A synthetic data integration framework to leverage external summary-level information from heterogeneous populations

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Abstract
There is a growing need for flexible general frameworks that integrate individual-level data with external summary information for improved statistical inference. External information relevant for a risk prediction model may come in multiple forms, through regression coefficient estimates or predicted values of the outcome variable. Different external models may use different sets of predictors and the algorithm they used to predict the outcome $Y$ given these predictors may or may not be known. The underlying populations corresponding to each external model may be different from each other and from the internal study population. Motivated by a prostate cancer risk prediction problem where novel biomarkers are measured only in the internal study, this paper proposes an imputation-based methodology, where the goal is to fit a target regression model with all available predictors in the internal study while utilizing summary information from external models that may have used only a subset of the predictors. The method allows for heterogeneity of covariate effects across the external populations. The proposed approach generates synthetic outcome data in each external population, uses stacked multiple imputation to create a long dataset with complete covariate information. The final analysis of the stacked imputed data is conducted by weighted regression. This flexible and unified approach can improve statistical efficiency of the estimated coefficients in the internal study, improve predictions by utilizing even partial information available from models that use a subset of the full set of covariates used in the internal study, and provide statistical inference for the external population with potentially different covariate effects from the internal population.

Keywords
data integration, prediction models, stacked multiple imputation, synthetic data
1 | INTRODUCTION

Increasingly, researchers are considering incorporating external information from large-scale studies to improve statistical inference rather than using the limited-sized individual-level data that are available to each investigator. It is often easier to have access to the summary information rather than the individual-level data due to restrictions on data privacy and sharing. Therefore, more and more emphasis has been devoted to developing general frameworks that integrate the individual-level data and the summary-level external information in a principled manner. Recent studies on this topic include incorporating external auxiliary information from large data, such as census or population-based biobank data, to improve the statistical inference of the internal study, assuming the model that relates the predictors is fully or partially shared between data sources, also known as transportability (Bareinboim & Pearl, 2013). Several methods to incorporate summary-level information from a single external data source using frequentist methods have been proposed (Chatterjee et al., 2016; Estes et al., 2017; Gu et al., 2019; Han & Lawless, 2019; Qin, 2000). Bayesian methods have also been suggested for this problem (Boonstra & Barbaro, 2020; Cheng et al., 2018, 2019; Antonelli et al., 2017). They are conceptually appealing as the information from the external study can be regarded as providing an informative prior distribution for the analysis of the individual level data. Bayesian approaches are not that simple to develop, as the parameters provided by the external study are not the parameters of interest, they can also be computationally expensive. Several studies have expanded the initial problem of incorporating a single external data source to multiple external data sources. Kundu et al. (2019) and Zhang et al. (2020) built upon the work of Chatterjee et al. (2016) to meta-analysis settings, while Gu et al. (2021) extended the work of Estes et al. (2017) by adaptively weighting multiple empirical Bayes estimators.

One challenge is accommodating the heterogeneity among different data sources, ignoring which would lead to potential estimation bias and misleading inference during data integration. Efforts have been made to address this issue. The framework proposed by Gu et al. (2021) assigns larger weights to the more compatible external data sources to incorporate valid supporting information into the internal study. Chen et al. (2021) used a penalty function to identify the difference of aggregate information among data sources. Yang and Ding (2020) employed a sensitivity parameter to quantify such systematic differences. Moreover, there could be other sources of information variation across the models. For example, different external studies may use different subsets of covariates, the underlying prediction model may be parametric or constructed by machine learning approaches, and the summary-level information may consist of estimated regression coefficients or of fitted predictions.

Although some of the existing approaches have considered the heterogeneity across data sources, the main focus has been on improving the statistical efficiency of the internal/main dataset with little attempt to make statistical inference on the external populations or allowing heterogeneous covariate effects across data sources. Wang et al. (2012) proposed a joint estimating procedure to merge longitudinal datasets while allowing different study-specific coefficients. The meta-analysis approach proposed by Kundu et al. (2019) used a generalized method of moments to estimate study-specific effects but only allows covariates that were measured in at least one of the external studies.

In this study, we consider the situation where moderately sized individual data are available from the internal study, and there are K populations (K ≥ 1), each of which provides some information about the relationship between the same outcome and a slightly different set of predictors. The goal is to fit a target regression model with all available predictors in the internal study while utilizing summary information from external models that may have used only a subset of the predictors. We propose a novel data integration and analysis strategy combining and extending two existing methods, the synthetic data method (Gu et al., 2019) and the stacked imputation method (Beesley & Taylor, 2021b). Our innovation includes extending Gu et al. (2019) to convert multiple external models into synthetic data, and proposing a stacked imputation strategy that includes Beesley and Taylor (2021b) as a special case, further allowing for heterogeneous covariate effects across populations. This flexible and unified data integration approach attains the following four objectives: (i) incorporating supporting information from a broad class of externally fitted predictive models or established risk calculators based on parametric regression or machine learning methods, as long as the external model can generate predicted outcomes given covariates; (ii) improving statistical efficiency of the estimated coefficients in the internal study; (iii) improving predictions by utilizing even partial information available from prediction models that uses a subset of the full set of covariates used in the internal study; (iv) making statistical inference for the external population with potentially different covariate effects from the internal population; and (v) developing open-source software through an R package for easy implementation.
The rest of the paper is organized as follows. In Section 2, we introduce the motivating example, where two new biomarkers that are measured in the internal study may be able to improve the risk prediction of high-grade prostate cancer. In Section 3, we introduce the proposed methodology and develop an R package to implement it. In Section 4, we apply the new method to the motivating example, where we build an expanded risk prediction model borrowing information from two external models. In Section 5, we evaluate the performance of the new method in a simulation study. Concluding remarks are presented in Section 6.

2 HIGH-GRADE PROSTATE CANCER RISK PREDICTION

Gleason grade is a score that is used to measure the severity of the prostate cancer at the time of diagnosis, where higher level represents worse prognosis. Several well-established risk calculators are available to predict the risk of high-grade prostate cancer (Gleason score over 6) in men undergoing a biopsy. For example, the Prostate Cancer Prevention Trial risk calculator (PCPThg) established from a United States population of size $N_{\text{PCPThg}} = 5,519$ (Thompson et al., 2006) and the European Randomized Study of Screening for Prostate Cancer risk calculator 3 (ERSPC) established from a European population of size $N_{\text{ERSPC}} = 3,624$ (Roobol et al., 2012) each used slightly different predictors to predict the same outcome through logistic regression models.

Specifically, PCPThg and ERSPC both used prostate-specific antigen level (PSA) and digital rectal examination findings (DRE) as predictors, and PCPThg also used age, race (African-American or not) and prior biopsy results, while ERSPC additionally used transrectal ultrasound prostate volume (TRUS-PV) with fitted models given by:

- PCPThg: $\logit(p_i) = -3.69 + 0.89\log_2(\text{PSA}_i) + \text{DRE}_i + 0.03\text{Age}_i + 0.96\text{Race}_i - 0.36\text{Biopsy}_i$;
- ERSPC: $\logit(p_i) = -3.16 + 1.18\log_2(\text{PSA}_i) + 1.81\text{DRE}_i - 1.51\log_2(\text{TRUS-PV})$,

where $p_i$ is the probability of observing high-grade prostate cancer for subject $i$. Both of these risk calculators were established from large datasets (18,882 men in PCPThg and 3,624 men in ERSPC) and have been evaluated in independent validation datasets.

In addition, new molecular biomarkers have been identified to be predictive of prostate cancer, two examples of which are prostate cancer antigen 3 (PCA3) and TMPRSS2:ERG (T2:ERG) gene fusions (Tomlins et al., 2015; Truong et al., 2013). In an internal dataset provided by Tomlins et al. (2015), we have 678 male patients who have complete data of all the predictors used in PCPThg and ERSPC, as well as PCA3 and T2:ERG gene fusions. Therefore, it is natural to consider using both the new biomarkers and the existing prostate cancer predictors to build an expanded risk calculator aiming for improved prediction performance. Since the data containing such new biomarkers are usually available on moderately sized samples with limited predictive power if being analyzed alone, incorporating established model information, such as the information from PCPThg and ERSPC, can potentially improve the prediction accuracy and is of great interest for precision prevention for men at risk of high-grade prostate cancer. Prior studies have shown promising risk discrimination by combining PCA3 and/or T2:ERG with PCPThg (Cheng et al., 2019; Gu et al., 2021; Tomlins et al., 2015).

In addition to the internal dataset, there is an independent dataset of size 1,174, which was collected from seven community clinics throughout the United States. This dataset will be used for validation. The baseline characteristics of each dataset is listed in Web supporting information Section 1. From this, we can see considerable differences in the distributions of some of the baseline variables across the datasets. We note especially that the population for the PCPThg study has lower risk, based on lower PSA values, and the prevalence of high-grade prostate cancer is also much lower in this study. We would like to propose a more flexible framework which first expands the existing prediction model to include new predictors in the internal population, and second boosts the estimation efficiency of the coefficients by incorporating externally fitted models, accounting for population heterogeneity.

3 MODELS AND METHODS

3.1 Notation

Let $Y$ denote the outcome of interest, which can be continuous, binary or of other types. Consider $X$ a set of $P$ routinely measured predictors and $B$ a set of $Q$ new predictors, for example, newly discovered biomarkers, where $B$ is only available in the internal study (i.e., $B$ are unmeasured predictors in all of the external studies). Let $I = (I_1, \ldots, I_K)$ denote the indicator vector representing $K$ external populations and $I_0$ represent the internal study.

We discuss the problem under the assumption that $Y|X, B$ is linear in $X$ and $B$. We consider the case where a moderate dataset of size $n$ with complete predictors $Y, X$ and $B$ is available to us from the internal study. For each external population $k \in \{1, \ldots, K\}$, a well-established reduced model for the same outcome $Y$ is also available, each of which may use a slightly different set of
predictors $X_k$, a subset of $X$. For example, if linear regression is used, the prediction model may look like:

$$E(Y|X_k) = X_k\beta_k = \beta_0 + \sum_{p=1}^{P} \beta_pX_p,$$

where $P_k \leq P$ is the dimension of $X_k$. We do not have access to the underlying individual-level data that was used to fit the external model but only have the summary information. This summary information can come in different forms that we summarize into two categories:

Category 1: Directly available in the form of an externally fitted regression model, along with the estimated model parameters $\hat{\beta}_k$.

Category 2: Any parametric or non-parametric model without knowing the exact form, for example, a fitted risk calculator that provides the risk probability $P(Y = 1|X_k)$ given $X_k$.

The target model of interest is a generalized linear model (GLM) including all $X$ and $B$ that allows for population-specific intercepts and $X$ coefficients in the following form:

$$g[\mathbb{E}(Y|X,B,I)] = \gamma_0 + \sum_{k=1}^{K} \gamma_k^{I_k} + \sum_{p=1}^{P} \gamma_{X_p}X_p$$

$$+ \sum_{k=1}^{K} \sum_{p=1}^{P} \gamma_{X_p}^{I_k}X_p + \sum_{q=1}^{Q} \gamma_{B_q}B_q,$$

where $g$ is the known link function. If one does not want to incorporate information from external studies, model (1) will reduce to the direct regression using internal data only:

$$g[\mathbb{E}(Y|X,B,I_0 = 1)] = \gamma_0 + \sum_{p=1}^{P} \gamma_{X_p}X_p + \sum_{q=1}^{Q} \gamma_{B_q}B_q.$$ (2)

Our goal is to estimate $\gamma$ in model (1). We assume that model (1) is correctly specified, which indicates that each external population can potentially differ in intercept and $X$ covariate effect as long as those $X$’s were used in the external model, while for covariates that are unmeasured in the $k$th model, we assume that the covariate effects are the same as the internal study. In addition, model (1) is a saturated model allowing all intercepts and $X$ covariates to differ across populations. In practice, given prior knowledge, we could reduce the number of unknown parameters to estimate by forcing some $\gamma_0^k$ and/or $\gamma_{X_p}^k$ to be zero. For example, a special case of model (1) is a logistic regression model that only allows population-specific intercepts, representing different prevalences and the same covariate effects in each population:

$$\text{logit}[\text{Pr}(Y = 1|X,B,I)] = \gamma_0 + \sum_{k=1}^{K} \gamma_k^{I_k}$$

$$+ \sum_{p=1}^{P} \gamma_{X_p}X_p + \sum_{q=1}^{Q} \gamma_{B_q}B_q.$$ (3)

We assume that the external models $Y|X_k$’s are the best-fitted models in the class of the reduced models that was considered, but this class of reduced models may not contain the true distribution of $Y|X_k$. One such example is when the full model is the logistic model shown in Equation (3), but the true distribution for $Y|X_k$’s are not logistic models as collapsibility does not hold for the logit link. We consider the fitted logistic model as the best-fitted model in the class.

### 3.2 Proposed synthetic data integration and analysis framework (SynDI)

We propose a synthetic data integration and analysis strategy, SynDI, that allows for heterogeneous $X$ covariate effects across the external populations, by first generating synthetic data for each external population, then using a stacked multiple imputation strategy to impute the missingness, and finally analyzing the imputed data through a heterogeneity-weighted regression. Figure 1 illustrates the proposed four-step strategy, along with the required assumptions in each step:

**Step 1: Convert each external summary-level information into a set of synthetic data.** We propose to leverage the external data information through a synthetic data approach, where the idea is to generate one set of synthetic data, $(\hat{Y}_k^{\text{syn}}, X_k^{\text{syn}})$, for each of the $k$th external study such that the distribution of $Y_k^{\text{syn}}|X_k^{\text{syn}}$ mimics the estimated conditional distribution $Y|X_k; \hat{\beta}_k$ in the $k$th study. These synthetic data will be combined with the internal data to jointly estimate the target parameter $\gamma$ in model (1). Since we want to borrow information from the conditional distribution $Y|X_k$ in the external population, the marginal distribution of $X$ in the synthetic data does not need to match the external study. Therefore, we create synthetic covariates following the same distribution as the internal covariates and the synthetic outcome is generated from the external model estimates.

Specifically, to create synthetic data for external study $k$, we first generate the synthetic covariates $X_k^{\text{syn}}$ by
replicating \( r_k \) times the internal data, where \( r_k \) is some positive integer. We will discuss the choice of \( r_k \) in the following paragraph. We then simulate the synthetic outcome \( \hat{Y}_{\text{syn}} \) using \( X_{\text{syn}} \) and the external summary information \( Y|X_k; \hat{\beta}_k \). Unmeasured predictors in the external populations (all \( B \) and some \( X \)'s) will be treated as missing data. Illustrated in Figure 1, step 1, assuming there are \( K = 2 \) external studies, since the external study 1 used \( X_1 \) and \( X_2 \) to predict \( Y \), we first replicate \( X_1, X_2 \) in the internal study \( r_1 \) times to create \( X_{\text{syn}}^1 \) of size \( n \times r_1 \); we then utilize the external model 1, \( Y|X_1, X_2; \hat{\beta}_1 \), to generate \( Y_{\text{syn}}^1 \); and lastly, the unmeasured predictors \( X_3 \) and \( B \) will remain missing. Similarly for the external study 2, we replicate the observed \( X_1, X_3 \) as \( X_{\text{syn}}^2 \), and create \( Y_{\text{syn}}^2 \). After combining the synthetic data with the target data, this combined dataset is of size \( N \times (P + Q + 1) \), where \( N = n \times (1 + r_1 + r_2 + \cdots + r_K) \).

Step 1 converts the external models into synthetic individual-level data, allowing for analyzing the observed internal data together with the synthetic external data. Similar ideas of creating synthetic data have been considered in survey methodologies (Reiter & Kinney, 2012), causal inference (Tan et al., 2021) and high-dimensional transfer learning (Gu et al., 2023). We follow the same procedure of creating synthetic data as introduced in Gu et al. (2019), and extend them to accommodate the case of multiple external models.

Gu et al. (2019) provided theoretical justification in special cases to show that the synthetic data method is equivalent to a constrained semi-parametric maximum likelihood approach (Chatterjee et al., 2016), and it is assumed that the external models were the best-fitted models in the class, but the class may not contain the true distribution (Assumption 1). They showed in finite sample size, the larger the number of replicates, \( r_k \), in each synthetic dataset, the more precision gain in the estimated coefficient of \( X \); when \( r_k \) goes to infinity, the precision gain by incorporating the \( k \)th external model will converge to a constant, under the assumption that the reduced external model \( Y|X_k \) is compatible with the target model \( Y|X, B \). Since this compatibility assumption is unlikely to be completely satisfied in practice, a pragmatic suggestion is to set the synthetic data size, that is, \( n \times r_k \), similar to the \( k \)th external study’s actual study size, if that is known, to limit the potential estimation bias of \( X_k \). By doing so, we also ensure that the amount of “information” about the \( Y|X_k \) model in the synthetic data is similar to the amount of “information” about the \( Y|X_k \) model in the external data. In essence this choice of \( r_k \) is performing a bias-variance trade-off. We will assess the performance of SynDI by varying \( r_k \) in the simulation studies in Section 5.

**Step 2:** For the combined dataset created in **Step 1**, multiply impute the missing covariates without using the outcome \( Y \) to create \( M \) imputed datasets.

To handle the missing covariates in the combined dataset created in Step 1, we propose to multiply impute the missingness through traditional multiple imputation by chained equation (MICE) while not involving the use of the outcome \( Y \) when creating the imputed covariates. The \( M \) imputed datasets will then be stacked together, constituting a stacked long dataset of size \( MN \times (P + Q + 1) \).
The idea of stacked imputation was proposed in Beesley and Taylor (2021b) to flexibly employ multiple imputation when the outcome is hard to adjust for in the imputation model, such as in the situation where the outcome is a censored survival time. The idea is to compute the imputingness using covariates only and analyze a weighted regression using weights proportional to probabilities derived from the outcome model, where in the following theoretical justification we briefly explain why we can achieve the same result as including the outcome in the imputation. Specifically, to fit a regression model $Y \mid X, B$ with missingness in $X = (X_{\text{mis}}, X_{\text{obs}})$ and $B$, the authors decomposed the MICE imputation model distribution into two terms, $f(Y|X_{\text{mis}}, B) = \alpha f(Y|X_{\text{mis}}, B_{\text{obs}}) f(Y|X_{\text{mis}}, X_{\text{obs}}, B) = f(Y|X_{\text{mis}}, B_{\text{obs}}) f(Y|X, B)$. They proposed first to use term 1 ignoring $Y$ to perform multiple imputation for the missingness, then to stack the imputed datasets, and finally to use term 2, which is proportional to the model of interest, to calculate a set of weights for a final weighted regression model. The weights are estimated through $f(Y|X, B; \hat{\gamma}_k)$, where $\hat{\gamma}_k$ is the direct regression estimates of model (2).

We apply this idea of stacked imputation in Step 2 and extend the weight calculation to allow for heterogeneous $X$ covariate effects in Step 3. Since our target model is $Y \mid X, B, I$, our imputation model becomes $f(Y|X_{\text{mis}}, B|Y_{\text{obs}}, I) \propto f(Y|X_{\text{mis}}, B|X_{\text{obs}}, I) f(Y|X, B, I)$. To implement multiple imputation in the blockwise missing structure, where some covariates are completely unobserved in one population, we assume that term 1 is the same across populations, that is, $f(Y|X_{\text{mis}}, B|X_{\text{obs}}, I) = f(Y|X_{\text{mis}}, B|X_{\text{obs}}, I)$ (Assumption 2). Detailed explanation of Assumption 2 can be found in the Web supporting information Section 2 and will be discussed later.

**Step 3: Calculate population-specific weights for each subject in the stacked long dataset.** The weights in term 2 above are proportional to the target model distribution $f(Y|X, B, I; \gamma)$, where initial estimates of $\gamma$ are needed to calculate the population-specific weights. Recall the internal estimates is $\hat{\gamma}_I$, and denote the external population estimates as $\hat{\gamma}_k$. In this step, we extend the original weights proposed in Beesley and Taylor (2021b) to population-specific weights proportional to $f(Y|X, B, I)$ for the internal population $I_0$ and each external population $I_k$, where Beesley and Taylor (2021b) becomes a special homogeneous-population case of ours when $I_0 = I_1 = \cdots = I_k$.

Specifically, for the internal population, we directly compute weights proportional to $f(Y|X, B; \hat{\gamma}_I)$. For the $k$th external population, $\hat{\gamma}_k$ from model $Y \mid X, B, I_k$; $\hat{\gamma}_I$ is not directly available since we only have the summary information on the reduced model $Y \mid X_k; \hat{\beta}_k$. Therefore, we treat the unmeasured covariates, $X_{(k)}$ and $B$, as the omitted covariates, assuming they have the same effects as the internal population. Neuhaus and Jewell (1993) argued that $\hat{\beta}_k$ would be biased due to omitting the covariates, and derived the algebraic relationship between $\hat{\beta}_k$ and the true effect of $X_k$. Following Neuhaus and Jewell (1993), we use the internal data and $\hat{\beta}_0$ to estimate the true effect of $X_k$, and thus compute $\hat{\gamma}_k = (\hat{\gamma}_I^X, \hat{\gamma}_X, \hat{\gamma}_{X(k)}^I, \hat{\beta}_B)^T$, where $\hat{\gamma}_I^X$ and $\hat{\gamma}_X$ are bias-corrected intercept and $X$ coefficients from $\hat{\beta}_0 = (\hat{\beta}_0^X, \hat{\beta}_X)^T$ while $\hat{\gamma}_{X(k)}^I$ and $\hat{\beta}_B$ are estimated coefficients from $\hat{\gamma}_I$. More details can be found in Web supporting information Section 3, along with two examples to derive the initial estimates for linear and logistic regression, respectively.

As described in Section 3.1, the summary information will be available in the form of either parameter estimates $\hat{\beta}_k$ (Category 1) or a risk calculator of unknown form that has the ability to estimate the probability of $Y = 1$ given $X_k$ (Category 2). In the case of Category 1, we can directly use $\hat{\beta}_k$. In the case of Category 2 where $\hat{\beta}_k$ does not exist, we follow the same procedure as in Category 1 but use an approximation $\hat{\beta}_k^{\text{syn}}$ instead. Specifically, we first create a large size of synthetic data $(Y_k^{\text{syn}}, X_k^{\text{syn}})$ as described in Step 1, and then we fit a GLM $Y_k^{\text{syn}} \mid X_k^{\text{syn}}$ with main effect using only the synthetic data, from which we obtain $\hat{\beta}_k^{\text{syn}}$. Further assessment can be found in simulation II of Section 5.

**Step 4: Estimate the target parameter $\gamma$ of model (1) through a weighted GLM using the stacked long dataset.** Given the stacked long dataset obtained in Step 2 and the weights calculated in Step 3, we can jointly fit a weighted regression of the target model (1) applied to the stacked long dataset to obtain the final point estimates of $\gamma$.

To measure the variation of $\hat{\gamma}$, we cannot use directly the variance estimator from the weighted regression nor the sandwich estimator, because they are biased as they do not account for the between-imputation variation (Beesley and Taylor, 2021b; Wood et al., 2008). Beesley and Taylor (2021a, 2021b) proposed three variance estimators. However, our numerical assessment reveals that the bias of these existing variance estimators increases with the synthetic data size, which conflicts with the fact that larger synthetic data size will provide more precise point estimates. Therefore, we propose a new bootstrap procedure by resampling the internal data and repeating Steps 1–4, which we show to have stable performance and outperform the existing variance estimators.

## 4 APPLICATION TO THE PROSTATE CANCER DATA

We apply SynDI to predict the risk of high-grade prostate cancer using an internal dataset containing patients
from three United States academic institutions (Tomlins et al., 2015) and two external risk calculators, PCPThg (Thompson et al., 2006) and ERSPC (Roobol et al., 2012) introduced in Section 2.

A total of 678 patients who had complete data were included in the internal dataset provided by Tomlins et al. (2015) (the prevalence of high-grade prostate cancer is 26.4%). In the internal individual-level data, in addition to all the predictors used in PCPThg and ERSPC, we also have data on two new biomarkers, PCA3 and T2:ERG gene fusions mentioned in Section 2. Therefore, in Table 1, we present the results of two target models using a total of eight predictors, including these two new biomarkers. One model only allows the intercept to be different across populations (“different intercept only” model corresponds to model [3]), and another flexible model allows all possible covariates that are used in the external populations to have population-specific effects (“different intercept and covariates” model that corresponds to model [1]). The detailed model forms can be found in the table legend. In Table 1, we present the point estimates (estimated standard deviation, SE) of each predictor. Using the validation dataset of $N_{\text{test}} = 1,174$, we also present the area under the curve (AUC) and the scaled Brier Score (BS) defined as $\frac{\sum_{i=1}^{N_{\text{test}}} (Y_i - \hat{Y}_i)^2}{\sum_{i=1}^{N_{\text{test}}} (Y_i - \bar{Y})^2}$, where $Y_i$ is the observed outcome for the $i^{th}$ patient in the validation data, and $\bar{Y} = \frac{1}{N_{\text{test}}} \sum_{i=1}^{N_{\text{test}}} Y_i$.

This table appears in color in the electronic version of this paper, and any mention of color refers to that version. The grey empty blocks in Table 1 imply that these predictors were not used in that specific external model, and thus in the proposed method we assume they have the same coefficient as the internal population (grey blocks with values). Results in Table 1 show that (i) for the internal population, we gain precision of the estimated coefficients by incorporating external model information (smaller SE highlighted in green), for example, in the different-intercept-only model, the bootstrap SE of log$_2$(PSA) reduces from 0.146 to 0.070, while it reduces for DRE from 0.299 to 0.139, compared to direct regression using internal data only; for the external population, when allowing population-specific effects (yellow blocks), (ii) we do not expect to see large precision gain due to variance-bias trade-off, for example, the precision gain of both log$_2$(PSA) and DRE we see in the different-intercept-only model diminishes in the different-intercept-and-covariates model, and (iii) the point estimates of the external populations are different from the internal population.

In the prediction metrics row, we show AUC (higher value represents better discrimination) and scaled BS (smaller value means improved accuracy) calculated using the validation cohort, where the red blocks imply slightly worse overall predictive performance of PCPThg population compared to direct regression, for example, 0.9% reduction of AUC. This may be because that the validation cohort has a moderately different population than the training cohort as it has different baseline distributions as noted by Tomlins et al. (2015), such as lower African-Americans proportion and higher DRE percentages, which may also explain why the fitted model for the European population has better performance on the validation data. Following the discussion about synthetic data size in Step 1, we create synthetic data for PCPThg and ERSPC, respectively, each with a similar size as its actual study size. Specifically, the synthetic data size is $678 \times 8 \approx 5,519 = N_{\text{PCPThg}}$ for PCPThg and $678 \times 5 \approx 3,624 = N_{\text{ERSPC}}$ for ERSPC. The larger synthetic sample size in PCPThg may also exacerbate the potential prediction bias in PCPThg.

## 5 SIMULATION STUDIES

While our proposed approach can handle any target model that belongs to the class of GLM, we focus on a binary outcome and logistic regression to evaluate the performance of SynDI and comparison methods. In all scenarios, the internal data are of size 200, while we vary the synthetic data size from the same size as the internal data to ten times the size for each external population. We compare SynDI with three methods, one benchmark method using the internal data only and two common approaches to analyze the combined dataset created in Step 1 of Section 3.2 where both of them include outcome $Y$ during imputation:

1. Internal-data-only (direct regression): fit the target model using the internal data only;
2. Proposed SynDI: we implement it through MICE in R software. For example, in Figure 1, Step 1, the imputation models for $X_2$, $X_3$, and $B$ are $(X_2|X_1,X_3,B)$, $(X_3|X_1,X_2,B)$, and $(B|X_1,X_2,X_3)$, respectively. Weights are calculated after imputation;
3. Fully conditionally specification (FCS): imputation through FCS by specifying an imputation model for each missing predictor conditional on all the observed covariates and the outcome $Y$, and iteratively generate imputed values (Van Buuren et al., 2006). For example, in Figure 1, Step 1, the imputation models for $X_2$, $X_3$, and $B$ are $(X_2|X_1,X_3,B,Y)$, $(X_3|X_1,X_2,B,Y)$, and $(B|X_1,X_2,X_3,Y)$, respectively;
4. Imputation by orders monotone blocks (IMB): a strategy that was designed to handle blockwise missingness (Li et al., 2014), the data structure we have in step 1. In our case, it sequentially imputes missing covariates starting with the one with the minimum missingness conditional on the observed data,
TABLE 1 Evaluated models for predicting the risk of high-grade prostate cancer.

|                   | PCPTg (Original) | PCPTg (Estimated) | ERSPC (Original) | ERSPC (Estimated) | Direct regression (REF) | Different intercept only | Different intercept and covariates ‡ |
|-------------------|------------------|-------------------|------------------|-------------------|-------------------------|-------------------------|--------------------------------------|
| Intercept         | -3.686           | -1.409 (.115)     | -3.16            | -1.391 (.111)     | -4.202 (.455)           | -4.157 (.456)           | -6.884 (.516)                      |
| log2(PSA)         | 0.894            | 0.735 (.124)      | 1.176            | 0.891 (.124)      | 0.885 (.146)            | 1.082 (.070)            | 1.082 (.070)                       |
| DRE               | 1                | 1.145 (.257)      | 1.813            | 1.306 (.269)      | 1.045 (.299)            | 1.118 (.139)            | 1.118 (.139)                       |
| Age               | 0.03             | 0.033 (.012)      |                  |                   |                         |                         |                                      |
| Biopsy            | -0.36            | -1.444 (.272)     |                  |                   |                         |                         |                                      |
| Race              | 0.96             | 0.442 (.288)      |                  |                   |                         |                         |                                      |
| log2(TRUS-PV)     |                  |                   | -1.514           | -1.697 (.225)     |                         |                         |                                      |
| log2(PCA3+1)      |                  |                   |                  |                   |                         |                         |                                      |
| log2(T2:ERG+1)    |                  |                   |                  |                   |                         |                         |                                      |
| Prediction metrics| 0.700            | 0.707             | 0.720            | 0.723             | 0.806 (REF)             | 0.804                   | 0.804                               |
| Brier score       | 1.059            | 0.987             | 0.954            | 0.994             | 0.903 (REF)             | 0.915                   | 0.977                               |

Note: Internal dataset of size n = 678; validation dataset of size Nval = 1,174; PCPTg, prostate cancer prevention trial risk calculator; ERSPC, the European Randomized Study of Screening for Prostate Cancer risk calculator; SE, the proposed bootstrap standard error from 500 replicates; grey represents certain predictor was not used in the external calculator, yellow represents population-specific effects that are different from the internal population, and red represents poor performance compared with direct regression. This table appears in color in the electronic version of this paper, and any mention of color refers to that version. Logit\((p_i) = g_0 + g_0^{PCPTg} + g_0^{ERSPC} + g_1^{PCPTg} \log_{2}(PSA) + g_1^{ERSPC} \log_{2}(PSA) + g_2^{PCPTg} \text{DRE} + g_2^{ERSPC} \text{DRE} + g_3^{PCPTg} \text{Age} + g_3^{ERSPC} \text{Age} + g_4^{PCPTg} \text{Biopsy} + g_4^{ERSPC} \text{Biopsy} + g_5^{PCPTg} \text{Race}_i + g_5^{ERSPC} \text{Race}_i \) (*). Logit\((p_i) = (\ast) + l_{PCPTg}^{I(REF)} \log_{2}(PSA) + l_{PCPTg}^{I(REF)} \text{DRE} + l_{PCPTg}^{I(REF)} \text{Age} + l_{PCPTg}^{I(REF)} \text{Biopsy} + l_{PCPTg}^{I(REF)} \text{Race}_i + l_{ERSPC}^{I(REF)} \log_{2}(PSA) + l_{ERSPC}^{I(REF)} \text{DRE} + l_{ERSPC}^{I(REF)} \text{Age} + l_{ERSPC}^{I(REF)} \text{Biopsy} + l_{ERSPC}^{I(REF)} \text{Race}_i \).
outcome, and newly imputed data. We implement IMB through MICE by specifying a different imputation model compared with FCS. For example, in Figure 1, Step 1, the imputation models for $X_2$, $X_3$, and $B$ are $(X_2 | X_1, Y)$, $(X_3 | X_1, X_2, Y)$, and $(B | X_1, X_2, X_3, Y)$, respectively.

$M = 100$ imputations are used for all multiple imputation. For FCS and IMB, we fit the same target model as SynDI but without weights, and calculate the variance via Rubin’s combining rules (Little & Rubin, 2002).

5.1 Simulation settings

We provide two representative examples in Simulations I and II to illustrate how to handle the two categories of external summary-level information, respectively (see summarized simulation settings in Figure 2). Additional simulation results to assess various settings and violations of assumptions can be found in Web supporting information Section 5.

- **Simulation I**: Idealized case where the internal data contain $Y, X_1, X_2, B_1$ (continuous), $B_2$ (binary), and two external models have been fitted to very large datasets that are sampled from the true data-generating mechanism. The external models provided parameter estimates $\beta_1$ and $\beta_2$ from logistic regression models $Y|X_1$ and $Y|X_1, X_2$, respectively. In all three populations, $X_1, X_2$, and $B_1$ follow a standard multivariate normal distribution with zero-mean, standard deviation 1, and 0.3 for all pairwise correlations, while $B_2$ follows a Bernoulli distribution $B_2|X_1, X_2, B_1 \sim$ Bern$(1 + \exp(0.1X_1 + 0.2X_2 + 0.3B_1))$. As shown in Figure 2, the three populations have similar generative outcome models with different intercepts, that is, $-1, 1, \text{and } 3$, which give prevalence of $Y = 1$ of $0.3, 0.57, \text{and } 0.81$, respectively. The target model is a logistic regression with different intercepts of the form $\text{logit}(P_r(Y = 1 | X, B, I)) = \gamma_0 + \gamma_{I1}I_1 + \gamma_{I2}I_2 + \gamma_{X1}X_1 + \gamma_{B1}B_1 + \gamma_{B2}B_2$. 

**Evaluation metrics**: Absolute bias, the estimated variance from proposed bootstrap method and other comparisons, and the empirical variance of point estimates.

- **Simulation II**: Compared to simulation I, the external model 2 in simulation II is derived by fitting a random forest model to a large dataset where the underlying generative model is a logistic regression model that contained quadratic and interaction terms. Specifically, the internal study contains complete data of $Y, X_1, X_2, X_3, X_4, B_1$ (continuous), $B_2$ (binary), and the two external models are available in different forms of summary information. External model 1 provides $\beta_1$ from a logistic regression model $Y|X_1, X_2, X_3$ and external model 2 provides the estimated probabilities of $Y = 1$ given $X_1, X_2, X_3$ and $X_4$ through a fitted random forest model. In all three populations, $X_1, X_2$, and $X_3$ follows a standard multivariate normal distribution with zero-mean, standard deviation 1. For all pairwise

![Figure 2](image-url)
correlations, while \( X_4 \) and \( B_1 \) each follows a conditional normal distribution, \( X_4|X_1, X_2, X_3 \sim N(0.2 \sum_{p=1}^{3} X_p, 1) \) and \( B_1|X \sim N(0.2 \sum_{p=1}^{3} X_p + 0.1 X_4, 1) \), and \( B_2 \) follows a Bernoulli distribution \( B_2|X, B_1 \sim Ber\{1 + \exp^{-0.2 \sum_{p=1}^{3} X_p + 0.1 (X_4 + B_1)}\} \), respectively. Similar to simulation I, the true generative distributions of \( Y \) in the internal and external population 1 shared the same main covariate effect but have different intercepts (–1 and 2, which corresponds to prevalence 0.3 and 0.65, respectively), while external model 2 additionally contains a quadratic term and an interaction (with intercept 3 corresponding to prevalence 0.73). The target model is a logistic regression with the form \( \hat{\Pr}(Y=1|X, B, I) = \gamma_0 + \gamma_0^I I_1 + \gamma_0^I I_2 + \sum_{p=1}^{4} \gamma_p X_p + \sum_{q=1}^{2} \gamma_q B_q \). As described in Step 3 of Section 3.2, \( \hat{\beta}_1 \) can be directly used to calculate weights for \( I_1 \), while we need to estimate \( \hat{\beta}_2^{\text{syn}} \) to calculate weights for \( I_2 \). To obtain \( \hat{\beta}_2^{\text{syn}} \), we first generate a large synthetic dataset \( \{Y_2^{\text{syn}}, X_2^{\text{syn}}\} \) by replicating the observed \( \{X_1, X_2, X_3, X_4\} \) and generating \( Y_2^{\text{syn}} \) values through the available random forest model, and then fit a main effect logistic model \( Y_2^{\text{syn}}|X_2^{\text{syn}} \) using only the synthetic data and ignoring the missing \( B_1 \) and \( B_2 \).

**Evaluation metrics:** Three prediction metrics over a validation data of size \( N_{\text{test}} = 2,000 \): sum of squared error (SSE) = \( \frac{1}{N_{\text{test}}} \sum_{i=1}^{N_{\text{test}}} (\hat{Y}_i - Y_0)^2 \), where \( \hat{Y}_i \) and \( Y_0 \) denote the estimated and true probability of \( Y_i = 1 \) given \( X_i \) and \( B_i \), respectively; AUC and BS.

### 5.2 Simulation Results

Figure 3 shows the average results of estimating \( \gamma \) from the target model across 500 simulated datasets for simulation I, including point estimates \( \hat{\gamma} \) in Figure 3A, variance estimators versus the empirical variance of \( \hat{\gamma} \) in Figure 3B, and the comparison of different variance estimators of \( \gamma \) in Figure 3C. This figure appears in color in the electronic version of this paper, and any mention of color refers to that version. Figure 3A shows that FCS (dark blue curve with crosses) and IMB (light blue curve with triangles) have similarly biased estimates, indicating these traditional imputation strategies involving the outcome variable cannot distinguish heterogeneous population effects, while SynDI (red curve with dots) always shows close results to the simulation truth (grey dashed curve) for all covariates, especially estimating \( X_2 \) and intercept of external population 2 when other methods show severe bias. Compared to the benchmark method (internal-data-only estimates in black solid curve), SynDI provides more accurate point estimates and additional estimation for the external populations.

In Figure 3B, each color denotes one method with a pair of curves, one solid curve with points of a shape representing the variance estimator and another dashed or dotted curve representing the Monte Carlo empirical variance of the point estimates. If the variance is correctly estimated, the solid curve should be approximately equal to the corresponding dashed or dotted one, which is true for all methods. All methods show precision gain in estimated \( X \) coefficients compared to the internal-data-only (the longer the distance to the internal-data-only curve, the larger the precision gain) while no precision gain in \( B \) covariates and the intercept due to no external added information and allowing population-specific effects, respectively. SynDI has over 50% efficiency gain in estimated \( X \) coefficients compared to the internal data. We see that FCS and IMB have larger precision gain in both estimated \( X \) coefficients than the proposed curve, which may be explained by bias-variance trade-off as they also have larger bias in the corresponding point estimates in Figure 3A. We will discuss its statistical rationale in Section 6.

Figure 3C shows the result of the proposed variance estimator and two comparisons, the Rubin’s rule variance estimator (StackImpute–Rubin) and the Louis information estimator (StackImpute–Louis), the variance estimators proposed by Beesley and Taylor (2021b). Gu et al. (2019) has shown that when the synthetic data size goes to infinity, the precision gain we achieve in \( X \) covariates will converge, which is shown as the gradually stable trend of the grey curve (Monte Carlo empirical variance of the point estimates, also serves as the empirical truth here). When the synthetic data size increases, the StackImpute–Louis estimator continuously underestimate the empirical truth of the variance estimates for all coefficients, and the StackImpute–Rubin estimator has similar pattern in estimating the variance of coefficients for \( X, B \) and the intercept of external study 1. On the contrary, the proposed variance estimator is empirically accurate for the \( X \) coefficients and slightly overestimated the variance for the intercepts and \( B \) coefficients. In particular, compared with other methods, the empirical bias of variance in SynDI can be up to ten times smaller than comparisons (e.g., 0.002 versus 0.02 in absolute bias), and the difference in bias could be even bigger when the synthetic data size is larger. Moreover, the proposed variance estimator is robust with increasing synthetic sample size whereas it increases for the other variance estimators. Note that the internal-data-only results (black solid curve) do not exist in external intercepts as they were not available in the internal data, whereas the bias of the internal data estimates is due to the small-sample bias compared with the simulation truth.

Figure 4 shows the result of Simulation II across increasing synthetic data size on a validation dataset, with three prediction metrics in the rows and three populations in the columns. In general, the results in Figure 4 are in
FIGURE 3  Visualization of simulation I results over increasing synthetic data size (A) point estimates of $\gamma$ (B) variance estimators vs. the empirical variance of $\hat{\gamma}$ (C) comparison of the proposed and the existing variance estimators of $\hat{\gamma}$. This figure appears in color in the electronic version of this paper, and any mention of color refers to that version.
FIGURE 4  Visualization of prediction metrics over increasing synthetic data size for simulation II. Larger area under the curve (AUC), smaller sum of squared error (SSE), and smaller Brier Score (BS) represent better prediction accuracy. This figure appears in color in the electronic version of this paper, and any mention of color refers to that version.

line with Figure 3A, implying that SynDI outperforms other methods when the external study is different from the internal study. Specifically, the first column indicates that all methods incorporating external information have consistently better prediction ability (larger AUC, smaller SSE, and smaller BS) than the internal-data-only method (the dashed grey curve). For the internal study, FCS/IMB performs similarly to SynDI as expected. Compared to others, SynDI performs similarly for external study 1 while it has clear superiority for external study 2. This is because the comparisons are unable to detect the heterogeneity in external studies, indicating that SynDI outperforms others when the true parameter values are different from the internal study values (SynDI has up to 41% more improvement in SSE and 19% more improvement in BS compared with FCS and IMB). SynDI shows a modest improvement in performance as the size of the synthetic data increases, for example, for $I_2$, SSE decreases 12.9% from 9.3 to 8.1 in SynDI, when the synthetic data size increases from 1 to 10.

6  |  DISCUSSION

6.1  |  Flexibility in external models and populations

The proposed approach adds to the existing research on integrating external summary information into the internal study. It can develop improved models and provide statistical inference not only for the internal population but also for the external populations. In the target model, the parameters measured in the external reduced models can differ from those of the internal population. This new strategy has the appealing feature of utilizing external information that comes in the form of a “black box” algorithm, that is, an algorithm that provides a predicted probability, but the underlying model is not necessarily simple or transparent or even known. The key aspect is that the external information allows the creation of synthetic data. In the subsequent paragraphs, we further summarize some key points and concluding remarks.

6.2  |  Using partial information through data integration

The proposed method can integrate summary information from multiple external models that each uses different covariates $X_k \in X$ into the current study. The simulation and real-data analysis showed expected results that we can only gain precision on estimated coefficient of $X$ but not the $B$ coefficients that are only available internally, even when $X$ and $B$ are correlated. This is consistent with the theoretical results in Dai et al. (2012) that the maximum likelihood estimation (MLE) estimator $\hat{\beta}$ and $\hat{\gamma}_B$ are always asymptotically independent under regularity conditions, where $\hat{\beta}$ is the estimates of intercept and $X$ coefficients in model $Y \mid X; \beta$ and $\hat{\gamma}_B$ is the estimated coefficient of $B$ from model $Y \mid X, B; \gamma$, respectively.
6.3 | Principled inference post-imputation

Although we discuss the framework under GLM, SynDI borrows strengths from the stacked multiple imputation (StackImpute) proposed by Beesley and Taylor (2021b), which can avoid incompatibility between the imputation model and the analysis model, and can be easily extended to accommodate complicated outcomes such as the time-to-event outcome in survival models. In SynDI, we introduce a bootstrap-typed variance estimation and compare it with the analytical variance estimators proposed in Beesley and Taylor (2021a, 2021b). In general, the bootstrap variance can provide more valid variance estimation but may be more computationally intense than others, while analytical estimates are fast to compute but may be biased. Based on simulation results, when the predictors have small covariate effects (simulation in Section 5.2 of Web supporting information), the bias of the analytical variance estimates is small.

6.4 | Improve not just current study but external model predictions

To our knowledge, few existing approaches can allow different population effects through regression analysis in data fusion, let alone improving external model predictions. Beyond regression analysis, several approaches were proposed in the causal inference and survival analysis field, aiming for a similar goal to incorporate supporting information from validation dataset into the main dataset and allowing heterogeneous treatment effects among different data sources (e.g., Chen et al., 2021; Antonelli et al., 2017; Yang & Ding, 2020). SynDI also allows readers to decide which covariate effects to differ across populations. Such decisions, allowing only intercept to differ or allowing all possible covariate effects to differ, depend on readers' prior knowledge about cross-population effects and research emphasis on variance-bias trade-off (i.e., more flexible model will lead to potentially less bias and larger variance estimation).

6.5 | Allow for violation of transportability assumption

The transportability assumption is common in data integration and causal inference when certain predictors are not mutually observed across populations (Rassler, 2004). Compared with more strict transportability assumed in literature, for example, transportability of the joint distri-

6.6 | Computational time

We list the running time for computing point and variance estimates in Table S1, where SynDI is more computationally expensive than other approaches due to the bootstrap procedure. In addition, Figure S1 shows that the running time of the point estimates is ignorable while the running time for the variance estimates increases with increasing synthetic data size. This is expected as we obtain the variance estimates through the bootstrap procedure, where the computing time of Step 2 (stacked multiple imputation) increases as the sample size increases.

6.7 | Limitations and future directions

SynDI assumes that the covariates that were not used in the external studies have the same effect as the internal study. Therefore, caution must be exercised when interpreting external populations’ results as the true underlying relationship is hard to verify without additional data from external populations. If possible, it is recommended to cross-validate the results using additional data sources from external populations. An interesting extension of SynDI is to accommodate the situation, where selection bias exists and selection probability or survey weights are available for each observation in the internal population. In theory, SynDI can be adapted to accommodate this by replacing the synthetic \( Y \) values with the inverse probability-weighted or survey weights-weighted synthetic \( Y \) values in Step 1 of the proposed strategy. Alternatively, instead of copying the whole internal \( X \)'s multiple times to create the same \( X \) distribution as the internal population, one can consider proportionally creating synthetic \( X \) through the given weights to recover the representative distribution in the external populations. Further investigation is needed to evaluate this.
Furthermore, if the exposure indicator is available as a covariate in all populations, one can also use the regression estimates from SynDi to calculate the estimated average causal effect by averaging over the joint distribution of $X$ and $B$.

In addition, the setting considered in this paper is different from the one in which the goal is causal inference about the effect of $X$ on $Y$ (e.g., Antonelli et al., 2017; McCandless et al., 2012) and the external study included confounders, $B$, but the internal study only had individual-level data on $Y$ and $X$. While this is an interesting problem, we do not see a way to extend SynDi to this different scenario. SynDi is not applicable in the revised setting where the external study contains unmeasured covariates in the internal study, because in SynDi, we first replicate the internal study contains unmeasured covariates in the internal study, because in SynDi, we first replicate the internal studies and then generate $\tilde{Y}_{\text{syn}}$ given $X_{\text{syn}}$. Following the same scenario, we would need $X_{\text{syn}}$ and $B_{\text{syn}}$ to generate $\tilde{Y}_{\text{syn}}$ for the external study. However, this is impossible without any individual-level information on $B$ covariates.

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**DATA AVAILABILITY STATEMENT**

Data from the illustrative example in this paper are not shared due to third-party data sharing restrictions and to protect patient privacy.

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**REFERENCES**

Antonelli, J., Zigler, C. & Dominici, F. (2017) Guided Bayesian imputation to adjust for confounding when combining heterogeneous data sources in comparative effectiveness research. *Biostatistics*, 18, 553–568.

Bareinboim, E. & Pearl, J. (2013) A general algorithm for deciding transportability of experimental results. *Journal of Causal Inference*, 1, 107–134.

Beesley, L.J. & Taylor, J. M.G. (2021a) Accounting for not-at-random missingness through imputation stacking. *Statistics in Medicine*, 40(27), 6118–6132.

Beesley, L.J. & Taylor, J. M.G. (2021b) A stacked approach for chained equations multiple imputation incorporating the substantive model. *Biometrics*, 77(4), 1342–1354.

Boonstra, P.S. & Barbaro, R.P. (2020) Incorporating historical models with adaptive Bayesian updates. *Biostat.*, 21(2), e47–e64.

Chatterjee, N., Chen, Y.H., Maas, P. & Carroll, R.J. (2016) Constrained maximum likelihood estimation for model calibration using summary-level information from external big data sources. *Journal of the American Statistical Association*, 111, 107–117.

Chen, Z., Ning, J., Shen, Y. & Qin, J. (2021) Combining primary cohort data with external aggregate information without assuming comparability. *Biometrics*, 77(3), 1024–1036.

Cheng, W., Taylor, J. M.G., Tomlins, T. & Mukherjee, B. (2019) Informing a risk prediction model for binary outcomes with external coefficient information. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, 68, 121–139.

Cheng, W., Taylor, J. M.G., Vokonas, P.S., Park, S.K. & Mukherjee, B. (2018) Improving estimation and prediction in linear regression incorporating external information from an established reduced model. *Statistics in Medicine*, 37, 1515–1530.

Dai, J.Y., Kooperberg, C., Leblanc, M. & Prentice, R.L. (2012) Two-stage testing procedures with independent filtering for genome-wide gene-environment interaction. *Biometrika*, 99, 929–944.

Estes, J.P., Mukherjee, B. & Taylor, J.M.G. (2017) Empirical Bayes estimation and prediction using summary-level information from external big data sources adjusting for violations of transportability. *Statistics in Biosciences*, 10, 568–586.

Gu, T., Lee, P.H. & Duan, R. (2023) COMMUTE: communication-efficient transfer learning for multi-site risk prediction. *Journal of Biomedical Informatics*, 137, 104243.

Gu, T., Taylor, J.M.G. & Mukherjee, B. (2019) Synthetic data method to incorporate external information into a current study. *Canadian Journal of Statistics*, 47, 580–603.

Gu, T., Taylor, J.M.G., & Mukherjee, B. (2021) A meta-inference framework to integrate multiple external models into a current study. *Biostatistics*, kxw017, https://doi.org/10.1093/biostatistics/kxw017.

Han, P. & Lawless, J.F. (2019) Empirical likelihood estimation using auxiliary summary information with different covariate distribution. *Statistics Sinica*, 29, 1321–1342.

Kundu, P., Tang, R. & Chatterjee, N. (2019) Generalized meta-analysis for multiple regression models across studies with disparate covariate information. *Biometrika*, 106, 567–585.

Li, F., Baccini, M., Mealli, F., Zell, E.R., Frangakis, C.E. & Rubin, D.B. (2014) Multiple imputation by ordered monotone blocks with application to the anthrax vaccine research program. *Journal of Computational and Graphical Statistics*, 23(3), 877–892.

Little, R.J.A. & Rubin, D.B. (2002) *Statistical analysis with missing data*, 2nd edition, Hoboken, NJ: John Wiley and Sons, Inc.

McCandless, L.C., Richardson, S. & Best, N. (2012) Adjustment for missing confounders using external validation data and propensity scores. *Journal of the American Statistical Association*, 107(497), 40–51.

Neuhaus, J. & Jewell, N. (1993) A geometric approach to assess bias due to omitted covariates in generalized linear models. *Biometrika*, 80, 807–815.

Qin, J. (2000) Combining parametric and empirical likelihoods. *Biometrika*, 87, 484–90.

Rassler, S. (2004) Data fusion: identification problems, validity, and multiple imputation. *Statistica Sinica*, 13, 153–171.

Reiter, J.P. & Kinney, S.K. (2012) Inferentially valid, partially synthetic data: generating from posterior predictive distributions not necessary. *Journal of Official Statistics*, 28(4), 583.
