Identifying individual predictive factors for treatment efficacy

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Identifying individual predictive factors for cancer immunotherapy efficacy

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Summary: Given the heterogeneous responses to cancer immunotherapy and the high cost of such treatments, there is an increasing interest in identifying, using pretreatment variables, patients that would likely benefit from them. Clearly, the success of such an endeavor will depend on the amount of information that the patient-specific variables convey about the individual causal treatment effect on the response of interest. In the present work, using causal inference and information theory, a strategy is proposed to evaluate individual predictive factors for cancer immunotherapy efficacy. In a first step, the methodology proposes a causal inference model to describe the joint distribution of the pretreatment predictors and the individual causal treatment effect. Further, in a second step, the so-called predictive causal information (PCI), a metric that quantifies the amount of information the pretreatment predictors convey on the individual causal treatment effects, is introduced and its properties are studied. The methodology is applied to identify predictors of therapeutic success for a therapeutic vaccine in advanced lung cancer. A user-friendly R library *EffectTreat* is provided to carry out the necessary calculations.

Key words: Causal inference; Multivariate predictors; Personalized medicine; Prediction of therapeutic success.

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1. Introduction

Medicine, as we know it today, is based on the idea of 'standard care', which provides patients with the best treatment for the general population or for the average patient. As a result, many clinicians use a 'one size fits all' approach. Specifically in cancer, patients are traditionally prescribed a predetermined first-line treatment, taking into account the indication and the degree of the cancer. However, the sustainability of the 'one size fits all' approach is questioned because of the complexity and uniqueness in which each individual tumor evolves. Therefore, the idea of giving a patient the right medicine at the right dose at the right time has become the golden dream of medical science in general and oncology in particular. With recent advances in cancer therapy, precision medicine has played an increasingly important role in the treatment of this malignancy (Wang and Wang, 2017). Now therapies can be designed to attack cancer cells more precisely through two main methods: selectively interrupting the pathways necessary for the survival or growth of cancer cells (targeted therapy) and artificially modulating the immune system of patients to generate a response against cancer cells (immunotherapy). To drive the transition from a traditional clinical practice model, precision medicine therapies will also require the joint development of diagnostic tools and the identification of key predictors to select the optimal treatment for individual patients (Dugger, Platt and Goldstein, 2018). However, despite recent advances in medical imaging, biomarkers, genetics and computer science, the difficulty of predicting the response to treatment of an individual patient remains a major challenge. For successful development of a drug that is tailored to a biomarker-defined patients, employment of appropriate statistical tools is paramount.

Attempts have been made to evaluate pretreatment predictors of therapeutic success using correlational techniques; methods like linear and logistic regression, discriminant analysis and boosting are often combined with measures of association like odds ratios and Pearson

correlations for evaluation purposes in this domain (Banerjee *et al.*, 2010; Honda *et al.*, 2014; Shin *et al.*, 2013; Spielmans *et al.*, 1983; van Loendersloot *et al.*, 2010; Zeller *et al.*, 2014). Regression models, the most used method, are able to include prognostic and predictive variables in an interaction with a treatment variable. A statistically significant and large interaction effect usually indicates potential subgroups that may have different responses to the treatment. However, this approach often fails to identify the correct subgroups due to large number of covariates and complex interactions among them. Other proposals to tackle the problem include tree-based partitioning and machine learning. Lipkovich, Dmitrienko and Agostino (2017) have made a comprehensive tutorial, Zhang *et al.* (2018) provide R codes to implement these methods and Kourou *et al.* (2015) presented a review of recent applications relevant to cancer prediction and prognosis.

In addition, another line of research has focused on the development of algorithms that determine optimal individualized treatment rules (ITR). For instance, Qian and Murphy (2011) constructed an optimal ITR that maximizes an empirical version of the mean response conditional on treatment and pretreatment covariates. The conditional mean approximation requires estimating a prediction model of the relationship between pretreatment prognostic variables, treatments and clinical outcome. Reduction in the mean response is related to the excess prediction error, through which an upper bound can be constructed for the mean reduction of the associated treatment rule. However, it has been argued that by inverting the model to find the optimal treatment rule, this method emphasizes prediction accuracy of the clinical response model instead of directly optimizing the decision rule (Zhao *et al.*, 2012). Zhao *et al.* (2012) circumvented the need for conditional mean modeling followed by inversion by directly estimating the decision rule that maximizes clinical response. In addition, these authors showed that the optimal treatment rule can be estimated within a weighted classification framework, where the weights are determined from the clinical

outcomes. Ma, Hobbs and Stingo (2015) provide an overview of statistical methods for establishing optimal treatment rules for personalized medicine and discuss specific examples in the contexts of oncology. These authors argued that the utility of these recent advances has not been fully recognized by the oncological community and that the available statistical methodology must evolve in order to optimally exploit the information on biomarkers for personalized cancer medicine.

Most importantly, before embarking on the development of ITRs, the existence problem should be addressed. Basically, one should determine if it is possible to develop such a rule based on a given set of pretreatment predictors in the first place. Alonso, Van der Elst and Molenberghs (2015) introduced a procedure to evaluate a pretreatment predictor of therapeutic success based on causal inference. Unlike Qian and Murphy (2011) and Zhao *et al.* (2012), these authors did not model the expected mean response as a function of treatment and pretreatment covariates, but focused on directly modeling the individual causal treatment effect as a function of a univariate pretreatment predictor. The main idea is to assess if it can actually predict treatment success for a specific patient. Furthermore, they argued that, rather counter intuitively, studying the association between the putative predictor and the response variable of interest in groups of patients that either receive or did not receive the treatment, is not sufficient to answer the relevant scientific question. Actually, a predictor exhibiting a strong and positive correlation with the most credible outcome to assess therapeutic success, the so-called true endpoint T, in the new treatment and control groups, may still carry no information whatsoever on the individual causal treatment effect on T. Using such a predictor to construct an ITR would be misleading, irrespectively of the procedure used to do it. A major limitation of their approach is that it can only cope with univariate pretreatment predictors. In the present work, using causal inference and information theory, a strategy is proposed to evaluate several individual predictive factors for

cancer immunotherapy efficacy. In a first step, the methodology proposes a causal inference model to describe the joint distribution of the pretreatment predictors and the individual causal treatment effect. Further, in a second step, the so-called predictive causal information (PCI), a metric that quantifies the amount of information the pretreatment predictors convey on the individual causal treatment effects, is introduced and its properties are studied. The identifiably problems associated with the use of causal inference models are approached via sensitivity analysis.

In Section 2, the causal-inference model underlying the evaluation strategy is introduced. A new validation metric, the so-called predictive causal information, is proposed in Section 3 where some of its properties are discussed. Some important identifiably issues are studied in Section 4 and a sensitivity analysis approach is introduced to handle the problem. The case study is presented and analyzed in Section 7 and some final comments are given in Section 8.

2. A causal inference model

In the following, T will denote the most credible outcome to assess therapeutic success, the so-called true endpoint, Z the treatment indicator and $\boldsymbol{S} = (S_1, S_2, \ldots, S_p)'$ a p-dimensional vector of putative pretreatment predictors. Rubin's model for causal inference assumes the existence, for each patient j, of two potential outcomes for the true endpoint: an outcome T_0 that would be observed under the control condition $Z = 0$ and an outcome T_1 that would be observed under the treatment condition $Z = 1$. T_0 and T_1 are potential outcomes in that they represent the outcomes of the patient had he received the treatment or control, respectively. Notice that, to simplify notation, the sub-index j has been omitted and this convention will be adopted throughout the manuscript.

Let us now consider for each patient the response vector $\boldsymbol{Y} = (\boldsymbol{T}', \boldsymbol{S}')'$ with $\boldsymbol{T} = (T_0, T_1)$. In the following, attention will be restricted to continuous outcomes. Although, in general, the use of only continuous variables may be seen as a limitation, this special case does appear

in important applications in this area like, for instance, the case study analyzed in this work. Extensions to more general scenarios are the subject of ongoing research. It will be further assumed that $\boldsymbol{Y} \sim N(\boldsymbol{\mu}, \boldsymbol{\Sigma})$, with

$$\boldsymbol{\Sigma} = \begin{pmatrix} \boldsymbol{\Sigma}_{TT} & \boldsymbol{\Sigma}_{TS} \\ \boldsymbol{\Sigma}_{ST} & \boldsymbol{\Sigma}_{SS} \end{pmatrix},$$

where

$$\boldsymbol{\Sigma}_{TT} = \begin{pmatrix} \sigma_{T0T0} & \sigma_{T0T1} \\ \sigma_{T0T1} & \sigma_{T1T1} \end{pmatrix}, \quad \boldsymbol{\Sigma}_{TS} = \begin{pmatrix} \sigma_{T0Sr} \\ \sigma_{T1Sr} \end{pmatrix}, \quad \boldsymbol{\Sigma}_{SS} = (\sigma_{SrSn}),$$

and $\sigma_{TrTn} = \text{cov}(T_r, T_n)$ $(r, n \in \{0, 1\})$, $\sigma_{TnSr} = \text{cov}(T_n, S_r)$ $(n = 0, 1,\ r = 1 \ldots p)$, $\sigma_{SrSn} = \text{cov}(S_r, S_n)$ $(n, r = 1 \ldots p)$. The variable $\Delta T = T_1 - T_0$ quantifies the individual causal treatment effect on the patient and, therefore, studying its relationship with the pretreatment predictor vector $\boldsymbol{S}$ is at the center of the evaluation strategy. In fact, when deciding on the appropriateness of an immunotherapy for a given patient one always, implicitly or explicitly, needs to consider an alternative intervention, for example, the best supportive care or another immunotherapy also registered for the use in the cancer indication of the patient. In such a scenario, one needs to compare the potential response of the patient to the immunotherapy with his potential response if he had received the alternative treatment or control ($Z = 0$). The so-called fundamental problem of causal inference states that, often in practice, only one of T_0 and T_1 is observed and, consequently, ΔT is not identifiable from the data (Holland, 1986).

Based on ΔT, one can define the expected or average causal treatment effect in the population of interest as $\beta = E(\Delta T)$. Rosenbaum and Rubin (1983) provided three identifiability conditions under which it is possible to obtain consistent estimators of the expected causal treatment effect. If Y denotes the response of interest and Y_z the potential outcome associated with $Z = z$ then the three identifiability conditions are: 1) Consistency: If $Z = z$ for a

given subject then $Y_z = Y$ for that subject, 2) Conditional exchangeability: This condition essentially states that there are no unmeasured confounders given data on baseline covariates L, that is, $Y_z \perp Z|L = l$ for each possible value z of Z and l of L and 3) Positivity: If $f_L(l) \neq 0$ then $f_{Z|L}(z|l) > 0$. It can easily be shown that in randomized clinical trials all conditions hold and the expected causal treatment effect can be estimated as $\beta = E(T|Z = 1) - E(T|Z = 0)$, where the conditional expectations are estimated using the observed means in the control and treated groups, respectively. The methodology proposed in the following sections is based only on the individual causal treatment effect ΔT and it is valid if consistency holds. Clearly, if consistency does not hold, then the potential outcomes are ill-defined and the methodology cannot be applied.

An ITR is given by a map $\tau : \boldsymbol{S} \rightarrow Z$. An optimal ITR is often defined as a rule that maximizes the expected value of $E(T|Z, \boldsymbol{S})$ (Qian and Murphy, 2011; Zhao *et al.*, 2012). In the present work, the focus is shifted from the conditional expected value of the response $E(T|Z, \boldsymbol{S})$ to a model that studies the relationship between ΔT and $\boldsymbol{S}$. It will also be illustrated that studying the relationship between $\boldsymbol{S}$ and T, based on the model $E(T|Z, \boldsymbol{S})$, may actually say very little about the relationship between ΔT and $\boldsymbol{S}$. Given that one is primarily interested in predicting the best treatment for each specific patient, setting the focus on the individual causal treatment effect seems to be the most natural approach.

To study the relationship between ΔT and $\boldsymbol{S}$ let us consider the vector $\boldsymbol{\psi} = (\Delta T, \boldsymbol{S}')'$. It can easily be shown that

$$\boldsymbol{\psi} = \begin{pmatrix} \Delta T \\ \boldsymbol{S} \end{pmatrix} = \boldsymbol{A}_\psi \boldsymbol{Y}, \tag{1}$$

where

$$\boldsymbol{A}_\psi = \begin{pmatrix} \boldsymbol{a}_1 & \boldsymbol{0}_p' \\ \boldsymbol{A}_0 & \boldsymbol{I}_p \end{pmatrix},$$

with $\boldsymbol{a}_1 = (-1\,1)$ a 1×2 matrix, $\mathbf{0}_p$ a p dimensional zero vector, $\boldsymbol{A}_0 = (\mathbf{0}_p\,\mathbf{0}_p)$ a $p \times 2$ matrix of zeros and $\boldsymbol{I}_p$ a p dimensional identity matrix. From the distributional assumptions for $\boldsymbol{Y}$ it follows that $\boldsymbol{\psi} \sim N\left(\boldsymbol{\mu}_\psi, \boldsymbol{\Sigma}_\psi\right)$, where $\boldsymbol{\mu}_\psi = (\beta, \boldsymbol{\mu}_S)$ and $\boldsymbol{\Sigma}_\psi = \boldsymbol{A}_\psi \boldsymbol{\Sigma} \boldsymbol{A}'_\psi$ with

$$\boldsymbol{\Sigma}_\psi = \begin{pmatrix} \boldsymbol{a}_1 \boldsymbol{\Sigma}_{TT} \boldsymbol{a}'_1 & \boldsymbol{a}_1 \boldsymbol{\Sigma}_{TS} \\ \boldsymbol{\Sigma}_{ST} \boldsymbol{a}'_1 & \boldsymbol{\Sigma}_{SS} \end{pmatrix}. \tag{2}$$

The scalar $\sigma_{\Delta T} = \boldsymbol{a}_1 \boldsymbol{\Sigma}_{TT} \boldsymbol{a}'_1 = \sigma_{T0T0} + \sigma_{T1T1} - 2\sqrt{\sigma_{T0T0}\sigma_{T1T1}}\,\rho_{T0T1}$ is the variance of the individual causal treatment effect ΔT, the $1 \times p$ vector $\boldsymbol{a}_1 \boldsymbol{\Sigma}_{TS} = (\sigma_{T1Sr} - \sigma_{T0Sr})$ $(r = 1 \ldots p)$ characterizes the association between ΔT and the pretreatment predictors and the covariance matrix $\boldsymbol{\Sigma}_{SS}$ describes the association structure of $\boldsymbol{S}$. In the following, a validation strategy will be proposed based on the previous causal inference model.

3. Predictive causal information

The primary objective of this work is to find a vector of pretreatment predictors $\boldsymbol{S}$ that conveys a substantial amount of information about the individual causal treatment effect ΔT. The mutual information between ΔT and $\boldsymbol{S}$ quantifies the amount of uncertainty in ΔT, expected to be removed if the value of $\boldsymbol{S}$ were known and, under the assumptions presented in Section 2, it is given by

$$I\left(\Delta T, \boldsymbol{S}\right) = -\frac{1}{2} \log\left(\frac{|\boldsymbol{\Sigma}_\psi|}{|\sigma_{\Delta T}||\boldsymbol{\Sigma}_{SS}|}\right),$$

where $|\boldsymbol{A}|$ denotes the determinant of matrix $\boldsymbol{A}$. Although it seems sensible to use this measure to quantitatively assess the validity of $\boldsymbol{S}$, the absence of an upper bound for $I\left(\Delta T, \boldsymbol{S}\right)$ hinders its interpretation. To solve this problem, we propose to use instead a normalized version of the mutual information, the so-called, squared informational coefficient of correlation (SICC) introduced by Linfoot (1957) and Joe (1989)

$$R^2_\psi = 1 - e^{-2I(\Delta T, \boldsymbol{S})} = 1 - \frac{|\boldsymbol{\Sigma}_\psi|}{|\sigma_{\Delta T}||\boldsymbol{\Sigma}_{SS}|}. \tag{3}$$

The SICC is always in the interval $[0, 1]$, is invariant under bijective transformations, and takes value zero if and only if ΔT and $\boldsymbol{S}$ are independent. Moreover, mutual information approaches infinity when the distribution of $(\Delta T, \boldsymbol{S})$ approaches a singular distribution, that is, $R^2_\psi \approx 1$ if and only if there exists an approximate functional relationship among ΔT and $\boldsymbol{S}$ (Joe, 1989). In the following, we will refer to (3) as the predictive causal information (PCI). Taking into account that $|\boldsymbol{\Sigma}_\psi| = |\boldsymbol{\Sigma}_{SS}||\sigma_{\Delta T|S}|$ where $\sigma_{\Delta T|S} = \boldsymbol{a}_1\boldsymbol{\Sigma}_{TT}\boldsymbol{a}_1' - \boldsymbol{a}_1\boldsymbol{\Sigma}_{TS}\boldsymbol{\Sigma}_{SS}^{-1}\boldsymbol{\Sigma}_{ST}\boldsymbol{a}_1'$ one gets

$$R^2_\psi = \frac{\boldsymbol{a}_1\boldsymbol{\Sigma}_{TS}\boldsymbol{\Sigma}_{SS}^{-1}\boldsymbol{\Sigma}_{ST}\boldsymbol{a}_1'}{\boldsymbol{a}_1\boldsymbol{\Sigma}_{TT}\boldsymbol{a}_1'}. \tag{4}$$

Notice further that, using the previous notation, $\sigma_{\Delta T|S} = \sigma_{\Delta T}\left(1 - R^2_\psi\right)$. The following lemma summarizes some properties of R^2_ψ that further justify its use as a validation metric in the present context.

LEMMA 1: *Let $\boldsymbol{\psi} = (\Delta T, \boldsymbol{S}')'$ denote the vector containing the individual causal treatment effect on T and the pretreatment predictor vector $\boldsymbol{S}$ with $\boldsymbol{\psi} \sim N\left(\boldsymbol{\mu}_\psi, \boldsymbol{\Sigma}_\psi\right)$ and $\boldsymbol{\Sigma}_\psi$ as given in (2). The coefficient R^2_ψ satisfies the following properties*

1. *R^2_ψ is invariant by bijective transformations of ΔT and $\boldsymbol{S}$*
2. *$0 \leqslant R^2_\psi \leqslant 1$*
3. *$R^2_\psi = 0$ if and only if $\sigma_{T0Sr} = \sigma_{T1Sr}$ for all $r = 1, 2 \ldots p$, where S_r denotes the r component of $\boldsymbol{S}$. If homoscedasticity is further assumed, i.e., if $\sigma_{T0T0} = \sigma_{T1T1} = \sigma_T$ then $R^2_\psi = 0$ if and only if $\rho_{T0Sr} = \rho_{T1Sr}$ for all r*
4. *$R^2_\psi = 1$ if and only if there exists a deterministic relationship between ΔT and $\boldsymbol{S}$*

Moreover, it can easily be shown that R^2_ψ is the maximum squared correlation between ΔT and a linear combination of $\boldsymbol{S}$, i.e., $R^2_\psi = \max_{\mathbf{t}}\left[\text{corr}\left(\Delta T, \boldsymbol{t}'\boldsymbol{S}\right)\right]^2$. Let us now assume that homocedasticity holds and $\rho_{T0Sr} = \rho_{T1Sr} = \gamma \approx 1$ for $r = 1, \ldots, p$, that means all pretreatment predictors are strongly associated with the true endpoint in the control

and treated groups (this association is typically studied based on model $E(T|Z, \boldsymbol{S})$). Item 3 in Lemma 1 shows that, rather counter-intuitively, such a multivariate predictor will carry no information whatsoever about the individual causal treatment effect ΔT and, therefore, developing meaningful ITRs based on it would be impossible, irrespectively of the methodology used for that purpose. These results are a natural extension of those presented in Alonso, Van der Elst and Molenberghs (2015). Actually, it follows naturally that if $p = 1$ then $R^2_\psi = \rho^2_\psi$, where $\rho_\psi = \text{corr}(\Delta T, S)$ is the coefficient introduced by these authors to quantify PCI in the univariate case. On the other hand, if the PCI is close to one then ΔT and $\boldsymbol{S}$ are almost deterministically related and the development of meaningful ITRs is now within reach. A proof of the lemma can be found in the Web-appendix.

Note that σ_{T0Sr} and σ_{T1Sr} are the covariances between the potential outcomes for the true endpoint T and the pretreatment predictors S_r. Under consistency, these covariances could in principle be estimated using information from patients that received and did not receive the treatment, respectively.

There are important reasons to move towards multivariate pretreatment predictors as the following lemma shows.

LEMMA 2: Let $\boldsymbol{S}_* = (\boldsymbol{S}', S_*)'$ be a new (p+1) dimensional predictor of therapeutic success, constructed by adding a new univariate predictor S_* to $\boldsymbol{S}$. Using obvious notation one has that $R^2_\psi \leqslant R^2_{\psi *}$.

Essentially, lemma 2 states that considering more pretreatment predictors can only improve our capacity to predict the individual causal treatment effect on the true endpoint and, consequently, multivariate pretreatment predictors are worth pursuing (proof provided in Web-based Supplementary Materials).

4. Predictive Causal Information (PCI): Some indentifiability issues

The quantification of PCI, as given by R^2_ψ, suffers from some important identifiability issues. In fact, even though $\mathbf{\Sigma}_{SS}$ is always identifiable and $\mathbf{\Sigma}_{TS}$ is identifiable under the weak assumption of consistency, the covariance matrix of the potential outcomes $\mathbf{\Sigma}_{TT}$ cannot be inferred from the data basically because, due to the fundamental problem of causal inference, the correlation between the potential outcomes ρ_{T0T1} is not estimable, with similar issues for correlations between potential surrogates.

To overcome this problem two strands of action are possible. First, one can try to define plausible identifiability conditions based on biological or subject-specific knowledge. For instance, in certain applications it may be plausible to assume that both potential outcomes are uncorrelated ($T_0 \perp T_1$). There are, however, some serious problems with this approach. Indeed, such subject-specific knowledge may not always be available and/or, as the fundamental problem of causal inference states, these biologically plausible assumptions can neither be proved nor disproved using data.

A second strategy is to implement a sensitivity analysis in which R^2_ψ is estimated across a fine grid of values for ρ_{T0T1}. In a first step, a grid of values $G = \{g_1,\ g_2,\ \ldots,\ g_k\}$ is considered for the unidentified correlation between the potential outcomes. Next, several $\mathbf{\Sigma}$ matrices are constructed fixing the identifiable correlations ρ_{T0S_r}, ρ_{T1S_r}, ρ_{SrSn} and variances σ_{T0T0}, σ_{T1T1}, σ_{SrSr} at their estimated values and considering all the values in G for ρ_{T0T1}. From all the previous $\mathbf{\Sigma}$ matrices only those that are positive-definite are used in the subsequent step. Finally, R^2_ψ is estimated based on these positive-definite matrices. The obtained vector R^2_ψ can intuitively be interpreted as a quantification of PCI across all plausible "realities", i.e., across those scenarios where the assumptions made for the unidentified correlation are compatible with the observed data. Further, the general behavior of R^2_ψ can subsequently be examined by quantifying the variability and the range of its estimates and in this way

the sensitivity of the results with respect to the unverifiable assumptions can be assessed. Notice that this approach does not preclude the use of subject-specific knowledge when it exists. For example, suppose we are comparing two different immunotherapy with the same specific target, so the correlation between the potential outcomes should be positive, then the grid $G = \{0,\ 0.05,\ \ldots,\ 0.95\}$ could be used for this correlation when carrying out the sensitivity analysis. In the present work, the sensitivity analysis approach will be adopted for the analysis of the case study.

5. Regression approach

As previously stated, the model $E\left(T|Z,\boldsymbol{S}\right)$ has played a central role in the methodologies developed for the evaluation and construction of ITRs. Unlike the previous strategies, the approach introduced in Section 3 uses individual causal treatment effects as the main building block for the analysis. However, the newly introduced methodology is intrinsically related to the model $E\left(T|Z,\boldsymbol{S}\right)$ and in the following this relationship will be studied in detail.

When interest is in the evaluation of predictors of therapeutic success, it is natural to allow for an interaction between the predictors contained in $\boldsymbol{S}$ and the treatment indicator Z thus, typically, the following model is considered

$$T = \beta_0 + \beta_1 Z + \sum_{k=1}^{p} \alpha_k S_k + \sum_{k=1}^{p} \gamma_k S_k Z + \varepsilon. \tag{5}$$

In model (5) the expected causal treatment effect (ECE) of Z on T, in the population under study, is given by $ECE(\boldsymbol{S}) = \beta_1 + \sum_{k=1}^{p} \gamma_k S_k$, i.e., it varies as a function of the pretreatment predictor $\boldsymbol{S}$ (Gelman and Hill, 2006). The vector of coefficients $\boldsymbol{\gamma}' = (\gamma_1, \gamma_2, \ldots, \gamma_p)$ fully captures the relationship between ECE and the pretreatment predictors. From (5) also follows $\sigma_{T1Sr} - \sigma_{T0Sr} = \sum_{k=1}^{p} \gamma_k \sigma_{SkSr}$ for all $r = 1, 2 \ldots p$. These expressions conform a system of p linear equations in p covariates that can be rewritten in matrix form as $\boldsymbol{a}_1 \boldsymbol{\Sigma}_{TS} = \boldsymbol{\gamma}' \boldsymbol{\Sigma}_{SS}$,

and has solution $\boldsymbol{\gamma}' = \boldsymbol{a}_1 \boldsymbol{\Sigma}_{TS} \boldsymbol{\Sigma}_{SS}^{-1}$ or, equivalently, $\boldsymbol{\gamma} = \boldsymbol{\Sigma}_{SS}^{-1} \boldsymbol{\Sigma}_{ST} \boldsymbol{a}_1'$. Substituting this value into (4) leads to the following lemma.

LEMMA 3: *Let us assume that the causal inference model introduced in Section 2 and the linear regression model given in (5) are both valid. If one further assumes that* $Z \perp \boldsymbol{S}$ *then* $R_\psi^2 = \dfrac{\boldsymbol{\gamma}' \boldsymbol{\Sigma}_{SS} \boldsymbol{\gamma}}{\sigma_{\Delta T}}$.

Details of the proof are provided in the Web-based Supplementary Materials. Given that $\boldsymbol{\Sigma}_{SS}$ is positive-definite, $\boldsymbol{\gamma}' \boldsymbol{\Sigma}_{SS} \boldsymbol{\gamma} \geqslant 0$, with equality if and only if $\boldsymbol{\gamma} = \mathbf{0}$. Thus, if the predictor is not valid at the individual level ($R_\psi^2 = 0$) then it will not be valid at the population level neither ($\boldsymbol{\gamma} = \mathbf{0}$) and vice versa. Consequently, a likelihood ratio test for the hypothesis $H_0 : \boldsymbol{\gamma} = \mathbf{0}$ involving only identifiable parameters, will also be a valid test for the hypothesis $H_0 : R_\psi^2 = 0$ involving an unidentifiable parameter. However, when one moves away from these extreme scenarios ($R_\psi^2 = 0$ and $\boldsymbol{\gamma} = \mathbf{0}$) important differences between both paradigms can emerge. For instance, low values of R_ψ^2 may occur when $\boldsymbol{\gamma} > \mathbf{0}$ if $\sigma_{\Delta T}$ is large relative to $\boldsymbol{\gamma}' \boldsymbol{\Sigma}_{SS} \boldsymbol{\gamma} \geqslant 0$.

The numerator in the expression for R_ψ^2 given in Lemma 3 is fully identifiable and the denominator only depends on one unidentifiable parameter, namely, ρ_{T0T1}. Moreover, R_ψ^2 will reach its maximum (minimum) when $\sigma_{\Delta T}$ reaches its minimum (maximum) and, hence,

$$\max_{\rho_{T0T1}} R_\psi^2 = R_{\psi max}^2 = \frac{\boldsymbol{\gamma}' \Sigma_{SS} \boldsymbol{\gamma}}{\left(\sqrt{\sigma_{T0T0}} - \sqrt{\sigma_{T1T1}}\right)^2},$$

$$\min_{\rho_{T0T1}} R_\psi^2 = R_{\psi min}^2 = \frac{\boldsymbol{\gamma}' \Sigma_{SS} \boldsymbol{\gamma}}{\left(\sqrt{\sigma_{T0T0}} + \sqrt{\sigma_{T1T1}}\right)^2}.$$

Probably, these maxima and minima will never be reached in practical situations. Indeed, $R_{\psi max}^2$ ($R_{\psi min}^2$) is reached only when $\rho_{T0T1} = -1$ ($\rho_{T0T1} = 1$) and, therefore, the distribution of $\boldsymbol{T}$ would be degenerate in such a situation. However, for any practically attainable value of ρ_{T0T1} one will always have $R_{\psi min}^2 < R_\psi^2 < R_{\psi max}^2$. Importantly, both $R_{\psi max}^2$ and $R_{\psi min}^2$ are identifiable from the data.

Note further that (5) implies $E(T|Z) = \beta_0 + \beta_1 Z + \boldsymbol{\alpha}'\boldsymbol{\mu}_S + Z\boldsymbol{\gamma}'\boldsymbol{\mu}_S$ with $\boldsymbol{\alpha}' = (\alpha_1, \alpha_2, \ldots, \alpha_p)$ and, hence, $\mu_{T0} = \beta_0 + \boldsymbol{\alpha}'\boldsymbol{\mu}_S$ and $\mu_{T1} = \beta_0 + \beta_1 + \boldsymbol{\alpha}'\boldsymbol{\mu}_S + \boldsymbol{\gamma}'\boldsymbol{\mu}_S$. Furthermore, under the identifiability conditions (i)–(iii) presented in Sectioin 2, $\beta = E(\Delta T) = \mu_{T1} - \mu_{T0} = \beta_1 + \boldsymbol{\gamma}'\boldsymbol{\mu}_S$ implying $\beta_1 = \beta - \boldsymbol{\gamma}'\boldsymbol{\mu}_S$. Plugging this expression into the equation for ECE leads to $ECE(\boldsymbol{S}) = \beta + \boldsymbol{\gamma}'(\boldsymbol{S} - \boldsymbol{\mu}_S)$. Finally, taking into account that $\boldsymbol{\gamma}' = \boldsymbol{a}_1\boldsymbol{\Sigma}_{TS}\boldsymbol{\Sigma}_{SS}^{-1}$ one gets

$$ECE(\boldsymbol{S}) = \beta + \boldsymbol{\gamma}'(\boldsymbol{S} - \boldsymbol{\mu}_S) = g(\boldsymbol{S}).$$

Thus, both methods provide the same point prediction for ΔT. However, unlike the regression approach, the causal inference approach allows quantifying the uncertainty of the prediction as $\sigma_{\Delta T|S} = \sigma_{\Delta T}\left(1 - R_\psi^2\right)$ and, even though $\sigma_{\Delta T|S}$ depends on unidentifiable parameters, the simulation approach described in Section 4 can be used to assess its value.

6. Is there a useful multivariate predictor?

In order to assign the best treatment to an individual patient, one needs to predict the individual causal treatment effect on that patient (ΔT), based on his vector of pretreatment predictors ($\boldsymbol{S}$). The prediction variance $\sigma_{\Delta T|S} = \sigma_{\Delta T}\left(1 - R_\psi^2\right)$ quantifies the accuracy of such a prediction and, ultimately, its practical utility. The formula for $\sigma_{\Delta T|S}$ raises some important issues. In fact, the right side of the equation is decomposed into two different elements. The second element depends on the multivariate predictor $\boldsymbol{S}$ through the value of R_ψ^2; the first element, however, is an intrinsic characteristic of the true-endpoint-treatment pair and is independent of the predictor. It is clear that the accuracy of the prediction (the inverse of the prediction variance) is a decreasing function of $\sigma_{\Delta T}$ and, consequently, if the individual causal treatment effect on the true endpoint has large variability, then a predictor should produce a close to one R_ψ^2 to have some predictive value. This hints on the fact that, for some true endpoints and treatments, the search for valid pretreatment predictors of therapeutic success, and/or the development of meaningful ITRs, may rather be a difficult

task. It also stresses the importance of multivariate predictors. Actually, as Lemma 2 states, increasing the dimension of $\boldsymbol{S}$ always leads to larger value for R^2_ψ and, hence, multivariate predictors may be the only hope for reaching meaningful predictions, when the individual responses to treatment are very variable.

Notice further that:

$$(\sqrt{\sigma_{T0T0}} - \sqrt{\sigma_{T1T1}})^2 \left(1 - R^2_\psi\right) \leqslant \sigma_{\Delta T|S} \leqslant (\sqrt{\sigma_{T0T0}} + \sqrt{\sigma_{T1T1}})^2 \left(1 - R^2_\psi\right). \qquad (6)$$

The upper bound in (6) can be used to assess the plausibility of finding a good predictor. Indeed, let us assume that one would like to keep the prediction variance under a certain value δ. Setting $\left(\sqrt{\sigma_{T0T0}} + \sqrt{\sigma_{T1T1}}\right)^2 \left(1 - R^2_\psi\right) \leqslant \delta$ leads to:

$$R^2_\delta = 1 - \frac{\delta}{\left(\sqrt{\sigma_{T0T0}} + \sqrt{\sigma_{T1T1}}\right)^2} \leqslant R^2_\psi.$$

The quantity R^2_δ is completely identifiable from the data (if negative it is set to zero and this inequality becomes trivial) and may be useful to assess the plausibility of finding good pretreatment predictors for a given true endpoint and treatment. Indeed, let us assume that a prediction variance $\sigma_{\Delta T|S} \leqslant \delta = 1.3$, is considered acceptable. Suppose further that for $\delta = 1.3$ the $R^2_{\delta=1.3} = 0.98$, then one would need to find a predictor that produces a PCI of at least 98% in order to keep the prediction variance smaller than 1.3. Arguably, such a predictor may be difficult to find. On the other hand, if for $\delta = 1.3$ a $R^2_{\delta=1.3} = 0.65$ is obtained then a predictor with a PCI of at least 65% will be capable of keeping the prediction variance smaller than the pre-specified δ. Therefore, although a $R^2_{\delta=1.3} = 0.65$ does not guarantee that a good predictor exists, it certainly makes its existence more plausible.

7. Case Study

7.1 *A clinical trial in advanced lung cancer*

The data come from a randomized clinical trial to assess the effect of a therapeutic vaccine to induce specific antibodies against the epidermal growth factor (EGF) in the treatment

of advanced non-small lung cancer patients. The experimental treatment CIMAvaxEGF was compared to the best supportive care (control treatment). In previous studies, laboratory results associated with the CIMAvaxEGF mechanism of action confirmed the vaccine is intended to induce antibodies against self EGFs that block EGF-EGFR interaction (Garcia *et al.*, 2008). On the other hand, it is known that the immune system deteriorates with cancer progression as a consequence of decreasing levels of functional T cells, down-regulation of the co-stimulatory molecules and expansion of hyporesponsive populations such as CD28-. The scientific community has been interested in finding markers, able to predict immune capacity and proper response to vaccination.

Peripheral blood samples were collected from patients before the treatment to assess immunological status. Three types of pretreatment markers were considered. Firstly, the basal EGF concentration in serum (S_1), that is a marker directly related with the mechanism of action of the vaccine. Secondly, immunosenescence markers previously reported as predictive biomarkers using a univariate approach (Saavedra *et al.*, 2016). Here we included the proportion of CD4+ (S_2), CD8+CD28- T cells (S_3), CD4/CD8 ratio (S_4) and the proportion of CD19+ B cells (S_5) as putative predictors of therapeutic success. Also we considered peripheral blood biomarkers associated with clinical outcome in patients with non-small cell lung cancer: the absolute lymphocyte count (S_6), the neutrophil-to-lymphocyte ratio (NLR:S_7), absolute eosinophil count (S_8), absolute monocyte count (S_9) and white blood cell count (S_{10}) (Tanizaki *et al.*, 2017). The time since trial inclusion till death was the true endpoint T of the study. The follow-up period started in July 2006 and ended in July 2016. By the end of the follow-up only 2 patients remained alive (only to censored values) and, for this reason, we consider time to death as a continuous random variable.

By design, only 52 patients from hospitals located in the city of Havana were included in the immunological study, of whom $n = 33$ had complete information. All missing values

were in the predictive biomarkers, due to logistic issues in the laboratory analyzing the samples. Therefore, in the following, it will be assumed that the missing data generating mechanism was missing completely at random (MCAR). The data were analyzed using the newly developed R package *EffectTreat* (freely available at http://cran.r-project.org/). For conciseness, in the present section no reference to the software is made but in the Supplementary Materials Web Appendix a more comprehensive analysis of the data is provided and the use of the R package *EffectTreat* is explained in detail.

7.2 *Data description.*

Table 1 shows the correlations between the different components of $\boldsymbol{S}$ and T under control (ρ_{T0Sr}) and experimental treatment (ρ_{T1Sr}) conditions. In the control group, all correlations were low and not significant, except for the absolute leucocyte count (S_{10}). In the treated group, significant correlations were observed for the proportion of CD4+ T cell (S_2) and CD4+/CD8+ ratio (S_4). The difference between both correlation coefficients was significant only for S_2 and S_{10}. Notice that, although no significant differences were observed, the correlations between S_5, S_6, S_9 and T_0/T_1 change from negative in the control to positive in the treated group. Given the relatively small sample size, the previous findings may indicate that patients who have higher CD19+ B cell, absolute limphocytes count and monocytes tend to have shorter survival times when they are treated with the best supportive care. In contrast, the patients under the same conditions, but treated with CIMAvaxEGF tend to live longer. In addition, the correlations between S_3, S_8 and T_0/T_1 change from positive in the control to negative in the treated group, which indicates that patients with more CD8+CD28- T cells and high absolute eosinophils count tend to live longer in the control group and less in the CIMAvaxEGF group. The correlations between S_1, S_7 and T were not significant in either group, that is, no differences were observed between control and treated

groups. The previous results, together with item 3 in Lemma 1, suggest that some of these predictors may be useful to construct a valid multivariate predictor of therapeutic success.

7.3 *Regression approach*

Several models with the structure given in (5) were fitted to the data. A model building exercise was carried out based on the AIC criterion and the final model included S_1: basal EGF Concentration, S_4: CD4+/CD8+ ratio, S_7: NLR, S_9: absolute monocyte count and their interaction with the treatment (for more details, see the supplementary materials). Table 2 shows the results for this model. The estimated average causal treatment effect was $ECE(\boldsymbol{S}) = 28.097 + 0.003\,S_1 - 21.776\,S_4 - 3.883\,S_7 - 0.840\,S_9$. A Likelihood Ratio Test indicated that the $\boldsymbol{S}$ by treatment interaction was significant ($p = 0.008$). Therefore, Lemma 3 guarantees that the PCI associated with the vector (S_1, S_4, S_7, S_9) will be strictly positive, i.e., $R^2_\psi > 0$. However, the previous analysis says nothing about the magnitude of the PCI for this 4-dimensional vector of pretreatment predictors and, consequently, it may still carry very little information about the individual causal treatment effect. To get an idea about the magnitude R^2_ψ the identifiable bounds $R = \left(R^2_{\psi min}, R^2_{\psi max}\right)$ were estimated as $R = (0.528, 1)$ and, therefore, the vector of pretreatment predictors (S_1, S_4, S_7, S_9) would produce a PCI of at least 0.53.

7.4 *Predictive causal information*

To quantify PCI, the algorithm introduced in Section 4 was used to estimate R^2_ψ across a set of plausible values for ρ_{T0T1}, the grid $G = \{-1,\ -0.99,\ -0.98,\ \ldots,\ 1\}$. All combinations including from one to ten predictors were evaluated. A total of 201 matrices were formed, based on the specified $\boldsymbol{\Sigma}_{TT}$, $\boldsymbol{\Sigma}_{TS}$, $\boldsymbol{\Sigma}_{SS}$ and the grid G. Only the positive-definite matrices were considered for the estimation of the PCI. Table 3 summarizes the results. For simplicity, only the results of the p-dimensional predictors ($p = 1 \ldots 10$) with the highest PCI are presented. The first line shows the measures of central tendency for the univariate predictor

with the highest average PCI, the second line shows the results for the bivariate predictor with the highest average PCI and so forth. Notice that the average R^2_ψ increases from 0.486, when only one predictor is considered, to 0.855 when the 10-dimensional predictor is used. Importantly, the minimum PCI obtained with the 6-dimensional predictor ($\min R^2_\psi = 0.727$) already exceeds the maximum value obtained for the best univariate predictor ($\max R^2_\psi = 0.694$). Lemma 2 in Section 3 states that the use of a multivariate predictor will always lead to a better prediction of the individual causal treatment effect on the true endpoint; this theoretical statement is now empirically illustrated in this case study.

The results obtained for the 6-dimensional predictor show that using the basal EGF concentration, the CD4+/CD8+ ratio, the proportion of CD4+ T cells, CD19+ B cell, Neutrophils-to-Lymphocyte ratio and the absolute monocyte count, lead to PCI values $R^2_\psi \geqslant 0.72$ across all "realities" compatible with the data at hand and, consequently, one may be able to construct meaningful ITRs based on these predictors.

As Lemma 2 clearly shows, the inclusion of more predictors will always lead to and increase in information about the individual causal treatment effect. However, measuring and collecting data on multiple predictors may increase the burden to clinical researchers and patients, and lead to higher costs. In situations where this is indeed the case, a thoughtful discussion of the advantages and disadvantages of using a high-dimensional multivariate predictor in that specific context will be needed. Such a discussion goes beyond the statistical framework provided by any specific evaluation strategy and clinical, economical and ethical considerations will need to be brought up as well.

8. Discussion

It may be argued that the future impact of PM on medical practice will largely depend on the construction of valid ITRs. However, before this, one should assess if the pretreatment predictors convey enough information about the individual causal treatment effect on the

response of interest. In the present work an evaluation metric, the so-called predictive causal information, was introduced to evaluate multivariate predictors of therapeutic success. The PCI has a simple yet appealing interpretation in terms of information gain. Unlike some previously introduced methodologies that require randomized data, the PCI is identifiable under the weaker condition of consistency. The properties of the PCI and its relationship with some previously introduced approaches was studied.

The case study showed the utility of the proposed methodology not only to identify the relevant individual predictive factors, but also to estimate the predictive probability of success and failure of treatment with an immunotherapy for a given patient. Specifically, it showed the relevance of taking into account together with the basal EGF concentration in serum, which is a measure directly related to the mechanism of action of the evaluated immunotherapy, the immunosenescence and inflammatory biomarkers, to predict the success of CIMAvaxEGF in the treatment of patients with advanced lung cancer. Previous studies evaluated (using a univariate approach) biomarkers to predict which patients will receive the greatest clinical benefits with CIMAvax-EGF (Garcia *et al.*, 2008; Saavedra *et al.*, 2016). In these studies, the biomarkers, as is common in medical research, where dichotomized using the median or an optimal cutpoint. This follows the clinical practice of labeling individuals as having or not an attribute. Nevertheless, it is well know in the methodological literature that dichotomization of continuous variables introduces major problems including loss of information, reduction in power and uncertainty in defining the cutpoint (Royston, Altman, and Sauerbrei, 2006). In this study we propose an adequate methodology for the treatment of biomarkers as continuous variables. Aditionally, to facilitate its implementation in practice the use of the R library *EffectTreat* is illustrated to perform the necessary calculations. In its current form, the PCI is only applicable when both the response and the predictors, are all continuous random variables. This is without doubt an important scenario but it does not

cover other equally relevant settings when the outcomes have different scale of measurement. Extensions to these other important settings are the subject of future research.

[Table 1 about here.]

[Table 2 about here.]

[Table 3 about here.]

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Supplementary Materials

Web Appendix A, referenced in Section 3 and Section 7, is available with this paper at the Biometrics website on Wiley Online Library.

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Table 1: Correlations between S_1 = Basal EGF concentration, S_2 = proportion of CD4+ T cell, S_3 = CD8+CD28- T cells , S_4 = CD4/CD8 ratio, S_5 = CD19 B cell, S_6 = absolute lymphocyte count, S_7 =neutrophil-to-lymphocyte ratio , S_8 =absolute eosinophil count, S_9 = absolute monocyte count,S_{10} = white blood cell count and T =the elapsed time since trial inclusion to death using the best supportive care in the control (T_0) and CIMAvaxEGF in the treatment (T_1) group, and significance of the difference of the correlations.

	T_0	T_1	Difference $r(S_x,\, T_0)$ and $r(S_x,\, T_1)$
S_1	0.192 ($p = 0.594$)	0.107 ($p = 0.628$)	$p = 0.421$
S_2	0.101 ($p = 0.781$)	0.687 ($p < 0.001$)	$p = 0.046$
S_3	0.046 ($p = 0.900$)	-0.357 ($p = 0.093$)	$p = 0.169$
S_4	0.423 ($p = 0.223$)	0.791 ($p < 0.001$)	$p = 0.078$
S_5	-0.125 ($p = 0.730$)	0.202 ($p = 0.355$)	$p = 0.225$
S_6	-0.048 ($p = 0.894$)	0.157 ($p = 0.473$)	$p = 0.318$
S_7	0.022 ($p = 0.952$)	0.192 ($p = 0.379$)	$p = 0.347$
S_8	0.138 ($p = 0.703$)	-0.023 ($p = 0.917$)	$p = 0.356$
S_9	-0.294 ($p = 0.410$)	0.323 ($p = 0.133$)	$p = 0.073$
S_{10}	-0.676 ($p = 0.031$)	-0.095 ($p = 0.665$)	$p = 0.049$

Table 2: Parameter estimates for regression model (5).

	β	$s.e.$	p
intercept	-46.638	25.064	0.075
Z	28.097	19.183	0.156
S_1: EGF	-0.007	0.011	0.530
S_4: CD4/CD8 ratio	45.785	9.234	< 0.001
S_7: NLR	8.204	5.344	0.138
S_9: Monocytes count	1.375	2.132	0.525
Z by S_1 interaction	0.003	0.008	0.688
Z by S_4 interaction	-21.776	6.911	0.004
Z by S_7 interaction	-3.883	4.060	0.349
Z by S_9 interaction	-0.840	2.064	0.688

Table 3: Summary statistics for R^2_ψ using the combinations of S_1 = Basal EGF concentration, S_2 = proportion of CD4+ T cell, S_3 = CD8+CD28- T cells , S_4 = CD4/CD8 ratio, S_5 = CD19 B cell, S_6 = absolute lymphocyte count, S_7 =neutrophil-to-lymphocyte ratio , S_8 =absolute eosinophil count, S_9 = absolute monocyte count,S_{10} = white blood cell count as pretreament predictors and T = The elapsed time since trial inclusion to death in the control (T_0) and CIMAvaxEGF treatment (T_1) groups.

	R^2_ψ			
S	Mean	Min	Median	Max
(S_2)	0.486	0.354	0.469	0.694
$(S_2,\ S_9)$	0.563	0.423	0.546	0.772
$(S_2,\ S_7,\ S_9)$	0.658	0.521	0.645	0.847
$(S_2,\ S_4,\ S_7,\ S_9)$	0.721	0.603	0.713	0.873
$(S_1,\ S_2,\ S_4,\ S_7,\ S_9)$	0.795	0.689	0.789	0.923
$(S_1,\ S_2,\ S_4,\ S_5,\ S_7,\ S_9)$	0.814	0.727	0.810	0.915
$(S_1,\ S_2,\ S_4,\ S_5,\ S_6,\ S_7,\ S_9)$	0.836	0.751	0.832	0.933
$(S_1,\ S_2,\ S_4,\ S_5,\ S_6,\ S_7,\ S_9,\ S_{10})$	0.847	0.796	0.846	0.902
$(S_1,\ S_2,\ S_4,\ S_5,\ S_6,\ S_7,\ S_8,\ S_9,\ S_{10})$	0.851	0.815	0.851	0.889
$(S_1,\ S_2,\ S_3,\ S_4,\ S_5,\ S_6,\ S_7,\ S_8,\ S_9,\ S_{10})$	0.855	0.825	0.854	0.886