Evaluating individualized treatment effect predictions: a new perspective on discrimination and calibration assessment

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Abstract

Personalized medicine constitutes a growing area of research that benefits from the many new developments in statistical learning. A key domain concerns the prediction of individualized treatment effects, and models for this purpose are increasingly common in the published literature. Aiming to facilitate the validation of prediction models for individualized treatment effects, we extend the classical concepts of discrimination and calibration performance to assess causal (rather than associative) prediction models. Working within the potential outcomes framework, we first evaluate properties of existing statistics (including the c-for-benefit) and subsequently propose novel model-based statistics. The main focus is on randomized trials with binary endpoints. We use simulated data to provide insight into the characteristics of discrimination and calibration statistics, and further illustrate all methods in a trial in acute ischemic stroke treatment. Results demonstrate that the proposed model-based statistics had the best characteristics in terms of bias and variance. While resampling methods to adjust for optimism of performance estimates in the development data were effective on average, they had a high variance across replications that limits their accuracy in any particular applied analysis. Thereto, individualized treatment effect models are best validated in external data rather than in the original development sample.

1 Introduction

The prediction of individualized treatment effect conditional on patient characteristics has received much interest recently [1, 2, 3, 4, 5, 6]. Such models typically predict a clinically relevant outcome under two different treatment conditions, and the difference between these predictions is attributed to the effect of treatment. This information is of clear interest in the context of clinical decision-making if the underlying model is of sufficient quality. However, the evaluation of individualized treatment effect (ITE) models is still a key methodological challenge and little guidance is currently available on how to quantify their performance [6].

In this paper, we focus on ITE models that contrast the effect of two treatment conditions on the risk of a binary endpoint. More specifically, we focus on assessment of their performance; guidance on their development is available elsewhere (e.g., [2, 6, 7]). Typical measures of prediction model performance with respect to outcome risk predictions include measures of calibration and
discrimination [8, 9, 10]. However, our specific interest here is in predictions of risk difference attributed to the effect of treatment (i.e., in absolute individualized treatment effect predictions). Although calibration and discrimination performance can also be assessed at the risk difference (treatment effect) level, existing measures (e.g., calibration intercept, calibration slope, c-statistic) do not apply without modification because individual treatment effects (in contrast to regular outcomes) are unobservable [6]. For this reason, a new c-statistic was recently proposed that applies to absolute treatment effect predictions in settings with a binary endpoint, along with a quantile-based assessment of calibration [11].

We expand on this previous work by casting the entire prediction and evaluation process in the potential outcomes framework [12, 13] and by developing model-based measures of discrimination and calibration performance with respect to individualized treatment effect predictions. Herein, the potential outcomes framework provides a way to deepen understanding of what is actually being measured. The model-based measures make more efficient use of the data without relying on matching on arbitrary cut-offs.

Section 2 sets the scene and describes the challenge of individualized causal prediction in terms of the potential outcomes framework. Subsequently, Section 3 and Section 4 describe existing and novel measures of discrimination and calibration performance with respect to absolute treatment effect respectively. Simulation results are provided for illustrative purposes. An applied example using data from the third International Stroke Trial (IST-3) [14] is described in Section 6. Lastly, Section 8 provides a general discussion.

2 Individualized treatment effect prediction

Most outcome prediction research focuses on capturing statistical association in absence of interventions. Individualized treatment effect (ITE) prediction is a different type of prediction since it has a causal interpretation: the quantity to be predicted is the effect caused by the treatment (or intervention, in a larger sense) on the outcome. Therefore, before moving to the performance measures of interest, this section shortly outlines causal prediction. Subsequently, issues surrounding the use of binomial outcome data for ITE modeling are shortly discussed (further details are available as online supplementary material A).

2.1 Causal prediction

To emphasize the causal nature of the predictions, it is helpful to write the individualized treatment effect of interest in terms of the potential outcomes framework [12, 13]. For treatment taking values \( a \in \mathcal{A}, Y^a \) denotes the potential outcome under treatment \( a \). When comparing two treatments, the ITE for individual \( i, \ldots, n \) can be defined as

\[
\delta(x_i) = \mathbb{E}(Y^a_i = 1 | X = x_i) - \mathbb{E}(Y^{a_i} = 1 | X = x_i)
\]

where \( x_i \) is a row vector of individual-level characteristics in matrix \( X \). The degree of granularity or individualization reflected by \( \delta(x_i) \) relates to the number of predictors included in \( X \), to the strength and shape of their association with the potential outcomes, and especially to the degree to which they have a differential effect across potential outcomes (i.e., modify the effect of treatment). Ideally, the set of measured individual-level characteristics includes all relevant characteristics with respect to individualized treatment effect. In practice however, this set of all relevant characteristics is often unknown and the best way forward is to aim for conditioning on the most important characteristics. Correspondingly, equation (1) reflects ITE as a conditional treatment effect for some set of characteristics.

Since in practice only one potential outcome is observed per individual [15], assumptions are required to estimate \( \delta(x_i) \) based on the observed data. These assumptions are discussed in detail elsewhere [6, 16]. In short, the key assumptions are exchangeability (the potential outcomes do not depend on the assigned treatment), consistency (the observed outcome under treatment \( a \in \mathcal{A} \) corresponds to the potential outcomes \( Y^{a_i} \)), and positivity (each individual has a non-zero probability of each treatment assignment. An additional assumption that eases inference is no interference (the potential outcomes for individual \( i \) do not depend on treatment assignment
to other individuals). Based on these assumptions, the individualized treatment effect can be identified given the observed data:

$$
\hat{\delta}(x_i) = \mathbb{E}(Y_{i}^{a=1} = 1 | X = x_i) - \mathbb{E}(Y_{i}^{a=0} = 1 | X = x_i)
$$

$$
= \mathbb{E}(Y_{i}^{a=1} = 1 | A = 1, X = x_i) - \mathbb{E}(Y_{i}^{a=0} = 1 | A = 0, X = x_i) \quad \text{(by exchangeability)}
$$

$$
= \mathbb{E}(Y_{i} = 1 | A = 1, X = x_i) - \mathbb{E}(Y_{i} = 1 | A = 0, X = x_i) \quad \text{(by consistency)} \quad (2)
$$

Equation (2) shows that ITE predictions ($\hat{\delta}(x_i)$) can be estimated using a prediction model for outcome risk $\mathbb{E}(Y_i = 1 | A = a, X = x_i)$. Many modeling tools can be used for this endeavor and the details are beyond the scope of this paper and are given elsewhere (e.g., [6, 17]).

2.2 Binary outcome data

Focusing on binary outcomes, we observe outcome $Y_i \in \{0, 1\}$ and covariate status $x_i$ for each individual $i$. In this context, the ITE estimate $\hat{\delta}(x_i)$ is a difference between two risk predictions ($p(Y_i = 1|A = 1, X = x_i) - p(Y_i = 1|A = 0, X = x_i)$). The range of $\hat{\delta}(x_i)$ includes all values in the $[-1,1]$ interval, while the observed difference between any two outcomes can only be one of $\{-1, 0, 1\}$. Therefore, in addition to the challenge that each individual only has an observed outcome for one treatment condition, the observations come with large and irreducible binomial error and hence provide only limited information. A further consideration with predictions for binary outcome data is that they are commonly non-linear functions of the covariates, and hence the effects of treatment and the covariates are usually not additive on the risk difference scale of interest here. Consequently, the resulting ITE predictions conflate variability from different sources: between-subject variability in $P(Y_i=0|X=x)$ and genuine treatment effect heterogeneity on the scale used for modeling. This is the price to pay for the benefit in terms of interpretation of measures on the scale of $\hat{\delta}(x)$ [18].

2.3 The challenge

In practice, the fundamentally limited nature of observed data when it comes to causal inference (i.e., with only one potential outcome being observed), the irreducible binomial error affecting the risk difference twice, and the challenge of model specification and estimation are all present at the same time. This evidently poses a challenge at the time of model development, but within the scope of this paper, it certainly also poses challenges during evaluation of models predicting individualized treatment effects. Most notably, and in contrast with regular prediction modeling, a direct comparison between predictions and observed outcomes is not feasible.

In this paper, we evaluate discrimination and calibration at the level of predicted individualized treatment effects. To this end, we first evaluate a recently introduced metric to assess discriminative performance [11] and subsequently propose alternative procedures that aim to alleviate some of the shortcomings. Thereafter, we address calibration of predicted treatment effect. With respect to the detection of overfitting (i.e., overly complex models that fail to generalize), we examine performance in both internal and external validation settings.

3 Discrimination for individualized treatment effects

Discriminative model performance reflects the degree to which model predictions are correctly rank-ordered and is a common performance measure in regular prediction modeling [9, 8]. In the context of outcome risk prediction, the observed outcomes provide an immediate reference to check rank-ordering at the level of the predictions. However, such a direct reference is not available for ITE models since individual treatment effects cannot be observed directly, which necessitates approximations. One of the possibilities is to use matching and is used in a recent proposal, the c-for-benefit, for a measure of discriminative performance on the ITE level [11]. The section shortly outlines the c-for-benefit and subsequently discusses its properties, limitations, and possible extensions.
3.1 C-for-benefit definition

In the setting of a two-arm study measuring a binary outcome of interest, the c-for-benefit aims to assess discrimination at the level of ITE predictions (referred to as ‘predicted [treatment] benefit’ in the original paper).\(^1\) The problem of unobserved individual treatment effects is approached from a matching perspective. One-to-one matching is used to match treated individuals to control individuals based on their predicted treatment effects. The subsequent data pairs hence consist of a treated individual and a control individual with similar predicted treatment effect. Observed treatment effect in the pair is defined as the difference in outcomes between these two individuals. Of note, observed (within-pair) treatment effect can only be \{-1,0,1\}. Subsequently, c-for-benefit has been defined as "the proportion of all possible pairs of matched individual pairs with unequal observed benefit in which the individual pair receiving greater treatment benefit was predicted to do so" [11]. The predicted treatment effect within each pair used in this definition is taken to be the (within-pair) average of predicted treatment effects. That is, for a pair comprising control individual \(i\) out of \(1, \ldots, n_i\) and treated individual \(j\) out of \(1, \ldots, n_j\), predicted treatment effects are taken to be

\[
\hat{\delta}_{ij}(x_i, x_j) = \left\{ (\hat{P}(Y_i|A_i = 1, X = x_i) - \hat{P}(Y_i|A_i = 0, X = x_i)) + (\hat{P}(Y_j|A_j = 1, X = x_j) - \hat{P}(Y_j|A_j = 0, X = x_j)) \right\}/2
\]

(3)

The ‘observed’ treatment effect is subsequently taken to be \(O_{ij} = Y_i - Y_j\). Therefore, the c-for-benefit is a regular concordance statistic (c-statistic) as commonly applied in survival data [19, 9], but applied to pairs of individuals that underwent different treatments. If the two (binary) outcomes in such a pair are discordant, then there supposedly is some evidence of a treatment effect (i.e., benefit or harm); conversely, there is no such evidence when the outcomes are concordant (i.e., the predicted treatment effect did not manifest as a difference in outcomes). The implicit assumption is that individual \(i\) and \(j\) are similar enough to serve as pseudo-observations of the unobserved potential outcomes. In the ideal case where \(x_i = x_j\) this is indeed the case, but such perfect matches are unlikely to be available for multivariable prediction models.\(^2\) An alternative (unsupervised) matching procedure that was proposed in the same paper is to match on covariates in terms of Mahalanobis distance.\(^3\) For the remainder of this paper, we will use cben-\(\hat{\delta}\) to refer to the original c-for-benefit using 1:1 matching on predicted treatment effect.

3.2 C-for-benefit challenges

Although the c-for-benefit has been applied on several occasions (e.g., [20, 21, 22]), its properties have not been fully elucidated. Van Klaveren et al. [11] recommended further work on its theoretical basis and simulations studies, which we here present. Evidently, many issues that apply to the regular concordance statistic also apply to the c-for-benefit. However, since the c-for-benefit relates to risk differences and depends on outcomes that cannot be observed directly, additional challenges arise which we outline below.

3.2.1 Difficult interpretation

As described, the c-for-benefit uses 1:1 matching and averages ITEs within each pair of matched individuals (i.e., \(\hat{\delta}_{ij}(x_i, x_j)\) in equation (3)). As we will see below (section 3.3), this average of two ITEs does not generally correspond to the treatment effect induced by the study design even if the model is correctly specified. Also, the observed outcome difference \(O_{ij}\) reflects more than just \(\hat{\delta}_{ij}(x_i, x_j)\) unless both control outcome risk and treated outcome risk are the same for matched individuals. These two issues obfuscate the interpretation of the index.

\(^1\)The original paper did not focus on the required conditions for causal interpretation of the predicted individualized treatment effects; here we assume that these assumptions, as described in Section 2.1, are met.

\(^2\)Note that we here forgo the notion of including all relevant covariates, since \(x_i = x_j\) is sufficient for the degree of individualization reflected by the model.

\(^3\) where the distance between \(x_i\) and \(x_j\) is defined as \(d(x_i, x_j) = \sqrt{(x_i - x_j)^T S^{-1}(x_i - x_j)}\) with \(S\) the covariance matrix of the covariates in \(X\)
3.2.2 Sensitivity to matching procedure

Two matching procedures were proposed for the c-for-benefit: i) based on \( \delta \) (i.e., minimize the distance between pairs \( \delta_i \) and \( \delta_j \), and ii) based on the Mahalanobis distance between covariate vectors\(^3\) [11]. In theory, matching on covariates \( X \) leads to appropriate matches on predicted treatment effects since the latter is a function of the covariates. However, the reverse is not true: matching on \( \hat{\delta} \) does not necessarily lead to appropriate matches on \( X \). The reason is that multiple configurations of \( X \) can give rise to the same value of \( \delta \), which does not satisfy equation (2). Importantly, this is even the case for a correctly specified model. The only setting in which matching on predicted ITEs is guaranteed to generate appropriate matches on \( X \) is when \( \hat{\delta} \) is a bijection of \( X \) (i.e., \( \hat{\delta} \) and \( X \) have a one-to-one correspondence). However, this is highly atypical in prediction modeling (e.g., a model with only one covariate that has a functional form with a strictly positive or negative first derivative). Also, both matching procedures were proposed for 1 : 1 matching, which requires either equal groups size for both study arms or loss of data. A simple remedy that stays close to the original idea is to perform repeated analysis with random sub-samples of the larger arm. Alternatively, the implementation of many-to-one matching (e.g., full matching) or many-to-many matching [23, 24, 25] might be implemented, but none of these has been studied in the context of the c-for-benefit.

3.3 Towards a more principled concordance statistic for benefit

The c-for-benefit compares concordance between differences in i) average predicted treatment effect within matched control-treated pairs \( \delta_{ij}(x_i, x_j) \) and ii) observed outcome differences within those same pairs \( O_{ij} \). However, in general \( \delta_{ij}(x_i, x_j) \neq E(O_{ij}|x_i, x_j) \) unless \( x_i = x_j \). This section decomposes \( E(O_{ij}|x_i, x_j) \) to find conditions under which unbiased comparison to ITE predictions is available. Thereto, for controls \( i \in 1, \ldots, n_i \) and treated individuals \( j \in 1, \ldots, n_j \) and writing \( g_0(x) \) for \( P(Y_i = 1|A = 0, X = x) \) and \( g_1(x) \) for \( P(Y_i = 1|A = 1, X = x) \),

\[
E(O_{ij}|x_i, x_j) = E(Y_j|x_j) - Y_i|x_i \\
= E(Y_j|x_j) - E(Y_i|x_i) \\
= g_1(x_j) - g_0(x_i) \quad (4) \\
= [g_0(x_j) + \delta(x_j)] - [g_0(x_i)] \quad (5) \\
= g_1(x_j) - [g_1(x_i) - \delta(x_i)] \quad (6)
\]

Hence, from equation (5) and given \( g_0(\cdot) \), the expected observed outcome difference between individual \( j \) receiving treatment and individual \( i \) receiving control equals the true equals the true individualized treatment effect for individuals sharing the same characteristics \( x \) as \( j \)

\[
E(O_{ij}|g_0(x_i), g_0(x_j)) = E(Y_j - g_0(x_j)) - \underbrace{E(Y_i - g_0(x_i))}_{\delta(x_j)} = \delta(x_j), \quad (7)
\]

and analogously, from equation (6) and given \( g_1(\cdot) \), the expected observed outcome difference between individual \( j \) receiving treatment and individual \( i \) receiving control equals the true individualized treatment effect for individuals sharing the same characteristics \( x \) as \( i \)

\[
E(O_{ij}|g_1(x_i), g_1(x_j)) = \underbrace{E(Y_j - g_1(x_j))}_{\delta(x_j)} - E(Y_i - g_1(x_i)) = \delta(x_i) \quad (8)
\]

Conditioning on \( g_0(\cdot) \) in equation (7) aims to achieve prognostic balance, which bears resemblance to prognostic score analysis [26, 27]. Conditioning on \( g_1(\cdot) \) in equation (8) is just the mirror image for \( g_1(\cdot) \). In practice, \( g_0(\cdot) \) and/or \( g_1(\cdot) \) will of course have to be estimated and the exact equalities will become approximations. For continuous outcomes, equation (7) allows evaluation of predictions \( \hat{\delta}(x_j) \) against residuals \( Y_j - \hat{g}_0(x_j) \) for \( j = 1, \ldots, n_j \), and equation (8) allows evaluation of predictions \( -\hat{\delta}(x_i) \) against residuals \( Y_i - \hat{g}_1(x_i) \) for \( i = 1, \ldots, n_i \).\(^4\) A key benefit of this approach

\(^4\)Either way, one arm can be used to estimate the relevant \( \hat{g}(\cdot) \) and the other arm to evaluate \( \hat{\delta}(\cdot) \). Alternatively, an external model \( \hat{g}(\cdot) \) might be used, but, as demonstrated in the simulation study, bias will be introduced if this external model does not fit the data well.
is that matching is not required. However, extension of such a residual-based approach to binary outcome data is not clear. Hence, we implemented a 1:1 matching procedure similar to ebben-δ, but with two important differences. First, matching was performed based on \( \hat{g}_0(\cdot) \) as opposed to predicted treatment effect. Thereby, whenever \( \hat{g}_0(x_i) = \hat{g}_0(x_{j}) \), the expected difference between \( Y_i \) and \( Y_j \) does equal \( \hat{\delta}(x_j) \) if the models for \( g_0 \) and \( g_1 \) are correct. Second, and following from the previous, this implementation evaluated concordance between \( \hat{\delta}(x_j) \) (as opposed to \( \hat{\delta}_j \)) and the corresponding \( O_j \)’s. We will further refer to this implementation as ebben-\( \hat{g}^0 \). Note that a mirror image alternative could be performed when matching on \( \hat{g}_1(\cdot) \); the choice between the two might be guided by the expected quality in terms of prediction accuracy of \( \hat{g}_0(\cdot) \) and \( \hat{g}_1(\cdot) \), and the size of the group in which ITE predictions will be evaluated.

3.4 Model-based c-statistics for individualized treatment effect

Extending earlier work on model-based concordance assessment in the context of risk prediction [28], we propose model-based concordance assessment on the level of absolute individualized treatment effect prediction. The concordance probability that we aim for is the probability that any randomly selected pair of patients (regardless of treatment assignment) has concordant ITE predictions and outcomes, divided by the probability that their outcomes are different. While the ITE predictions are clearly defined (equation (2)), the outcomes (individualized treatment effects) are never observed directly and can be approximated in multiple ways. The model-based approach is to use the model’s predictions of the potential outcomes when deriving the concordance statistic. Therefore, it reflects the concordance statistic that would be expected under the assumption that the model is correct and given a specific set of data. Note that all information required for a model-based estimate is in the model, so there is no problem with respect to unobserved potential outcomes.

Let us first define concordance between ITE predictions and potential outcome patterns in line with the c-for-benefit. As above, take an event \( Y = 1 \) to be harmful. For a randomly selected individual \( k \) with a lower predicted ITE than another individual \( l \) (\( \hat{\delta}_k < \hat{\delta}_l \), where \( k, l \in 1, \ldots, n \) and \( k \neq l \)), treatment is predicted to be more beneficial (or less harmful) for individual \( k \) as compared to individual \( l \). The potential outcome patterns that are concordant with \( \hat{\delta}_k < \hat{\delta}_l \) are

1. \( Y_{k}^{a=1} = 0, Y_{k}^{a=0} = 1, Y_{l}^{a=1} = 0, Y_{l}^{a=0} = 0 \) (benefit for \( k \), no benefit for \( l \))
2. \( Y_{k}^{a=0} = 0, Y_{k}^{a=0} = 1, Y_{l}^{a=1} = 1, Y_{l}^{a=0} = 1 \) (benefit for \( k \), no benefit for \( l \))
3. \( Y_{k}^{a=0} = 0, Y_{k}^{a=0} = 1, Y_{l}^{a=1} = 1, Y_{l}^{a=0} = 0 \) (benefit for \( k \), harm for \( l \))
4. \( Y_{k}^{a=1} = 0, Y_{k}^{a=0} = 0, Y_{l}^{a=1} = 1, Y_{l}^{a=0} = 0 \) (no benefit for \( k \), harm for \( l \))
5. \( Y_{k}^{a=1} = 1, Y_{k}^{a=0} = 0, Y_{l}^{a=1} = 1, Y_{l}^{a=0} = 0 \) (no benefit for \( k \), harm for \( l \)).

The corresponding estimated probabilities of these patterns follow easily from the model(s) for both potential outcomes. For instance, for the first pattern: \( [1 - \hat{P}(Y_{k}^{a=1} = 1)] \cdot [1 - \hat{P}(Y_{l}^{a=1} = 1)] \cdot [1 - \hat{P}(Y_{l}^{a=0} = 1)] \). The sum of the five patterns is further referred to as \( \hat{P}_{\text{benefit},k,l} \). Likewise, let \( \hat{P}_{\text{harm},k,l} \) denote the total probability of observing relative harm for case \( k \) with respect to case \( l \), which can be obtained in a similar manner. Returning to our definition of concordance probability, the probability of concordant ITE predictions and potential outcomes for two randomly chosen patients \( k \) and \( l \) for any given model can be written as

\[
P(\text{concordant}) = \frac{1}{n(n-1)} \sum_k \sum_{l \neq k} \left[ I(\hat{\delta}_k < \hat{\delta}_l)\hat{P}_{\text{benefit},k,l} + I(\hat{\delta}_k > \hat{\delta}_l)\hat{P}_{\text{harm},k,l} \right] 
\]  

(9)

Subsequently, the model-based probability of a potential outcome pattern reflecting either relative benefit or relative harm for a randomly selected pair of patients is

\[
\hat{P}(\text{treatment effect in potential outcomes}) = \frac{1}{n(n-1)} \sum_k \sum_{l \neq k} \left[ \hat{P}_{\text{benefit},k,l} + \hat{P}_{\text{harm},k,l} \right],
\]

(10)

and hence the concordance probability is

\[
\frac{\sum_k \sum_{l \neq k} \left[ I(\hat{\delta}_k < \hat{\delta}_l)\hat{P}_{\text{benefit},k,l} + I(\hat{\delta}_k > \hat{\delta}_l)\hat{P}_{\text{harm},k,l} \right]}{\sum_k \sum_{l \neq k} \left[ \hat{P}_{\text{benefit},k,l} + \hat{P}_{\text{harm},k,l} \right]} 
\]  

(11)
A formulation that allows for ties \( \hat{\delta}_k = \hat{\delta}_l \) and avoids the need to derive \( \hat{P}_{\text{harm},k,l} \) is, in line with the Harrell’s c-statistic [19, 9],

\[
\text{mbcb} = \frac{\sum_k \sum_{l \neq k} \left[ I(\hat{\delta}_k < \hat{\delta}_l)\hat{P}_{\text{benefit},k,l} + \frac{1}{2} I(\hat{\delta}_k = \hat{\delta}_l)\hat{P}_{\text{benefit},k,l} \right]}{\sum_k \sum_{l \neq k} \hat{P}_{\text{benefit},k,l}}
\]  

(12)

We propose the model-based c-for-benefit (mbcb) as a model-based alternative to the c-for-benefit, hence the name. Estimating both \( \delta(x) \) and \( \hat{P}_{\text{benefit},k,l} \) from the same model, the mbcb provides the theoretical concordance probability between ITE predictions and potential outcomes that would be achieved if the model is correct. Important to note, such a model-based statistic only depends on the observed outcomes in the development data through the model, and hence does not provide any insight into model fit. For instance, estimating both \( \delta(x) \) and \( \hat{P}_{\text{benefit},k,l} \) from some ITE model \( \hat{\delta}_m \) in new data \( D \), the mbcb would return the expected concordance probability for \( \hat{\delta}_m \) at the ITE-level as based on the distribution of \( X \) in \( D \), and assuming \( \hat{\delta}_m \) is correct; it does not depend on the outcomes measured in \( D \). In other words, it provides a case-mix adjusted (\textit{i.e.}, adjusted for the sampled \( X \)) expected mbcb for new data [28]. This is of interest since concordance statistics are known to be sensitive to case-mix. For instance, discriminative performance in terms of a concordance statistic for a new sample that is truncated in terms of \( X \) (\textit{e.g.}, due to inclusion criteria) will be lower, even if the model is perfectly adequate, just because it is harder to discriminate in the new sample [29]. Hence, the case-mix adjusted expected mbcb is a better reference than the mbcb in the development data when validating a model. To obtain a validation estimate of ITE-level concordance probability (\textit{i.e.}, without assuming that the ITE model is correct), the estimator for \( \hat{P}_{\text{benefit},k,l} \) should be based on independent validation data that were not used for ITE model development. The main goal is to obtain estimates of \( \hat{P}_{\text{benefit},k,l} \) as accurate as possible for the new data, since these take the role of the ‘observed’ outcomes for the model-based c-for-benefit. A way to do so it by refitting the original ITE model in the independent data and using the resulting outcome risk predictions to calculate \( \hat{P}_{\text{benefit},k,l} \).

4 Calibration of individualized treatment effect predictions

A calibration measure reflects the degree to which predictions (predicted treatment effect) agree with observations (observed treatment effect). Several routes can be taken when interest is in predicted individualized treatment effect.

(A) Classical calibration: compare predicted outcome risk under the assigned treatment conditions versus observed outcomes.

(B) Within-arm classical calibration: classical calibration within treatment arms.

(C) Quantile-group calibration of average individualized versus observed treatment effect.

(D) Model-based calibration of individualized versus observed treatment effect.

Method (A) has been described at length in the literature (\textit{e.g.}, [8, 9, 10]) and method (B) is a straightforward extension. Both have the disadvantage that they do not directly assess absolute treatment effect: overall calibration of outcome risk may look good when prognostic factors are well modeled and explain most of the outcome risk, even though a comparatively small (but possibly important) treatment effect is not well represented.

A common way to proceed in the direction of direct predicted treatment effect evaluation is to form quantile groups of the predictions and to compare (average) predicted and observed treatment effect within these groups [11, 6] (method ((C))). However, the cut-off points to form these groups are always arbitrary and smooth model-based calibration plots have become the preferred method of choice in regular (outcome risk) calibration assessment [10]. This leaves method (D) which, in theory, provides the desired direct ITE assessment while avoiding the disadvantages associated with cut-offs. However, to our knowledge, such a method has not been described yet. We propose a model-based approach that isolates the calibration of \( \hat{\delta} \) based on equation (7).

According to equation (7), \( E(Y_j - \hat{y}_0(x_j)) \) can be directly compared against predictions \( \hat{\delta}(x_j) \) for treated individuals \( j \in 1, \ldots, n_j \). In case of dichotomous \( Y_j \), a natural way to do so is to model \( Y_j \).
with offset $\hat{g}_0(x_j)$. For instance, for a logistic model, a calibration model could be formulated as

$$\logit(Y_j) = \beta_0 + \beta_1 \hat{d}_{lp}(x_j) + \hat{g}_{p,0}(x_j)$$  \hspace{1cm} (13)

where $\hat{d}_{lp}(x_j) = \logit(\hat{g}_1(x_j)) - \logit(\hat{g}_0(x_j))$ and $\hat{g}_{p,0}(x_j) = \logit(\hat{g}_0(x_j))$. The anticipated intercept $\beta_0$ and slope $\beta_1$ in case of a perfect prediction are 0 and 1 respectively, as for regular prognostic model calibration \[8, 9\]. Assuming that $\hat{g}_0(x_j)$ is correct, the estimated slope $\beta_1$ directly reflects ITE overfitting (slope below 1) or underfitting (slope above 1), and the estimated intercept $\beta_0$ reflects average error in the ITE predictions. When $\hat{g}_0(x_j)$ is misspecified, $\beta_0$ and $\beta_1$ amalgamate ITE calibration and errors in $\hat{g}_{p,0}(x_j)$. Given the importance of $\hat{g}_0(x_j)$, which essentially anchors the ITE predictions, it might be preferable to derive predictions $\hat{g}_0$ based on a new model fitted in the external control arm data to reduce bias in the assessment of ITE calibration. A more direct way to assess average error in predicted ITEs is to examine the difference between observed and expected average treatment effect: $[\frac{1}{n_j} \sum_j Y_j - \frac{1}{n} \sum_i Y_i] - [\frac{1}{n_j} \sum_j \hat{g}_1(x_j) - \frac{1}{n} \sum_i \hat{g}_0(x_i)]$.

As a side note, continuous outcomes $Y_j$ allow for direct analysis of residuals $Y_j - \hat{g}_0(x_j)$ by means of a linear regression model.

$$Y_j - \hat{g}_0(x_j) = \beta_0 + \beta_1 \hat{d}(x_j) + \epsilon_j$$  \hspace{1cm} (14)

for individuals $j \in 1, \ldots, n_j$ and with $\epsilon_j \sim N(0, \sigma^2)$. The anticipated intercept, slope, and procedure to derive calibration in the large are the same as for (13). In addition to model-based evaluation, a smooth curve such as a loess (locally estimated scatterplot smoothing) estimate can be drawn through a scatterplot of $Y_j - \hat{g}_0(x_j)$ versus $\hat{d}(x_j)$ to provide a visual evaluation of ITE calibration for continuous outcomes.

### 5 Simulation study

A simulation study was performed with the aim to compare performance of the different discrimination and calibration measures for ITE predictions discussed across varying sample sizes. The simulation study was performed and reported in line with recommendations by Morris et al. \[30\] and using R statistical software version 4.2 \[31\].

#### 5.1 Simulation study procedures

**Data generating mechanisms:** Synthetic trial data were simulated for a trial comparing two treatments on a binary outcome. Covariates $x_1$ and $x_2$ were generated from independent standard normal distributions and treatment assignment was 1:1 independent of $X$. Data were simulated for both potential outcomes based on a logistic data generating mechanism (DGM) according to model

$$\logit(P(Y_{i}^{A=a} = 1)) = -1 - 0.75a_i + x_{i1} + 0.5a_i x_{i2}$$  \hspace{1cm} (15)

for a population of size 100,000, and will be further referred to as DGM-1. DGM-1 includes main effects of treatment and $X_1$ and an interaction between treatment and $X_2$. For each of $n_{aim} = 500$ simulation runs, development (D) and validation data (V1) sets of size 500, 750, and 1000 were randomly drawn from the population. Marginal event probabilities were $P(Y_{i}^{a=0}) \approx 0.31$ and $P(Y_{i}^{a=1}) \approx 0.20$. Additionally, independent validation sets of 1000 cases (V2) were sampled from a population of size 100,000 generated from a second DGM (DGM-2) with changes in the coefficients to reflect a different population

$$\logit(P(Y_{i}^{A=a} = 1)) = -0.5 - 0.5a_i + 0.75x_{i1} + 0.25x_{i2} + 0.25a_i x_{i1} + 0.25a_i x_{i2}.$$  \hspace{1cm} (16)

Marginal event probabilities for the second DGM were $P(Y_{i}^{a=0}) \approx 0.39$ and $P(Y_{i}^{a=1}) \approx 0.31$. With differences in both average treatment effect and heterogeneity of treatment effect between DGM-1 and DGM-2, a model developed in a sample from DGM-1 should not perform well in individuals from DGM-2.

**Estimands:** For discrimination, our estimand $\theta_d$ is the concordance statistic between ITE predictions and the true probabilities to observe benefit. For a fixed ITE model, a given data generating
mechanism, and a fixed matrix of observed covariates, this is exactly the definition of the mbcb in equation (12) when substituting true the value of $P_{\text{benefit,k,l}}$ (know from the DGM) for the estimated $\hat{P}_{\text{benefit,k,l}}$. This provides the expected ITE concordance statistic with the expectation taken over repeated samples of the potential outcomes. Due to its dependence on the matrix of observed covariates in a sample, it is further referred to as the ‘sample reference’. For the estimand in the population, the mbcb is a considerable computational burden due to the fast-growing number of observation pairs with increasing sample size. Instead, the ‘population reference’ was not based on the expectation over potential outcomes given the covariates, but on a single sample of the potential outcomes. Hence it is still unbiased with respect to the true estimand in the population. Further details are provided in online supplementary material B) and also show the relation between the mbcb and Harrell’s c-statistics [19, 9] applied to ITE predictions and simulations of both potential outcomes for each individual.

For calibration performance, our estimands were the calibration intercept $\beta_0$ and calibration slope $\beta_1$ as defined in equation (13). The true values follow directly from equation (13) when taking, for $j \in 1, \ldots, n_j$, the known probabilities $P(Y_j=1)$ based on the appropriate DGM, $\hat{\delta}_p(x_j)$ as the sample-based ITE predictions under evaluation, and $\hat{g}_{p,0}(x_j)$ based on known probabilities $P(Y_j=0)$. Both a sample reference (the value of the estimand for the distribution of $X$ in the given sample) and a population reference (the value of the estimand for the distribution of $X$ in the population) were derived.

**Methods:** The ITE model fitted to the development data was a logistic regression model estimated by means of maximum likelihood of the form

$$\logit(P(Y_i = 1)) = \beta_0 + \beta_1 a_i + \beta_2 x_{i1} + \beta_3 x_{i2} + \beta_4 a_i x_{i1} + \beta_5 a_i x_{i2}$$  (17)

Discrimination performance was assessed by means of the c-for-benefit using 1:1 benefit matching (cben-$\delta$), the c-for-benefit using 1:1 matching on predicted outcome risk under the control treatment (cben-$\hat{\gamma}^0$), and the mbcb. Calibration performance was assessed according to equation (13). Each of the performance measures was evaluated (1) without correction in the same samples as in which the ITE model was developed (sample D, apparent performance[9]), (2) in interval validation using bootstrap 0.632+ adjustment (3) in interval validation using bootstrap optimism correction, (4) in external validation samples V1, (5) in external validation data samples V2, (6) in the external population from DGM-1, and (7) in the external population from DGM-2. A more detailed account of the procedures in available in online supplementary material C.

**Performance measures:** Writing $\theta_s$ for the reference value in simulation run $s$, and $\hat{\theta}_s$ for the corresponding estimate, performance measures were averaged across simulations $s = 1, \ldots, n_{sim}$ in terms of bias $\frac{1}{n_{sim}} \sum_{s=1}^{n_{sim}} (\hat{\theta}_s - \theta_s)$ and root mean squared prediction error $\sqrt{\frac{1}{n_{sim}} \sum_{s=1}^{n_{sim}} (\theta_s - \hat{\theta}_s)^2}$.

**Additional reference:** For calibration evaluation only, a ‘naive’ population reference value was derived for each ITE model to demonstrate that ITE calibration heavily relies on the accuracy of control outcome risk predictions ($\hat{g}_0$). This reference does not correspond to an estimand of interest, but instead corresponds to ‘naive’ adjustment for $\hat{g}_0$ as predicted by the evaluated ITE model (i.e., instead of $\hat{g}_0$ as predicted from a local model in data independent from the development data). Thereby, it serves to illustrate the large-sample error that occurs under misspecification of the model for $\hat{g}_0$.

**5.2 Discrimination results**

Figure 1 and Table 1 show the main simulation results with respect to the discrimination statistics. Tabulated results corresponding to Figure 1 are available as online supplementary Table D.1. First, note that the sample reference and population reference show near perfect agreement across all panels. This shows that the estimand in a validation sample generalized well to entire population (i.e., did not greatly depend on the specific sample of covariate values in a given validation sample).

With respect to the estimates, and starting with apparent evaluations (top left), all statistics showed optimism with respect to the reference standards, which decreased with increasing sample size. As expected, direct evaluation in new data from the same DGM (top-middle) removes optimism for cben-$\delta$ and cben-$\hat{\gamma}^0$, and did not remove optimism in the model-based c-for-benefit. The latter preserves overfitting since it only estimates the c-statistic that would be obtained for the
new data if the model were correct. Note that the estimated cben-δ in V1 was actually too low, indicating bias in the estimator.

As shown in the bootstrap panels in Figure 1, both types of bootstrap evaluations adjusted for optimism in apparent evaluations. On average, bias was almost eliminated from cben-γ0 and the mbcb. For cben-δ the bootstrap adjusted estimates were too low, which is in line the findings in V1. Nonetheless, bootstrap procedures were generally not able to decrease the root mean squared prediction error between the estimated statistic and population reference statistic (Table 1). The 0.632+ procedure for the cben-γ0 forms an exception, decreasing both bias and rmse for all sample sizes.

With respect to evaluation in new data from a different DGM (top-right), the large systematic error for cben-γ0 and mbcb is apparent. For the cben-γ0, this is because it relies on predictions ̂g0 for 1:1 matching that are not suitable for the data at hand. Consequently, the observed outcome difference within matched pairs cannot be fully attributed to treatment, resulting in biased estimates. For the mbcb, this actually a feature, showing the expected model performance adjusted to the case-mix in V2 assuming the ITE model is correct. Local estimates of ̂Pbenefit,k,l are required for actual external validation. Lastly, the original cben-δ was a little too low (as in V1), but still quite close to the reference standards, with 1:1 matching on ̂δ apparently reasonable for this DGM.

Sub-figures and rows indicated with a star (in Figure 1 and Table 1) show the results after local estimation of control outcome risk (for the cben-γ0) and ̂Pbenefit,k,l (for the mbcb). For the cben-γ0, this is required for accurate matching in new data. For the mbcb, local estimates of ̂Pbenefit,k,l are always required for validation purposes. For both V1 and V2, this results in essentially unbiased estimates for both the cben-γ0 and the mbcb. However, rmse of the cben-γ0 was still large and the mbcb is clearly to be preferred in terms of error when compared against the population reference estimates.

Summarizing, the cben-δ showed some bias in all settings but was very stable throughout. Both the cben-γ0 and mbcb were essentially unbiased when evaluated in external data, but only the latter was sufficiently precise to also outperform the cben-δ in terms of rmse. Lastly, bootstrap procedures removed optimism across the board, but also increased variability.

| Statistic   | cben-δ   | cben-γ0   | mbcb       |
|-------------|----------|-----------|------------|
| Development data |          |           |            |
| Apparent    | 0.036, 0.031, 0.025 | 0.045, 0.035, 0.030 | **0.035, 0.027, 0.023** |
| 0.632+      | 0.041, 0.035, 0.030 | 0.037, 0.030, 0.026 | 0.039, 0.030, 0.027 |
| Opt. corrected | 0.042, 0.036, 0.030 | 0.046, 0.036, 0.031 | 0.037, 0.029, 0.026 |
| External    |          |           |            |
| DGM-1       | 0.028, 0.028, 0.028 | 0.032, 0.030, 0.030 | 0.036, 0.027, 0.023 |
| DGM-2       | 0.023, 0.024, 0.024 | 0.042, 0.043, 0.041 | 0.085, 0.079, 0.076 |
| DGM-1*      | na       | 0.031, 0.030, 0.031 | **0.024, 0.023, 0.024** |
| DGM-2*      | na       | 0.028, 0.028, 0.029 | **0.022, 0.023, 0.022** |

Table 1: Root mean squared error against population reference as averaged over simulation runs for each measure and for each of the sample sizes (500, 750, and 1000; left to right). * after local estimation of control outcome risk (for cben-γ0) and ̂Pbenefit,k,l (for mbcb). Bold numbers denote the best performance for each sample size in the following groups: development data, external data from DGM-1, and external data from DGM-2.

### 5.3 Calibration results

Simulation results for the calibration estimates are shown in Figure 2 (slopes), online supplementary material Figure D.1 (intercepts) and Table 2. Tabulated results corresponding to these figures is in online supplementary Tables D.2 and D.3. As expected, the apparent intercept and slope evaluations were uniformly 0 and 1 respectively. While this is a useful check of procedures, it also

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5External data set V1 is an exception, since the DGM was exactly the same as for the development set, but this is never known in practice.
Figure 1: Simulation results for the discrimination statistics in terms of mean c-statistic ± 1 SD. Top row: apparent evaluations in the original data (left), new data from the same DGM (middle), and new data from a different DGM (right). Bottom row, left to right: adjusted evaluations in the original data (bootstrap corrected 0.632+ and optimism correction), adjusted evaluations in new data from the same DGM, and adjusted evaluations in new data from a different DGM.

illustrates a challenge in calibration procedures: the apparent assessment is not just optimistic, but wholly uninformative.

Naive calibration assessment in V1 (i.e., with offset $\hat{g}_{lp,0}(x_j)$ based on the ITE model under evaluation) showed optimistic slope estimates. Performing the same assessment in the whole population for DGM-1 (‘population naive’) gave similarly biased estimates. These findings are exaggerated when assessing calibration in V2, with the naive findings for all sample sizes seemingly very good, yet with large deviation from the true slopes for either the sample reference (i.e., given the distribution of covariates in the validation data) or the population reference. Both bootstrap procedures removed optimism from apparent estimates, but the 0.632+ estimate was on average 0.062 too low for all sample sizes. Optimism correction performed better and was on average 0.036 below the population reference. Nonetheless, in terms of rmse, bootstrap estimates were all worse than the non-informative apparent evaluation. This implies that there does not seem to be enough information in a single sample to obtain reliable ITE calibration estimates.

The only consistently unbiased estimates were obtained in external data V1 and V2 after locally estimating a model for $\hat{g}_{lp,0}(x_j)$ in the control arm. Note that this approach does not use data twice, since the ITE calibration model is fitted in the treated arm only. Regardless of sample size or data generating mechanism, these estimates were almost unbiased and had the best rmse as compared to any of the other estimates. The only exception was for n1000 in V1, which had a similar rmse based on the original model for $g_{lp,0}(x_j)$. Since D and V1 are both from DGM-1, re-estimation of $g_{lp,0}(x_j)$ is only beneficial if V1 has a larger control arm, which was the case for n500 and n750 for D. Nonetheless, since rmse is on the scale of the estimates, the absolute size of the errors was still large, casting doubt on the practical utility of ITE calibration.

Summarizing, relying on the ITE model for predictions $\hat{g}_{lp,0}(x_j)$ (control outcome risk) can induce large bias and local estimation of $g_{lp,0}(x_j)$ in independent data is preferable. Bootstrap estimates
removed optimism and performed well in terms of bias, but were highly variable for particular data sets, which limits practical applicability. In external validation data, performance of the ITE calibration metrics provided a large improvement over apparent and bootstrap estimated in terms of both bias and root mean squared prediction error.

Figure 2: Simulation results for the ITE calibration slope estimates (mean ± 1 SD). Top row: apparent evaluations in the original data (left), new data from the same DGM (middle), and new data from a different DGM (right). Bottom row, left to right: adjusted evaluations in the original data (bootstrap corrected 0.632+ and optimism correction), adjusted evaluations in new data from the same DGM, and adjusted evaluations in new data from a different DGM.

6 Applied example: the third International Stroke Trial

Patients with an ischemic stroke have sudden onset of neurological symptoms due to a blood clot that narrows or blocks an artery that supplies the brain. A key component in the emergency medical treatment of these patients includes clot-busting drug alteplase (intravenous thrombolysis recombinant tissue-type plasminogen activator) [32].

The third International Stroke Trial (IST-3) was a randomized trial and investigated the benefits and harms of intravenous thrombolysis with alteplase in acute ischemic stroke [14]. This large trial included 3035 patients receiving either alteplase or placebo in a 1:1 ratio. The primary outcome was proportion of patients that was alive and independent at 6-month follow-up, which we used as outcome of interest here. Primary analyses of the treatment effect were performed by with logistic regression adjusted for linear effects of age, National Institutes of Health stroke scale (NIHSS) score, time from onset of stroke symptoms to randomization, and presence (vs absence) of ischemic change on the pre-randomization brain scan according to expert assessment. This analysis showed weak evidence of an effect (OR 1.13, 95% CI 0.95-1.35), but subgroup analyses suggested possibly heterogeneous treatment effect by age, NIHSS score, and predicted probability of a poor outcome.

For illustrative purposes, we here compare a main effects logistic regression model similar to the original adjusted analysis (model 1) with a model where all covariate-treatment interactions were included (model 2). The outcome was coded as 0 for those independent and alive after 6 months
Statistic $\hat{\beta}_0$ $\hat{\beta}_1$

**Development data**

|            |       |       |
|------------|-------|-------|
| Apparent   | 0.563, 0.378, 0.319 | 0.724, 0.491, 0.409 |
| 0.632+     | na    | 0.893, 0.679, 0.573 |
| Opt. corrected | 0.627, 0.450, 0.384 | 0.817, 0.600, 0.506 |

**External**

|           |       |       |
|-----------|-------|-------|
| DGM-1     | 0.367, 0.336, 0.315 | 0.473, 0.413, 0.386 |
| DGM-2     | 0.924, 0.911, 0.898 | 0.730, 0.701, 0.665 |
| DGM-1*    | 0.337, 0.322, 0.319 | 0.412, 0.375, 0.393 |
| DGM-2*    | 0.373, 0.284, 0.269 | 0.455, 0.316, 0.332 |

Table 2: Root mean squared error against population reference as averaged over simulation runs for calibration intercept and slope estimates for each of the sample sizes (500, 750, and 1000; left to right). * after local estimation of control outcome risk. Bold numbers denote the best performance for each sample size in the following groups: development data, external data from DGM-1, and external data from DGM-2.

and 1 otherwise. The included variables were treatment, age, NIHSS, time (from onset of stroke symptoms to randomization), and imaging status (presence vs absence of ischemic change on the pre-randomization brain scan). Continuous variables age, NIHSS, and time, were modeled using smoothing splines. We also included covariate-treatment interactions for these variables. Continuous variables age, NIHSS, and time, were modeled using smoothing splines with shrinkage. We also included covariate-treatment interactions for these variables. Models were fitted using the mgcv package in R with defaults smoothing parameter selection based on generalized cross-validation [33]. All in all, this applied example illustrates different ways to assess the quality of individualized treatment effect predictions. The evaluated models were emphatically chosen for this purpose and were not developed in collaboration with clinical experts in the field. Hence, they are not meant to me applied in practice.

The exact parameter estimates for both models are not of key interest, but the apparent performance with respect to outcome risk prediction was good for both: c-statistics were 0.826 and 0.831 for model 1 and 2 respectively, with accompanying Brier scores of 0.160 and 0.158 and Nagelkerke $R^2$ of 0.389 and 0.402. The Spearman correlation between outcome risk predictions for both models, conditional on the assigned treatments, was 0.99.

| Model     | cben-$\tilde{\delta}$ | cben-$\tilde{y}$ | mbcb | $\hat{\beta}_0$ | $\hat{\beta}_1$ |
|-----------|------------------------|------------------|------|----------------|----------------|
| **Apparent** |                        |                  |      |                |                |
| M1        | 0.488                  | 0.489            | 0.510| -0.117         |                |
| M2        | 0.562                  | 0.570            | 0.567| 0.011          | 1.071          |
| **bootstrap 0.632+** |                        |                  |      |                |                |
| M1        | 0.489                  | 0.499            | 0.505|                |                |
| M2        | 0.535                  | 0.559            | 0.536|                | 0.522          |
| **Optimism corrected** |                        |                  |      |                |                |
| M1        | 0.485                  | 0.475            | 0.507| -0.068         |                |
| M2        | 0.534                  | 0.544            | 0.518| -0.022         | 0.895          |

Table 3: Applied example discrimination and calibration statistics for predicted individualized treatment effect.

Nonetheless, the range of predicted ITEs (i.e., on the risk difference scale) was very different. Model 1 predicted ITEs with median -0.020 (IQR -0.027, -0.011 and range -0.029, 0.000), while model 2 predicted ITEs with median -0.026 (IQR -0.059, 0.027 and range -0.811, 0.213). That is, the predicted treatment effect was very similar across individuals when predicted by model 1 (assuming a constant treatment effect on the log odds scale), but not when predicted by model 2 (assuming a heterogeneous treatment effect on the log odds scale). Table 3 shows the apparent and bootstrap corrected results for discrimination and calibration assessment at the ITE level for
the applied example as averaged over 1000 bootstrap samples.

With respect to ITE discrimination, both apparent and bootstrap-corrected discrimination estimates favored model 2 over model 1, with model 1 estimates around the no discriminative ability value of 0.5. If model 2 were entirely correct, the expected c for benefit for samples with similar characteristics was estimated to be 0.567 (apparent mbcb). While we know that model 2 is just a model and not exactly correct, this value is relevant since it provides the upper bound of ITE concordance for the combination of model and data. Subsequently, the bootstrap procedures uncovered evidence of overfitting of ITE’s and provided downward adjusted estimates.

Calibration slope estimates suggested that model 2 ITE estimates are more heterogeneous than justified by the data, and require shrinkage. The amount of shrinkage suggested varies considerably between the 0.632+ and optimism corrected estimates. Based on the simulation study, optimism correction was already conservative and was to be preferred over the 0.632+ slope which were yet more conservative. Note that the calibration slope for model 1 is not estimable (since the ITEs have no variability on the logit scale) and the intercept estimate for model 1 clearly show that the degree of predicted benefit is underestimated.

In summary, the results indicate that model 1 did not provide useful differentiation in terms of ITEs. While the discriminative ability of model 2 seems modest, clear benchmarks are lacking. After updating based on the optimism corrected calibration estimates, model 2 ITE predictions may still be meaningful, having a median of -0.02 (IQR -0.52, 0.02 and range -0.58, 0.19). Comparing the 1969 patients predicted to have benefit ($\hat{\delta}_{model2} < 0$) with the remaining 1066 patients ($\hat{\delta}_{model2} \geq 0$), the first were older [median(IQR) age 83 (78-87) vs 73 (63-82)], had worse symptoms [median(IQR) nihss 15(10-20) vs 6(4-9)], were treated earlier [median(IQR) time in hours 3.5 (2.5-4.9) vs 4.2 (3.6-4.8)], were more likely to have visual infarction on imaging (43% vs 36%), and had a less favorable outcome on average (alive and independent after 6 months in 23% vs 58% respectively).

7 Software

R package iteval (https://github.com/jeroenhoogland/iteval) provides a free software implementation on the freely available R software environment for statistical computing [31] for the cben-$\delta$, cben-$\delta^0$, mbcb, and calibration measures as defined in this paper.

8 Discussion

Measures of calibration and discrimination have a long history in the context of prediction models for observed outcome data, especially of the binary type. However, the evaluation of individualized treatment effect (ITE) prediction models is more challenging, first and foremost because of the causal nature of the predictions and the ensuing unobservable nature of individualized treatment effects. In this paper, we utilized the potential outcomes framework [13] to obtain insight into existing performance measures [11] and to develop novel measures of discrimination and calibration for ITE prediction models. We proposed model-based statistics to address challenges of existing methods. Importantly, these statistics are applicable regardless of the modeling approach used to generate ITE predictions, as long as predictions for each potential outcome are available. This means that our methods are usable for both statistical, as well as machine learning methods. Also, while the primary focus was on dichotomous outcomes, we also provided residual-based approaches for continuous outcome models. As such, our work provides generally applicable tools for the endeavor of ITE prediction model evaluation [6].

With respect to discriminative ability, the model-based c-for-benefit (mbcb) provides both a normal performance measure and an expected (case-mix adjusted) reference level for new data. The latter is relevant since concordance probabilities are known to be sensitive to case-mix [29]. Also, bootstrap procedures are available to adjust for optimism during model development. In the simulation study, the mbcb estimates were best in terms of both bias and root mean squared error across simulation settings. Both matching-based measures of discriminative performance had specific downsides. The original cben-$\delta$ has a difficult interpretation and was downward biased in the simulation study, but was very stable throughout. The adaptations implemented in the
cben-\hat{g}^0 did remove the bias, but at the cost of much larger variability. We hypothesize that the stability of the mbcb is due to the lack of a need for a matching algorithm. The large variability of cben-\hat{g}^0 likely relates to strong reliance of the matching procedure on the accuracy of predicted control outcome risk.

With respect to calibration, the potential outcomes framework provided a model-based method that evaluates ITE prediction in the treated individuals, against an offset of prediction outcome risk under control treatment. Compared to traditional calibration measures at the level of the outcome of interest, calibration of ITE predictions has the additional challenge that ITEs are in fact relative effects. As such, correct calibration of ITEs depends on correct calibration of outcome risk under control treatment. In line, local updating of the model predicting control outcome risk proved paramount for valid assessment of ITE calibration.

A key finding for both ITE discrimination and calibration measures was that bootstrap procedures were able to remove optimism \(\text{i.e. reduce bias}\), but that the increase in variance of the estimator generally led to increased root mean squared error. This implies that external data is required to accurately assess ITE predictions. The underlying reason is the need for local estimates \(\text{i.e. independent of the ITE model under evaluation}\) of control and treated outcome risk. While these steps were incorporated in the bootstrap procedures, they are necessarily noisy since they have to rely on only 36.8% of the data for any particular bootstrap run.

While this paper focused on measures specifically targeting ITE predictions, in practice we recommend assessing prediction performance with respect to the observed outcomes first \[9, 8\]. For instance, performance with respect to outcome risk can be evaluated in the control arm and in the treated arm separately. If performance is good, one can move on to ITE evaluation. The motivation for this hierarchy is that ITEs reflect differences and that they hence compound errors in both potential outcome predictions.

Limitations of the current work include the limited nature of the simulation study which was mainly performed for illustrative purposes. While both discrimination and calibration are well researched in classical settings, their application to ITE predictions is relatively novel. While we did elucidate several aspects of ITE prediction model evaluation in terms of discrimination and calibration, important questions remain. These include questions with respect to the best strategy for model comparison, the uncertainty of the estimated statistics, the relation between discrimination and calibration on the outcome risk level and the ITE level, and the relation between discrimination and calibration statistics and clinical usefulness of the models. With respect to uncertainty estimates, bootstrap procedures provide a good option, but many of the challenges are still open.

In terms of future research, it would be interesting to evaluate whether some level of grouping is beneficial for the evaluation of model performance. Paradoxically, the aim for precision underlying the development of ITE models may hamper the possibility to evaluate them, since individual level treatment effects are inherently unobservable, and their evaluation hence involves approximations based on the very model under evaluation. Also, especially in the binary event case, even if individual-level treatment effects would be observable, they would still be very noisy. This is the underlying reason that the c-statistics for benefit are so much lower than c-statistics on the outcome level.

Summarizing, we used the potential outcomes framework to obtain insight into measures of discrimination and calibration at the level of individualized treatment effect predictions. This allowed for a principled examination of existing measures and a proposal of new measures that may enrich the toolbox for ITE model evaluation. Further research is necessary to improve understanding of the exact characteristics of these measures under varying conditions with respect to sample size, degree of treatment effect heterogeneity, and explained variation.

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Data Availability Statement

Data for the International Stroke Trial-3 applied example are publicly available [34]. R package iteval is available on GitHub (https://github.com/jeroenhoogland/iteval) and provides functions to derive the cben-δ, cben-γ, mbcb, and calibration measures as defined in this paper. Github repository iteval-sims (https://github.com/jeroenhoogland/iteval-sims) provides the required files and instructions for replication of the simulation study.

References

[1] D. M. Kent, E. Steyerberg, and D. van Klaveren, “Personalized evidence based medicine: predictive approaches to heterogeneous treatment effects,” BMJ, p. k4245, 2018.

[2] D. M. Kent, D. van Klaveren, J. K. Paulus, R. D’Agostino, S. Goodman, R. Hayward, J. P. Ioannidis, B. Patrick-Lake, S. Morton, M. Pencina, G. Raman, J. S. Ross, H. P. Selker, R. Varadhan, A. Vickers, J. B. Wong, and E. W. Steyerberg, “The Predictive Approaches to Treatment effect Heterogeneity (PATH) Statement: Explanation and Elaboration,” Annals of Internal Medicine, vol. 172, pp. W1–W25, Jan. 2020.

[3] S. Senn, “Statistical pitfalls of personalized medicine,” Nature, vol. 563, pp. 619–621, Nov. 2018.

[4] A. Rekkas, J. K. Paulus, G. Raman, J. B. Wong, E. W. Steyerberg, P. R. Rijnbeek, D. M. Kent, and D. van Klaveren, “Predictive approaches to heterogeneous treatment effects: a scoping review,” BMC Medical Research Methodology, vol. 20, p. 264, Dec. 2020.

[5] L. Lin, M. Sperrin, D. A. Jenkins, G. P. Martin, and N. Peek, “A scoping review of causal methods enabling predictions under hypothetical interventions,” Diagnostic and Prognostic Research, vol. 5, p. 3, Dec. 2021.

[6] J. Hoogland, J. IntHout, M. Belias, M. M. Rovers, R. D. Riley, F. E. Harrell Jr, K. G. M. Moons, T. P. A. Debray, and J. B. Reitsma, “A tutorial on individualized treatment effect prediction from randomized trials with a binary endpoint,” Statistics in Medicine, p. sim.9154, Aug. 2021.

[7] S. Wager and S. Athey, “Estimation and Inference of Heterogeneous Treatment Effects using Random Forests,” Journal of the American Statistical Association, vol. 113, pp. 1228–1242, July 2018.

[8] E. W. Steyerberg, Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. Statistics for Biology and Health, Cham: Springer International Publishing, 2019.

[9] F. E. Harrell, Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis. Springer series in statistics, Cham Heidelberg New York: Springer, second ed., 2015. OCLC: 922304565.

[10] B. Van Calster, D. J. McLernon, M. van Smeden, L. Wynants, E. W. Steyerberg, and On behalf of Topic Group ‘Evaluating diagnostic tests and prediction models’ of the STRATOS initiative, “Calibration: the Achilles heel of predictive analytics,” BMC Medicine, vol. 17, p. 230, Dec. 2019.

[11] D. van Klaveren, E. W. Steyerberg, P. W. Serruys, and D. M. Kent, “The proposed ‘concordance-statistic for benefit’ provided a useful metric when modeling heterogeneous treatment effects,” Journal of Clinical Epidemiology, vol. 94, pp. 59–68, 2018.

[12] D. B. Rubin, “Estimating causal effects of treatments in randomized and nonrandomized studies.,” Journal of Educational Psychology, vol. 66, no. 5, pp. 688–701, 1974.
[13] D. B. Rubin, “Causal Inference Using Potential Outcomes: Design, Modeling, Decisions,” *Journal of the American Statistical Association*, vol. 100, pp. 322–331, Mar. 2005.

[14] The IST-3 collaborative group, “The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial,” *The Lancet*, vol. 379, pp. 2352–2363, June 2012.

[15] P. Holland, “Statistics and Causal Inference,” *Journal of the American Statistical Association*, vol. 81, no. 396, pp. 945–960, 1986.

[16] M. A. Hernán and J. M. Robins, *Causal Inference: What If*. Boca Raton: Chapman & Hall/CRC, Feb. 2020.

[17] A. Lamont, M. D. Lyons, T. Jaki, E. Stuart, D. J. Feaster, K. Thamaratnam, D. Oberski, H. Ishwaran, D. K. Wilson, and M. L. Van Horn, “Identification of predicted individual treatment effects in randomized clinical trials,” *Statistical Methods in Medical Research*, vol. 27, no. 1, pp. 142–157, 2018.

[18] E. J. Murray, E. C. Caniglia, S. A. Swanson, S. Hernández-Díaz, and M. A. Hernán, “Patients and investigators prefer measures of absolute risk in subgroups for pragmatic randomized trials,” *Journal of Clinical Epidemiology*, vol. 103, pp. 10–21, Nov. 2018.

[19] F. E. Harrell and R. M. Califf, “Evaluating the Yield of Medical Tests,” *JAMA*, vol. 247, p. 4, May 1982.

[20] A. P. Bress, T. Greene, C. G. Derington, J. Shen, Y. Xu, Y. Zhang, J. Ying, B. K. Bellows, W. C. Cushman, P. K. Whelton, N. M. Pajewski, D. Reboussin, S. Beddu, R. Hess, J. S. Herrick, Z. Zhang, P. Kohn, R. W. Yeh, S. Basu, W. S. Weintraub, and A. E. Moran, “Patient Selection for Intensive Blood Pressure Management Based on Benefit and Adverse Events,” *Journal of the American College of Cardiology*, vol. 77, pp. 1977–1990, Apr. 2021.

[21] M. K. Olsen, K. M. Stechuchak, E. Z. Oddone, L. J. Damschroder, and M. L. Maciejewski, “Which patients benefit most from completing health risk assessments: comparing methods to identify heterogeneity of treatment effects,” *Health Services and Outcomes Research Methodology*, Feb. 2021.

[22] T. Duan, P. Rajpurkar, D. Laird, A. Y. Ng, and S. Basu, “Clinical Value of Predicting Individual Treatment Effects for Intensive Blood Pressure Therapy: A Machine Learning Experiment to Estimate Treatment Effects from Randomized Trial Data,” *Circulation: Cardiovascular Quality and Outcomes*, vol. 12, Mar. 2021.

[23] P. R. Rosenbaum, “A Characterization of Optimal Designs for Observational Studies,” *Journal of the Royal Statistical Society: Series B (Methodological)*, vol. 53, pp. 597–610, July 1991.

[24] B. B. Hansen, “Full Matching in an Observational Study of Coaching for the SAT,” *Journal of the American Statistical Association*, vol. 99, pp. 609–618, Sept. 2004.

[25] J. Colannino, M. Damian, F. Hurtado, S. Langerman, H. Meijer, S. Ramawami, D. Souvaine, and G. Toussaint, “Efficient Many-To-Many Point Matching in One Dimension,” *Graphs and Combinatorics*, vol. 23, pp. 169–178, June 2007.

[26] B. B. Hansen, “The prognostic analogue of the propensity score,” *Biometrika*, vol. 95, pp. 481–488, Feb. 2008.

[27] T. Nguyen and T. P. Debray, “The use of prognostic scores for causal inference with general treatment regimes,” *Statistics in Medicine*, vol. 38, pp. 2013–2029, May 2019.

[28] D. van Klaveren, M. Gönen, E. W. Steyerberg, and Y. Vergouwe, “A new concordance measure for risk prediction models in external validation settings: A new Concordance Measure for External Validation of Risk Models,” *Statistics in Medicine*, vol. 35, pp. 4136–4152, Oct. 2016.

[29] D. Nieboer, T. van der Ploeg, and E. W. Steyerberg, “Assessing Discriminative Performance at External Validation of Clinical Prediction Models,” *PLOS ONE*, vol. 11, p. e0148820, Feb. 2016.
A Binomial outcome data

A.1 Absolute risk, risk difference, and binomial error

Focusing on binary outcomes, assume we observe outcome $Y_i \in \{0, 1\}$ and covariate status $x_i$ for each individual $i$. Using data on $n$ individuals, we can model the outcome risk $P(Y_i = 1|A = a_i, X = x_i)$. There are two sources of error when using such a model to predict binary outcomes. There is the reducible error in modeling the risk (i.e., how well the modelled probability approximates the actual probability of an event), and there is the irreducible error in the difference between the actual probability of an event and its manifestation as a 0 or 1 outcome (binomial error).

Adding to this, actual interest is in the difference in outcome risk under different treatment assignment $a \in \{0, 1\}$. That is, interest is in $P(Y_i = 1|A = 1, X = x_i) - P(Y_i = 1|A = 0, X = x_i)$. The range of possible true (and estimated) treatment effects (risk differences) includes all values in the $[-1, 1]$ interval, but the observed difference between any two outcomes can only be one of $\{-1, 0, 1\}$. An example may be helpful to appreciate the large influence of irreducible error in this setting. For instance, regardless of any modeling, assume that an active treatment (as compared to a control condition) reduces outcome risk from 25% to 20% for a certain individual. Moreover, assume that these probabilities are known exactly and that this individual can be observed unconfounded.

For instance, $P(Y^0 = 0, Y^1 = 0) = (1 - P(Y^0 = 0))(1 - P(Y^1 = 0)) = (1 - 0.25)(1 - 0.2) = 0.6$
A.2 Scale matters

Models that predict the risk of a binary event commonly make use of a link function in order to map a function of the covariates in $\mathbb{R}$ onto the probability scale [35]. Such link functions, such as the logit or inverse Gaussian, are inherently non-linear and hence do not preserve additivity. Consequently, a treatment effect that is constant (i.e., does not vary with other covariates) before applying the link function shall vary with other covariates on the risk scale and vice versa. As an example, we write $h^{-1}$ for an inverse link function and take control risk to be a function $f(\cdot)$ of only one random variable $X$ (i.e., $P(Y_{a=0}|X=x) = h^{-1}(f(X))$). Subsequently, assume a constant (homogeneous) relative treatment effect $d$ such that $P(Y_{a=1}|X=x) = h^{-1}(f(X) + d)$, then the absolute treatment effect necessarily depends on $X$, since

$$
\delta(x) = P(Y_{a=1}|X=x) - P(Y_{a=0}|X=x) = h^{-1}[f(X) + d] - h^{-1}[f(X)] = h^{-1}(d)
$$

unless $h^{-1}(\cdot)$ is linear. Consequently, between-individual variability (i.e., variability in terms of $X$) directly changes control outcome risk and affects the absolute effect of $d$ on the probability scale even if $d$ is constant. For instance, a constant treatment effect on the log-odds scale translates into heterogeneous treatment effect on the risk difference scale. Thereby, relatively simple treatment effect structures may lead to meaningful between-individual treatment effect variability at the risk difference level if there is large variability in $h^{-1}(f(X))$ [6, 36]. In addition, treatment effect may interact with $X$ in the domain of $h^{-1}(\cdot)$, i.e., we may directly model treatment effect heterogeneity. These two sources of variability in $\delta(x)$ can no longer be discerned when evaluating just the estimates $\hat{\delta}(x)$. Hence, the benefit in terms of interpretation of measures on the scale of $\delta(x)$ [18], as of interest in this paper, has a price in that they conflate variability in $\delta(x)$ from different sources: between-subject variability in $P(Y_{a=0}|X=x)$ and genuine treatment effect heterogeneity on the scale used for modeling.

B Discrimination estimand

Harrell’s c-statistic [19, 9] can be applied to ordered predictions and (possibly censored) ordered outcomes. Applying Harrell’s c-statistic with ITE predictions and within-individual differences in potential outcomes $Y_{a=1} - Y_{a=0}$ as simulated from some data generating mechanism, the equation for the concordance probability can be written as

$$
c_{\delta, \text{ben}} = \frac{\sum_k \sum_{l \neq k} [I(\hat{\delta}_k < \hat{\delta}_l)\text{ben}_{kl} + \frac{1}{2}I(\hat{\delta}_k = \hat{\delta}_l)\text{ben}_{kl}]}{\sum_k \sum_{l \neq k} \text{ben}_{kl}} \tag{B.1}
$$

with

$$
\text{ben}_{kl} = I([Y_{k}^{a=1} - Y_{k}^{a=0}] < [Y_{l}^{a=1} - Y_{l}^{a=0}]) \tag{B.2}
$$

However, the within-individual differences in sampled potential outcomes $Y_{k}^{a=1} - Y_{k}^{a=0}$ are just a single manifestation of treatment effect for covariate matrix $X$, and interest is in the expected value over repeated samples of potential outcomes given $X$. Taking this expectation $E_{Y^{a=1}\mid X}$ over equation (B.1) does not affect ITE predictions, since these are invariant conditional on a fixed ITE model and fixed $X$. For $\text{ben}_{kl}$,

$$
E_{Y^{a=1}\mid X}(\text{ben}_{kl}) = E_{Y^{a=1}\mid X}(I([Y_{k}^{a=1} - Y_{k}^{a=0}] < [Y_{l}^{a=1} - Y_{l}^{a=0}]))
$$

$$
= P([Y_{k}^{a=1} - Y_{k}^{a=0}] < [Y_{l}^{a=1} - Y_{l}^{a=0}])
$$

$$
= P_{\text{benefit},k,l} \quad \text{(as defined in Section 3.4)} \tag{B.3}
$$

In turn, substituting an estimate of $P_{\text{benefit},k,l}$ for $\text{ben}_{kl}$ in equation (B.1) gives the equation for the nmbc (equation (12)). Instead substituting the true probabilities $P_{\text{benefit},k,l}$, as known in a simulation context given the data generating mechanism, provides the expected value for the ITE concordance statistic for a given data generating mechanism, a fixed matrix of observed covariate values $X$, and a fixed ITE model. Therefore, it was used as the estimand value of the ITE concordance statistic for a given sample (denoted 'sample reference').
When the sample size is very large, such as for the simulated populations of size 100,000, calculation of the mbcb is computationally very intensive and an approximation based on $\hat{c}_{\delta, \text{ben}}$ (equation (B.1)) is accurate. Note that $\hat{c}_{\delta, \text{ben}}$ is still unbiased, but of course more variable.

C Performance evaluation details

C.1 Apparent performance

Apparent ITE model performance was evaluated, without any adjustment, in the development sample D in which the ITE model was fitted. Consequently, apparent estimates can be expected to be optimistic. For apparent calibration performance of a logistic ITE model based on maximum likelihood estimation, note that the estimates will invariably be $\hat{\beta}_0 = 0$ and $\hat{\beta}_1 = 1$ since the calibration model is of the exact same type. All in all, apparent performance was primarily assessed to show the need for internal validation procedures that correct for optimism or, better yet, new data.

C.2 Internal validation

Discrimination

Internal validation was performed based on a non-parametric bootstrapping procedure based on 100 bootstrap samples. Performance estimates were based on either a 0.632+ method [37] adapted for application in the context of c-statistics or on optimism correction [9]. The adapted 0.632+ method provides a weighted average of apparent performance and average out-of-sample performance as based on predictions from bootstrap models for the cases not in the bootstrap sample. Writing $\hat{c}_{\text{app}}$ (scalar) for the apparent c-statistic and $\hat{c}_{\text{oos}}$ (scalar) for the average out-of-sample c-statistic across bootstrap replications,

$$\hat{c}_{\text{oos}} = \left\{ \begin{array}{ll} \min(\gamma, \hat{c}_{\text{oos}}), & \hat{c}_{\text{app}} \geq \gamma \\ \max(\gamma, \hat{c}_{\text{oos}}), & \hat{c}_{\text{app}} < \gamma \end{array} \right. \quad (C.1)$$

$$R = \left\{ \begin{array}{ll} |\hat{c}_{\text{app}} - \hat{c}_{\text{oos}}|, & |\hat{c}_{\text{oos}} - \gamma| < |\hat{c}_{\text{app}} - \gamma| \\ 0, & \text{otherwise} \end{array} \right. \quad (C.2)$$

$$w = \frac{0.632}{1 - 0.368R} \quad (C.3)$$

$$\hat{c}_{0.632+} = \hat{c}_{\text{app}}(1 - w) + w\hat{c}_{\text{oos}} \quad (C.4)$$

where $\gamma$ is the value of the statistic for an uninformative model (so $\gamma = 0.5$ for c-statistics), and $w$ is a weight that depends on the discrepancy between apparent and out-of-sample performance. To prevent that $R$ falls outside of the (0, 1), we avoid the possibility of bootstrap correction towards a point beyond the no information threshold by replacement of $\hat{c}_{\text{oos}}$ with $\hat{c}'_{\text{oos}}$ throughout, with

$$\hat{c}'_{\text{oos}} = \left\{ \begin{array}{ll} \min(\gamma, \hat{c}'_{\text{oos}}), & \hat{c}_{\text{app}} \geq \gamma \\ \max(\gamma, \hat{c}'_{\text{oos}}), & \hat{c}_{\text{app}} < \gamma \end{array} \right. \quad (C.5)$$

Subsequently, $R$ reflect the degree of overfitting and ranges from zero to one, with $w$ depending only on $R$ and ranging from 0.632 and 1. Thereby, $\hat{c}_{0.632+}$ moves towards $\hat{c}'_{\text{oos}}$ when the amount of overfitting ($|\hat{c}_{\text{app}} - \hat{c}'_{\text{oos}}|$) is large with respect to the models gain relative to no information ($|\hat{c}_{\text{app}} - \gamma|$). The choice to use $\hat{c}'_{\text{oos}}$ instead of $\hat{c}'_{\text{oos}}$ in (C.5) was to avoid correction of an apparent estimate beyond the no information threshold.

Alternatively, optimism correction estimates optimism as the average difference between performance of bootstrap models as evaluated in a) the original full data set D and b) within the bootstrap sample. In case of overfitting, the discrepancy between the two will increase. The apparent estimate is subsequently corrected for this bootstrap estimate of optimism.
Obtaining either the 0.632+ or optimism corrected estimates for cben-$\hat{\delta}$ and cben-$\hat{g}^0$ is straightforward. One subtlety is that in case of unequal group sizes (treated vs control), the average over 1000 repeated analyses of subsamples of the larger arm was taken to accommodate for 1:1 matching. For the model-based estimates, a choice with respect to the estimation of $\hat{P}_{\text{benefit},k,l}$ has to be made with respect to out-of-sample evaluation. To avoid bias, the out-of-sample evaluation of $\hat{P}_{\text{benefit},k,l}$ for the 0.632+ estimate was based on a model for $\hat{g}_0$ and $\hat{g}_1$ is the out-of-sample cases (with the same specification as the model under evaluation). For the optimism correction, $\hat{P}_{\text{benefit},k,l}$ for the whole of D was based on the ITE model as developed in the full sample D. That is, the 0.632+ model-based c-statistic estimates were obtained from (1) out-of-sample predictions $\hat{\delta}(x_{i,\text{oos}})$ from bootstrap models and (2) $\hat{P}_{\text{benefit},k,l}$ based on an out-of-sample model. Optimism corrected model-based c-statistic estimates were obtained from (1) predictions $\hat{\delta}(x_i)$ from bootstrap models and $\hat{P}_{\text{benefit},k,l}$ based on the development model.

**Calibration**

Bootstrap evaluation of the calibration parameters was also performed. A 0.632+ estimate was derived for the slope estimates in analogy to the derivation for c-statistics, but using $\gamma = 0$ for the value that slope $\beta_1$ takes for an uninformative model. Out-of-sample estimates of $\hat{g}_0(\cdot)$ were based on a model fitted in just the out-of-sample controls to serve as an offset in the calibration model fitted in the out-of-sample treated arm. A 0.632+ estimate for the calibration intercept parameter is not readily available since a $\gamma$ value for a non-informative intercept cannot be defined. Optimism corrected bootstrap estimates were obtained for both intercepts and slopes. Estimates of $\hat{g}_0(\cdot)$ in the bootstrap sample were based on the bootstrap model and estimates $\hat{g}_0(\cdot)$ in the original data were based on the original ITE model fitted in development data D.

### C.3 External validation

**Discrimination**

External validation was performed in both V1 (DGM-1) and V2 (DGM-2). ITE predictions can be evaluated directly using cben-$\hat{\delta}$. For cben-$\hat{g}^0$, which matches based on predicted control outcome risk $\hat{g}_0(\cdot)$, a key question is whether $\hat{g}_0(\cdot)$ may best be based on the ITE model or on a new model fitted in the control arm of the external data. In practice, the accuracy of $\hat{g}_0(\cdot)$ based on the ITE model can be assessed in the control arm of the external data. If not satisfactory, a new model for $\hat{g}_0(\cdot)$ can be derived in the external data for use with the cben-$\hat{g}^0$. The latter option was taken for the simulation study based on a refitting of the relevant parts of model (17) in the control arm (i.e., omitting parameters relating to a which equal 0 for controls) of the external data. Note that fitting a new model will in general remove bias, but may have a high cost in terms of variance if the external data set is small. For the model-based c-for-benefit (mcb), the accuracy of $\hat{P}_{\text{benefit},k,l}$, and hence the underlying $\hat{g}_0(\cdot)$ and $\hat{g}_1(\cdot)$, is paramount. In the mcb, $\hat{P}_{\text{benefit},k,l}$ is the sole carrier of information from the external data and acts as the reference for ITE predictions under evaluation. In line with the procedure for the cben-$\hat{g}^0$, performance with respect $\hat{g}_0(\cdot)$ and $\hat{g}_1(\cdot)$ can be examined in the external data (control arm and treated arm respectively) and may indicate the need for a new model. Again, the latter option was chosen for the simulation study. Note that D, V1 and V2 were always of equal size, such that there was the benefit of possibly reducing bias while avoiding the possible harm of increased variance. Finally, note that while cben-$\delta$, cben-$\hat{g}^0$, and the mcb focus on $\hat{\delta}(x_i)$, inadequate prediction performance with respect to $\hat{g}_0(\cdot)$ and/or $\hat{g}_1(\cdot)$ is an ominous sign for ITE model performance. Nonetheless, the attention with respect to accurate potential outcome prediction in the external data is required even if only to reliably show bad performance with respect to $\hat{\delta}(x_i)$.

**Calibration**

Direct calibration assessment in external data exactly followed the lines of apparent calibration assessment with all predictions (both $\hat{\delta}_g(x_j)$ and $\hat{g}_{p,0}(x_j)$) based on the ITE model as derived in D and applied in V1 and V2. Adjusted estimates were obtained based on local predictions $\hat{g}_{p,0}(x_j)$ based on a refitting of the relevant parts of model (17) in the control arm (i.e., omitting parameters relating to a which equal 0 for controls) of the external data.

**Calibration**

As for discrimination, the estimands as defined in Section 5 reflect the target reference parameter values for a specific ITE model as evaluated in a specific sample (D, V1 or V2). To remove dependence of the performance measure on a (small) sample, population reference values were
derived per data generating mechanism as for the discrimination measures. Derivation was exactly analogous to the description under ‘estimands’ in Section 5. In addition, a naive population reference for calibration assessment that mirrored assessment in D (\textit{i.e.}, naive referring to adjustment based on $\hat{g}_0(\cdot)$ based on the ITE model instead of independent data). Therein, this naive population reference helps to remove the influence of sample size from the assessment of bias due to misspecification of $\hat{g}_0(\cdot)$. 
D Additional simulation study results

D.1 Discrimination

| Statistic       | cben-δ | cben-\(\hat{y}\) | mbcb | sample ref. | population ref. |
|-----------------|--------|----------------|------|------------|-----------------|
| Development data, n=500 |        |                 |      |            |                 |
| Apparent        | 0.587  | 0.599          | 0.598| 0.578      | 0.580           |
| 0.632+          | 0.568  | 0.583          | 0.576| 0.578      | 0.580           |
| Opt. corrected  | 0.569  | 0.581          | 0.578| 0.578      | 0.580           |
| External, n=500 |        |                 |      |            |                 |
| DGM-1           | 0.569  | 0.581          | 0.598| 0.578      | 0.580           |
| DGM-2           | 0.518  | 0.551          | 0.598| 0.520      | 0.520           |
| DGM-1*          | 0.580  | 0.578          | 0.578| 0.578      | 0.580           |
| DGM-2*          | 0.521  | 0.520          | 0.520| 0.520      | 0.520           |
| Development data, n=750 |        |                 |      |            |                 |
| Apparent        | 0.584  | 0.595          | 0.594| 0.582      | 0.584           |
| 0.632+          | 0.572  | 0.585          | 0.580| 0.582      | 0.584           |
| Opt. corrected  | 0.572  | 0.583          | 0.580| 0.582      | 0.584           |
| External        |        |                 |      |            |                 |
| DGM-1           | 0.574  | 0.584          | 0.594| 0.582      | 0.584           |
| DGM-2           | 0.520  | 0.533          | 0.594| 0.520      | 0.520           |
| DGM-1*          | 0.581  | 0.582          | 0.582| 0.582      | 0.584           |
| DGM-2*          | 0.523  | 0.523          | 0.520| 0.520      | 0.520           |
| Development data, n=1000 |      |                 |      |            |                 |
| Apparent        | 0.581  | 0.594          | 0.592| 0.584      | 0.586           |
| 0.632+          | 0.573  | 0.585          | 0.582| 0.584      | 0.586           |
| Opt. corrected  | 0.573  | 0.584          | 0.582| 0.584      | 0.586           |
| External        |        |                 |      |            |                 |
| DGM-1           | 0.575  | 0.584          | 0.592| 0.584      | 0.586           |
| DGM-2           | 0.518  | 0.552          | 0.592| 0.521      | 0.521           |
| DGM-1*          | 0.584  | 0.585          | 0.584| 0.584      | 0.586           |
| DGM-2*          | 0.521  | 0.520          | 0.521| 0.521      | 0.521           |

Table D.1: Mean over simulation runs for each discrimination measure and for each of the sample sizes (500, 750, and 1000; left to right). *) After local estimation of control outcome risk (for cben-\(\hat{y}\)) and \(P_{benefit,k,l}\) (for mbcb).

D.2 Calibration
Figure D.1: Simulation results for the ITE calibration intercept estimates (mean ± 1 SD). Top row: apparent evaluations in the original data (left), new data from the same DGM (middle), and new data from a different DGM (right). Bottom row, left to right: adjusted evaluations in the original data (bootstrap corrected 0.632+ and optimism correction), adjusted evaluations in new data from the same DGM (middle), and adjusted evaluations in new data from a different DGM (right).
| Statistic                        | $\beta_0$ | population naive | sample ref. | population ref. |
|---------------------------------|-----------|------------------|-------------|-----------------|
| **Development data, n=500**     |           |                  |             |                 |
| Apparent                        | 0.000     | -0.046           | -0.105      | -0.107          |
| 0.632⁺                          |           |                  |             |                 |
| Opt. corrected                  | -0.108    | -0.046           | -0.105      | -0.107          |
| **External, n=500**             |           |                  |             |                 |
| DGM-1                           | -0.052    | -0.046           | -0.108      | -0.107          |
| DGM-2                           | 0.687     | 0.694            | -0.140      | -0.140          |
| DGM-1*                          | -0.109    | -0.103           | -0.108      | -0.107          |
| DGM-2*                          | -0.162    | -0.154           | -0.140      | -0.140          |
| **Development data, n=750**     |           |                  |             |                 |
| Apparent                        | 0.000     | -0.011           | -0.034      | -0.037          |
| 0.632⁺                          |           |                  |             |                 |
| Opt. corrected                  | -0.063    | -0.011           | -0.034      | -0.037          |
| **External**                    |           |                  |             |                 |
| DGM-1                           | -0.031    | -0.011           | -0.038      | -0.037          |
| DGM-2                           | 0.746     | 0.727            | -0.100      | -0.100          |
| DGM-1*                          | -0.064    | -0.043           | -0.038      | -0.037          |
| DGM-2*                          | -0.088    | -0.105           | -0.100      | -0.100          |
| **Development data, n=1000**    |           |                  |             |                 |
| Apparent                        | 0.000     | 0.007            | -0.011      | -0.010          |
| 0.632⁺                          |           |                  |             |                 |
| Opt. corrected                  | -0.036    | 0.007            | -0.011      | -0.010          |
| **External**                    |           |                  |             |                 |
| DGM-1                           | -0.006    | 0.007            | -0.009      | -0.010          |
| DGM-2                           | 0.748     | 0.745            | -0.102      | -0.101          |
| DGM-1*                          | -0.003    | 0.009            | -0.009      | -0.010          |
| DGM-2*                          | -0.094    | -0.096           | -0.102      | -0.101          |

Table D.2: Mean over simulation runs for calibration intercept estimates each of the sample sizes (500, 750, and 1000; left to right). *) after local estimation of control outcome risk.
| Statistic                  | $\beta_1$ | population naive | sample ref. | population ref. |
|---------------------------|-----------|------------------|-------------|-----------------|
| **Development data, n=500** |           |                  |             |                 |
| Apparent                  | 1.000     | 0.907            | 0.856       | 0.853           |
| 0.632 ±                   | 0.785     | 0.907            | 0.856       | 0.853           |
| Opt. corrected            | 0.831     | 0.907            | 0.856       | 0.853           |
| **External, n=500**       |           |                  |             |                 |
| DGM-1                     | 0.932     | 0.907            | 0.852       | 0.853           |
| DGM-2                     | 0.908     | 0.913            | 0.384       | 0.383           |
| DGM-1*                    | 0.868     | 0.843            | 0.852       | 0.853           |
| DGM-2*                    | 0.374     | 0.379            | 0.384       | 0.383           |
| **Development data, n=750** |           |                  |             |                 |
| Apparent                  | 1.000     | 0.942            | 0.939       | 0.935           |
| 0.632 ±                   | 0.878     | 0.942            | 0.939       | 0.935           |
| Opt. corrected            | 0.901     | 0.942            | 0.939       | 0.935           |
| **External**              |           |                  |             |                 |
| DGM-1                     | 0.956     | 0.942            | 0.935       | 0.935           |
| DGM-2                     | 0.989     | 0.948            | 0.426       | 0.425           |
| DGM-1*                    | 0.920     | 0.907            | 0.935       | 0.935           |
| DGM-2*                    | 0.455     | 0.416            | 0.426       | 0.425           |
| **Development data, n=1000** |           |                  |             |                 |
| Apparent                  | 1.000     | 0.981            | 0.990       | 0.991           |
| 0.632 ±                   | 0.930     | 0.981            | 0.990       | 0.991           |
| Opt. corrected            | 0.939     | 0.981            | 0.990       | 0.991           |
| **External**              |           |                  |             |                 |
| DGM-1                     | 0.992     | 0.981            | 0.992       | 0.991           |
| DGM-2                     | 0.993     | 0.985            | 0.439       | 0.439           |
| DGM-1*                    | 1.004     | 0.991            | 0.992       | 0.991           |
| DGM-2*                    | 0.443     | 0.435            | 0.439       | 0.439           |

Table D.3: Mean over simulation runs for calibration slope estimates each of the sample sizes (500, 750, and 1000; left to right). *) after local estimation of control outcome risk.