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Genomic and clinical predictors for improving estimator precision in randomized trials of breast cancer treatments

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ABSTRACT

Background: The hope that genomic biomarkers would dramatically and immediately improve care for common, complex diseases has been tempered by slow progress in their translation beyond bioinformatics. We propose a novel use of genomic information where the goal is to improve estimator precision in a randomized trial. We analyze the potential precision gains from the popular MammaPrint genomic signature and clinical variables in simulations of randomized trials analyzed using covariate adjustment.
Methods: We apply an estimator for the average treatment effect in the trial that adjusts for prognostic baseline variables to improve precision [1]. This precision gain can be translated directly into sample size reduction and corresponding cost savings. We conduct simulation studies based on resampling genomic and clinical data of breast cancer patients from four publicly available observational studies.
Results: Separate simulation studies were conducted based on each of the four data sets, with sample sizes ranging from 115 to 307. Adjusting only for clinical variables provided gains of −1%, 5%, 6%, 17%, compared to the unadjusted estimator. Adjusting only for the MammaPrint genomic signature provided gains of 2%, 4%, 4%, 5%. Simultaneously adjusting for clinical variables and the genomic signature provided gains of 2%, 6%, 7%, 16%. The differences between precision gains from adjusting for genomic plus clinical variables, versus only clinical variables, were −1%, 0%, 1%, 3%.
Conclusions: Adjusting only for clinical variables led to substantial precision gains (at least 5%) in three of the four data sets, with a 1% precision loss in the remaining data set. These gains were unchanged or increased when sample sizes were doubled in our simulations. The precision gains due to incorporating genomic information, beyond the gains from adjusting for clinical variables, were not substantial.

1. Introduction

The announcement of the Precision Medicine Initiative [2] stated that “Precision medicine's more individualized, molecular approach to cancer will enrich and modify, but not replace, the successful staples of oncology – prevention, diagnostics, some screening methods, and effective treatments – while providing a strong framework for accelerating the adoption of precision medicine in other spheres.” In the realm of genomic biomarker development, this mandate puts an explicit focus on “enrichment”, i.e. how much *additional* information a new marker can provide to supplement the standard course of care. The uncertain value of genomic measurements for improving clinical practice has been a critical roadblock in the translation of genomic markers to the clinic [3], in addition to problems with reproducibility [4], interpretability [5], and cost [6]. A small number of laboratory tests based on genomic signatures have been approved for clinical use. Tests such as MammaPrint [7], Oncotype DX [8], and Prosigna [9] rely on measurement of expression for a set of genes that are associated with differential survival and severity of breast cancer cases.

It is difficult to evaluate the clinical value that these genomic signatures add beyond standard clinical factors measured for all breast cancer patients, such as age, estrogen receptor status, tumor size, and tumor grade. It is also known that tests based on genomic signatures are not part of the standard of care in many cases [10]; [3]. Ongoing clinical trials are being performed to ascertain the value of some of these signatures to make adaptive treatment decisions [11]. We propose to evaluate the use of genomic signatures in a different setting by considering the prognostic value added from adjusting for a genomic signature in a randomized clinical trial of a new treatment versus control.

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In a randomized trial the primary analysis typically involves estimating the average treatment effect. Adjusting for baseline variables that are prognostic for the outcome can lead to improved precision in estimating the average treatment effect at large sample sizes (i.e., asymptotically as sample size grows). Yang and Tsiatis [12] showed that for continuous outcomes and a linear model with main terms, the analysis of covariance (ANCOVA) estimator is guaranteed to be consistent and as or more precise than the standard unadjusted estimator, even if the linear model is not correctly specified, i.e., the true distribution of the outcome given baseline covariates may be much more complex than the linear model used, and still the guarantee holds.

More recently, estimators with the same desirable property as the ANCOVA procedure have been extended to binary and count outcomes; see Cao et al. [13]; Tan [14]; Rotnitzky et al. [15] and Gruber and van der Laan [16]. Colantuoni and Rosenblum [1] provide a review of these recent estimators, which are designed to estimate an average treatment effect in the general setting of an observational study, where the probability of being assigned to treatment is not randomized and must be learned from the data. These estimators may also be applied to randomized trials, where their guarantees on improved precision require fewer assumptions than in an observational study since in a randomized trial the assignment probability is known (and set by design).

The above estimators all have the aforementioned consistency and precision guarantee. One difference among them is that the estimators of Colantuoni and Rosenblum [12]; Tan [14]; and Colantuoni and Rosenblum [1] do not require solving a non-convex (and therefore computationally challenging) optimization problem; however, the benefit of solving such a problem, as done by the estimators of Cao et al. [13]; Rotnitzky et al. [15] and Gruber and van der Laan [16]; is that they have potential for further precision gains, so there is a computation versus precision tradeoff.

The precision gains provided by adjusting for baseline variables depend on how correlated the baseline variables are with the outcome and the degree of chance imbalance in the baseline variables across the treatment groups. To the best of our knowledge, the value of such adjustment has not yet been assessed using simulations based on resampling from breast cancer patient data sets, as we do here. We resample in a way that preserves correlations between baseline variables and the outcome in order to give a realistic assessment (as best as we can using simulations and our data sets) of the magnitude of precision gains likely to be observed in practice.

We aim to determine the prognostic value of clinical and/or genomic variables measured at baseline (pre-randomization). Of particular interest is the additional gain from adjusting for the genomic signature beyond that obtained by adjusting for standard clinical baseline variables. Our definition of precision gain in this setting equals the percent sample size reduction from using the adjusted estimator compared to the unadjusted estimator in order to attain the same power, asymptotically. Although perhaps not as groundbreaking of a result as once hoped, this approach represents a realistic attempt to assess the value of the information provided by a genomic signature.

2. Methods

2.1. Data

Microarray data used to validate the MammaPrint model [17] were gathered as described in the appendix of Marchionni et al. [18]. The MammaPrint validation data set consists of 307 breast cancer patients. Table 1 summarizes the key clinical factors recorded for these patients as well as their MammaPrint risk prediction, which is a binary classification based on the risk score calculated by the MammaPrint model [7]. We dropped 11 patients whose estrogen receptor (ER) status or tumor grade were unknown and conducted our analysis using the 296 remaining patients.

Table 1
MammaPrint validation data set. ER - estrogen receptor status, Grade - tumor severity grading (3 is most severe), Five-Year Recurrence - whether or not cancer has reappeared after five years, MammaPrint risk prediction - high or low risk for cancer recurrence. Age and Tumor Size are given as means with standard deviations in parentheses.

Characteristic	Summary
n	307
Age (years)	47.08 (7.27)
Five-Year Recurrence	
Yes	47
No	260
Tumor Size (mm)	21.48 (7.71)
Grade	
1	47
2	126
3	126
Unknown	8
ER	
+	212
−	90
Unknown	5
MammaPrint Risk Prediction	
High	194
Low	113

We also conduct simulations based on three external breast cancer data sets described in the Supplementary Material. These are called GSE19615, GSE11121, GSE7390, with sample sizes 115, 200, 198, respectively.

2.2. Statistical method to adjust for baseline covariates

We define the average treatment effect to be the difference between the population mean of the primary outcome under assignment to treatment and the population mean under assignment to control. The term “covariate adjustment” means that information from baseline variables is used to improve the precision in estimating the average treatment effect. This is done by adjusting for chance imbalances in baseline variables between treatment and control arms. Since our focus is improved precision for estimating the average treatment effect, we do not consider effects within subgroups; investigating the latter is an area for future research.

Increased precision for estimation of the average treatment effect can lead to a trial with fewer participants and shorter duration, compared to a trial with the same power that uses a less precise estimator. This is because the sample size for a trial is typically selected in order to achieve a desired power, e.g., 80% or 90%, at an alternative (e.g., the minimum, clinically meaningful effect size); using a more precise estimator leads to a smaller required sample size to achieve the power goal. More precise estimators can be used to reduce the sample size even when the average treatment effect is zero, which is the setting of our simulation study. This can be achieved by prespecifying the sample size as that which achieves a desired power at a given alternative, taking into account the percent variance reduction from using the adjusted estimator compared to the unadjusted estimator. A more flexible approach is to use information based monitoring, where the trial runs until a preplanned information level has accrued (see, e.g., Jennison and Turnbull [19]. Information with respect to a given estimator, defined as the reciprocal of its variance, accrues faster for estimators with greater precision, leading to smaller sample sizes.