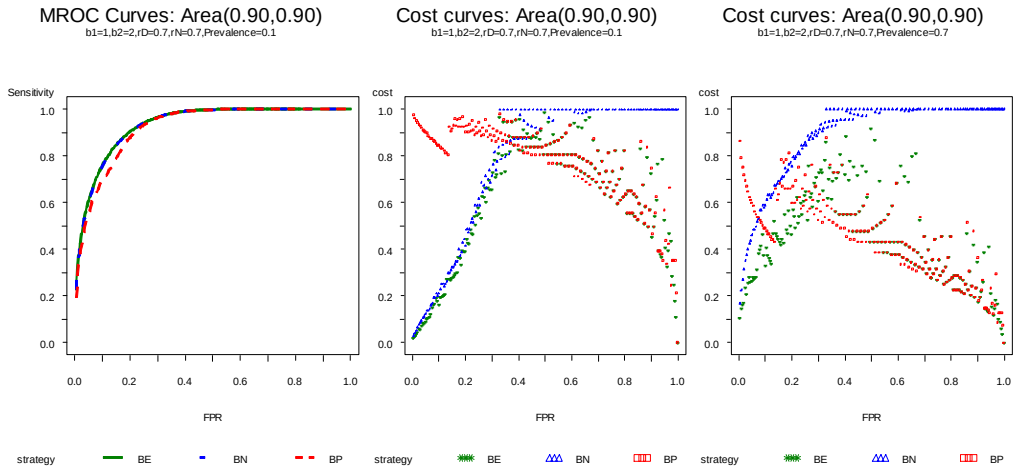

Figure A5.1b: (b1=1, b2=2)

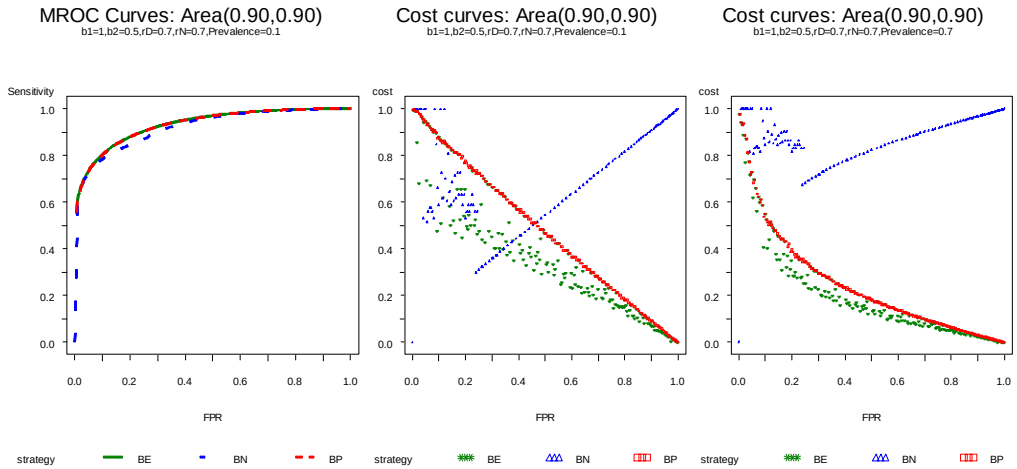

Figure A5.1c: (b1=1, b2=0.5)

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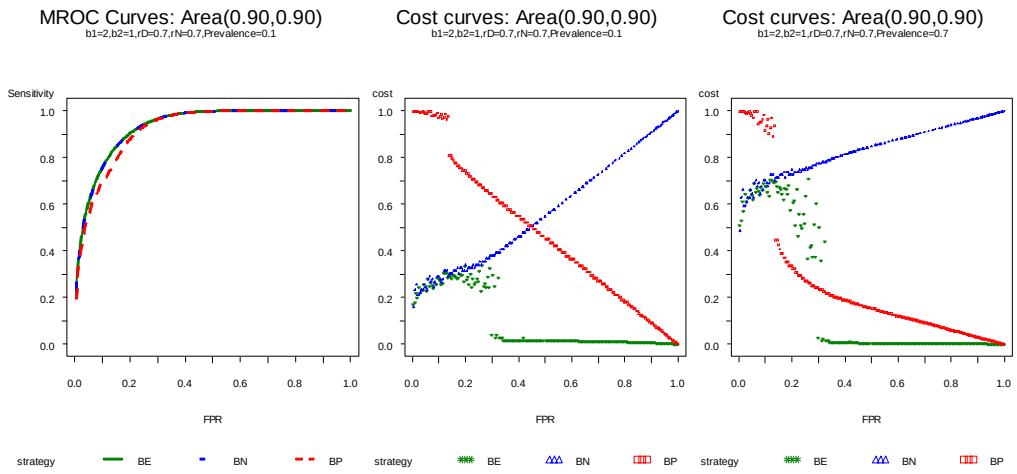

Figure A5.1d: (b1=2, b2=1)

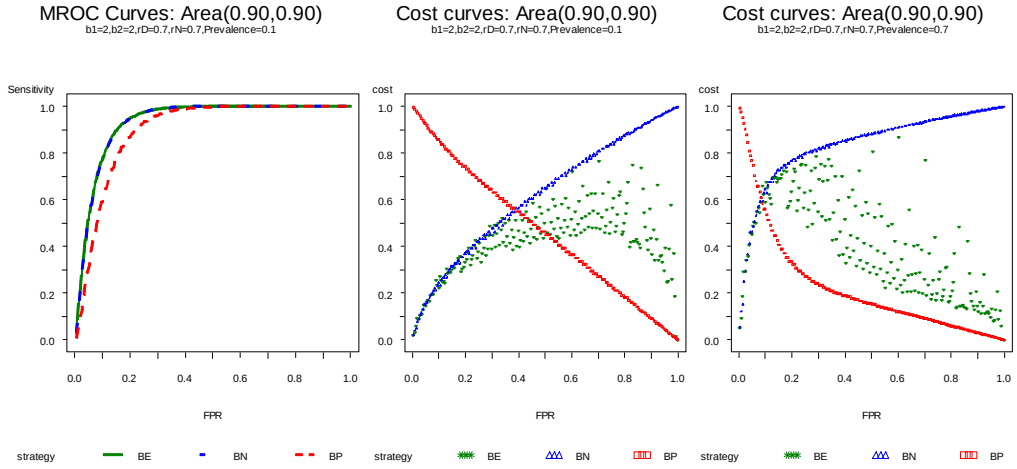

Figure A5.1e: (b1=2, b2=2)

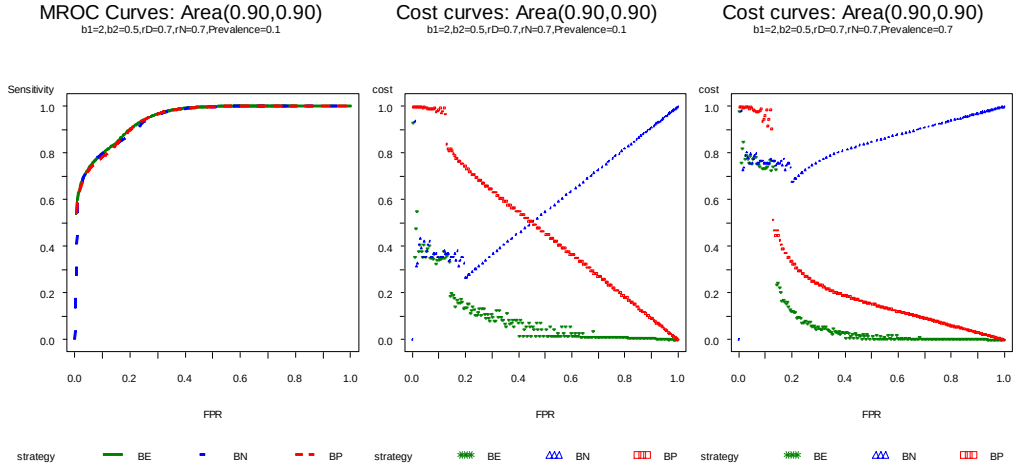

Figure A5.1f: (b1=2, b2=0.5)

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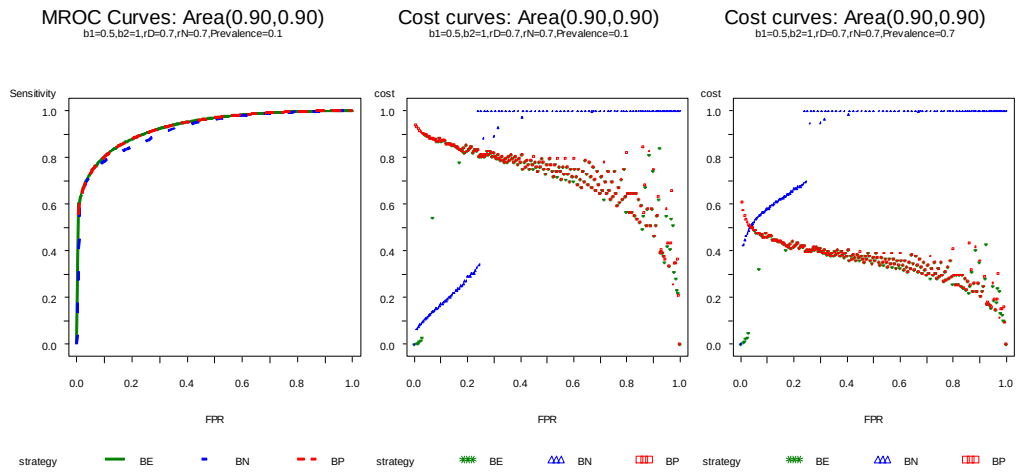

Figure A5.1g: (b1=0.5, b2=1)

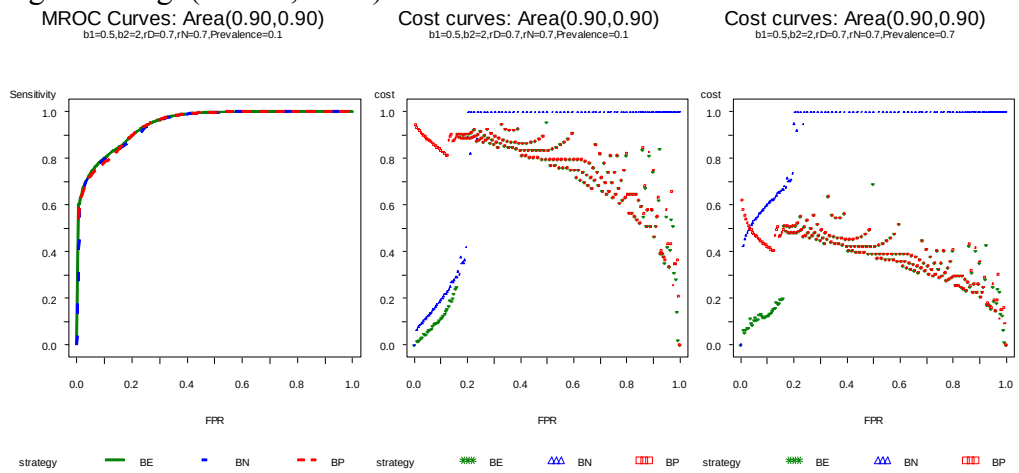

Figure A5.1h: (b1=0.5, b2=2)

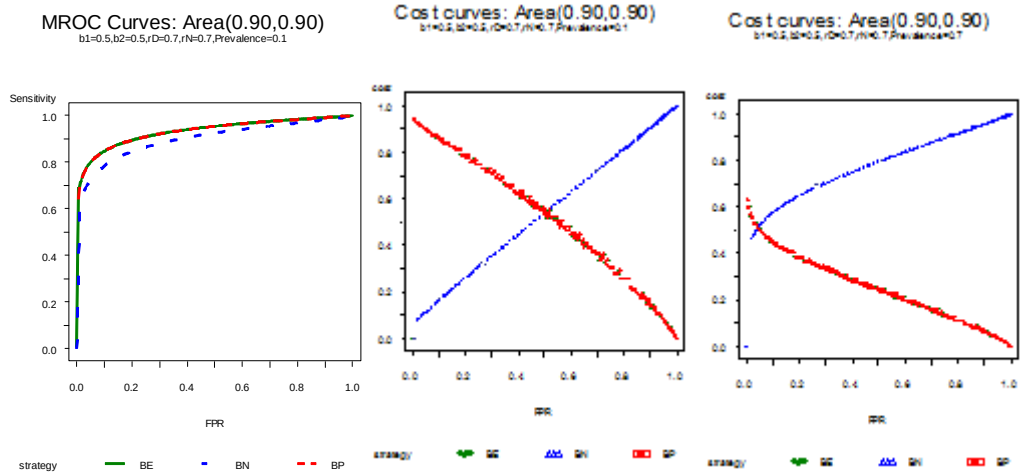

Figure A5.1i: (b1=0.5, b2=0.5)

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A5.2 AUC1 = 0.70, AUC2 = 0.90

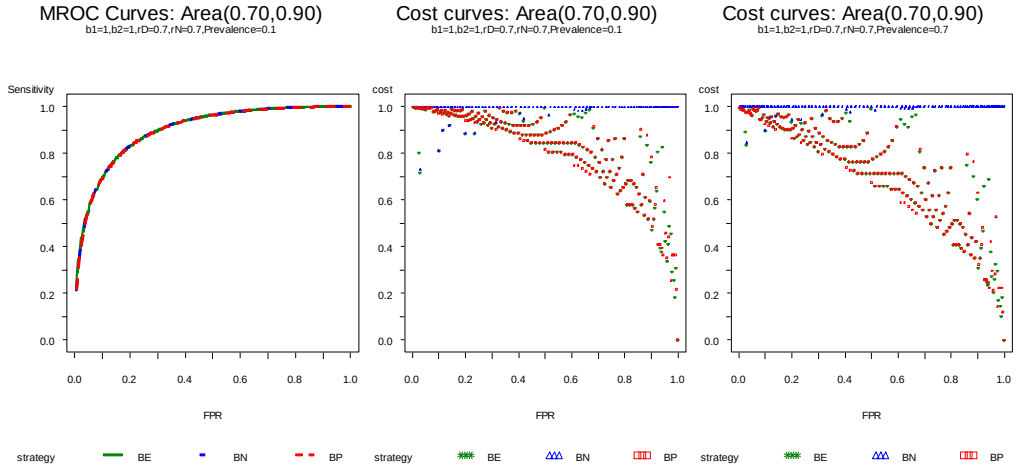

Figure A5.2a: (b1=1, b2=1)

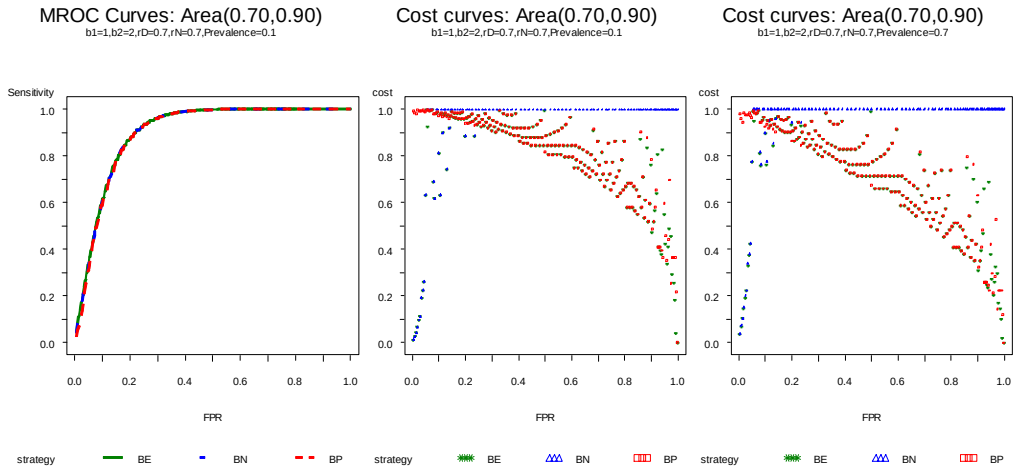

Figure A5.2b: (b1=1, b2=2)

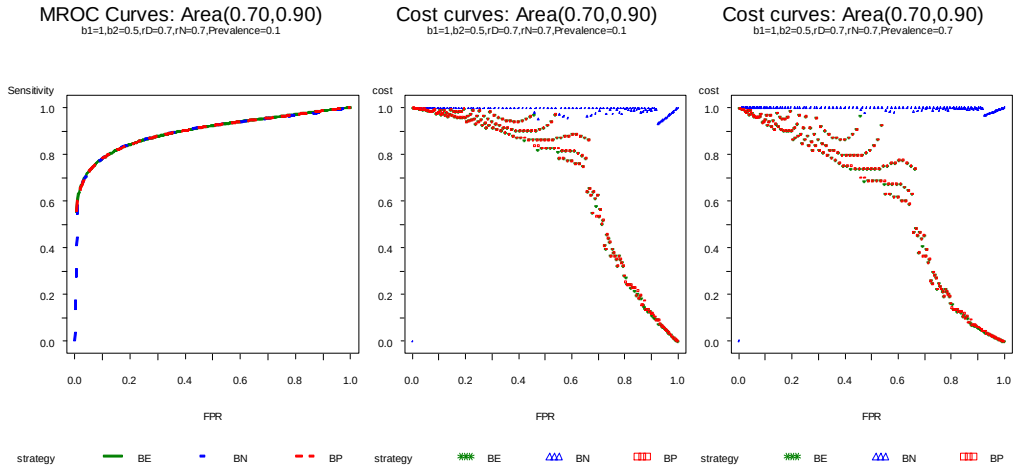

Figure A5.2c: (b1=1, b2=0.5)

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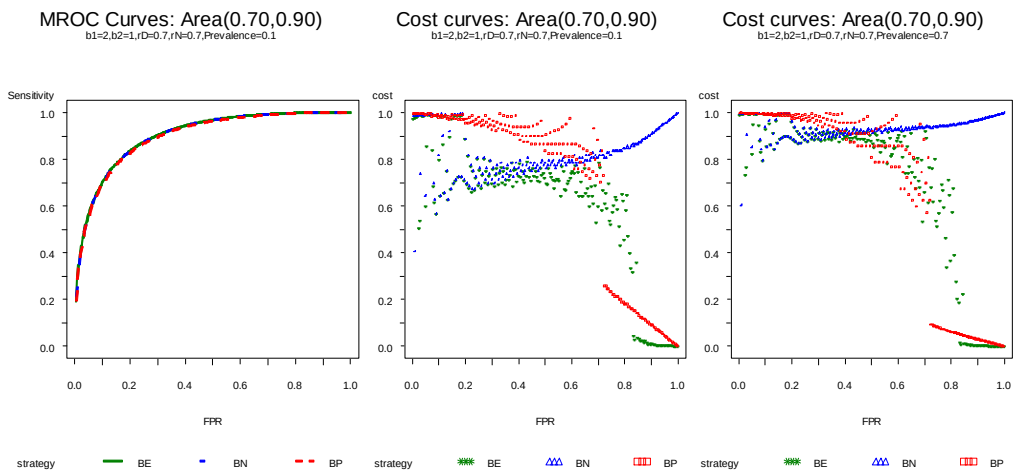

Figure A5.2d: (b1=2, b2=1)

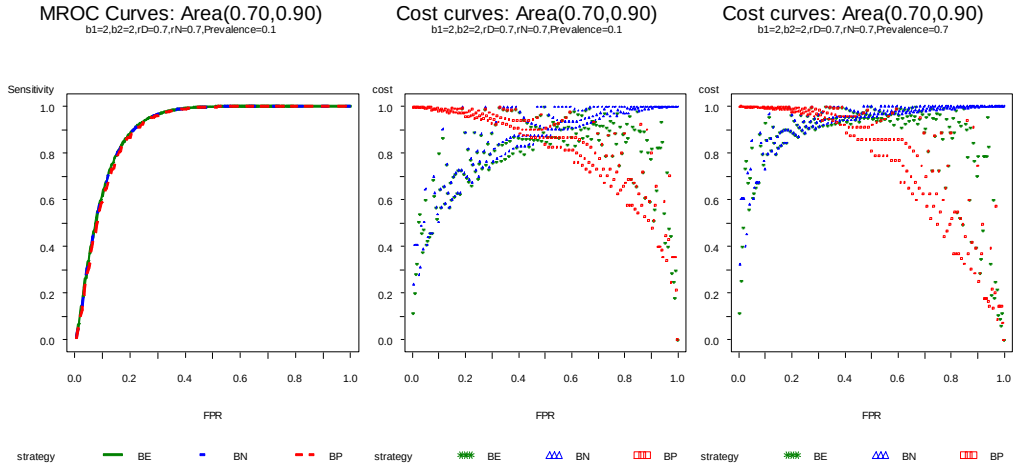

Figure A5.2e: (b1=2, b2=2)

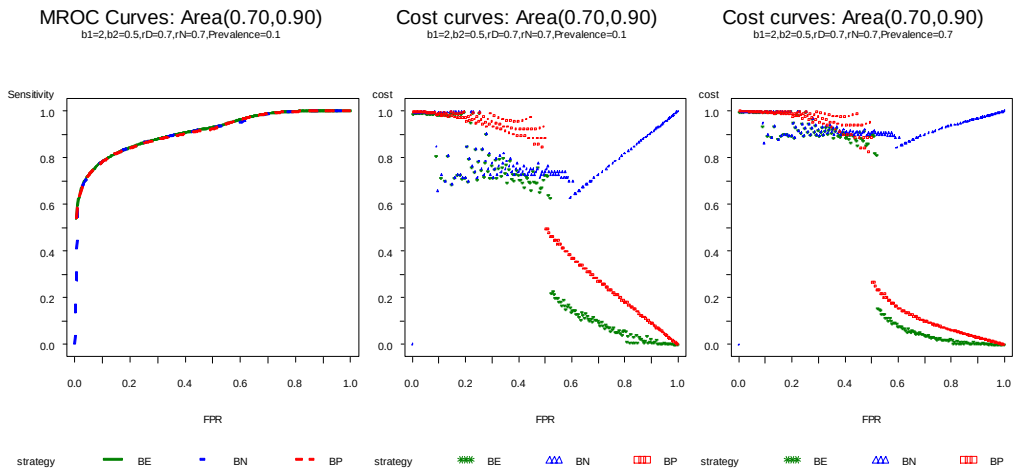

Figure A5.2f: (b1=2, b2=0.5)

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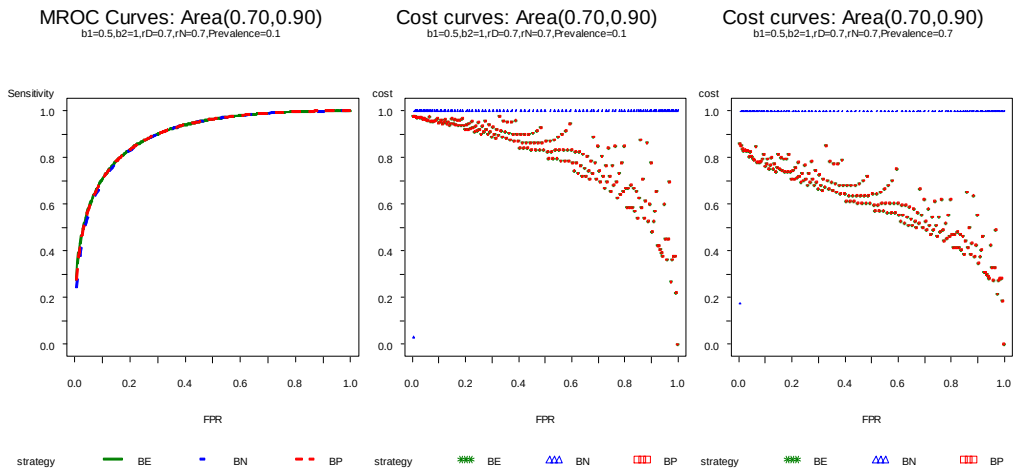

Figure A5.2g: (b1=0.5, b2=1)

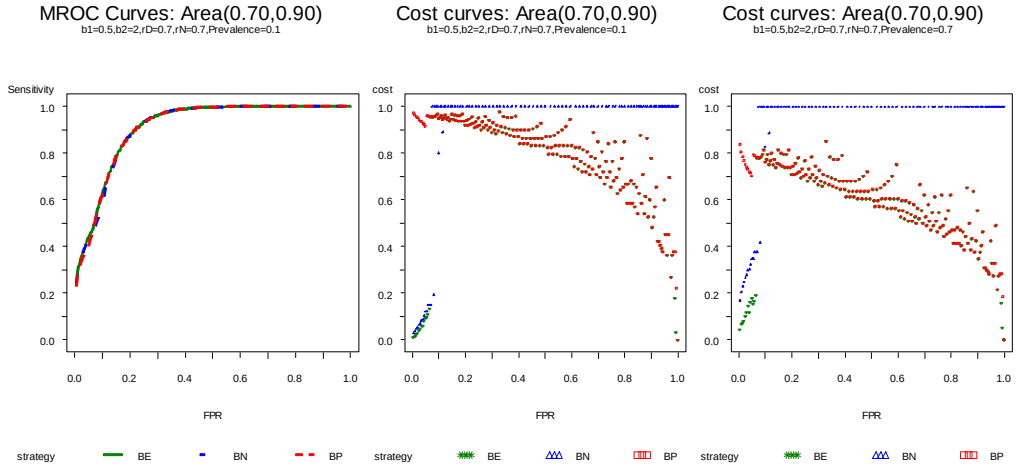

Figure A5.2h: (b1=0.5, b2=2)

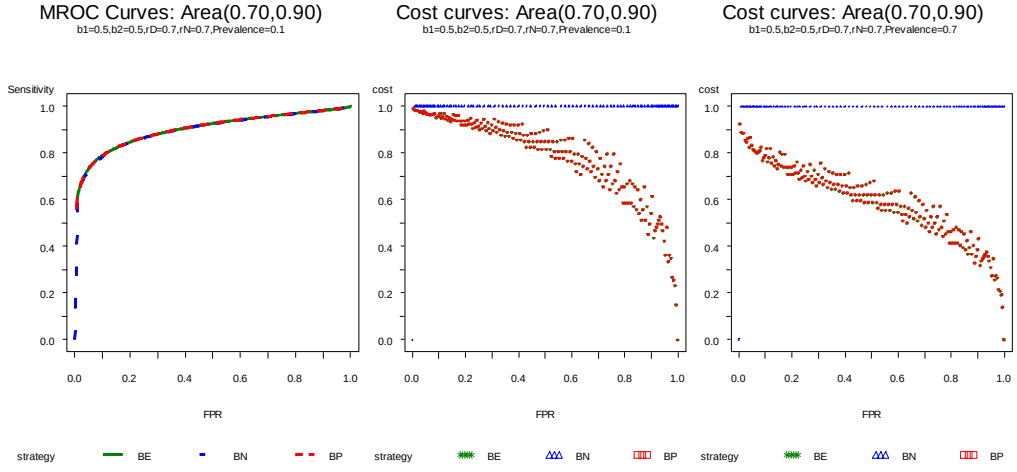

Figure A5.2i: (b1=0.5, b2=0.5)

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A5.3 AUC1 = 0.70, AUC2 = 0.70

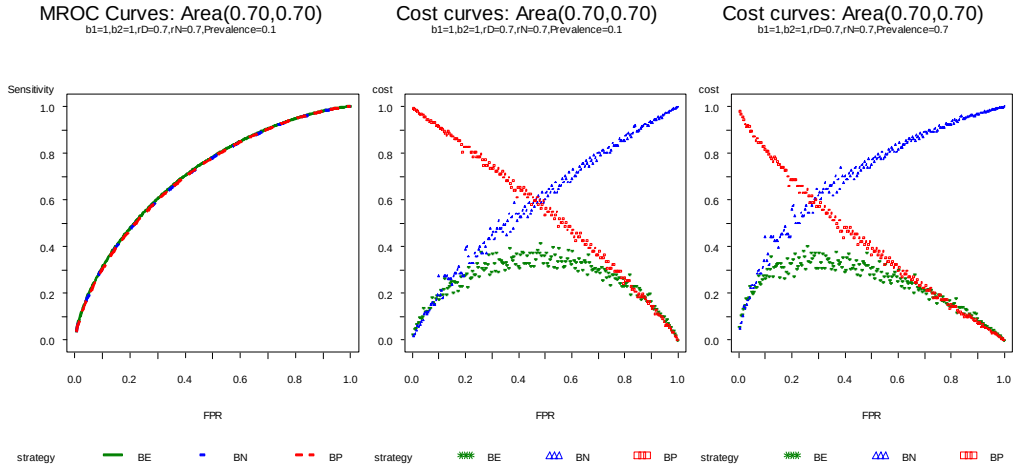

Figure A5.3a: (b1=1, b2=1)

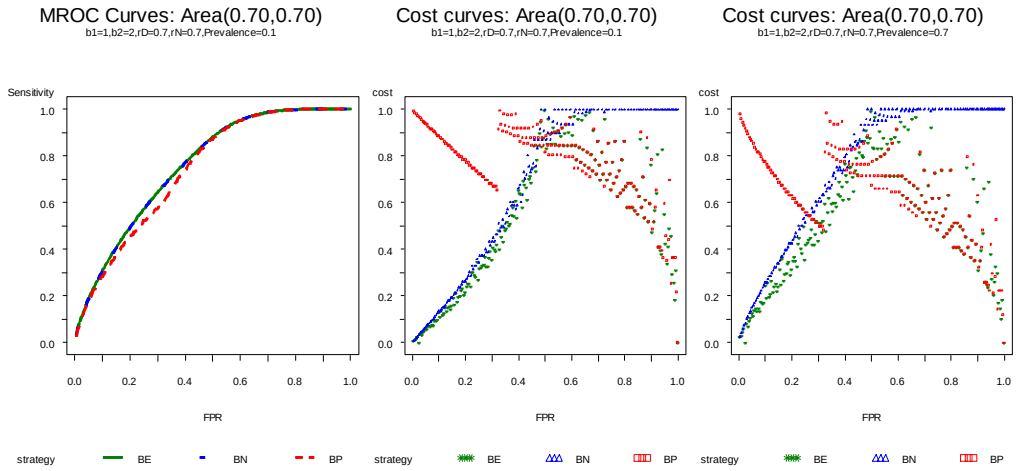

Figure A5.3b: (b1=1, b2=2)

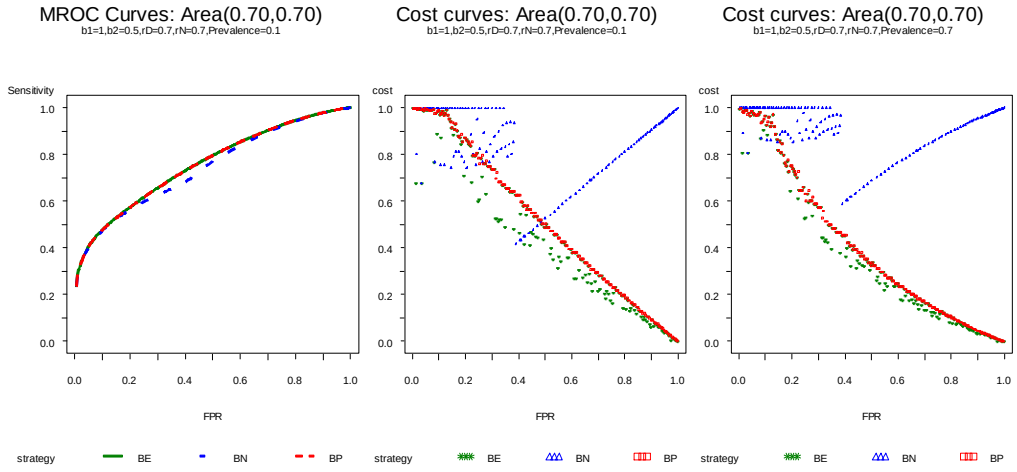

Figure A5.3c: (b1=1, b2=0.5)

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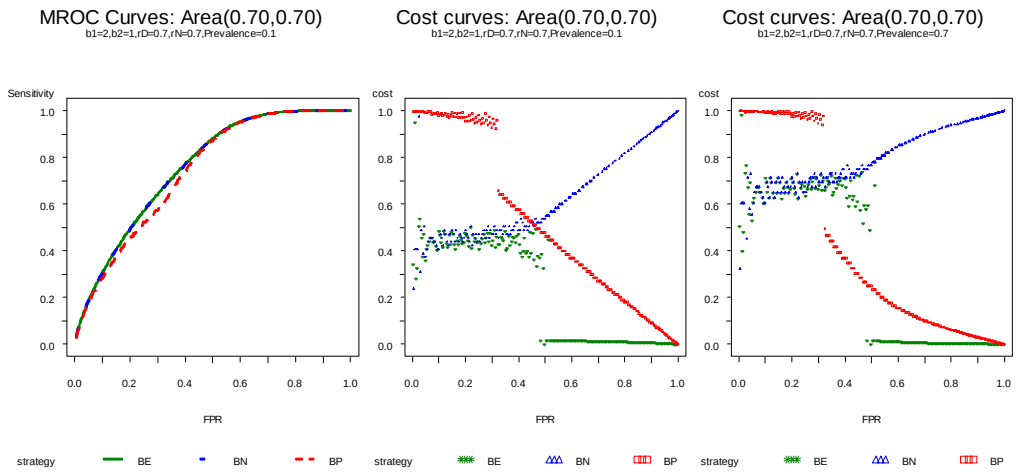

Figure A5.3d: (b1=2, b2=1)

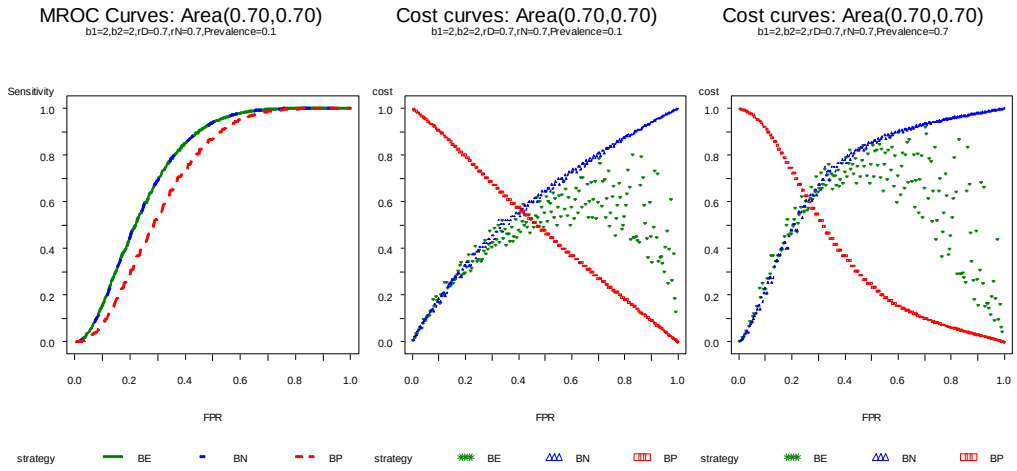

Figure A5.3e: (b1=2, b2=2)

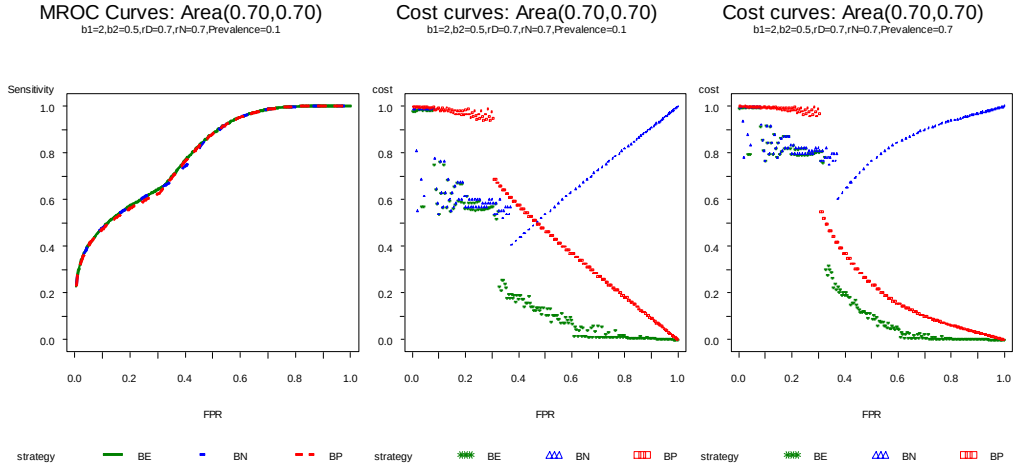

Figure A5.3f: (b1=2, b2=0.5)

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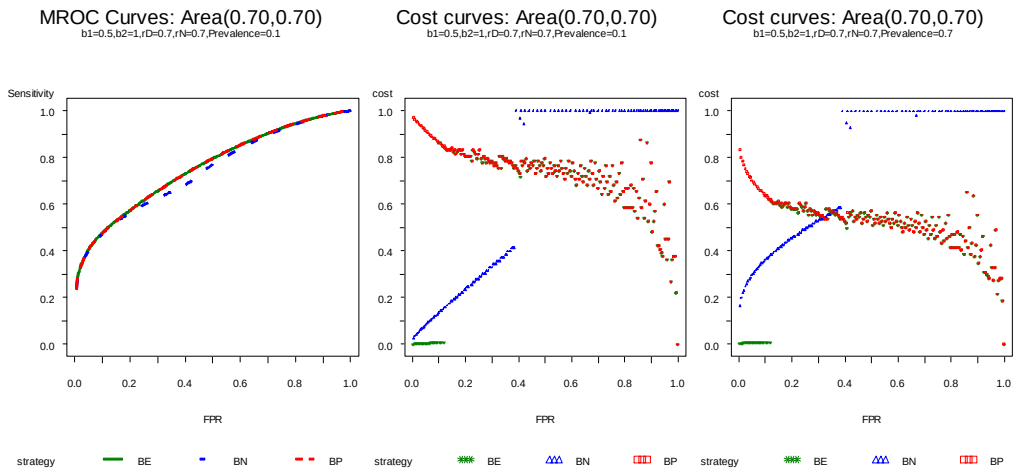

Figure A5.3g: (b1=0.5, b2=1)

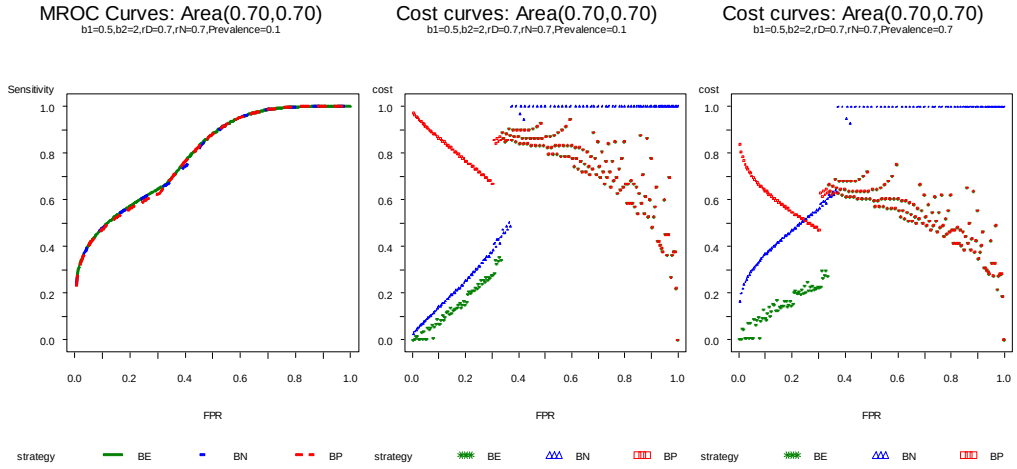

Figure A5.3h: (b1=0.5, b2=2)

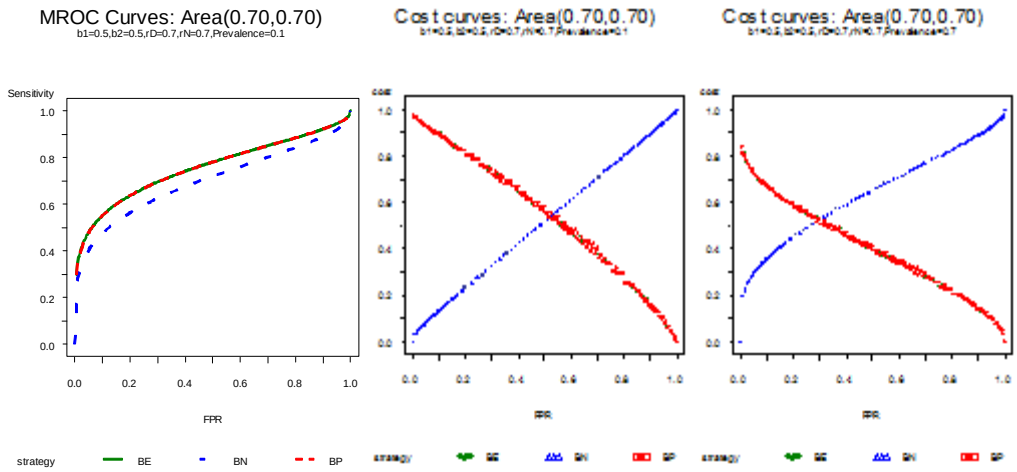

Figure A5.3i: (b1=0.5, b2=0.5)

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Appendix B

Graphs (q=0.999)

The two plots in the top show MCMROC curves and cost curves when disease prevalence is low (prevalence = 0.1) and below show MCMROC curves and cost curves when disease prevalence is high (prevalence = 0.7).

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B1 Independent of the tests , B1.1 AUC1 = 0.90, AUC2 = 0.90

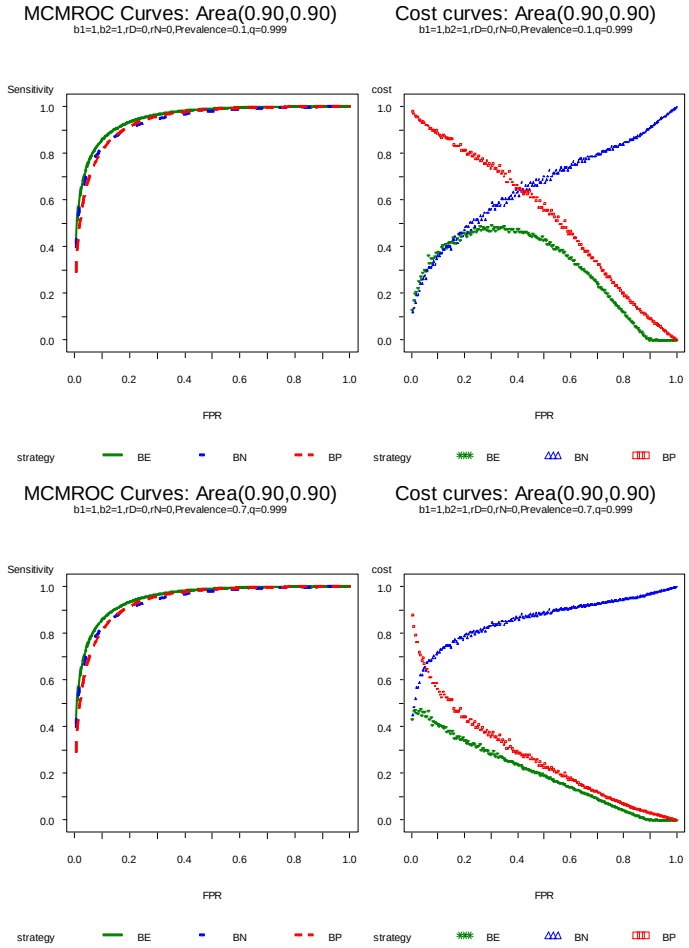
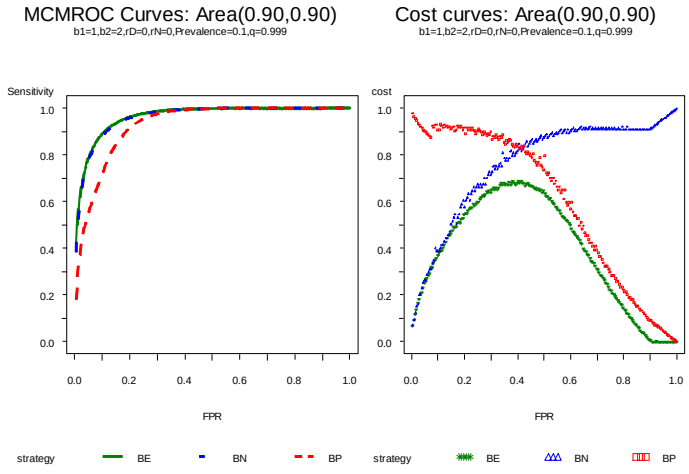


Figure B1.1a: (b1=1, b2=1)



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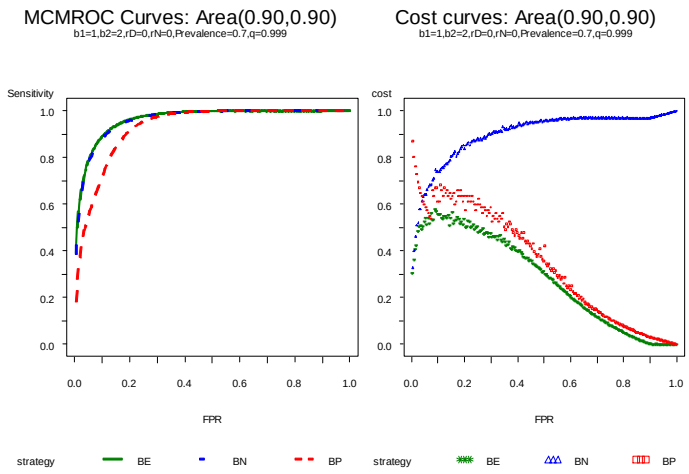

Figure B1.1b: (b1=1, b2=2)

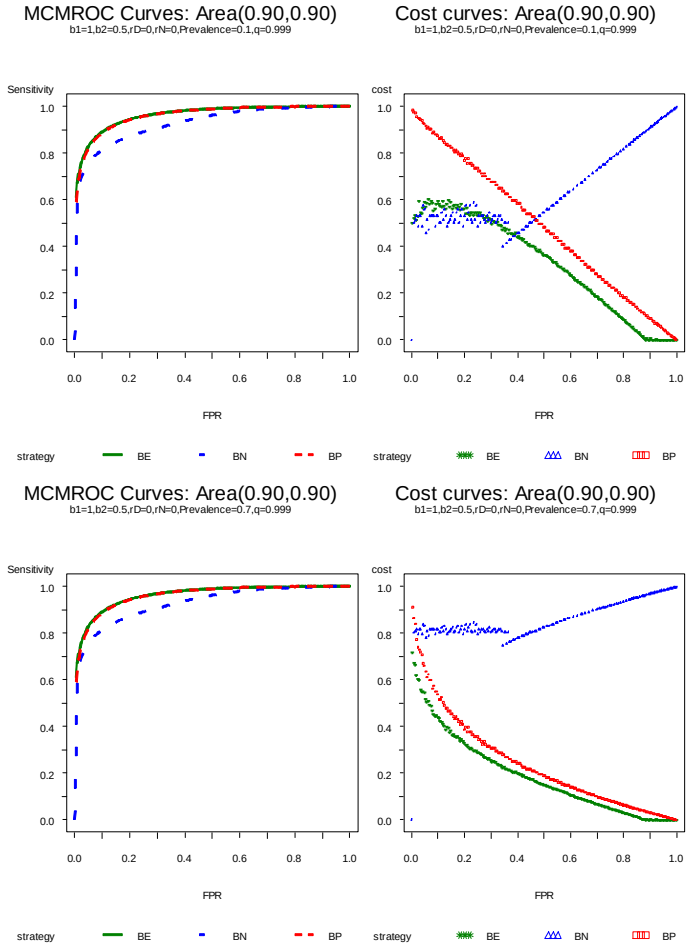

Figure B1.1c: (b1=1, b2=0.5)

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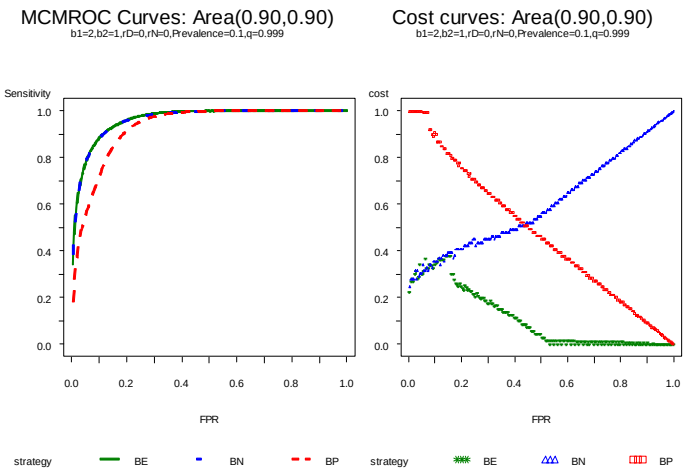


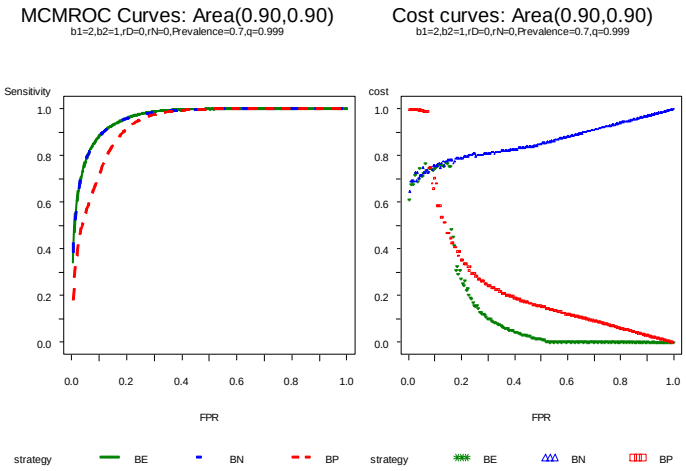
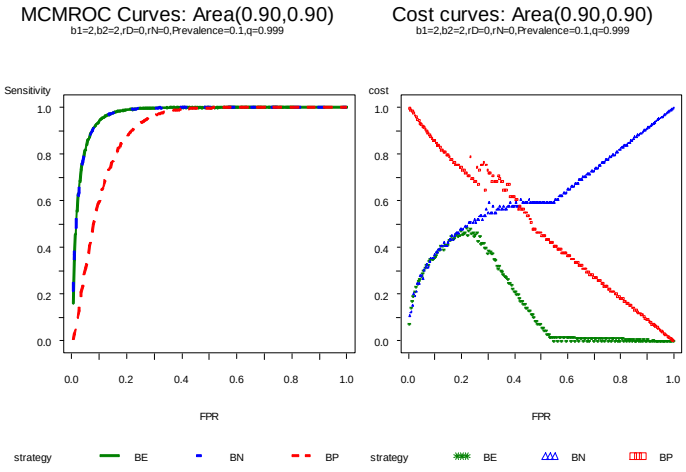


Figure B1.1d: (b1=2, b2=1)



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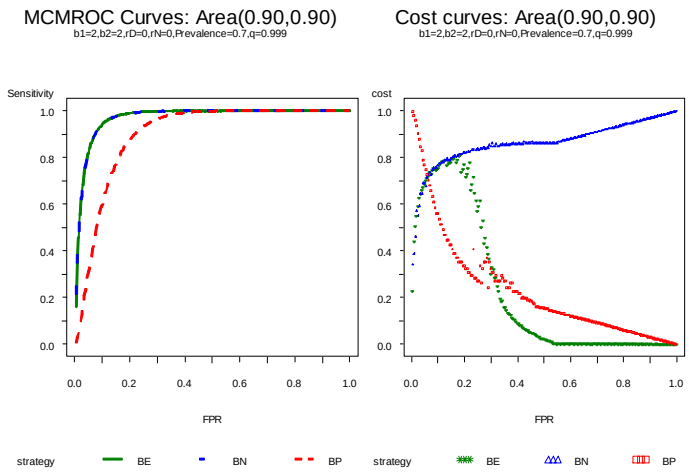
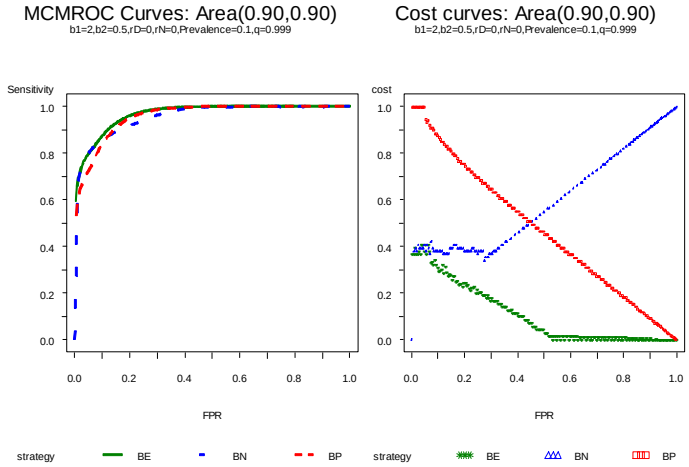


Figure B1.1e: (b1=2, b2=2)



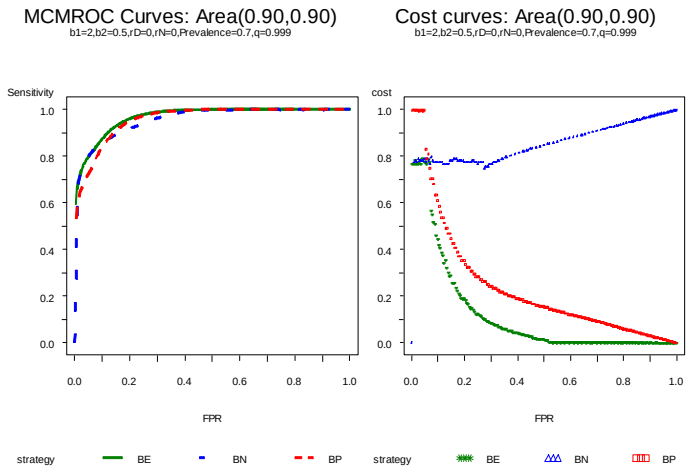


Figure B1.1f: (b1=2, b2=0.5)

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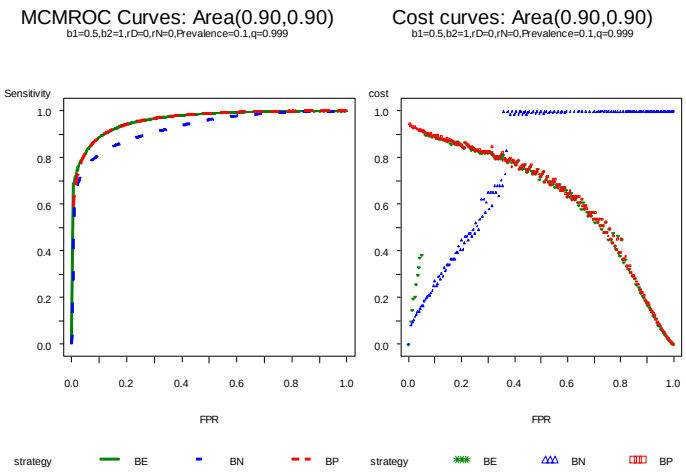


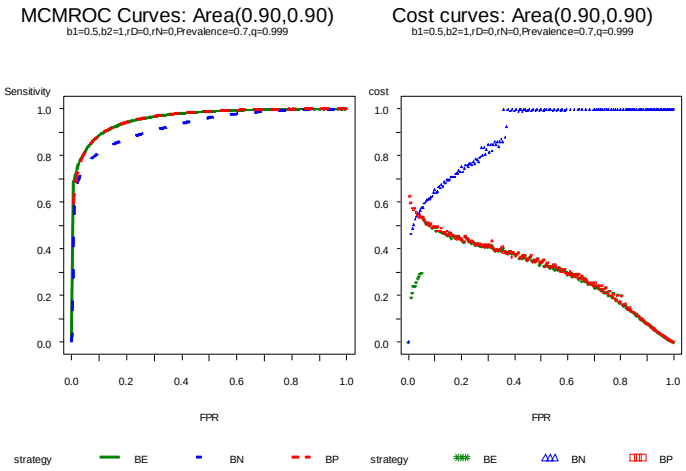
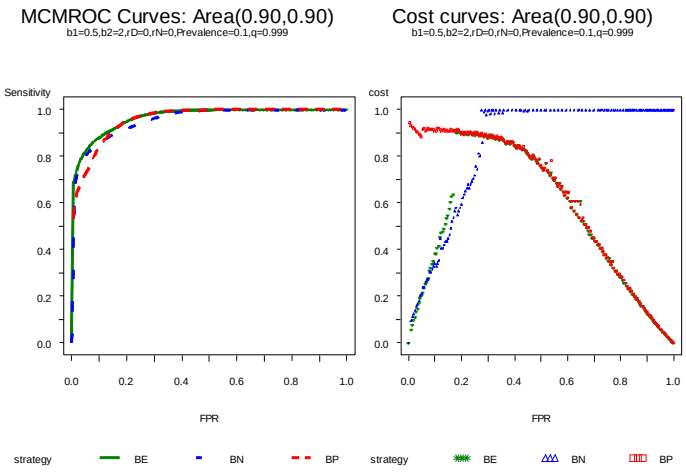


Figure B1.1g: (b1=0.5, b2=1)



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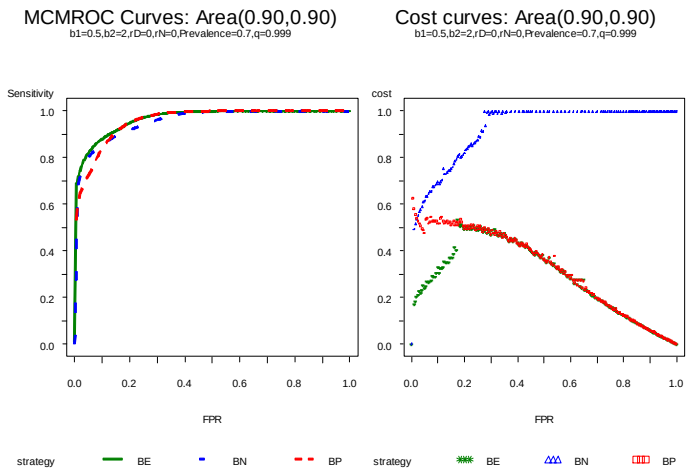
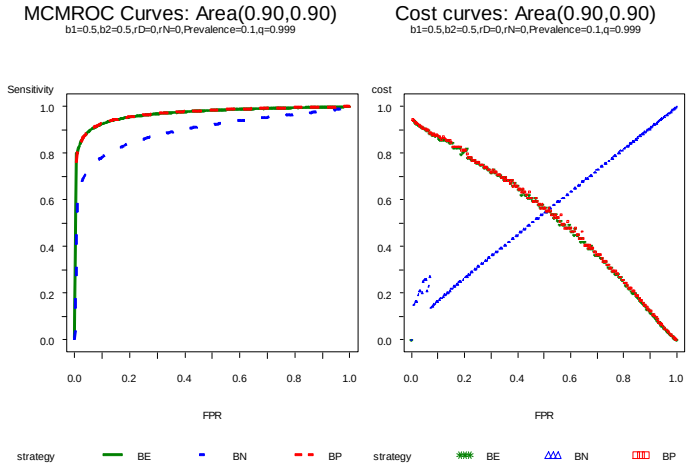


Figure B1.1h: (b1=0.5, b2=2)



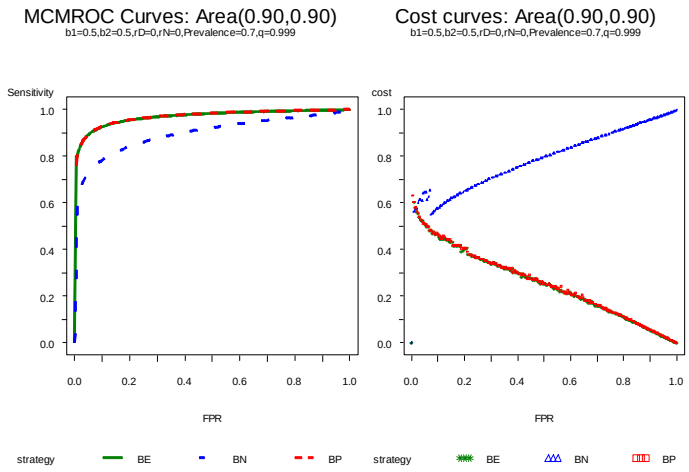


Figure B1.1i: (b1=0.5, b2=0.5)

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.2 AUC1 = 0.70, AUC2 = 0.90

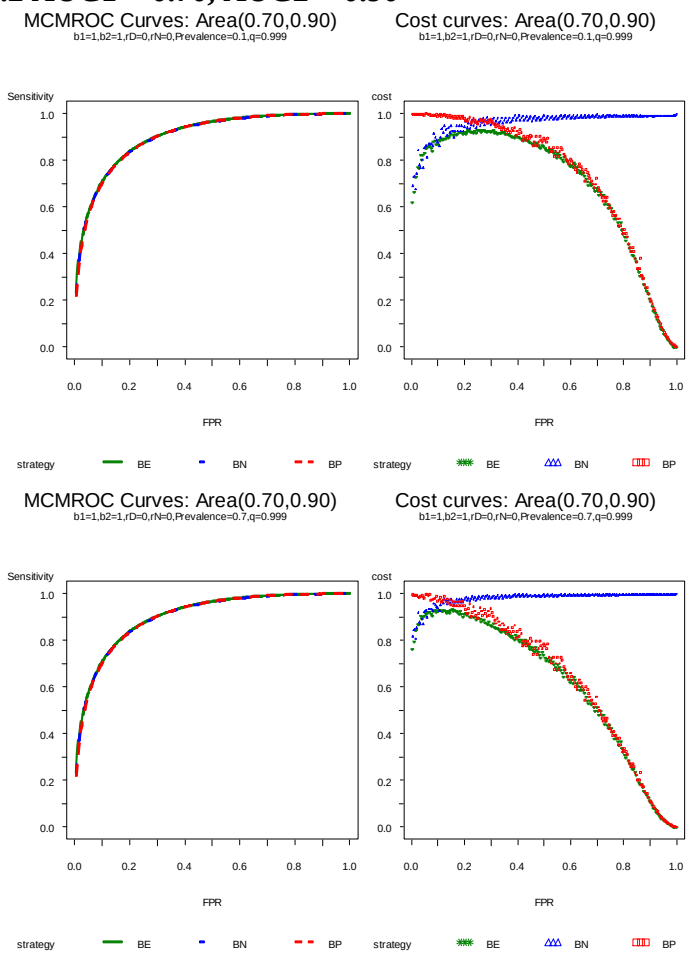
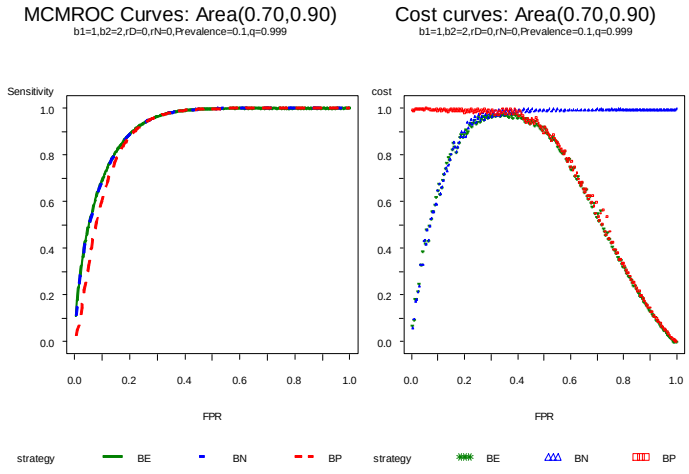


Figure B1.2a: (b1=1, b2=1)



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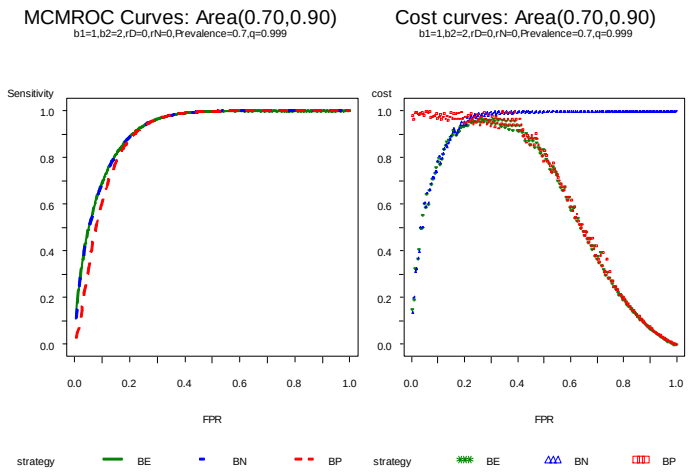

Figure B1.2b: (b1=1, b2=2)

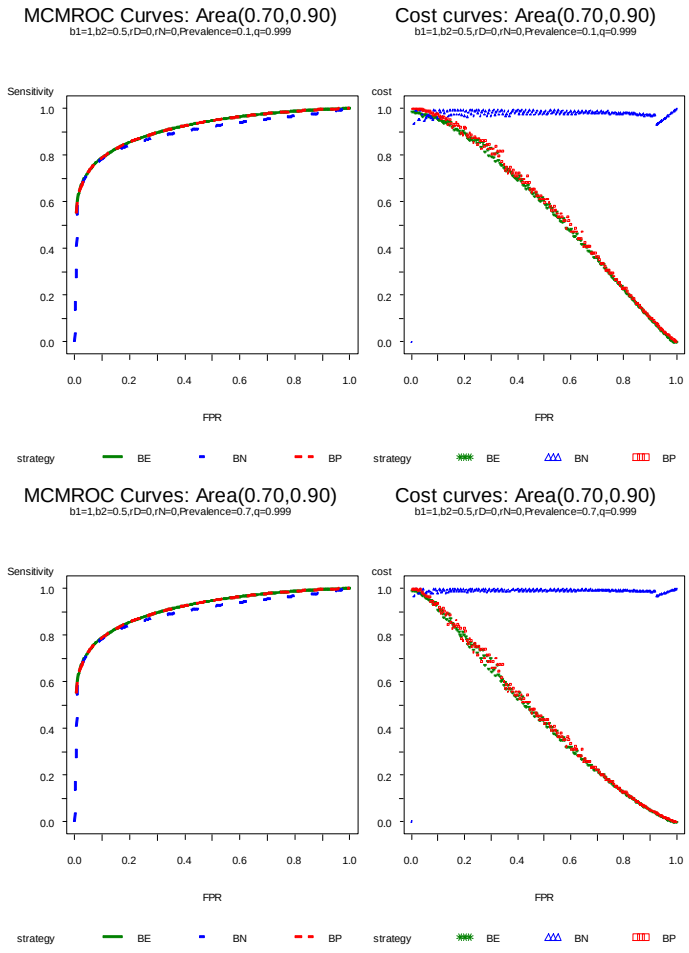

Figure B1.2c: (b1=1, b2=0.5)

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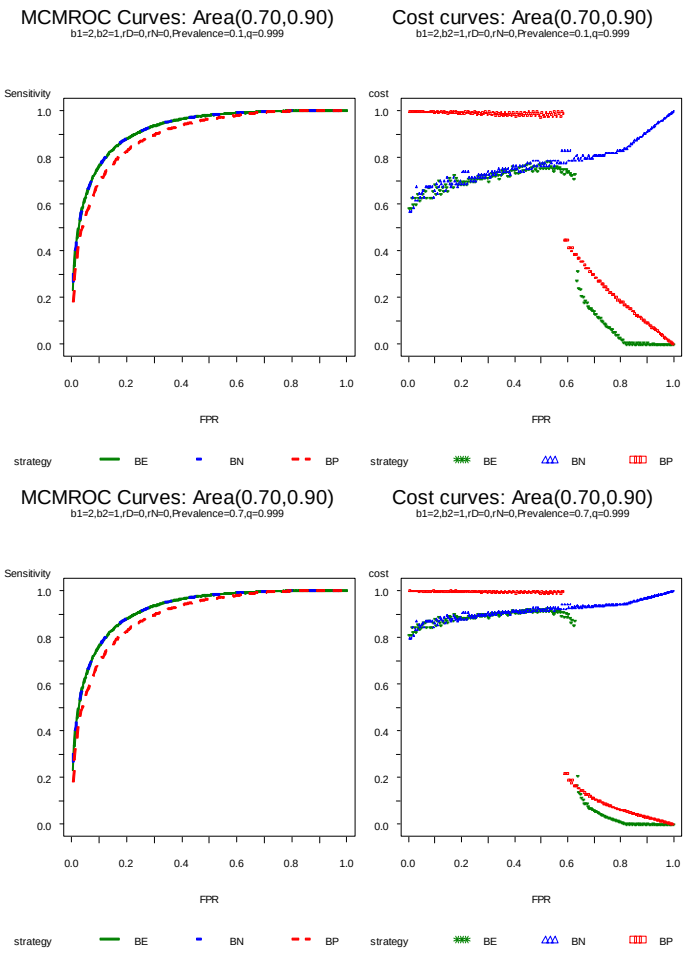
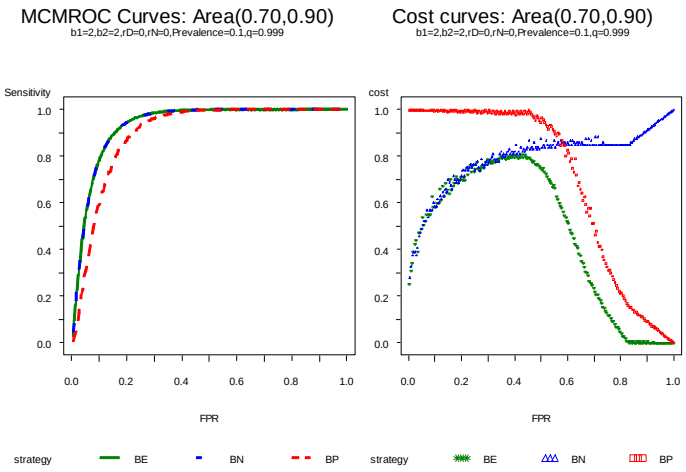


Figure B1.2d: (b1=2, b2=1)



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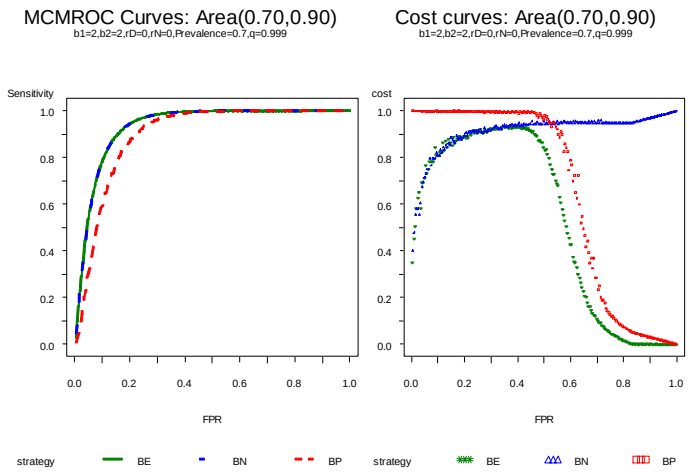
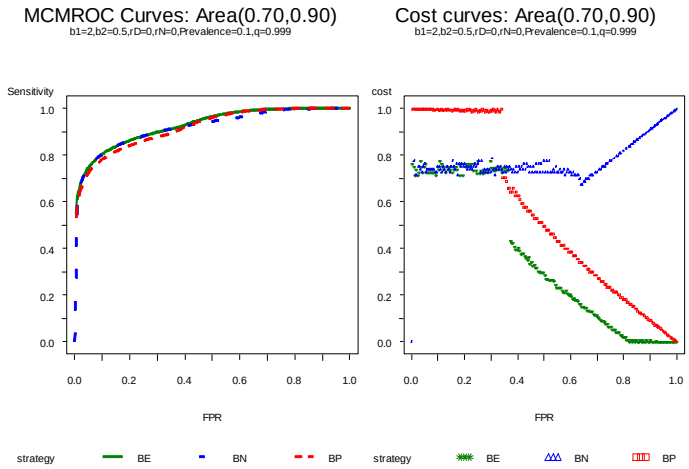


Figure B1.2e: (b1=2, b2=2)



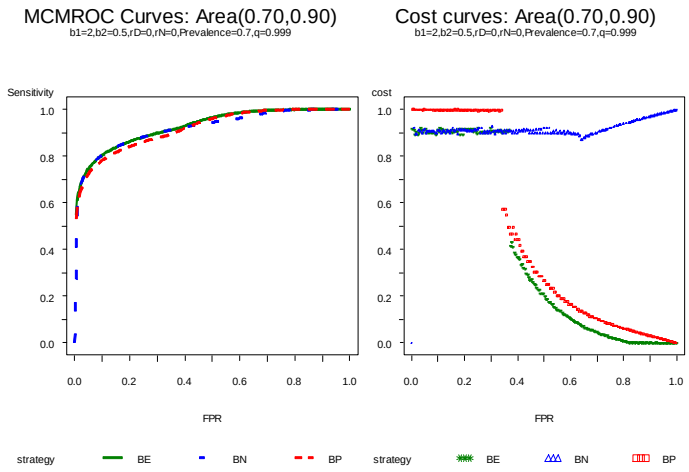


Figure B1.2f: (b1=2, b2=0.5)

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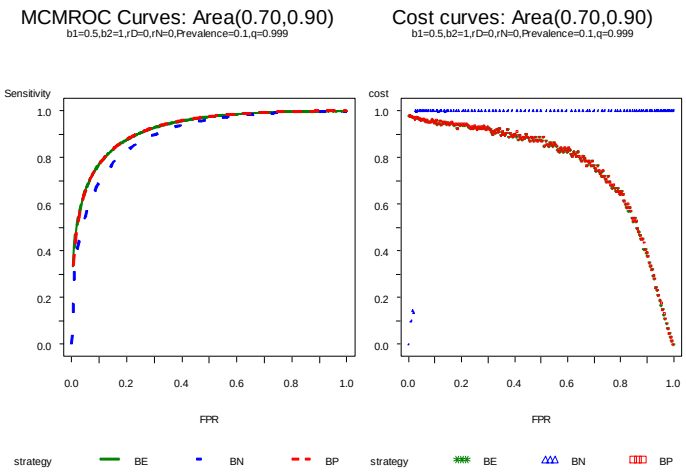


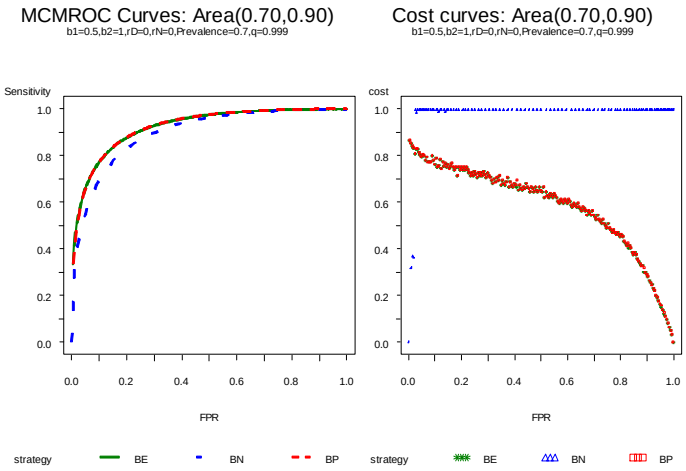
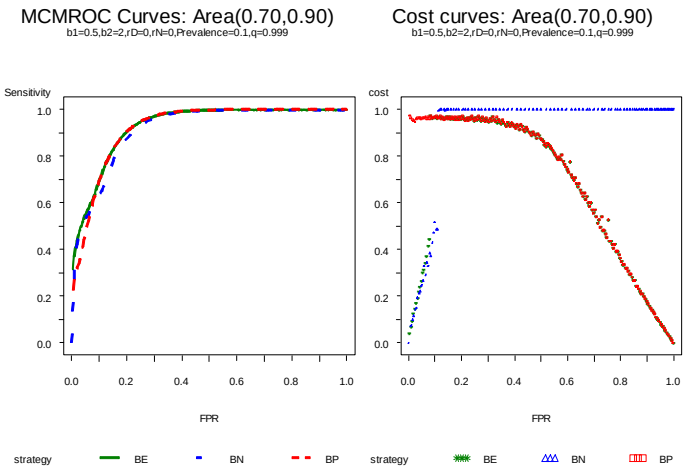


Figure B1.2g: (b1=0.5, b2=1)



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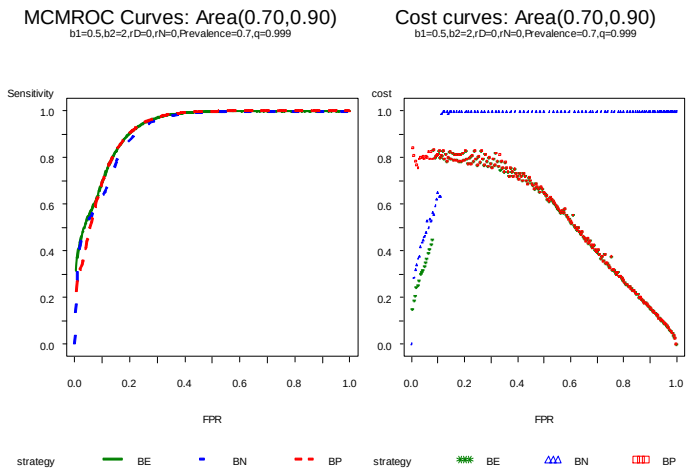
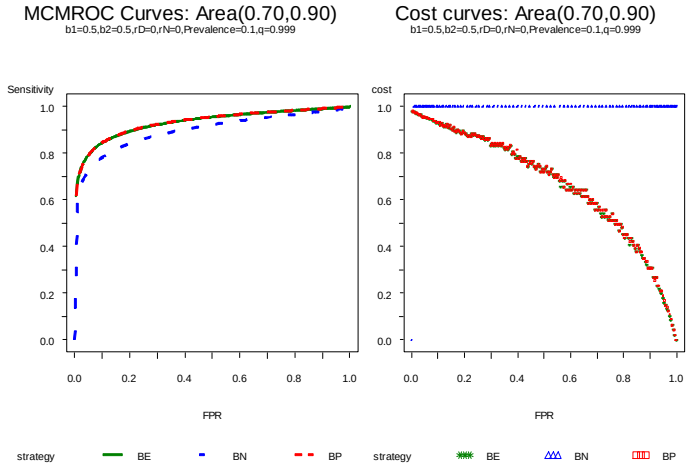


Figure B1.2h: (b1=0.5, b2=2)



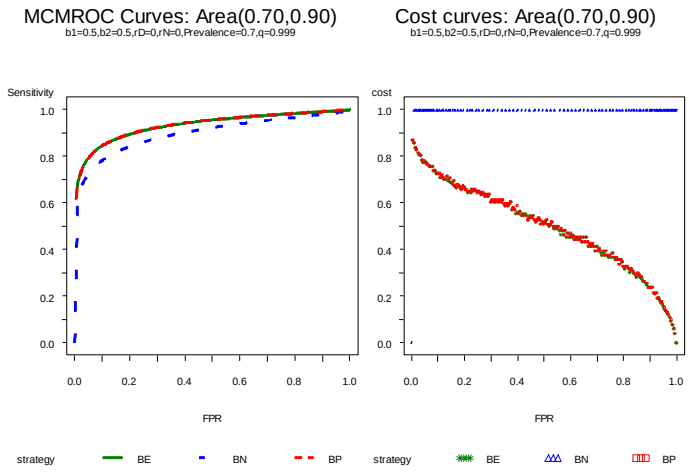


Figure B1.2i: (b1=0.5, b2=0.5)

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B1.3 AUC1 = 0.70, AUC2 = 0.70

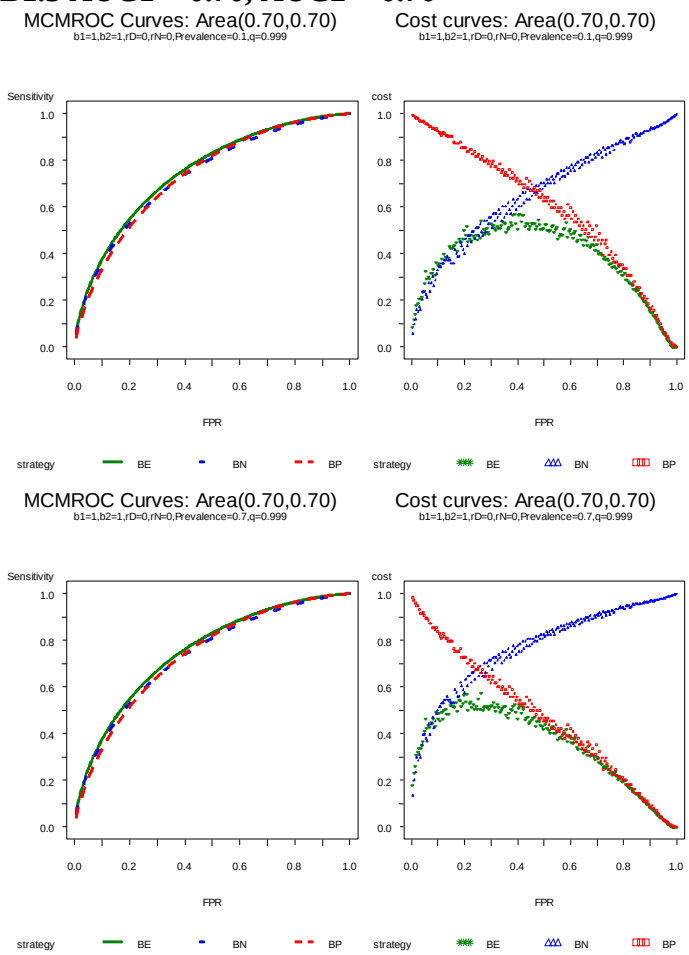
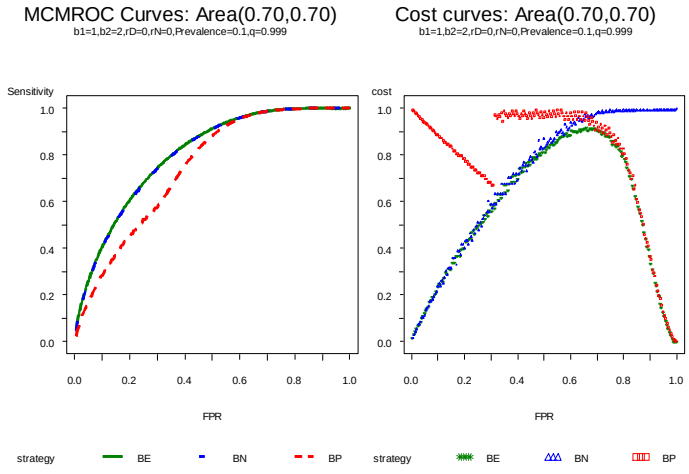


Figure B1.3a: (b1=1, b2=1)



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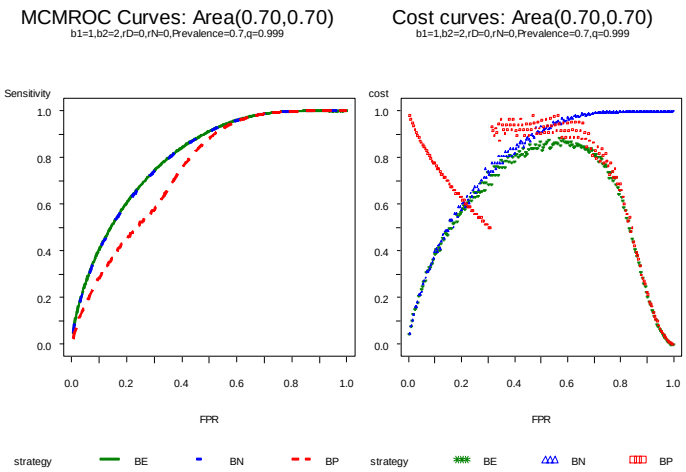

Figure B1.3b: (b1=1, b2=2)

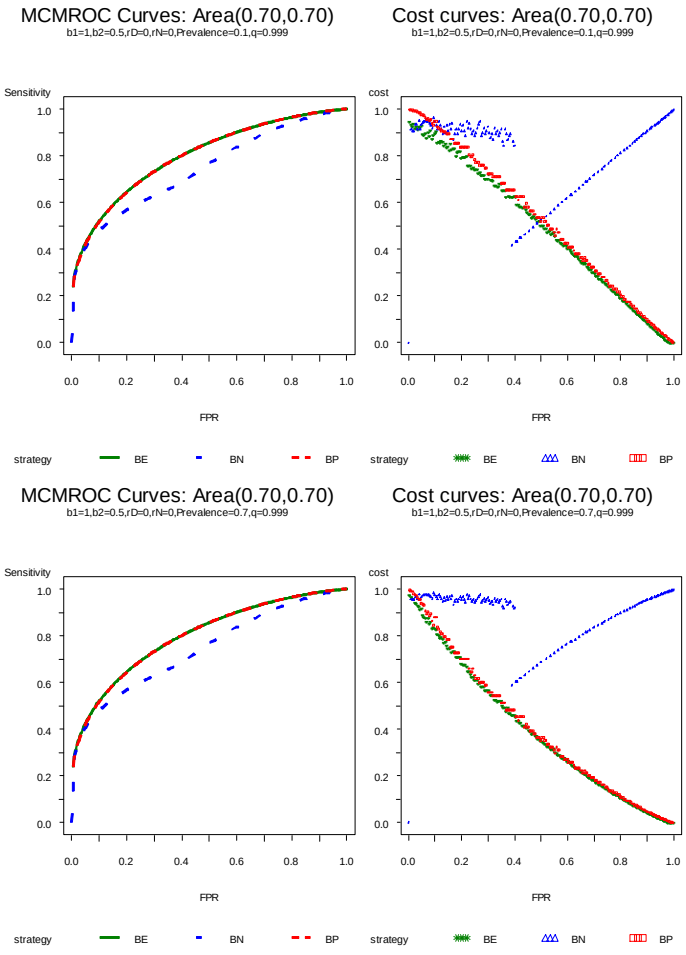

Figure B1.3c: (b1=1, b2=0.5)

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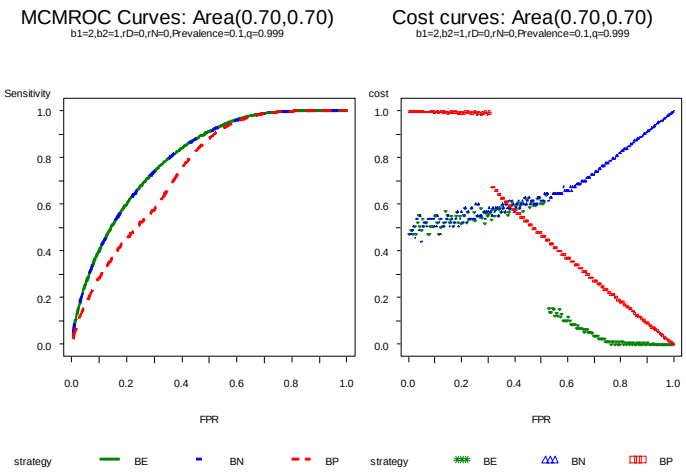


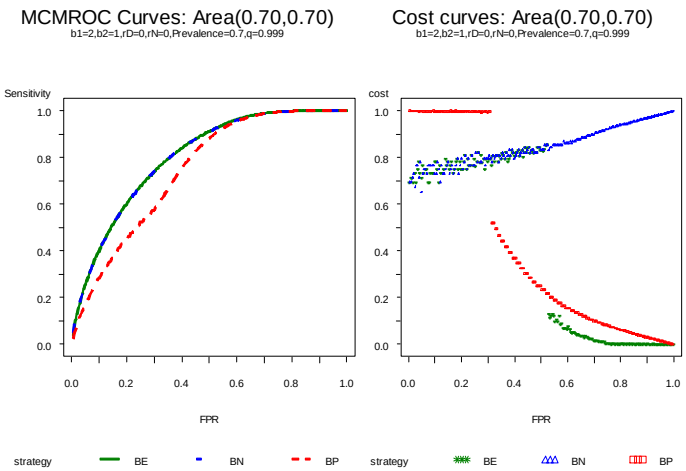
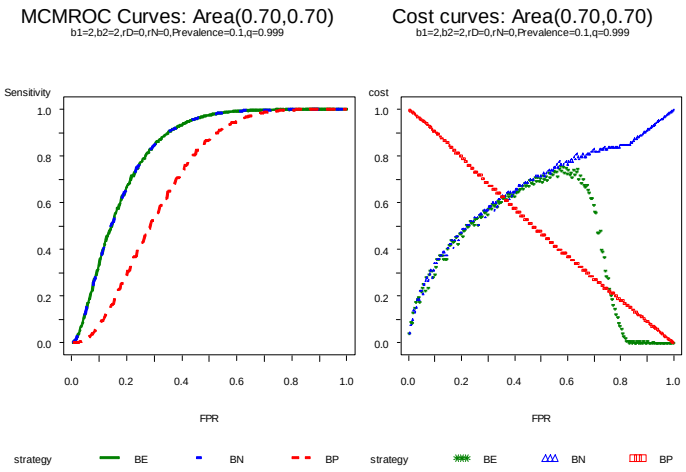


Figure B1.3d: (b1=2, b2=1)



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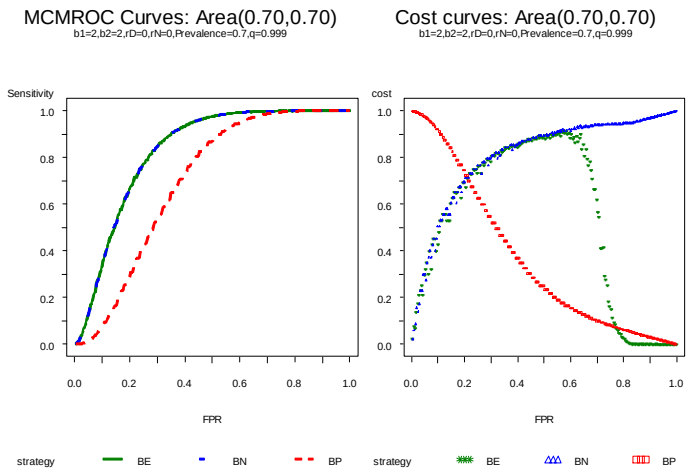

Figure B1.3e: (b1=2, b2=2)

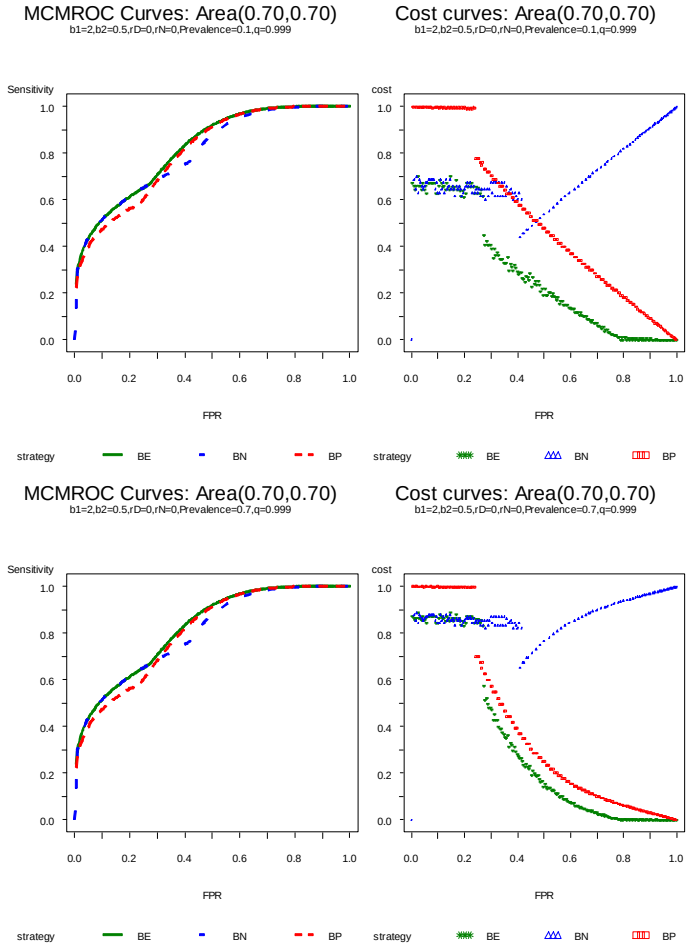

Figure B1.3f: (b1=2, b2=0.5)

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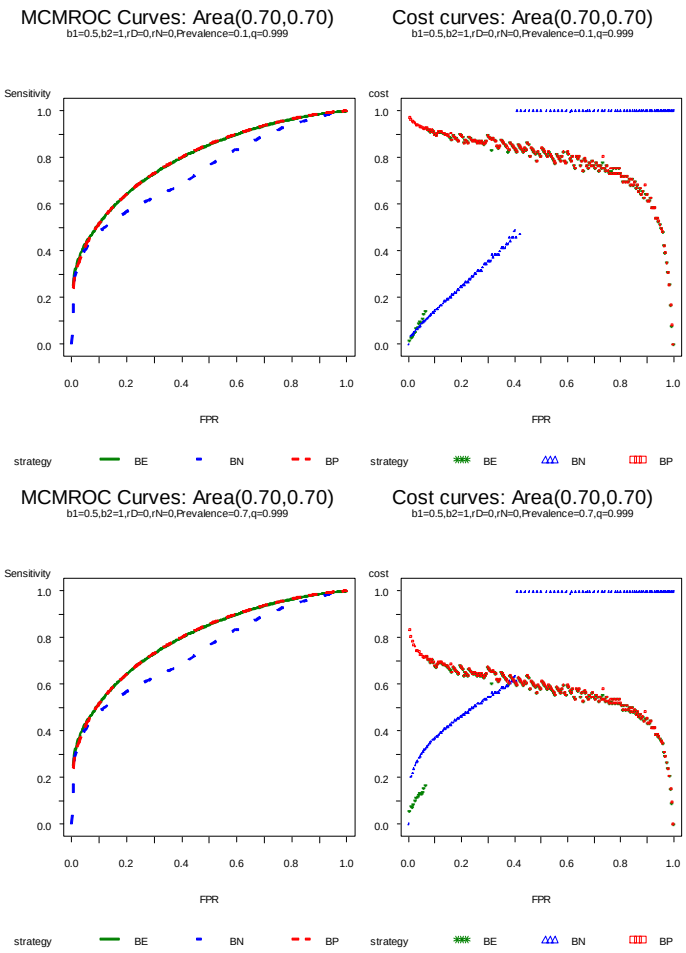
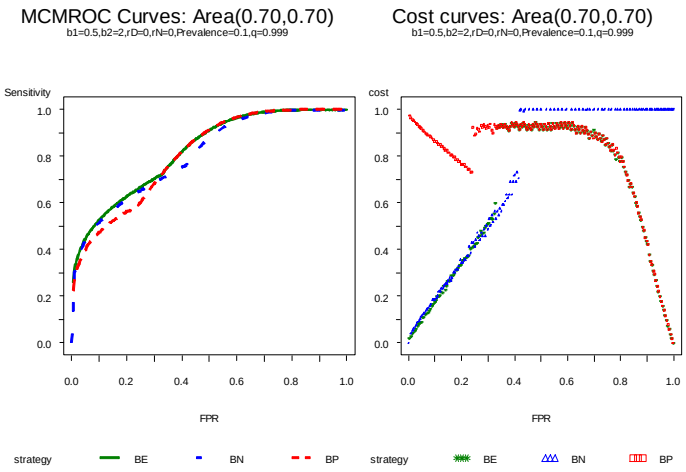


Figure B1.3g: (b1=0.5, b2=1)



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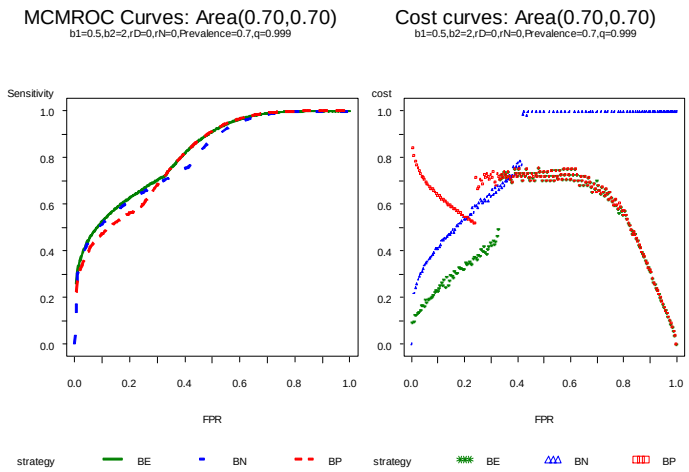
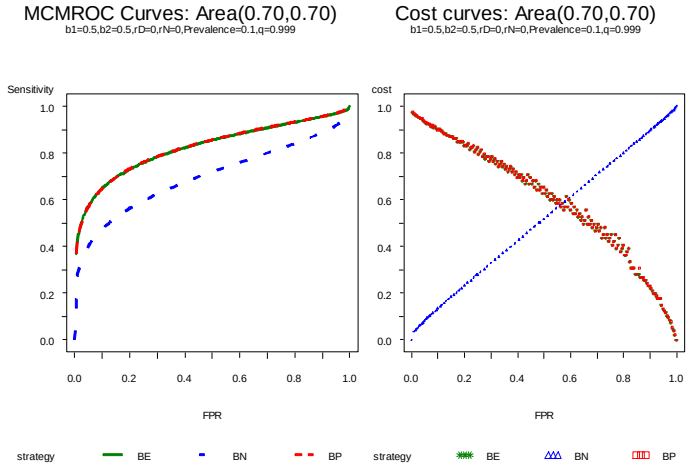


Figure B1.3h: (b1=0.5, b2=2)



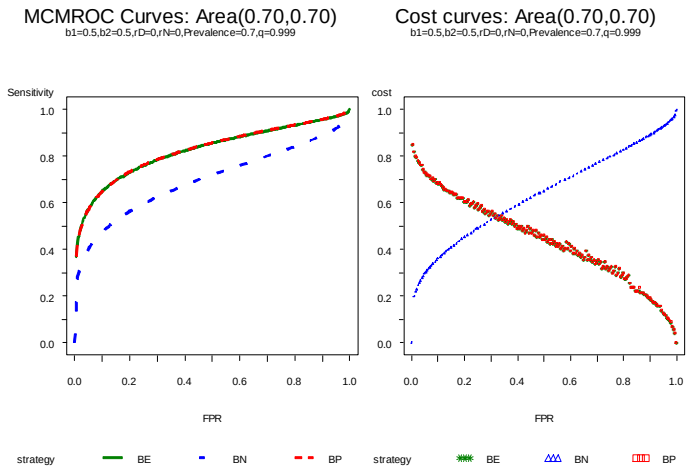


Figure B1.3i: (b1=0.5, b2=0.5)

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B2 Dependent of the tests $(\rho_D = 0.3, \rho_N = 0.3)$

B2.1 AUC1 = 0.90, AUC2 = 0.90

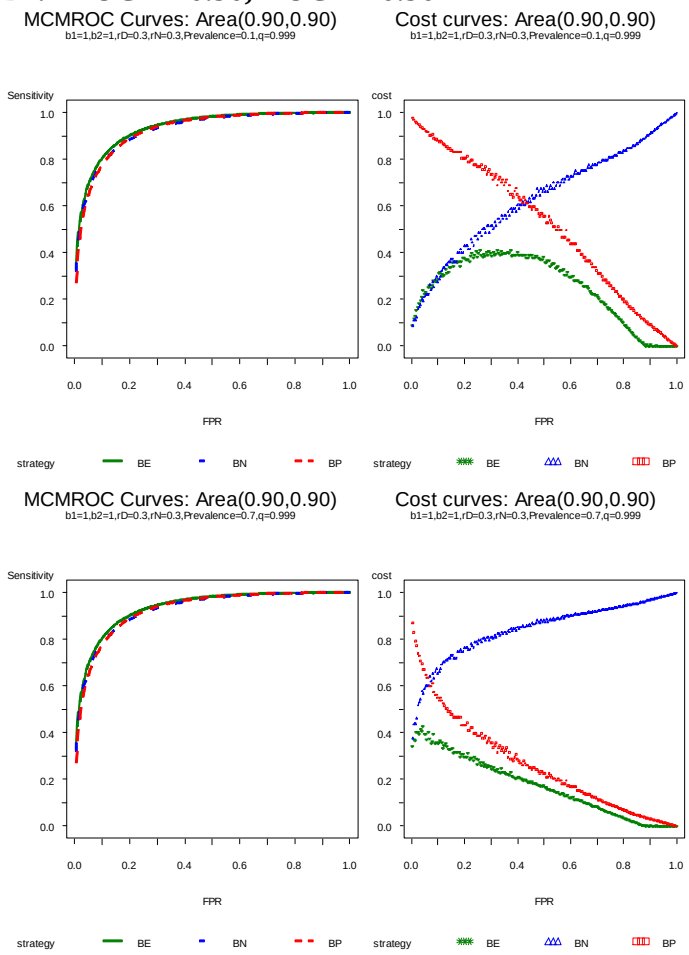
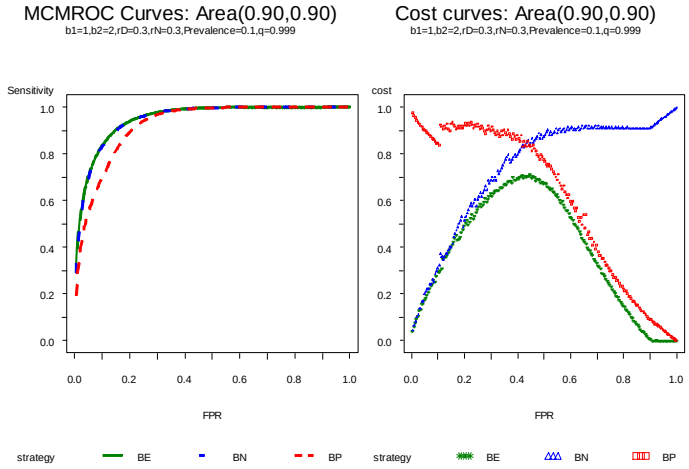


Figure B2.1a: (b1=1, b2=1)



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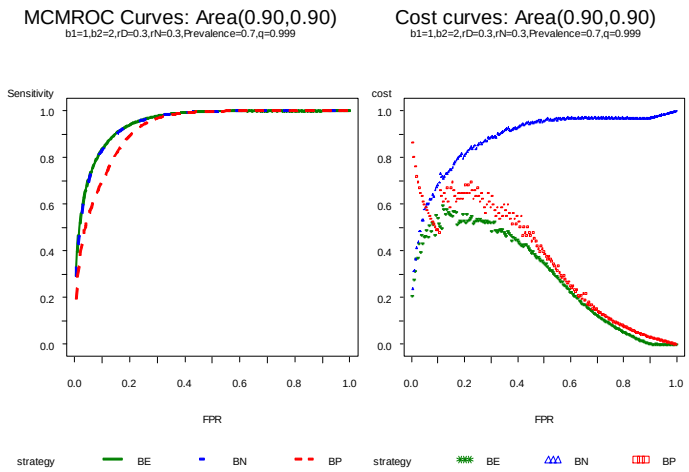

Figure B2.1b: (b1=1, b2=2)

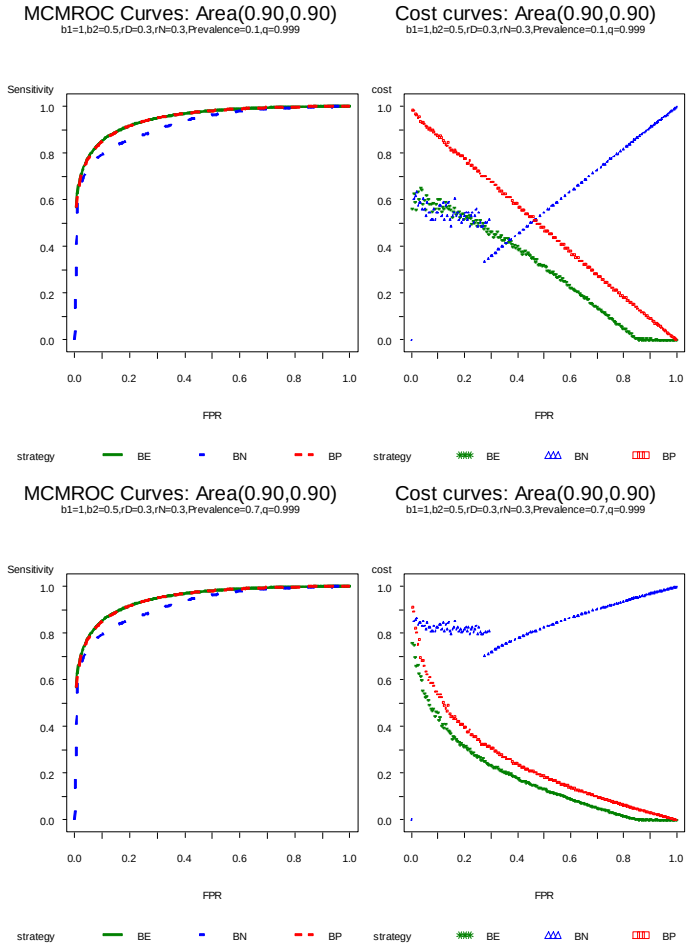

Figure B2.1c: (b1=1, b2=0.5)

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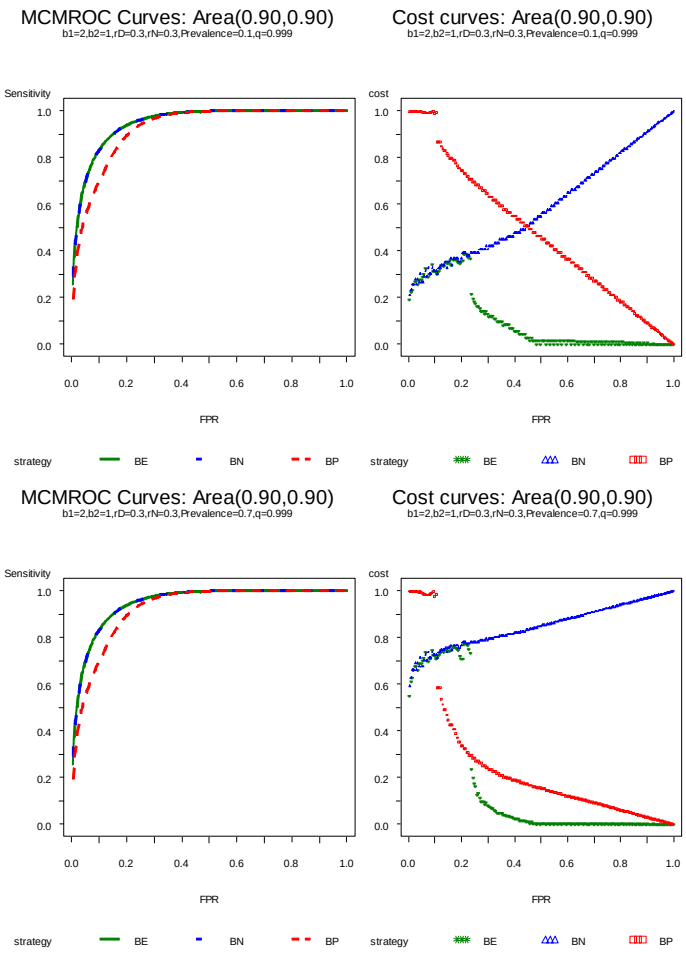
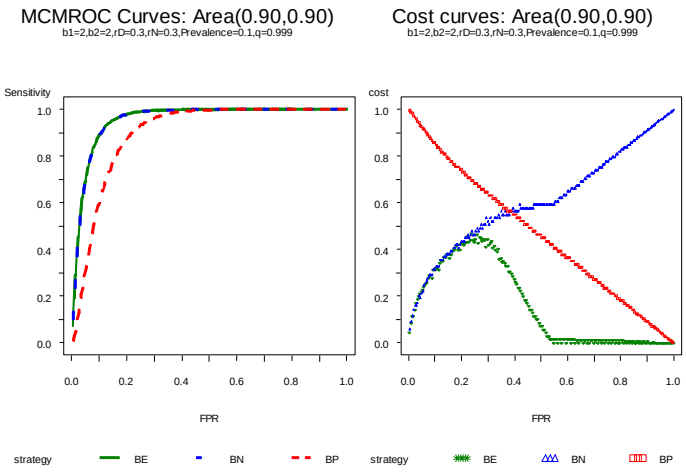


Figure B2.1d: (b1=2, b2=1)



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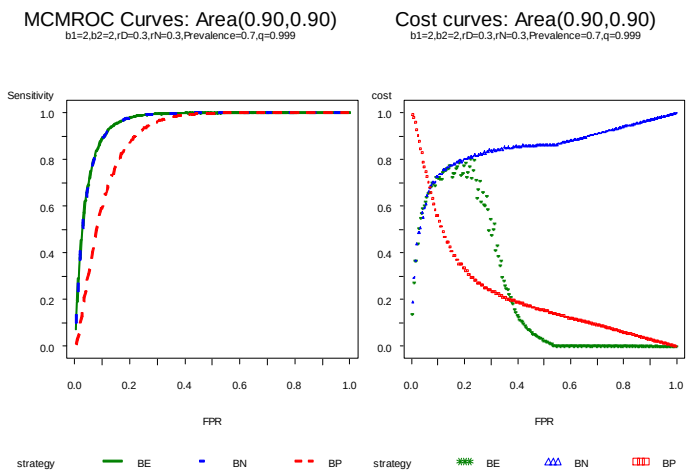

Figure B2.1e: (b1=2, b2=2)

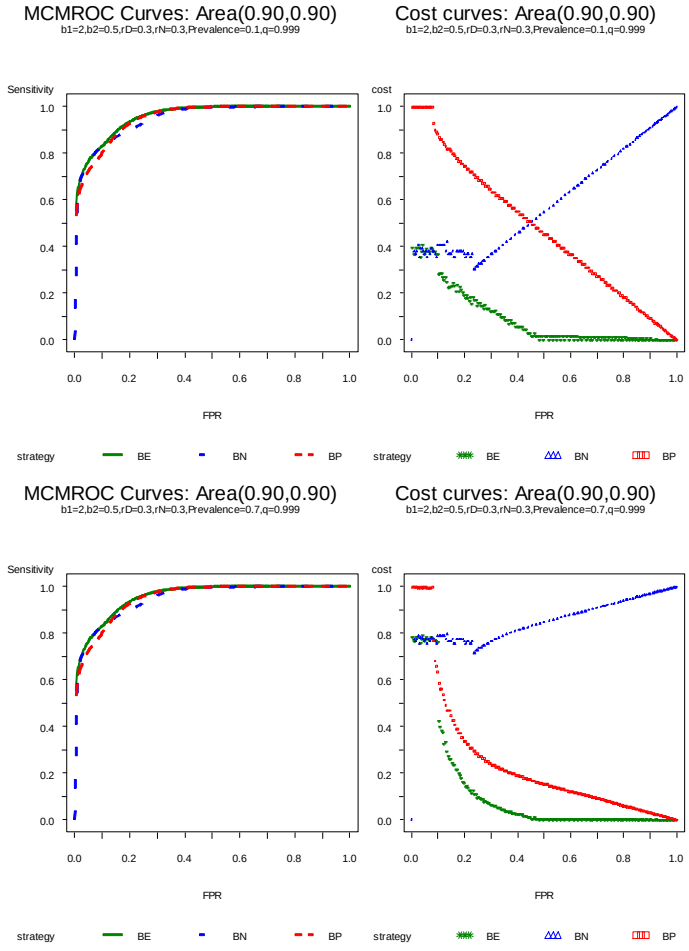

Figure B2.1f: (b1=2, b2=0.5)

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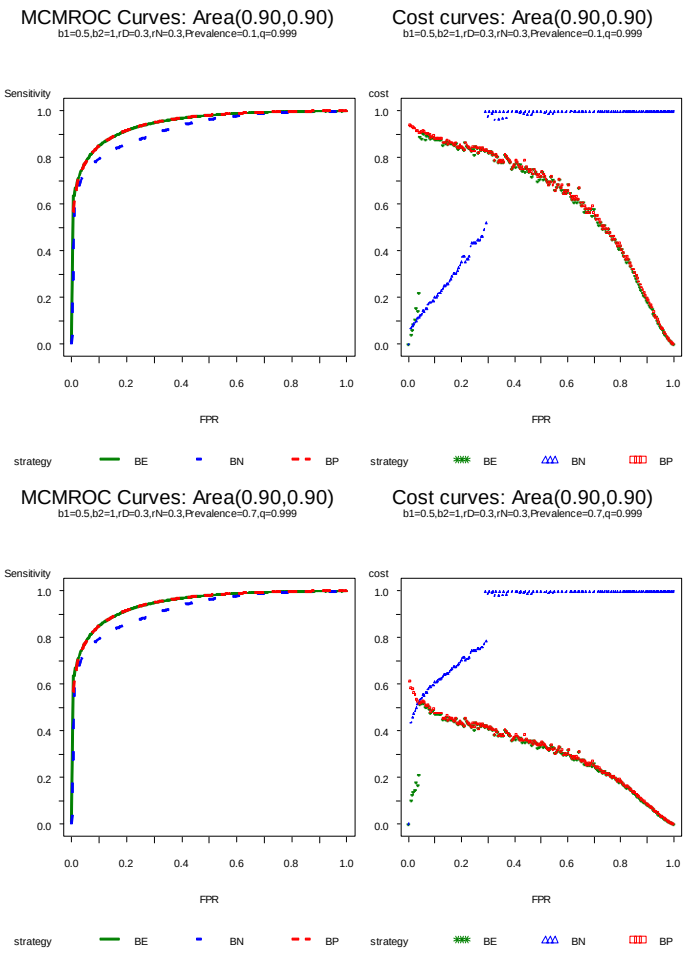
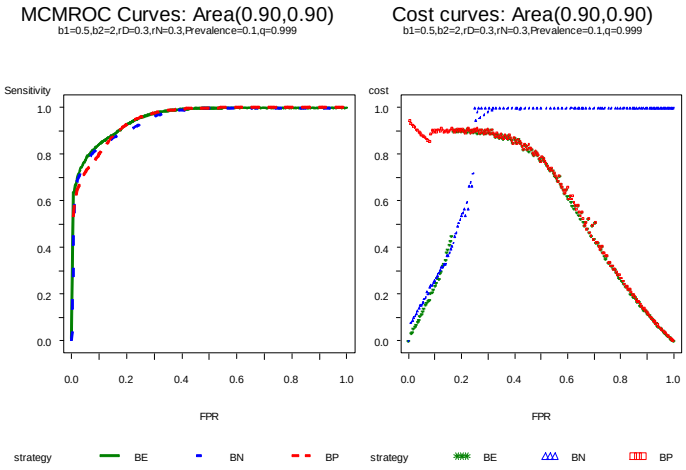


Figure B2.1g: (b1=0.5, b2=1)



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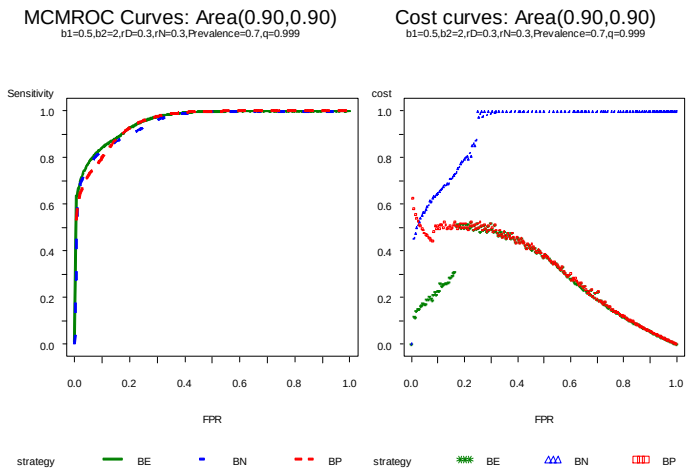
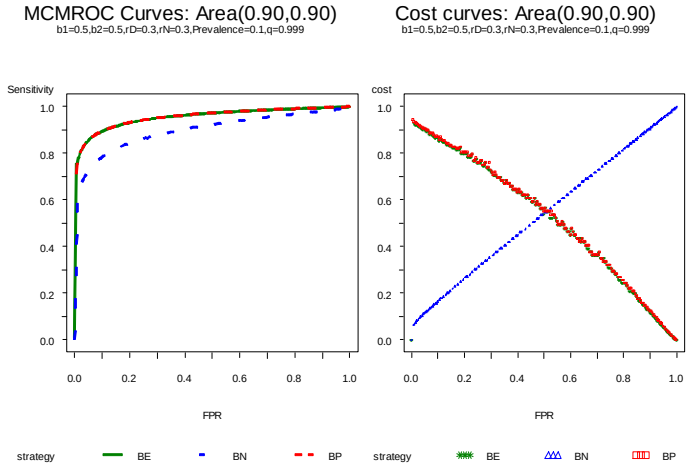


Figure B2.1h: (b1=0.5, b2=2)



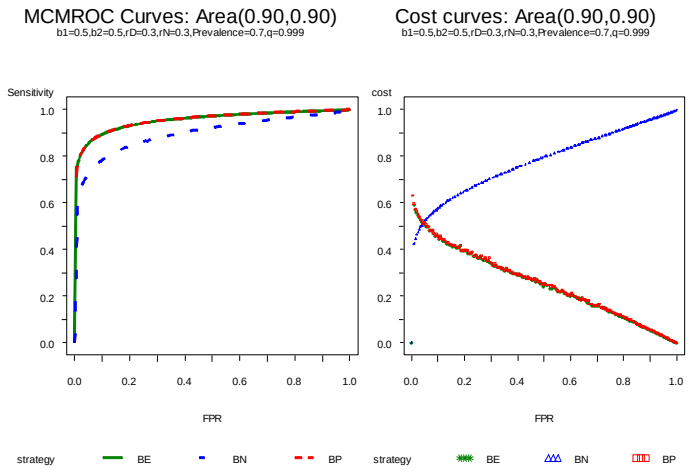


Figure B2.1i: (b1=0.5, b2=0.5)

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B2.2 AUC1 = 0.70, AUC2 = 0.90

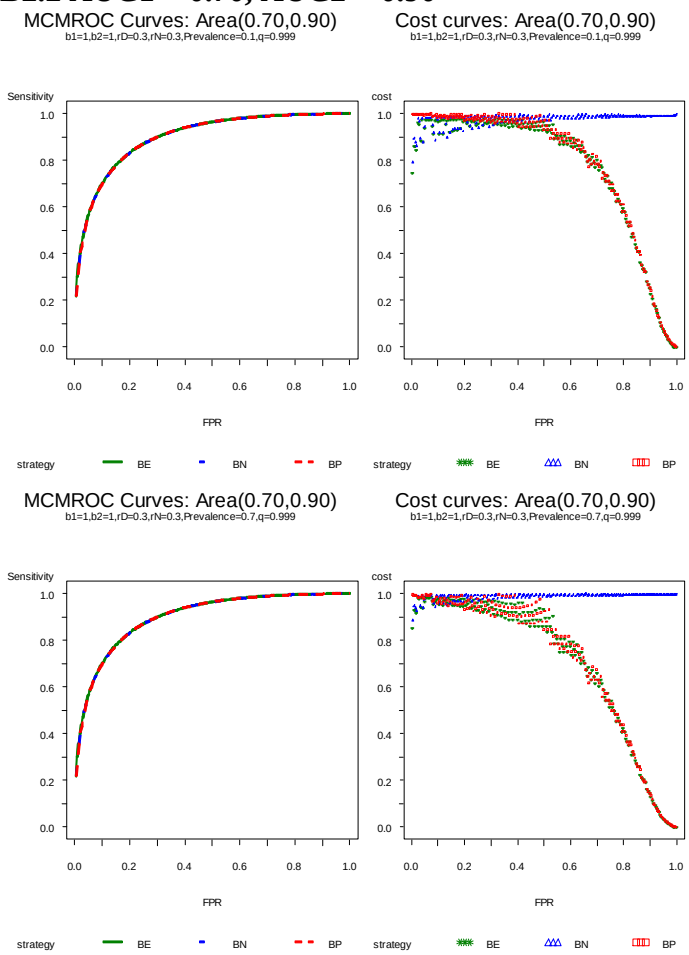
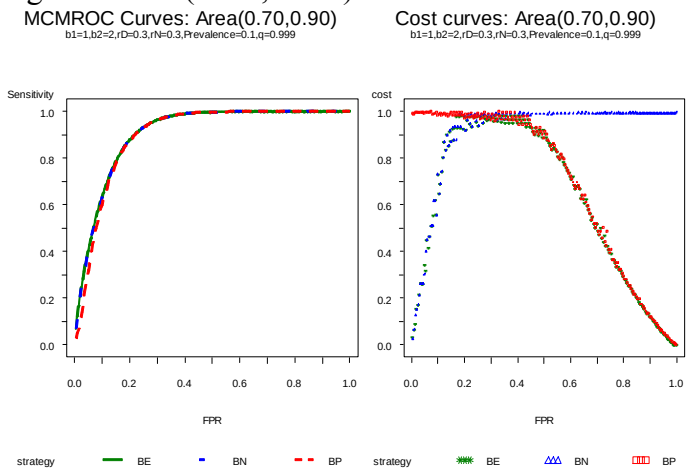


Figure B2.2a: (b1=1, b2=1)



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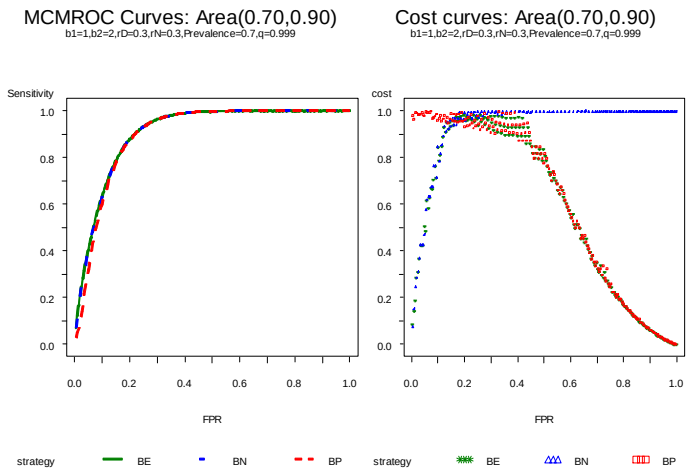

Figure B2.2b: (b1=1, b2=2)

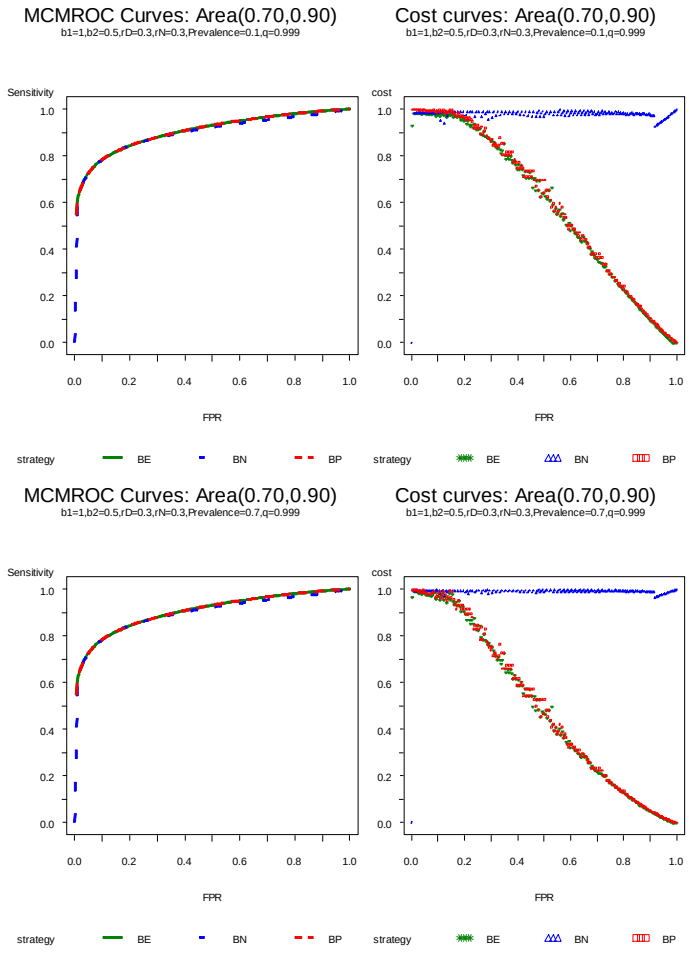

Figure B2.2c: (b1=1, b2=0.5)

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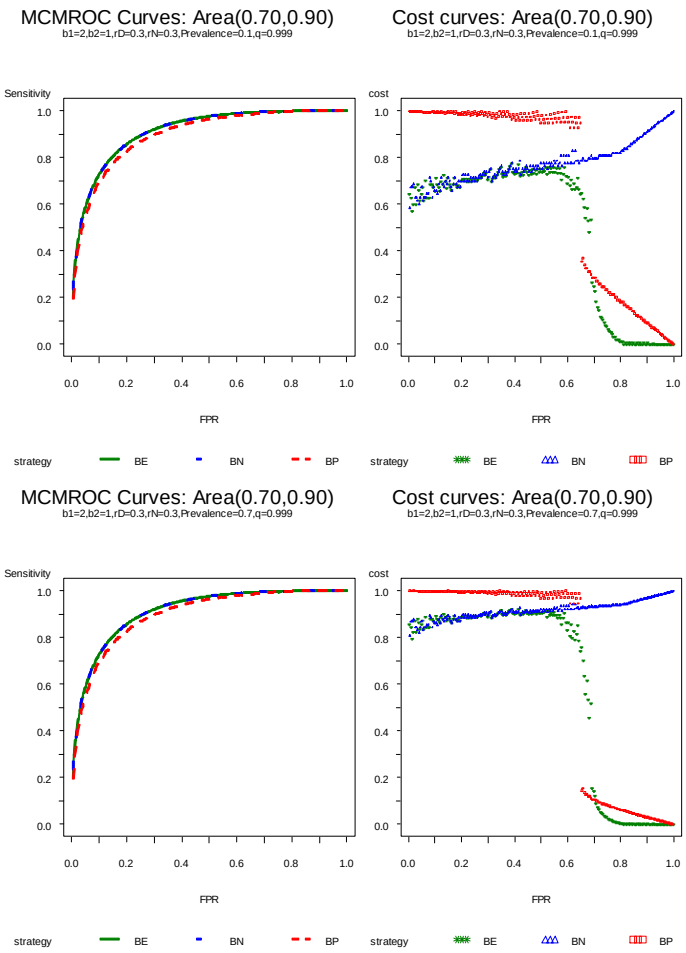
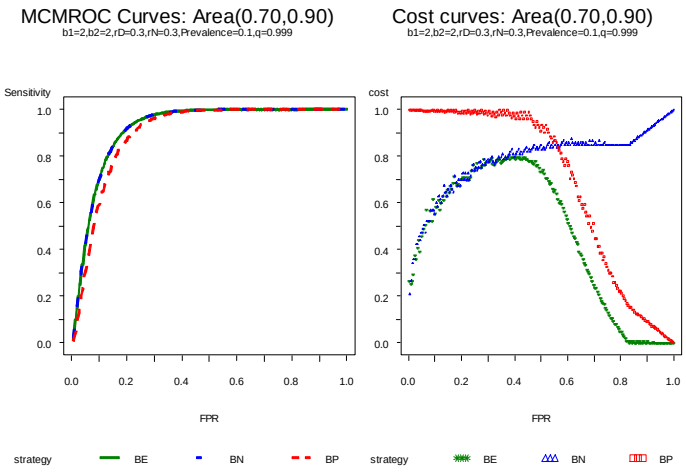


Figure B2.2d: (b1=2, b2=1)



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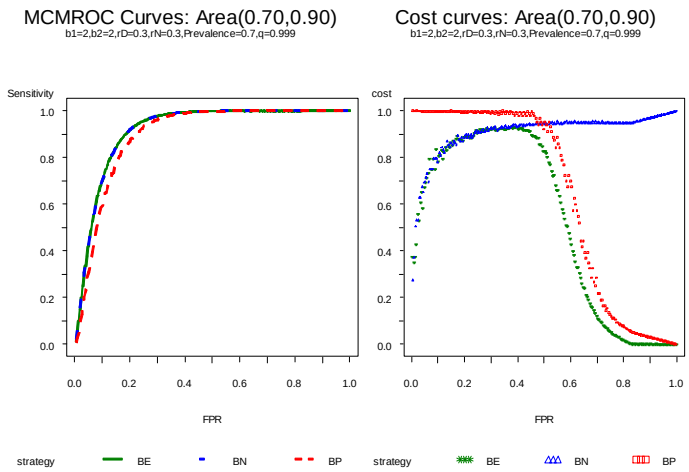
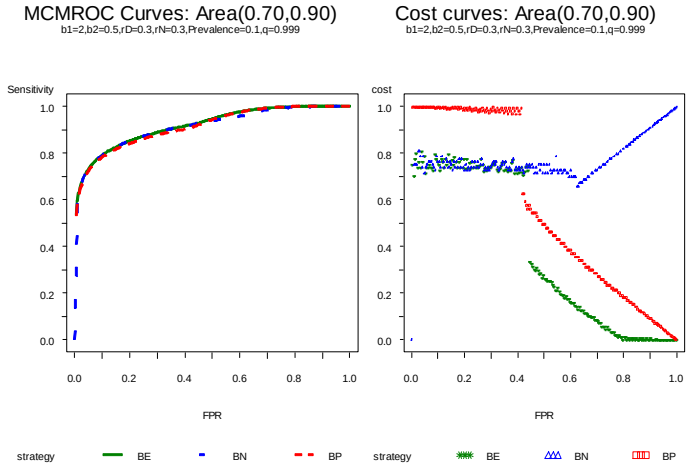


Figure B2.2e: (b1=2, b2=2)



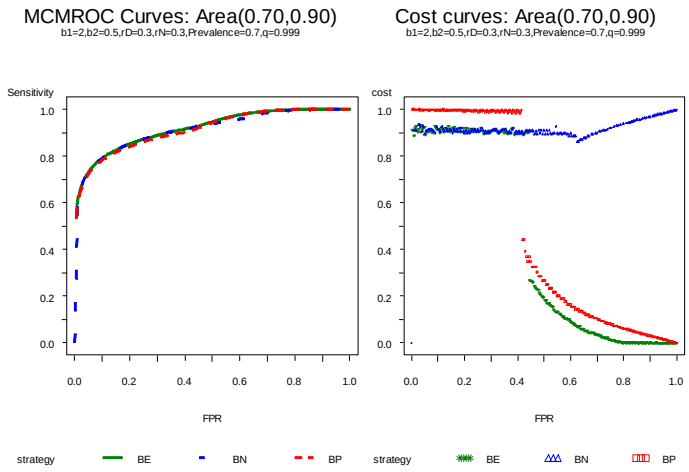


Figure B2.2f: (b1=2, b2=0.5)

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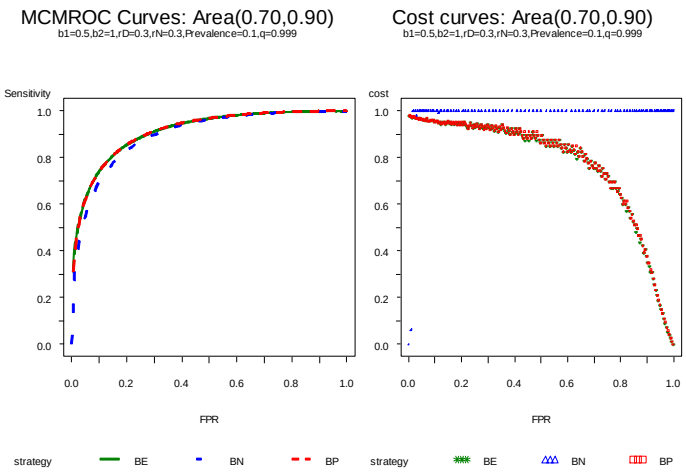


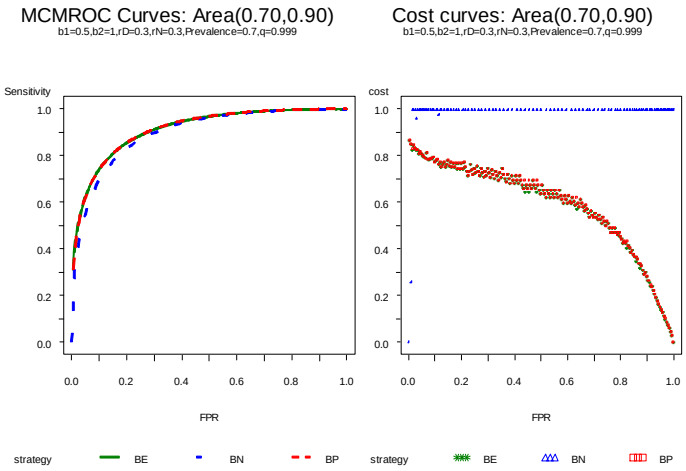
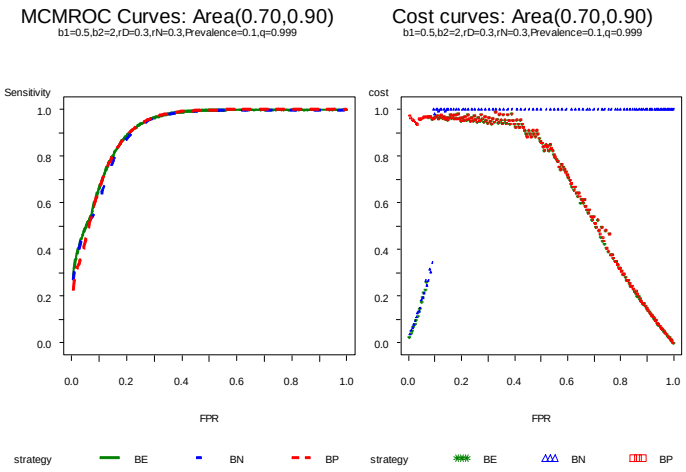


Figure B2.2g: (b1=0.5, b2=1)



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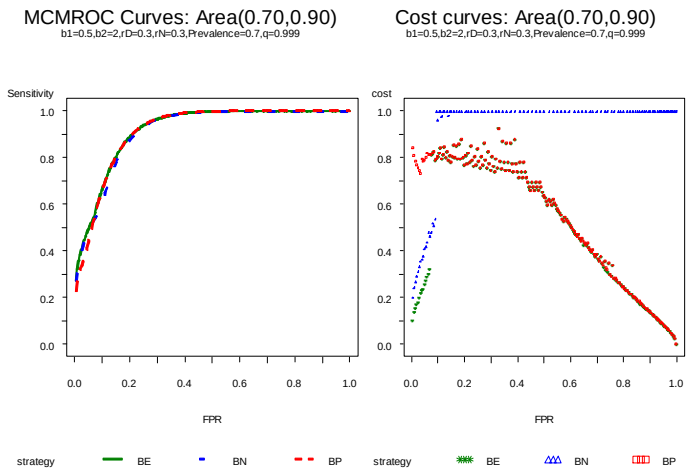
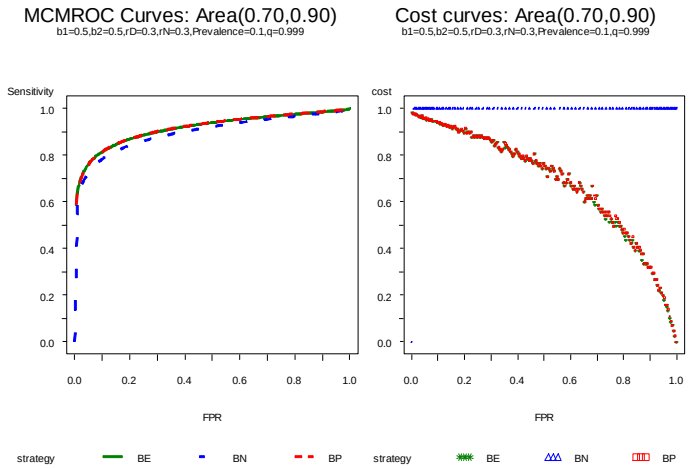


Figure B2.2h: (b1=0.5, b2=2)



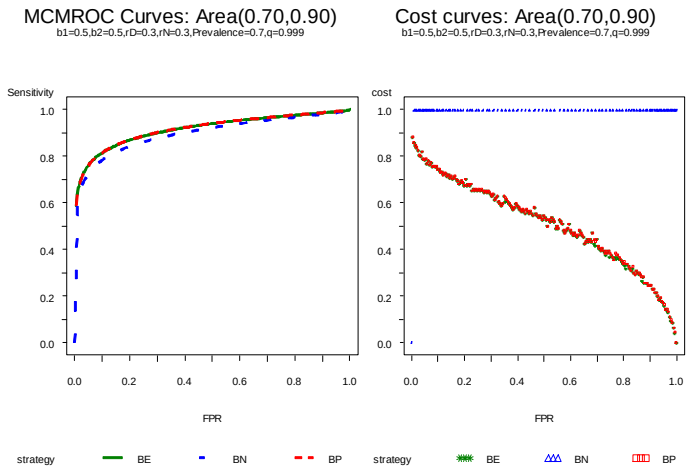


Figure B2.2i: (b1=0.5, b2=0.5)

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B2.3 AUC1 = 0.70, AUC2 = 0.70

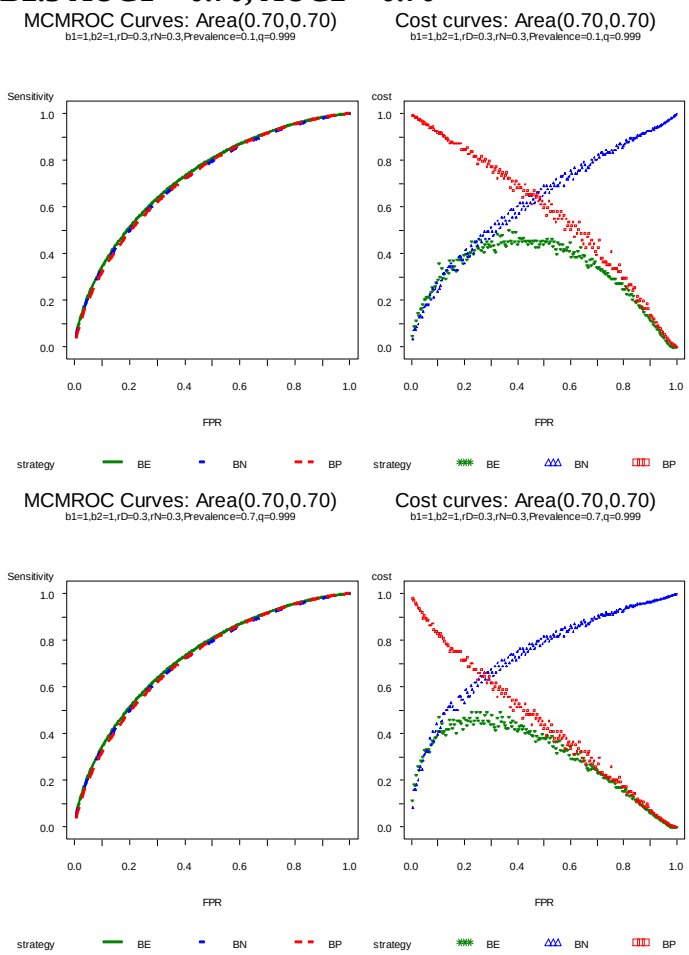
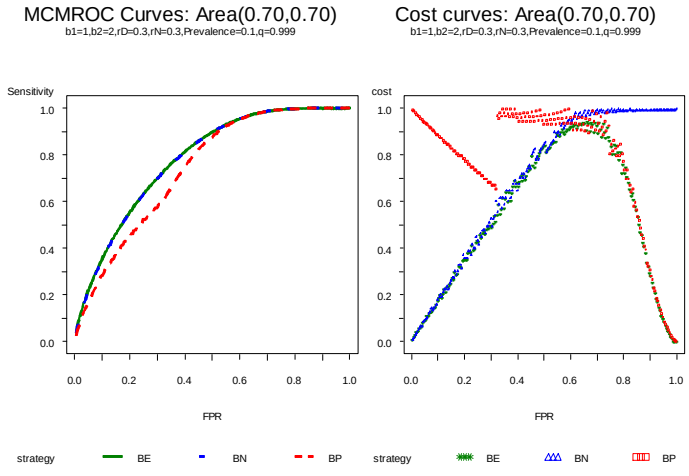


Figure B2.3a: (b1=1, b2=1)



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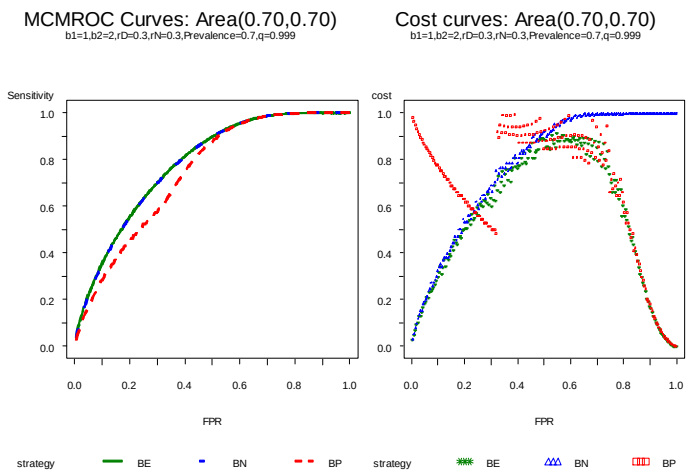

Figure B2.3b: (b1=1, b2=2)

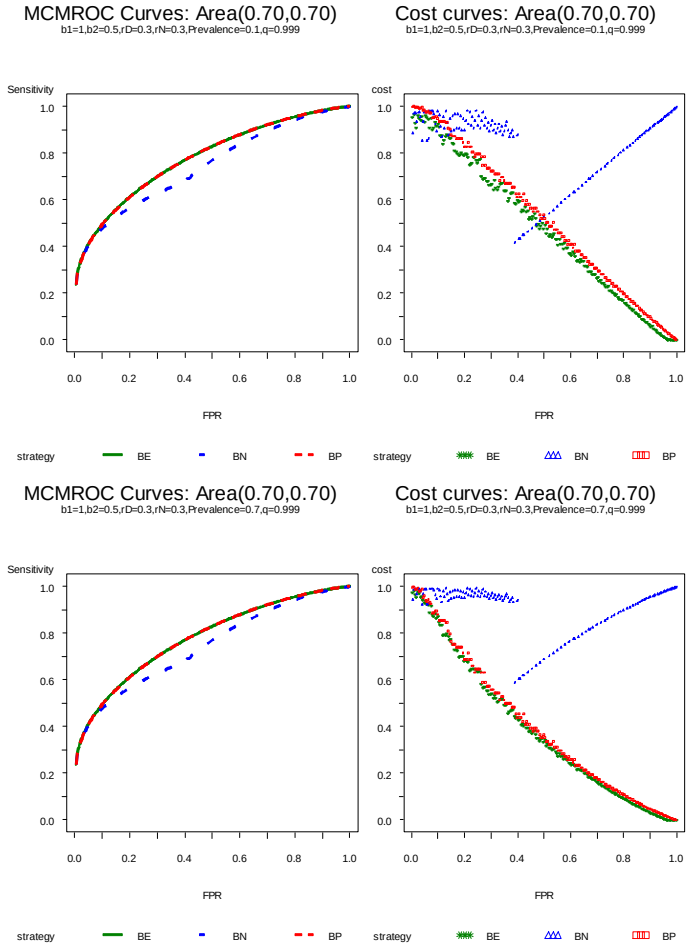

Figure B2.3c: (b1=1, b2=0.5)

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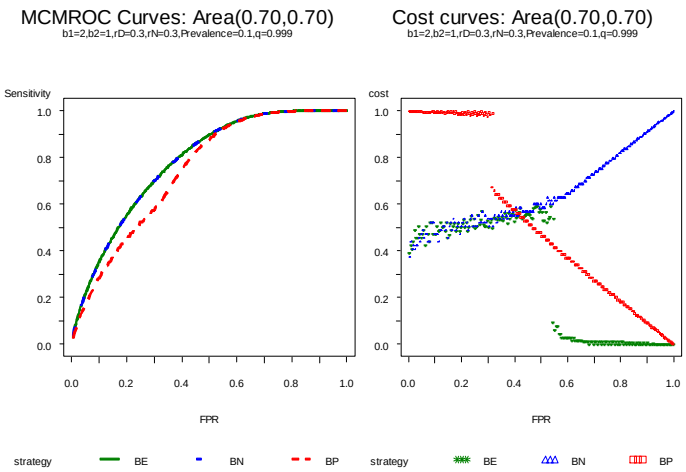


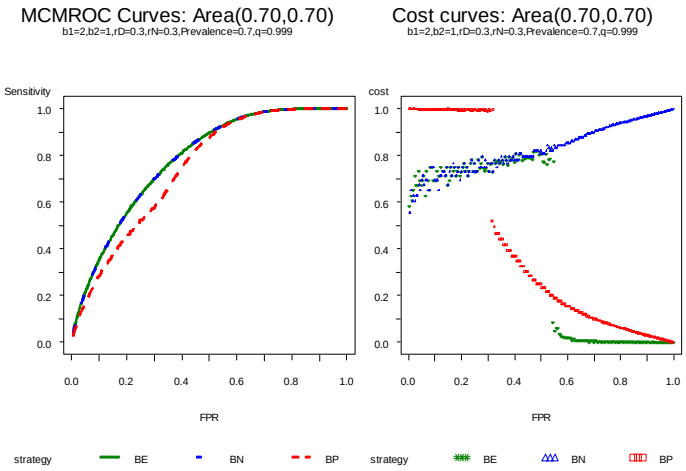
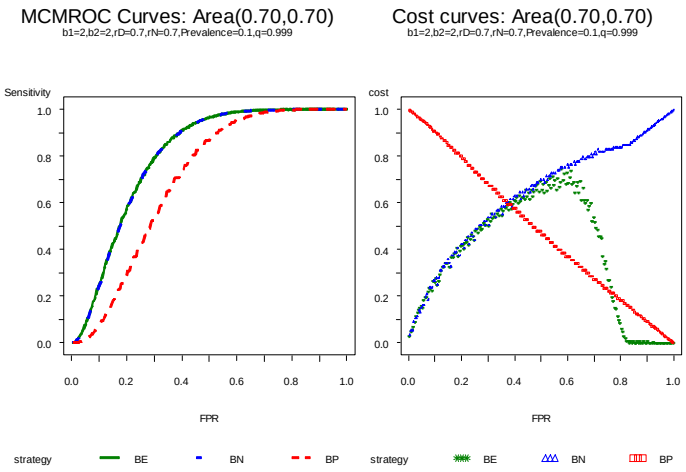


Figure B2.3d: (b1=2, b2=1)



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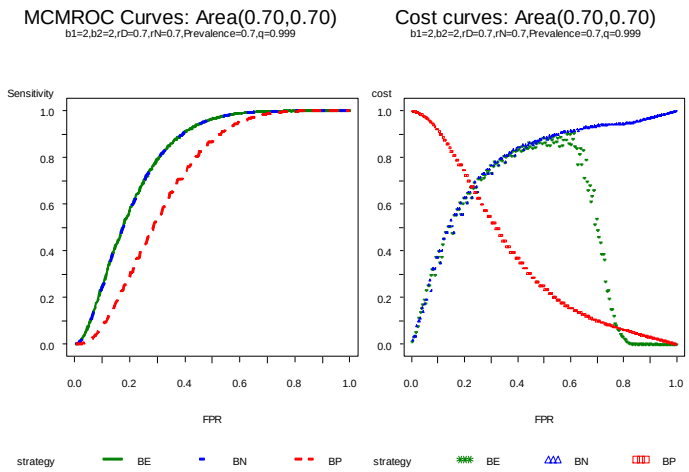

Figure B2.3e: (b1=2, b2=2)

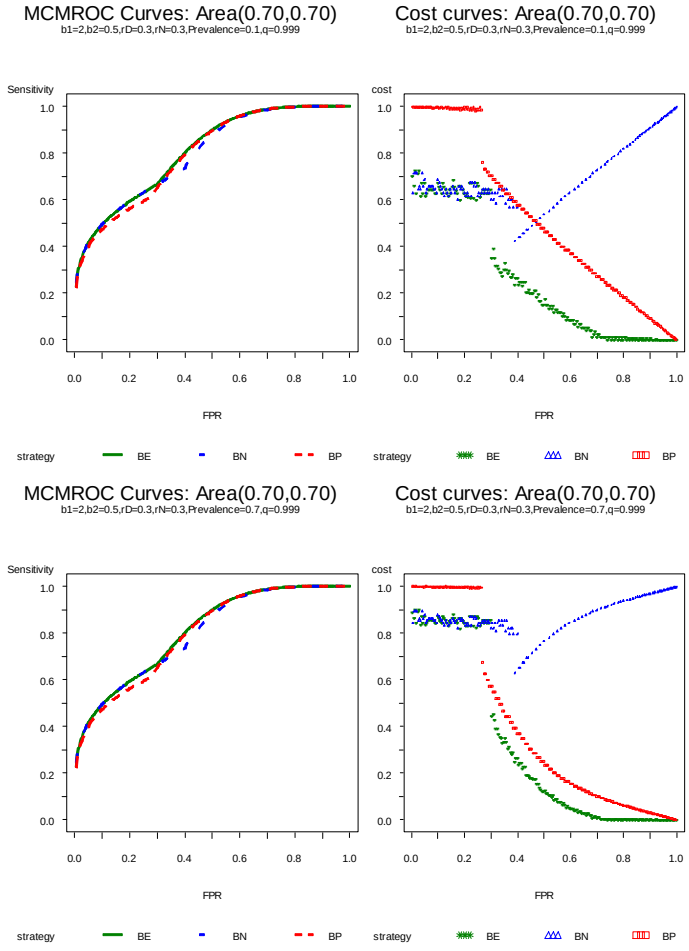

Figure B2.3f: (b1=2, b2=0.5)

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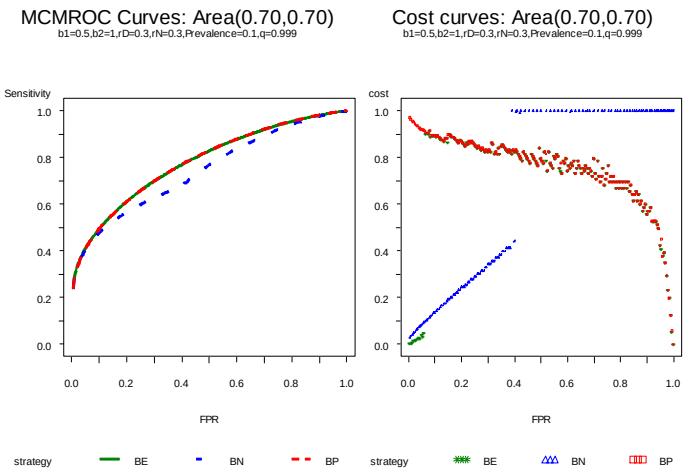


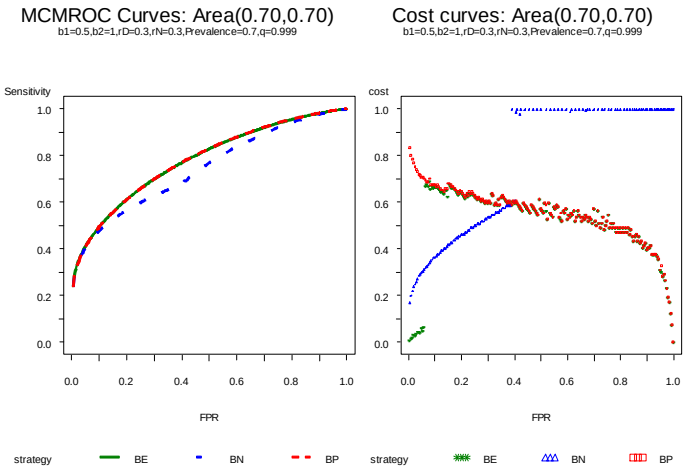
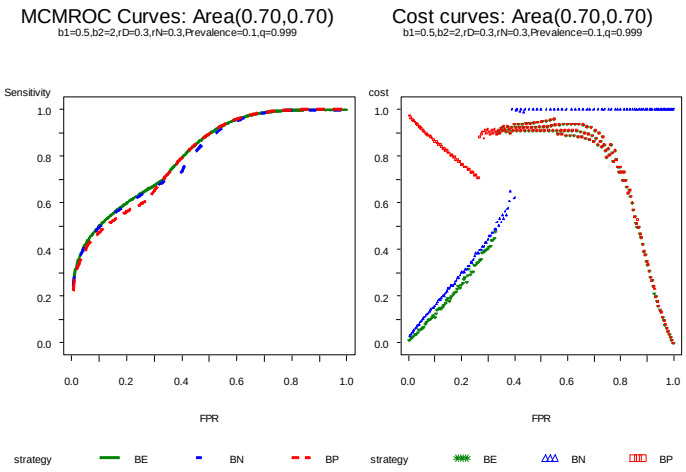


Figure B2.3g: (b1=0.5, b2=1)



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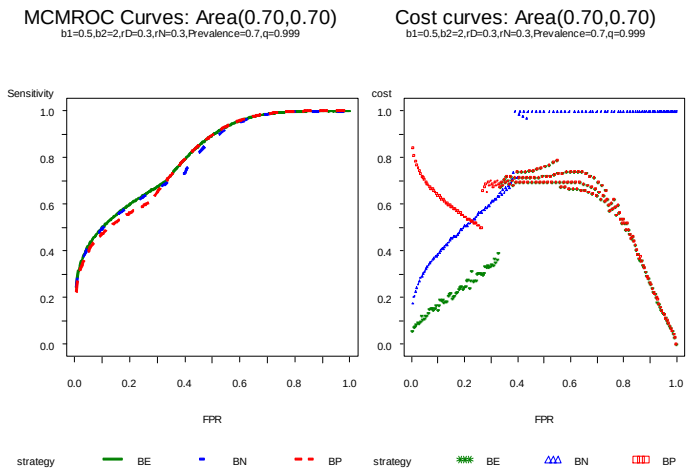
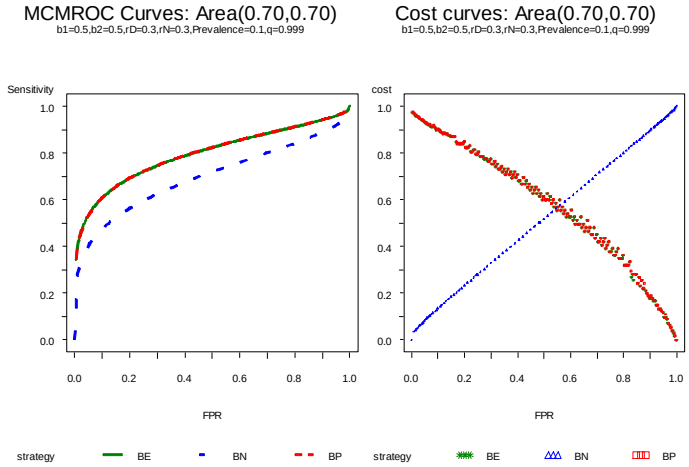


Figure B2.3h: (b1=0.5, b2=2)



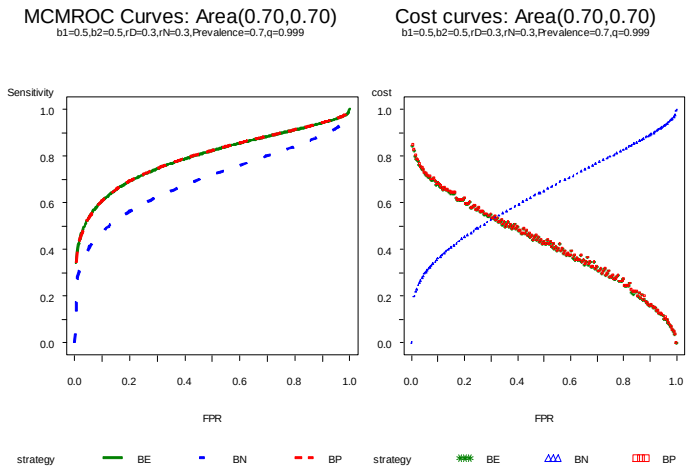


Figure B2.3i: (b1=0.5, b2=0.5)

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B3 Dependent of the tests $(\rho_D = 0.3, \rho_N = 0.7)$

B3.1 AUC1 = 0.90, AUC2 = 0.90

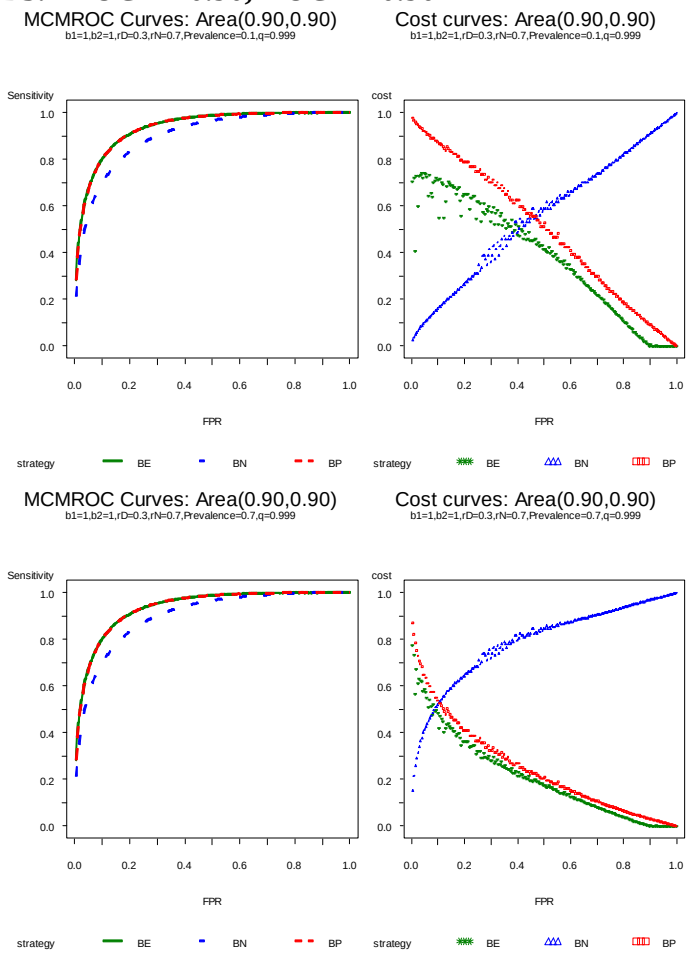
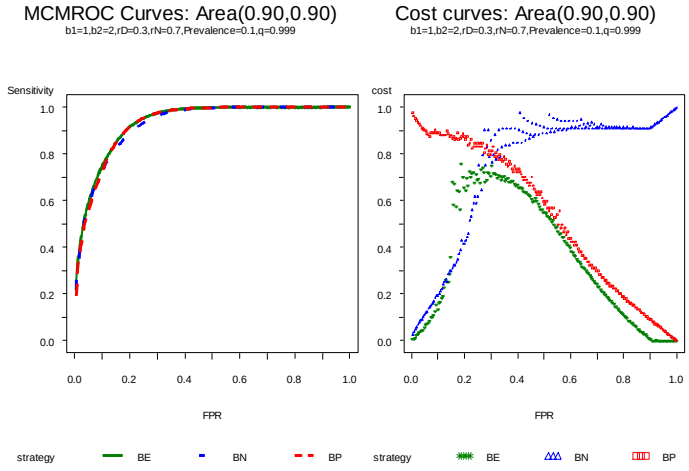


Figure B3.1a: (b1=1, b2=1)



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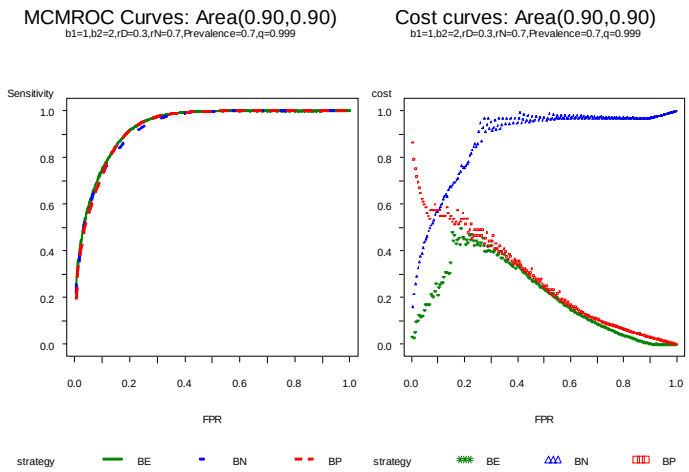

Figure B3.1b: (b1=1, b2=2)

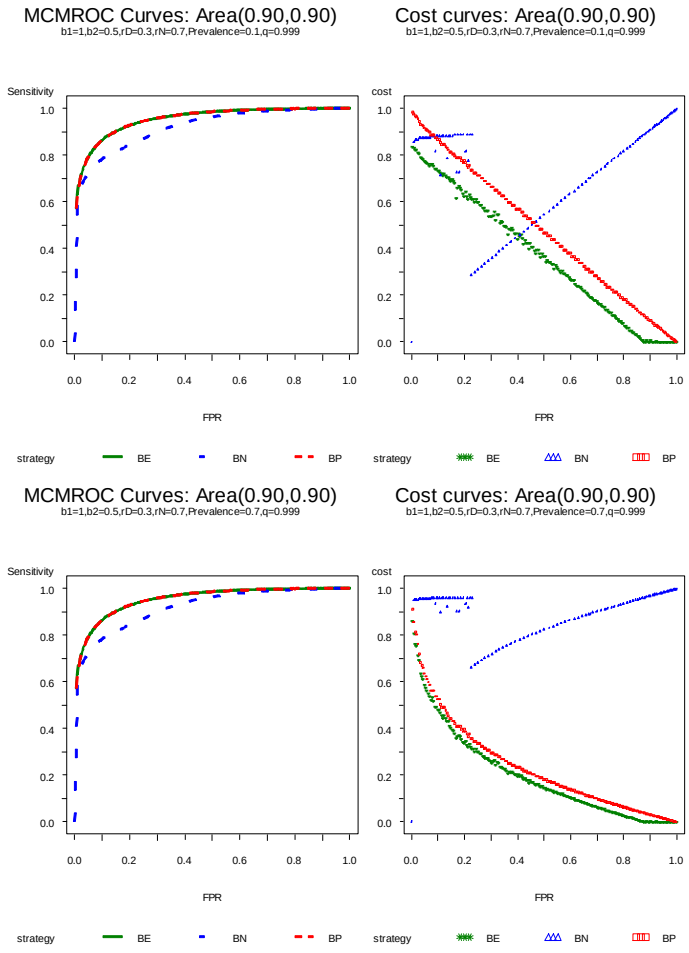

Figure B3.1c: (b1=1, b2=0.5)

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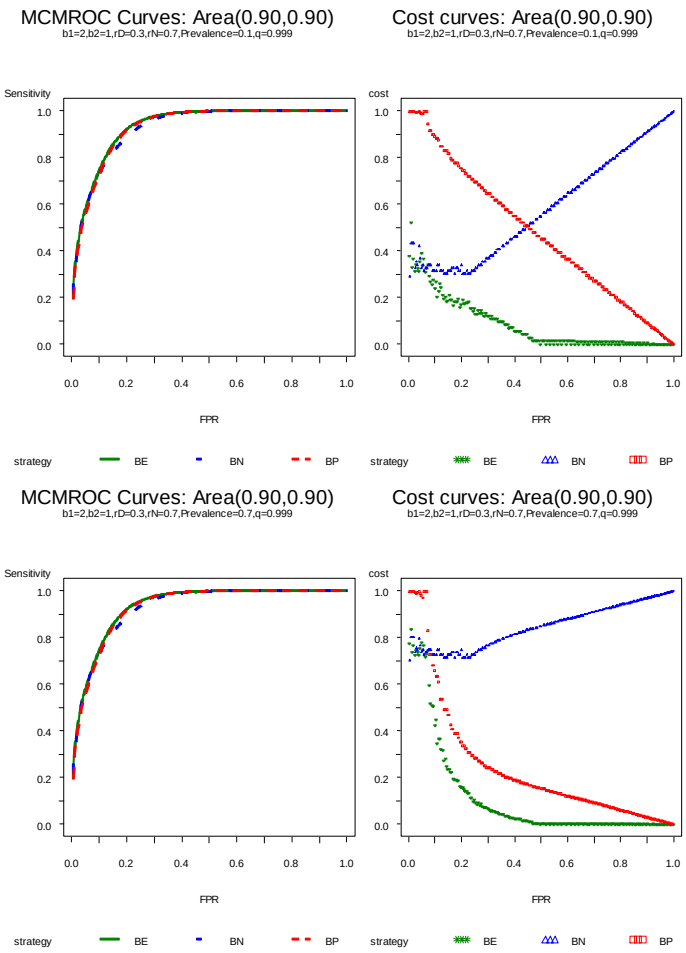
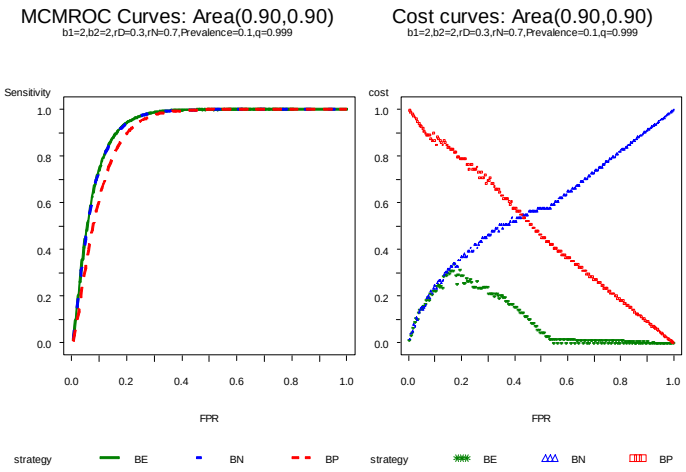


Figure B3.1d: (b1=2, b2=1)



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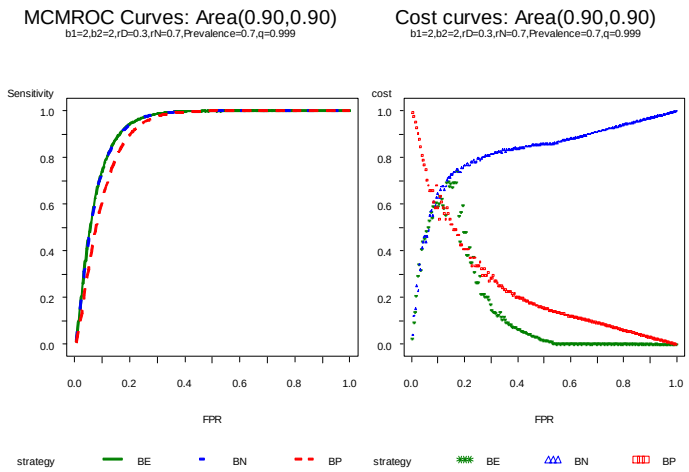

Figure B3.1e: (b1=2, b2=2)

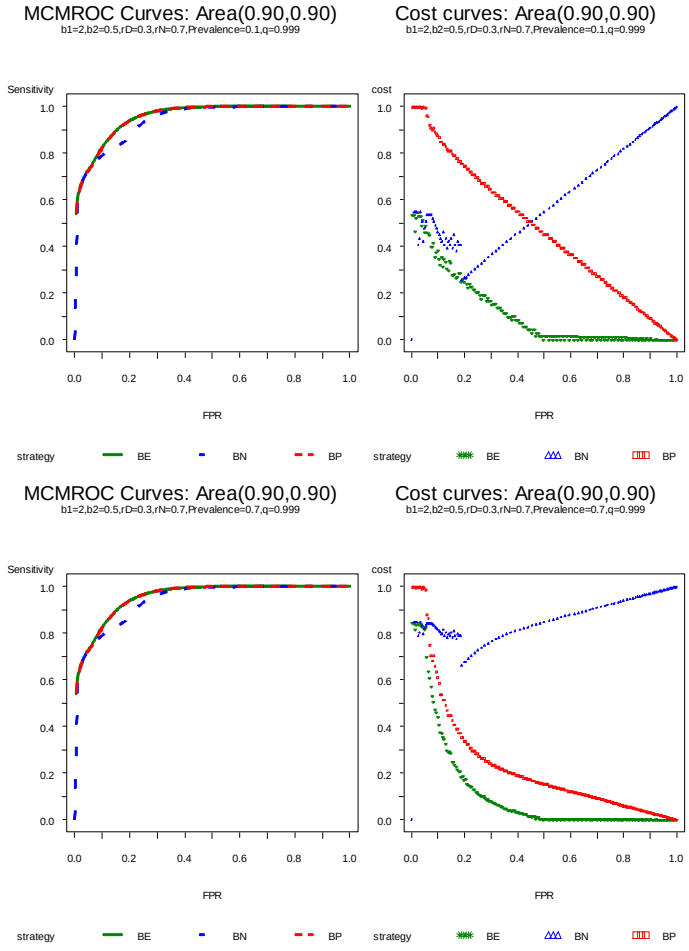

Figure B3.1f: (b1=2, b2=0.5)

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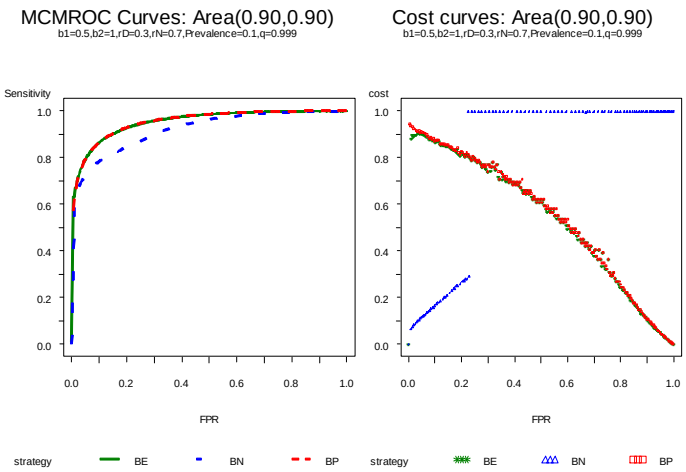


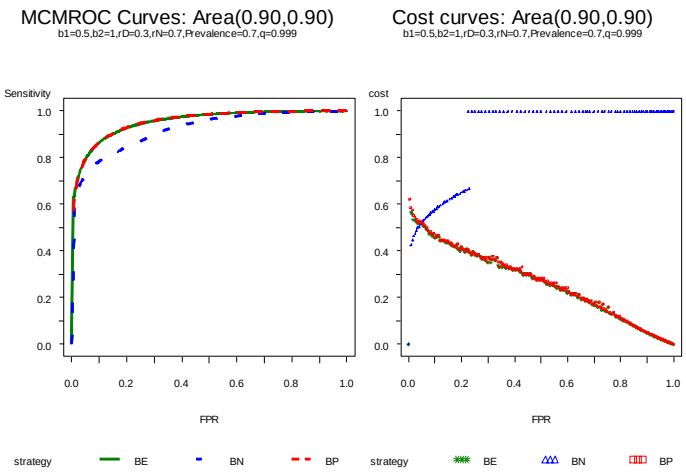
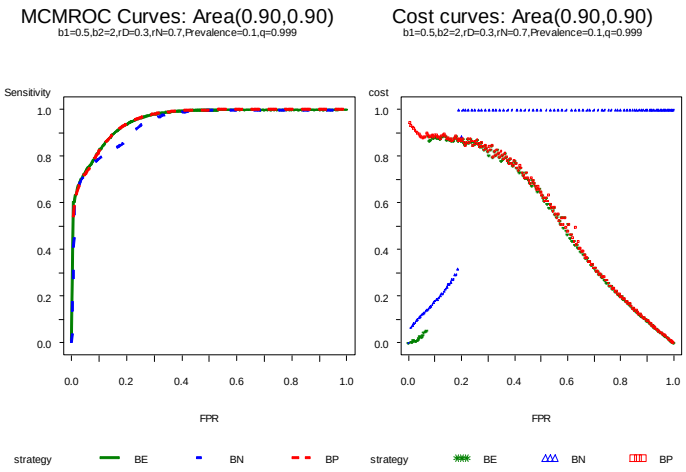


Figure B3.1g: (b1=0.5, b2=1)



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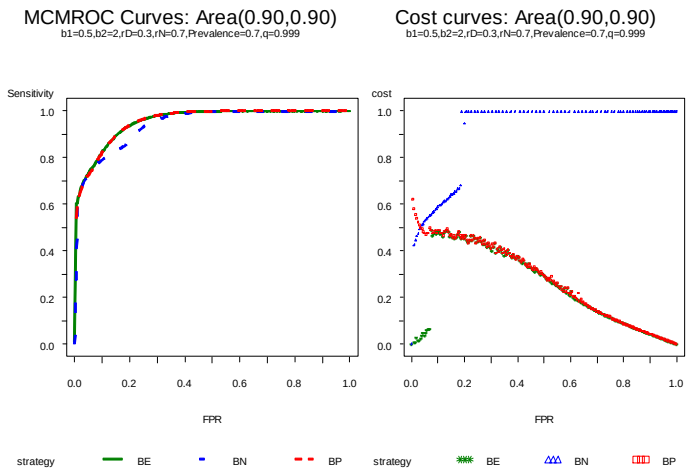
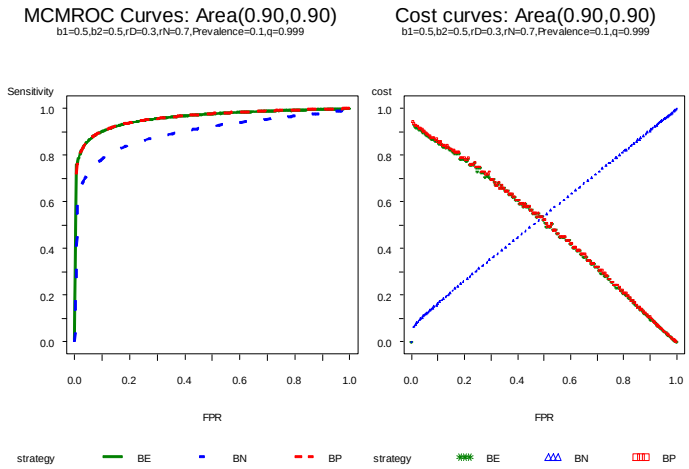


Figure B3.1h: (b1=0.5, b2=2)



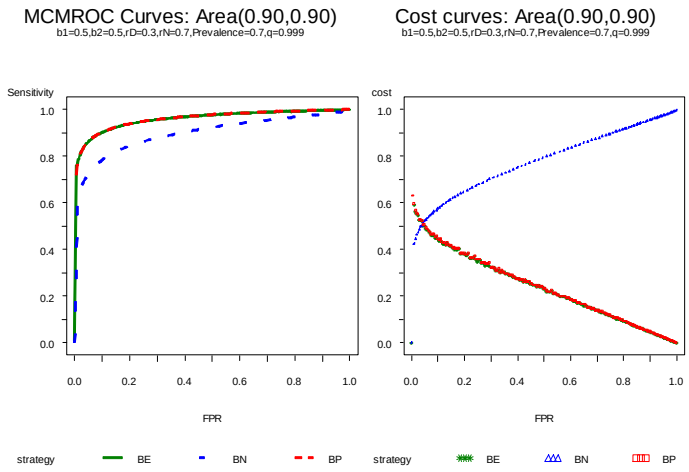


Figure B3.1i: (b1=0.5, b2=0.5)

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B3.2 AUC1 = 0.70, AUC2 = 0.90

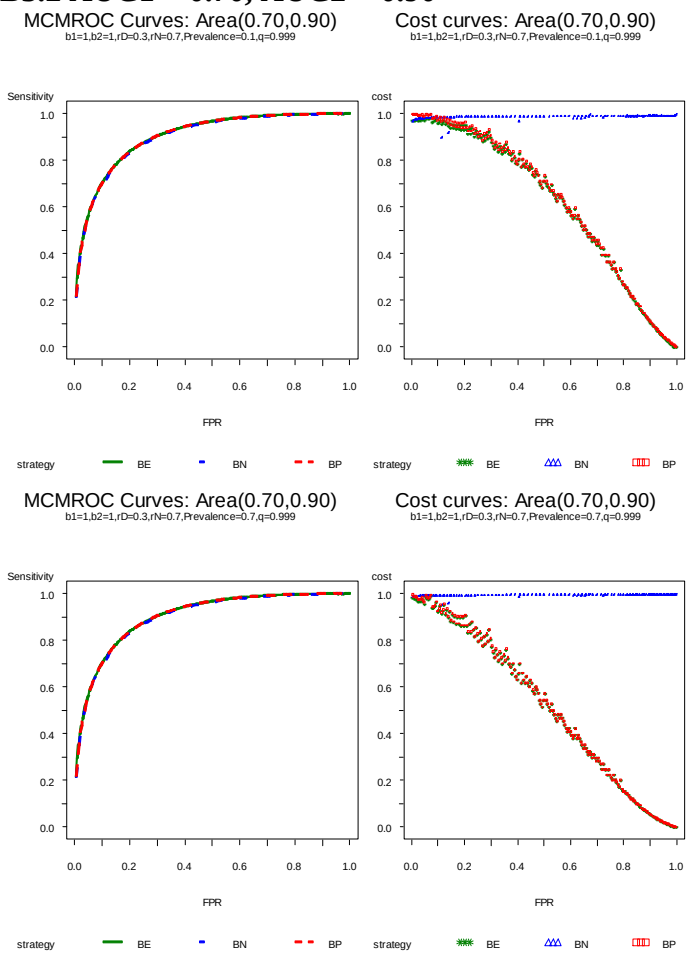
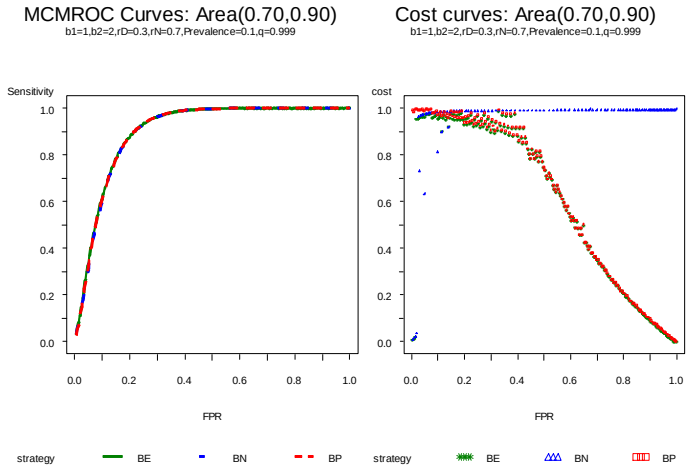


Figure B3.2a: (b1=1, b2=1)



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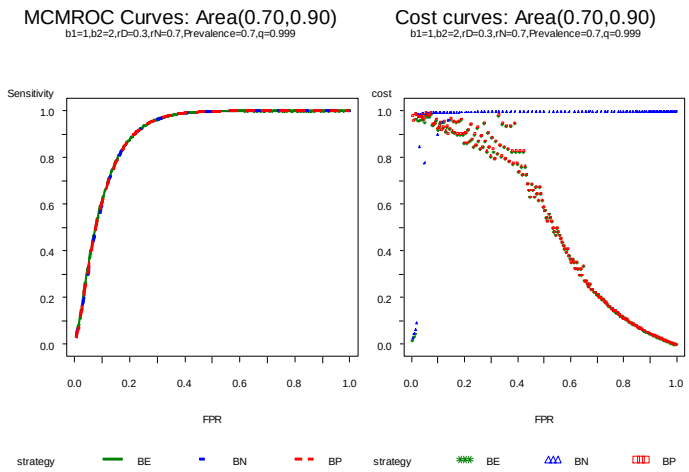
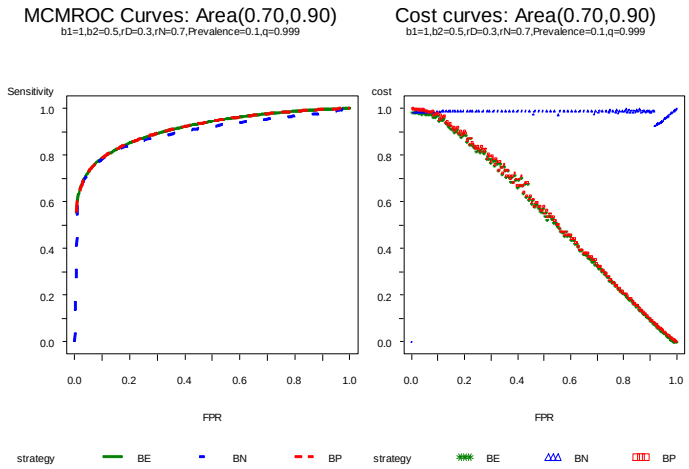


Figure B3.2b: (b1=1, b2=2)



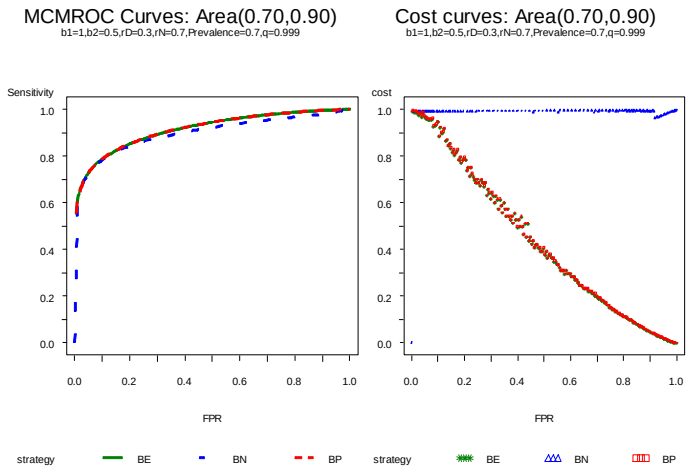


Figure B3.2c: (b1=1, b2=0.5)

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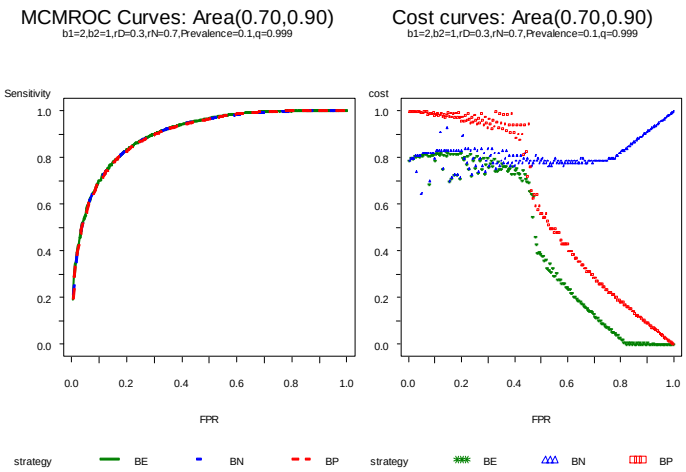


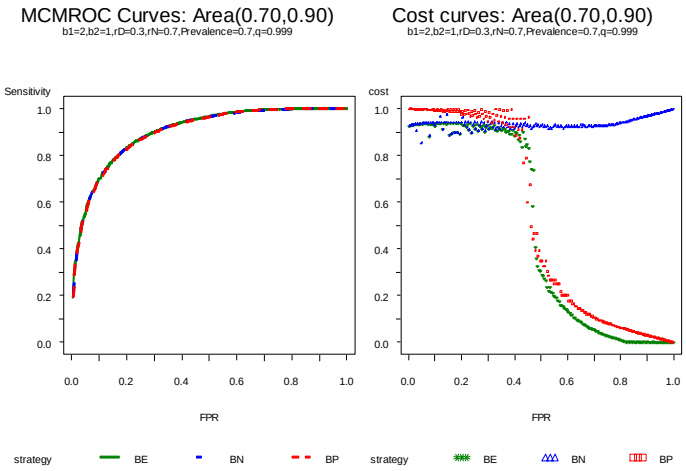
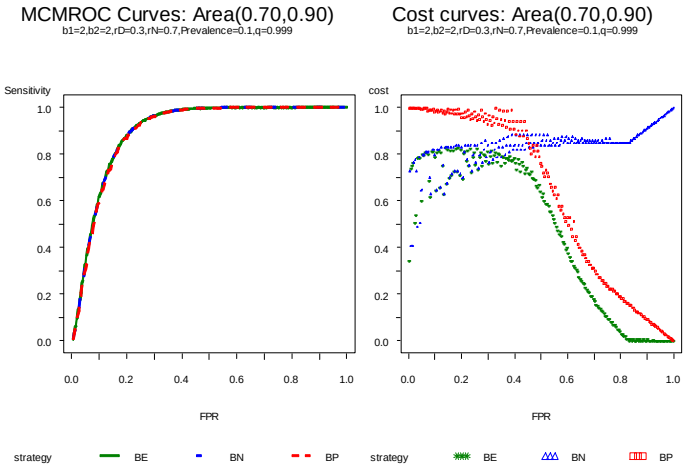


Figure B3.2d: (b1=2, b2=1)



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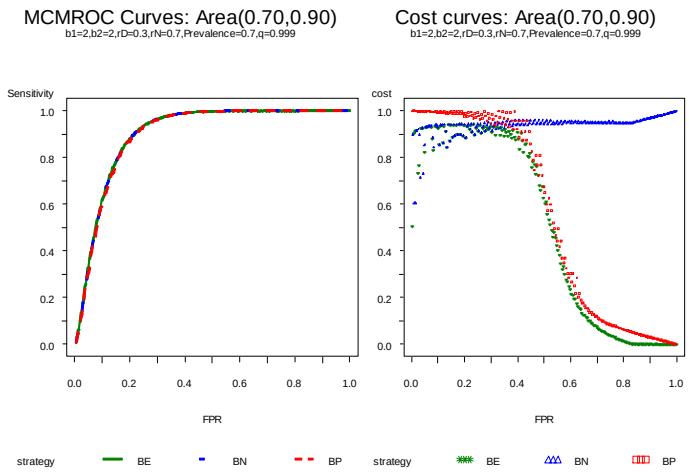
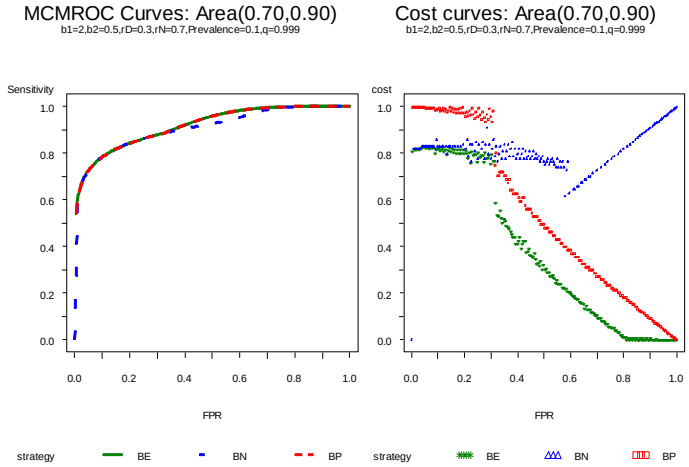


Figure B3.2e: (b1=2, b2=2)



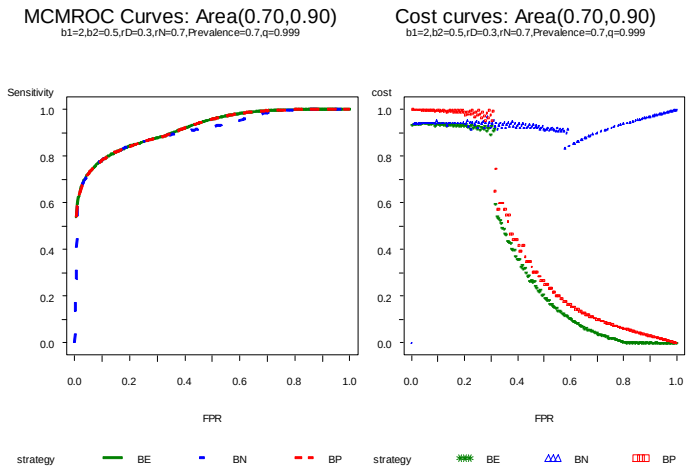


Figure B3.2f: (b1=2, b2=0.5)

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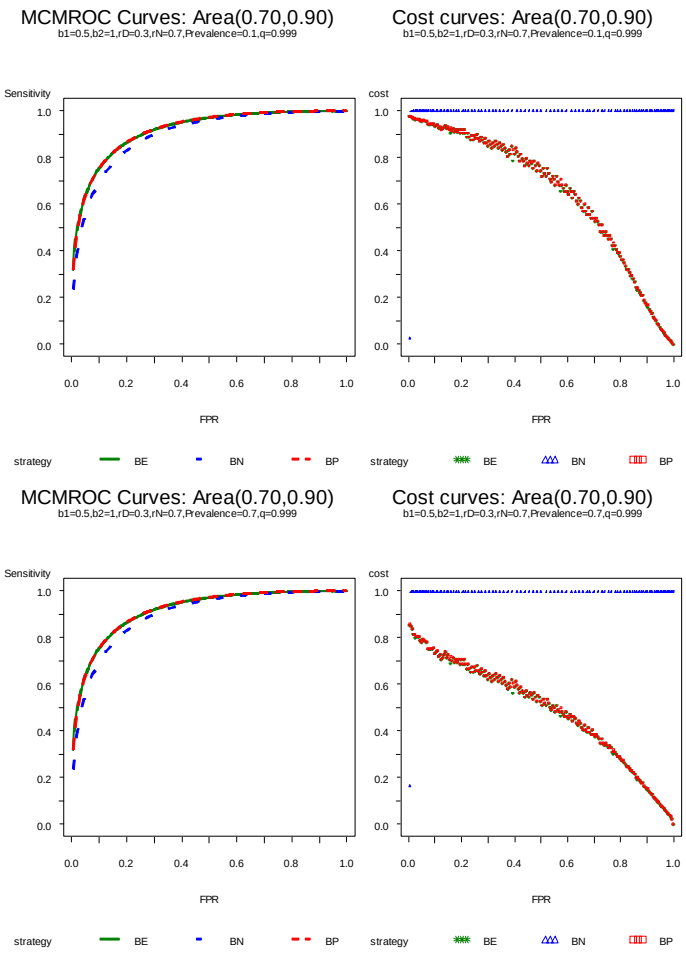
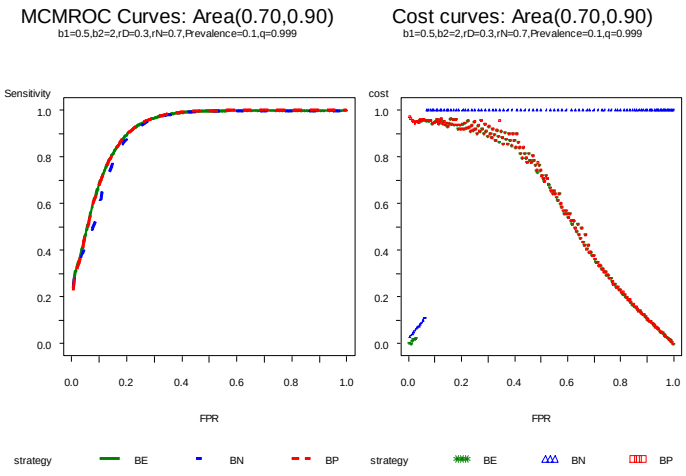


Figure B3.2g: (b1=0.5, b2=1)



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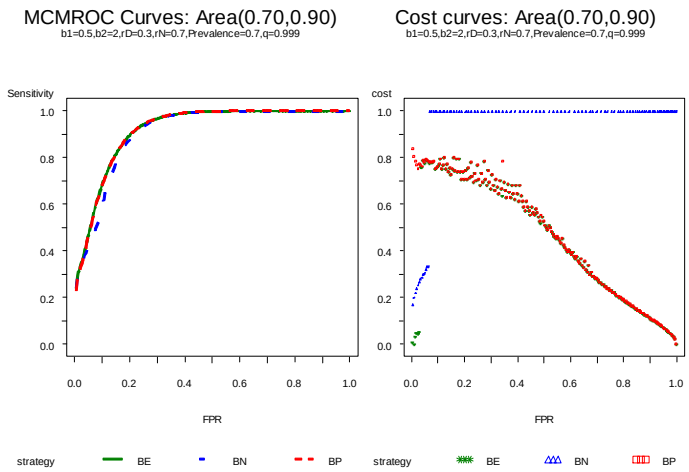
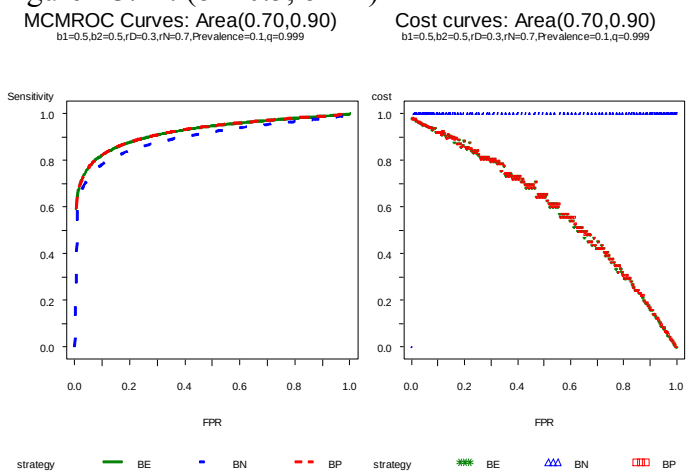


Figure B3.2h: (b1=0.5, b2=2)



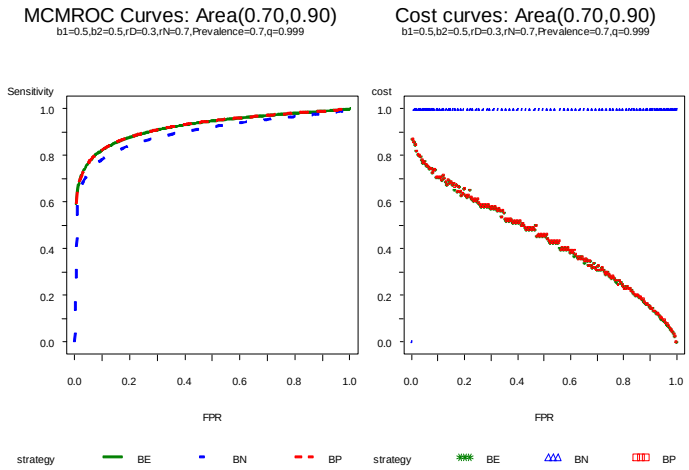


Figure B3.2i: (b1=0.5, b2=0.5)

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B3.3 AUC1 = 0.70, AUC2 = 0.70

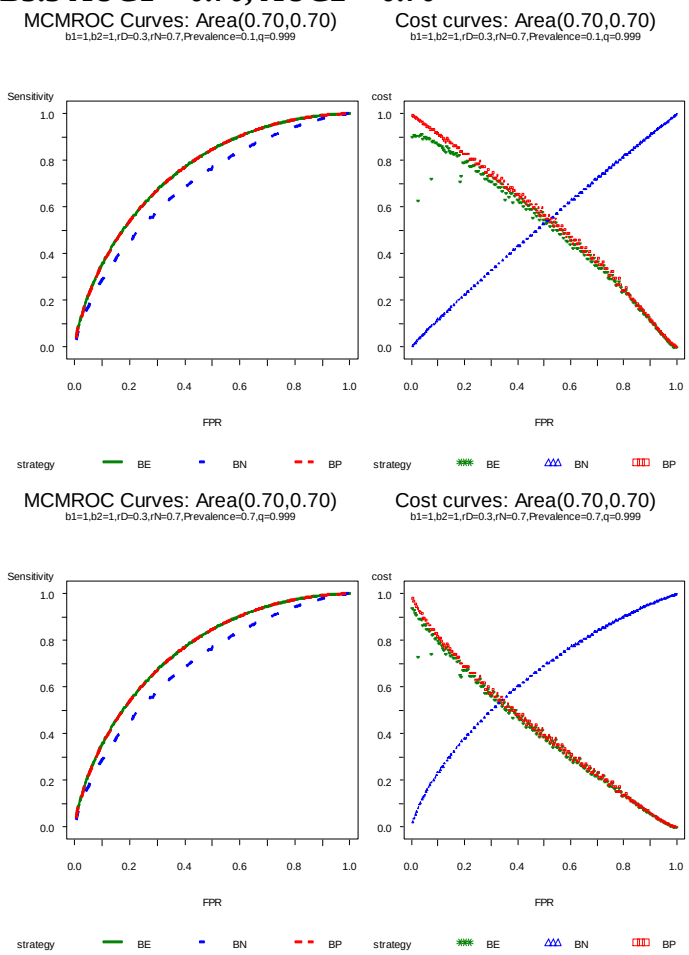
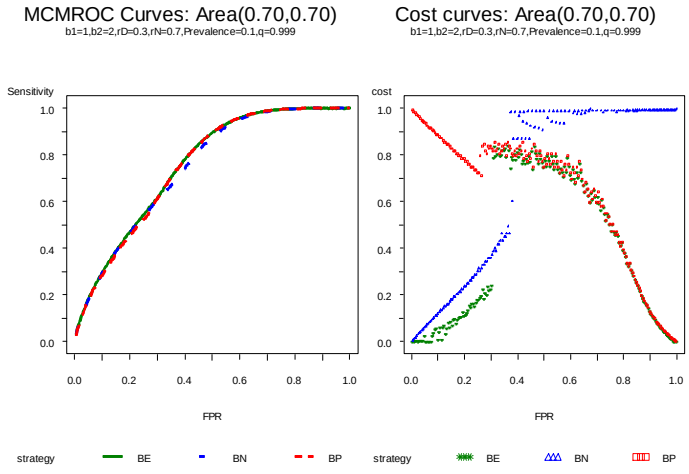


Figure B3.3a: (b1=1, b2=1)



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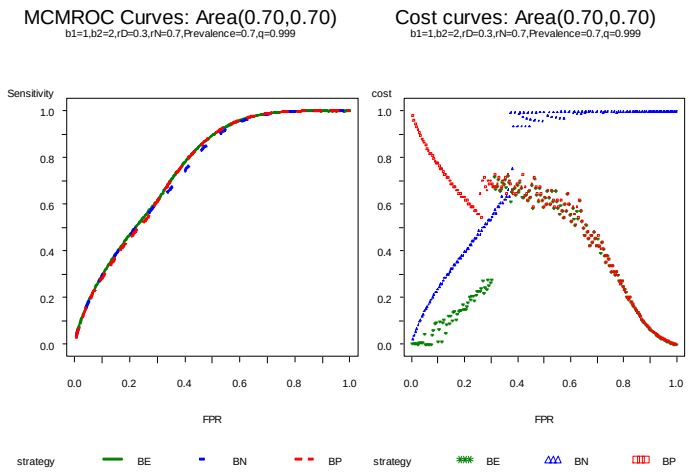

Figure B3.3b: (b1=1, b2=2)

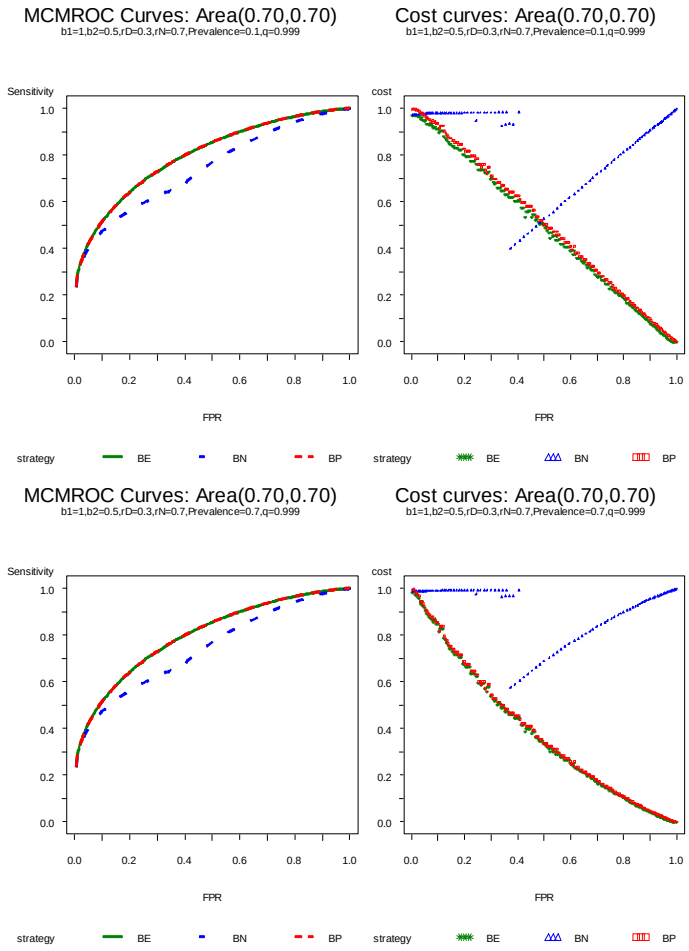

Figure B3.3c: (b1=1, b2=0.5)

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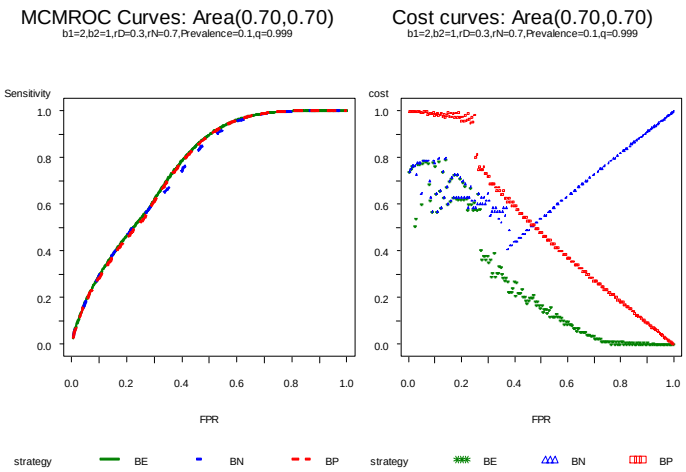


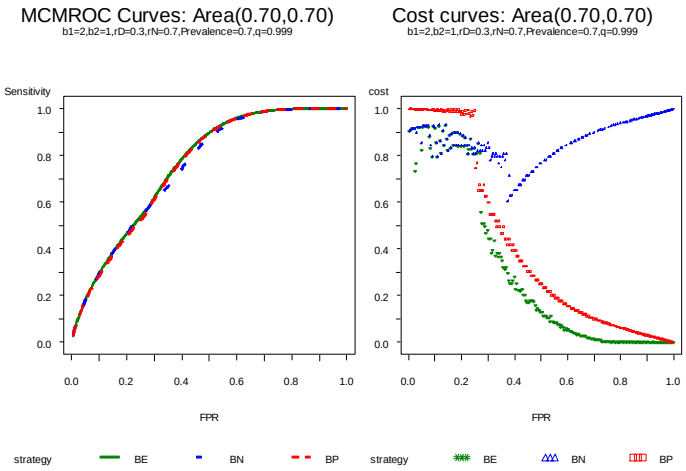
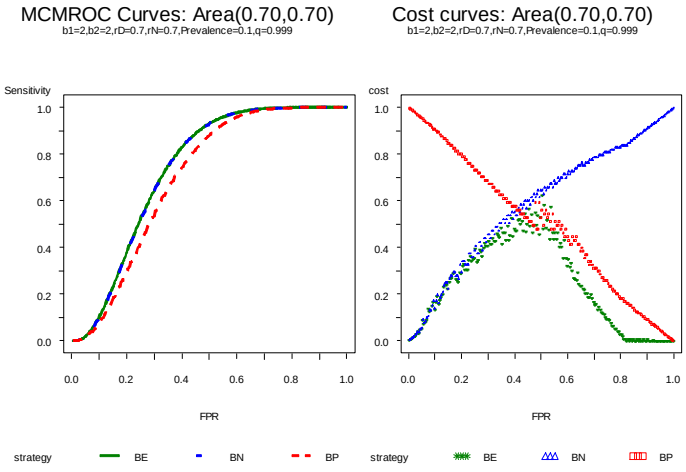


Figure B3.3d: (b1=2, b2=1)



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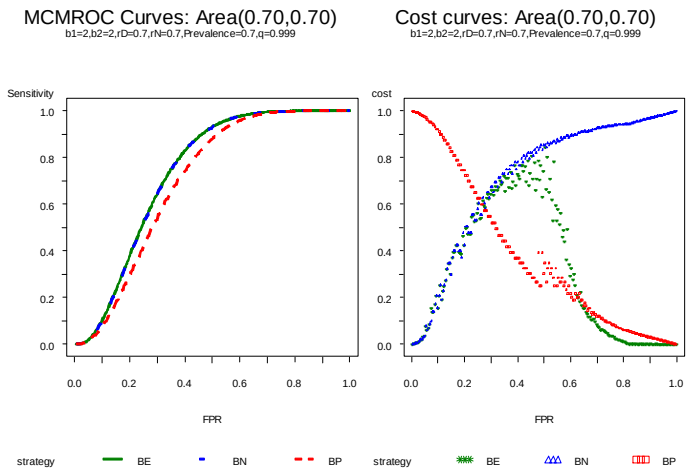

Figure B3.3e: (b1=2, b2=2)

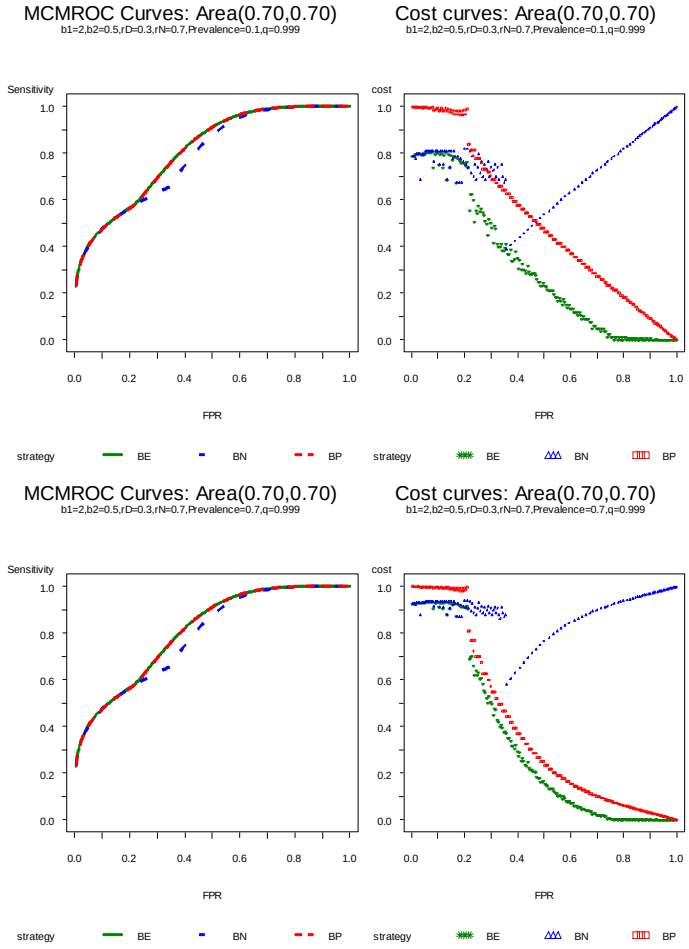

Figure B3.3f: (b1=2, b2=0.5)

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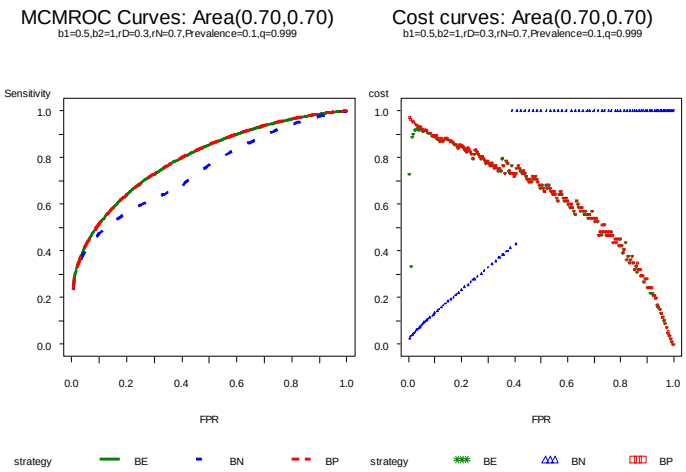


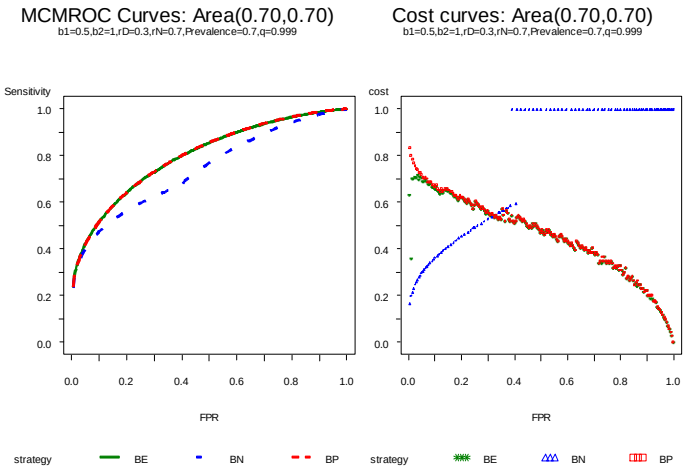
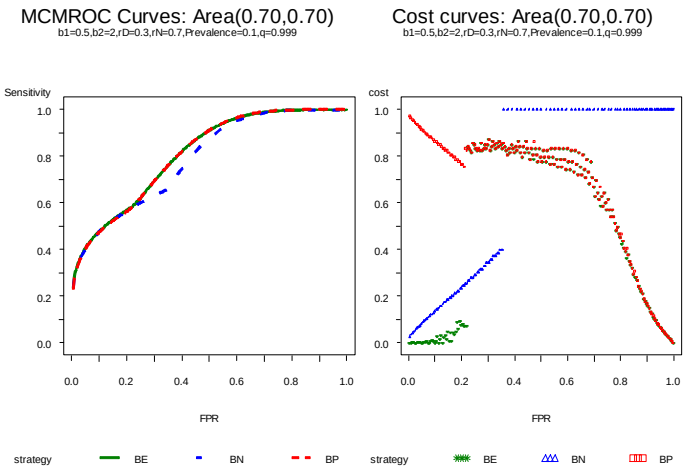


Figure B3.3g: (b1=0.5, b2=1)



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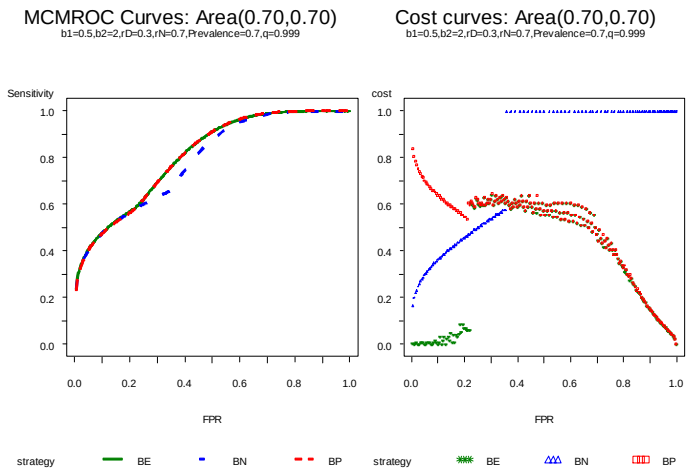
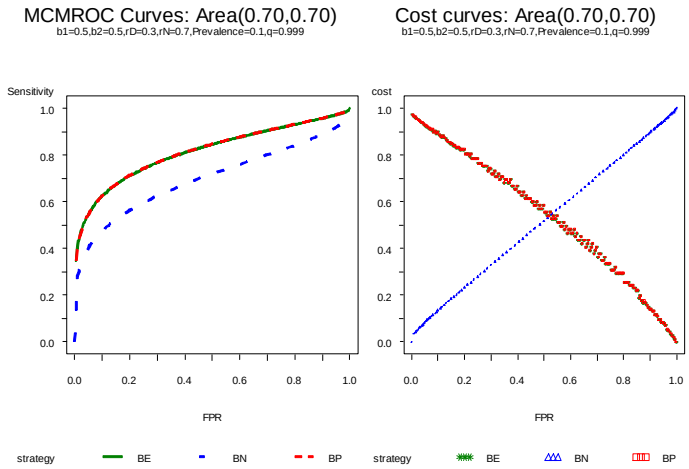


Figure B3.3h: (b1=0.5, b2=2)



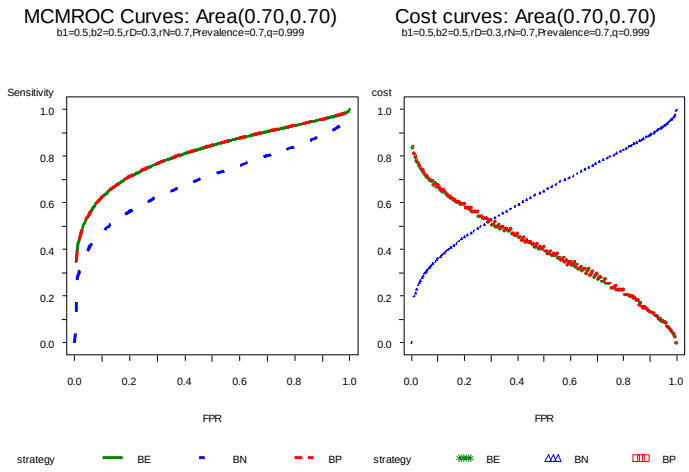


Figure B3.3i: (b1=0.5, b2=0.5)

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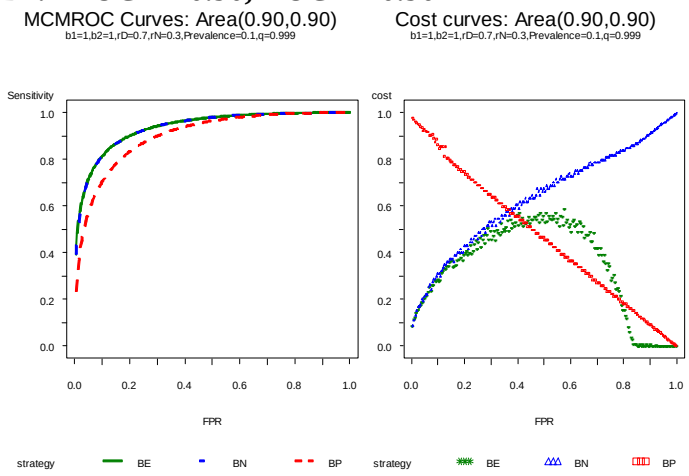
B4 Dependent of the tests $(\rho_D = 0.7, \rho_N = 0.3)$

B4.1 AUC1 = 0.90, AUC2 = 0.90



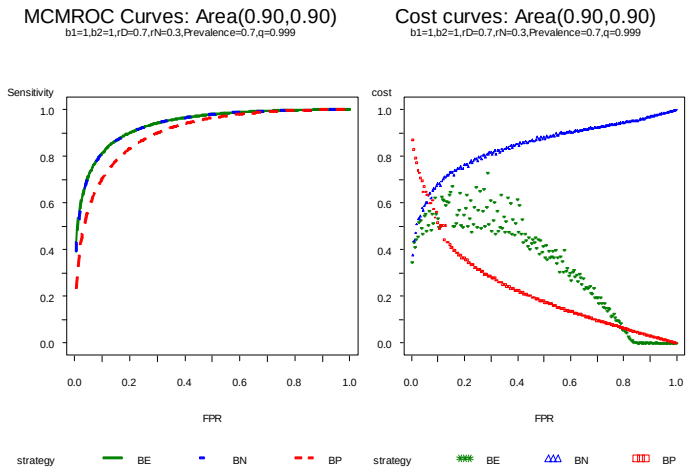
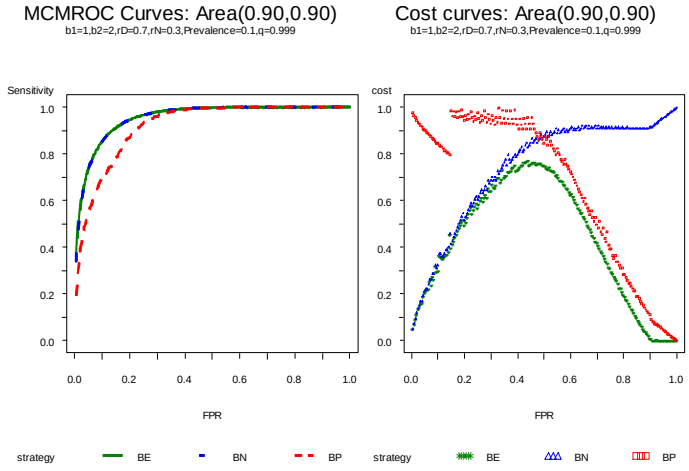


Figure B4.1a: (b1=1, b2=1)



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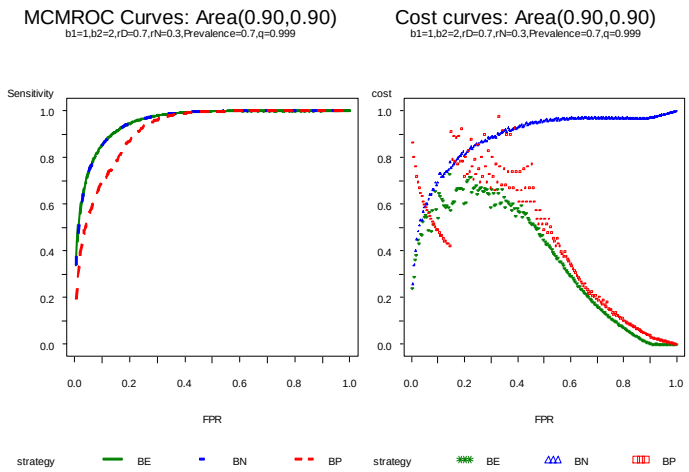

Figure B4.1b: (b1=1, b2=2)

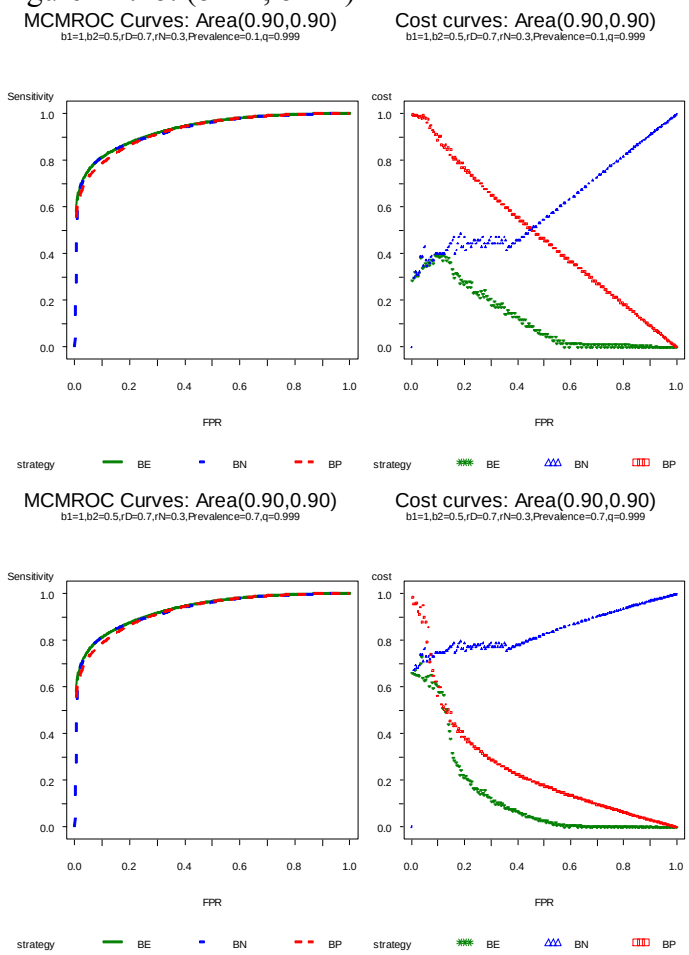

Figure B4.1c: (b1=1, b2=0.5)

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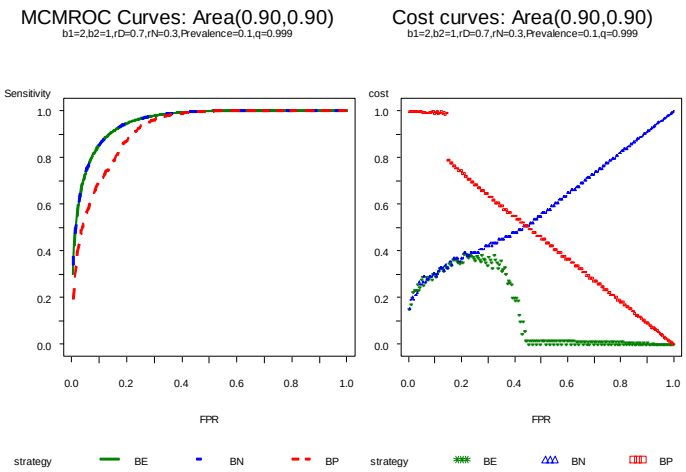


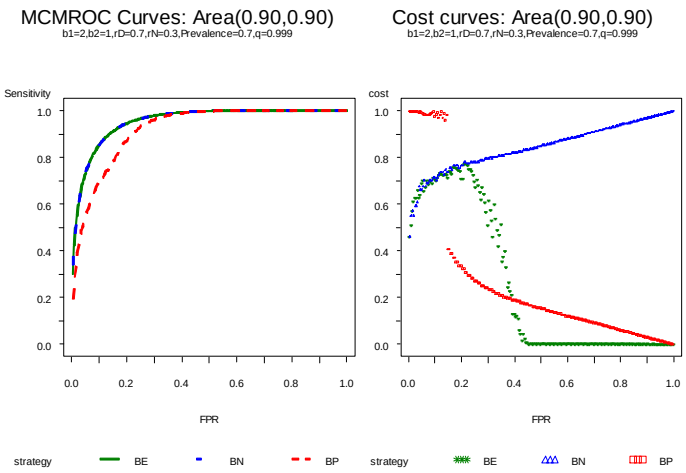
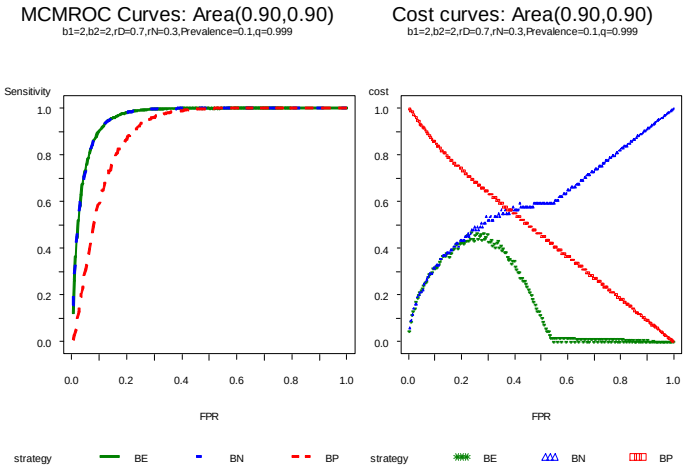


Figure B4.1d: (b1=2, b2=1)



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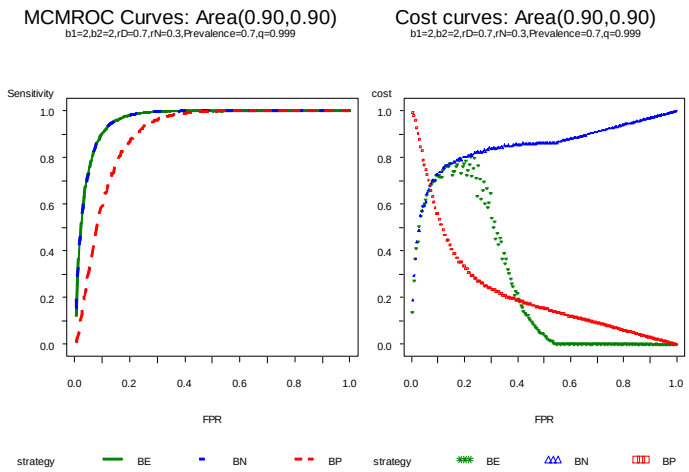
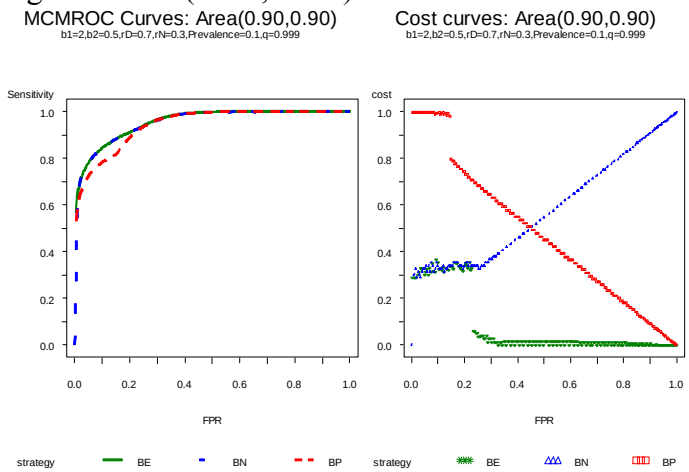


Figure B4.1e: (b1=2, b2=2)



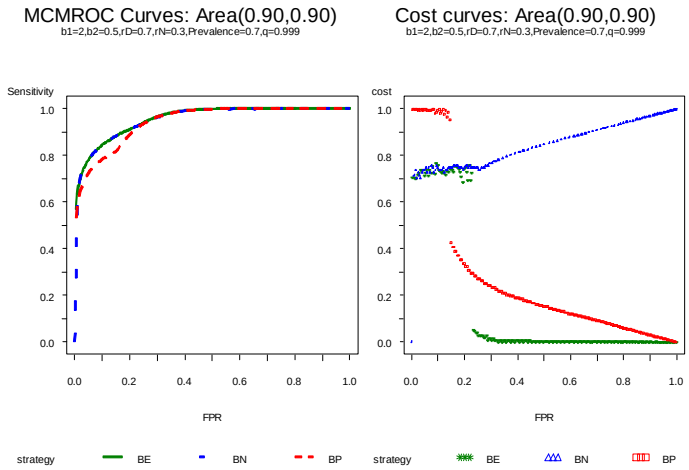


Figure B4.1f: (b1=2, b2=0.5)

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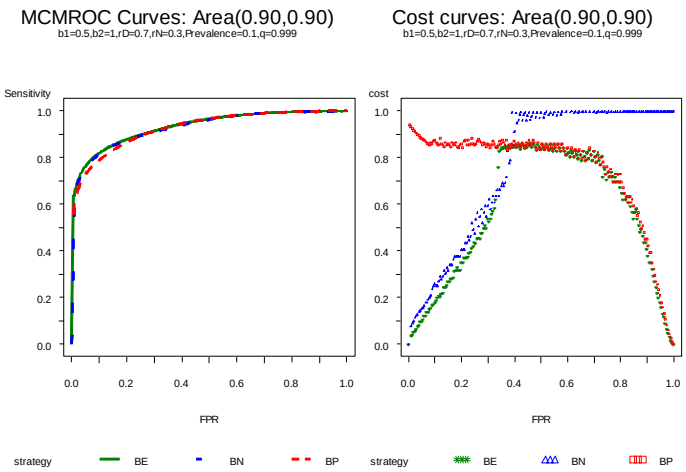


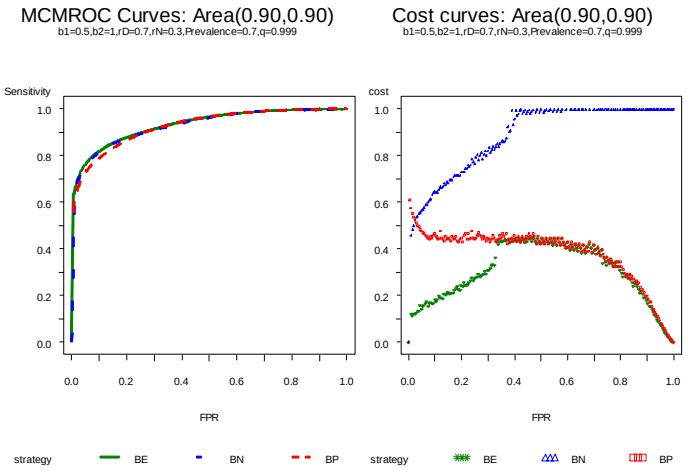
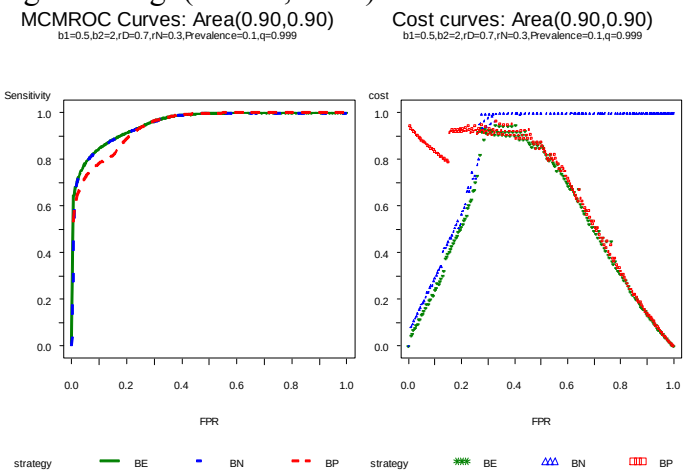


Figure B4.1g: (b1=0.5, b2=1)



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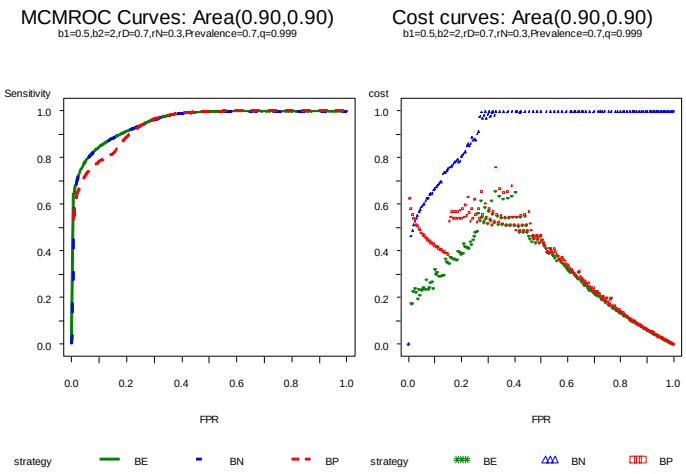

Figure B4.1h: (b1=0.5, b2=2)

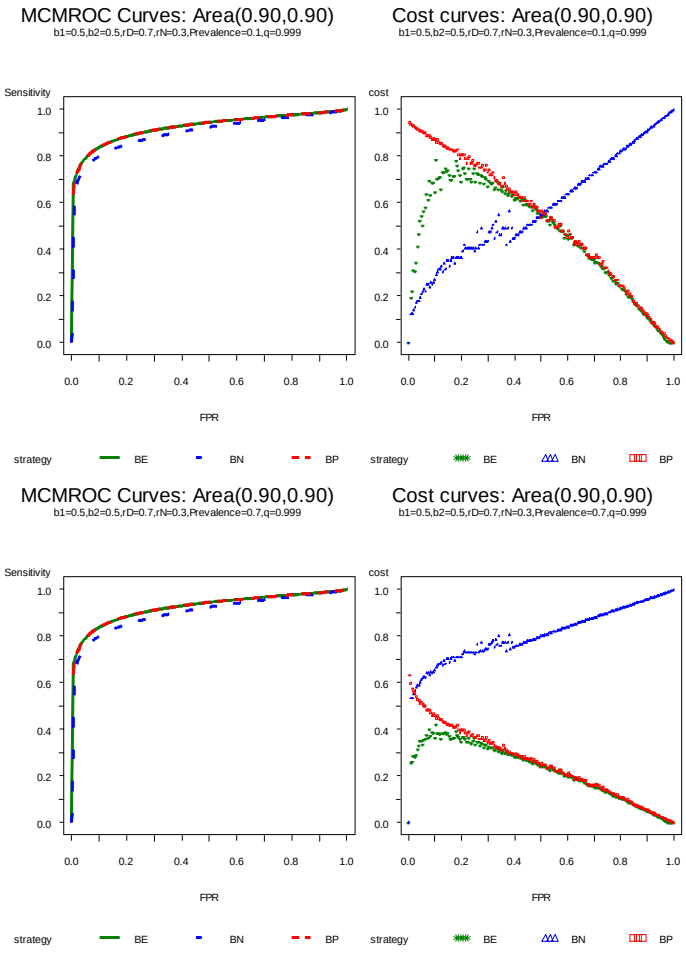

Figure B4.1i: (b1=0.5, b2=0.5)

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B4.2 AUC1 = 0.70, AUC2 = 0.90

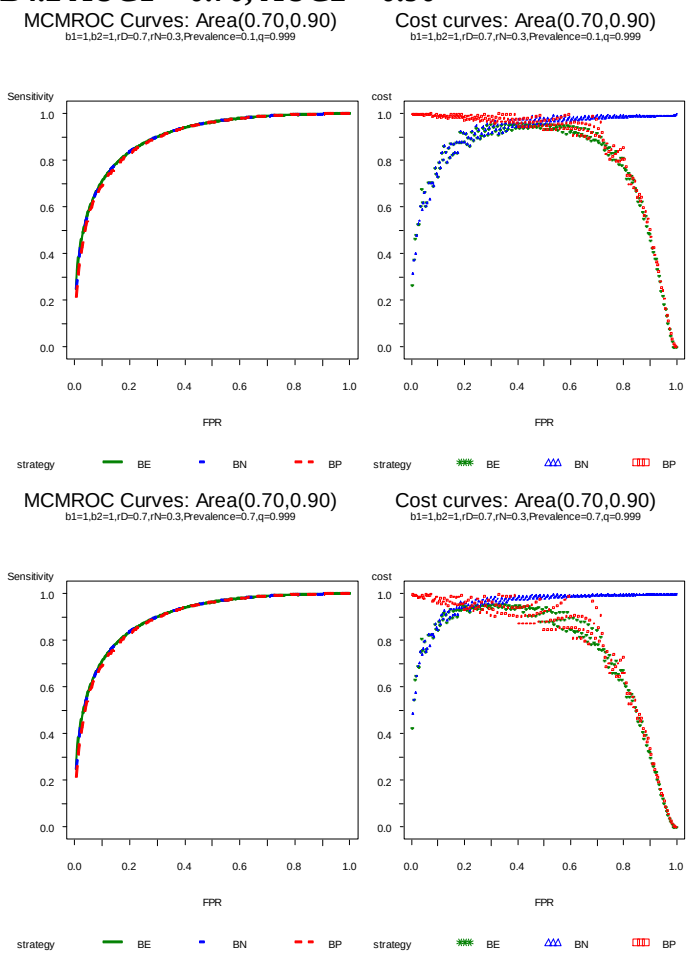
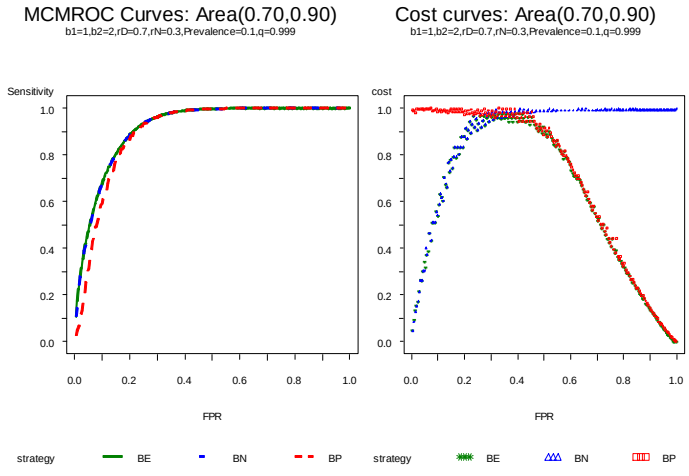


Figure B4.2a: (b1=1, b2=1)



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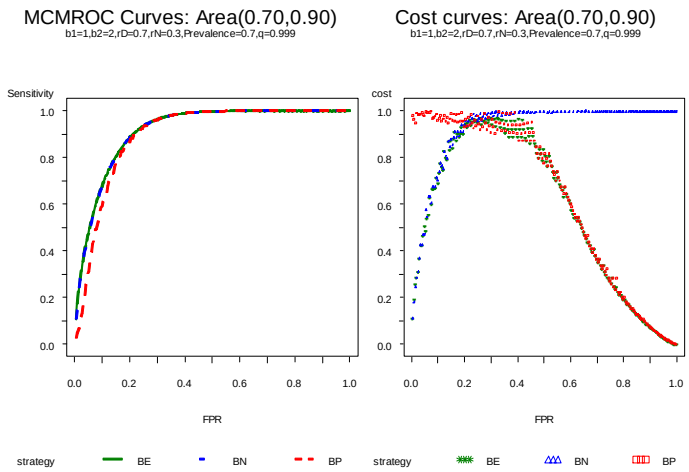

Figure B4.2b: (b1=1, b2=2)

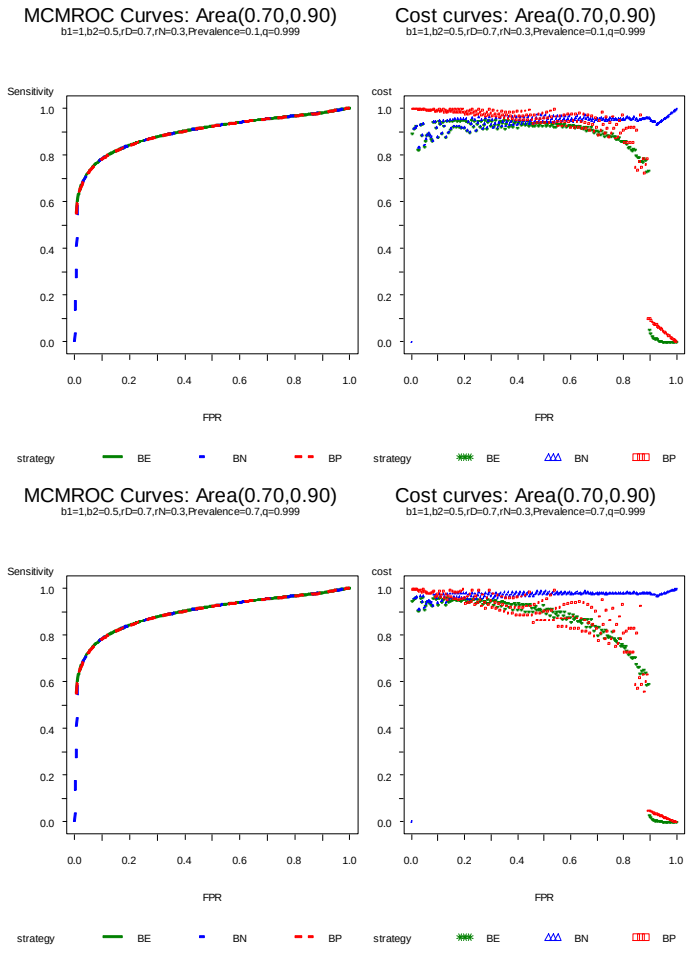

Figure B4.2c: (b1=1, b2=0.5)

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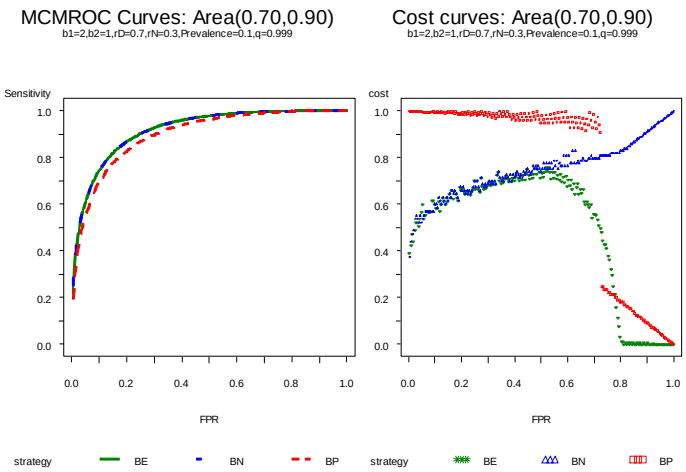


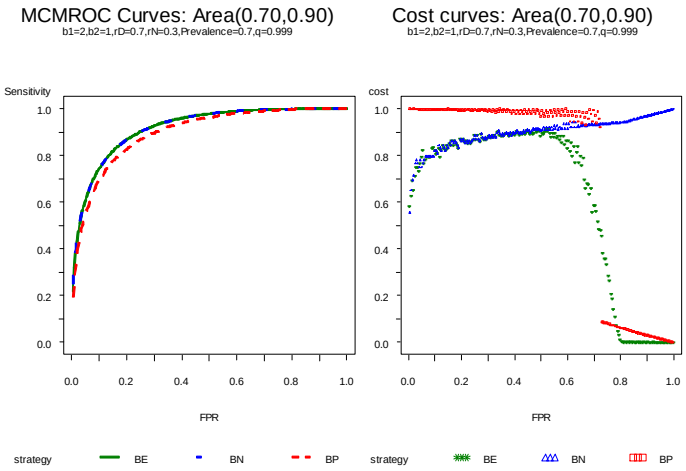
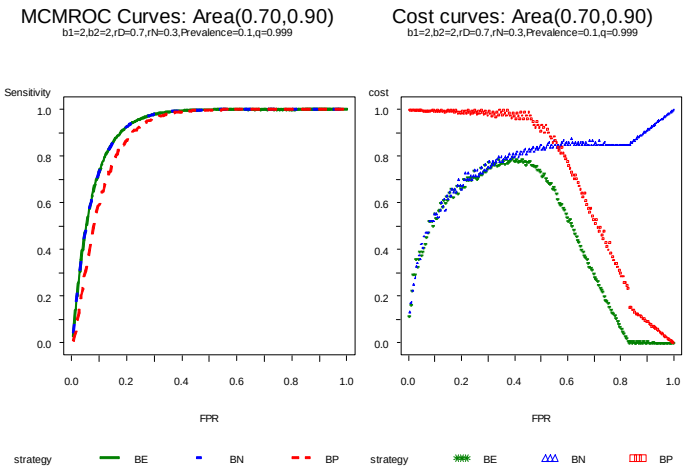


Figure B4.2d: (b1=2, b2=1)



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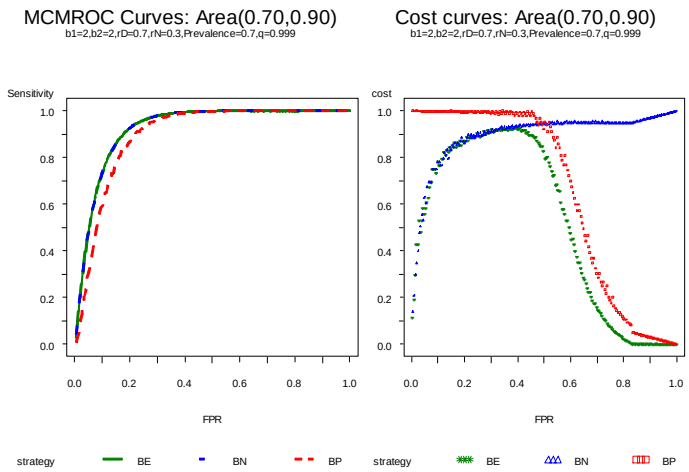

Figure B4.2e: (b1=2, b2=2)

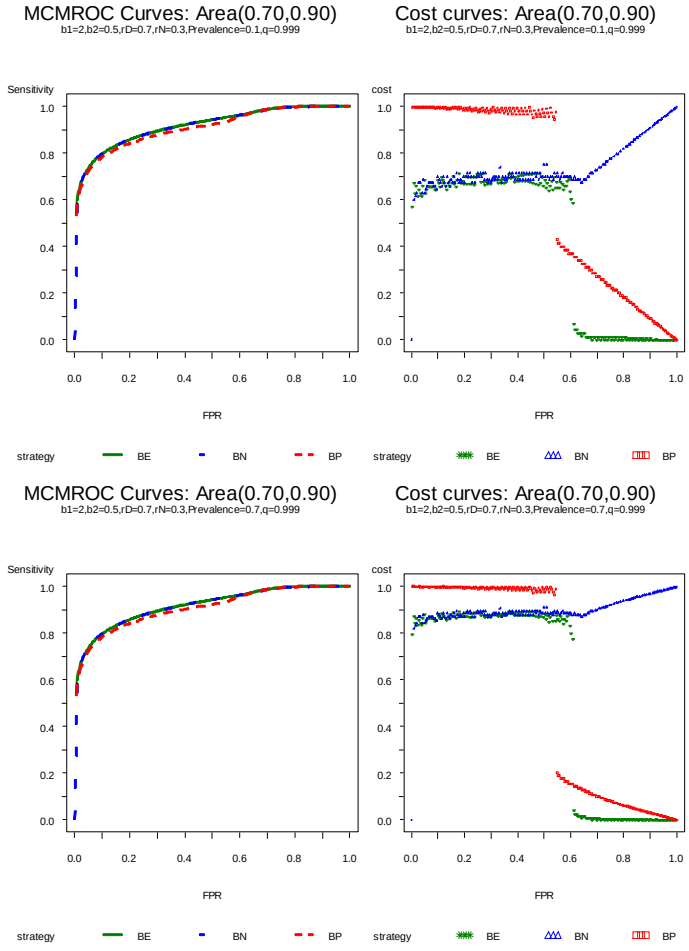

Figure B4.2f: (b1=2, b2=0.5)

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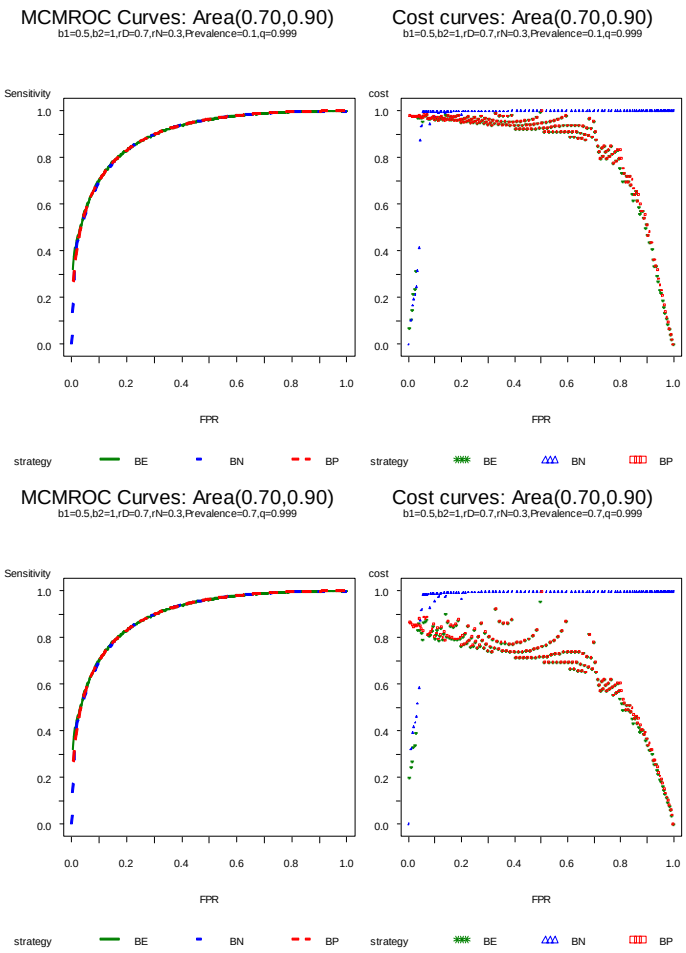
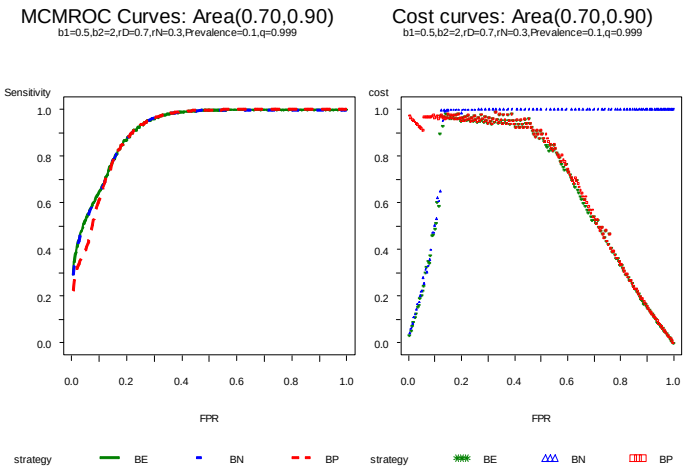


Figure B4.2g: (b1=0.5, b2=1)



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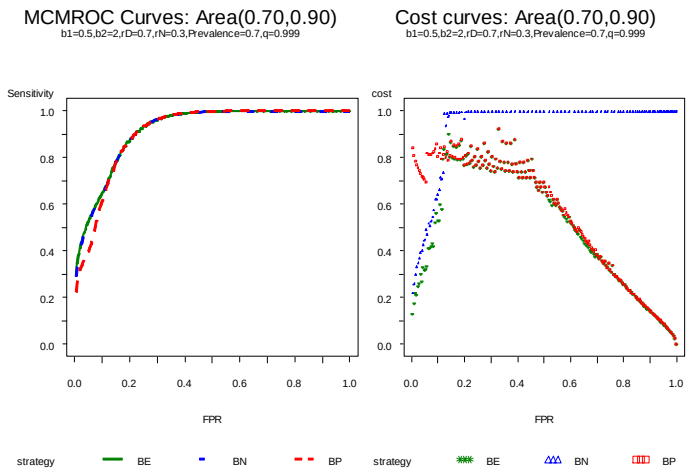
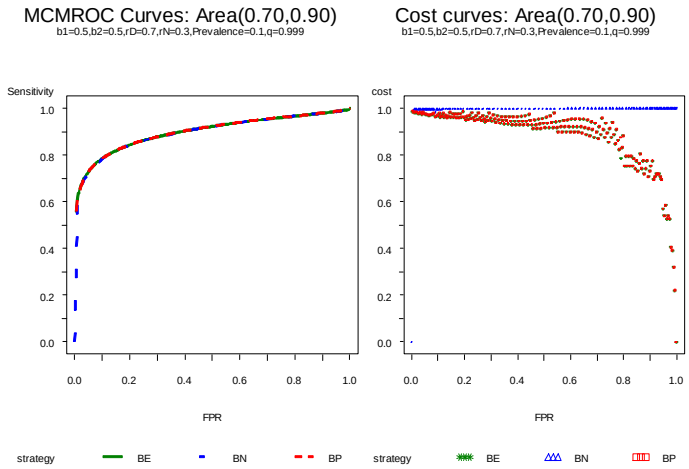


Figure B4.2h: (b1=0.5, b2=2)



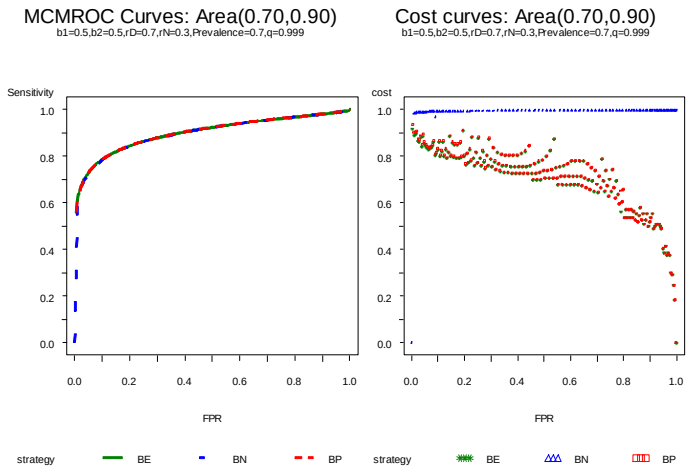


Figure B4.2i: (b1=0.5, b2=0.5)

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B4.3 AUC1 = 0.70, AUC2 = 0.70

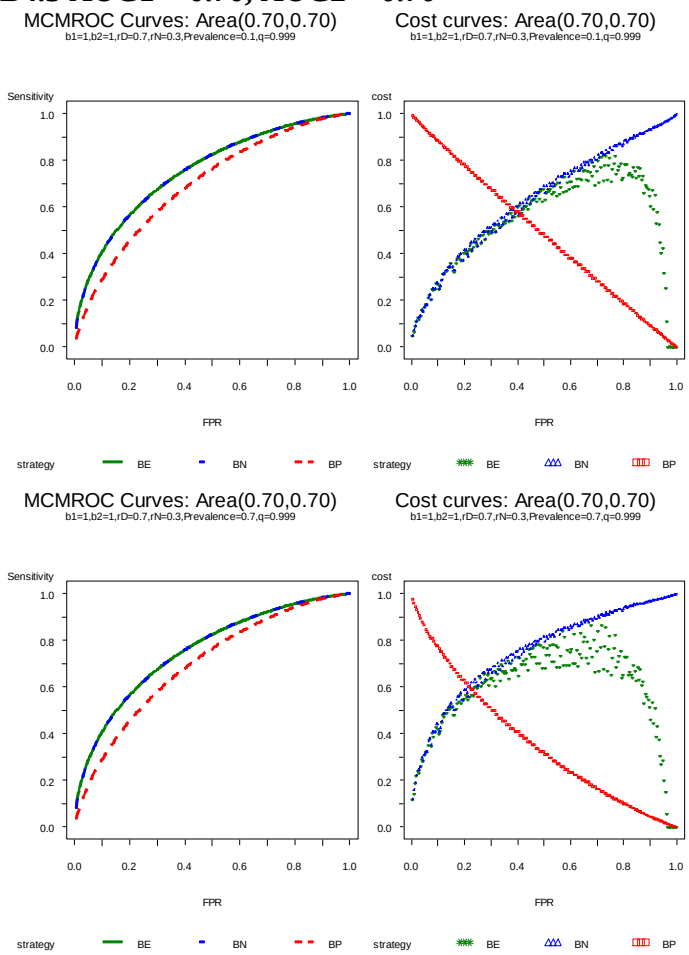
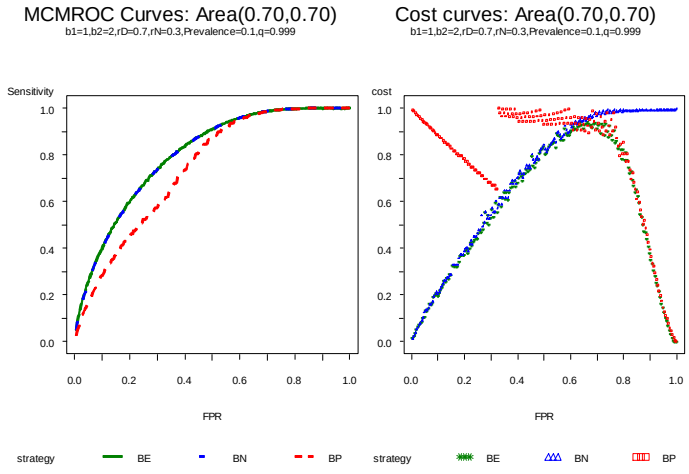


Figure B4.3a: (b1=1, b2=1)



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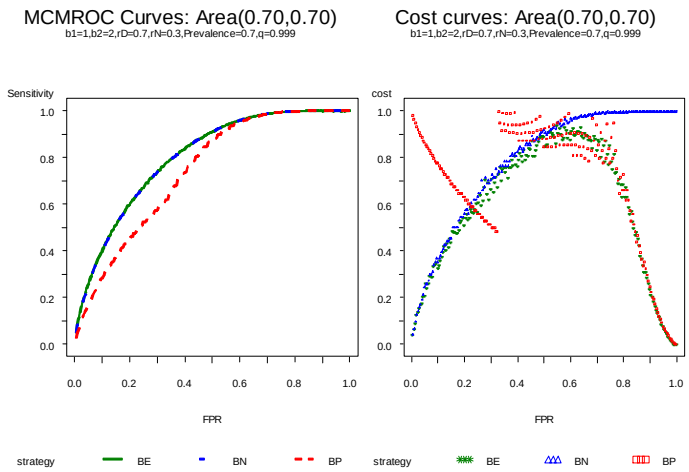

Figure B4.3b: (b1=1, b2=2)

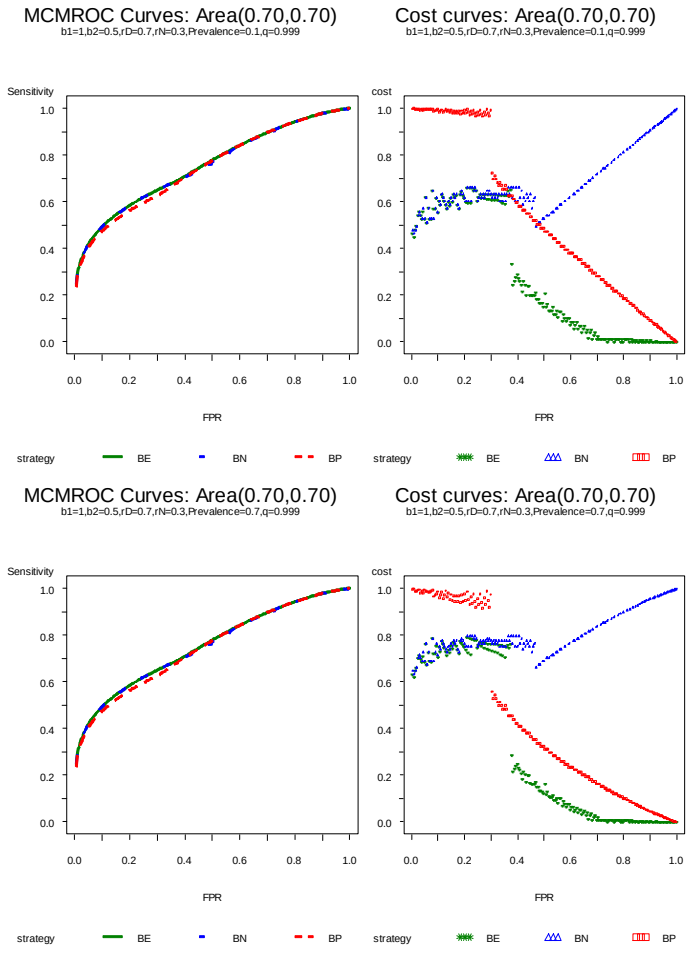

Figure B4.3c: (b1=1, b2=0.5)

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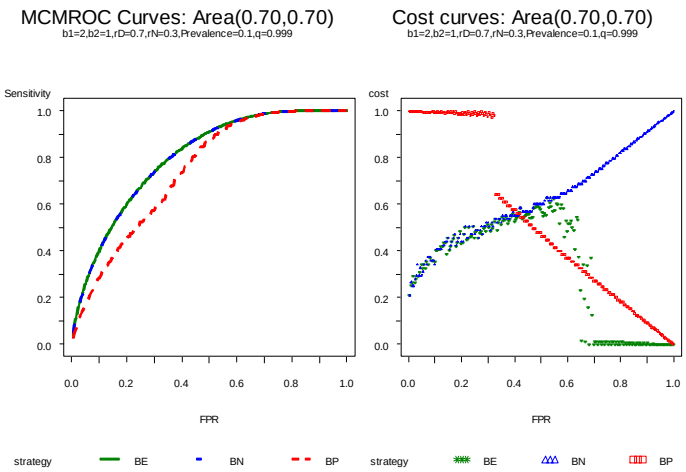


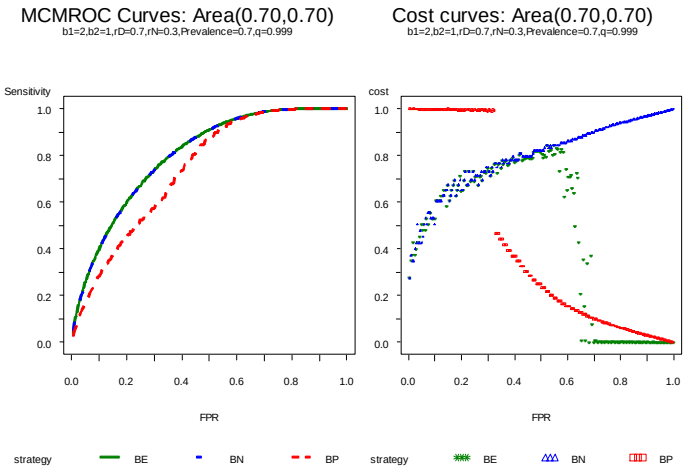
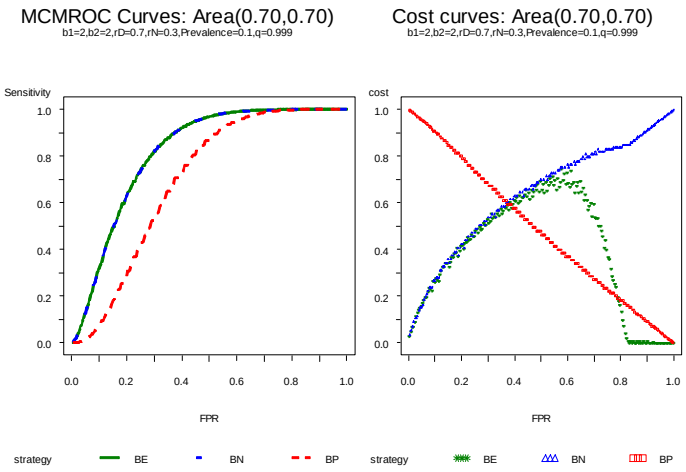


Figure B4.3d: (b1=2, b2=1)



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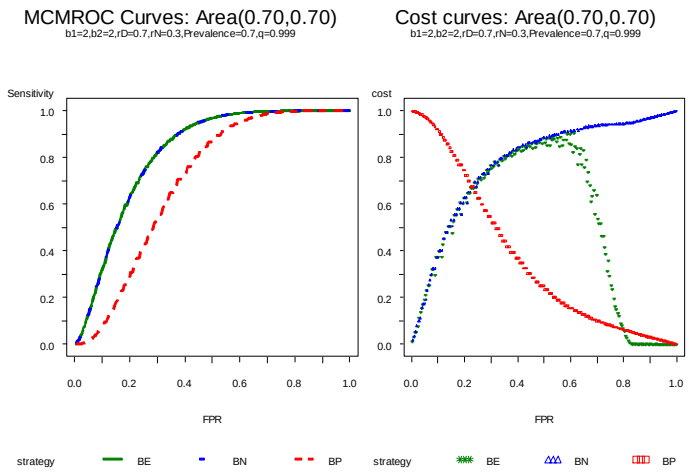

Figure B4.3e: (b1=2, b2=2)

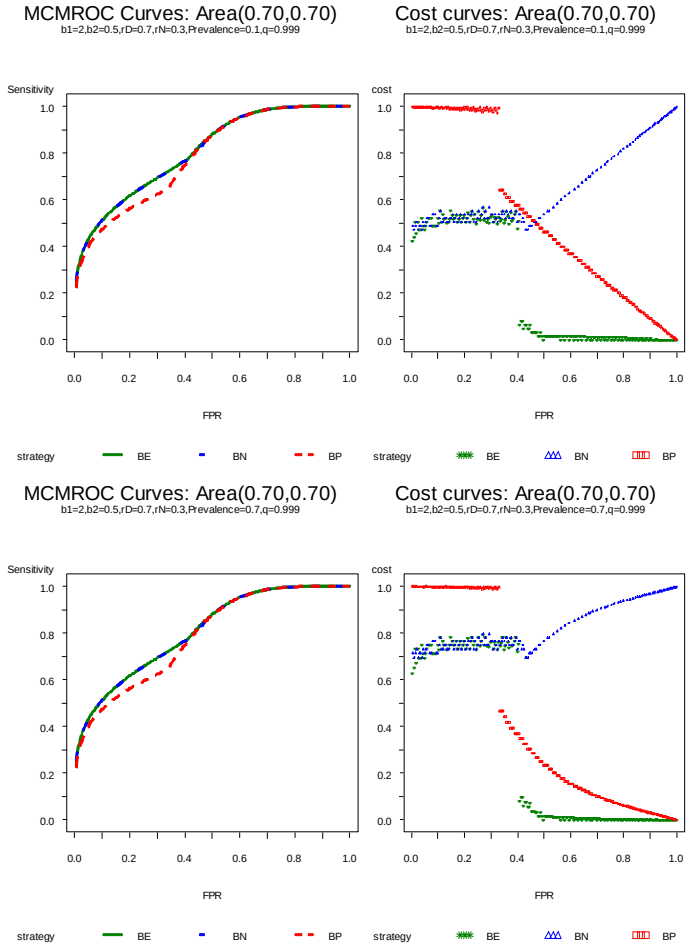

Figure B4.3f: (b1=2, b2=0.5)

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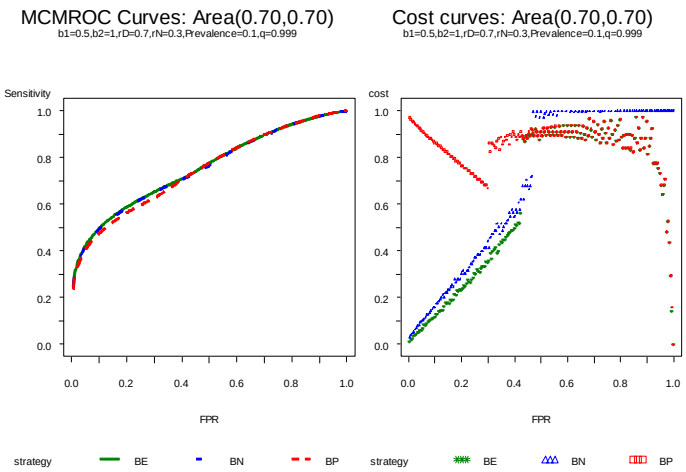


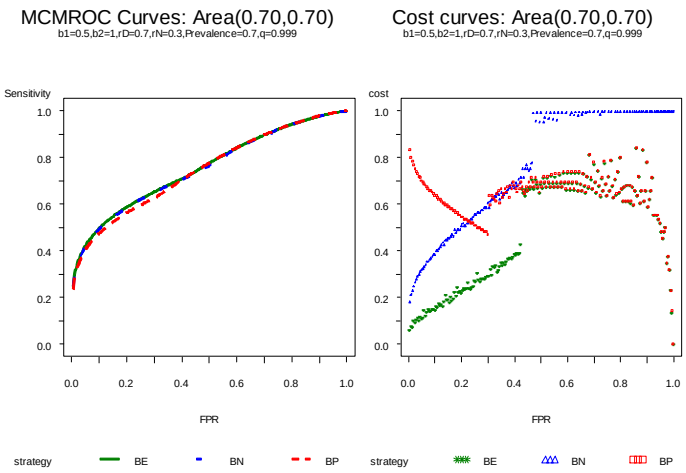
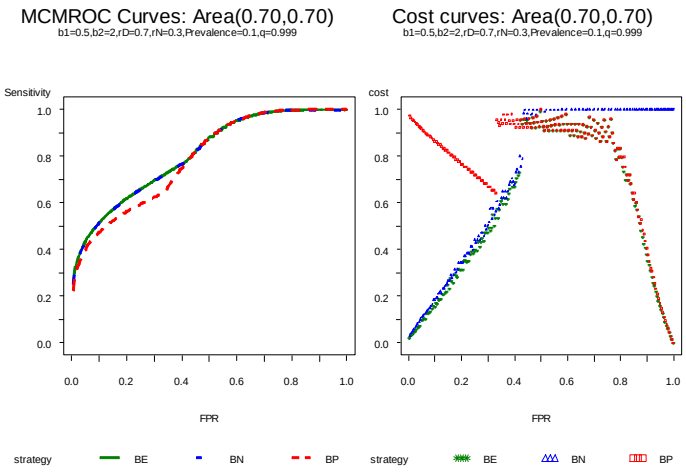


Figure B4.3g: (b1=0.5, b2=1)



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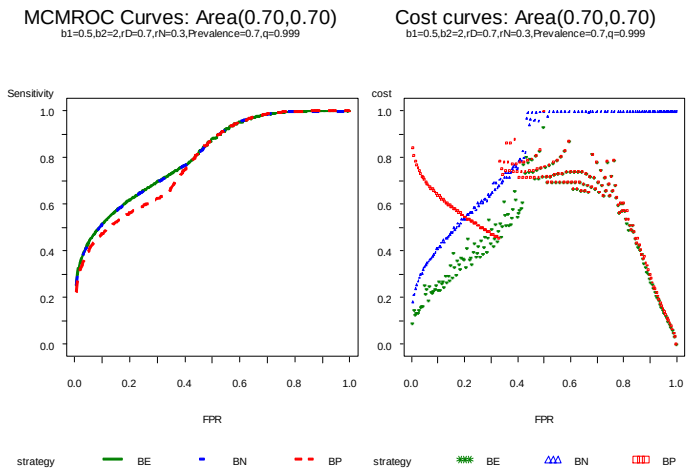
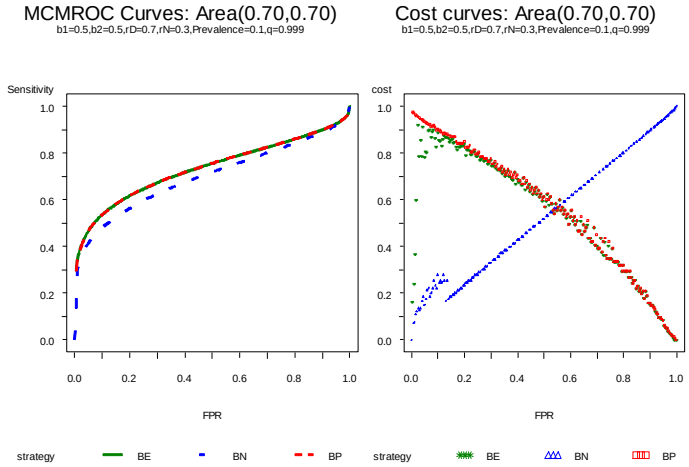


Figure B4.3h: (b1=0.5, b2=2)



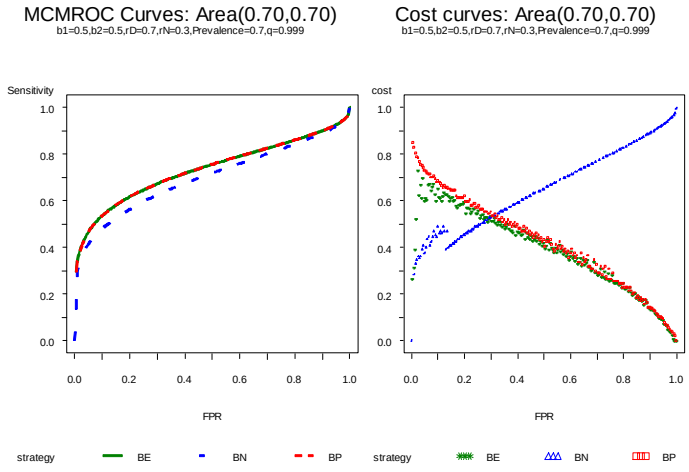


Figure B4.3i: (b1=0.5, b2=0.5)

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B5 Dependent of the tests $(\rho_D = 0.7, \rho_N = 0.7)$

B5 .1 AUC1 = 0.90, AUC2 = 0.90

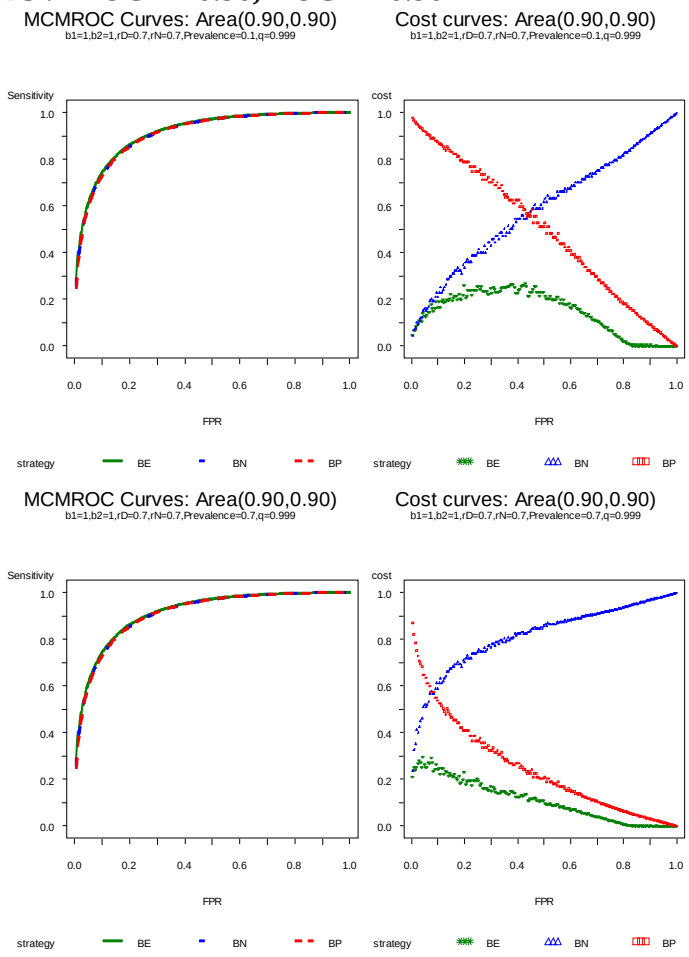
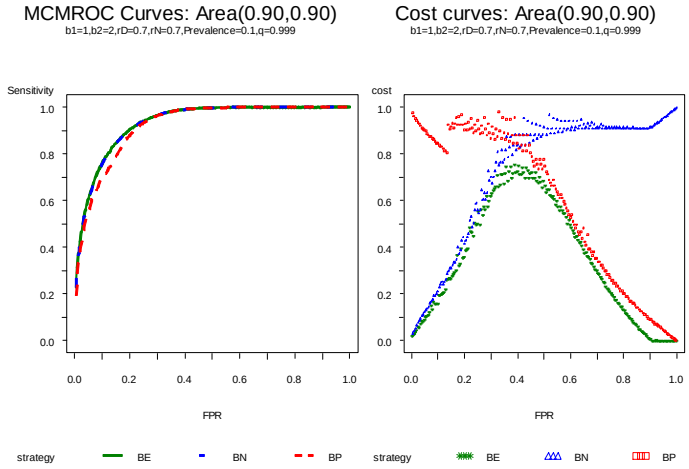


Figure B5 .1a: (b1=1, b2=1)



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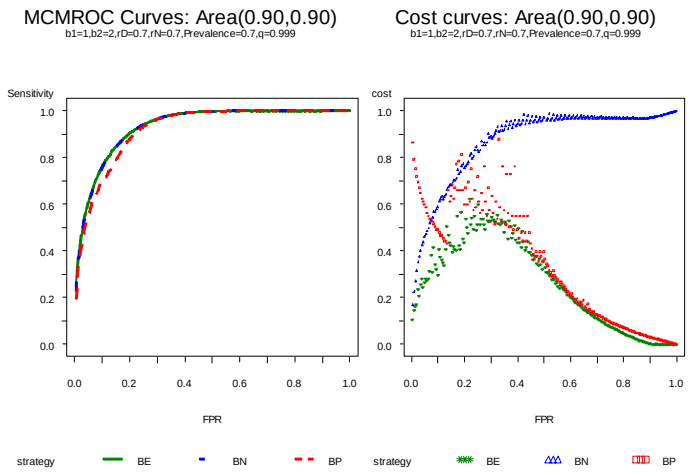

Figure B5 .1b: (b1=1, b2=2)

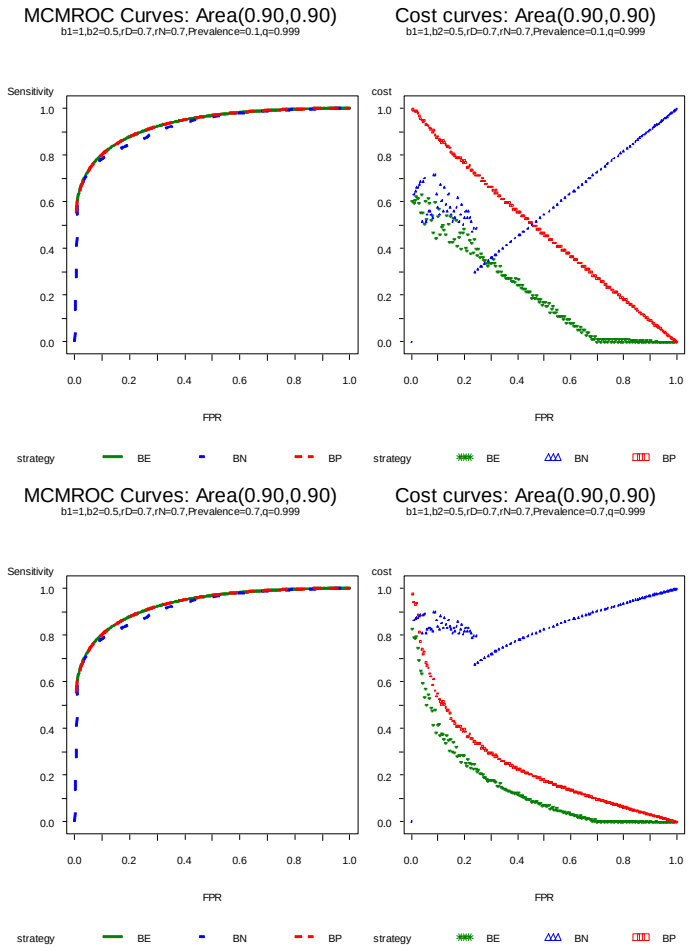

Figure B5 .1c: (b1=1, b2=0.5)

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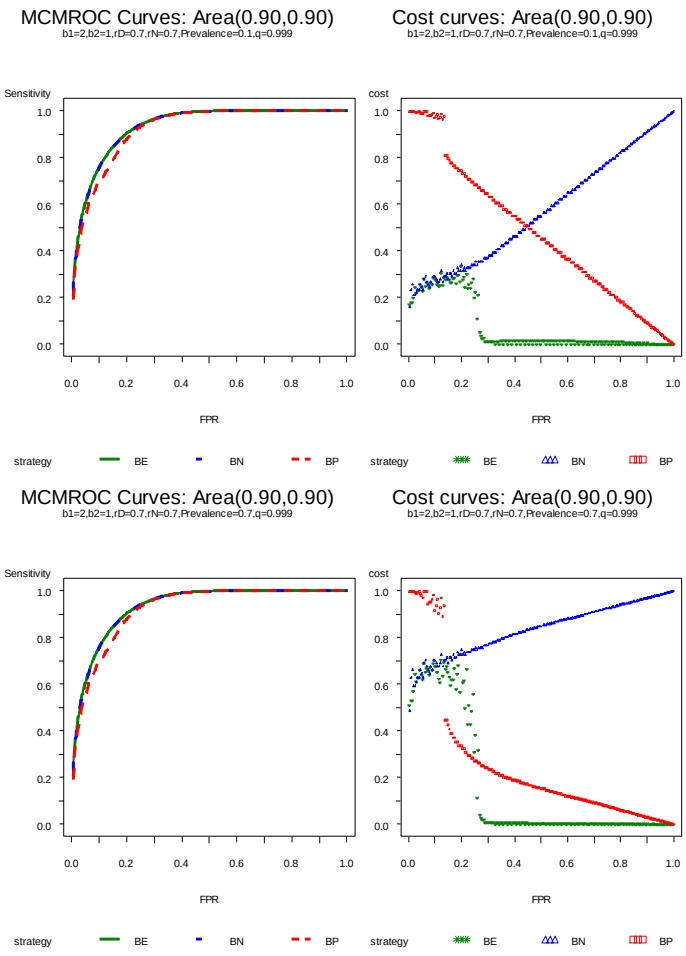
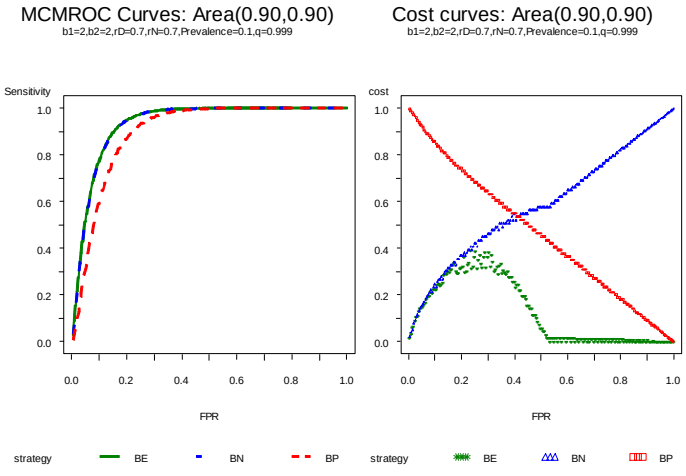


Figure B5 .1d: (b1=2, b2=1)



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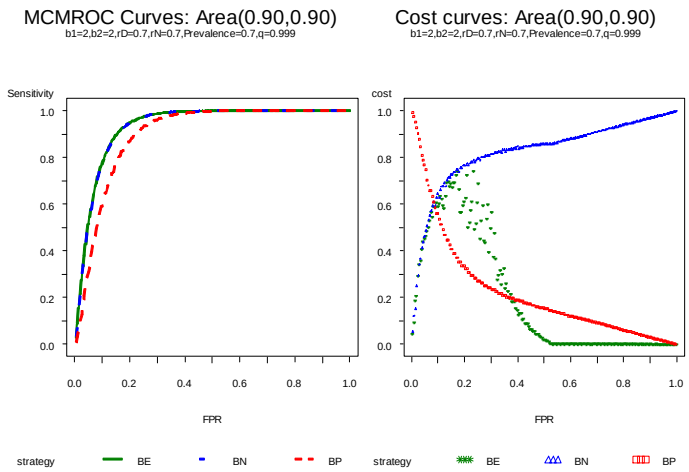

Figure B5 .1e: (b1=2, b2=2)

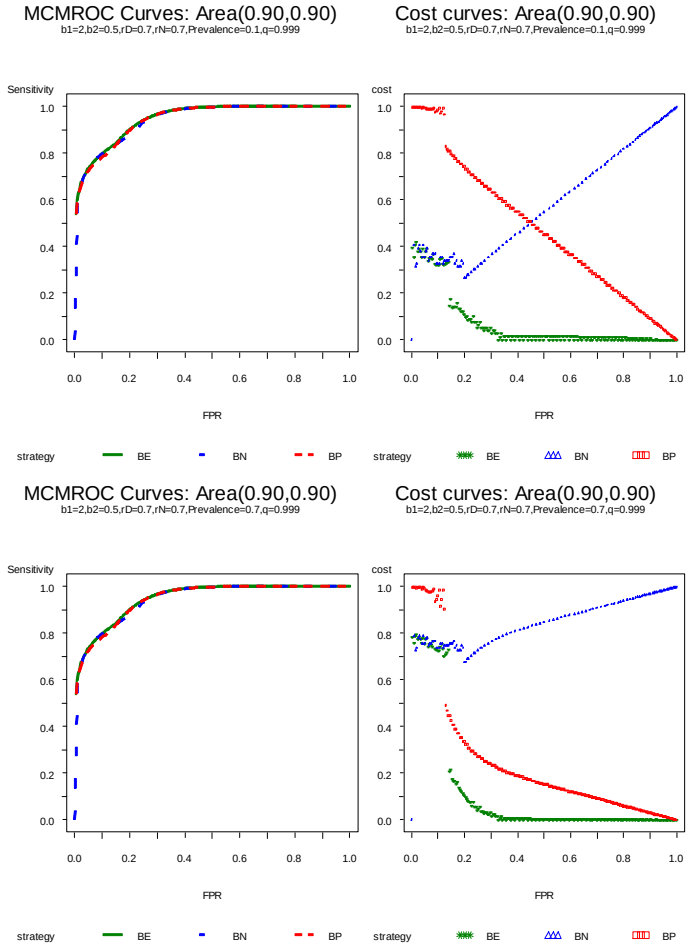

Figure B5 .1f: (b1=2, b2=0.5)

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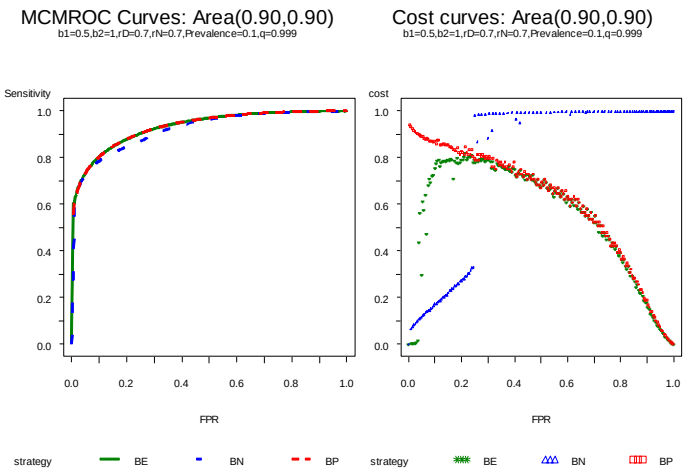


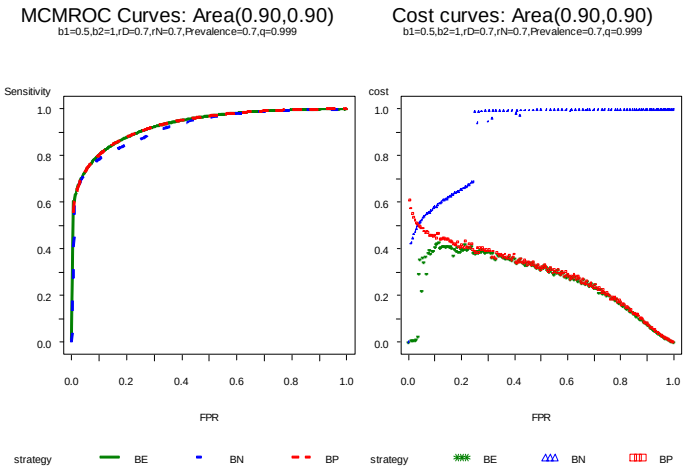
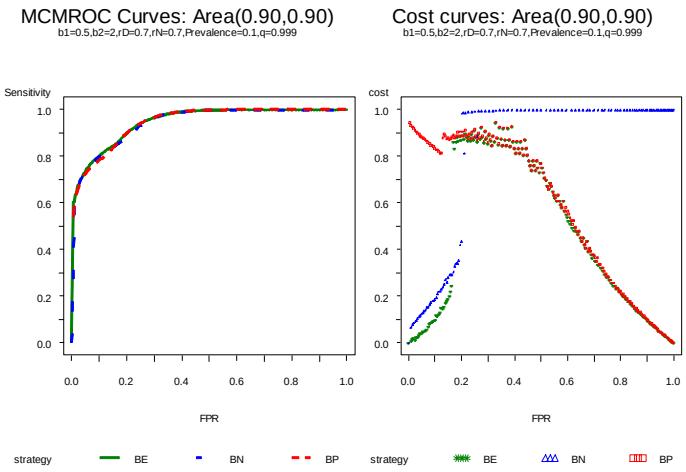


Figure B5 .1g: (b1=0.5, b2=1)



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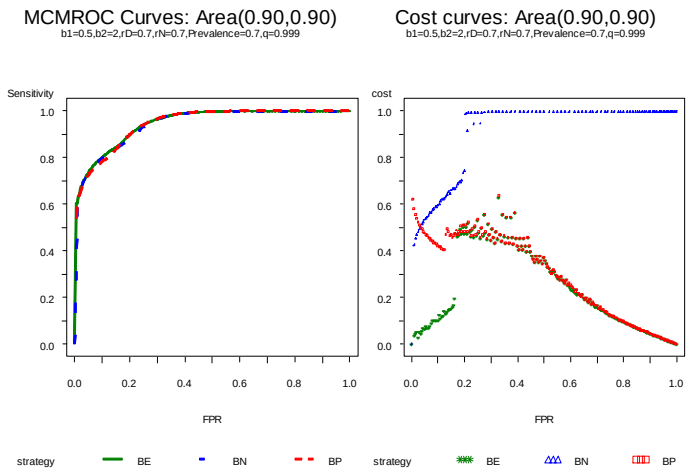
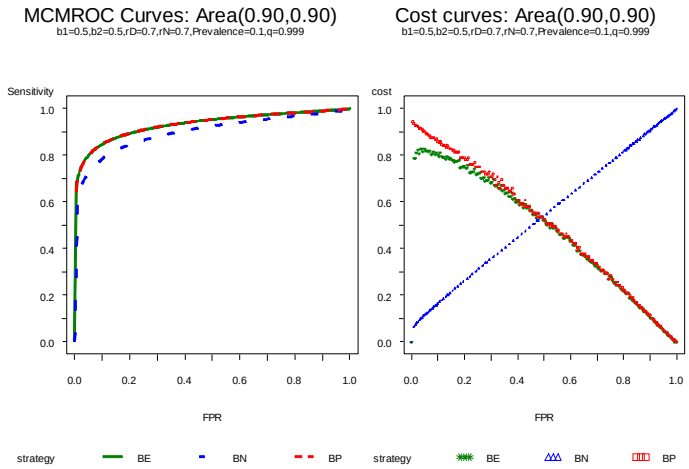


Figure B5 .1h: (b1=0.5, b2=2)



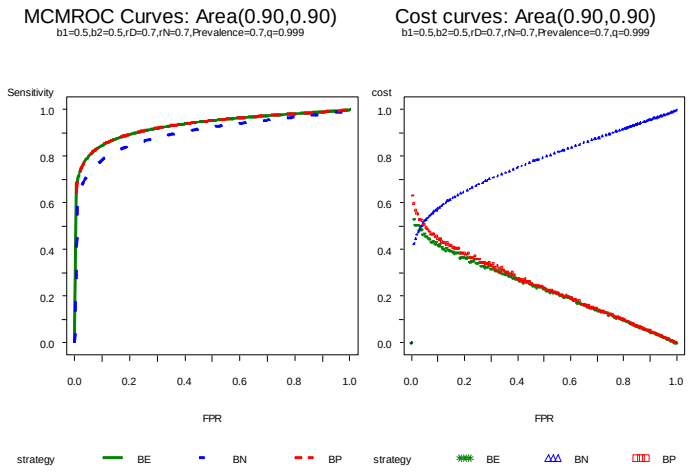


Figure B5 .1i: (b1=0.5, b2=0.5)

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B5 .2 AUC1 = 0.70, AUC2 = 0.90

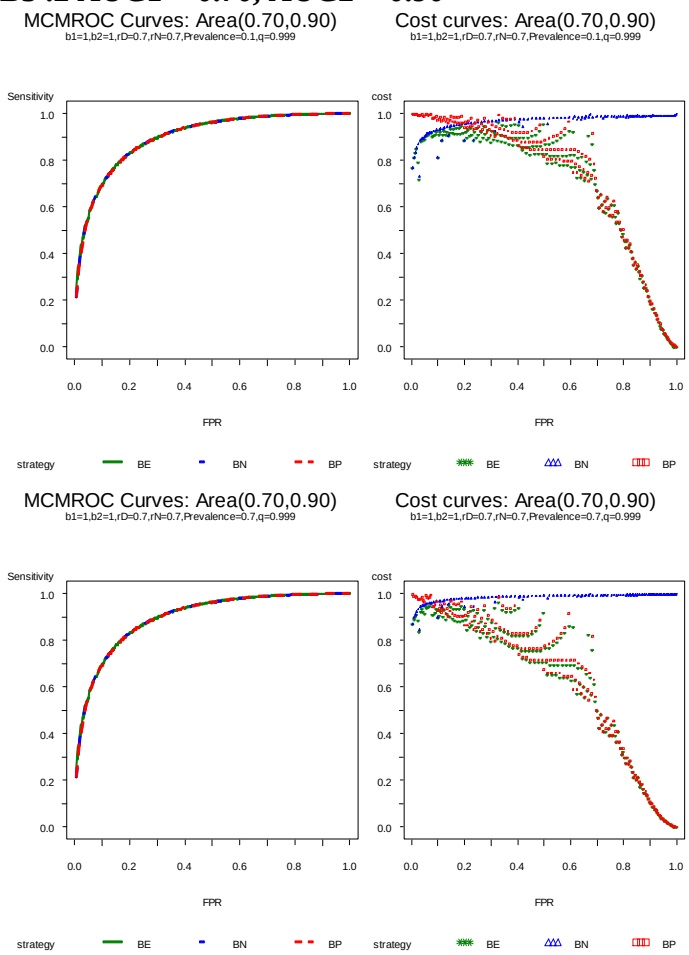
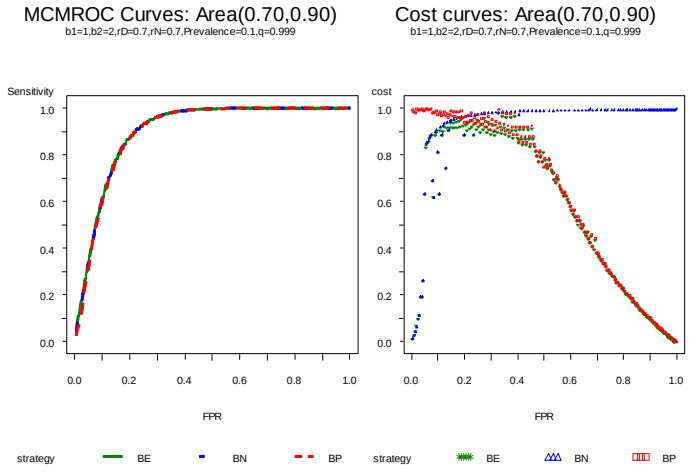


Figure B5 .2a: (b1=1, b2=1)



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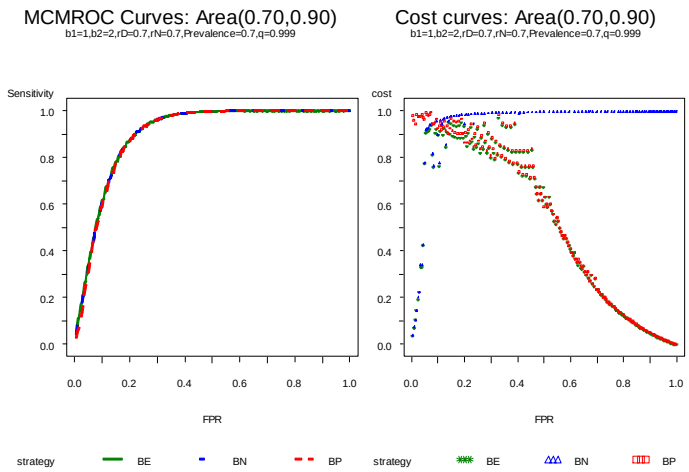

Figure B5 .2b: (b1=1, b2=2)

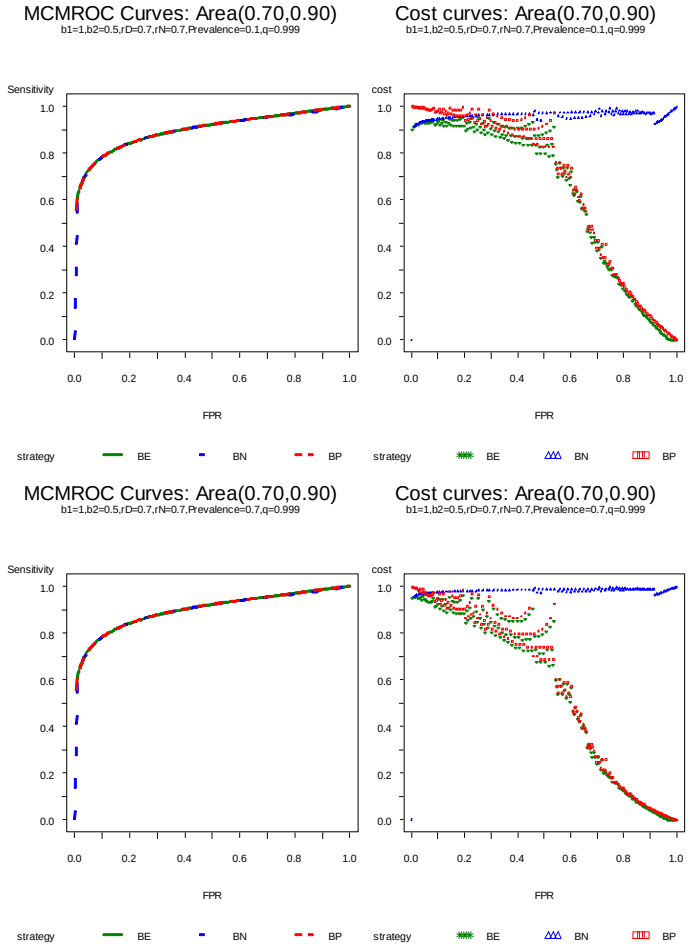

Figure B5 .2c: (b1=1, b2=0.5)

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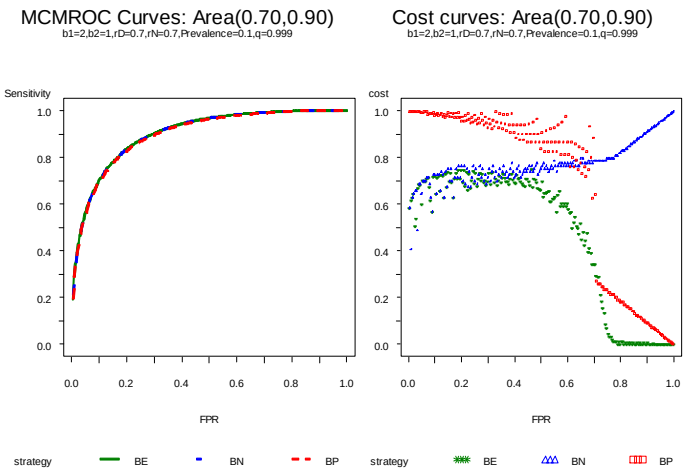


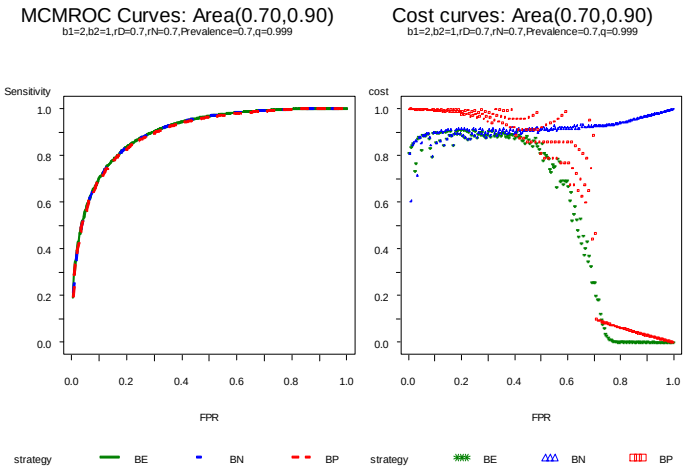
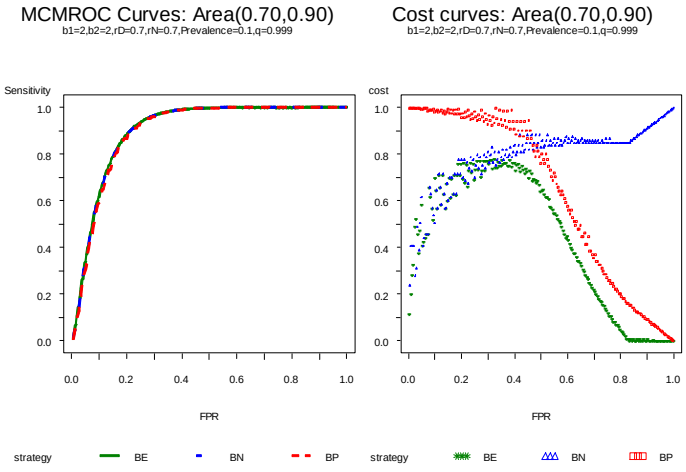


Figure B5 .2d: (b1=2, b2=1)



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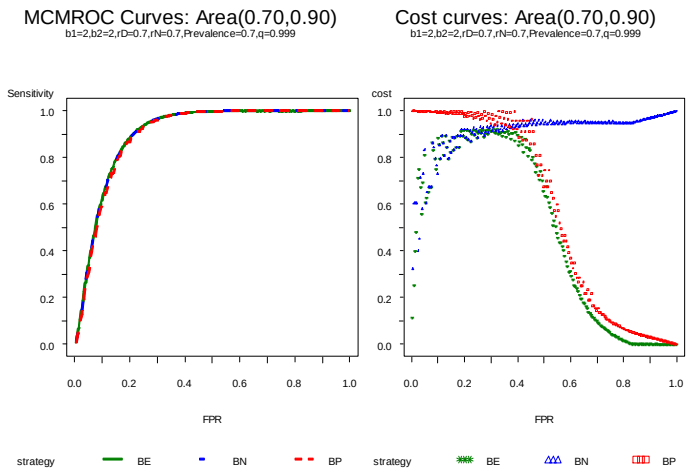

Figure B5 .2e: (b1=2, b2=2)

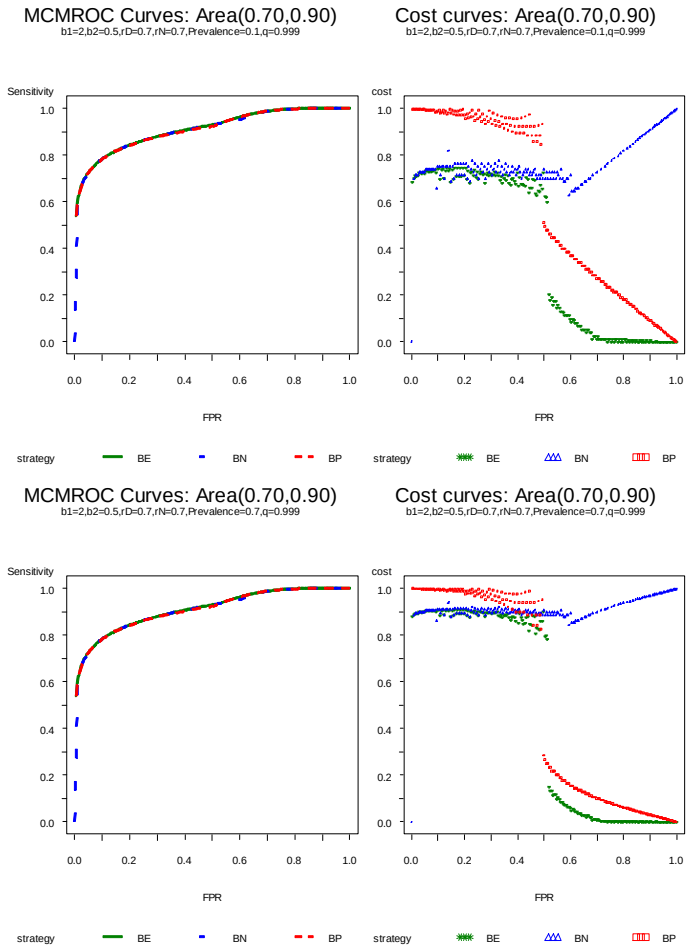

Figure B5 .2f: (b1=2, b2=0.5)

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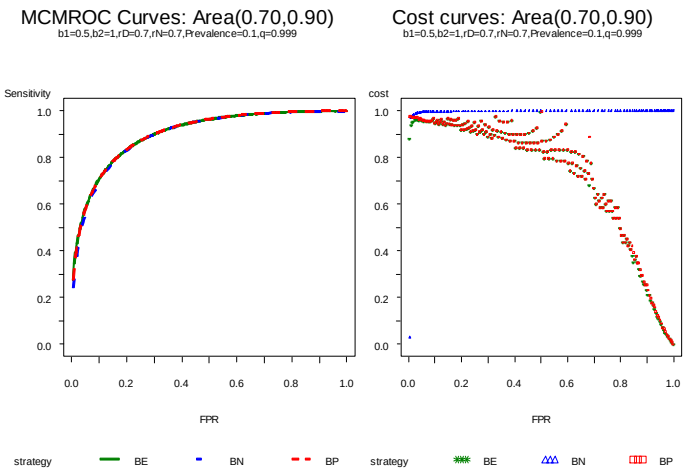


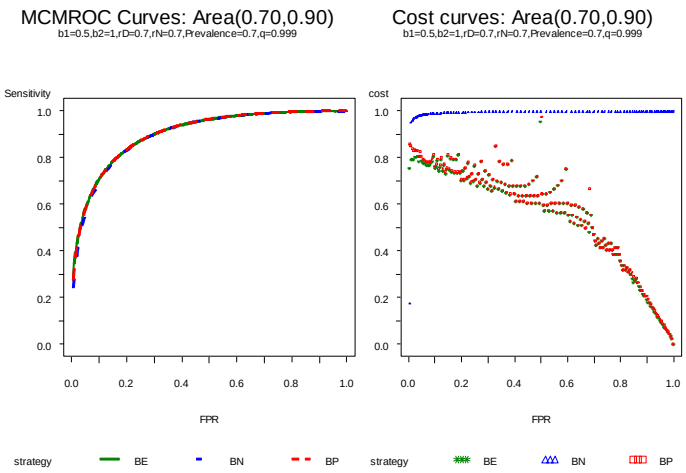
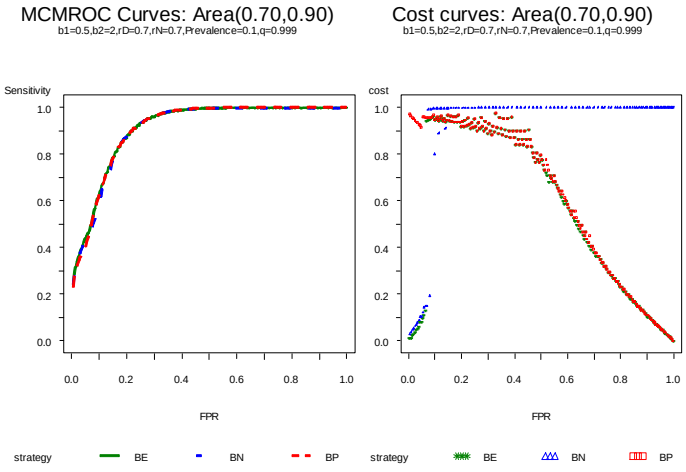


Figure B5 .2g: (b1=0.5, b2=1)



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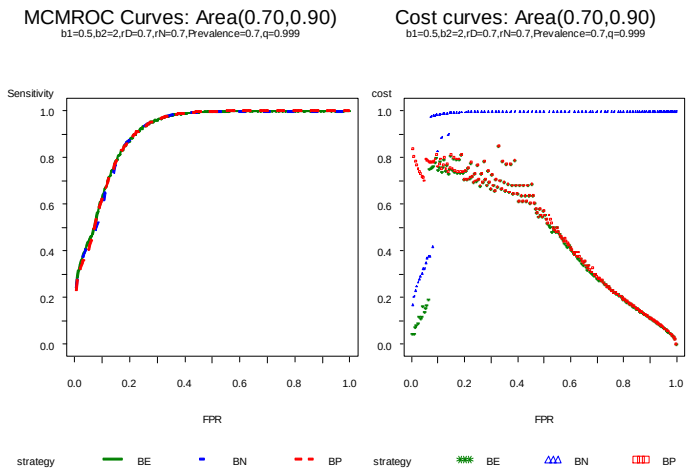
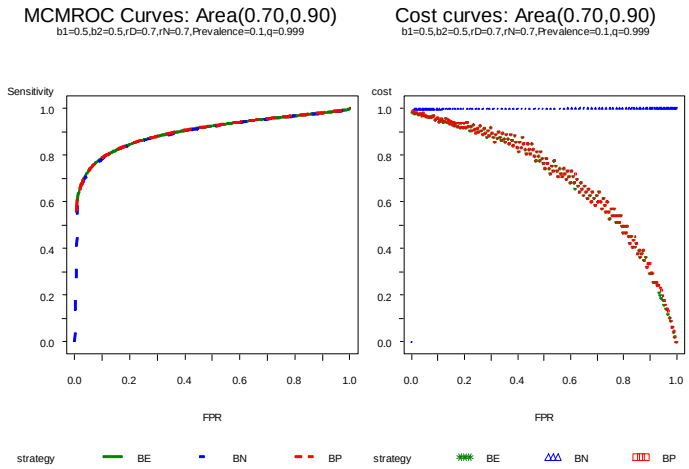


Figure B5 .2h: (b1=0.5, b2=2)



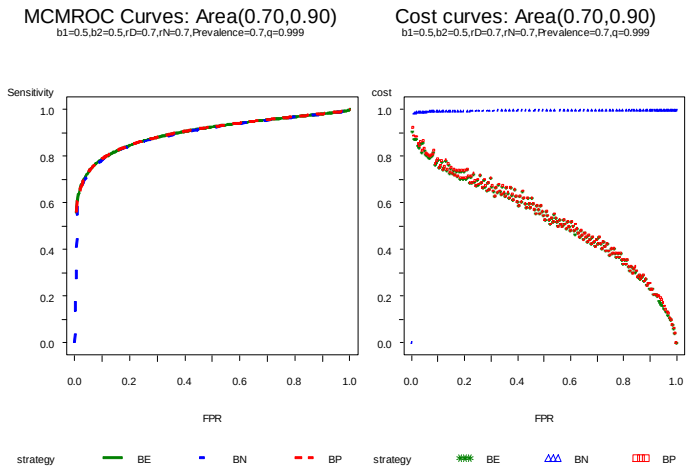


Figure B5 .2i: (b1=0.5, b2=0.5)

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B5 .3 AUC1 = 0.70, AUC2 = 0.70

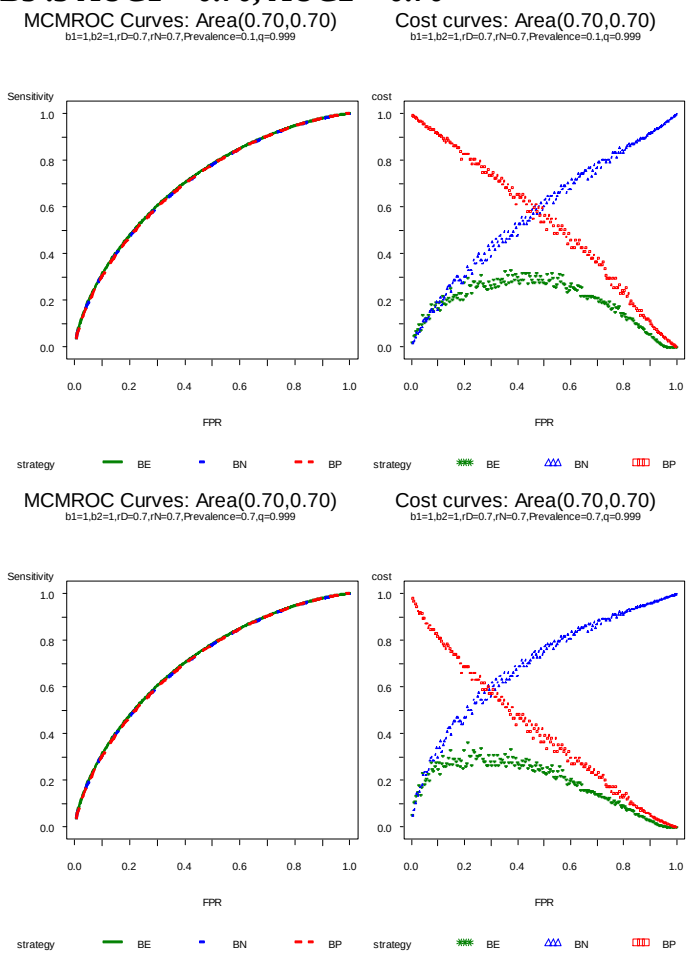
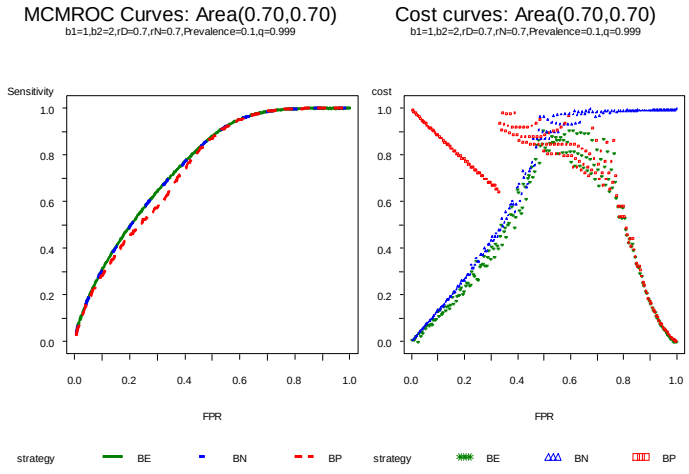


Figure B5 .3a: (b1=1, b2=1)



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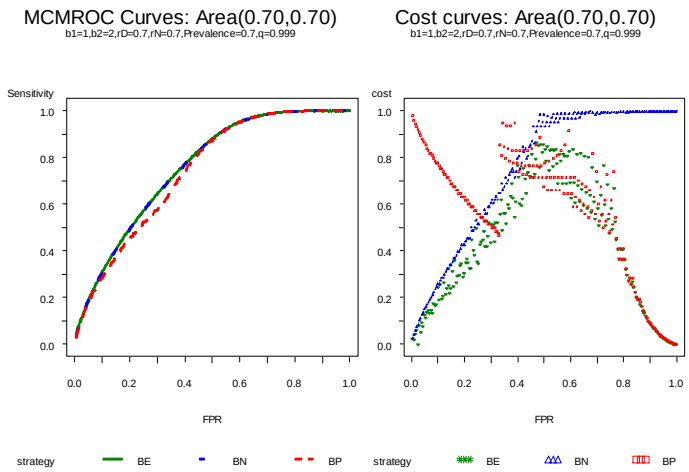
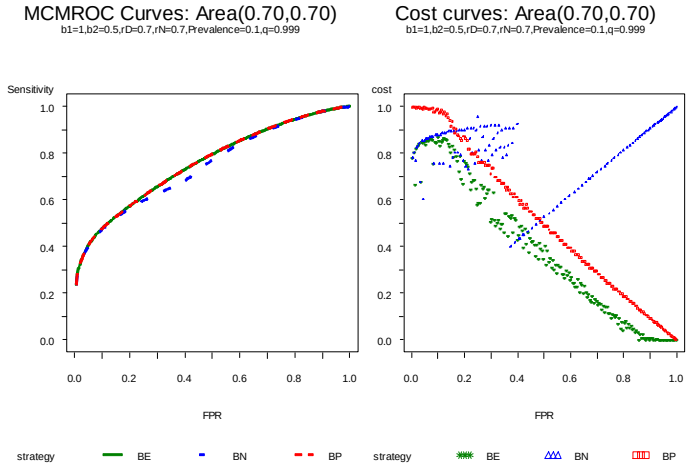


Figure B5 .3b: (b1=1, b2=2)



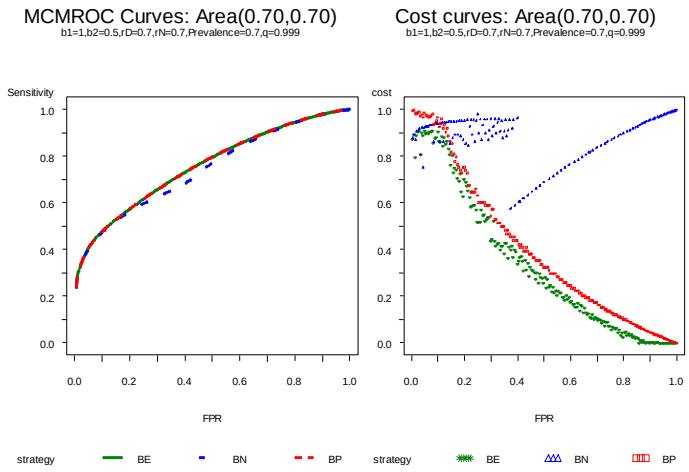


Figure B5 .3c: (b1=1, b2=0.5)

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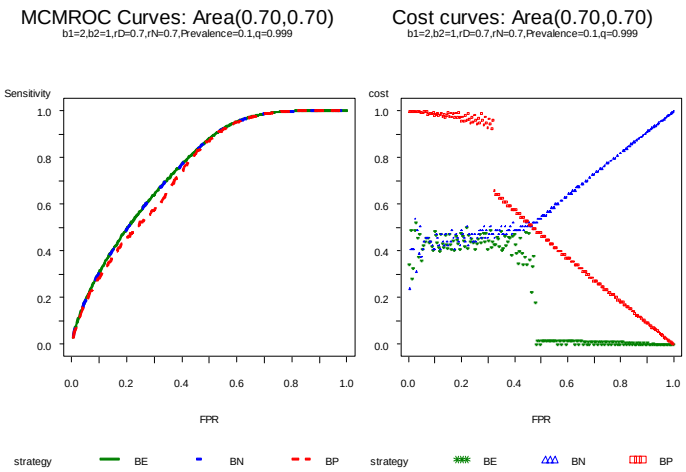


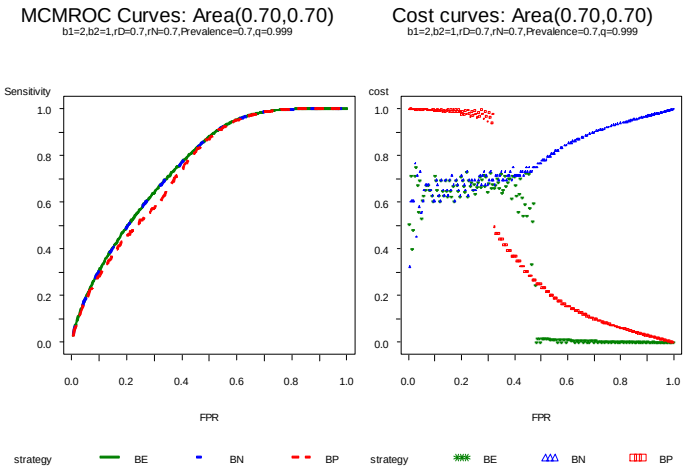
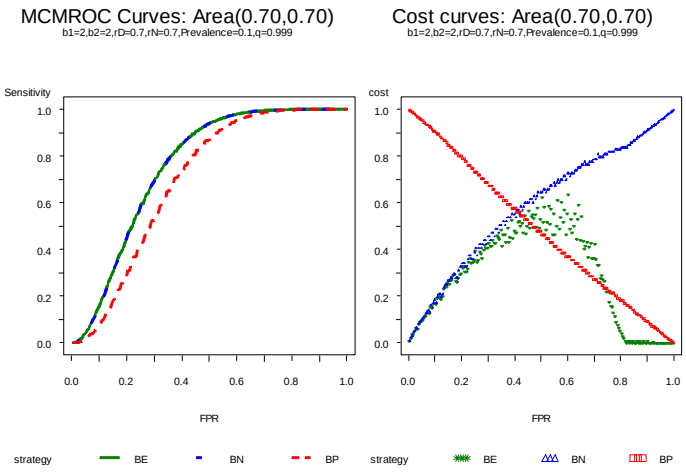


Figure B5 .3d: (b1=2, b2=1)



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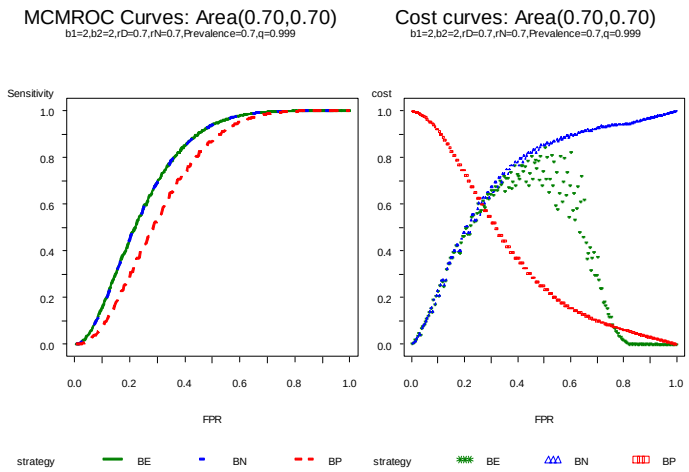

Figure B5 .3e: (b1=2, b2=2)

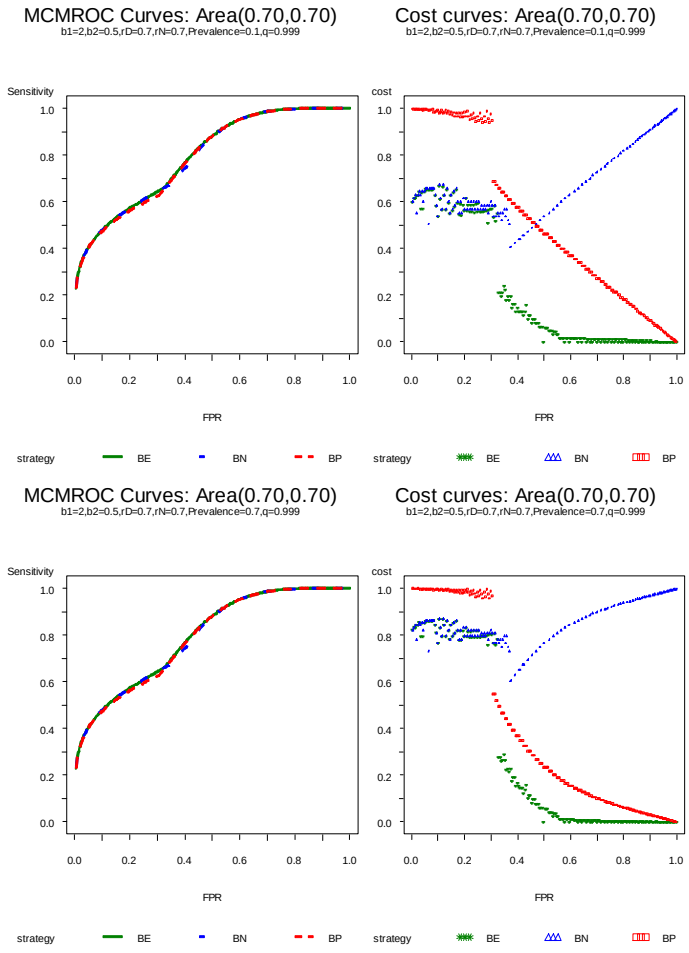

Figure B5 .3f: (b1=2, b2=0.5)

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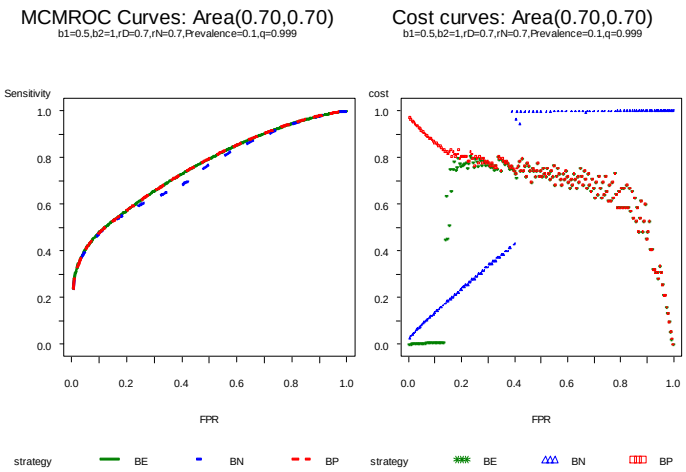


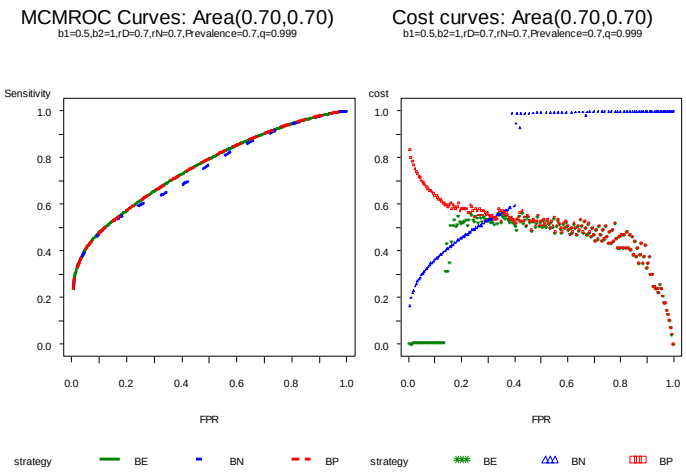
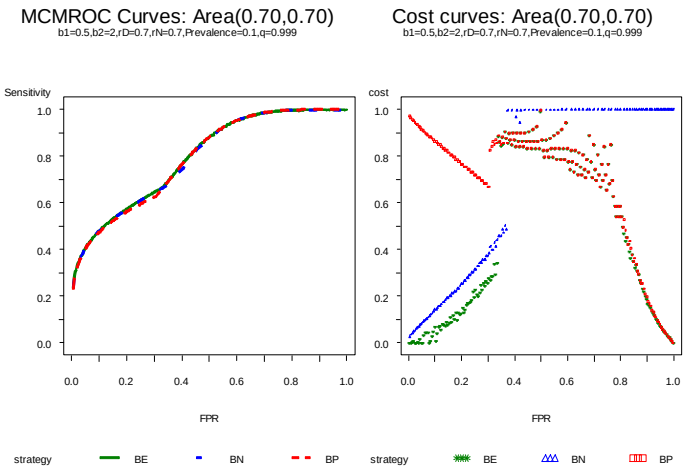


Figure B5 .3g: (b1=0.5, b2=1)



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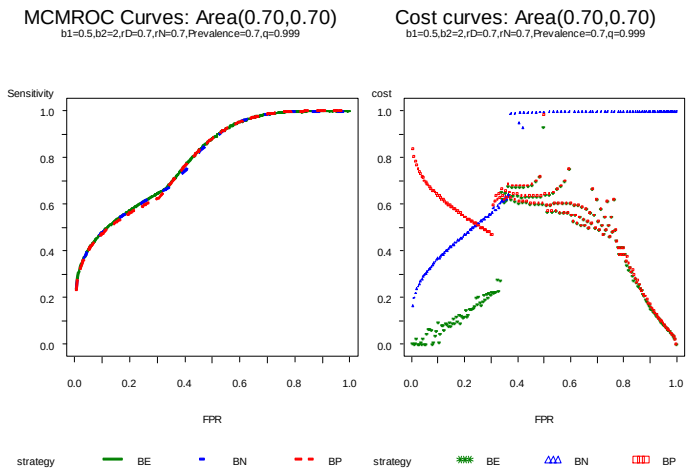
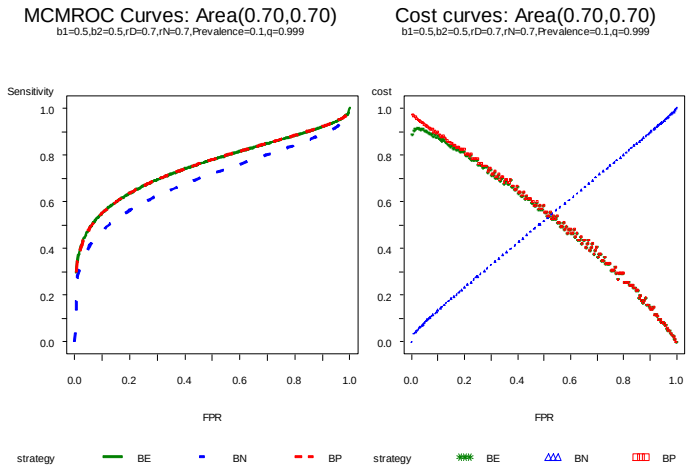


Figure B5 .3h: (b1=0.5, b2=2)



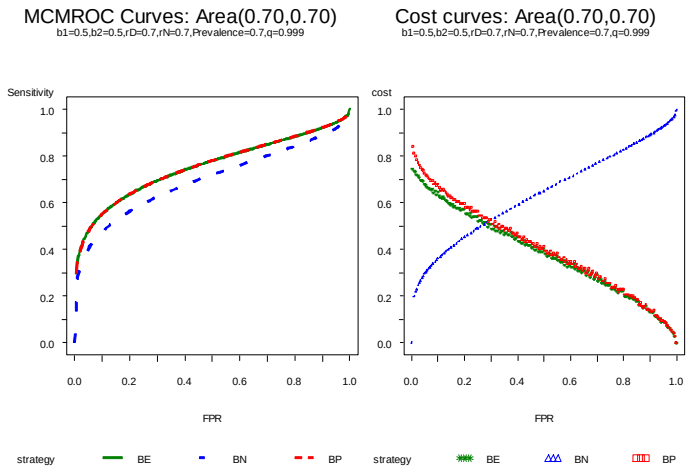


Figure B5 .3i: (b1=0.5, b2=0.5)

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Appendix C

Graphs (q=0.95)

The two plots in the top show MCMROC curves and cost curves when disease prevalence is low (prevalence = 0.1) and below show MCMROC curves and cost curves when disease prevalence is high (prevalence = 0.7).

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C1 Independent of the tests $(\rho_D = 0, \rho_N = 0)$

C1.1 AUC1 = 0.90, AUC2 = 0.90

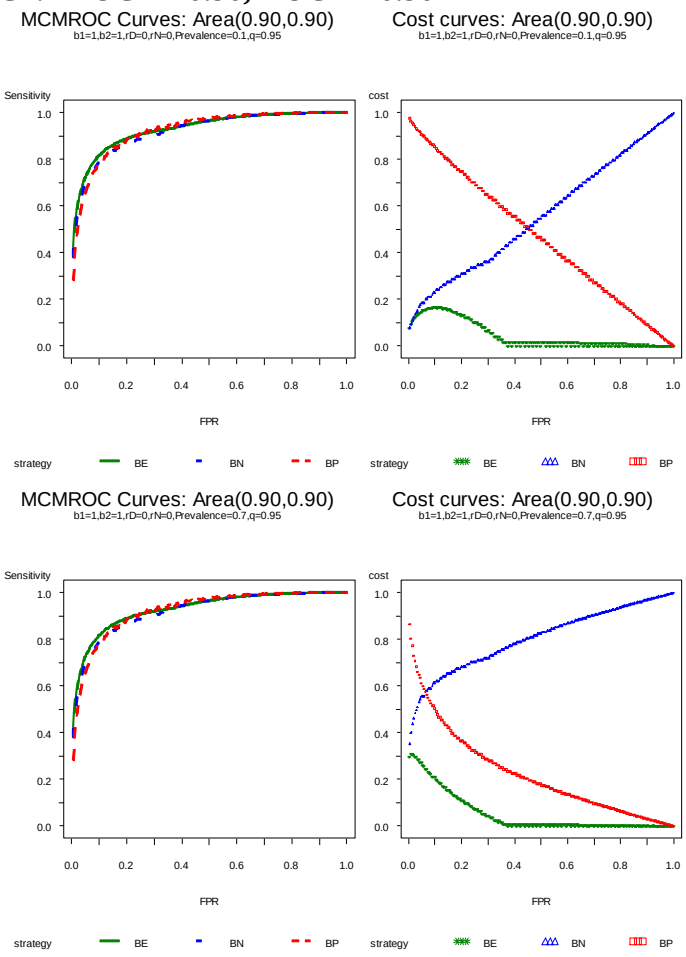
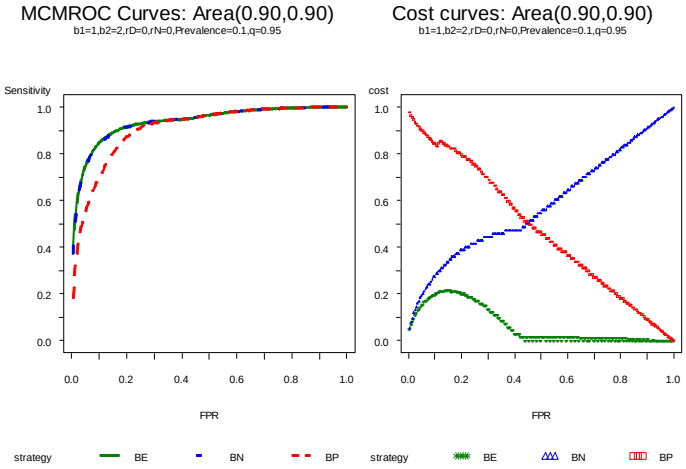


Figure C1.1a: (b1=1, b2=1)



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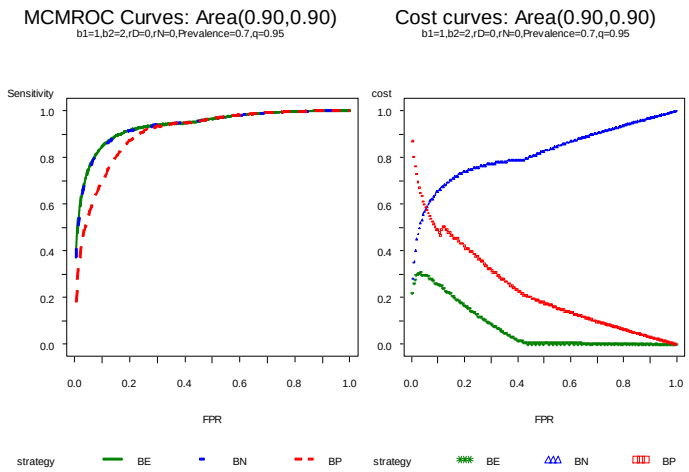
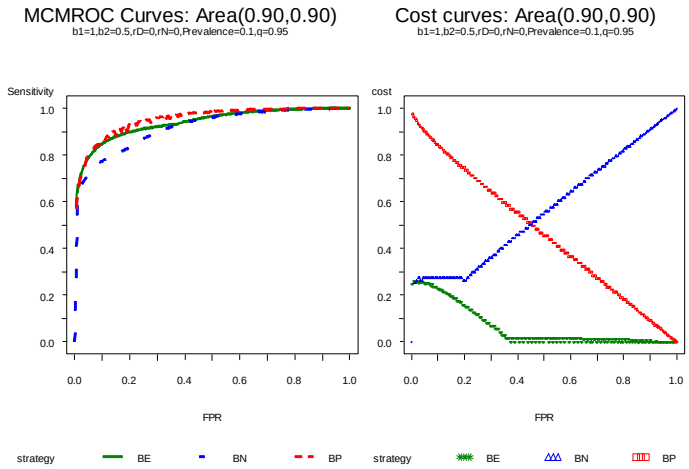


Figure C1.1b: (b1=1, b2=2)



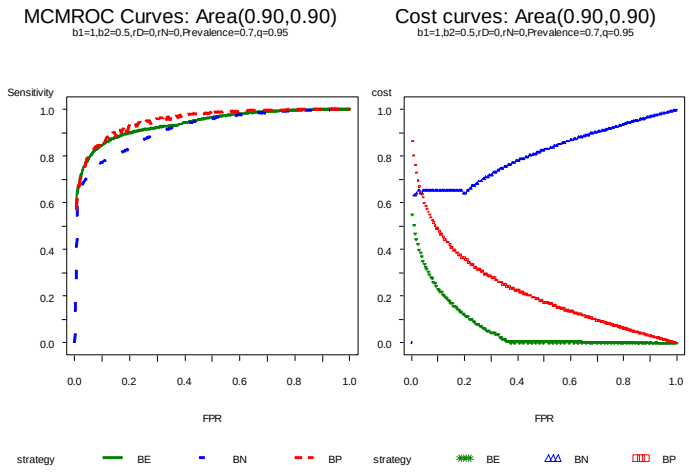


Figure C1.1c: (b1=1, b2=0.5)

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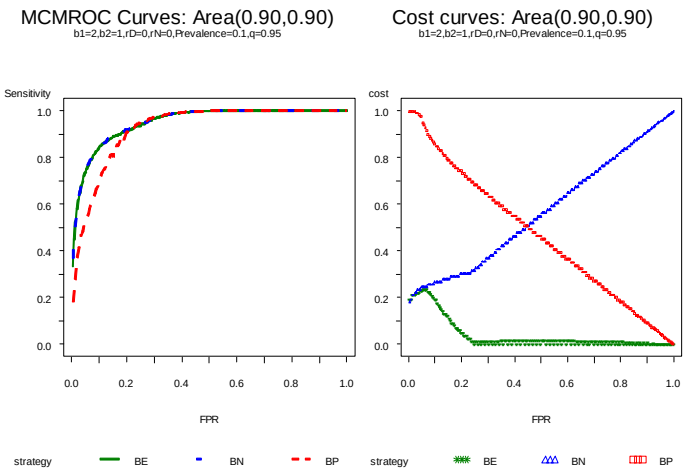


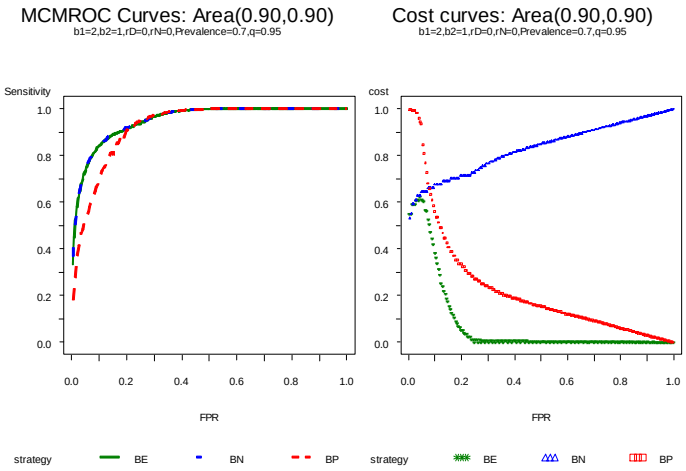
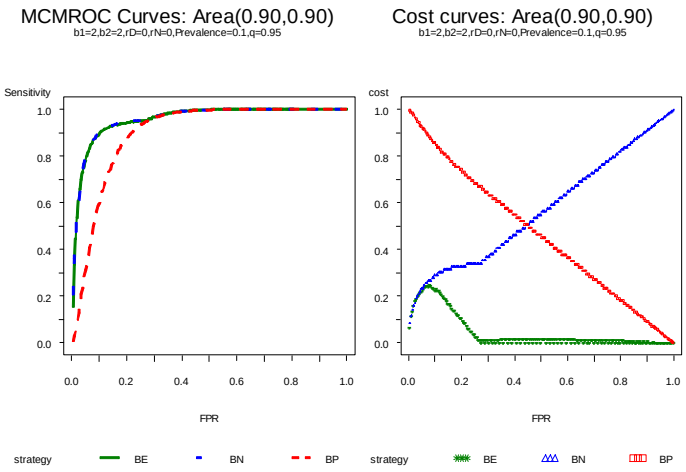


Figure C1.1d: (b1=2, b2=1)



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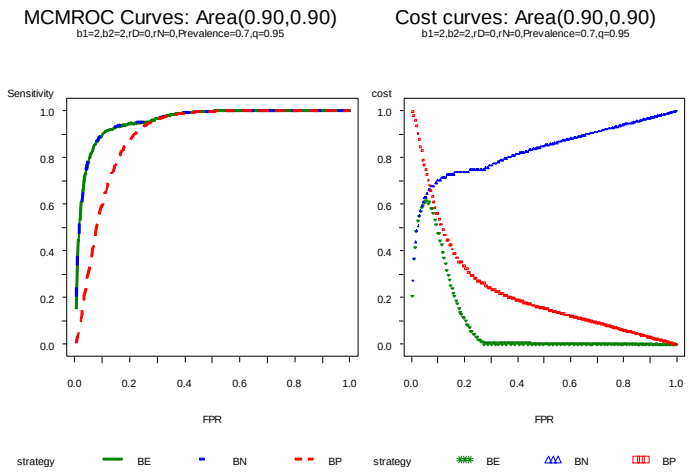

Figure C1.1e: (b1=2, b2=2)

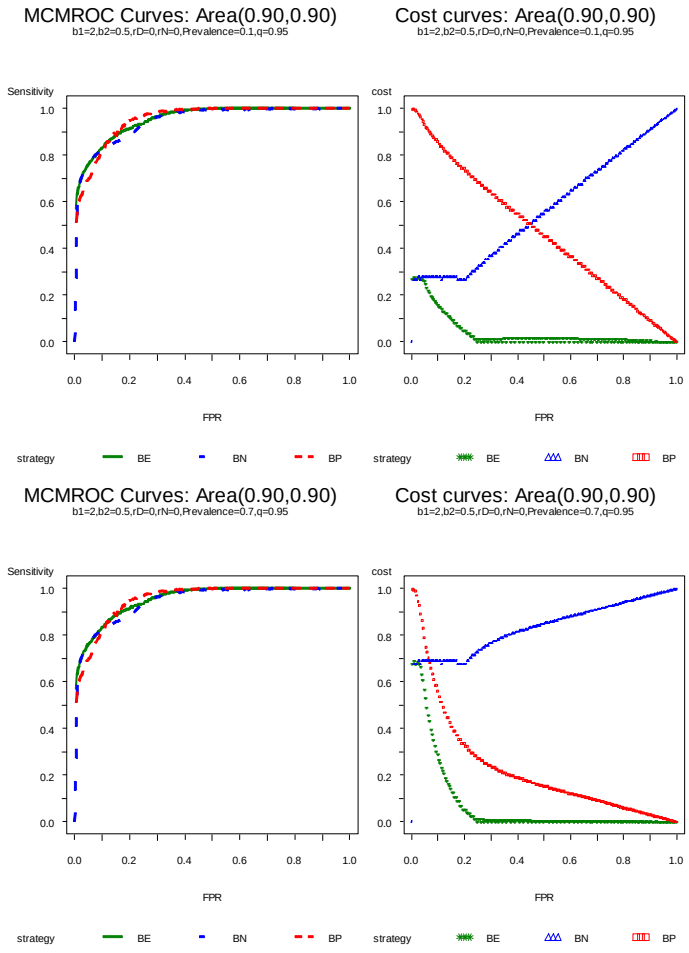

Figure C1.1f: (b1=2, b2=0.5)

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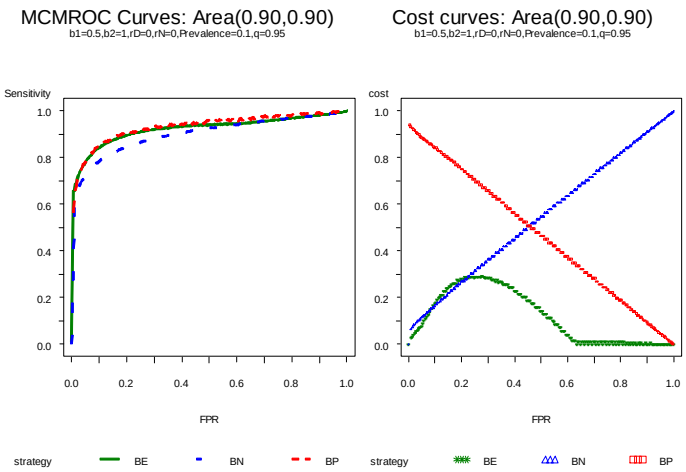


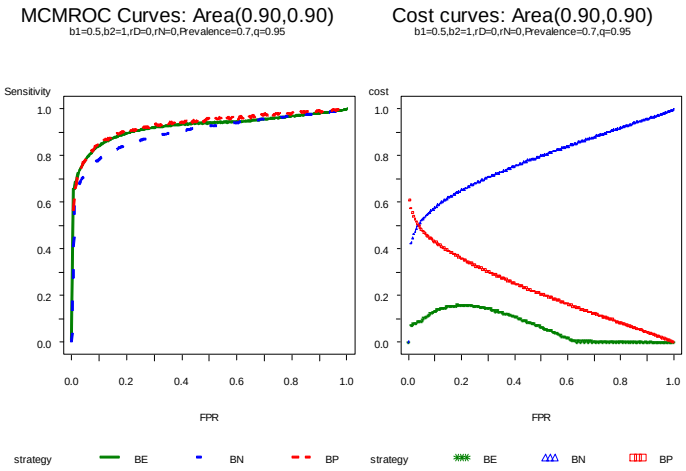
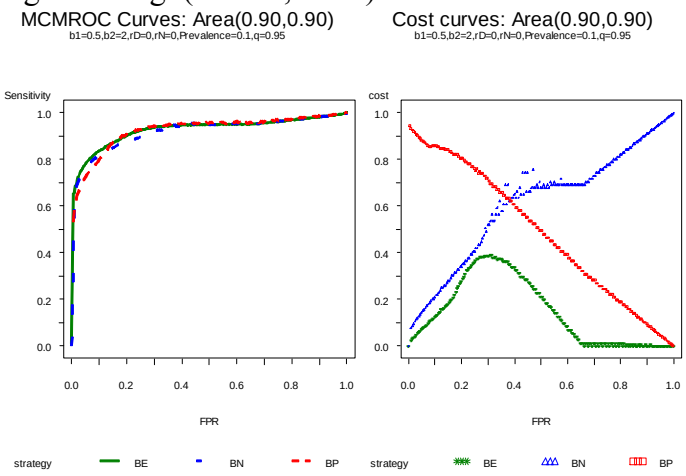


Figure C1.1g: (b1=0.5, b2=1)



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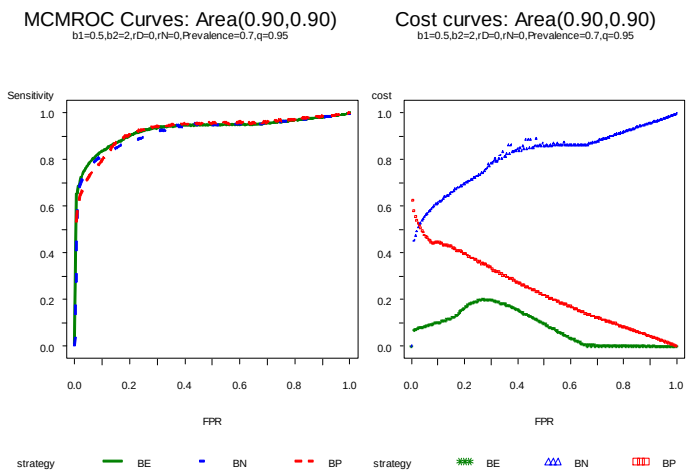
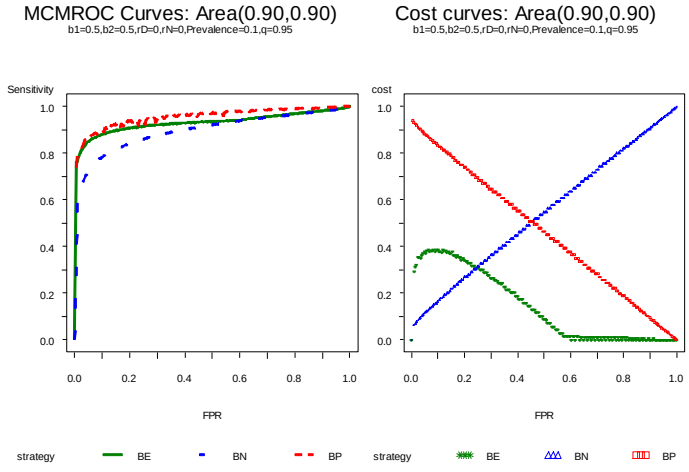


Figure C1.1h: (b1=0.5, b2=2)



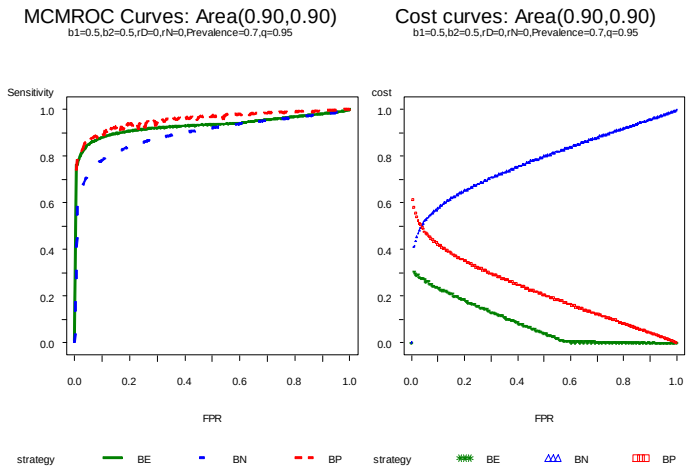


Figure C1.1i: (b1=0.5, b2=0.5)

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C1.2 AUC1 = 0.70, AUC2 = 0.90

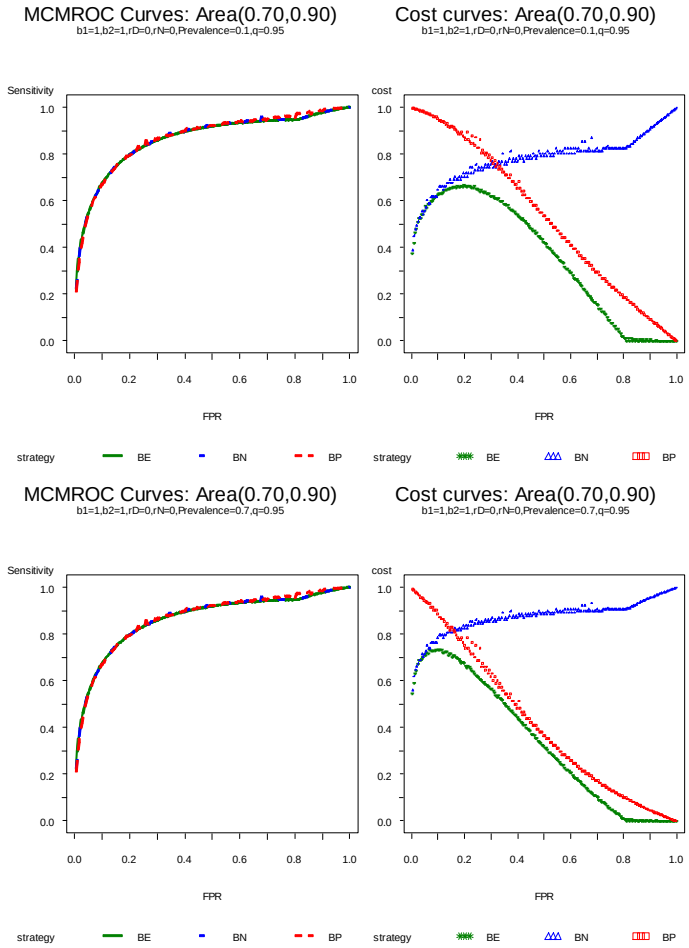
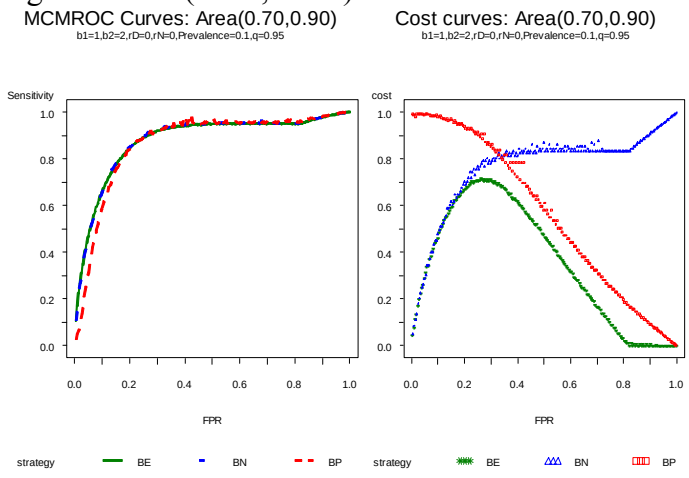


Figure C1.2a: (b1=1, b2=1)



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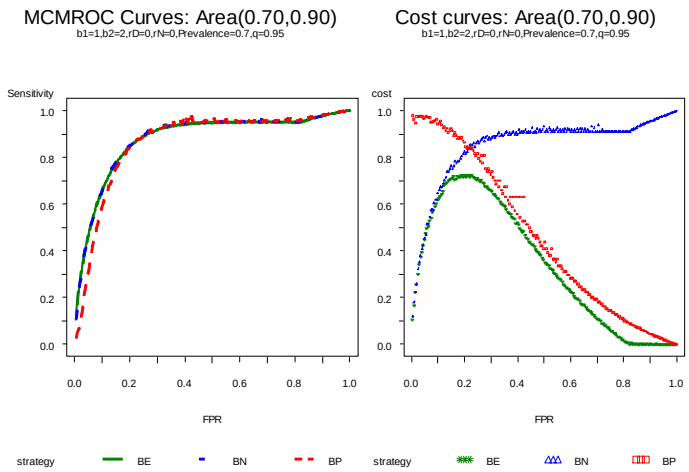

Figure C1.2b: (b1=1, b2=2)

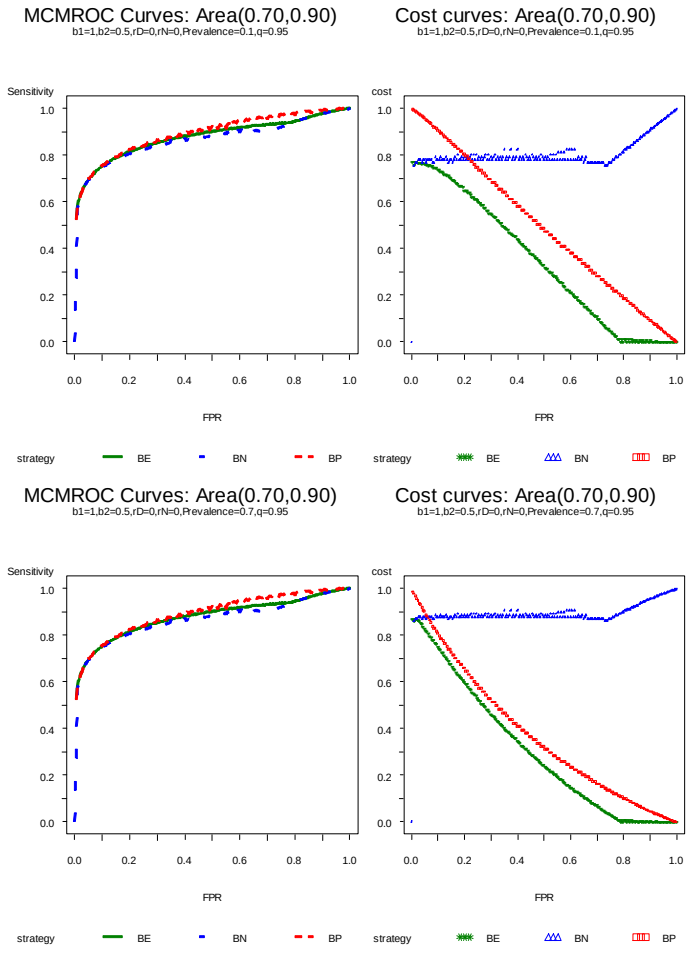

Figure C1.2c: (b1=1, b2=0.5)

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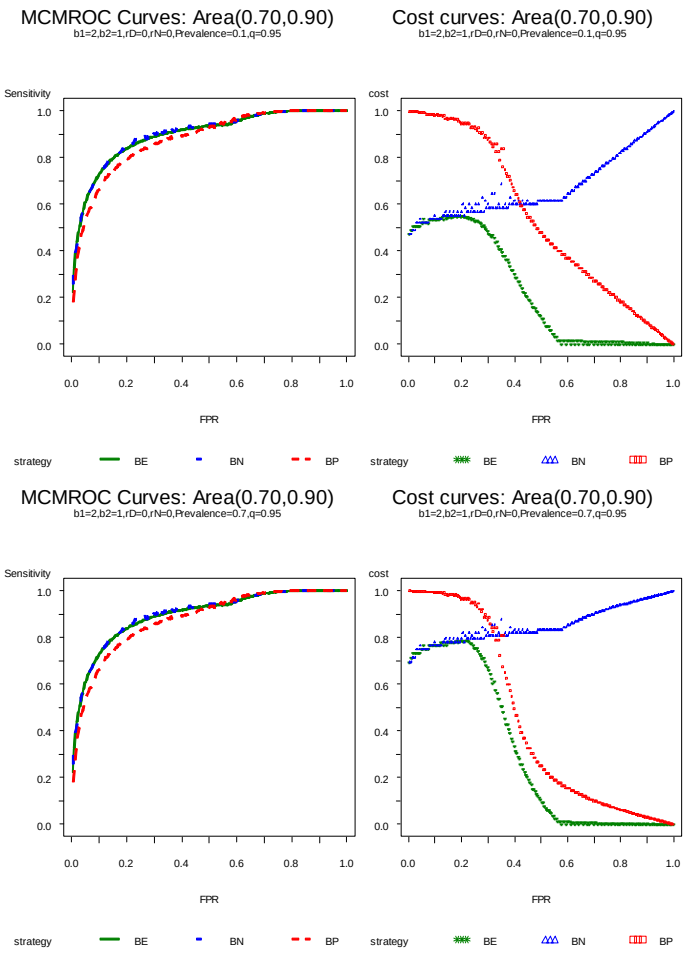
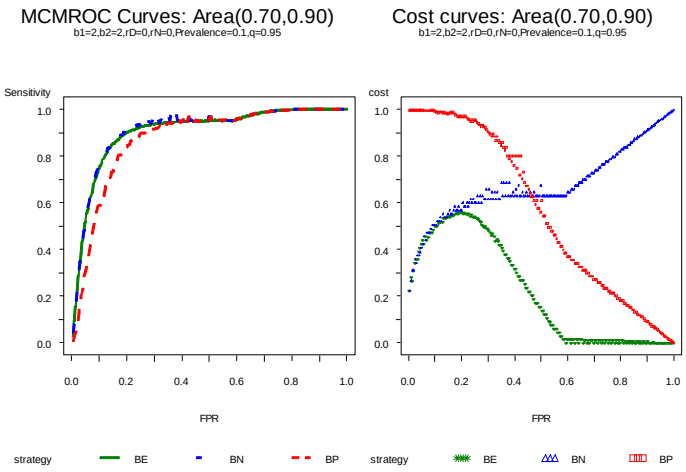


Figure C1.2d: (b1=2, b2=1)



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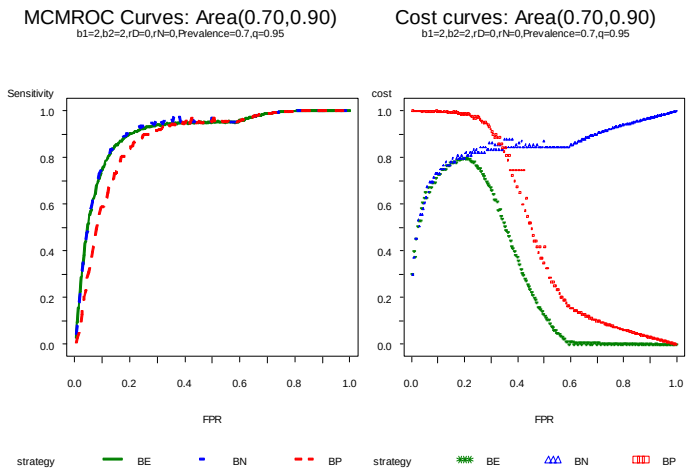
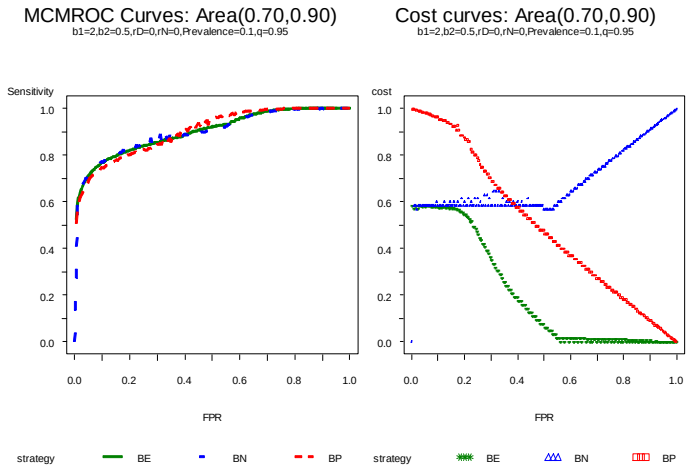


Figure C1.2e: (b1=2, b2=2)



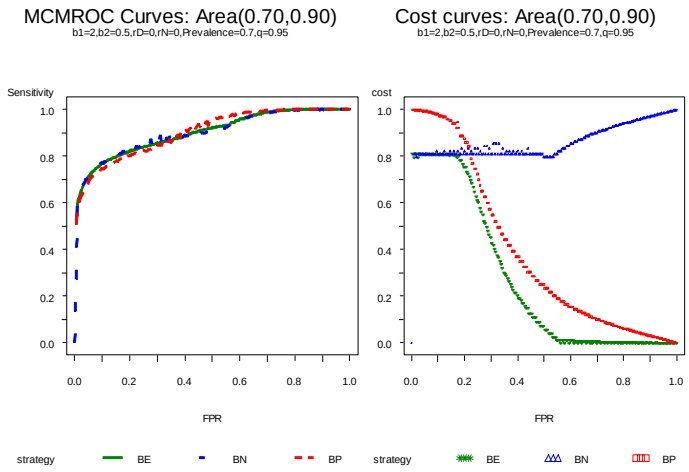


Figure C1.2f: (b1=2, b2=0.5)

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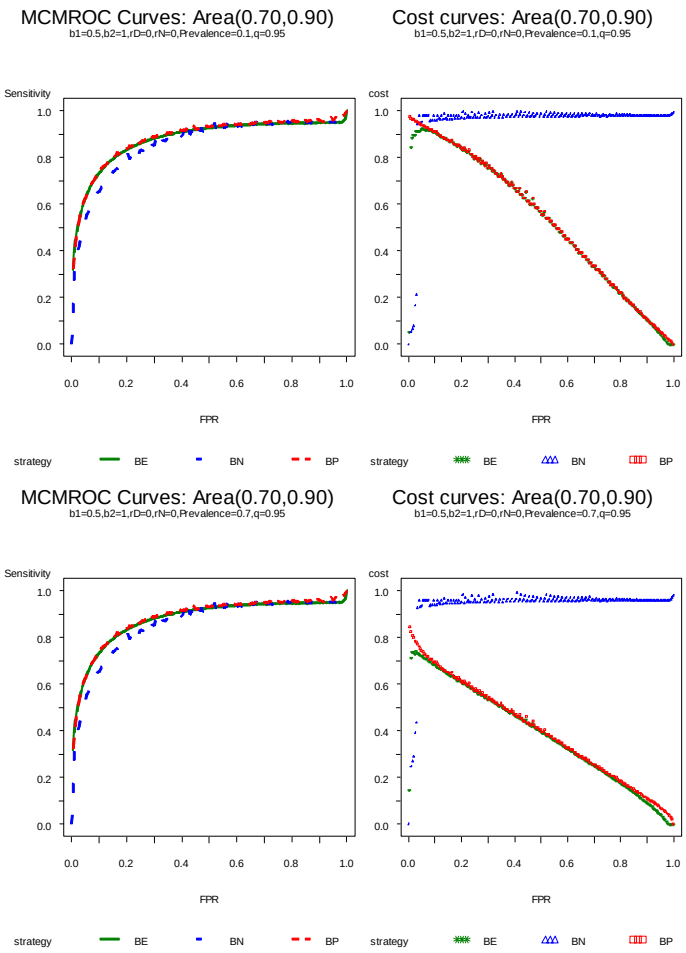
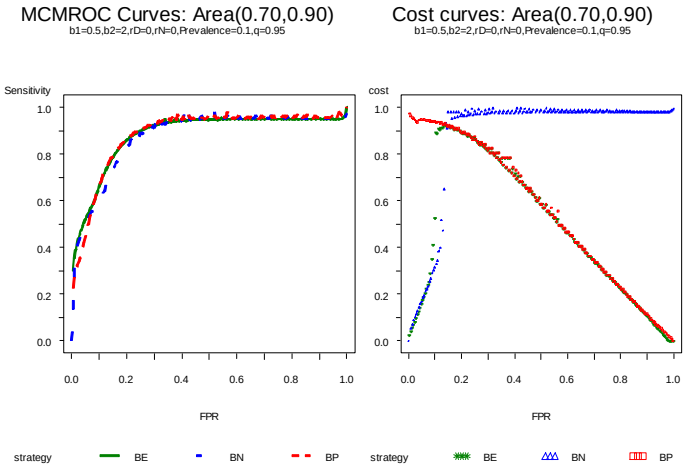


Figure C1.2g: (b1=0.5, b2=1)



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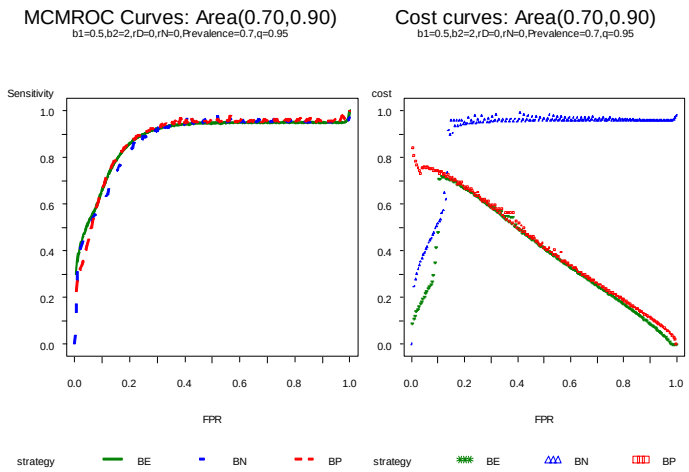
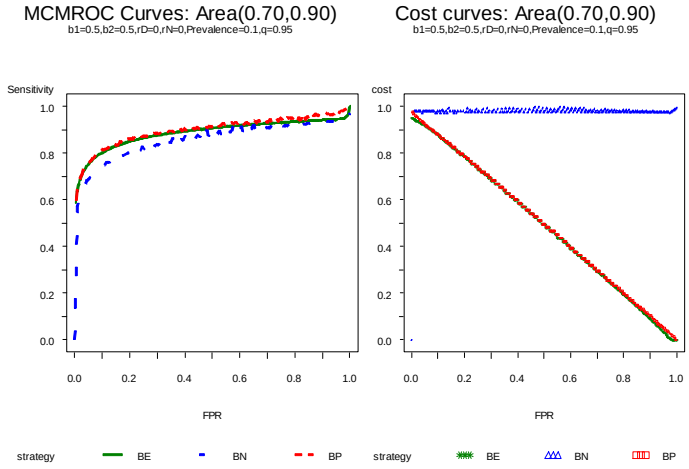


Figure C1.2h: (b1=0.5, b2=2)



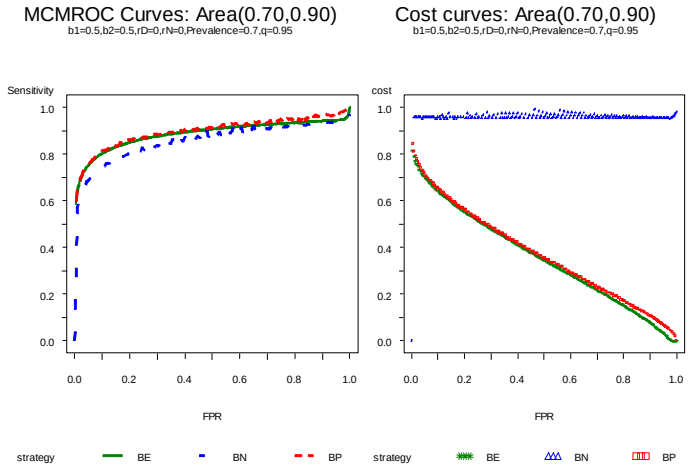


Figure C1.2i: (b1=0.5, b2=0.5)

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C1.3 AUC1 = 0.70, AUC2 = 0.70

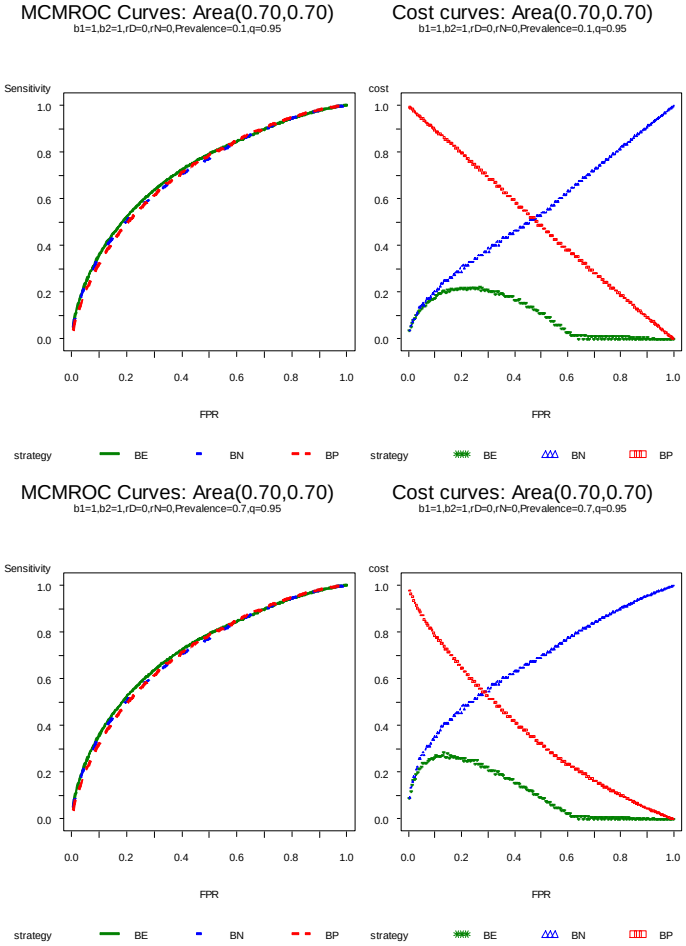
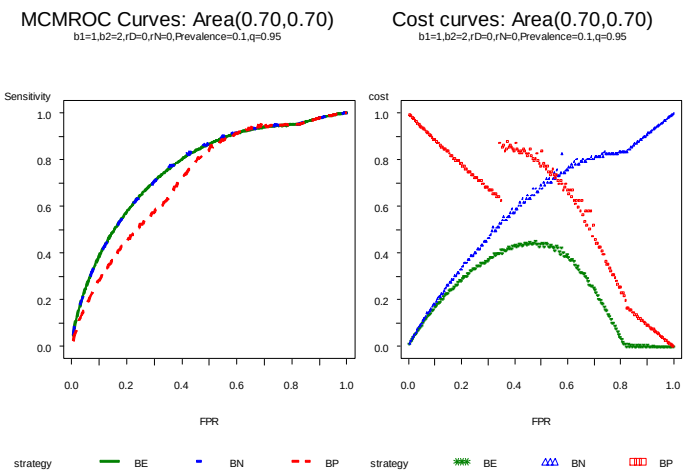


Figure C1.3a: (b1=1, b2=1)



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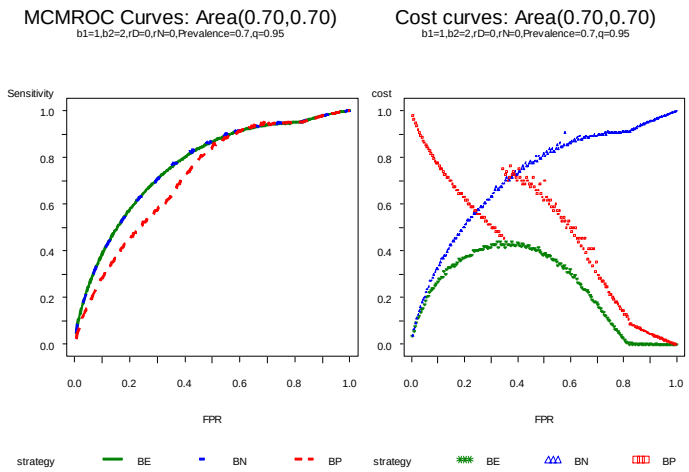

Figure C1.3b: (b1=1, b2=2)

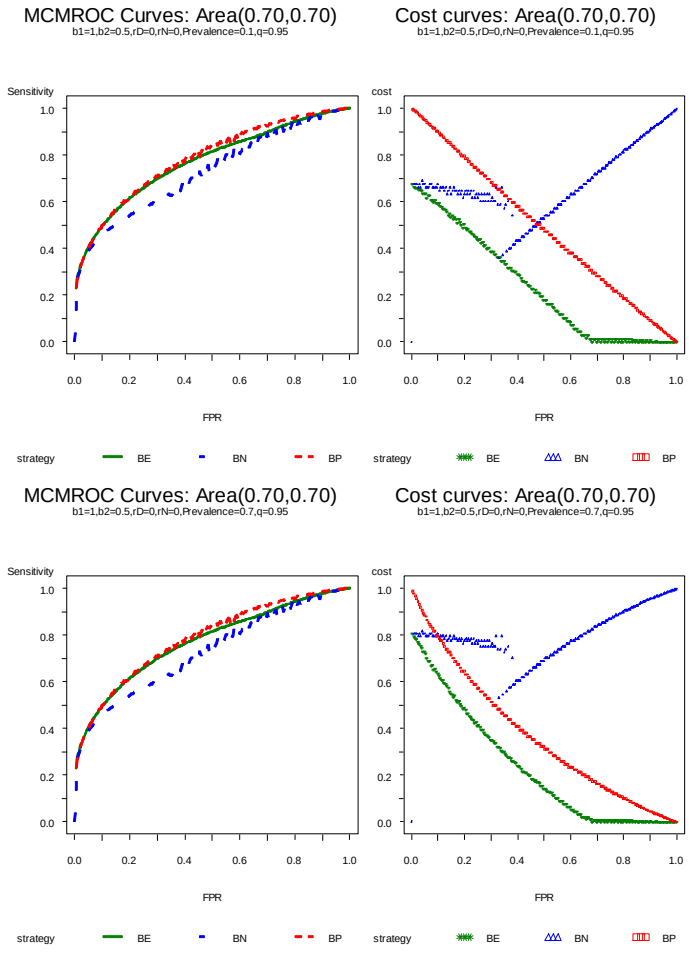

Figure C1.3c: (b1=1, b2=0.5)

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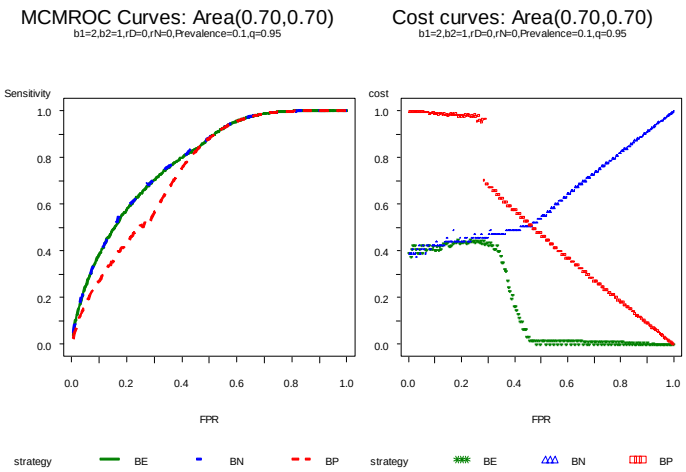


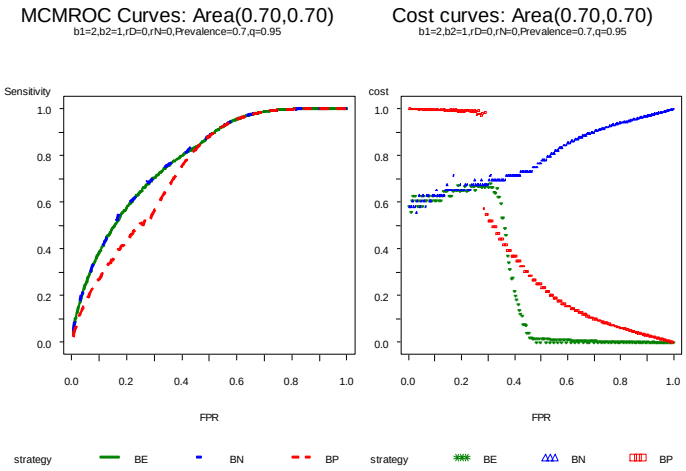
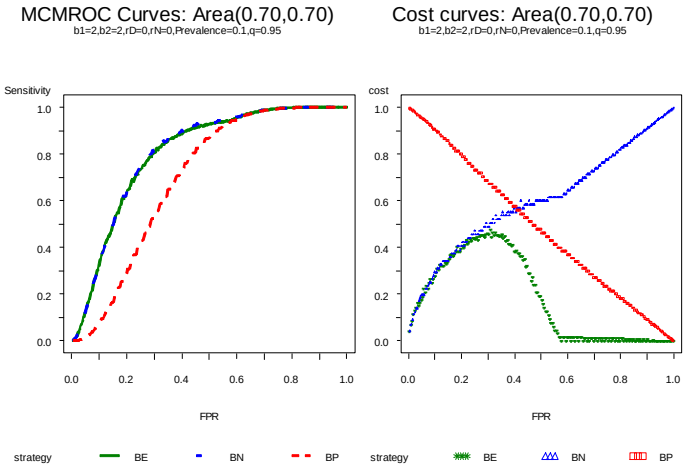


Figure C1.3d: (b1=2, b2=1)



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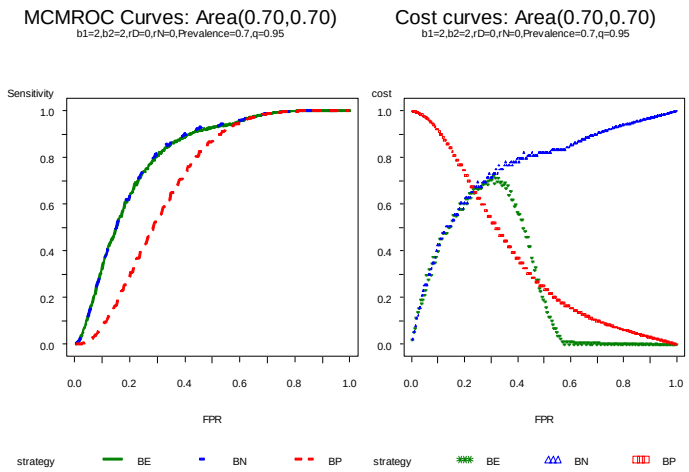

Figure C1.3e: (b1=2, b2=2)

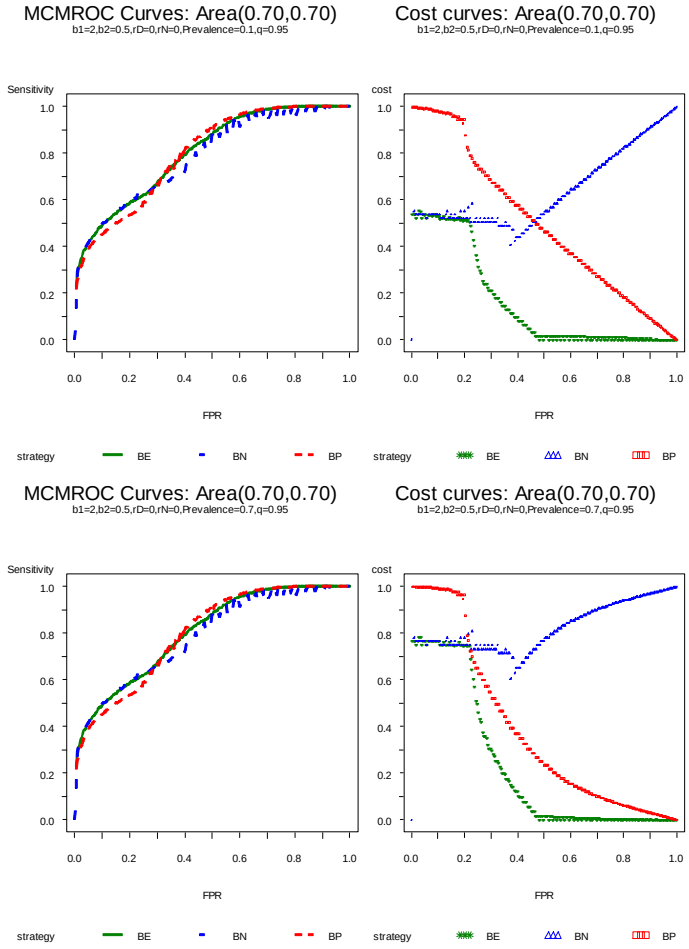

Figure C1.3f: (b1=2, b2=0.5)

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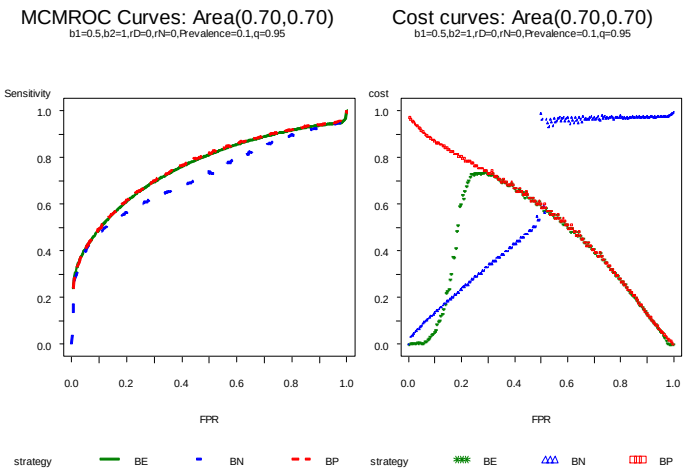


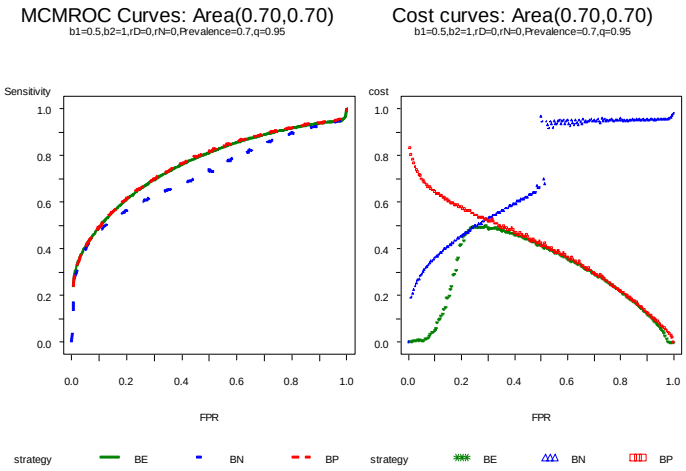
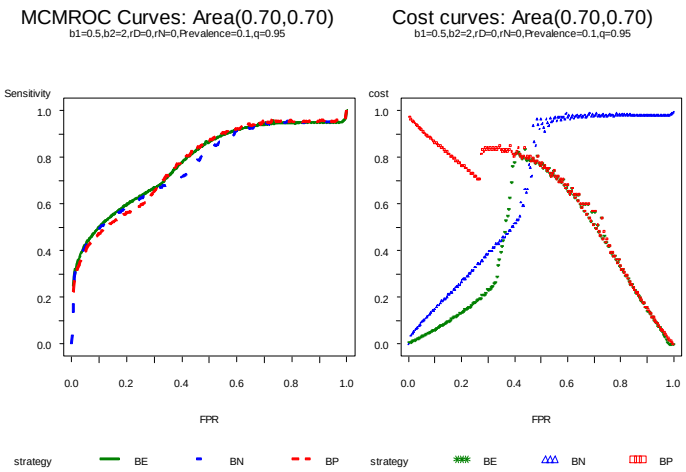


Figure C1.3g: (b1=0.5, b2=1)



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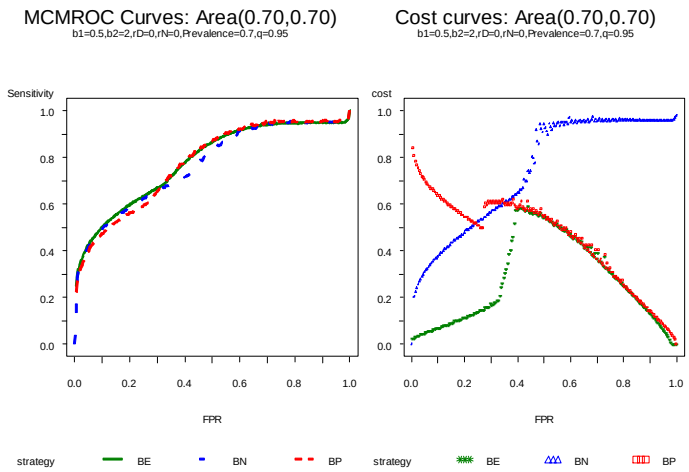
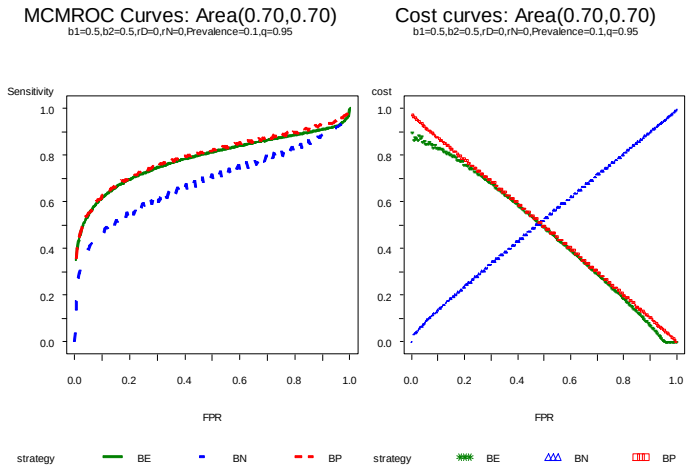


Figure C1.3h: (b1=0.5, b2=2)



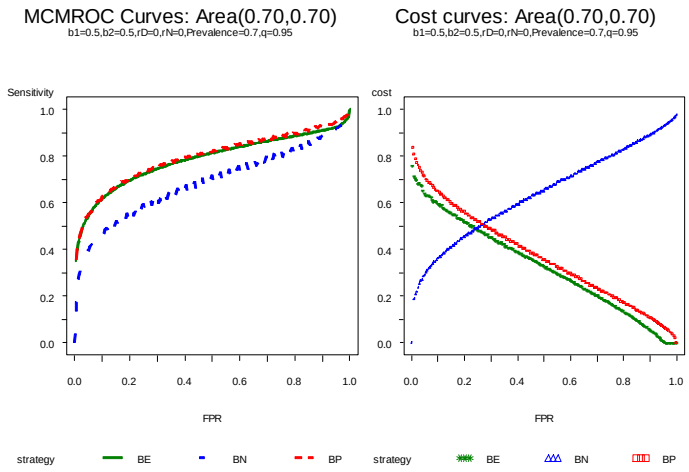


Figure C1.3i: (b1=0.5, b2=0.5)

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C2 Dependent of the tests ($\rho_D = 0.3, \rho_N = 0.3$)

C2. 1 AUC1 = 0.90, AUC2 = 0.90

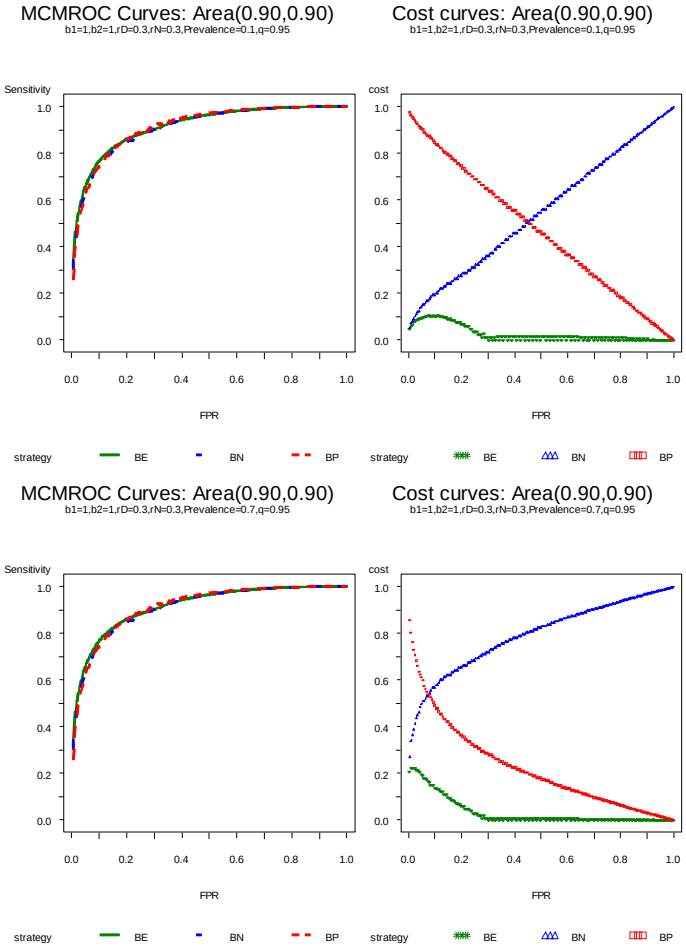
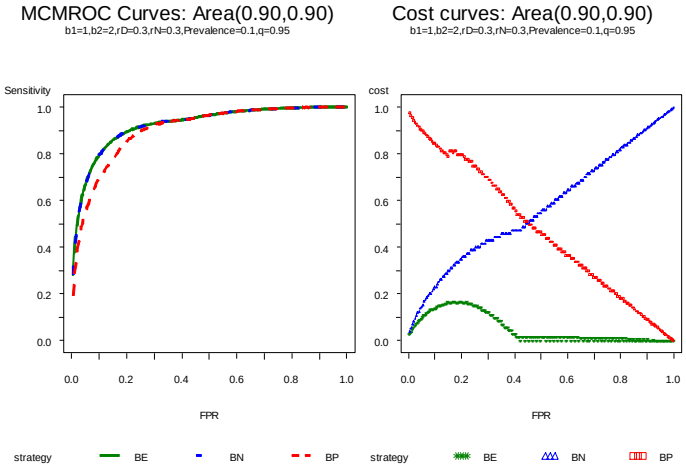


Figure C2. 1a: (b1=1, b2=1)



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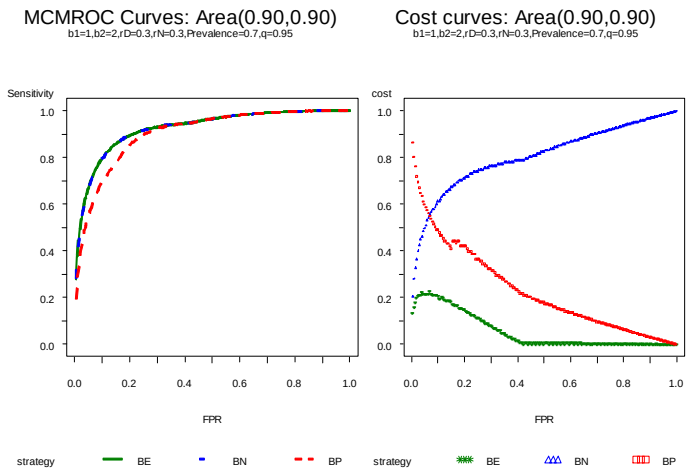
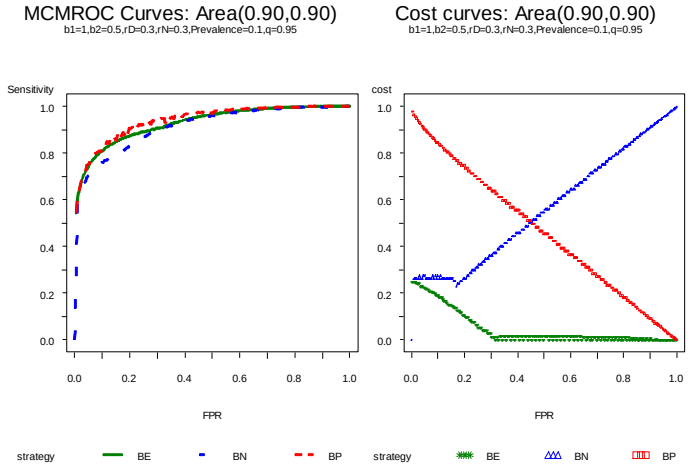


Figure C2. 1b: (b1=1, b2=2)



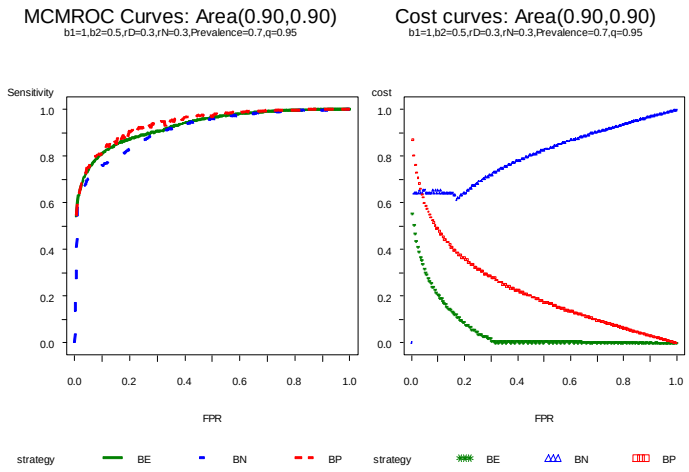


Figure C2. 1c: (b1=1, b2=0.5)

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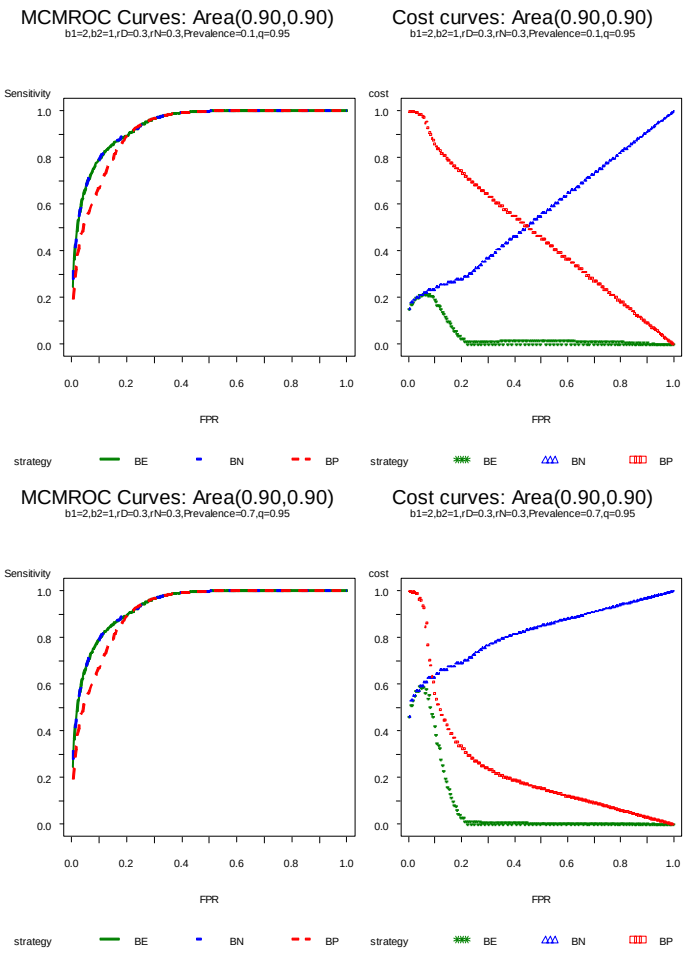
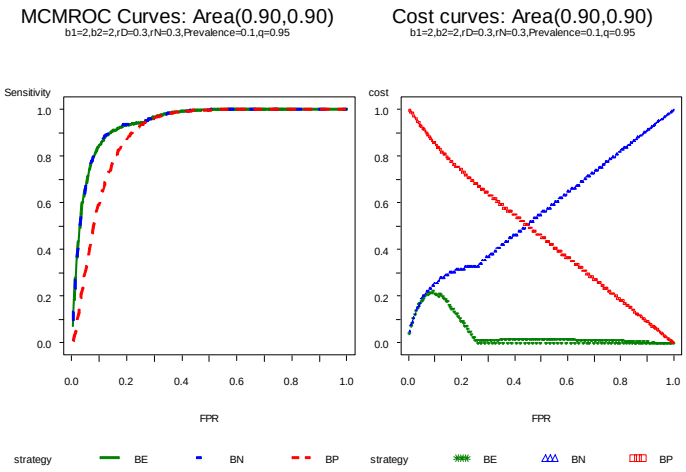


Figure C2. 1d: (b1=2, b2=1)



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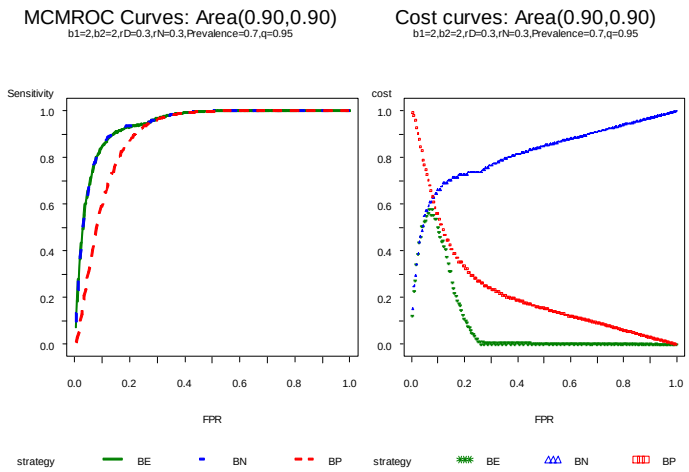
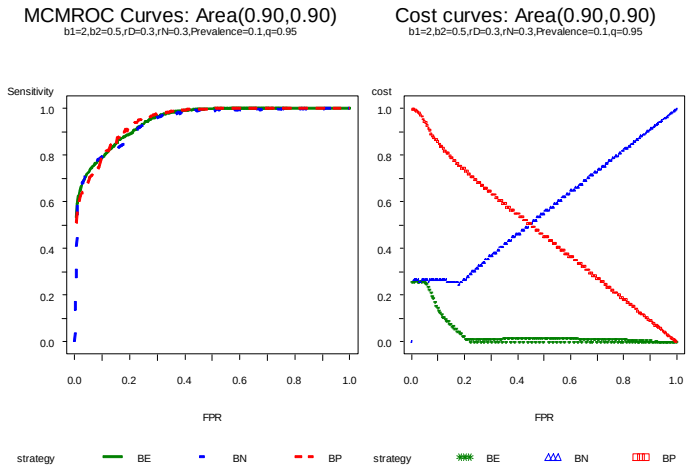


Figure C2. 1e: (b1=2, b2=2)



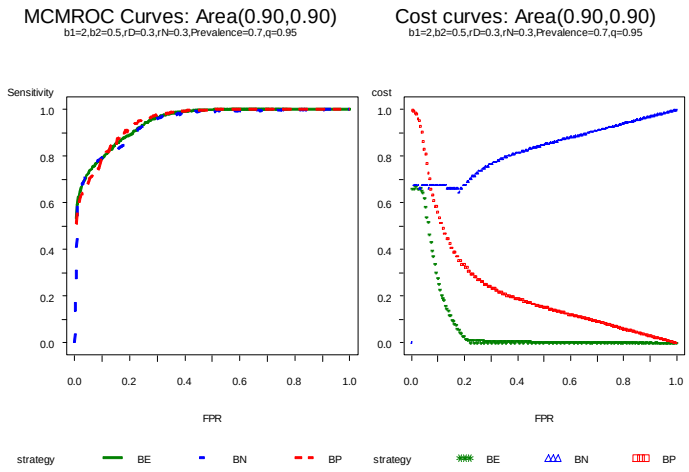


Figure C2. 1f: (b1=2, b2=0.5)

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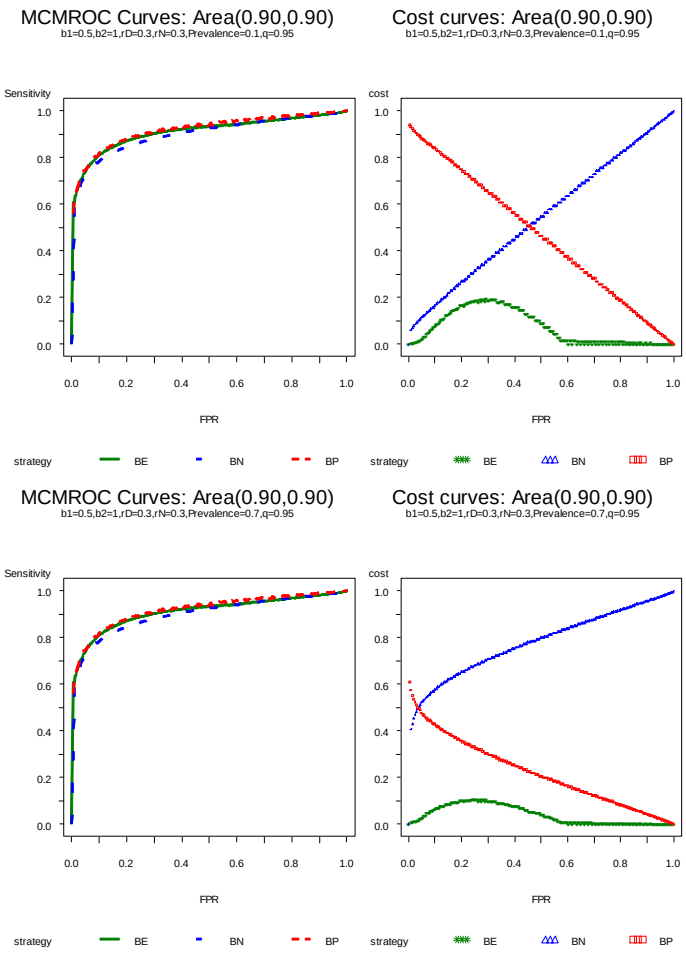
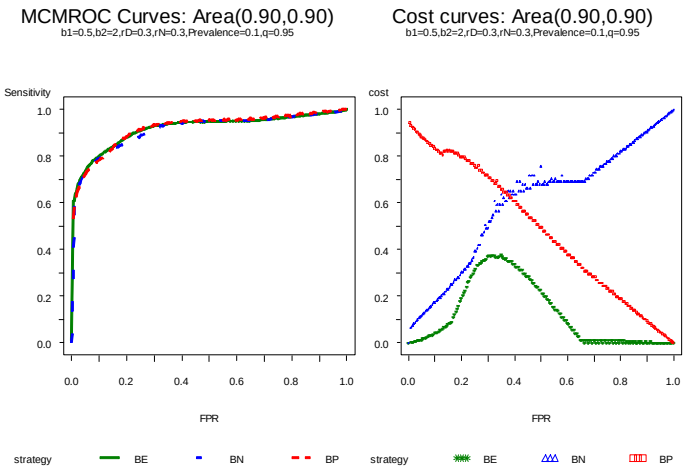


Figure C2. 1g: (b1=0.5, b2=1)



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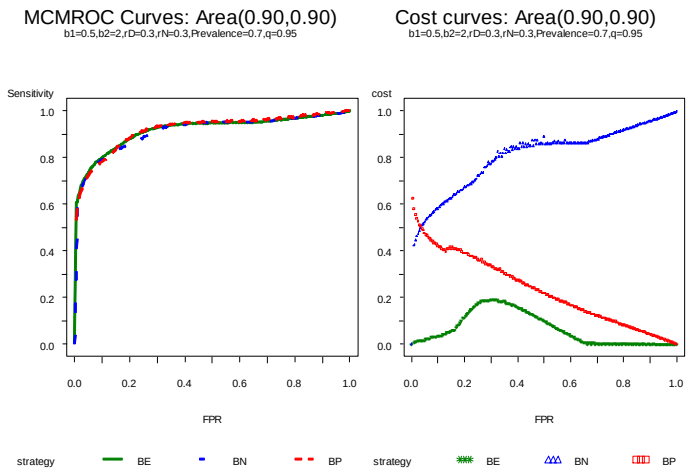
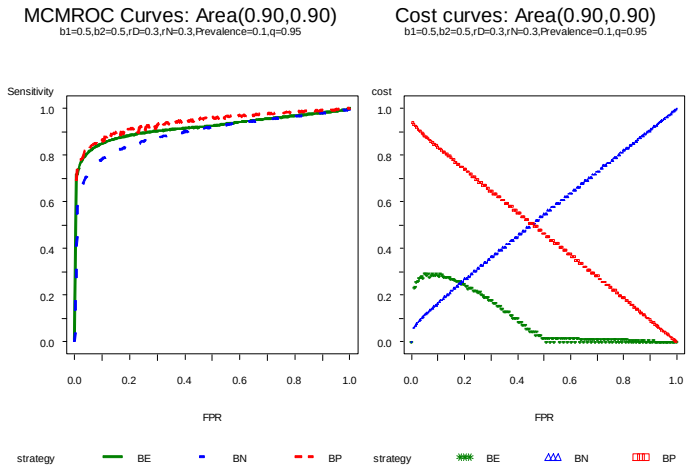


Figure C2. 1h: (b1=0.5, b2=2)



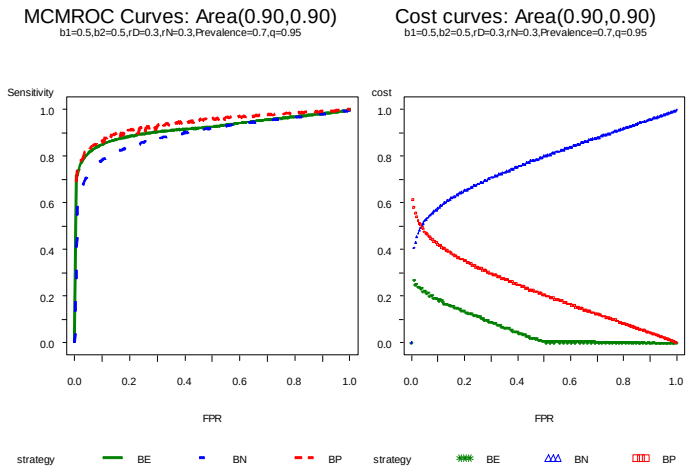


Figure C2. 1i: (b1=0.5, b2=0.5)

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C2. 2 AUC1 = 0.70, AUC2 = 0.90

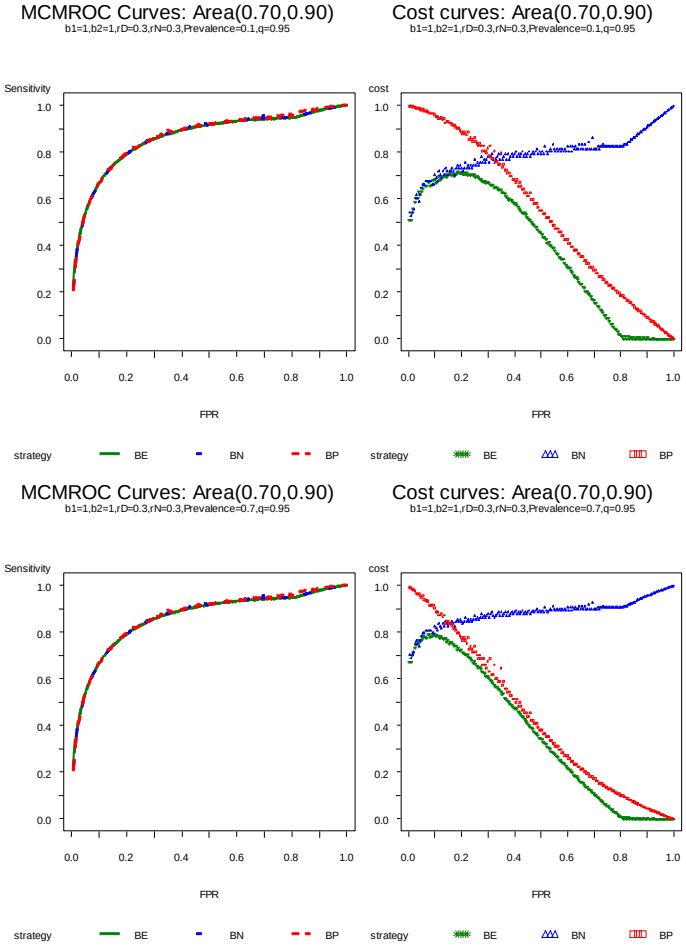
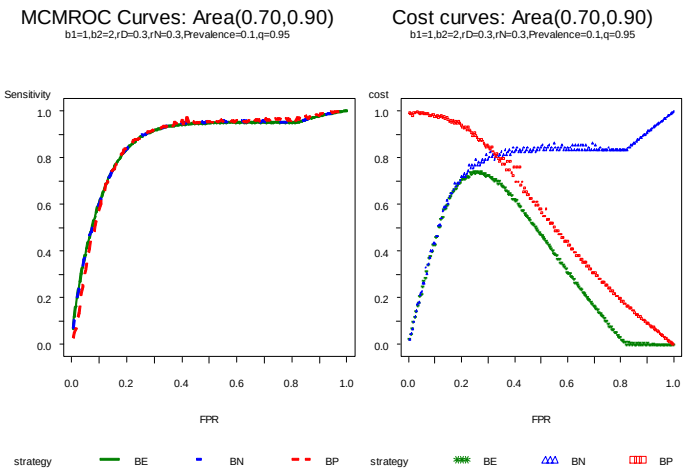


Figure C2. 2a: (b1=1, b2=1)



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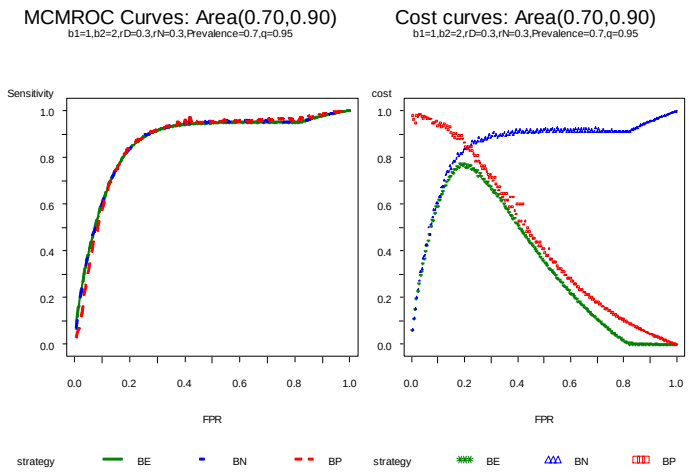
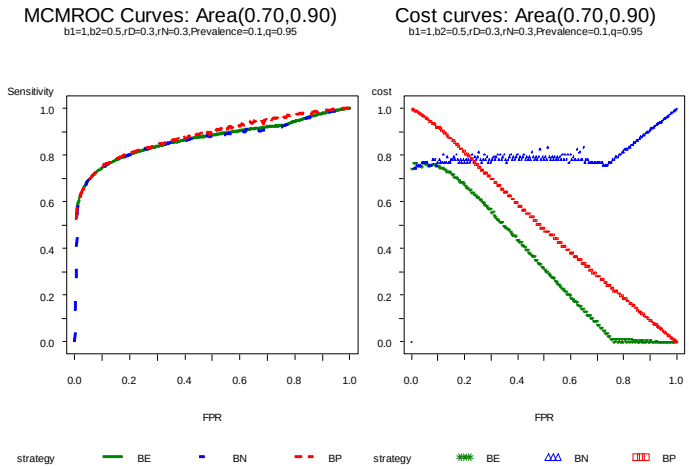


Figure C2. 2b: (b1=1, b2=2)



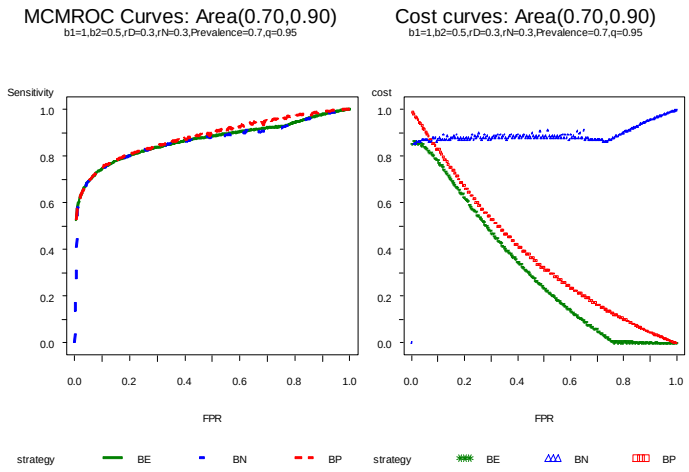


Figure C2. 2c: (b1=1, b2=0.5)

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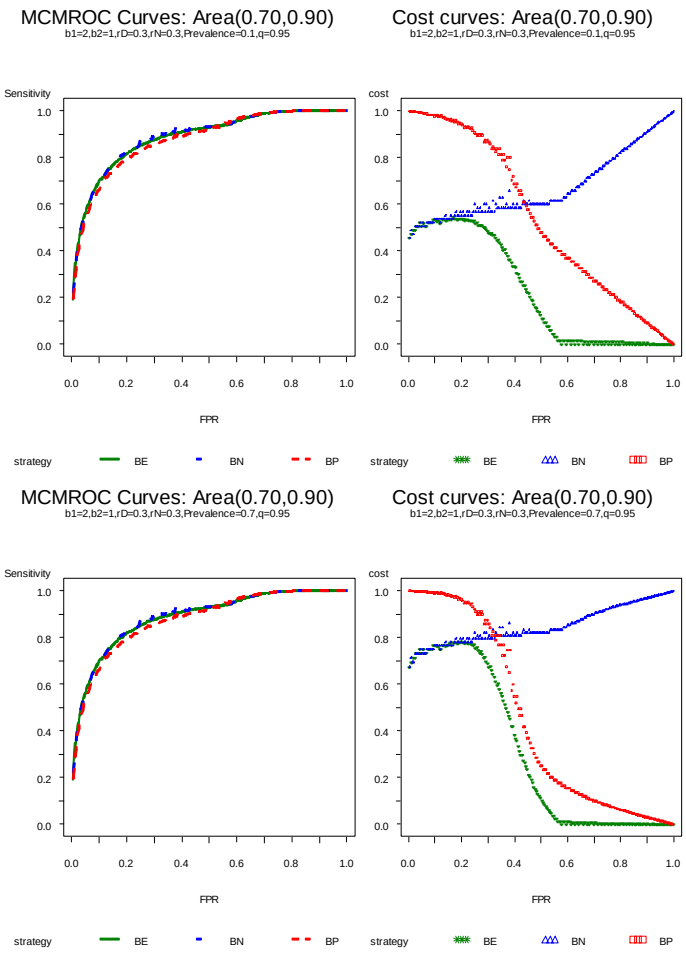
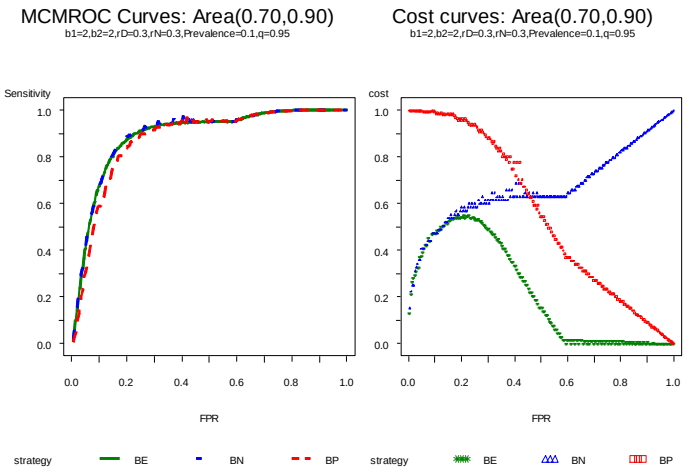


Figure C2. 2d: (b1=2, b2=1)



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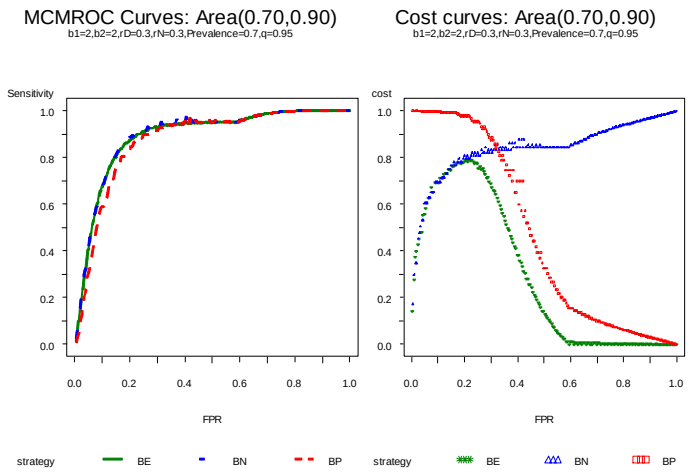

Figure C2. 2e: (b1=2, b2=2)

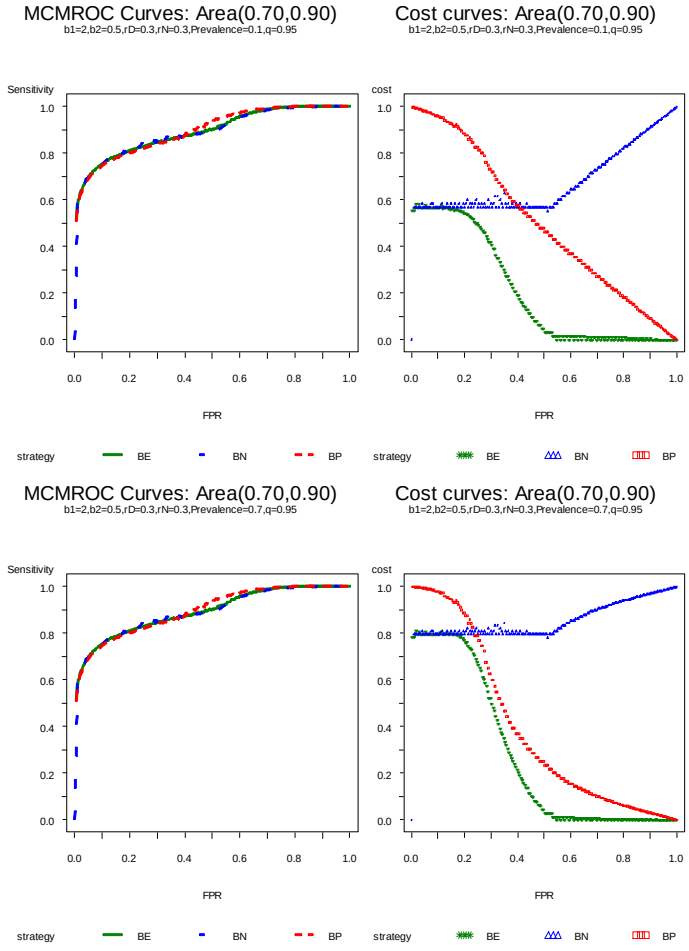

Figure C2. 2f: (b1=2, b2=0.5)

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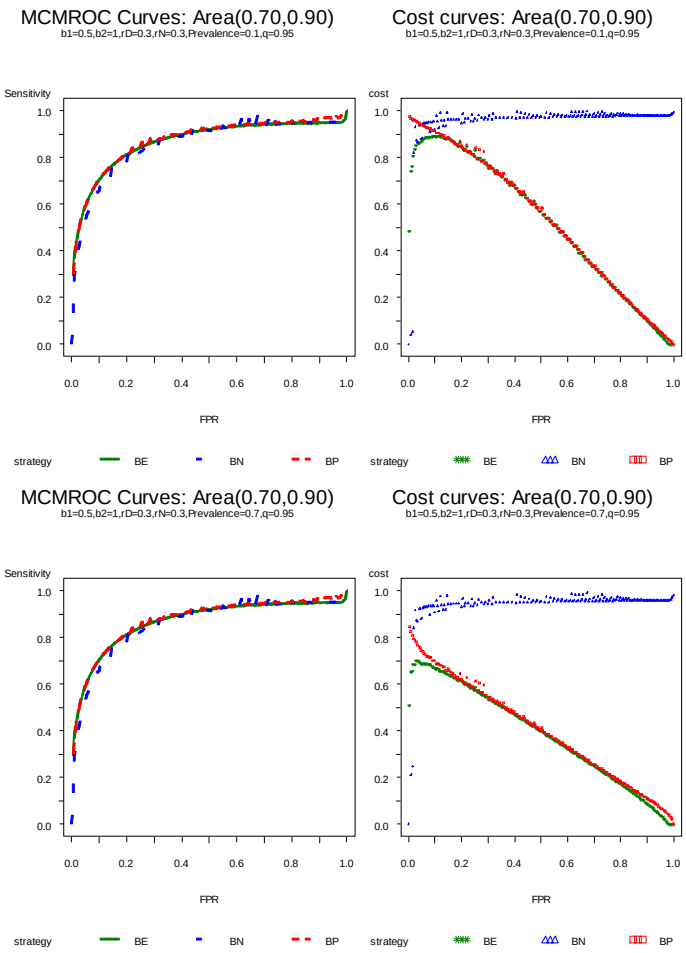
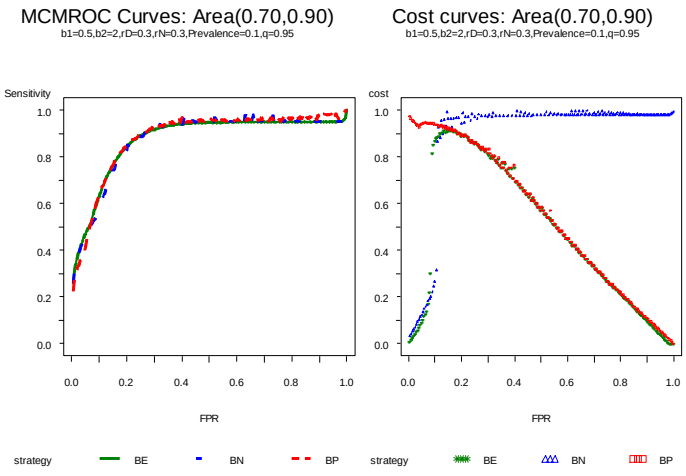


Figure C2. 2g: (b1=0.5, b2=1)



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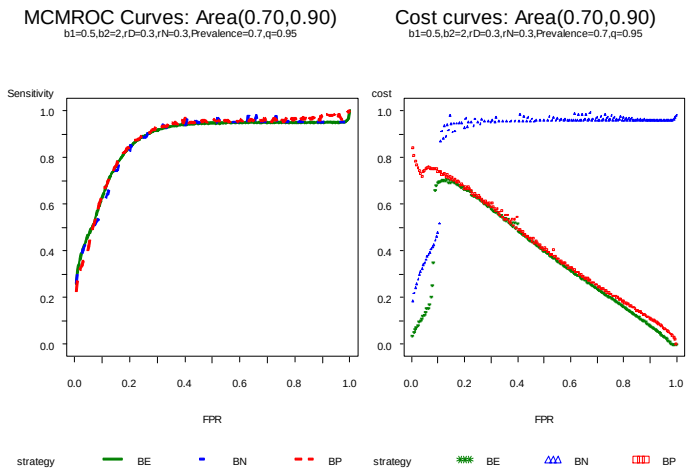
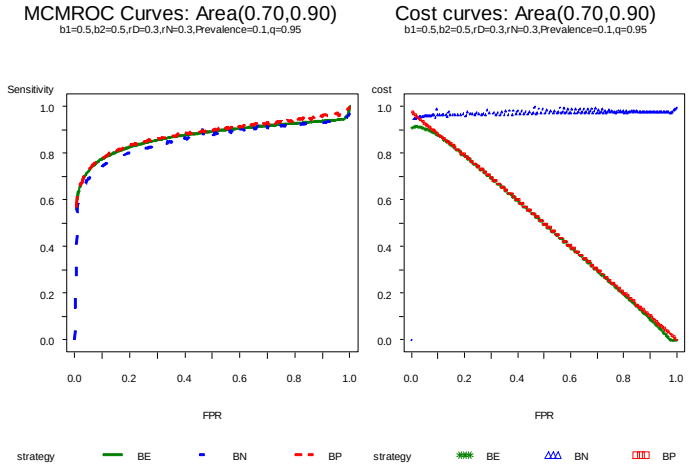


Figure C2. 2h: (b1=0.5, b2=2)



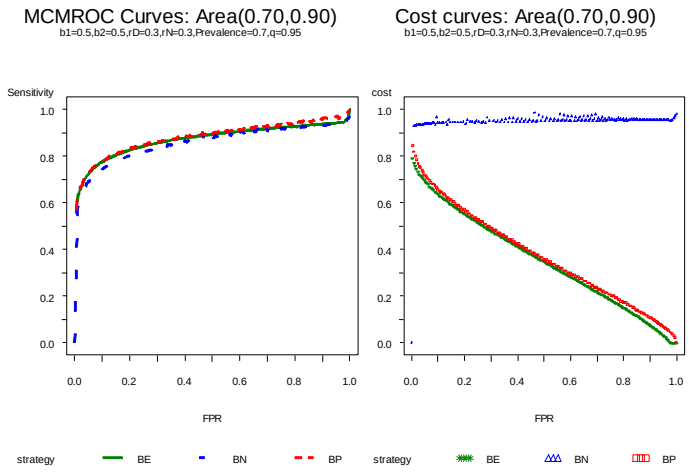


Figure C2. 2i: (b1=0.5, b2=0.5)

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C2. 3 AUC1 = 0.70, AUC2 = 0.70

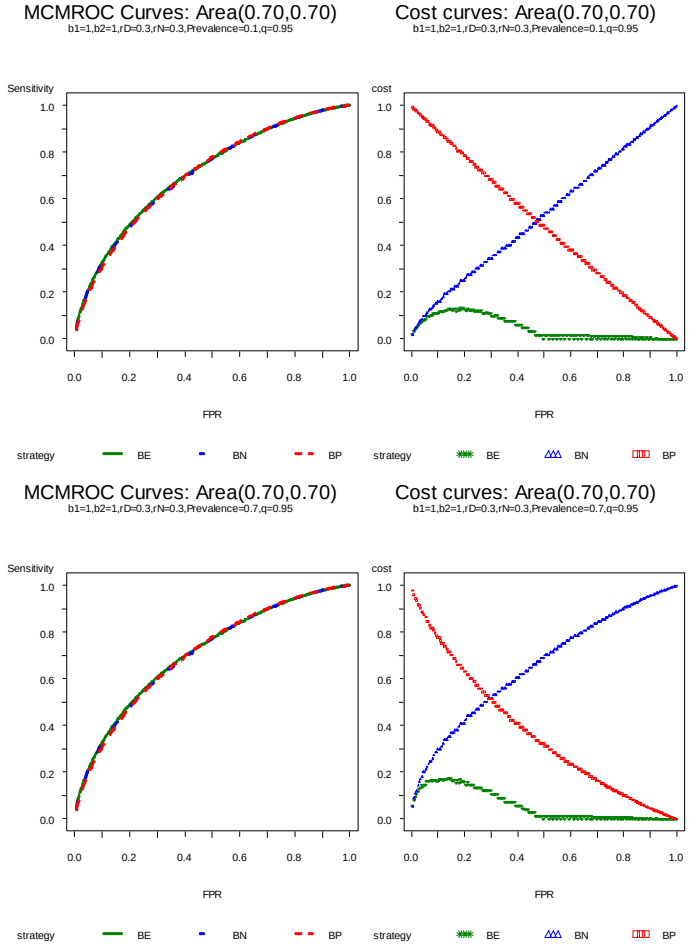
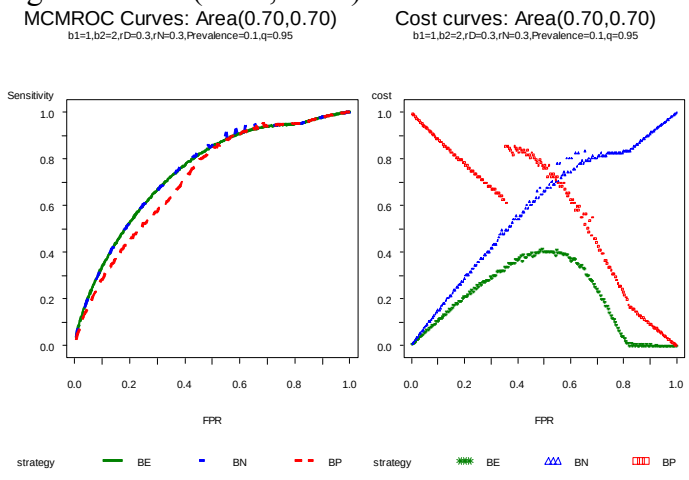


Figure C2. 3a: (b1=1, b2=1)



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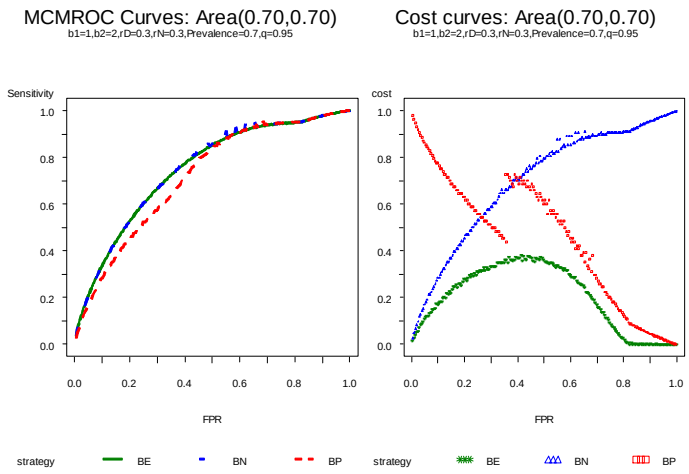

Figure C2. 3b: (b1=1, b2=2)

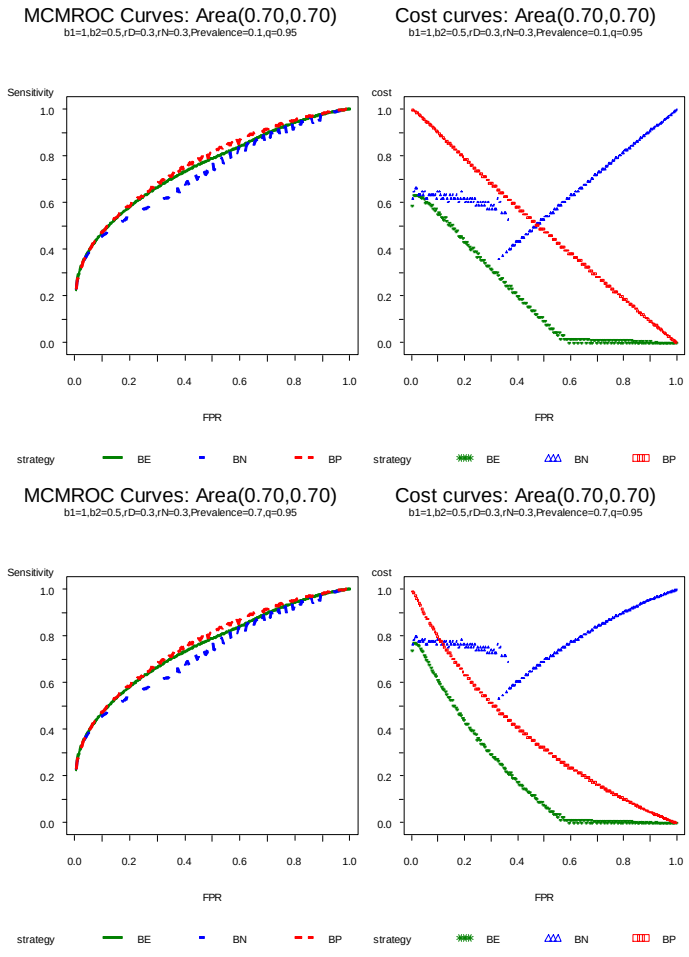

Figure C2. 3c: (b1=1, b2=0.5)

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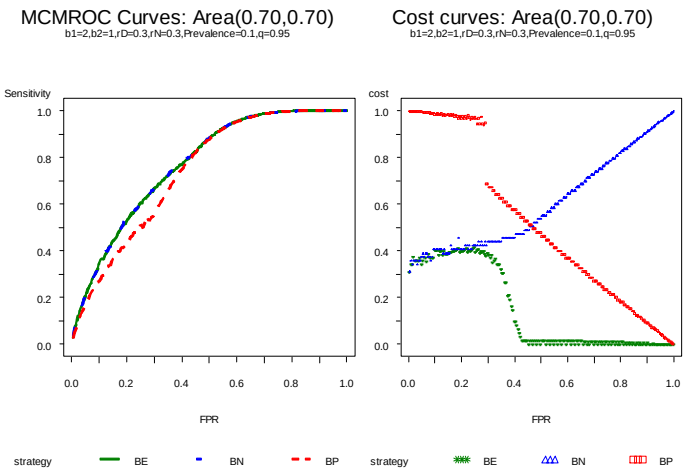


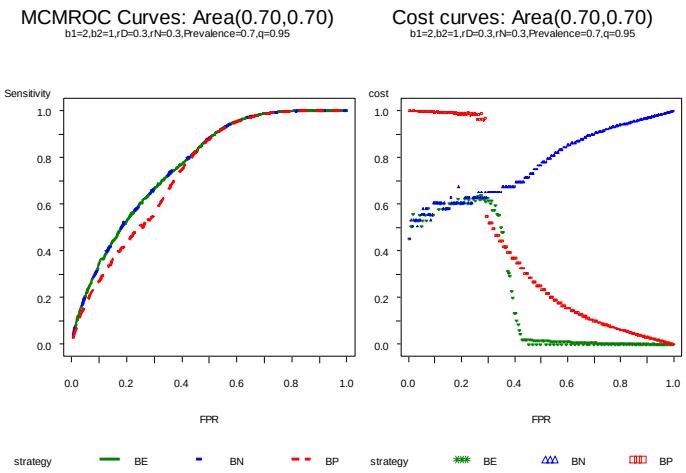
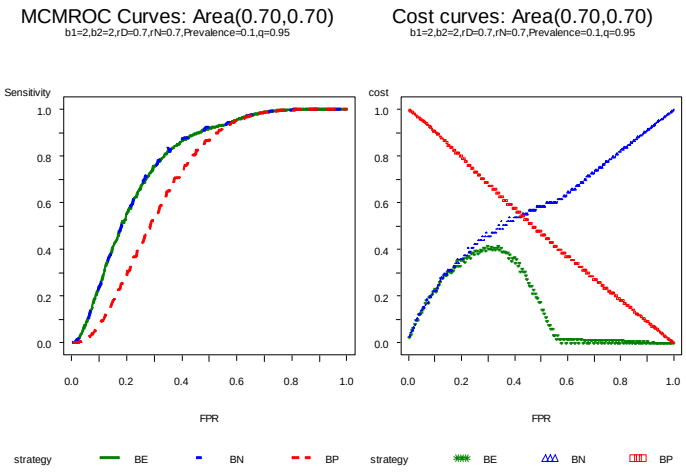


Figure C2. 3d: (b1=2, b2=1)



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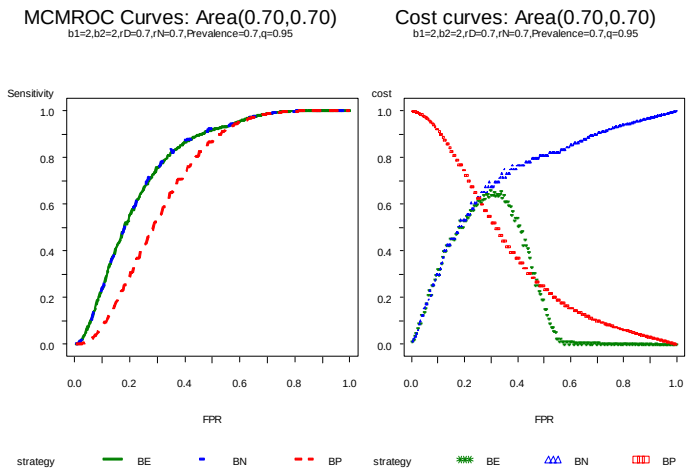
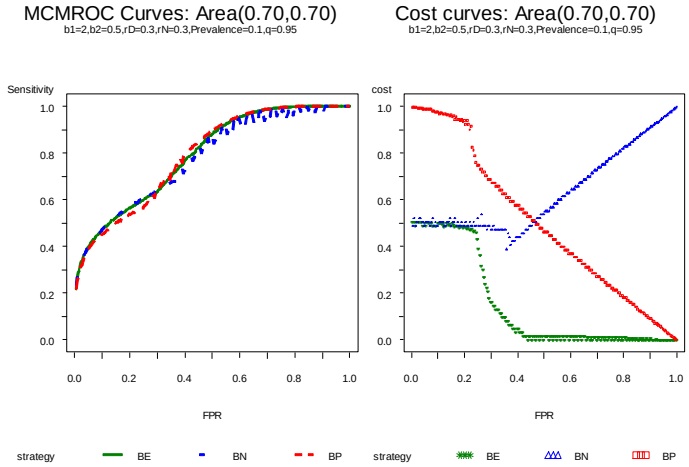


Figure C2. 3e: (b1=2, b2=2)



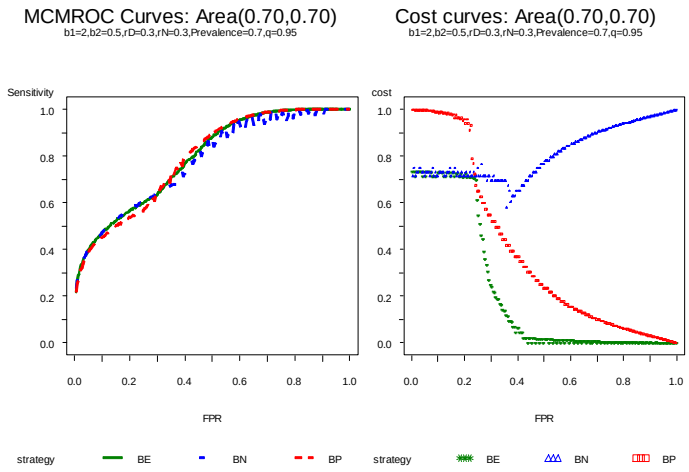


Figure C2. 3f: (b1=2, b2=0.5)

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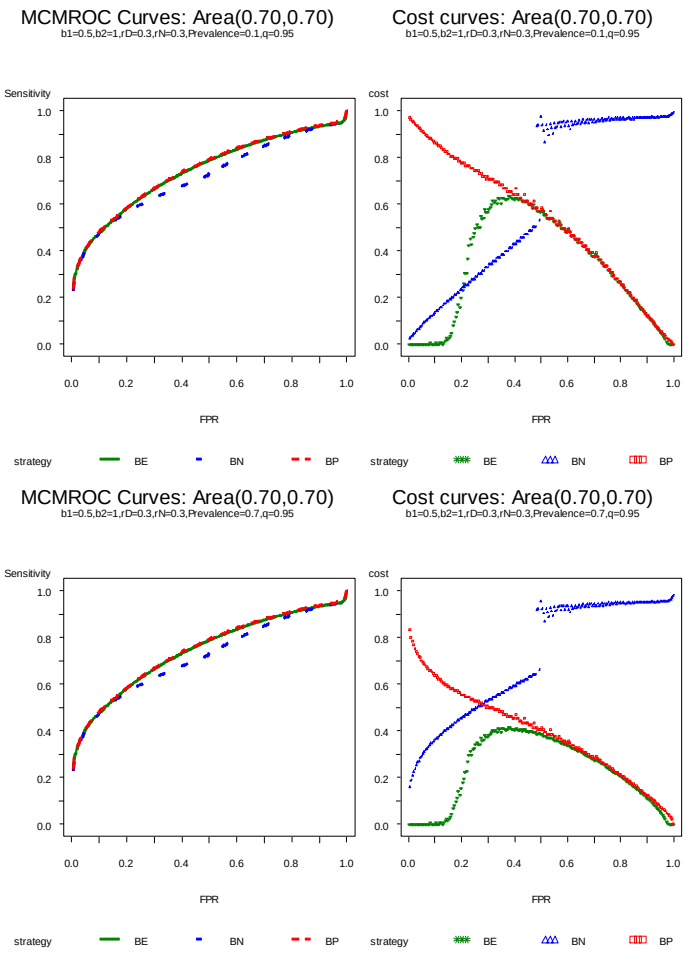
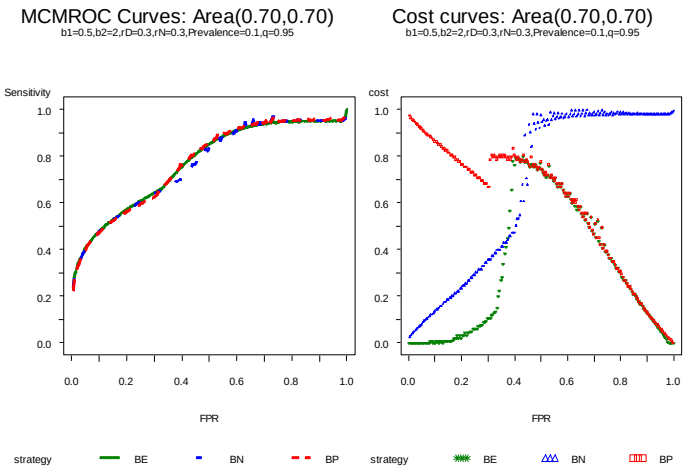


Figure C2. 3g: (b1=0.5, b2=1)



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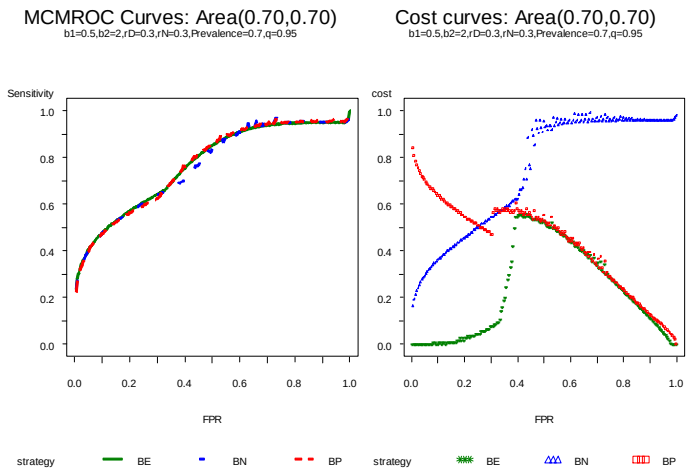
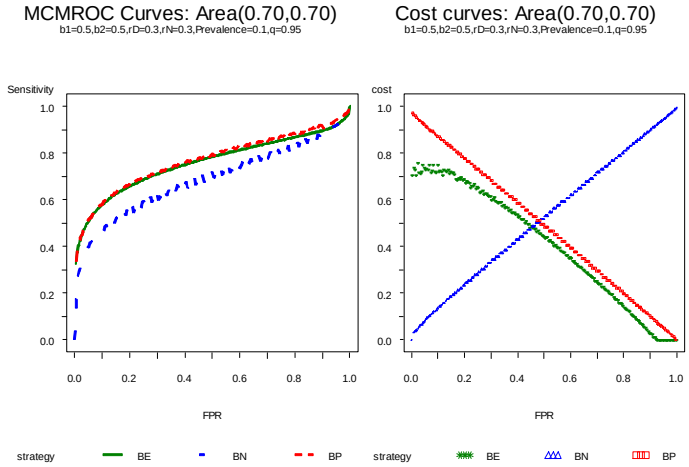


Figure C2. 3h: (b1=0.5, b2=2)



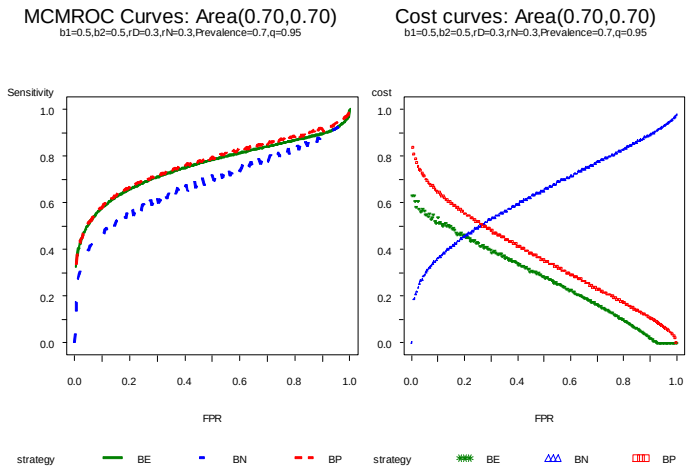


Figure C2. 3i: (b1=0.5, b2=0.5)

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C3 Dependent of the tests $(\rho_D = 0.3, \rho_N = 0.7)$

C3. 1 AUC1 = 0.90, AUC2 = 0.90

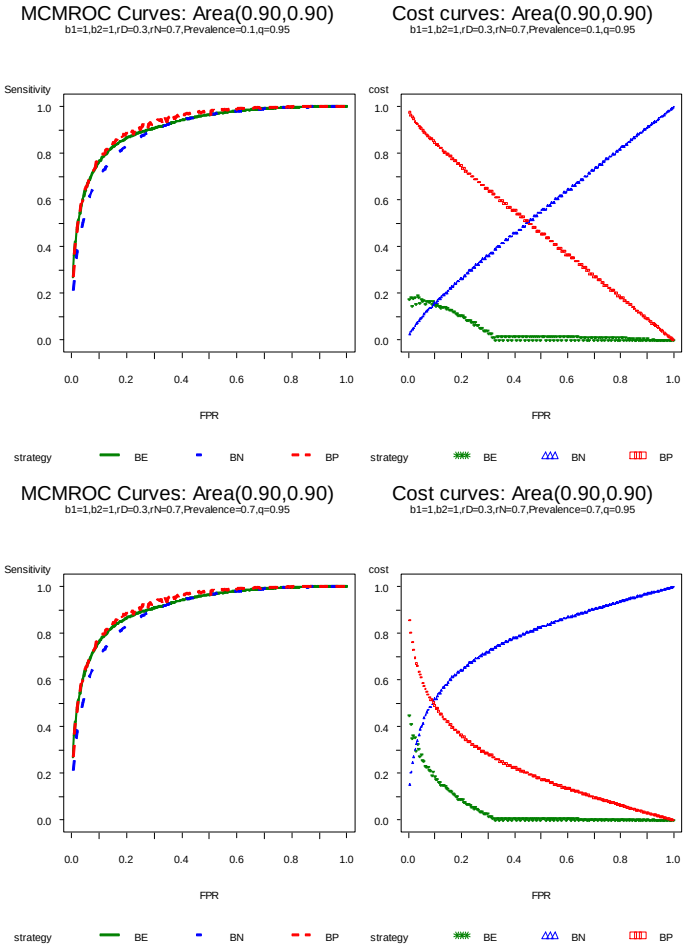
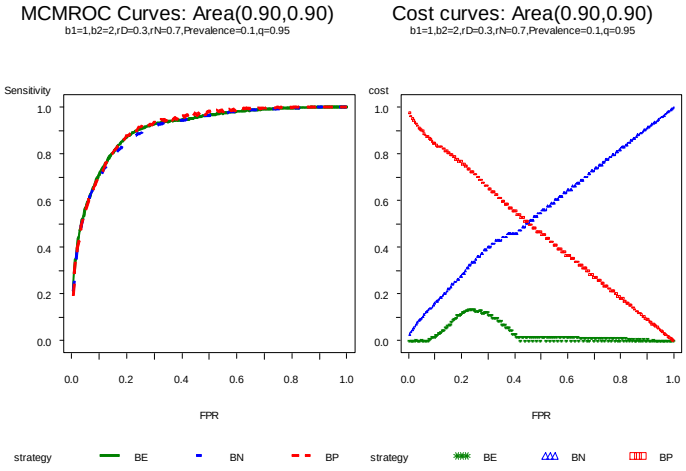


Figure C3. 1a: (b1=1, b2=1)



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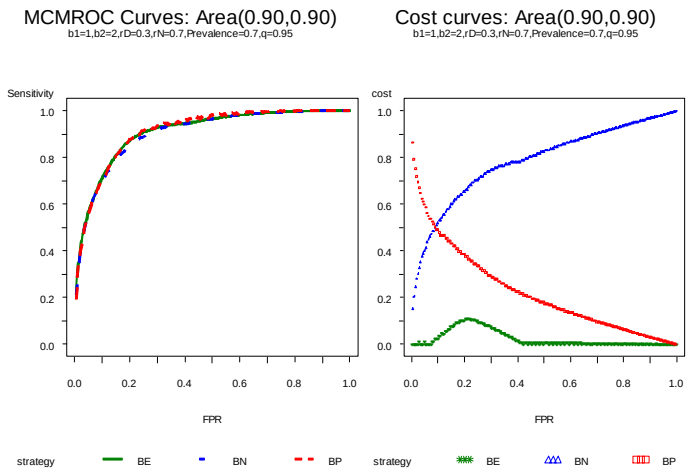
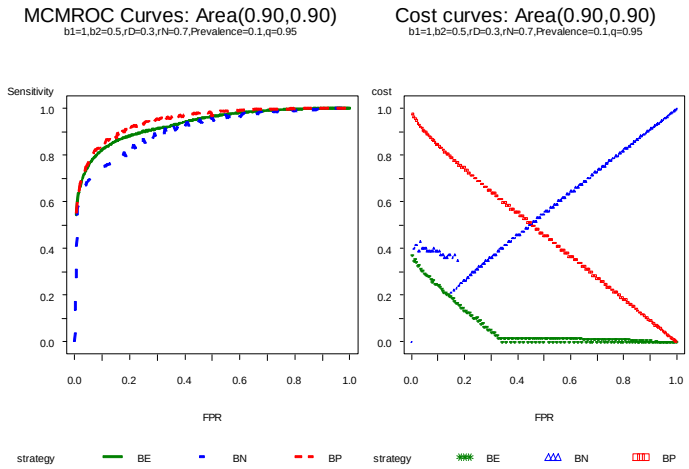


Figure C3. 1b: (b1=1, b2=2)



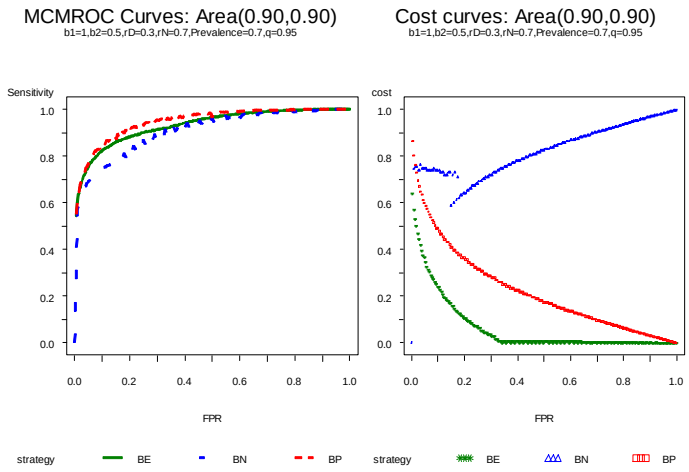


Figure C3. 1c: (b1=1, b2=0.5)

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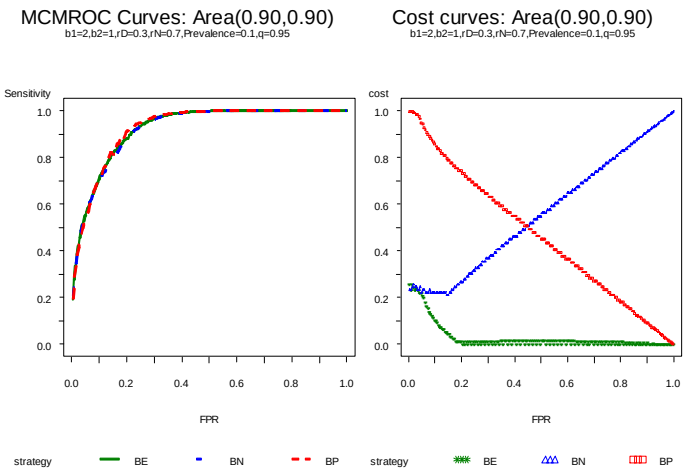


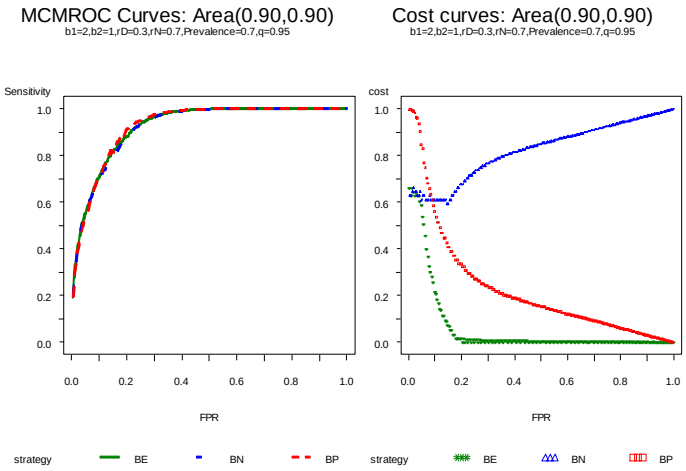
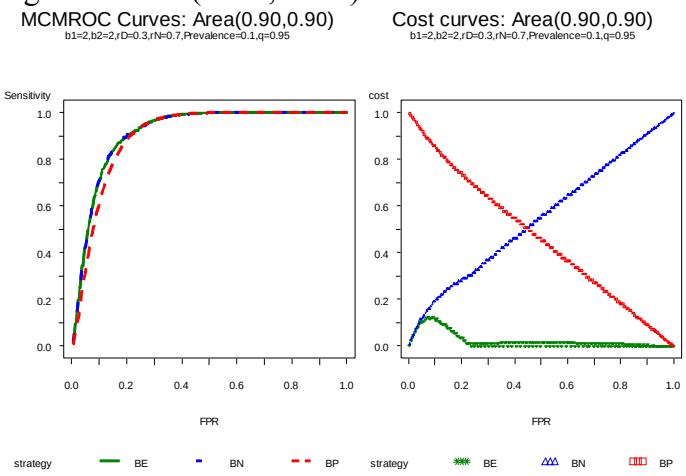


Figure C3. 1d: (b1=2, b2=1)



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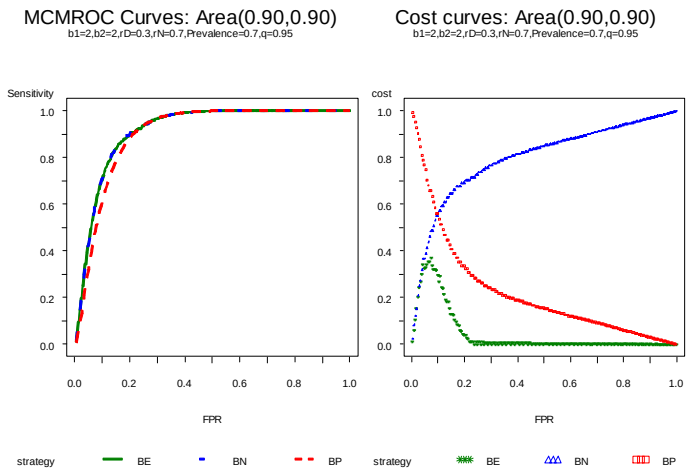
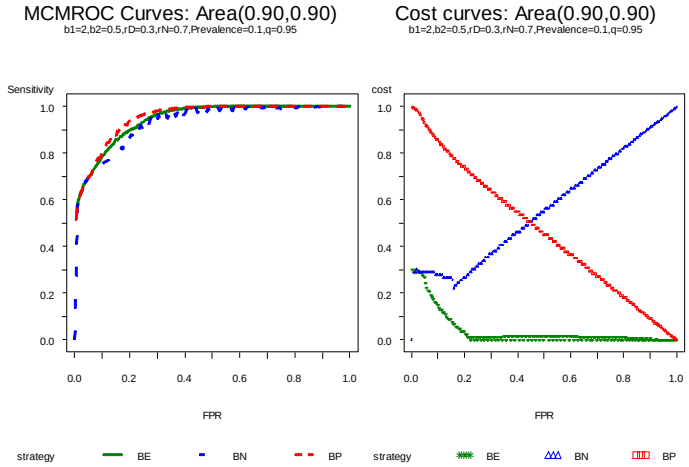


Figure C3. 1e: (b1=2, b2=2)



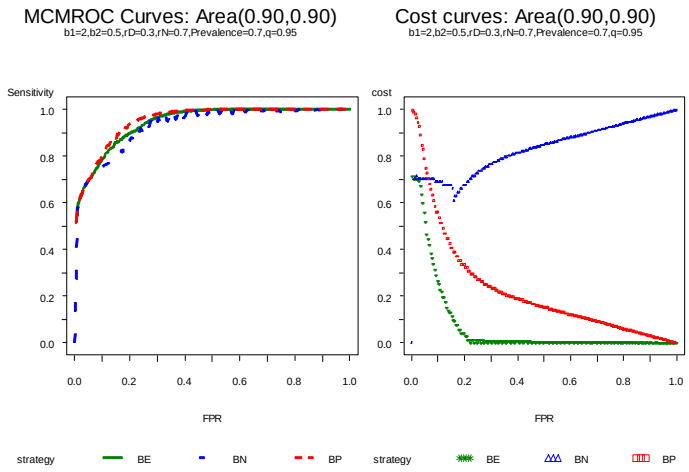


Figure C3. 1f: (b1=2, b2=0.5)

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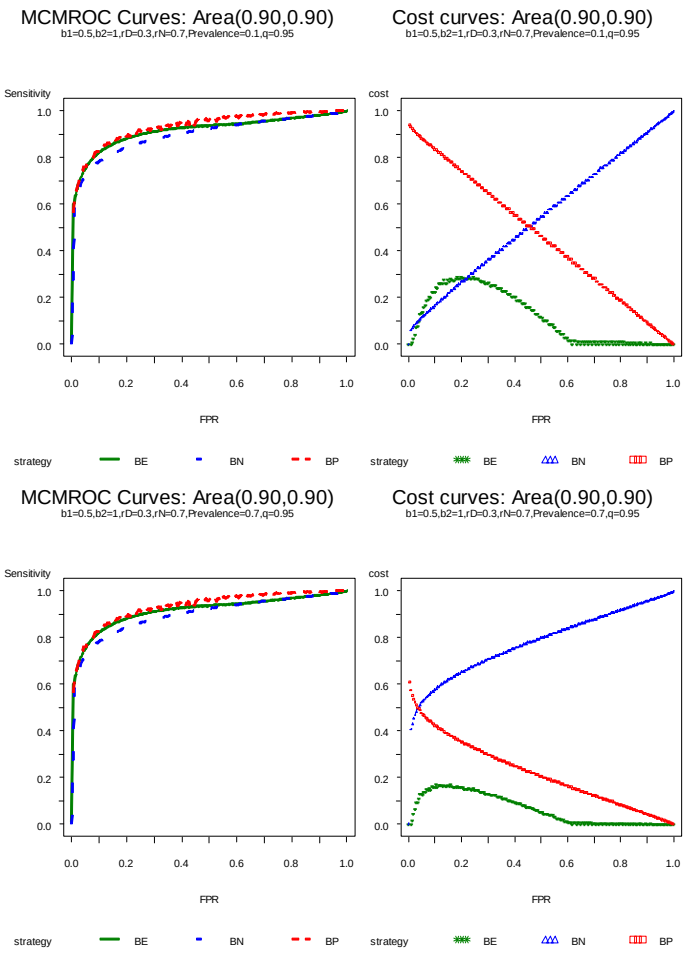
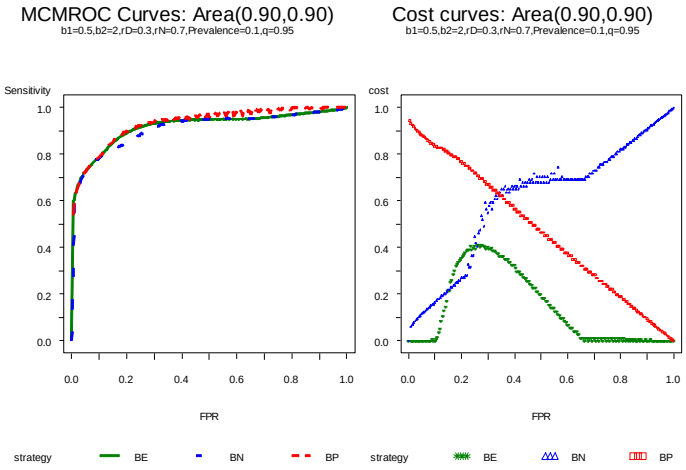


Figure C3. 1g: (b1=0.5, b2=1)



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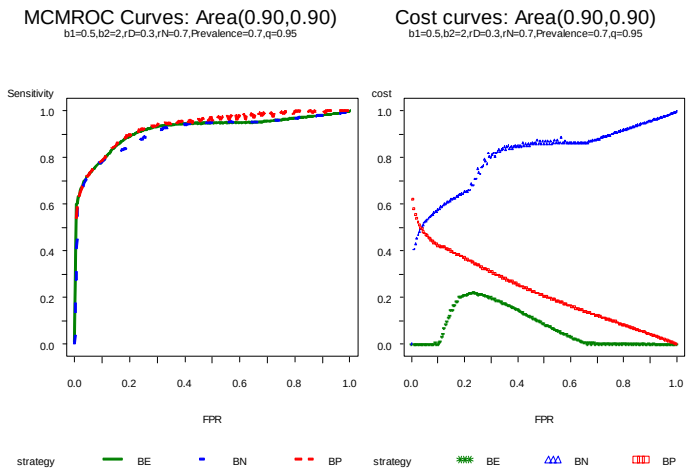
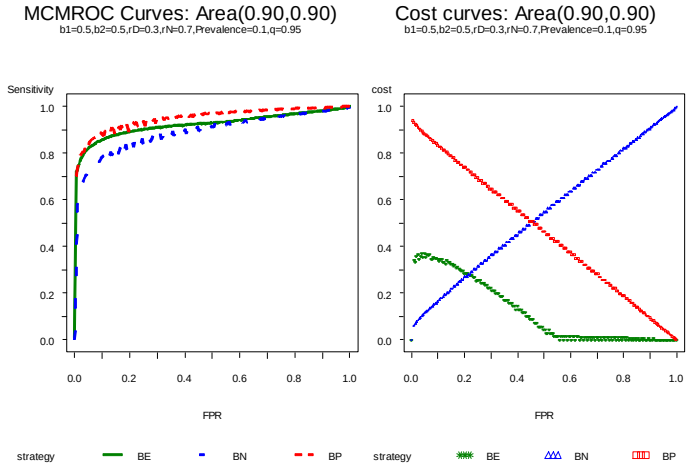


Figure C3. 1h: (b1=0.5, b2=2)



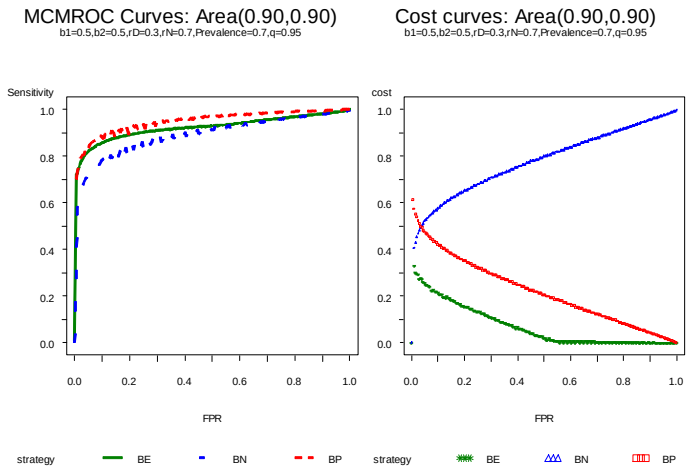


Figure C3. 1i: (b1=0.5, b2=0.5)

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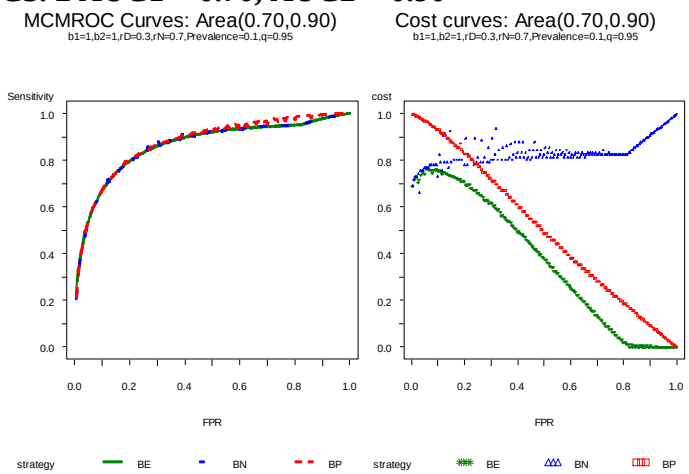
C3. 2 AUC1 = 0.70, AUC2 = 0.90



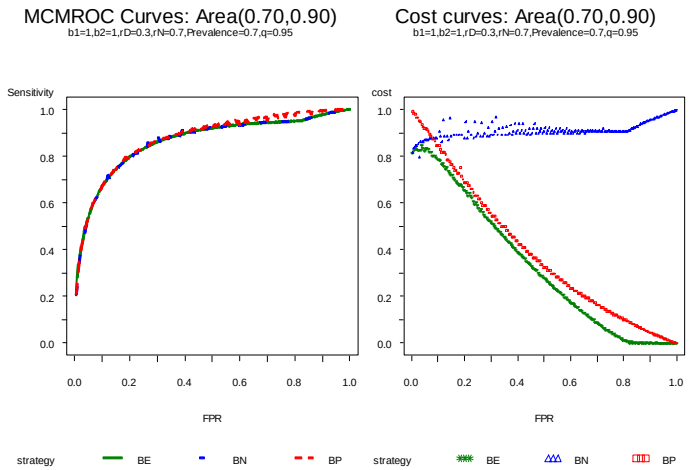
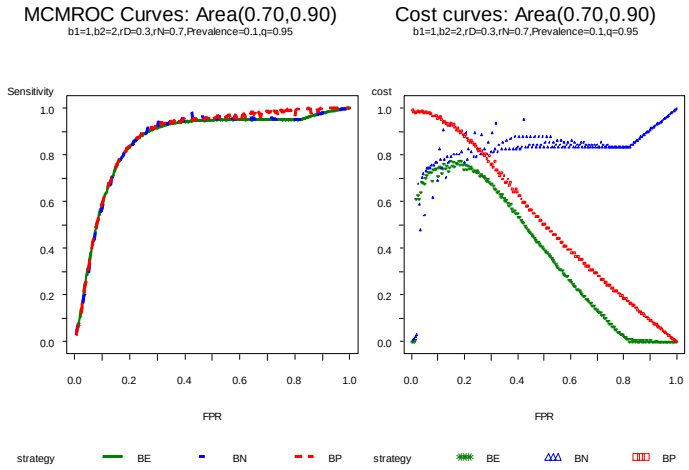


Figure C3. 2a: (b1=1, b2=1)



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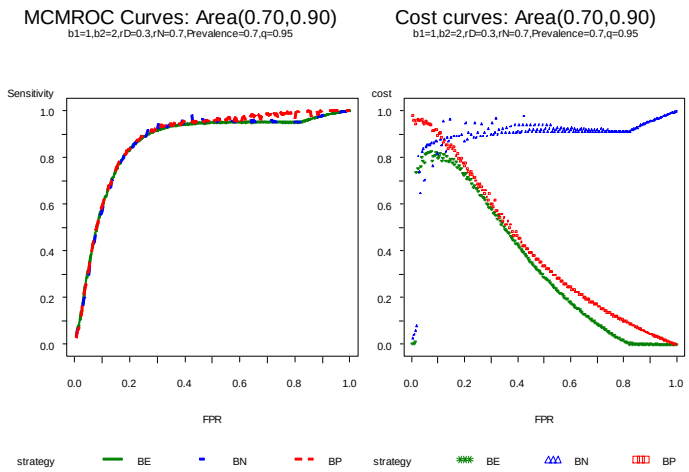
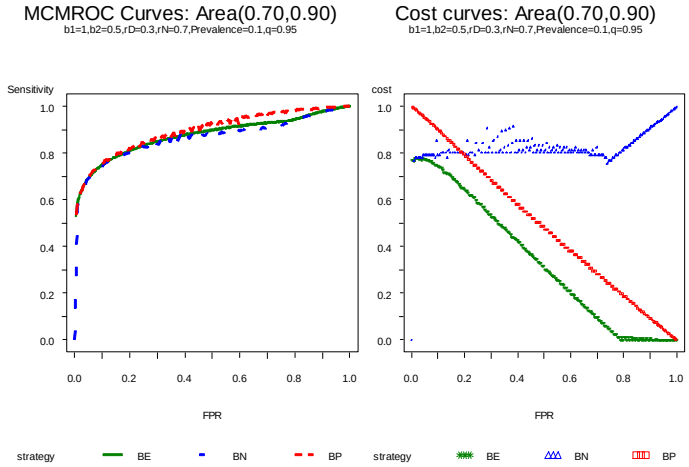


Figure C3. 2b: (b1=1, b2=2)



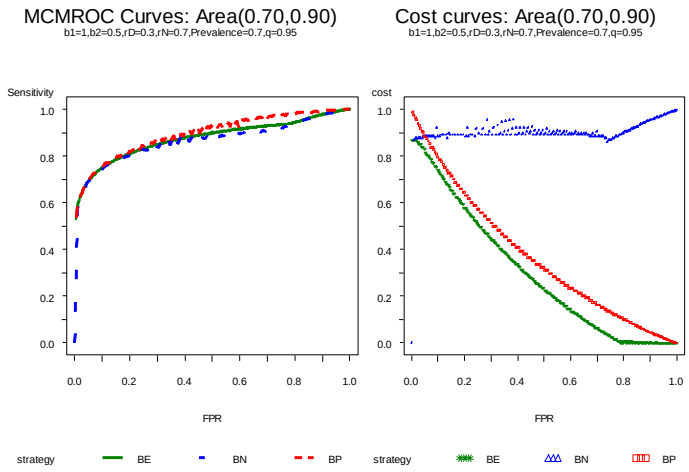


Figure C3. 2c: (b1=1, b2=0.5)

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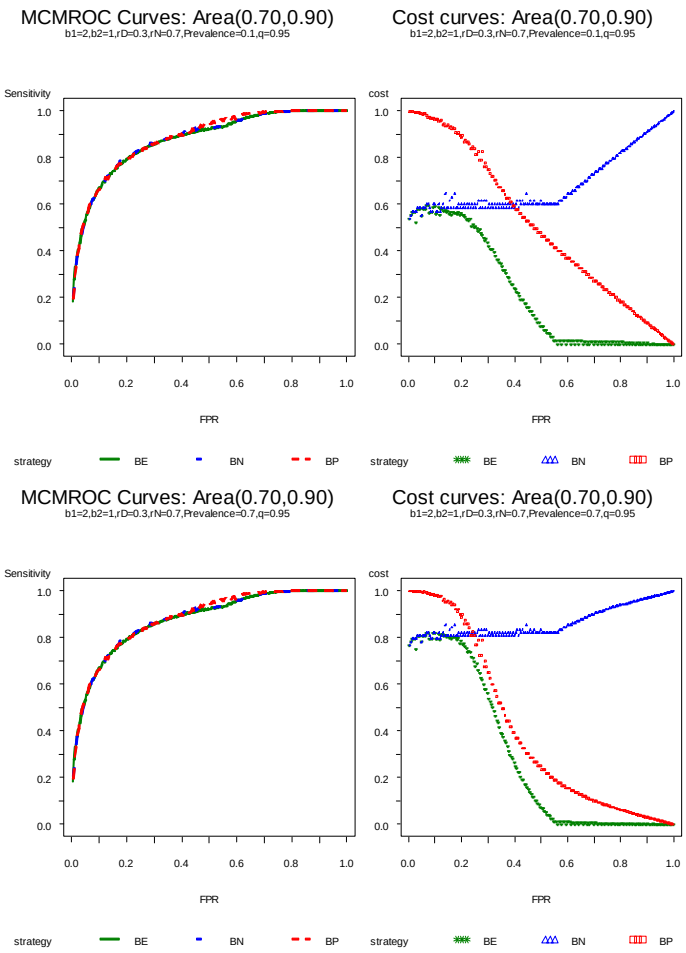
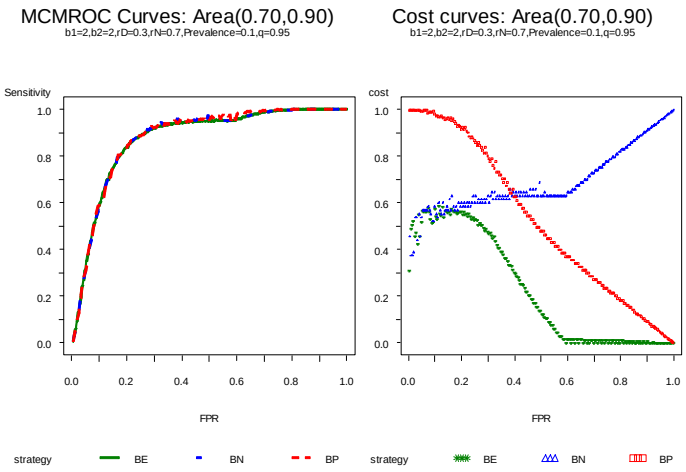


Figure C3. 2d: (b1=2, b2=1)



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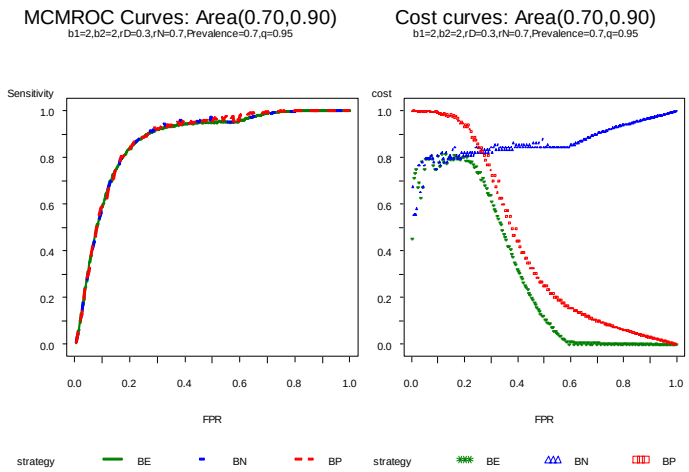

Figure C3. 2e: (b1=2, b2=2)

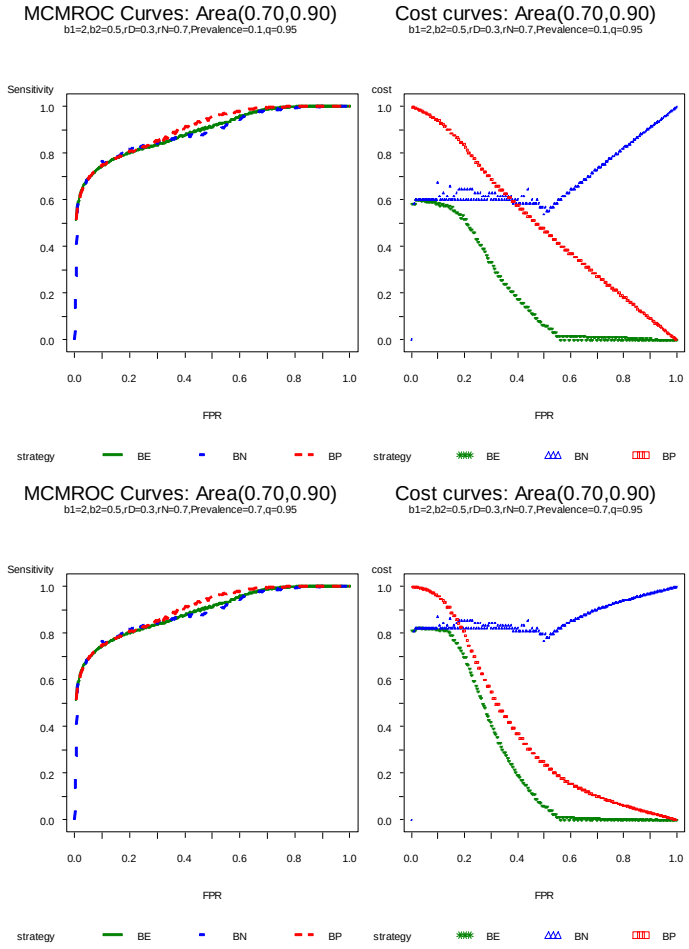

Figure C3. 2f: (b1=2, b2=0.5)

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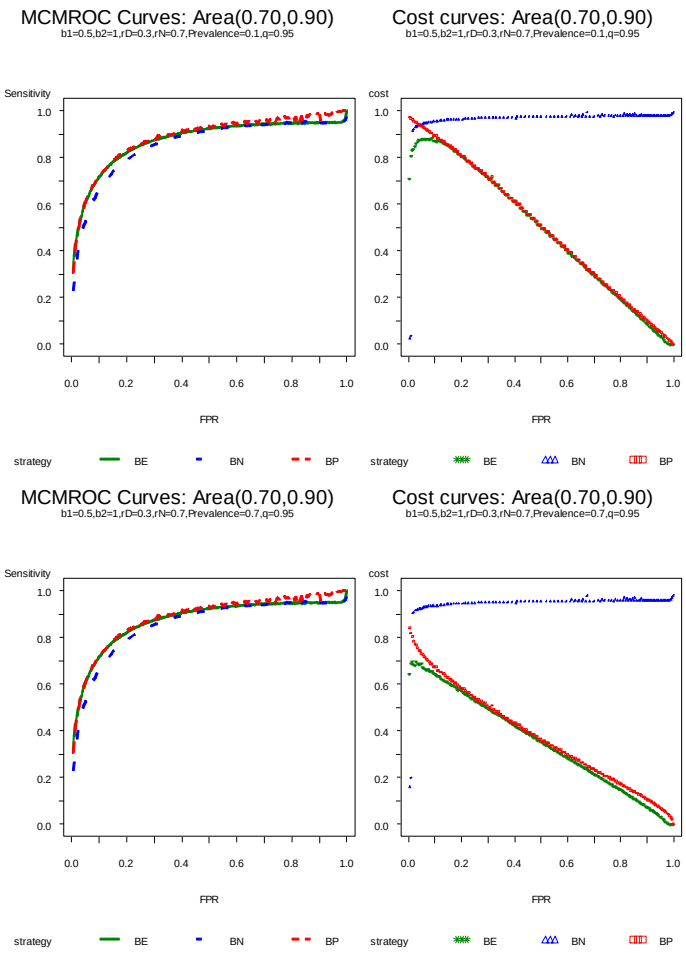
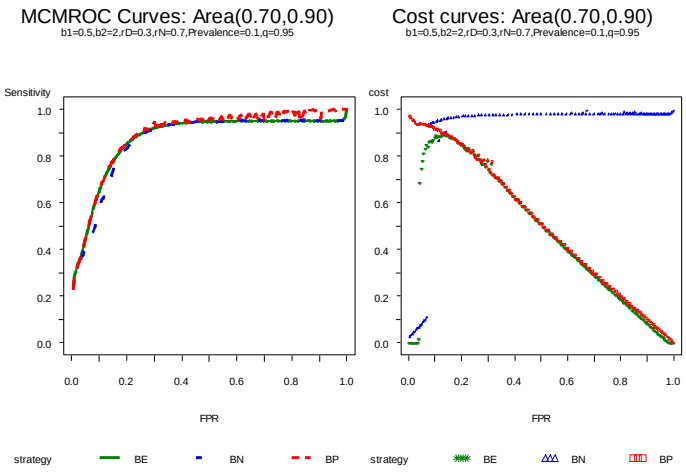


Figure C3. 2g: (b1=0.5, b2=1)



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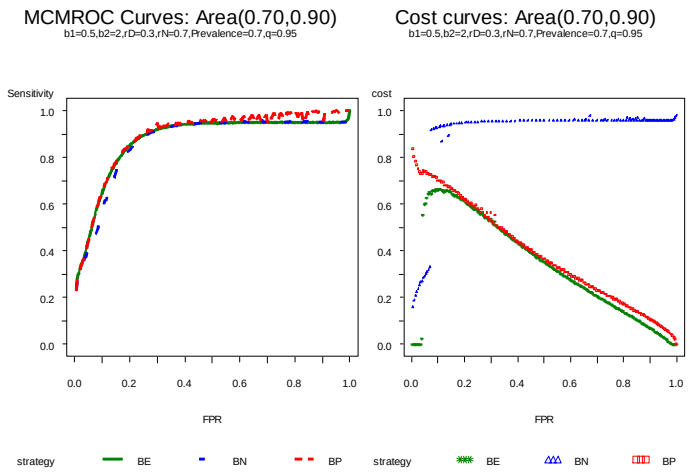
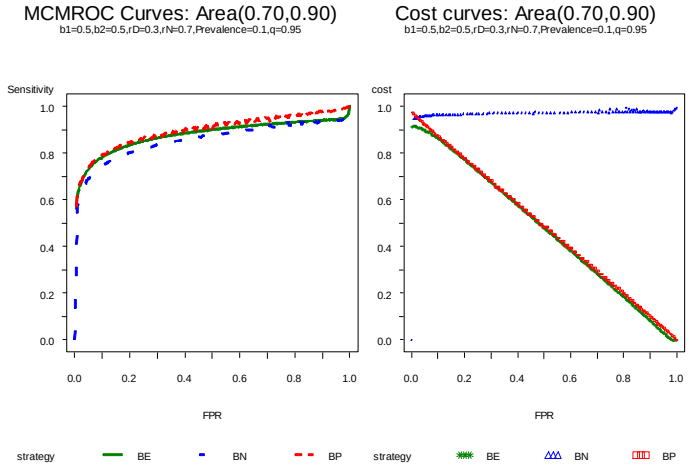


Figure C3. 2h: (b1=0.5, b2=2)



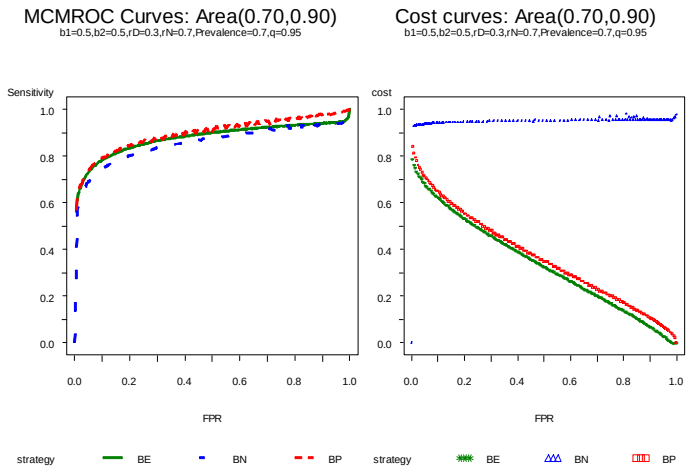


Figure C3. 2i: (b1=0.5, b2=0.5)

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C3. 3 AUC1 = 0.70, AUC2 = 0.70

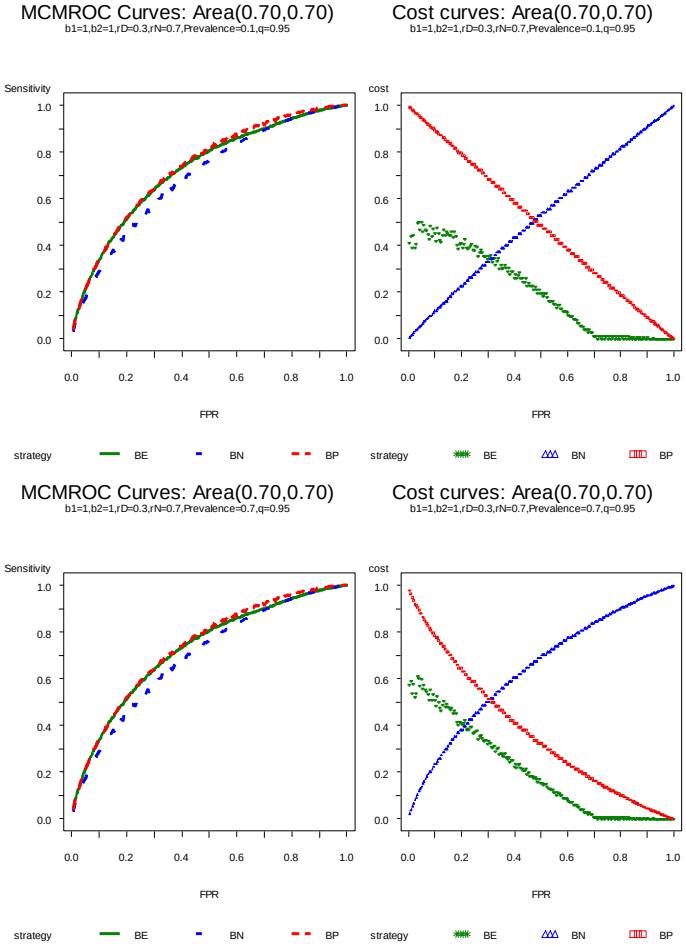
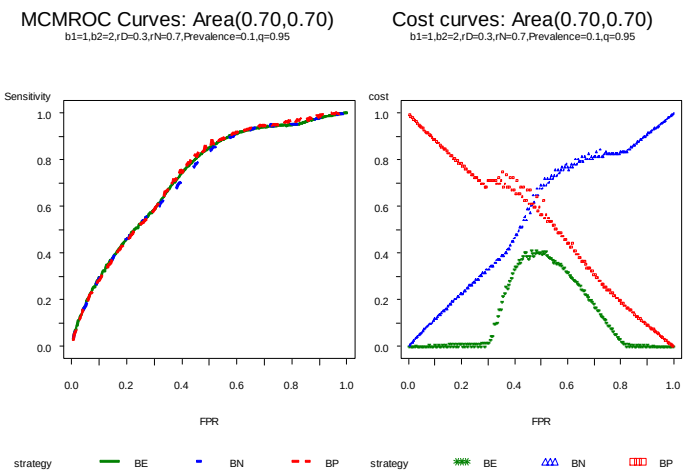


Figure C3. 3a: (b1=1, b2=1)



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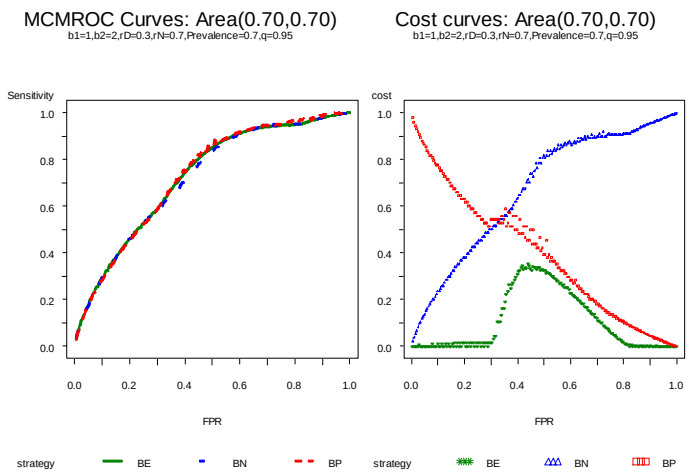
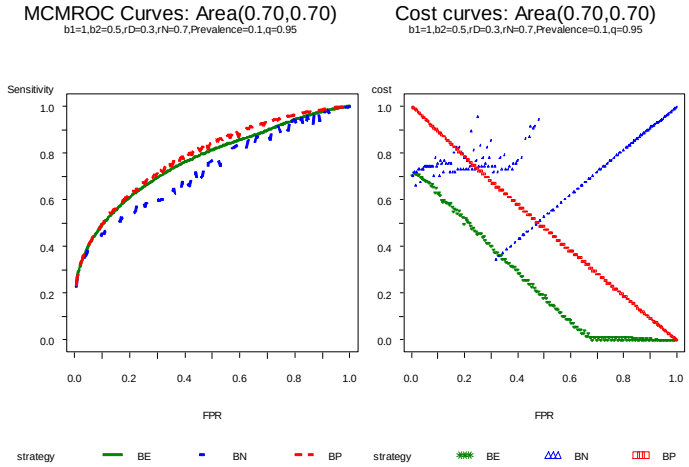


Figure C3. 3b: (b1=1, b2=2)



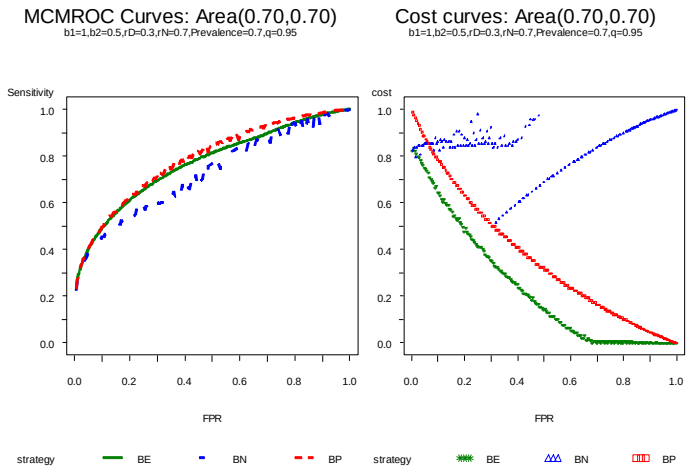


Figure C3. 3c: (b1=1, b2=0.5)

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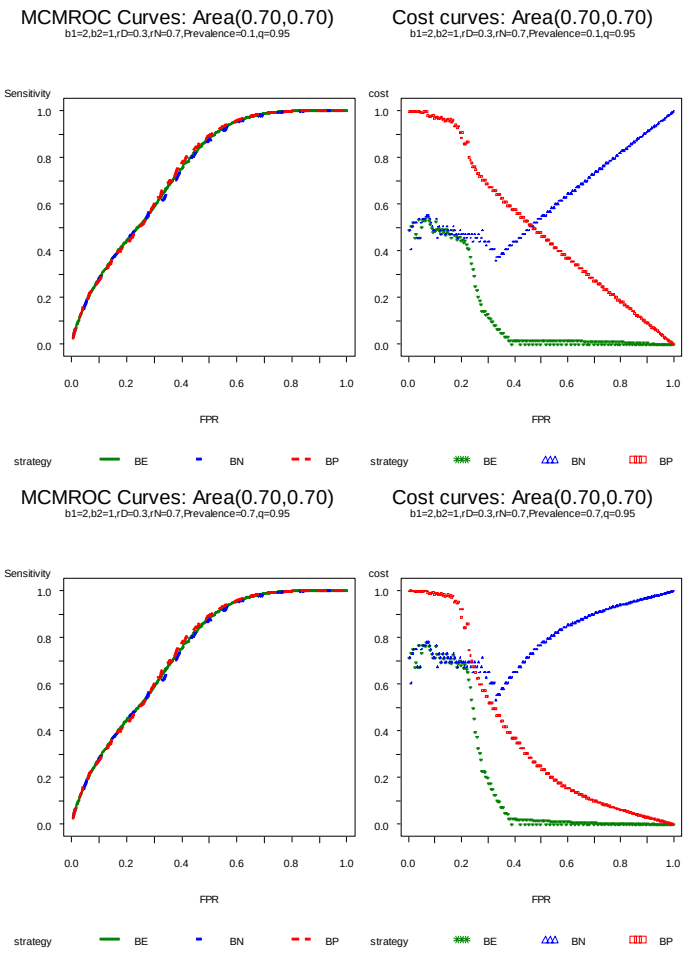
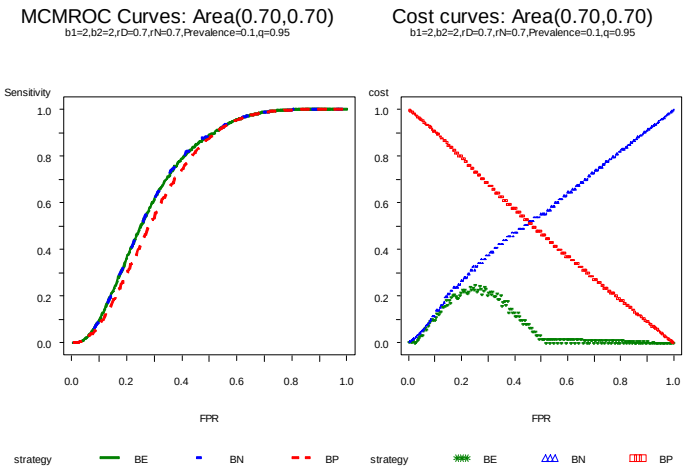


Figure C3. 3d: (b1=2, b2=1)



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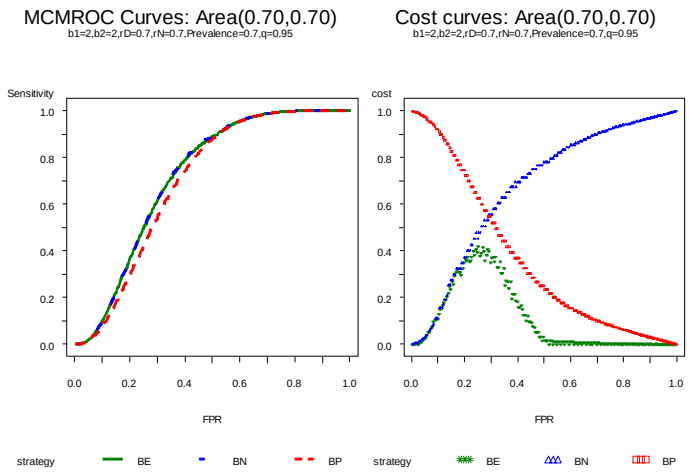

Figure C3. 3e: (b1=2, b2=2)

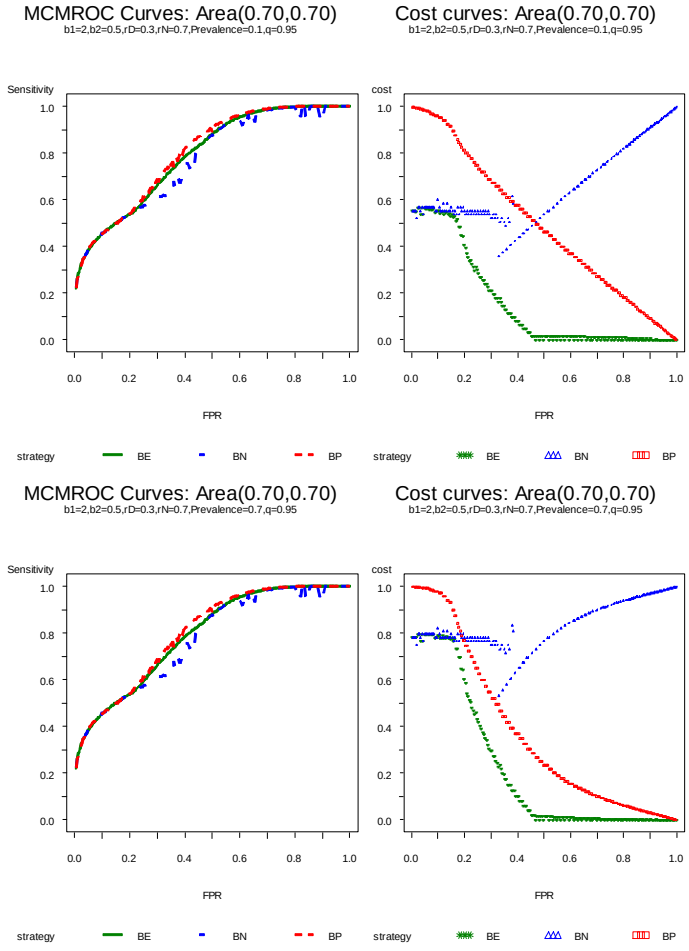

Figure C3. 3f: (b1=2, b2=0.5)

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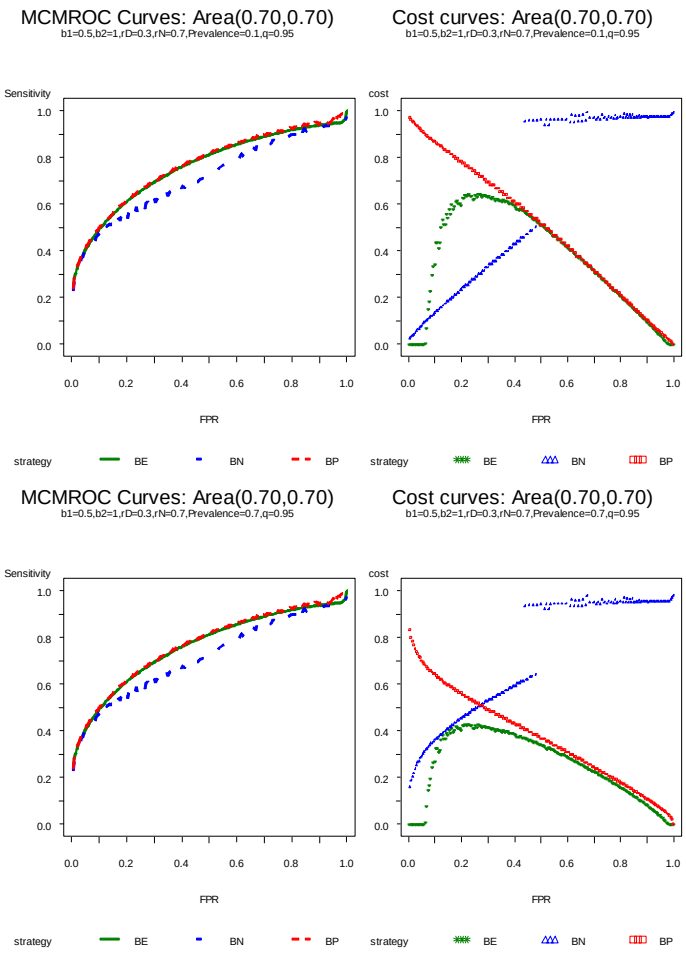
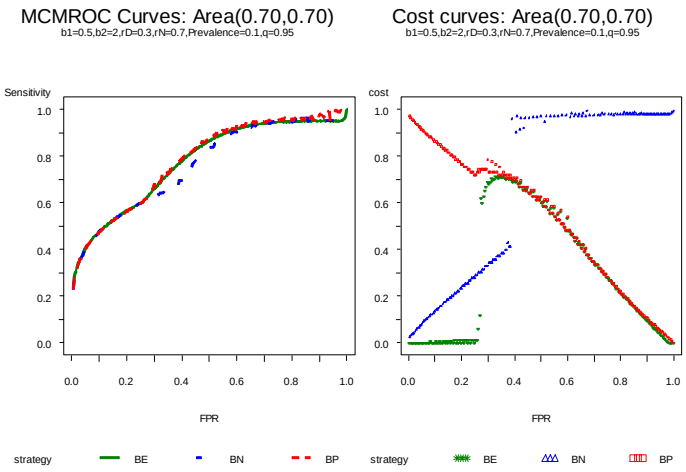


Figure C3. 3g: (b1=0.5, b2=1)



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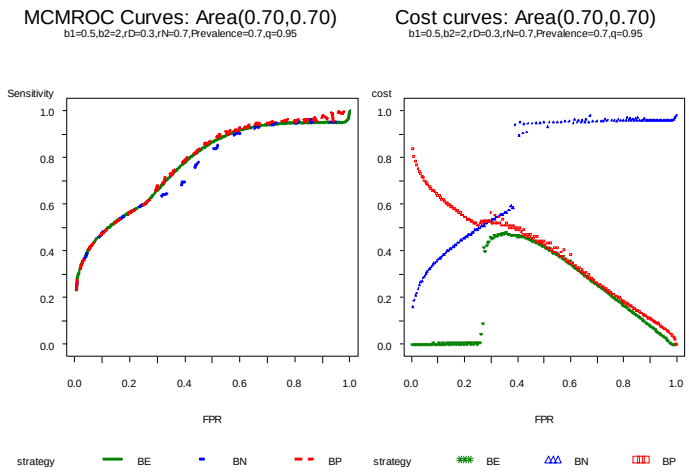
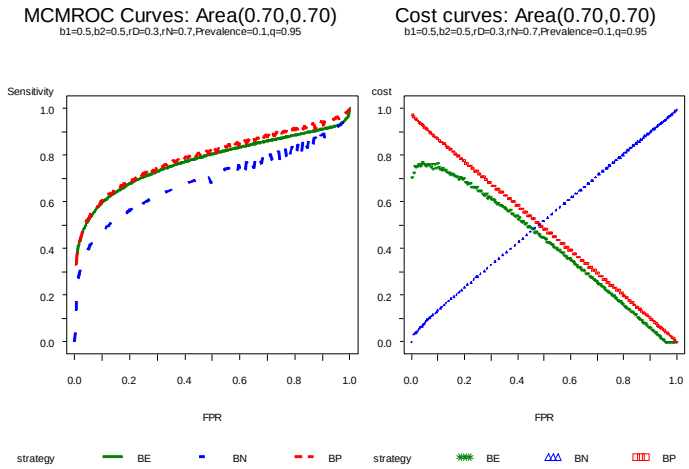


Figure C3. 3h: (b1=0.5, b2=2)



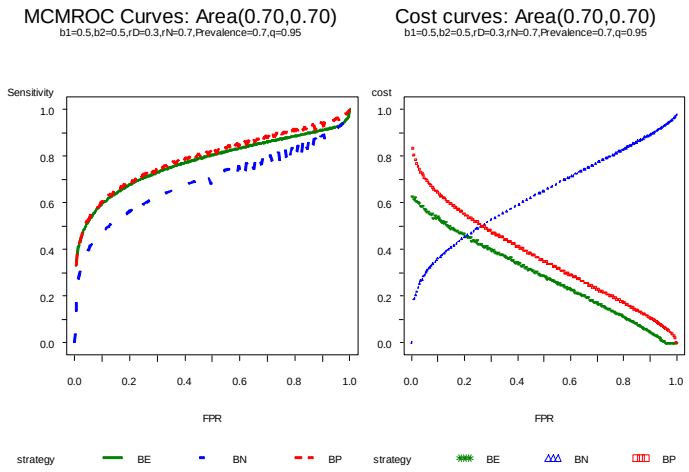


Figure C3. 3i: (b1=0.5, b2=0.5)

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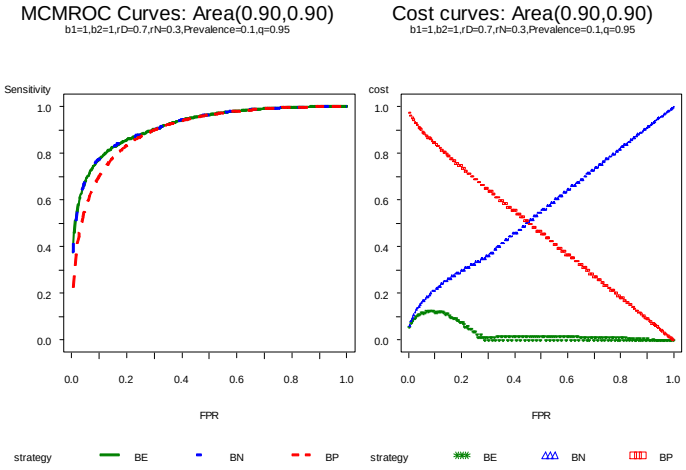
C4 Dependent of the tests $(\rho_D = 0.7, \rho_N = 0.3)$

C4. 1 AUC1 = 0.90, AUC2 = 0.90



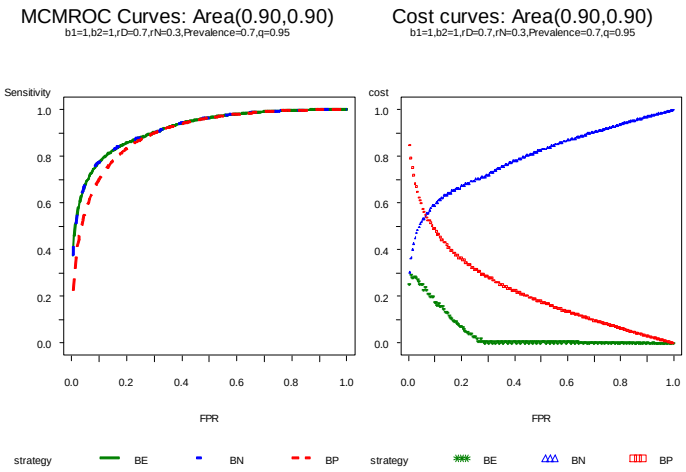
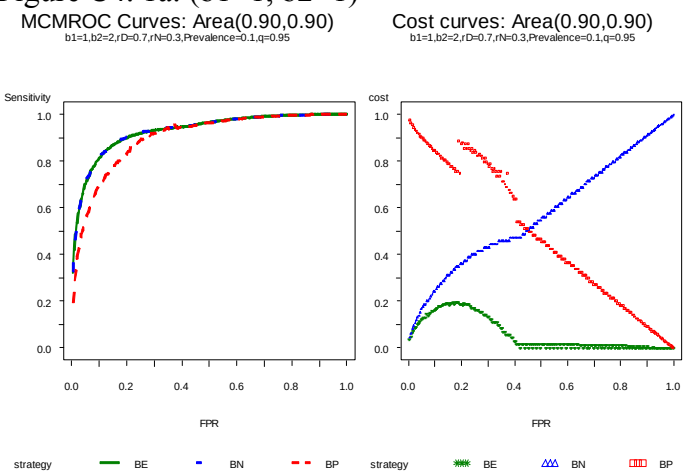


Figure C4. 1a: (b1=1, b2=1)



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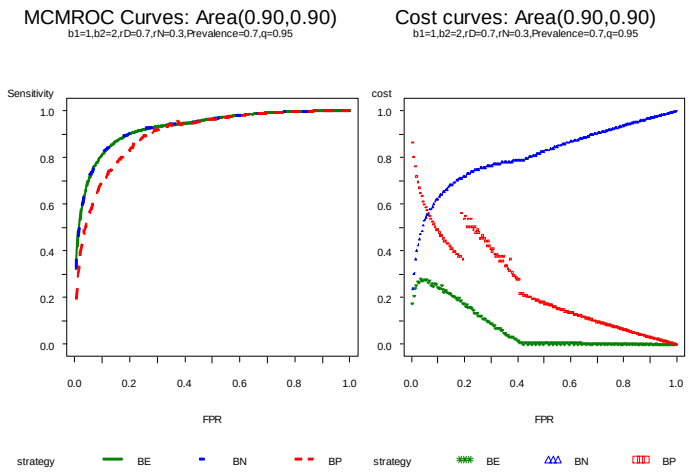

Figure C4. 1b: (b1=1, b2=2)

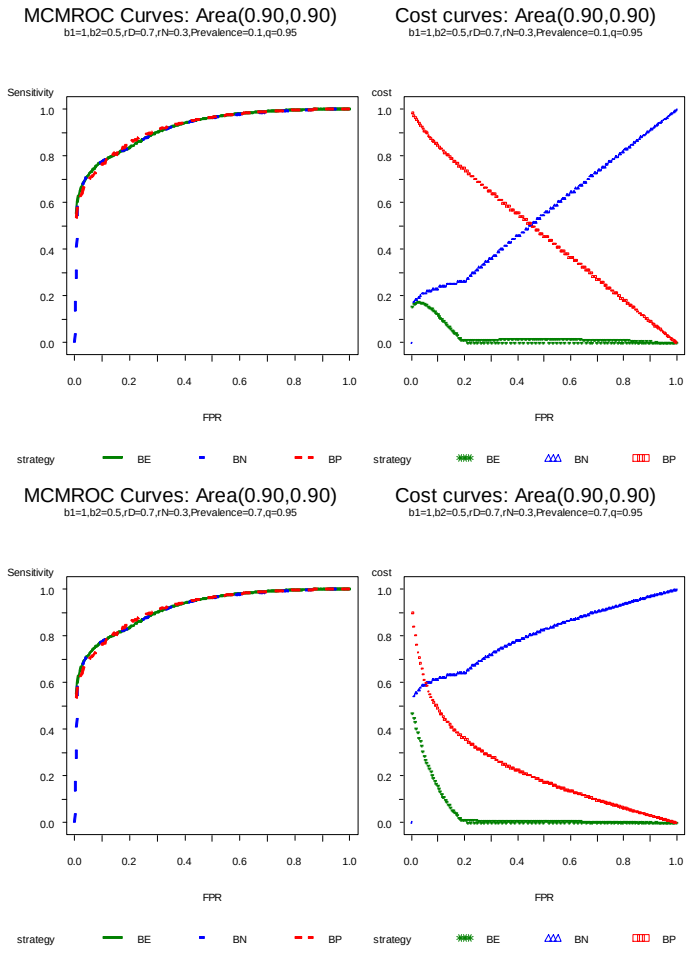

Figure C4. 1c: (b1=1, b2=0.5)

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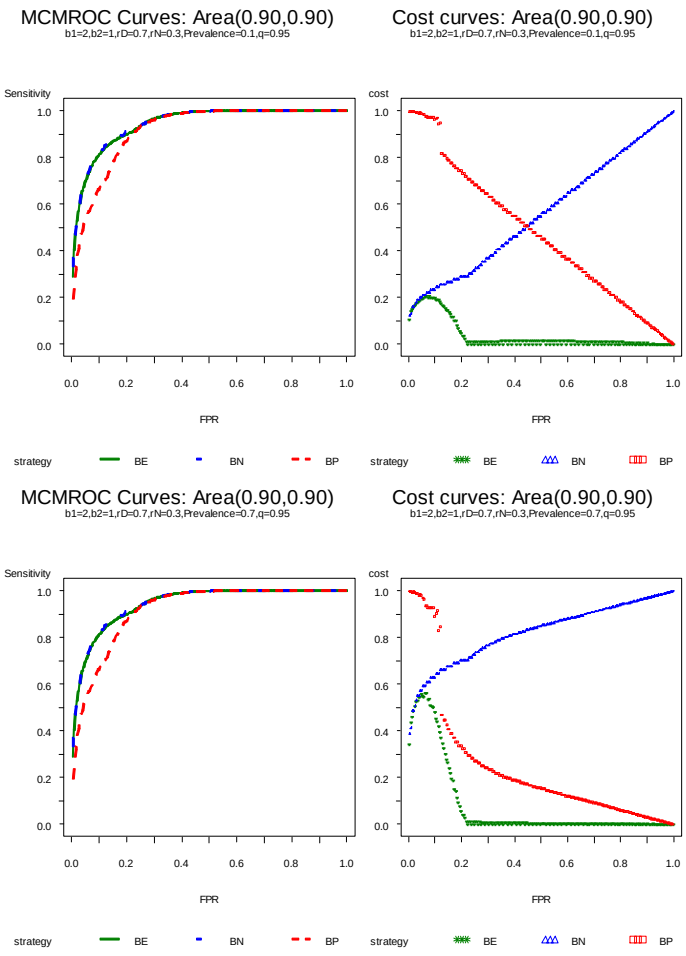
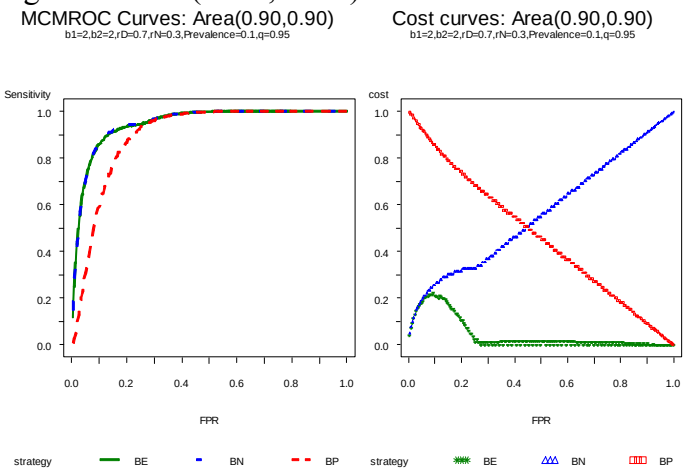


Figure C4. 1d: (b1=2, b2=1)



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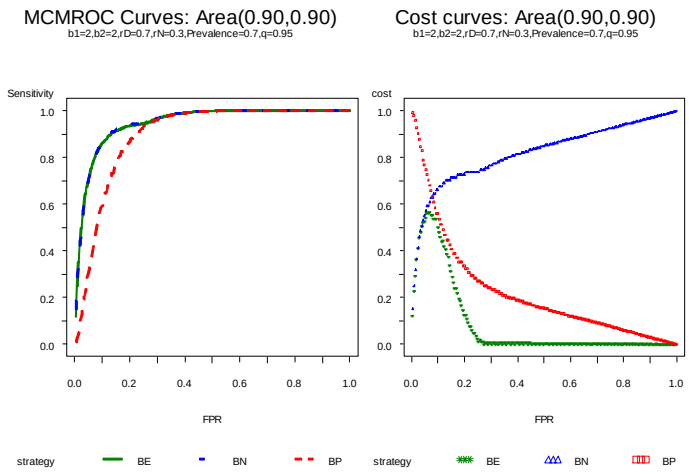

Figure C4. 1e: (b1=2, b2=2)

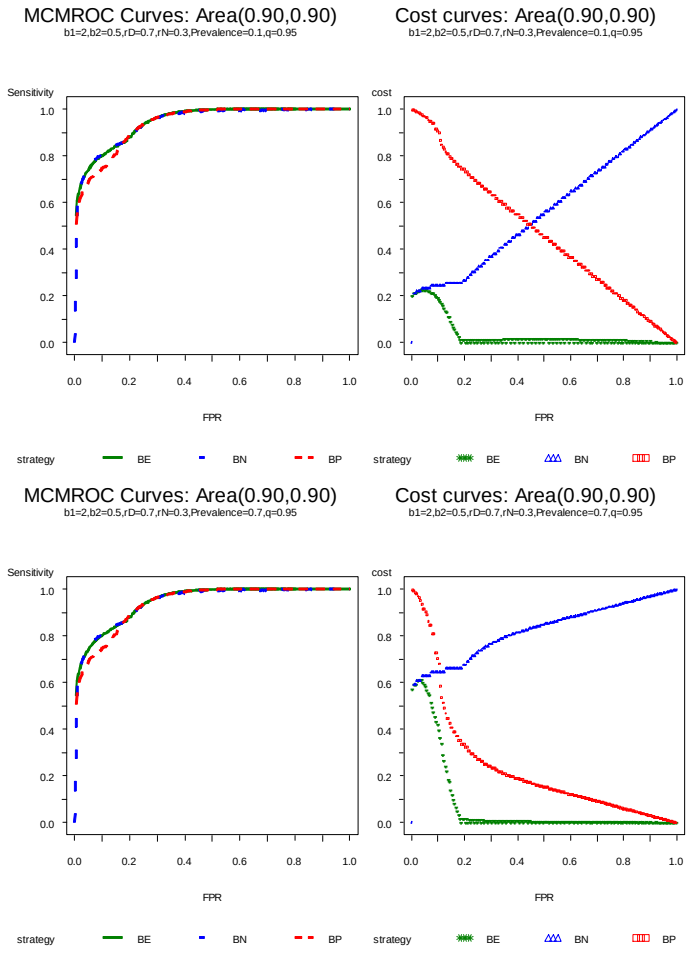

Figure C4. 1f: (b1=2, b2=0.5)

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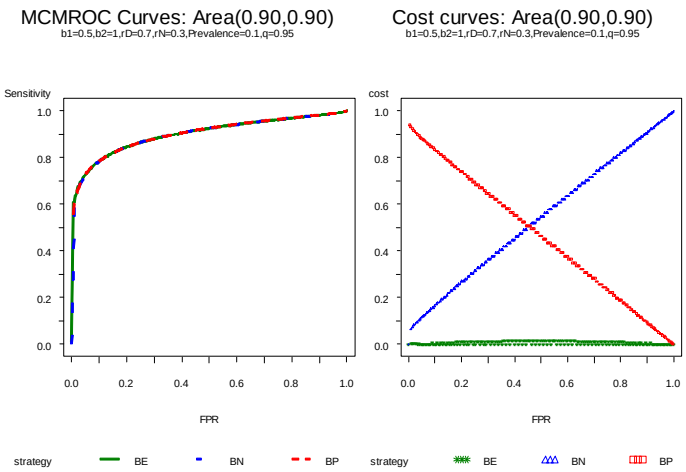


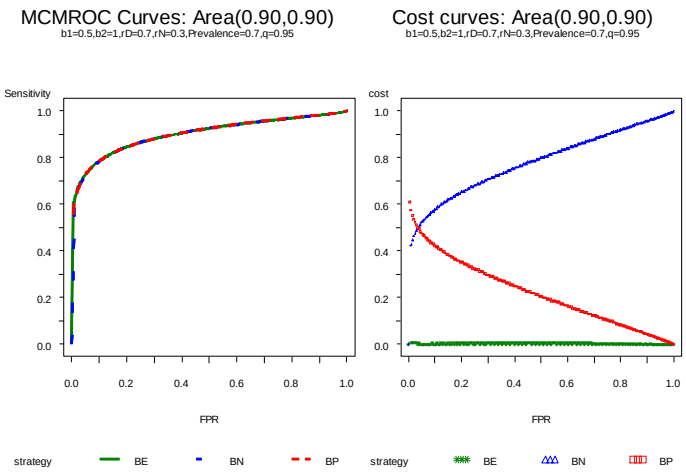
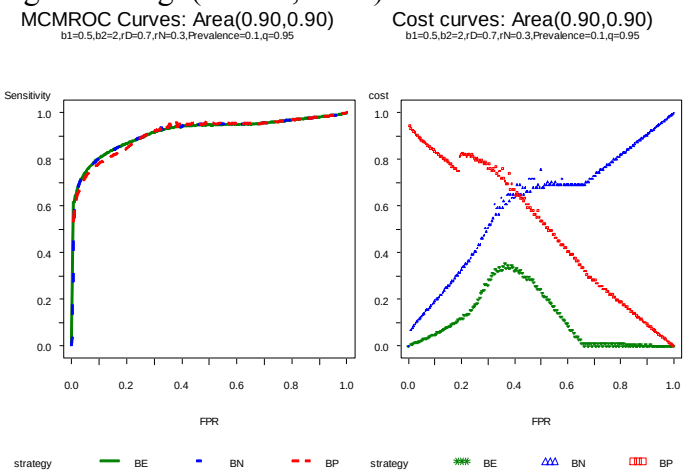


Figure C4. 1g: (b1=0.5, b2=1)



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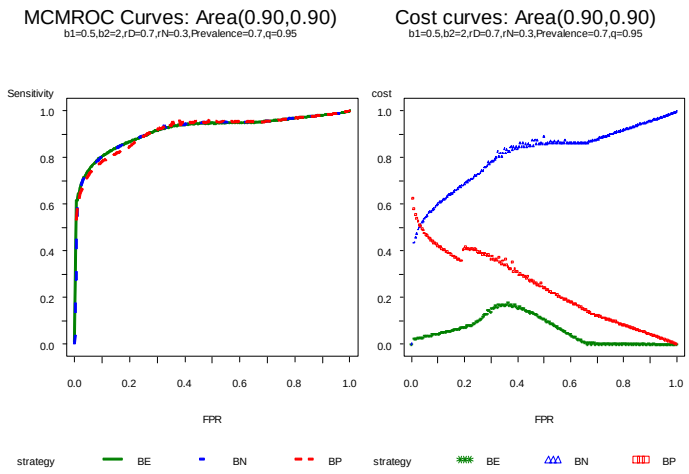
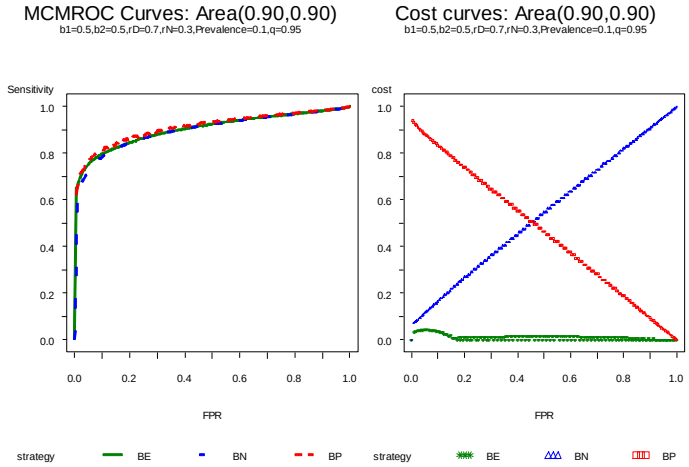


Figure C4. 1h: (b1=0.5, b2=2)



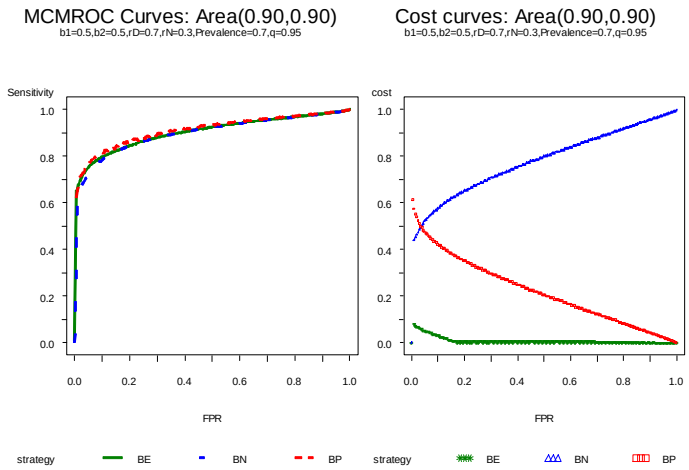


Figure C4. 1i: (b1=0.5, b2=0.5)

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C4. 2 AUC1 = 0.70, AUC2 = 0.90

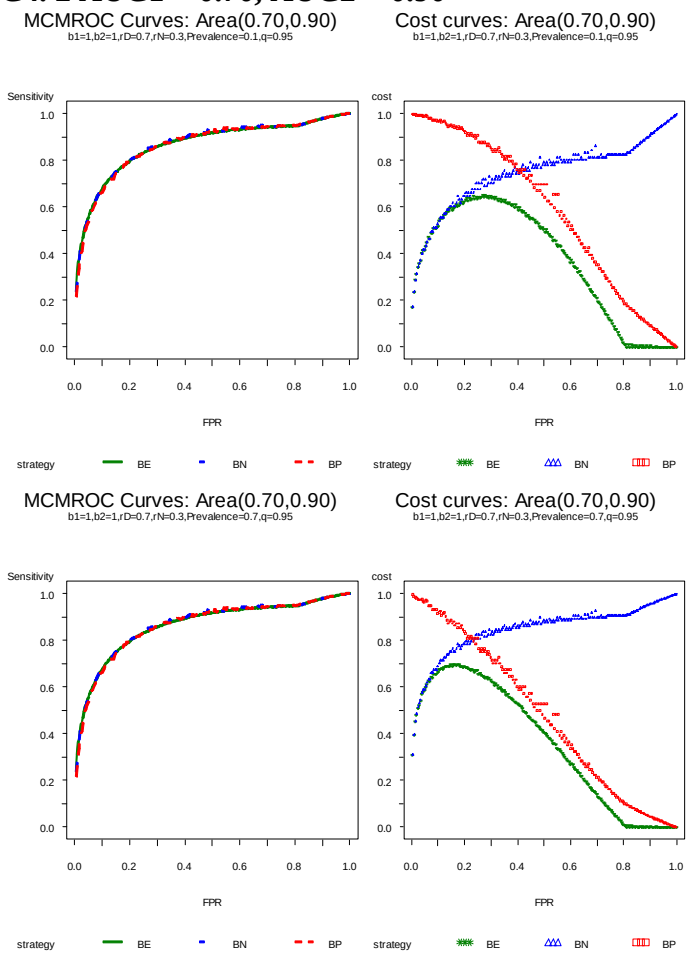
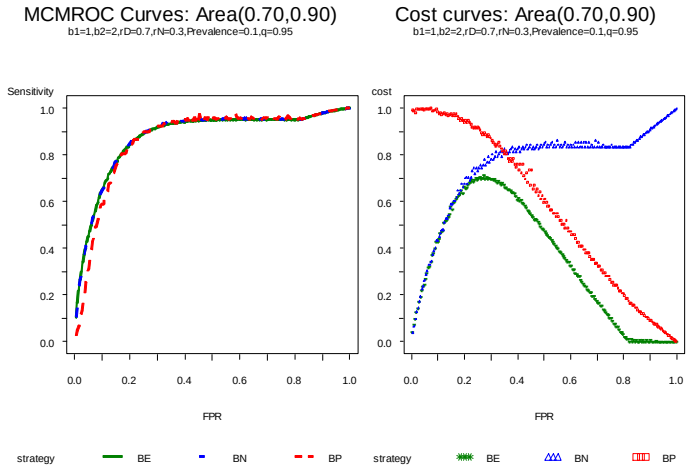


Figure C4. 2a: (b1=1, b2=1)



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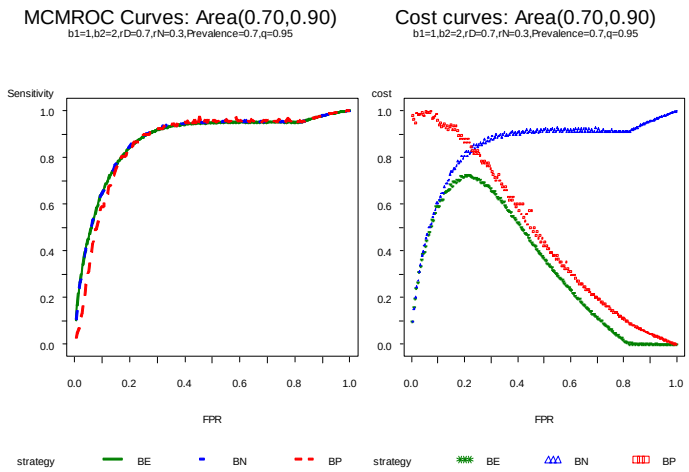

Figure C4. 2b: (b1=1, b2=2)

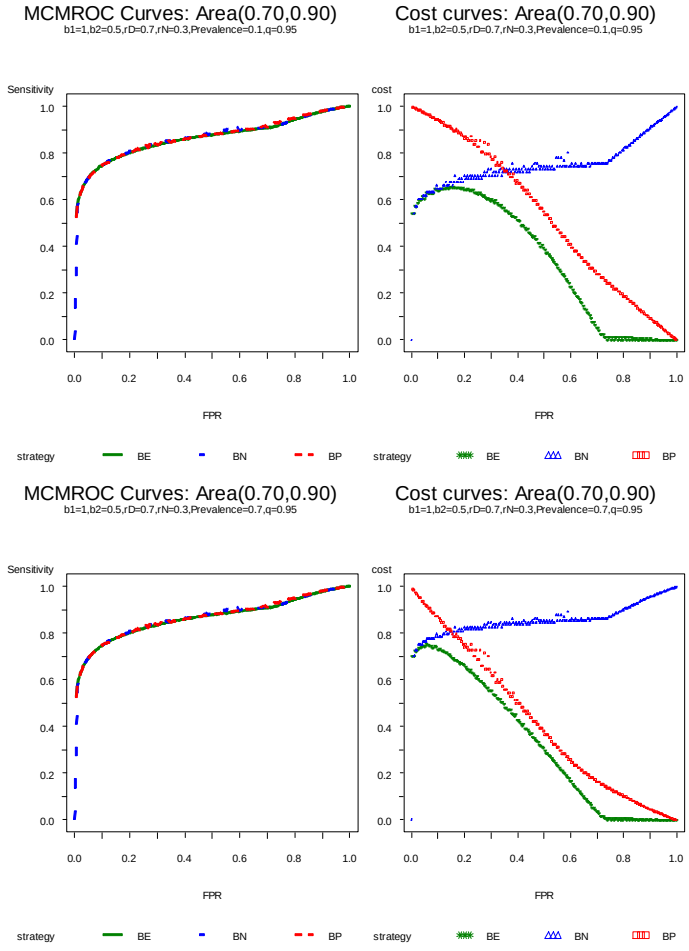

Figure C4. 2c: (b1=1, b2=0.5)

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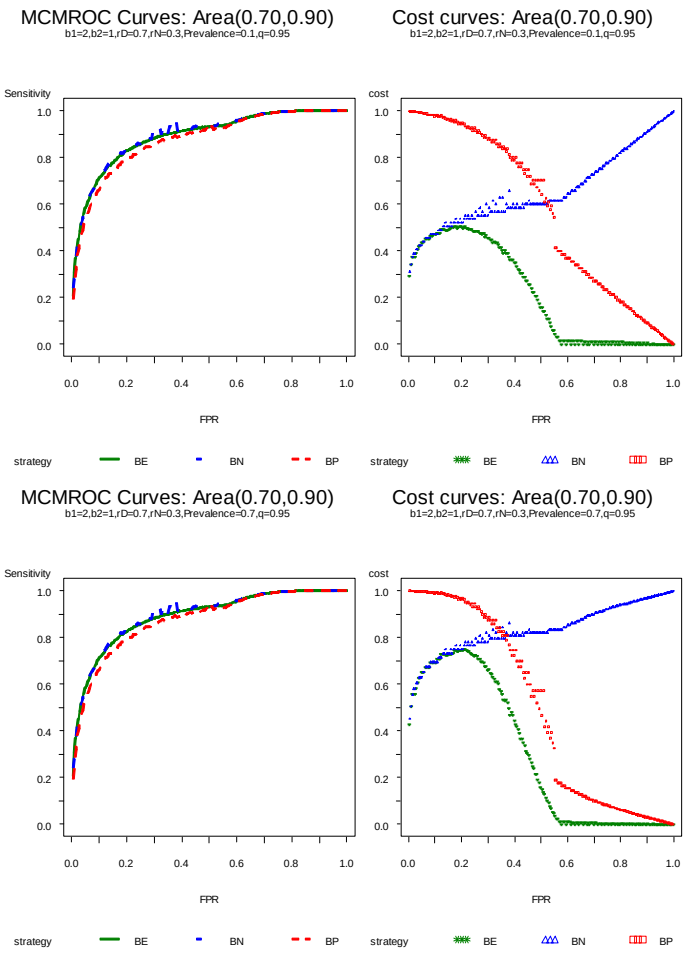
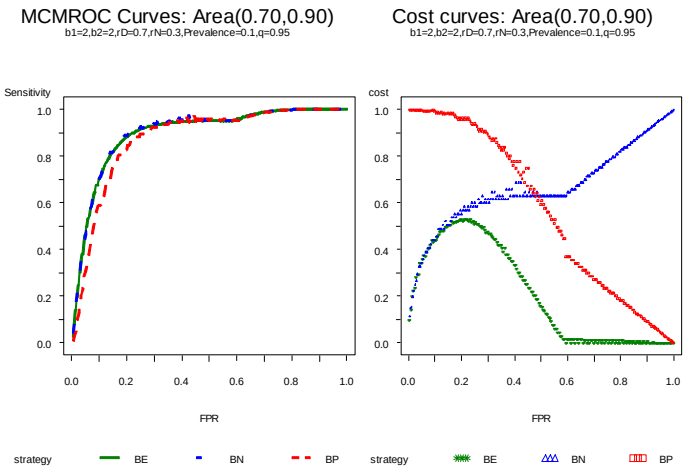


Figure C4. 2d: (b1=2, b2=1)



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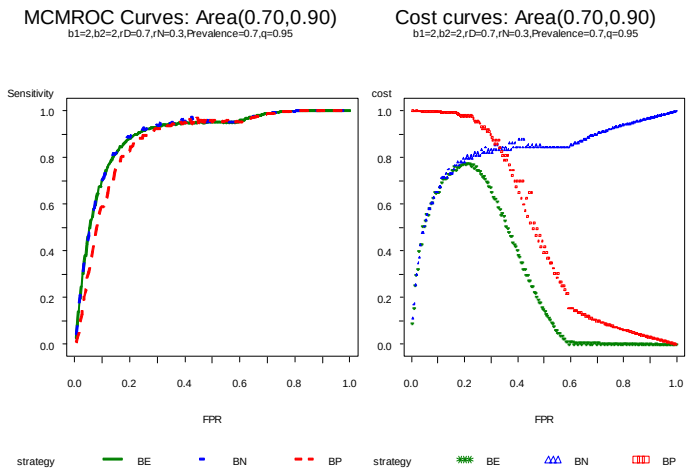
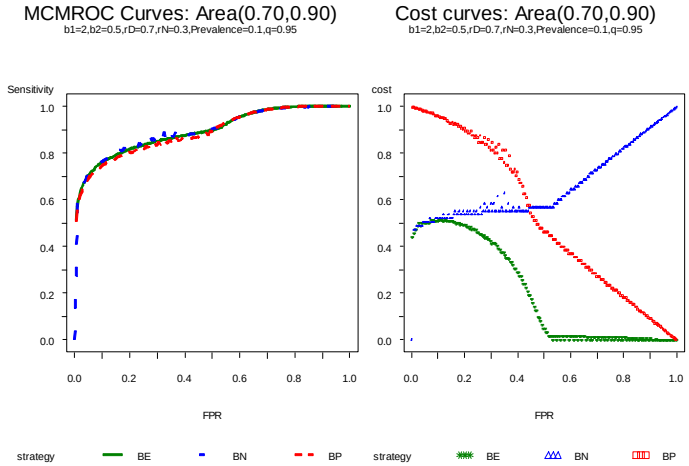


Figure C4. 2e: (b1=2, b2=2)



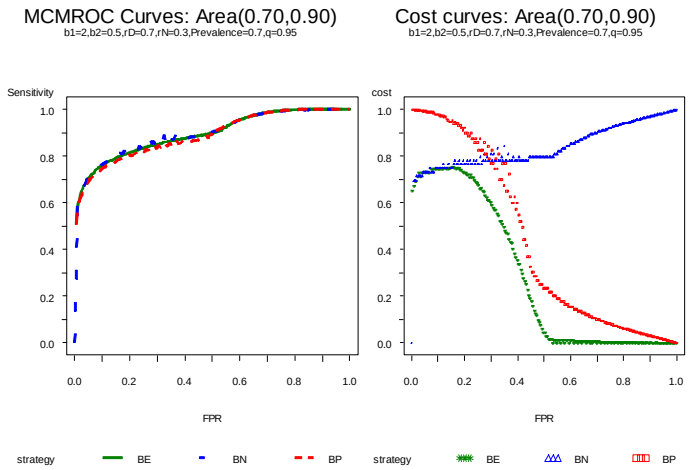


Figure C4. 2f: (b1=2, b2=0.5)

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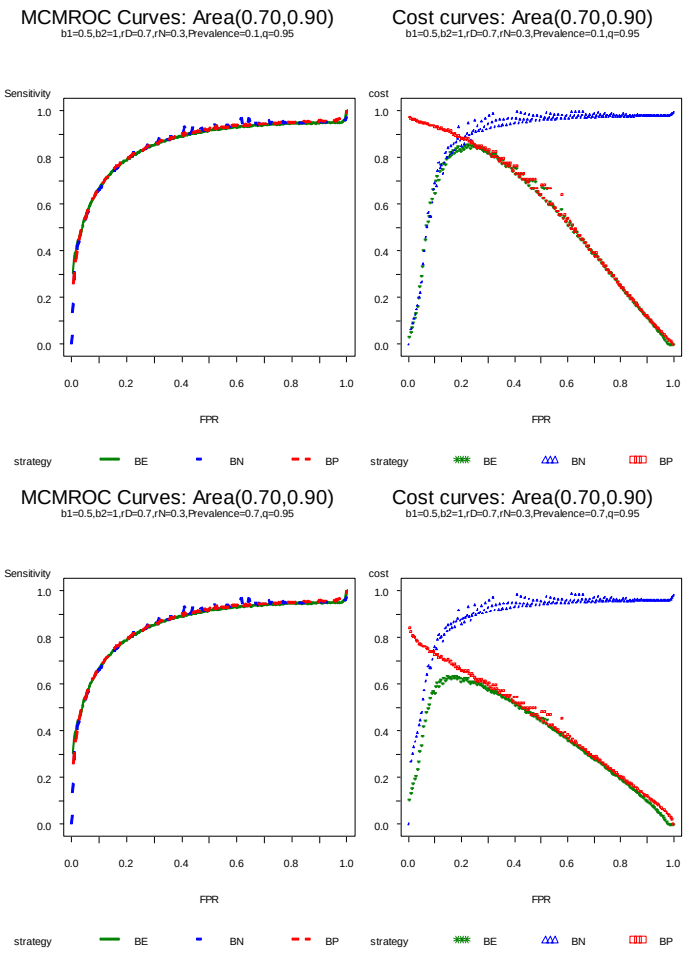
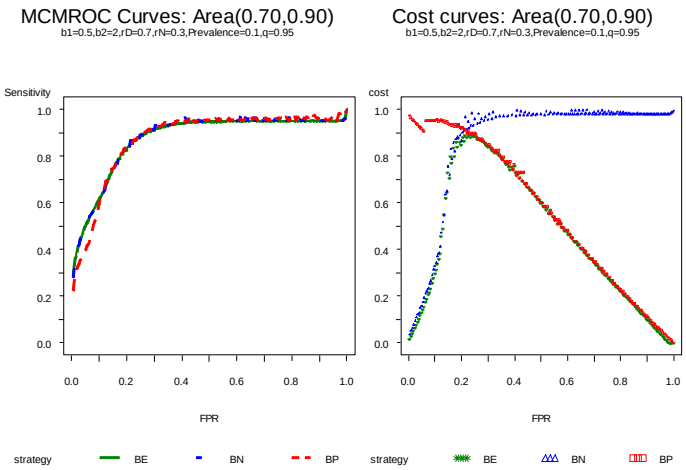


Figure C4. 2g: (b1=0.5, b2=1)



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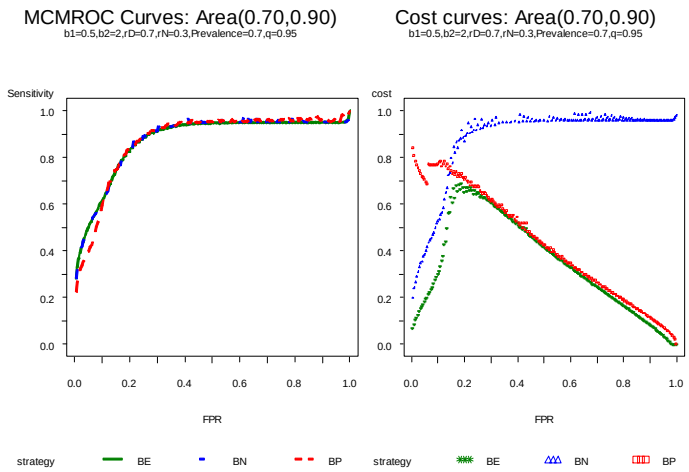
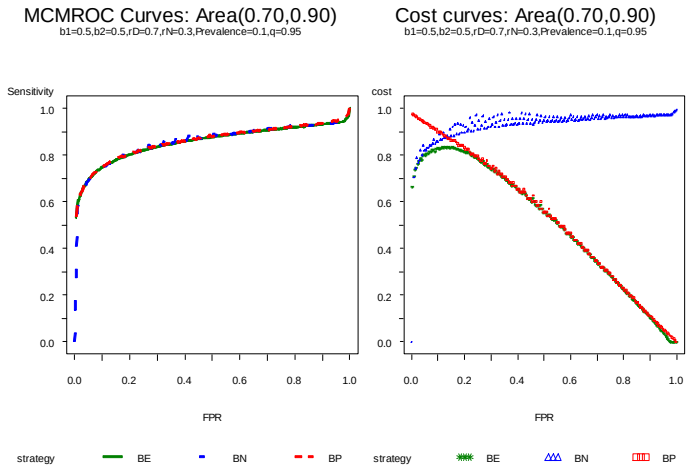


Figure C4. 2h: (b1=0.5, b2=2)



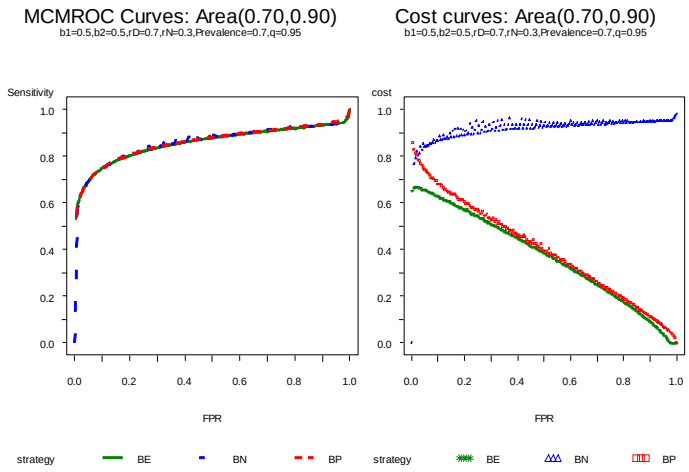


Figure C4. 2i: (b1=0.5, b2=0.5)

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C4. 3 AUC1 = 0.70, AUC2 = 0.70

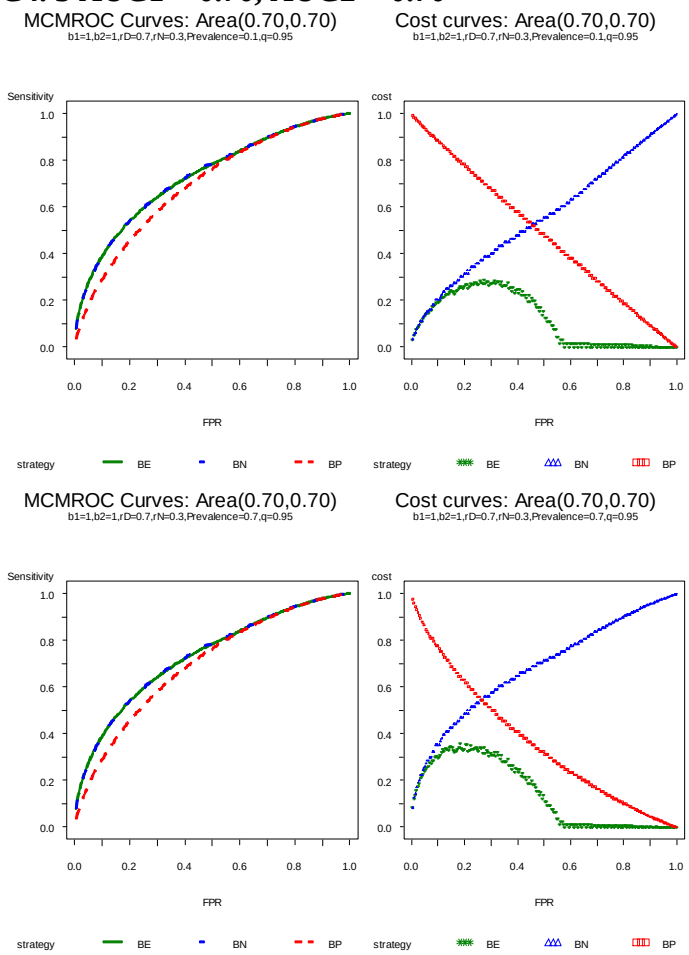
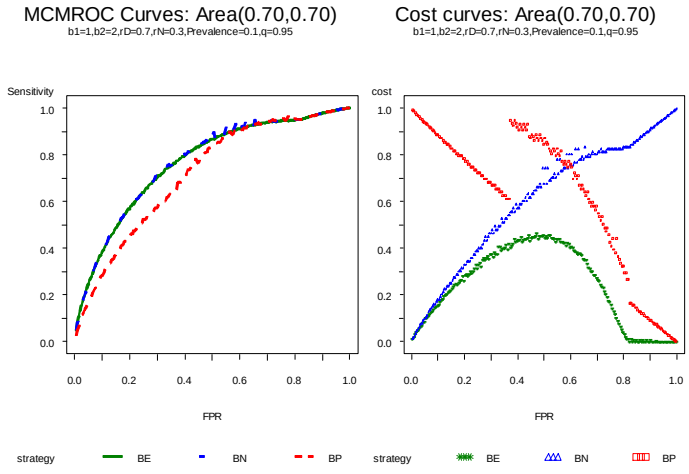


Figure C4. 3a: (b1=1, b2=1)



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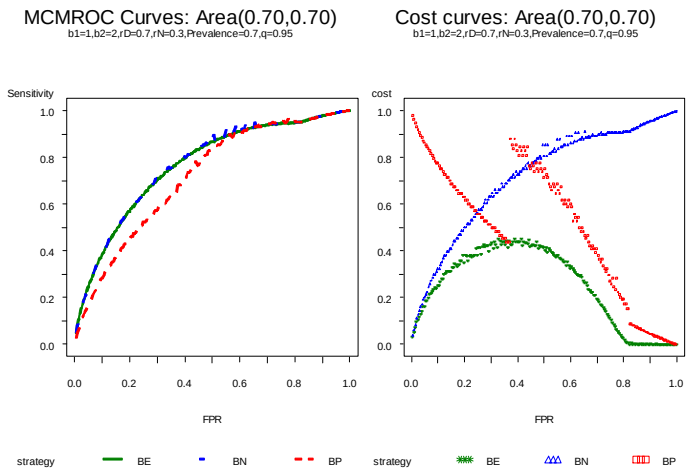
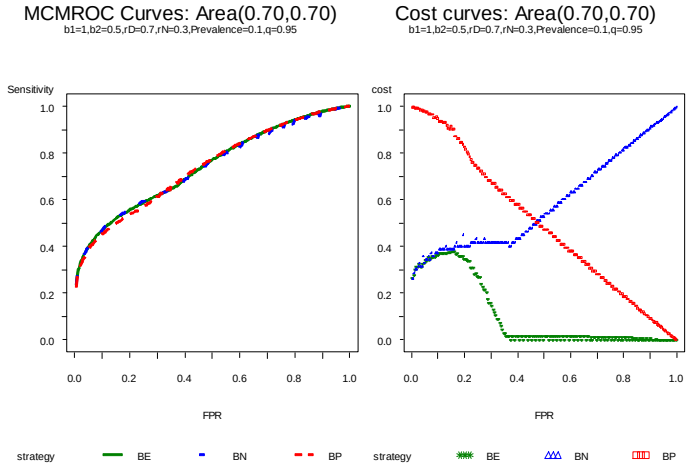


Figure C4. 3b: (b1=1, b2=2)



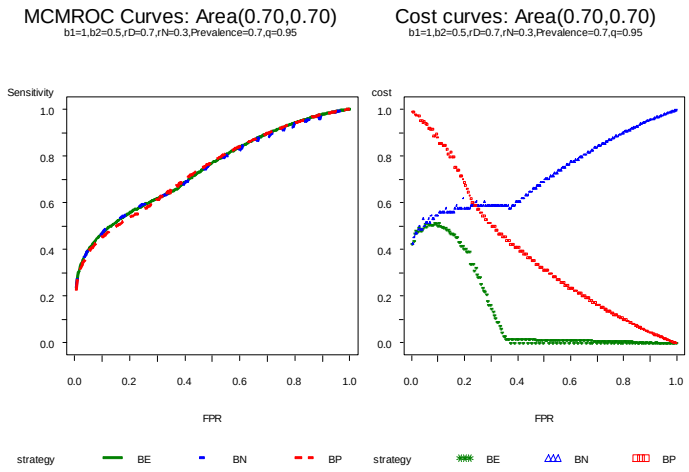


Figure C4. 3c: (b1=1, b2=0.5)

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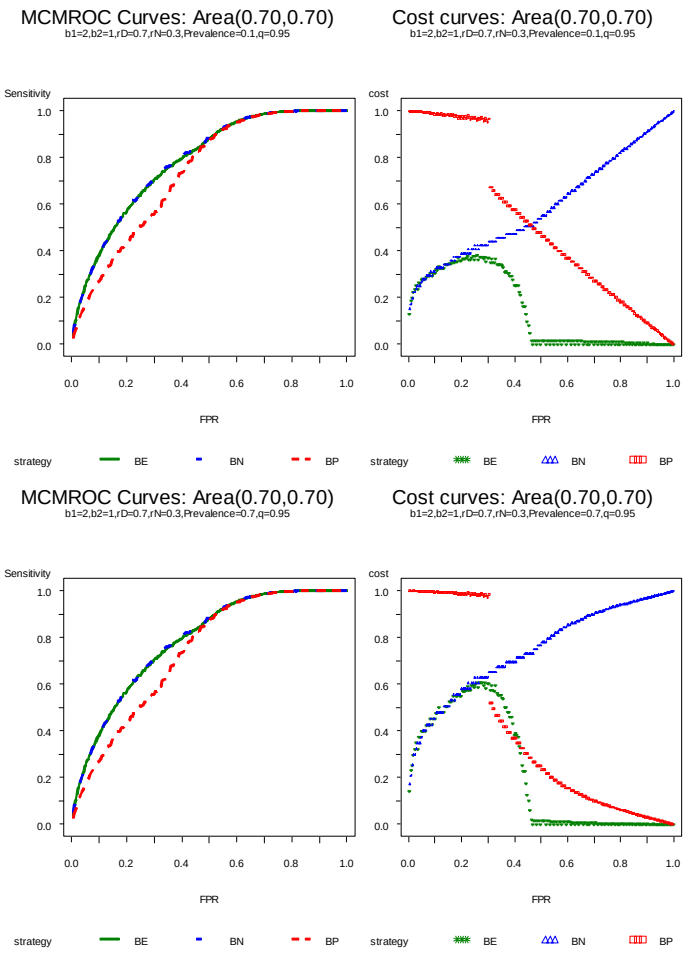
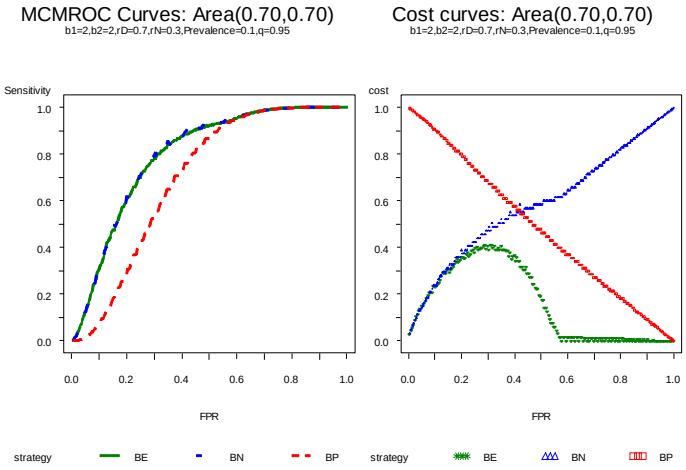


Figure C4. 3d: (b1=2, b2=1)



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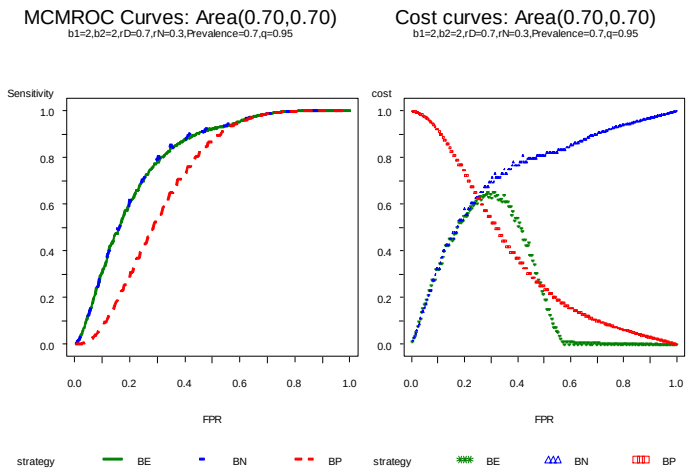

Figure C4. 3e: (b1=2, b2=2)

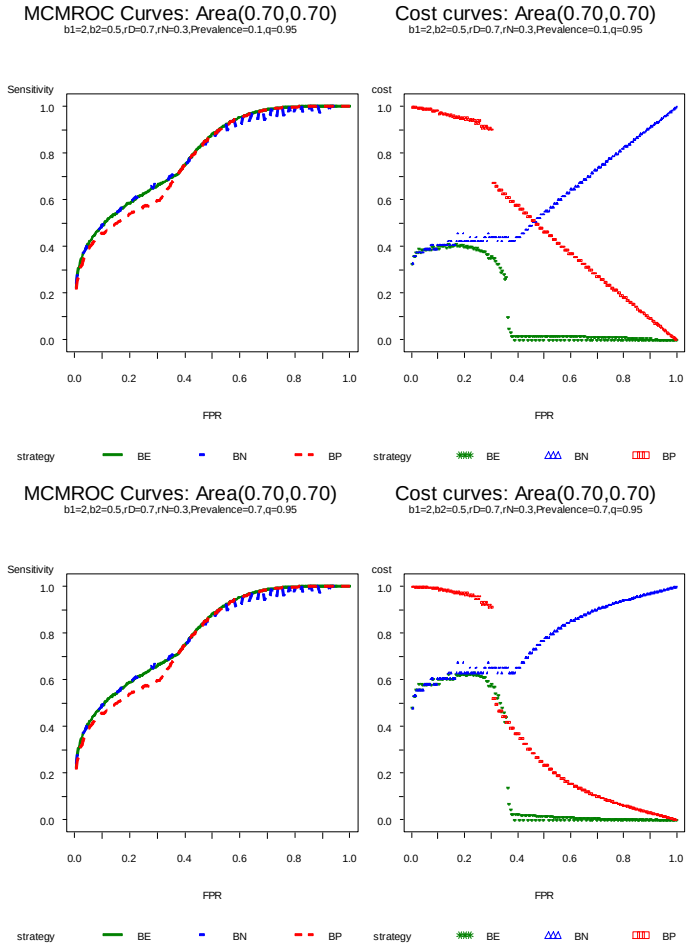

Figure C4. 3f: (b1=2, b2=0.5)

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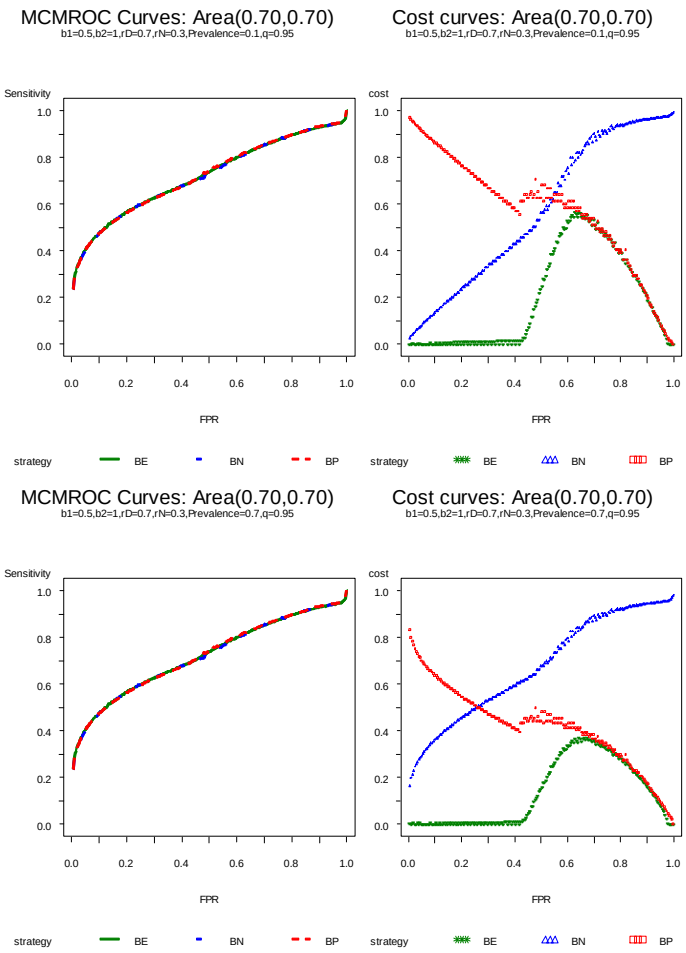
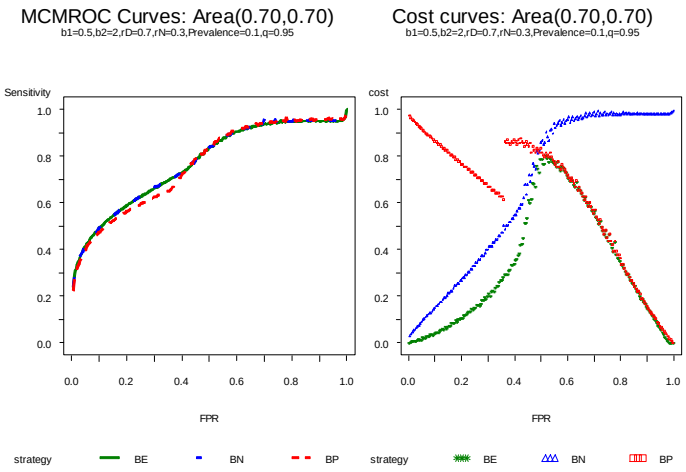


Figure C4. 3g: (b1=0.5, b2=1)



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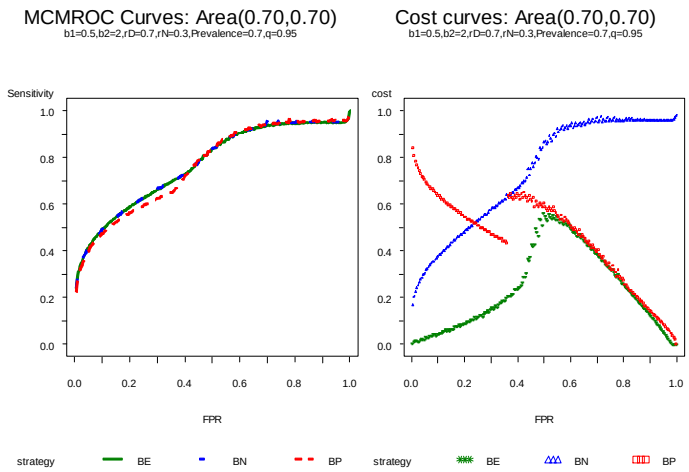
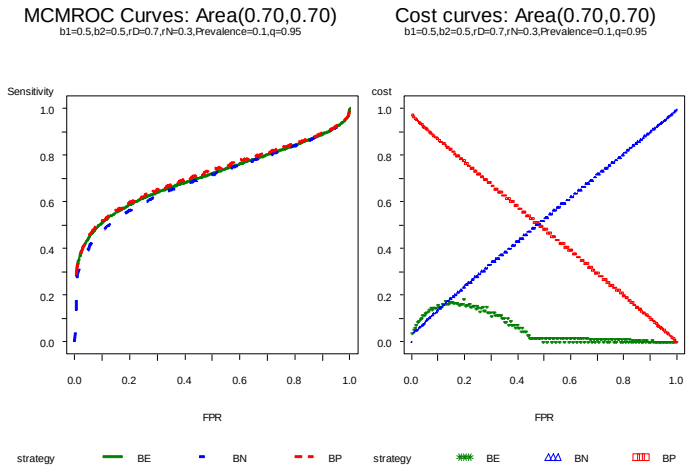


Figure C4. 3h: (b1=0.5, b2=2)



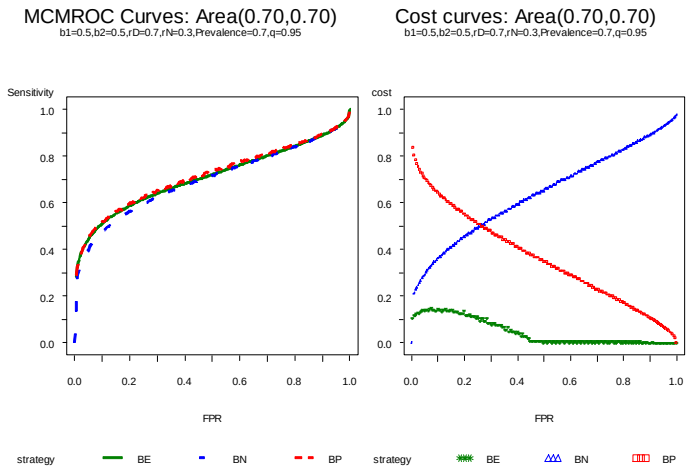


Figure C4. 3i: (b1=0.5, b2=0.5)

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C5 Dependent of the tests $(\rho_D = 0.7, \rho_N = 0.7)$

C5. 1 AUC1 = 0.90, AUC2 = 0.90

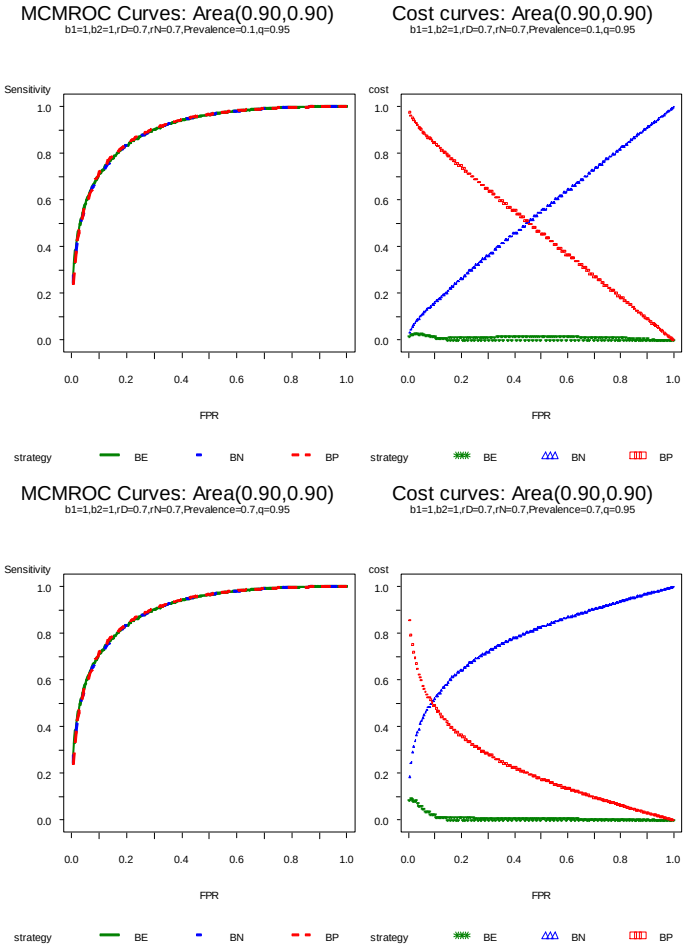
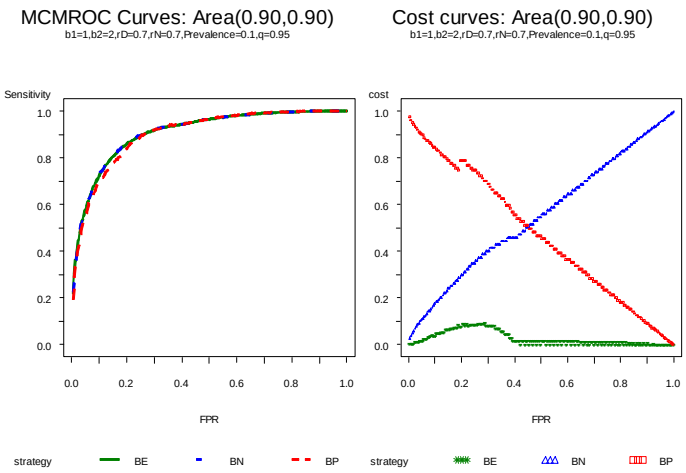


Figure C5. 1a: (b1=1, b2=1)



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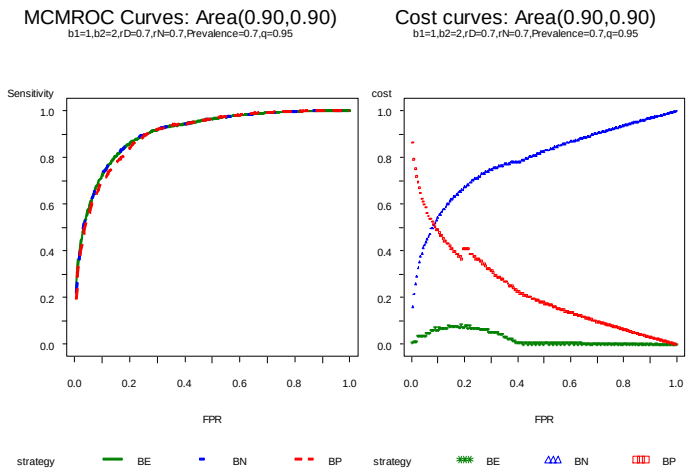
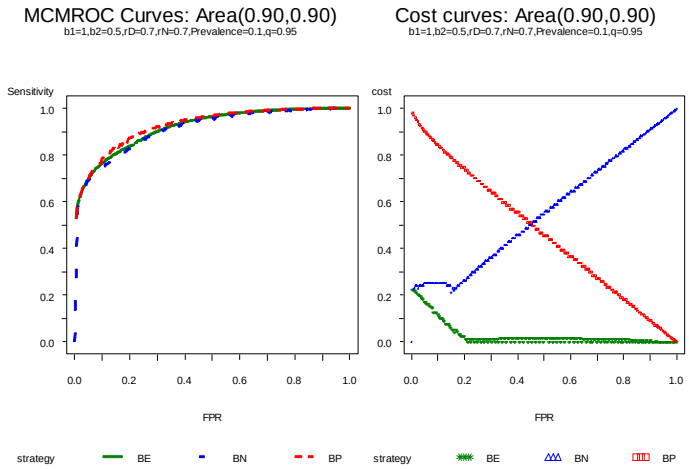


Figure C5. 1b: (b1=1, b2=2)



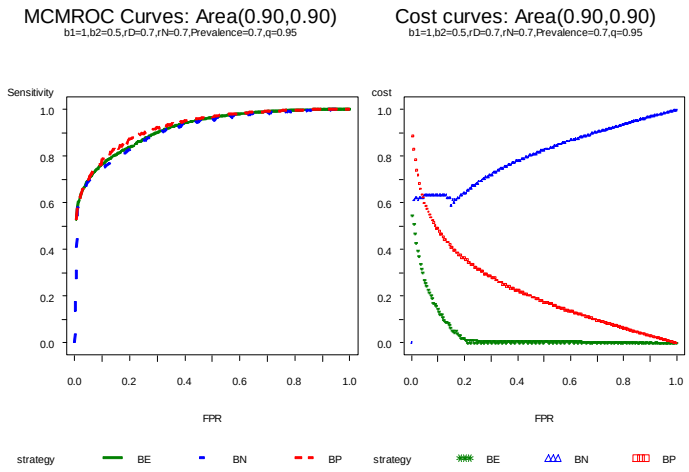


Figure C5. 1c: (b1=1, b2=0.5)

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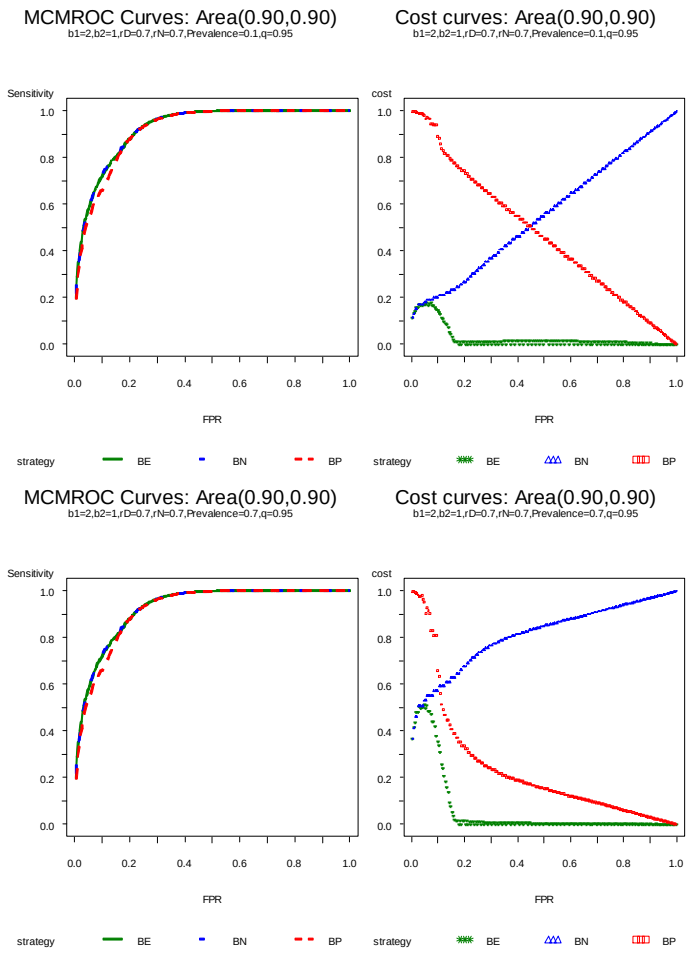
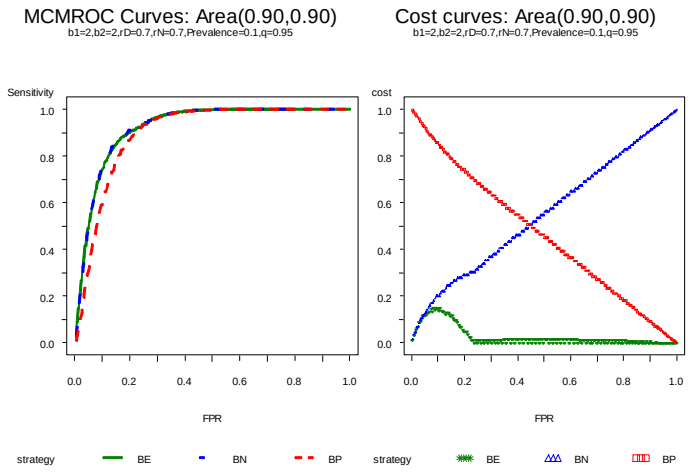


Figure C5. 1d: (b1=2, b2=1)



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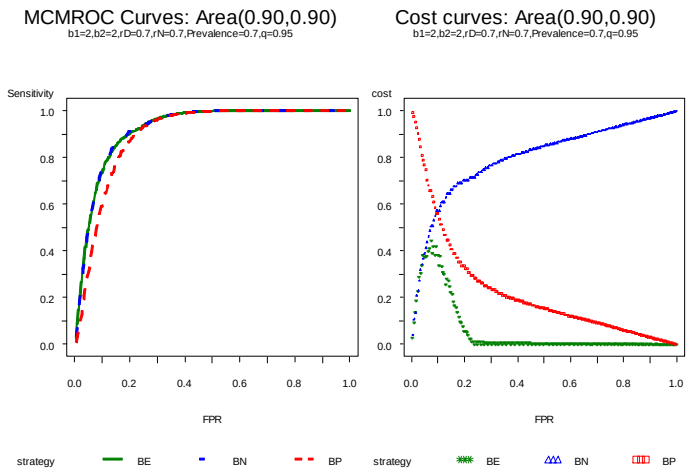

Figure C5. 1e: (b1=2, b2=2)

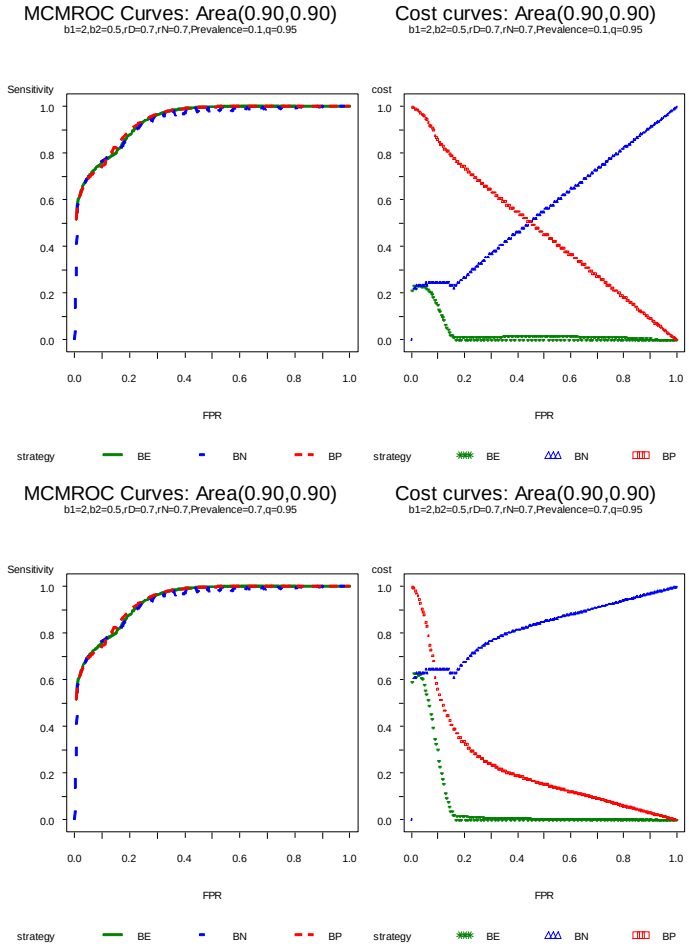

Figure C5. 1f: (b1=2, b2=0.5)

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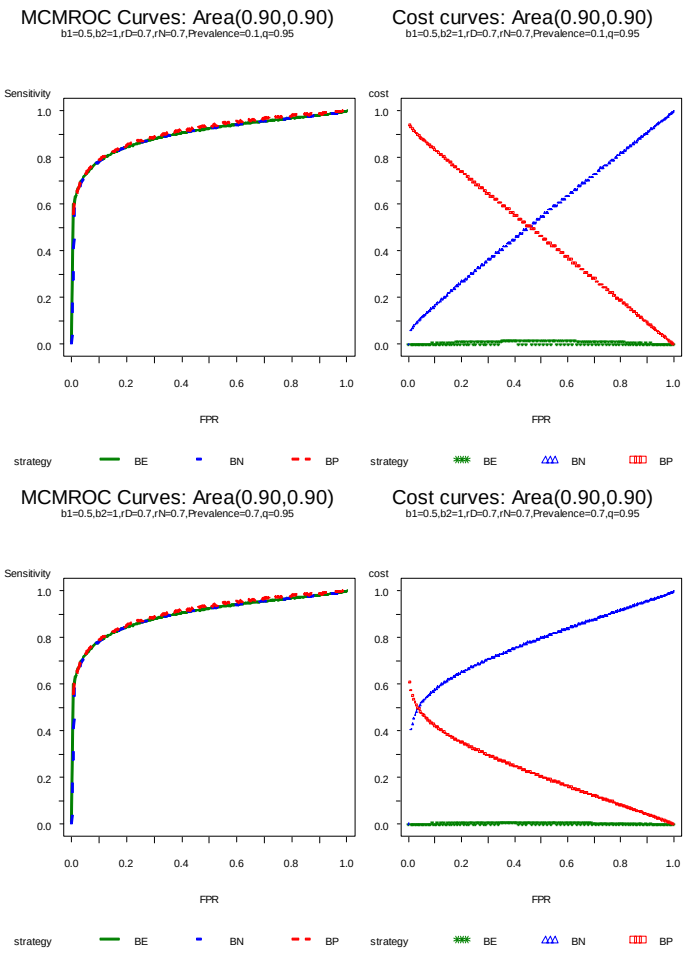
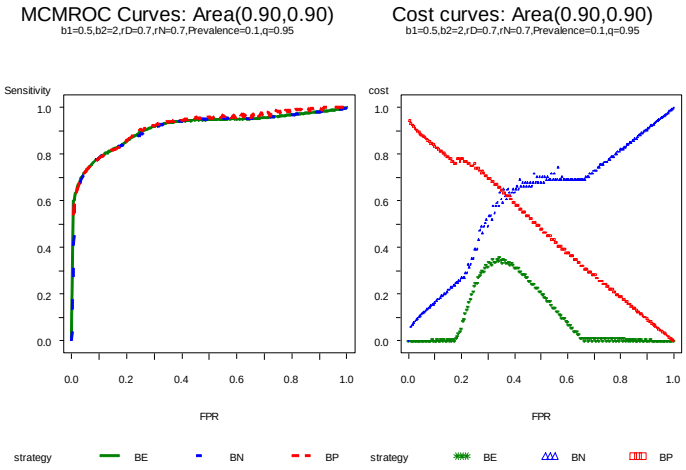


Figure C5. 1g: (b1=0.5, b2=1)



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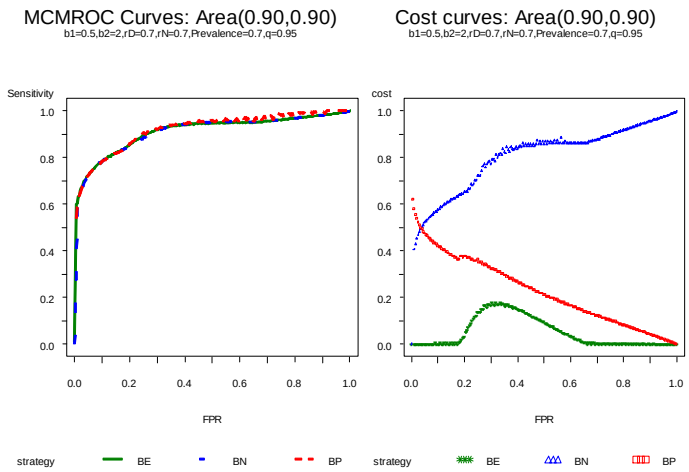
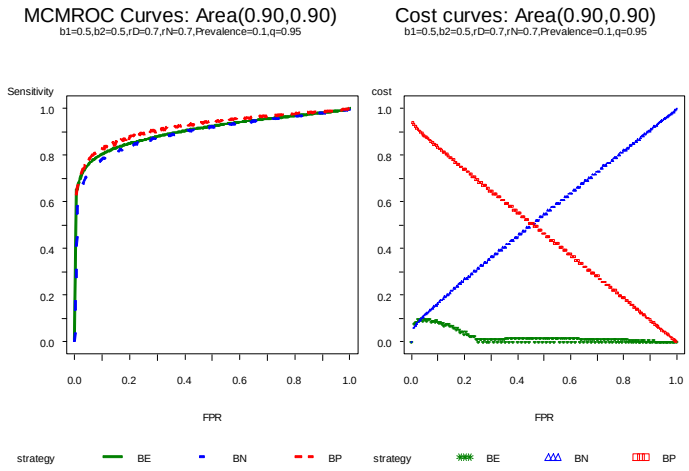


Figure C5. 1h: (b1=0.5, b2=2)



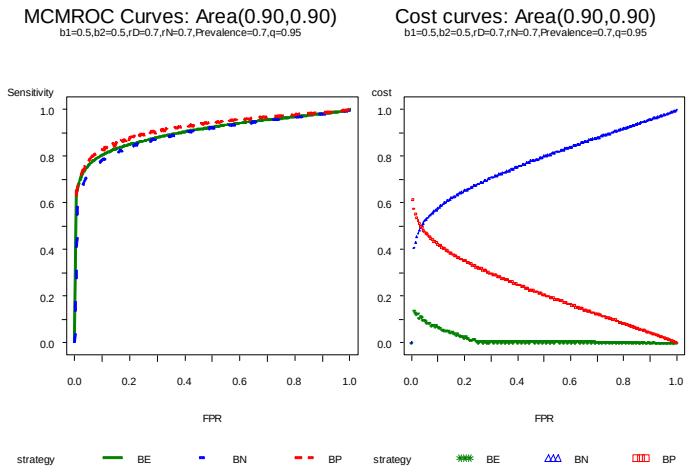


Figure C5. 1i: (b1=0.5, b2=0.5)

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. 2 AUC1 = 0.70, AUC2 = 0.90

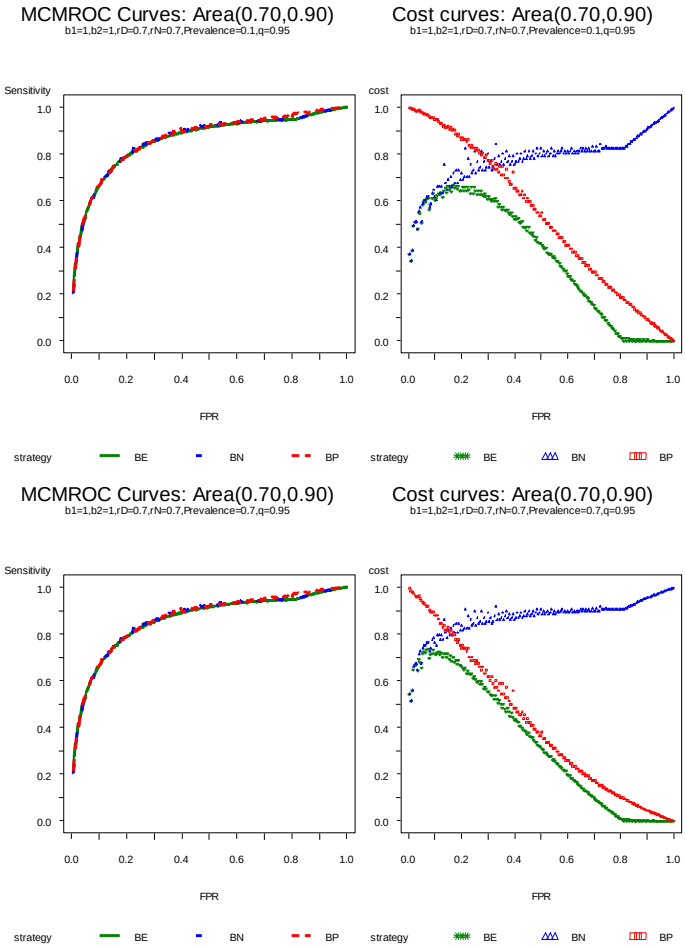
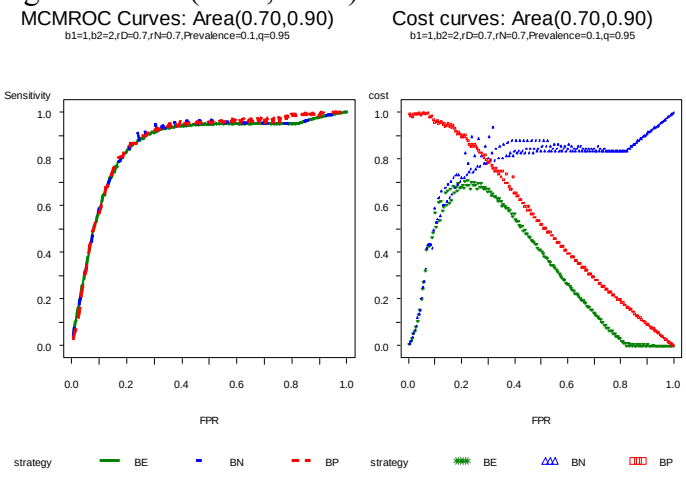


Figure C5. 2a: (b1=1, b2=1)



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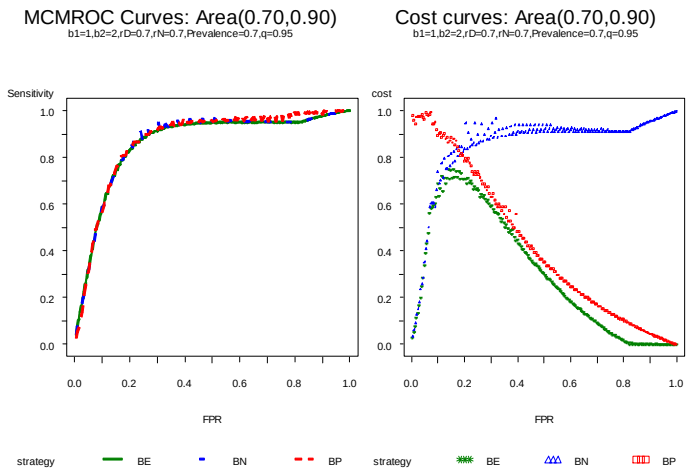
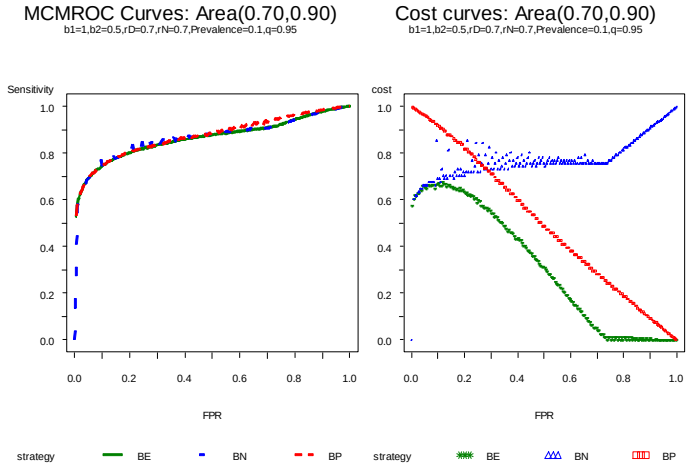


Figure C5. 2b: (b1=1, b2=2)



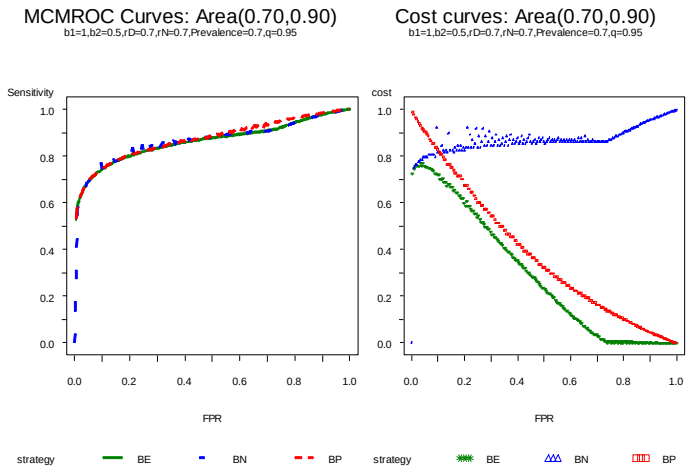


Figure C5. 2c: (b1=1, b2=0.5)

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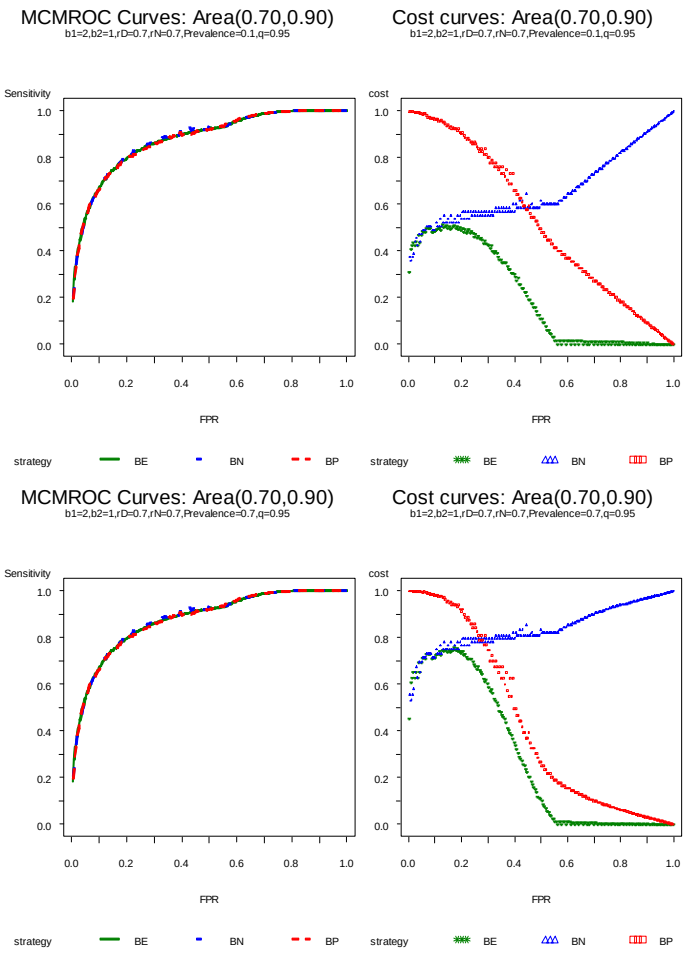
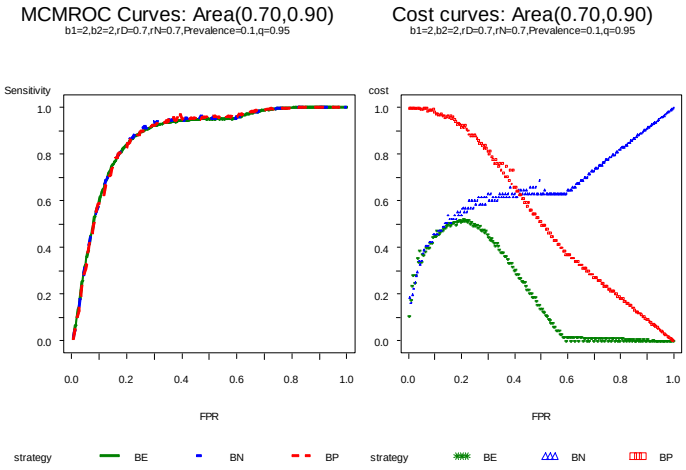


Figure C5. 2d: (b1=2, b2=1)



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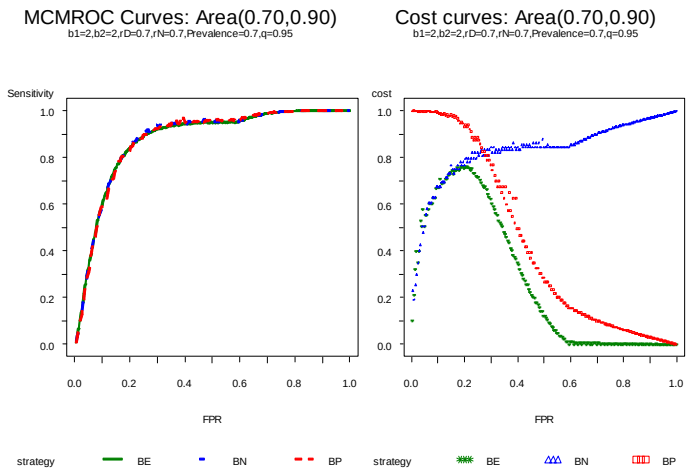
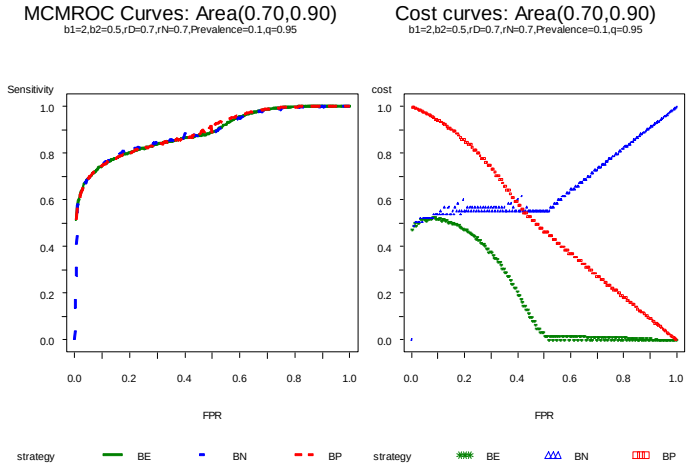


Figure C5. 2e: (b1=2, b2=2)



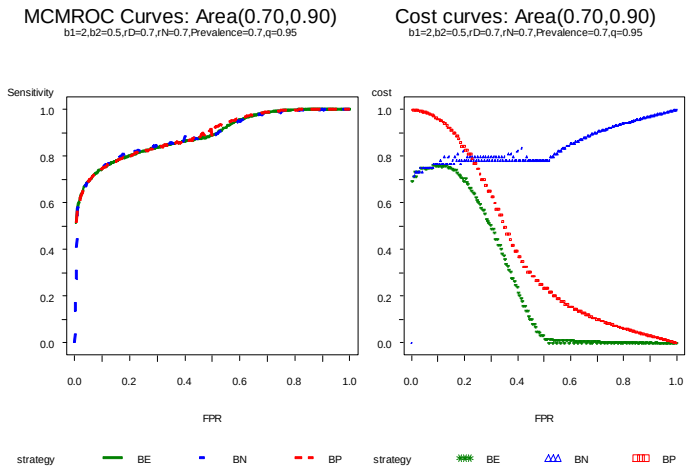


Figure C5. 2f: (b1=2, b2=0.5)

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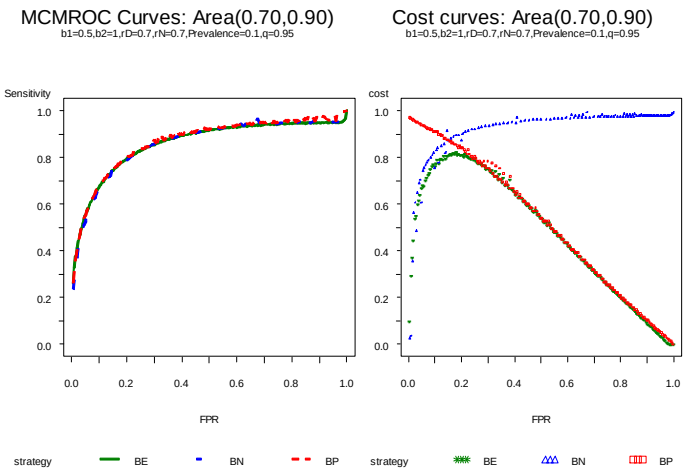


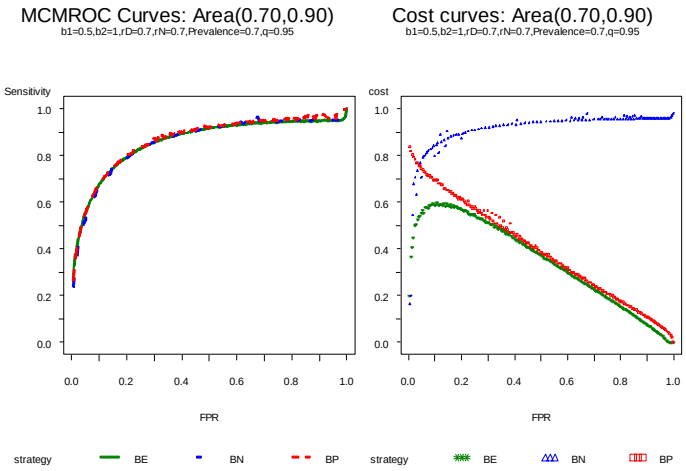
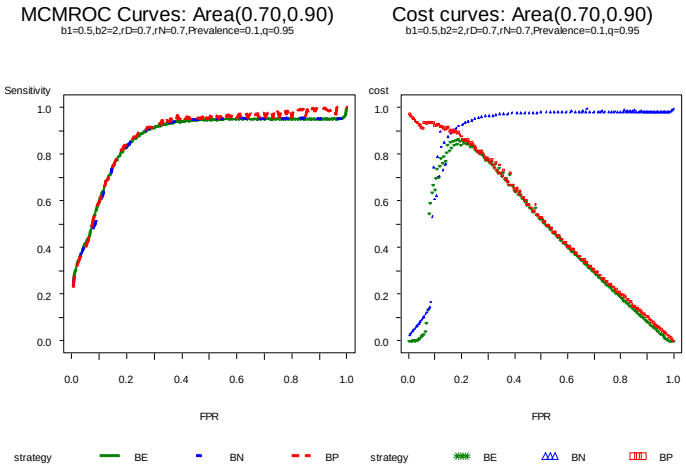


Figure C5. 2g: (b1=0.5, b2=1)



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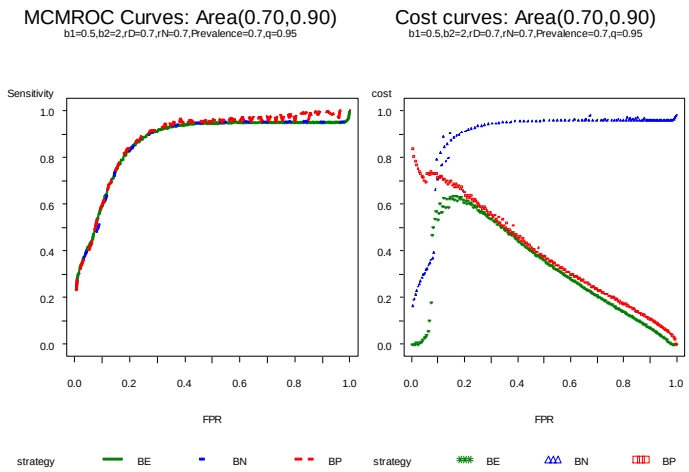

Figure C5. 2h: (b1=0.5, b2=2)

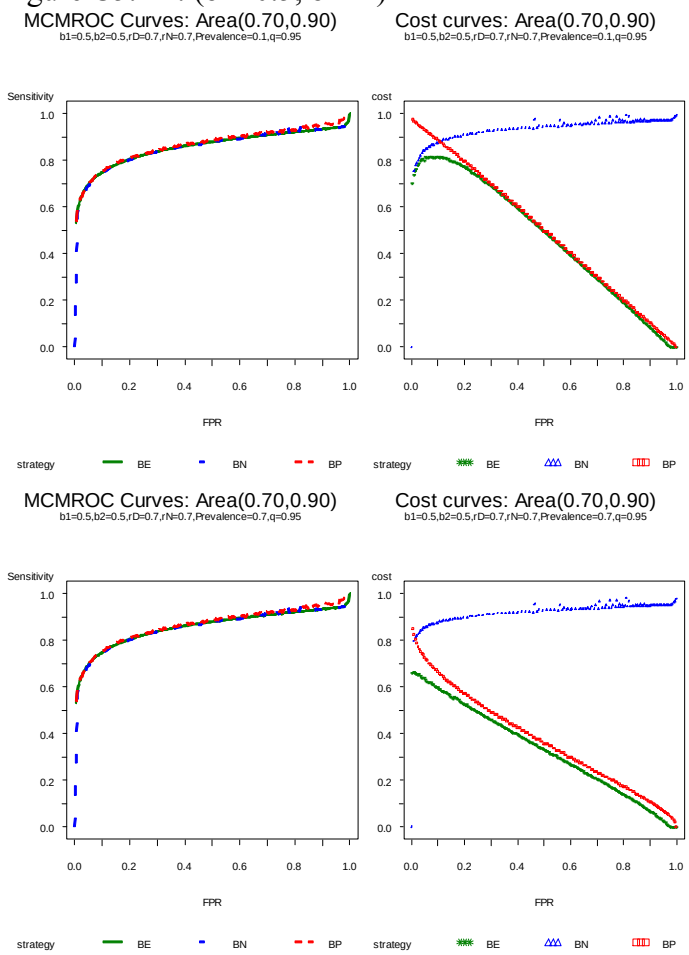

Figure C5. 2i: (b1=0.5, b2=0.5)

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C5. 3 AUC1 = 0.70, AUC2 = 0.70

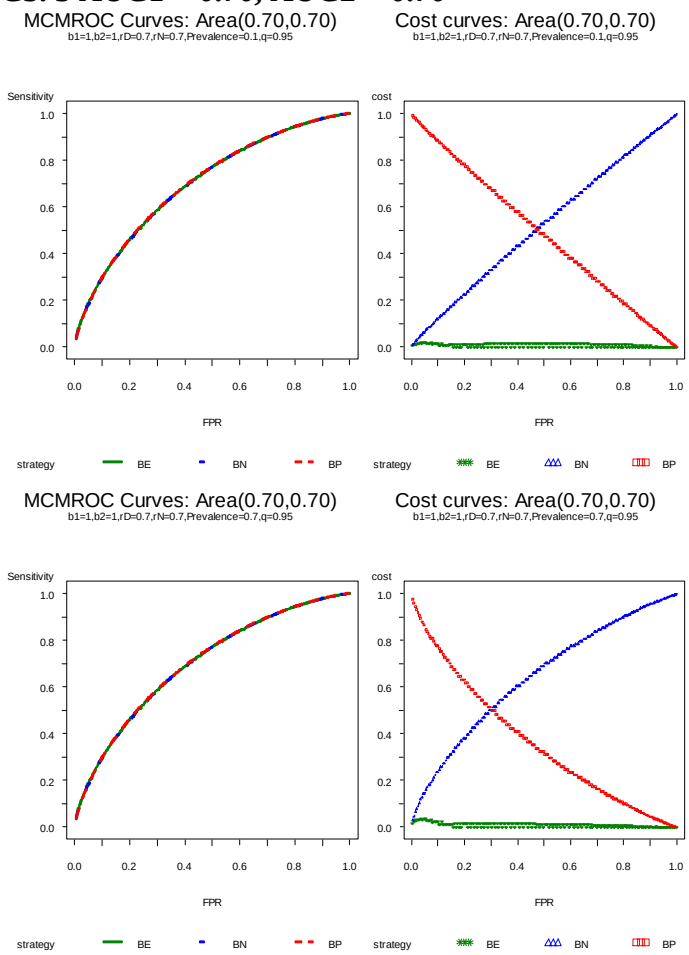
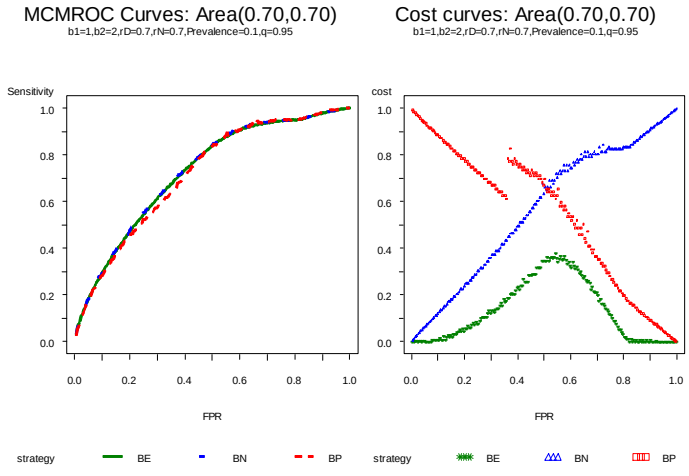


Figure C5. 3a: (b1=1, b2=1)



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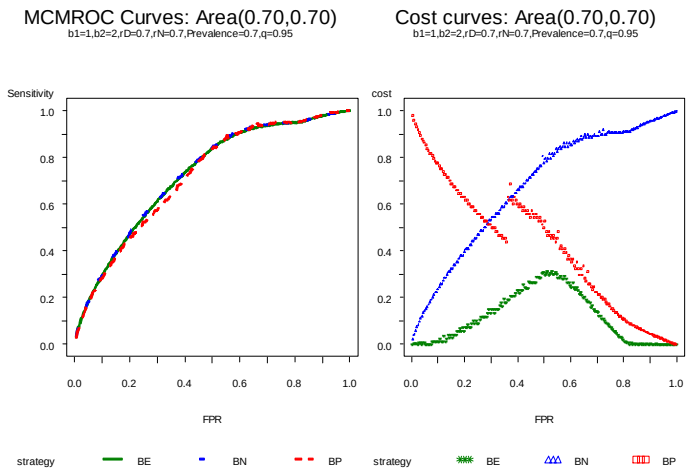
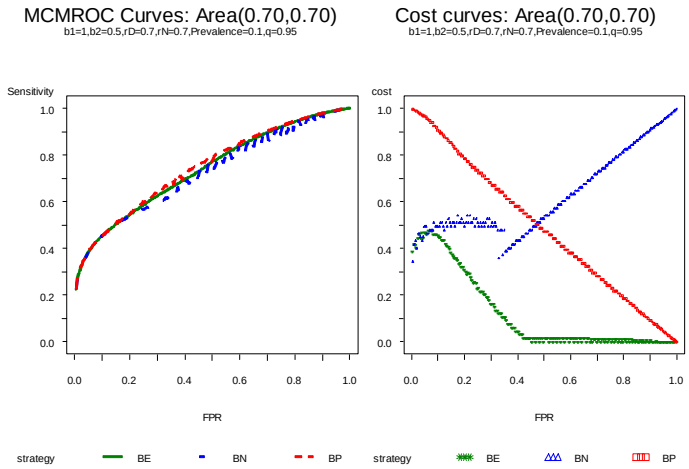


Figure C5. 3b: (b1=1, b2=2)



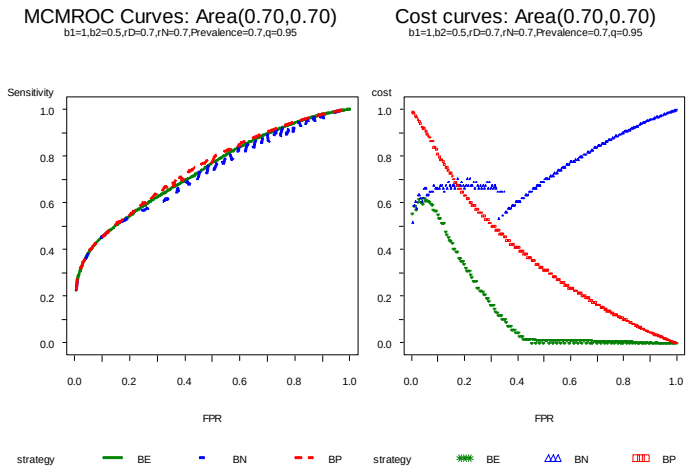


Figure C5. 3c: (b1=1, b2=0.5)

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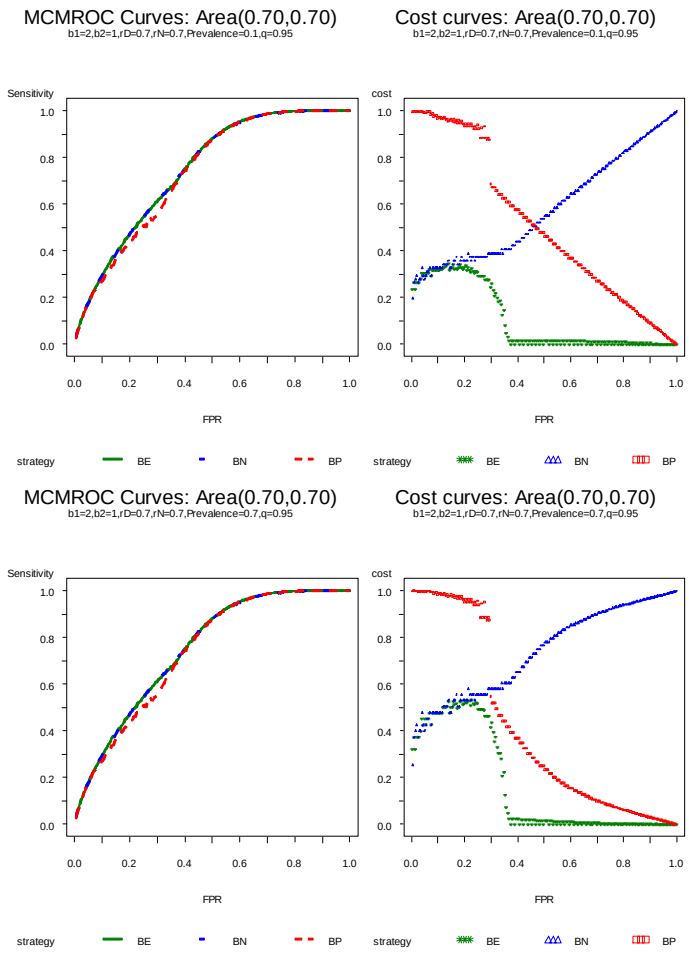
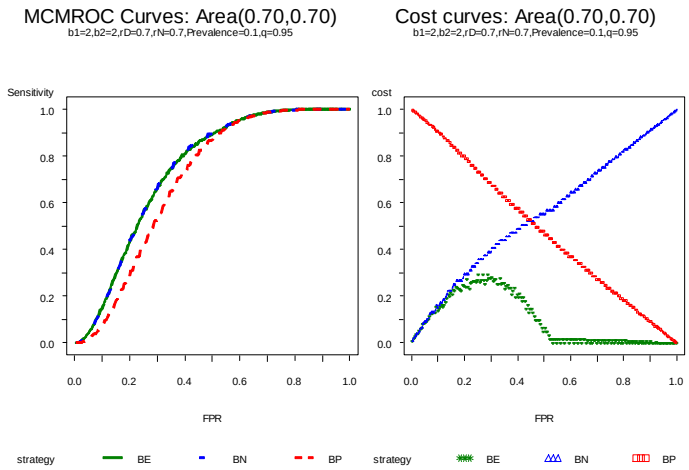


Figure C5. 3d: (b1=2, b2=1)



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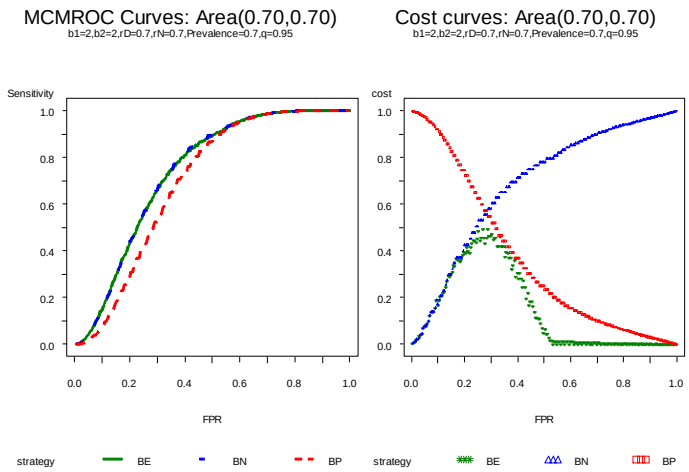

Figure C5. 3e: (b1=2, b2=2)

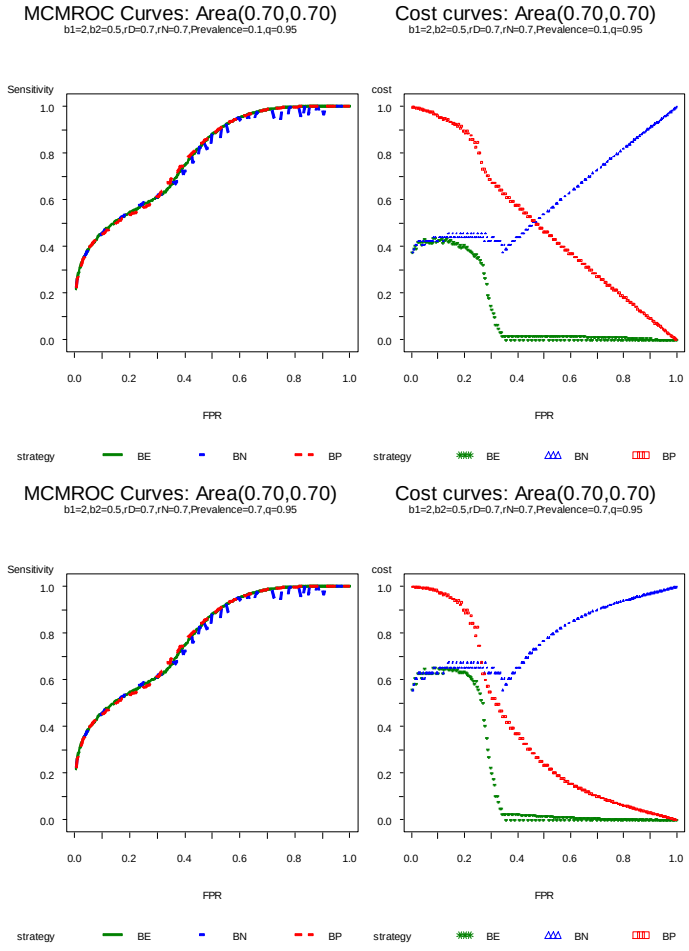

Figure C5. 3f: (b1=2, b2=0.5)

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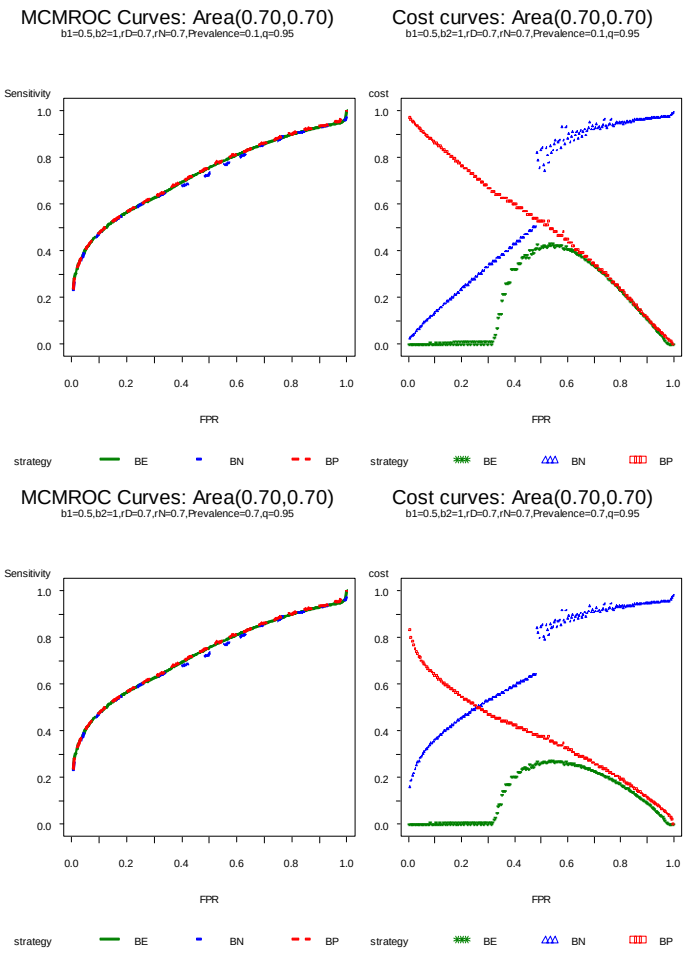
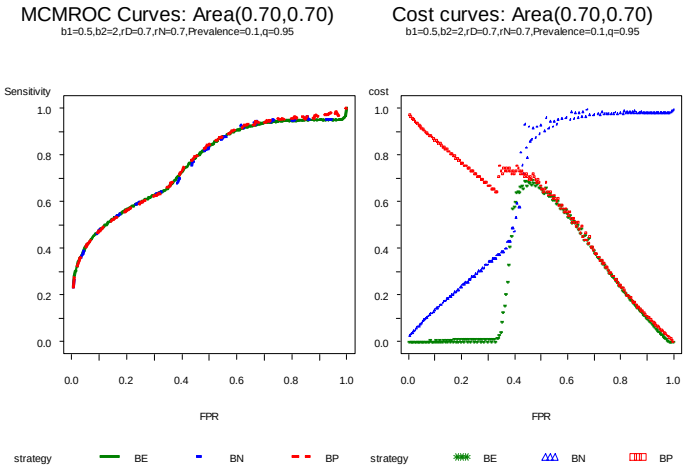


Figure C5. 3g: (b1=0.5, b2=1)



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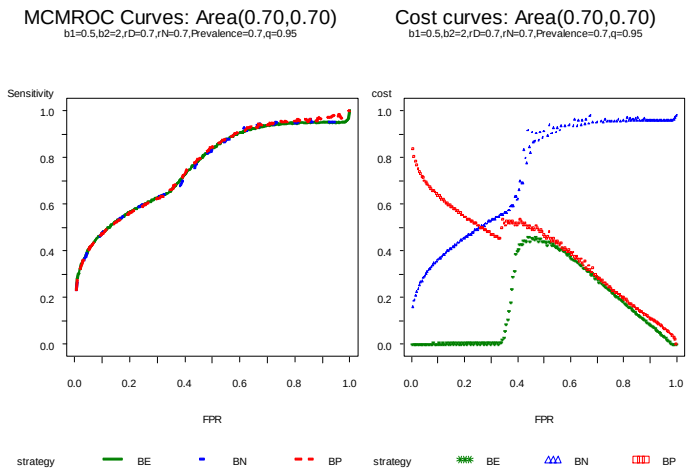
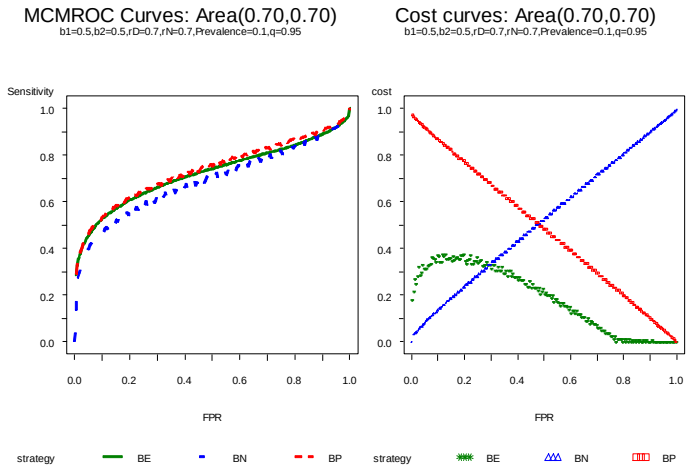


Figure C5. 3h: (b1=0.5, b2=2)



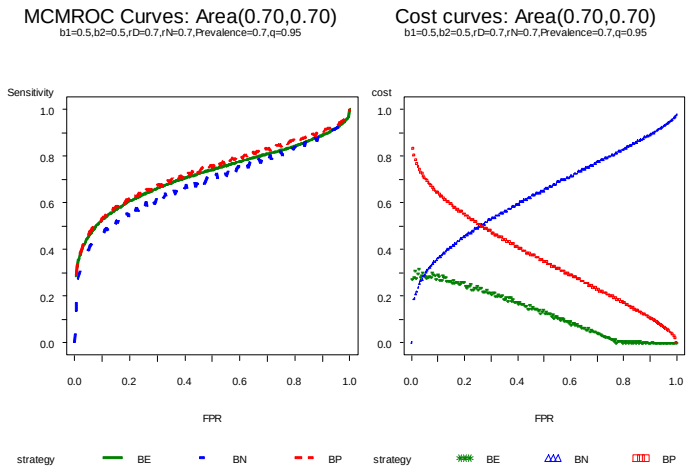


Figure C5. 3i: (b1=0.5, b2=0.5)

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Appendix D

SAS programs

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D1: Define permanent SAS formats

```
libname FORMAT 'C:\project';
run;
proc format LIBRARY = FORMAT ;
value lessthan (multilabel)
0-0.005      = '<=0.005'
0-0.01 = '<=0.01'
0-0.015      = '<=0.015'
0-0.02 = '<=0.02'
0-0.025      = '<=0.025'
0-0.03 = '<=0.03'
0-0.035      = '<=0.035'
0-0.04 = '<=0.04'
0-0.045      = '<=0.045'
0-0.05 = '<=0.05'
0-0.055      = '<=0.055'
0-0.06 = '<=0.06'
0-0.065      = '<=0.065'
0-0.07 = '<=0.07'
0-0.075      = '<=0.075'
0-0.08 = '<=0.08'
0-0.085      = '<=0.085'
0-0.09 = '<=0.09'
0-0.095      = '<=0.095'
0-0.10 = '<=0.1'
0-0.105      = '<=0.105'
0-0.11 = '<=0.11'
0-0.115      = '<=0.115'
0-0.12 = '<=0.12'
0-0.125      = '<=0.125'
0-0.13 = '<=0.13'
0-0.135      = '<=0.135'
0-0.14 = '<=0.14'
0-0.145      = '<=0.145'
0-0.15 = '<=0.15'
0-0.155      = '<=0.155'
0-0.16 = '<=0.16'
0-0.165      = '<=0.165'
0-0.17 = '<=0.17'
0-0.175      = '<=0.175'
0-0.18 = '<=0.18'
```

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0-0.185 = '<=0.185'
0-0.19 = '<=0.19'
0-0.195 = '<=0.195'
0-0.2 = '<=0.2'
0-0.205 = '<=0.205'
0-0.21 = '<=0.21'
0-0.215 = '<=0.215'
0-0.22 = '<=0.22'
0-0.225 = '<=0.225'
0-0.23 = '<=0.23'
0-0.235 = '<=0.235'
0-0.24 = '<=0.24'
0-0.245 = '<=0.245'
0-0.25 = '<=0.25'
0-0.255 = '<=0.255'
0-0.26 = '<=0.26'
0-0.265 = '<=0.265'
0-0.27 = '<=0.27'
0-0.275 = '<=0.275'
0-0.28 = '<=0.28'
0-0.285 = '<=0.285'
0-0.29 = '<=0.29'
0-0.295 = '<=0.295'
0-0.30 = '<=0.3'
0-0.305 = '<=0.305'
0-0.31 = '<=0.31'
0-0.315 = '<=0.315'
0-0.32 = '<=0.32'
0-0.325 = '<=0.325'
0-0.33 = '<=0.33'
0-0.335 = '<=0.335'
0-0.34 = '<=0.34'
0-0.345 = '<=0.345'
0-0.35 = '<=0.35'
0-0.355 = '<=0.355'
0-0.36 = '<=0.36'
0-0.365 = '<=0.365'
0-0.37 = '<=0.37'
0-0.375 = '<=0.375'
0-0.38 = '<=0.38'
0-0.385 = '<=0.385'
0-0.39 = '<=0.39'
0-0.395 = '<=0.395'
0-0.40 = '<=0.4'
0-0.405 = '<=0.405'
0-0.41 = '<=0.41'

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0-0.415 = '<=0.415'
0-0.42 = '<=0.42'
0-0.425 = '<=0.425'
0-0.43 = '<=0.43'
0-0.435 = '<=0.435'
0-0.44 = '<=0.44'
0-0.445 = '<=0.445'
0-0.45 = '<=0.45'
0-0.455 = '<=0.455'
0-0.46 = '<=0.46'
0-0.465 = '<=0.465'
0-0.47 = '<=0.47'
0-0.475 = '<=0.475'
0-0.48 = '<=0.48'
0-0.485 = '<=0.485'
0-0.49 = '<=0.49'
0-0.495 = '<=0.495'
0-0.50 = '<=0.50'
0-0.505 = '<=0.505'
0-0.51 = '<=0.51'
0-0.515 = '<=0.515'
0-0.52 = '<=0.52'
0-0.525 = '<=0.525'
0-0.53 = '<=0.53'
0-0.535 = '<=0.535'
0-0.54 = '<=0.54'
0-0.545 = '<=0.545'
0-0.55 = '<=0.55'
0-0.555 = '<=0.555'
0-0.56 = '<=0.56'
0-0.565 = '<=0.565'
0-0.57 = '<=0.57'
0-0.575 = '<=0.575'
0-0.58 = '<=0.58'
0-0.585 = '<=0.585'
0-0.59 = '<=0.59'
0-0.595 = '<=0.595'
0-0.60 = '<=0.6'
0-0.605 = '<=0.605'
0-0.61 = '<=0.61'
0-0.615 = '<=0.615'
0-0.62 = '<=0.62'
0-0.625 = '<=0.625'
0-0.63 = '<=0.63'
0-0.635 = '<=0.635'
0-0.64 = '<=0.64'

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0-0.645 = '<=0.645'
0-0.65 = '<=0.65'
0-0.655 = '<=0.655'
0-0.66 = '<=0.66'
0-0.665 = '<=0.665'
0-0.67 = '<=0.67'
0-0.675 = '<=0.675'
0-0.68 = '<=0.68'
0-0.685 = '<=0.685'
0-0.69 = '<=0.69'
0-0.695 = '<=0.695'
0-0.70 = '<=0.7'
0-0.705 = '<=0.705'
0-0.71 = '<=0.71'
0-0.715 = '<=0.715'
0-0.72 = '<=0.72'
0-0.725 = '<=0.725'
0-0.73 = '<=0.73'
0-0.735 = '<=0.735'
0-0.74 = '<=0.74'
0-0.745 = '<=0.745'
0-0.75 = '<=0.75'
0-0.755 = '<=0.755'
0-0.76 = '<=0.76'
0-0.765 = '<=0.765'
0-0.77 = '<=0.77'
0-0.775 = '<=0.775'
0-0.78 = '<=0.78'
0-0.785 = '<=0.785'
0-0.79 = '<=0.79'
0-0.795 = '<=0.795'
0-0.80 = '<=0.8'
0-0.805 = '<=0.805'
0-0.81 = '<=0.81'
0-0.815 = '<=0.815'
0-0.82 = '<=0.82'
0-0.825 = '<=0.825'
0-0.83 = '<=0.83'
0-0.835 = '<=0.835'
0-0.84 = '<=0.84'
0-0.845 = '<=0.845'
0-0.85 = '<=0.85'
0-0.855 = '<=0.855'
0-0.86 = '<=0.86'
0-0.865 = '<=0.865'
0-0.87 = '<=0.87'

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```
0-0.875          = '<=0.875'
0-0.88  = '<=0.88'
0-0.885          = '<=0.885'
0-0.89  = '<=0.89'
0-0.895          = '<=0.895'
0-0.900          =  '<=0.9'
0-0.905          = '<=0.905'
0-0.91  = '<=0.91'
0-0.915          = '<=0.915'
0-0.92  = '<=0.92'
0-0.925          = '<=0.925'
0-0.93  = '<=0.93'
0-0.935          = '<=0.935'
0-0.94  = '<=0.94'
0-0.945          = '<=0.945'
0-0.95  = '<=0.95'
0-0.955          = '<=0.955'
0-0.96  = '<=0.96'
0-0.965          = '<=0.965'
0-0.97  = '<=0.97'
0-0.975          = '<=0.975'
0-0.98  = '<=0.98'
0-0.985          = '<=0.985'
0-0.99  = '<=0.99'
0-0.995          = '<=0.995'
0-1.00  = '<=1';run;
```

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D2: Generating MROC/MCMROC and cost curves

```
libname bios 'C:\ project \r0r0\90_90\b1b1';run;
LIBNAME FRMT 'C:\ project';run;
OPTIONS FMTSEARCH=(FRMT);run;
*****************************************BP*****;
data rocBP;
do c1=-3 to 4.81 by 0.04;
do c2=-3 to 4.81 by 0.04;
Sensitivity = 1-probbnrm((c1-1.81)/1,(c2-1.81)/1, 0);
FP = 1-probbnrm((c1-0)/1,(c2-0)/1, 0);
FPR = ceil(FP*200)/200 + (FP=0);
costp01 = (probnorm((c1-1.81)/1 ))* 0.1 + (probnorm((c1-0)/1 ))*(1-0.1) ;
costp07 = (probnorm((c1-1.81)/1 ))* 0.7 + (probnorm((c1-0)/1 ))*(1-0.7) ;
output;
end;
end;
run;quit;
proc sort data=rocBP; by FP;run;
proc means data=rocBP max noprint nway;
var Sensitivity; class FP ;
output out=mrocBP (drop=_type_ _freq_ FP)
            max=MTPR
            maxid(Sensitivity(c1))=c1
      maxid(Sensitivity(c2))=c2
      maxid(Sensitivity(Sensitivity))=Sensitivity
      maxid(Sensitivity(costp01))=costp01
      maxid(Sensitivity(costp07))=costp07;
format FP lessthan.;
run;
data mrocBP;set mrocBP;FPR=_n_/200;run;
/********************** MCMROC******************/
proc sort data=rocBP; by FPR;run;
proc sort data=mrocBP; by FPR ;run;
data mrocBPq;
merge rocBP mrocBP;
by FPR;
run;
**************q=1 PREV=0.1*************************;
data mrocBPq1;
set mrocBPq ;
TPRmaxq = 1 * MTPR ;
if Sensitivity >= TPRmaxq then q=1;
else q=0;
if q=0 then delete;
run;
```

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```
proc sort data=mrocBPq1; by FPR costp01 descending Sensitivity ;run;
proc means data=mrocBPq1  min noprint nway;
var costp01; class FP ;
output out=mincq1BPp01 (drop=_type_ _freq_ FP)
     min=cost
     minid(costp01(c1))=c1
     minid(costp01(c2))=c2
     minid(costp01(FPR))=FPR
     minid(costp01(MTPR))=MTPR
     minid(costp01(TPRmaxq))=TPRmaxq
     minid(costp01(Sensitivity))=Sensitivity;
format FP lessthan.;
run; ******************q=1 PREV=0.7*************************;
proc sort data=mrocBPq1; by FPR costp07 descending Sensitivity ;run;
proc means data=mrocBPq1  min noprint nway;
var costp07; class FP ;
output out=mincq1BPp07 (drop=_type_ _freq_ FP)
     min=cost
     minid(costp07(c1))=c1
     minid(costp07(c2))=c2
     minid(costp07(FPR))=FPR
     minid(costp07(MTPR))=MTPR
     minid(costp07(TPRmaxq))=TPRmaxq
     minid(costp07(Sensitivity))=Sensitivity;
format FP lessthan.;
run;
*****************q=0.95 PREV=0.1******;
data mrocBPq95;
set mrocBPq ;
TPRmaxq = 0.95 * MTPR ;
if Sensitivity >= TPRmaxq then q=1;
else q=0;
if q=0 then delete;
run;
proc sort data=mrocBPq95; by FPR costp01 descending Sensitivity ;run;
proc means data=mrocBPq95  min noprint nway;
var costp01; class FP ;
output out=mincq95BPp01 (drop=_type_ _freq_ FP)
     min=cost
     minid(costp01(c1))=c1
     minid(costp01(c2))=c2
     minid(costp01(FPR))=FPR
     minid(costp01(MTPR))=MTPR
     minid(costp01(TPRmaxq))=TPRmaxq
     minid(costp01(Sensitivity))=Sensitivity;
format FP lessthan.;
```

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```
run;
*********************************************q=1 PREV=0.7***;
proc sort data=mrocBPq95; by FPR costp07 descending Sensitivity ;run;
proc means data=mrocBPq95  min noprint nway;
var costp07; class FP ;
output out=mincq95BPp07 (drop=_type_ _freq_ FP)
     min=cost
     minid(costp07(c1))=c1
     minid(costp07(c2))=c2
     minid(costp07(FPR))=FPR
     minid(costp07(MTPR))=MTPR
     minid(costp07(TPRmaxq))=TPRmaxq
     minid(costp07(Sensitivity))=Sensitivity;
format FP lessthan.;
run;
*********************************************BN*****;
data rocBN;
do c1=-3 to 4.81 by 0.04;
do c2=-3 to 4.81 by 0.04;
Sensitivity = 1-cdf('NORMAL',(c1-1.81)/1 ,0,1)-cdf('NORMAL',(c2-1.81)/1 ,0,1) +
probbnrm((c1-1.81)/1,(c2-1.81)/1, 0);
FP = 1-cdf('NORMAL',(c1-0)/1 ,0,1)-cdf('NORMAL',(c2-0)/1 ,0,1) + probbnrm((c1-
0)/1,(c2-0)/1, 0);
FPR = ceil(FP*200)/200 + (FP=0);
costp01 = (1-probnorm((c1-1.81)/1 )) * 0.1 +  (1-probnorm((c1-0)/1 ))*(1-0.1) ;
costp07 = (1-probnorm((c1-1.81)/1 )) * 0.7 +  (1-probnorm((c1-0)/1 ))*(1-0.7) ;
output;
end;
end;
run;
proc sort data=rocBN; by FP;run;
proc means data=rocBN max noprint nway;
var Sensitivity; class FP / mlf;
output out=mrocBN (drop=_type_ _freq_ FP)
          max=MTPR
          maxid(Sensitivity(c1))=c1
     maxid(Sensitivity(c2))=c2
     maxid(Sensitivity(Sensitivity))=Sensitivity
     maxid(Sensitivity(costp01))=costp01
     maxid(Sensitivity(costp07))=costp07;
format FP lessthan.;
run;
data mrocBN;set mrocBN;FPR=_n_/200;run;
/************************************* MCMROC****/
proc sort data=rocBN; by FPR;run;
proc sort data=mrocBN; by FPR ;run;
```

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```
data mrocBNq;
merge rocBN mrocBN;
by FPR;
run;
*********************************************q=1 PREV=0.1***;
data mrocBNq1;
set mrocBNq ;
TPRmaxq = 1 * MTPR ;
if Sensitivity >= TPRmaxq then q=1;
else q=0;
if q=0 then delete;
run;
proc sort data=mrocBNq1; by FPR costp01 descending Sensitivity ;run;
proc means data=mrocBNq1  min noprint nway;
var costp01; class FP ;
output out=mincq1BNp01 (drop=_type_ _freq_ FP)
     min=cost
     minid(costp01(c1))=c1
     minid(costp01(c2))=c2
     minid(costp01(FPR))=FPR
     minid(costp01(MTPR))=MTPR
     minid(costp01(TPRmaxq))=TPRmaxq
     minid(costp01(Sensitivity))=Sensitivity;
format FP lessthan.;
run;
*********************************************q=1 PREV=0.7*****;
proc sort data=mrocBNq1; by FPR costp07 descending Sensitivity ;run;
proc means data=mrocBNq1  min noprint nway;
var costp07; class FP ;
output out=mincq1BNp07 (drop=_type_ _freq_ FP)
     min=cost
     minid(costp07(c1))=c1
     minid(costp07(c2))=c2
     minid(costp07(FPR))=FPR
     minid(costp07(MTPR))=MTPR
     minid(costp07(TPRmaxq))=TPRmaxq
     minid(costp07(Sensitivity))=Sensitivity;
format FP lessthan.;
run;
*********************************************q=0.95 PREV=0.1*****;
data mrocBNq95;
set mrocBNq ;
TPRmaxq = 0.95 * MTPR ;
if Sensitivity >= TPRmaxq then q=1;
else q=0;
if q=0 then delete;
```

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```
run;
proc sort data=mrocBNq95; by FPR costp01 descending Sensitivity ;run;
proc means data=mrocBNq95  min noprint nway;
var costp01; class FP ;
output out=mincq95BNp01 (drop=_type_ _freq_ FP)
     min=cost
     minid(costp01(c1))=c1
     minid(costp01(c2))=c2
     minid(costp01(FPR))=FPR
     minid(costp01(MTPR))=MTPR
     minid(costp01(TPRmaxq))=TPRmaxq
     minid(costp01(Sensitivity))=Sensitivity;
format FP lessthan.;
run;
********************q=1 PREV=0.7**********************;
proc sort data=mrocBNq95; by FPR costp07 descending Sensitivity ;run;
proc means data=mrocBNq95  min noprint nway;
var costp07; class FP ;
output out=mincq95BNp07 (drop=_type_ _freq_ FP)
     min=cost
     minid(costp07(c1))=c1
     minid(costp07(c2))=c2
     minid(costp07(FPR))=FPR
     minid(costp07(MTPR))=MTPR
     minid(costp07(TPRmaxq))=TPRmaxq
     minid(costp07(Sensitivity))=Sensitivity;
format FP lessthan.;
run;

******BE*************************************************************;
data rocBE;
do c1=-3 to 4.81 by 0.04;
do c2=-3 to c1 by 0.04;
do c3=-3 to 4.81 by 0.04;
Sensitivity = 1-cdf('NORMAL',(c2-1.81)/1 ,0,1) + probbnrm((c2-1.81)/1,(c3-1.81)/1, 0) -
probbnrm((c1-1.81)/1,(c3-1.81)/1, 0);
FP = 1-cdf('NORMAL',(c2-0)/1 ,0,1) + probbnrm((c2-0)/1,(c3-0)/1, 0) - probbnrm((c1-
0)/1,(c3-0)/1, 0);
FPR = ceil(FP*200)/200 + (FP=0);
costp01 =(probnorm((c1-1.81)/1 )-probnorm((c2-1.81)/1 ))*0.1 + (probnorm((c1-0)/1 )-
probnorm((c2-0)/1 ))*(1-0.1) ;
costp07 =(probnorm((c1-1.81)/1 )-probnorm((c2-1.81)/1 ))*0.7 + (probnorm((c1-0)/1 )-
probnorm((c2-0)/1 ))*(1-0.7) ;
output;
end;
end;
```

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```
end;
run;
proc sort data=rocBE; by FP;run;
proc means data=rocBE max noprint nway;
var Sensitivity; class FP / mlf;
output out=mrocBE (drop=_type_ _freq_ FP)
            max=MTPR
            maxid(Sensitivity(c1))=c1
      maxid(Sensitivity(c2))=c2
            maxid(Sensitivity(c3))=c3
      maxid(Sensitivity(Sensitivity))=Sensitivity
      maxid(Sensitivity(costp01))=costp01
      maxid(Sensitivity(costp07))=costp07;
format FP lessthan.;
run;
data mrocBE;set mrocBE;FPR=_n_/200;run;
/************************************* MCMROC*****/
proc sort data=rocBE; by FPR;run;
proc sort data=mrocBE; by FPR ;run;
data mrocBEq;
merge rocBE mrocBE;
by FPR;
run;
*********************************************q=1 PREV=0.1*********;
data mrocBEq1;
set mrocBEq ;
TPRmaxq = 1 * MTPR ;
if Sensitivity >= TPRmaxq then q=1;
else q=0;
if q=0 then delete;
run;
proc sort data=mrocBEq1; by FPR costp01 descending Sensitivity ;run;
proc means data=mrocBEq1  min noprint nway;
var costp01; class FP ;
output out=mincq1BEp01 (drop=_type_ _freq_ FP)
     min=cost
     minid(costp01(c1))=c1
     minid(costp01(c2))=c2
     minid(costp01(c3))=c3
     minid(costp01(FPR))=FPR
     minid(costp01(MTPR))=MTPR
     minid(costp01(TPRmaxq))=TPRmaxq
     minid(costp01(Sensitivity))=Sensitivity;
format FP lessthan.;
run;
******************q=1 PREV=0.7*********************************;
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```
proc sort data=mrocBEq1; by FPR costp07 descending Sensitivity ;run;
proc means data=mrocBEq1  min noprint nway;
var costp07; class FP ;
output out=mincq1BEp07 (drop=_type_ _freq_ FP)
     min=cost
     minid(costp07(c1))=c1
     minid(costp07(c2))=c2
          minid(costp01(c3))=c3
     minid(costp07(FPR))=FPR
     minid(costp07(MTPR))=MTPR
     minid(costp07(TPRmaxq))=TPRmaxq
     minid(costp07(Sensitivity))=Sensitivity;
format FP lessthan.;
run;
**********q=0.95 PREV=0.1**********;
data mrocBEq95;
set mrocBEq ;
TPRmaxq = 0.95 * MTPR ;
if Sensitivity >= TPRmaxq then q=1;
else q=0;
if q=0 then delete;
run;
proc sort data=mrocBEq95; by FPR costp01 descending Sensitivity ;run;
proc means data=mrocBEq95  min noprint nway;
var costp01; class FP ;
output out=mincq95BEp01 (drop=_type_ _freq_ FP)
     min=cost
     minid(costp01(c1))=c1
     minid(costp01(c2))=c2
          minid(costp01(c3))=c3
     minid(costp01(FPR))=FPR
     minid(costp01(MTPR))=MTPR
     minid(costp01(TPRmaxq))=TPRmaxq
     minid(costp01(Sensitivity))=Sensitivity;
format FP lessthan.;
run;
**********q=1 PREV=0.7**********;
proc sort data=mrocBEq95; by FPR costp07 descending Sensitivity ;run;
proc means data=mrocBEq95  min noprint nway;
var costp07; class FP ;
output out=mincq95BEp07 (drop=_type_ _freq_ FP)
     min=cost
     minid(costp07(c1))=c1
     minid(costp07(c2))=c2
          minid(costp01(c3))=c3
     minid(costp07(FPR))=FPR
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```
    minid(costp07(MTPR))=MTPR
    minid(costp07(TPRmaxq))=TPRmaxq
    minid(costp07(Sensitivity))=Sensitivity;
format FP lessthan.;
run;
*********************************************q=0.999 *****;
data mrocBPq999;
set mrocBPq ;
TPRmaxq = 0.999 * MTPR ;
if Sensitivity >= TPRmaxq then q=1;
else q=0;
if q=0 then delete;
run;
proc sort data=mrocBPq999; by FPR costp01 descending Sensitivity ;run;
proc means data=mrocBPq999  min noprint nway;
var costp01; class FP ;
output out=mincq999BPp01 (drop=_type_ _freq_ FP)
    min=cost
    minid(costp01(c1))=c1
    minid(costp01(c2))=c2
    minid(costp01(FPR))=FPR
    minid(costp01(MTPR))=MTPR
    minid(costp01(TPRmaxq))=TPRmaxq
    minid(costp01(Sensitivity))=Sensitivity;
format FP lessthan.;
run;
**********q=1 PREV=0.7**********;
proc sort data=mrocBPq999; by FPR costp07 descending Sensitivity ;run;
proc means data=mrocBPq999  min noprint nway;
var costp07; class FP ;
output out=mincq999BPp07 (drop=_type_ _freq_ FP)
    min=cost
    minid(costp07(c1))=c1
    minid(costp07(c2))=c2
    minid(costp07(FPR))=FPR
    minid(costp07(MTPR))=MTPR
    minid(costp07(TPRmaxq))=TPRmaxq
    minid(costp07(Sensitivity))=Sensitivity;
format FP lessthan.;
run;
**********************q=0.999 PREV=0.1**********************;
data mrocBNq999;
set mrocBNq ;
TPRmaxq = 0.999 * MTPR ;
if Sensitivity >= TPRmaxq then q=1;
else q=0;
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```
if q=0 then delete;
run;
proc sort data=mrocBNq999; by FPR costp01 descending Sensitivity ;run;
proc means data=mrocBNq999  min noprint nway;
var costp01; class FP ;
output out=mincq999BNp01 (drop=_type_ _freq_ FP)
     min=cost
     minid(costp01(c1))=c1
     minid(costp01(c2))=c2
     minid(costp01(FPR))=FPR
     minid(costp01(MTPR))=MTPR
     minid(costp01(TPRmaxq))=TPRmaxq
     minid(costp01(Sensitivity))=Sensitivity;
format FP lessthan.;
run;
**********************************************q=1 PREV=0.7***;
proc sort data=mrocBNq999; by FPR costp07 descending Sensitivity ;run;
proc means data=mrocBNq999  min noprint nway;
var costp07; class FP ;
output out=mincq999BNp07 (drop=_type_ _freq_ FP)
     min=cost
     minid(costp07(c1))=c1
     minid(costp07(c2))=c2
     minid(costp07(FPR))=FPR
     minid(costp07(MTPR))=MTPR
     minid(costp07(TPRmaxq))=TPRmaxq
     minid(costp07(Sensitivity))=Sensitivity;
format FP lessthan.;
run;
**********************************************q=0.999 PREV=0.1**;
data mrocBEq999;
set mrocBEq ;
TPRmaxq = 0.999 * MTPR ;
if Sensitivity >= TPRmaxq then q=1;
else q=0;
if q=0 then delete;
run;
proc sort data=mrocBEq999; by FPR costp01 descending Sensitivity ;run;
proc means data=mrocBEq999  min noprint nway;
var costp01; class FP ;
output out=mincq999BEp01 (drop=_type_ _freq_ FP)
     min=cost
     minid(costp01(c1))=c1
     minid(costp01(c2))=c2
          minid(costp01(c3))=c3
     minid(costp01(FPR))=FPR
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    minid(costp01(MTPR))=MTPR
    minid(costp01(TPRmaxq))=TPRmaxq
    minid(costp01(Sensitivity))=Sensitivity;
format FP lessthan.;
run;
*********************************************q=1 PREV=0.7***;
proc sort data=mrocBEq999; by FPR costp07 descending Sensitivity ;run;
proc means data=mrocBEq999  min noprint nway;
var costp07; class FP ;
output out=mincq999BEp07 (drop=_type_ _freq_ FP)
    min=cost
    minid(costp07(c1))=c1
    minid(costp07(c2))=c2
        minid(costp01(c3))=c3
    minid(costp07(FPR))=FPR
    minid(costp07(MTPR))=MTPR
    minid(costp07(TPRmaxq))=TPRmaxq
    minid(costp07(Sensitivity))=Sensitivity;
format FP lessthan.;
run;
*******************q=1,Prevalence=0.1,MROC curves **************;
data mincq1BEp01; set mincq1BEp01;strategy='BE';run;
data mincq1BNp01; set mincq1BNp01;strategy='BN';run;
data mincq1BPp01; set mincq1BPp01;strategy='BP';run;
data bios.mcmrocq1p01;
set mincq1BEp01 mincq1BNp01 mincq1BPp01;
run;
data mincq1BEp07; set mincq1BEp07;strategy='BE';run;
data mincq1BNp07; set mincq1BNp07;strategy='BN';run;
data mincq1BPp07; set mincq1BPp07;strategy='BP';run;
data bios.mcmrocq1p07;
set mincq1BEp07 mincq1BNp07 mincq1BPp07;
run;
data mincq95BEp01; set mincq95BEp01;strategy='BE';run;
data mincq95BNp01; set mincq95BNp01;strategy='BN';run;
data mincq95BPp01; set mincq95BPp01;strategy='BP';run;
data bios.mcmrocq95p01;
set mincq95BEp01 mincq95BNp01 mincq95BPp01;
run;
data mincq95BEp07; set mincq95BEp07;strategy='BE';run;
data mincq95BNp07; set mincq95BNp07;strategy='BN';run;
data mincq95BPp07; set mincq95BPp07;strategy='BP';run;
data bios.mcmrocq95p07;
set mincq95BEp07 mincq95BNp07 mincq95BPp07;
run;
data mincq999BEp01; set mincq999BEp01;strategy='BE';run;
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data mincq999BNp01; set mincq999BNp01;strategy='BN';run;
data mincq999BPp01; set mincq999BPp01;strategy='BP';run;
data bios.mcmrocq999p01;
set mincq999BEp01 mincq999BNp01 mincq999BPp01;
run;
data mincq999BEp07; set mincq999BEp07;strategy='BE';run;
data mincq999BNp07; set mincq999BNp07;strategy='BN';run;
data mincq999BPp07; set mincq999BPp07;strategy='BP';run;
data bios.mcmrocq999p07;
set mincq999BEp07 mincq999BNp07 mincq999BPp07;
run;
ODS rtf FILE = 'C:\sim\r0r0\90_90\b1b1\q1q95final.rtf'  style=journal2;
goptions reset=all vsize=2.5 hsize=1.9 htitle=.8 htext=.4;
axis1 w=1 order=(0 to 1 by 0.2) major=(h=.2) minor =(n=1); axis2 w=1 order=(0 to 1 by
0.2) major=(h=.2) minor =(n=1);
SYMBOL1 v=none COLOR=green INTERPOL=join LINE=1 h=1 w=2;
SYMBOL2 v=none COLOR=blue INTERPOL=join LINE=35 h=1 w=2;
SYMBOL3 v=none COLOR=red INTERPOL=join LINE=2 h=1 w=2;
LEGEND1 position= (BOTTOM CENTER OUTSIDE)  shape=symbol(1.2,.5) ;
proc gplot data=bios.mcmrocq1p01;
plot Sensitivity * FPR = strategy / vaxis=axis1 haxis=axis2 LEGEND = LEGEND1;
title1 'MROC Curves: Area(0.90,0.90)';
title2 'b1=1,b2=1,rD=0,rN=0,Prevalence=0.1';
run;
goptions reset=global vsize=2.5 hsize=1.7 htitle=.8 htext=.4;
axis1 order=(0 to 1 by 0.2) major=(h=.2) minor =(n=1); axis2 order=(0 to 1 by 0.2)
major=(h=.2) minor =(n=1);
SYMBOL1 c=black v=: COLOR=green h=.2 w=.2;
SYMBOL2 c=black v=triangle COLOR=blue h=.1 w=.1;
SYMBOL3 c=black v=square COLOR=red h=.1 w=.1;
LEGEND1 position= (BOTTOM CENTER OUTSIDE)  shape=symbol(.8,.5) ;
proc gplot data=bios.mcmrocq1p01;
plot cost * FPR = strategy/ vaxis=axis1 haxis=axis2 LEGEND = LEGEND1;
title1 'Cost curves: Area(0.90,0.90)';
title2 'b1=1,b2=1,rD=0,rN=0,Prevalence=0.1';
run;
/**********************************Prevalence=0.7***************/
goptions reset=all vsize=2.5 hsize=1.9 htitle=.8 htext=.4;
axis1 w=1 order=(0 to 1 by 0.2) major=(h=.2) minor =(n=1); axis2 w=1 order=(0 to 1 by
0.2) major=(h=.2) minor =(n=1);
SYMBOL1 v=none COLOR=green INTERPOL=join LINE=1 h=1 w=2;
SYMBOL2 v=none COLOR=blue INTERPOL=join LINE=35 h=1 w=2;
SYMBOL3 v=none COLOR=red INTERPOL=join LINE=2 h=1 w=2;
LEGEND1 position= (BOTTOM CENTER OUTSIDE)  shape=symbol(1.2,.5) ;
proc gplot data=bios.mcmrocq1p07;
plot Sensitivity * FPR = strategy / vaxis=axis1 haxis=axis2 LEGEND = LEGEND1;
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title1 'MROC Curves: Area(0.90,0.90)';
title2 'b1=1,b2=1,rD=0,rN=0,Prevalence=0.7';
run;
goptions reset=global vsize=2.5 hsize=1.7 htitle=.8 htext=.4;
axis1 order=(0 to 1 by 0.2) major=(h=.2) minor =(n=1); axis2 order=(0 to 1 by 0.2)
major=(h=.2) minor =(n=1);
SYMBOL1 c=black v=: COLOR=green h=.2 w=.2;
SYMBOL2 c=black v=triangle COLOR=blue h=.1 w=.1;
SYMBOL3 c=black v=square COLOR=red h=.1 w=.1;
LEGEND1 position= (BOTTOM CENTER OUTSIDE)  shape=symbol(.8,.5) ;
proc gplot data=bios.mcmrocq1p07;
plot cost * FPR = strategy/ vaxis=axis1 haxis=axis2 LEGEND = LEGEND1;
title1 'Cost curves: Area(0.90,0.90)';
title2 'b1=1,b2=1,rD=0,rN=0,Prevalence=0.7';
run;
******************q=0.999,Prevalence=0.1, MCMROC curves ****;
goptions reset=all vsize=2.5 hsize=1.9 htitle=.8 htext=.4;
axis1 w=1 order=(0 to 1 by 0.2) major=(h=.2) minor =(n=1); axis2 w=1 order=(0 to 1 by
0.2) major=(h=.2) minor =(n=1);
SYMBOL1 v=none COLOR=green INTERPOL=join LINE=1 h=1 w=2;
SYMBOL2 v=none COLOR=blue INTERPOL=join LINE=35 h=1 w=2;
SYMBOL3 v=none COLOR=red INTERPOL=join LINE=2 h=1 w=2;
LEGEND1 position= (BOTTOM CENTER OUTSIDE)  shape=symbol(1.2,.5) ;
proc gplot data=bios.mcmrocq999p01;
plot Sensitivity * FPR = strategy / vaxis=axis1 haxis=axis2 LEGEND = LEGEND1;
title1 'MCMROC Curves: Area(0.90,0.90)';
title2 'b1=1,b2=1,rD=0,rN=0,Prevalence=0.1,q=0.999';
run;
goptions reset=global vsize=2.5 hsize=1.7 htitle=.8 htext=.4;
axis1 order=(0 to 1 by 0.2) major=(h=.2) minor =(n=1); axis2 order=(0 to 1 by 0.2)
major=(h=.2) minor =(n=1);
SYMBOL1 c=black v=: COLOR=green h=.2 w=.2;
SYMBOL2 c=black v=triangle COLOR=blue h=.1 w=.1;
SYMBOL3 c=black v=square COLOR=red h=.1 w=.1;
LEGEND1 position= (BOTTOM CENTER OUTSIDE)  shape=symbol(.8,.5) ;
proc gplot data=bios.mcmrocq999p01;
plot cost * FPR = strategy/ vaxis=axis1 haxis=axis2 LEGEND = LEGEND1;
title1 'Cost curves: Area(0.90,0.90)';
title2 'b1=1,b2=1,rD=0,rN=0,Prevalence=0.1,q=0.999';
run;
/*****************************************Prevalence=0.7***/
goptions reset=all vsize=2.5 hsize=1.9 htitle=.8 htext=.4;
axis1 w=1 order=(0 to 1 by 0.2) major=(h=.2) minor =(n=1); axis2 w=1 order=(0 to 1 by
0.2) major=(h=.2) minor =(n=1);
SYMBOL1 v=none COLOR=green INTERPOL=join LINE=1 h=1 w=2;
SYMBOL2 v=none COLOR=blue INTERPOL=join LINE=35 h=1 w=2;
```

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```
SYMBOL3 v=none COLOR=red INTERPOL=join LINE=2 h=1 w=2;
LEGEND1 position= (BOTTOM CENTER OUTSIDE)  shape=symbol(1.2,.5) ;
proc gplot data=bios.mcmrocq999p07;
plot Sensitivity * FPR = strategy / vaxis=axis1 haxis=axis2 LEGEND = LEGEND1;
title1 'MCMROC Curves: Area(0.90,0.90)';
title2 'b1=1,b2=1,rD=0,rN=0,Prevalence=0.7,q=0.999';
run;
goptions reset=global vsize=2.5 hsize=1.7 htitle=.8 htext=.4;
axis1 order=(0 to 1 by 0.2) major=(h=.2) minor =(n=1); axis2 order=(0 to 1 by 0.2)
major=(h=.2) minor =(n=1);
SYMBOL1 c=black v=: COLOR=green h=.2 w=.2;
SYMBOL2 c=black v=triangle COLOR=blue h=.1 w=.1;
SYMBOL3 c=black v=square COLOR=red h=.1 w=.1;
LEGEND1 position= (BOTTOM CENTER OUTSIDE)  shape=symbol(.8,.5) ;
proc gplot data=bios.mcmrocq999p07;
plot cost * FPR = strategy/ vaxis=axis1 haxis=axis2 LEGEND = LEGEND1;
title1 'Cost curves: Area(0.90,0.90)';
title2 'b1=1,b2=1,rD=0,rN=0,Prevalence=0.7,q=0.999';
run;
**********q=0.95,Prevalence=0.1, MCMROC curves ****;
goptions reset=all vsize=2.5 hsize=1.9 htitle=.8 htext=.4;
axis1 w=1 order=(0 to 1 by 0.2) major=(h=.2) minor =(n=1); axis2 w=1 order=(0 to 1 by
0.2) major=(h=.2) minor =(n=1);
SYMBOL1 v=none COLOR=green INTERPOL=join LINE=1 h=1 w=2;
SYMBOL2 v=none COLOR=blue INTERPOL=join LINE=35 h=1 w=2;
SYMBOL3 v=none COLOR=red INTERPOL=join LINE=2 h=1 w=2;
LEGEND1 position= (BOTTOM CENTER OUTSIDE)  shape=symbol(1.2,.5) ;
proc gplot data=bios.mcmrocq95p01;
plot Sensitivity * FPR = strategy / vaxis=axis1 haxis=axis2 LEGEND = LEGEND1;
title1 'MCMROC Curves: Area(0.90,0.90)';
title2 'b1=1,b2=1,rD=0,rN=0,Prevalence=0.1,q=0.95';
run;
goptions reset=global vsize=2.5 hsize=1.7 htitle=.8 htext=.4;
axis1 order=(0 to 1 by 0.2) major=(h=.2) minor =(n=1); axis2 order=(0 to 1 by 0.2)
major=(h=.2) minor =(n=1);
SYMBOL1 c=black v=: COLOR=green h=.2 w=.2;
SYMBOL2 c=black v=triangle COLOR=blue h=.1 w=.1;
SYMBOL3 c=black v=square COLOR=red h=.1 w=.1;
LEGEND1 position= (BOTTOM CENTER OUTSIDE)  shape=symbol(.8,.5) ;
proc gplot data=bios.mcmrocq95p01;
plot cost * FPR = strategy/ vaxis=axis1 haxis=axis2 LEGEND = LEGEND1;
title1 'Cost curves: Area(0.90,0.90)';
title2 'b1=1,b2=1,rD=0,rN=0,Prevalence=0.1,q=0.95';
run;
/****************************************Prevalence=0.7*/
goptions reset=all vsize=2.5 hsize=1.9 htitle=.8 htext=.4;
```

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```
axis1 w=1 order=(0 to 1 by 0.2) major=(h=.2) minor =(n=1); axis2 w=1 order=(0 to 1 by
0.2) major=(h=.2) minor =(n=1);
SYMBOL1 v=none COLOR=green INTERPOL=join LINE=1 h=1 w=2;
SYMBOL2 v=none COLOR=blue INTERPOL=join LINE=35 h=1 w=2;
SYMBOL3 v=none COLOR=red INTERPOL=join LINE=2 h=1 w=2;
LEGEND1 position= (BOTTOM CENTER OUTSIDE)  shape=symbol(1.2,.5) ;
proc gplot data=bios.mcmrocq95p07;
plot Sensitivity * FPR = strategy / vaxis=axis1 haxis=axis2 LEGEND = LEGEND1;
title1 'MCMROC Curves: Area(0.90,0.90)';
title2 'b1=1,b2=1,rD=0,rN=0,Prevalence=0.7,q=0.95';
run;
goptions reset=global vsize=2.5 hsize=1.7 htitle=.8 htext=.4;
axis1 order=(0 to 1 by 0.2) major=(h=.2) minor =(n=1); axis2 order=(0 to 1 by 0.2)
major=(h=.2) minor =(n=1);
SYMBOL1 c=black v=: COLOR=green h=.2 w=.2;
SYMBOL2 c=black v=triangle COLOR=blue h=.1 w=.1;
SYMBOL3 c=black v=square COLOR=red h=.1 w=.1;
LEGEND1 position= (BOTTOM CENTER OUTSIDE)  shape=symbol(.8,.5) ;
proc gplot data=bios.mcmrocq95p07;
plot cost * FPR = strategy/ vaxis=axis1 haxis=axis2 LEGEND = LEGEND1;
title1 'Cost curves: Area(0.90,0.90)';
title2 'b1=1,b2=1,rD=0,rN=0,Prevalence=0.7,q=0.95';
run;quit;
ods rtf close;
```

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D3: Optimal Operating points

```
libname bios 'C:\project\r0r0\90_90\b1b1';run;
LIBNAME FRMT 'C:\ project';run;
OPTIONS FMTSEARCH=(FRMT);run;
/********************** Generalized Youden index  **/
/****************** REV=0.1, cb=0.01, slope=0.1 ,q=1***/
data Optimalq1p01cb01p1;
set bios.mcmrocq1p01;
GYI = Sensitivity - ((1-0.1)/(0.1))*0.01*FPR;
run;
data Optimalq1p01cb01p1;
set Optimalq1p01cb01p1;
where cost <= 0.75;
run;
proc sort data=         Optimalq1p01cb01p1;by strategy;
run;
proc means data=Optimalq1p01cb01p1 max noprint;
var GYI;
by strategy;
output out=MGYIcq1p01cb01p1 (drop=_type_ _freq_)
      maxid(GYI(c1))=c1
            maxid(GYI(c2))=c2  maxid(GYI(c3))=c3
      max=MGYI
      maxid(GYI(Sensitivity))= Sensitivity
      maxid(GYI(FPR))= FPR
      maxid(GYI(cost))=cost;
run;
/************************************** REV=0.1, cb=0.11,slope=1
,q=1*************************************************************************
*******/
data Optimalq1p01cb11p1;
set bios.mcmrocq1p01;
GYI = Sensitivity - ((1-0.1)/(0.1))*0.11*FPR;
run;
data Optimalq1p01cb11p1;
set Optimalq1p01cb11p1;
where cost <= 0.75;
run;
proc sort data=         Optimalq1p01cb11p1;by strategy;
run;
proc means data=Optimalq1p01cb11p1 max noprint;
var GYI;
by strategy;
output out=MGYIcq1p01cb11p1 (drop=_type_ _freq_)
      maxid(GYI(c1))=c1
```

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```
        maxid(GYI(c2))=c2  maxid(GYI(c3))=c3
    max=MGYI
    maxid(GYI(Sensitivity))= Sensitivity
    maxid(GYI(FPR))= FPR
    maxid(GYI(cost))=cost;
run;
/************************************* REV=0.1, cb=0.33,slope=3
,q=1*************************************************************************
*******/
data Optimalq1p01cb33p1;
set bios.mcmrocq1p01;
GYI = Sensitivity - ((1-0.1)/(0.1))*0.33*FPR;
run;
data Optimalq1p01cb33p1;
set Optimalq1p01cb33p1;
where cost <= 0.75;
run;
proc sort data=        Optimalq1p01cb33p1;by strategy;
run;
proc means data=Optimalq1p01cb33p1 max noprint;
var GYI;
by strategy;
output out=MGYIcq1p01cb33p1 (drop=_type_ _freq_)
    maxid(GYI(c1))=c1
        maxid(GYI(c2))=c2  maxid(GYI(c3))=c3
    max=MGYI
    maxid(GYI(Sensitivity))= Sensitivity
    maxid(GYI(FPR))= FPR
    maxid(GYI(cost))=cost;
run;
/************************************* REV=0.1, cb=1,slope=9
,q=1*************************************************************************
*******/
data Optimalq1p01cb10p1;
set bios.mcmrocq1p01;
GYI = Sensitivity - ((1-0.1)/(0.1))*1*FPR;
run;
data Optimalq1p01cb10p1;
set Optimalq1p01cb10p1;
where cost <= 0.75;
run;
proc sort data=        Optimalq1p01cb10p1;by strategy;
run;
proc means data=Optimalq1p01cb10p1 max noprint;
var GYI;
by strategy;
```

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```
output out=MGYIcq1p01cb10p1 (drop=_type_ _freq_)
      maxid(GYI(c1))=c1
            maxid(GYI(c2))=c2  maxid(GYI(c3))=c3
      max=MGYI
      maxid(GYI(Sensitivity))= Sensitivity
      maxid(GYI(FPR))= FPR
      maxid(GYI(cost))=cost;
run;
/************************************** REV=0.1*/
ods rtf file="C:\sim\r0r0\90_90\b1b1\final GYI\75\MGYIcost75bp1.rtf" ;
ods rtf ;
proc print data = MGYIcq1p01cb01p1;       run;
ods rtf ;
proc print data = MGYIcq1p01cb11p1;       run;
ods rtf ;
proc print data = MGYIcq1p01cb33p1; run;
ods rtf ;
proc print data = MGYIcq1p01cb10p1; run;
ods rtf close;
/********************************** Generalized Youden index  ***/
/****************** REV=0.1, cb=0.23,slope=0.1 ,q=1**/
data Optimalq1p07cb23p7;
set bios.mcmrocq1p07;
GYI = Sensitivity - ((1-0.7)/(0.7))*0.23*FPR;
run;
data Optimalq1p07cb23p7;
set Optimalq1p07cb23p7;
where cost <= 0.75;
run;
proc sort data=         Optimalq1p07cb23p7;by strategy;
run;
proc means data=Optimalq1p07cb23p7 max noprint;
var GYI;
by strategy;
output out=MGYIcq1p07cb23p7 (drop=_type_ _freq_)
      maxid(GYI(c1))=c1
            maxid(GYI(c2))=c2  maxid(GYI(c3))=c3
      max=MGYI
      maxid(GYI(Sensitivity))= Sensitivity
      maxid(GYI(FPR))= FPR
      maxid(GYI(cost))=cost;
run;
/****************************** REV=0.1, cb=1,slope=0.43 ,q=1**/
data Optimalq1p07cb1p7;
set bios.mcmrocq1p07;
GYI = Sensitivity - ((1-0.7)/(0.7))*1*FPR;
```

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```
run;
data Optimalq1p07cb1p7;
set Optimalq1p07cb1p7;
where cost <= 0.75;
run;
proc sort data=         Optimalq1p07cb1p7;by strategy;
run;
proc means data=Optimalq1p07cb1p7 max noprint;
var GYI;
by strategy;
output out=MGYIcq1p07cb1p7 (drop=_type_ _freq_)
      maxid(GYI(c1))=c1
            maxid(GYI(c2))=c2  maxid(GYI(c3))=c3
      max=MGYI
      maxid(GYI(Sensitivity))= Sensitivity
      maxid(GYI(FPR))= FPR
      maxid(GYI(cost))=cost;
run;
/****************** REV=0.1, cb=2.33,slope=1 ,q=1***/
data Optimalq1p07cb233p7;
set bios.mcmrocq1p07;
GYI = Sensitivity - ((1-0.7)/(0.7))*2.33*FPR;
run;
data Optimalq1p07cb233p7;
set Optimalq1p07cb233p7;
where cost <= 0.75;
run;
proc sort data=         Optimalq1p07cb233p7;by strategy;
run;
proc means data=Optimalq1p07cb233p7 max noprint;
var GYI;
by strategy;
output out=MGYIcq1p07cb233p7 (drop=_type_ _freq_)
      maxid(GYI(c1))=c1
            maxid(GYI(c2))=c2  maxid(GYI(c3))=c3
      max=MGYI
      maxid(GYI(Sensitivity))= Sensitivity
      maxid(GYI(FPR))= FPR
      maxid(GYI(cost))=cost;
run;
/************************************** REV=0.1, cb=7,slope=3 ,q=1**/
data Optimalq1p07cb70p7;
set bios.mcmrocq1p07;
GYI = Sensitivity - ((1-0.7)/(0.7))*7*FPR;
run;
data Optimalq1p07cb70p7;
```

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```
set Optimalq1p07cb70p7;
where cost <= 0.75;
run;
proc sort data=          Optimalq1p07cb70p7;by strategy;
run;
proc means data=Optimalq1p07cb70p7 max noprint;
var GYI;
by strategy;
output out=MGYIcq1p07cb70p7 (drop=_type_ _freq_)
      maxid(GYI(c1))=c1
            maxid(GYI(c2))=c2  maxid(GYI(c3))=c3
      max=MGYI
      maxid(GYI(Sensitivity))= Sensitivity
      maxid(GYI(FPR))= FPR
      maxid(GYI(cost))=cost;
run;
/************************************** REV=0.7**/
ods rtf file="C:\sim\r0r0\90_90\b1b1\final GYI\75\MGYIcost75bp7.rtf" ;
ods rtf ;
proc print data = MGYIcq1p07cb23p7;       run;
ods rtf ;
proc print data = MGYIcq1p07cb1p7;        run;
ods rtf ;
proc print data = MGYIcq1p07cb233p7; run;
ods rtf ;
proc print data = MGYIcq1p07cb70p7; run;
ods rtf close;
```

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Vita

Anwar Ahmed has earned a bachelor of sciences in Applied Statistics and Demography from Gezira University, Sudan. In 2004, he received a master of sciences in Statistics from Virginia Commonwealth University. He began studies in Biostatistics at Virginia Commonwealth University in the fall of 2005. During his first year, he assisted with teaching statistical methods to medical and graduate students. He worked four years as Statistical Consultant at VCU technology services, helping many students on their dissertation and faculty on their research. As of June 2010, he has earned a Ph.D. in Biostatistics from Virginia Commonwealth University.

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