Flexible variable selection in the presence of missing data

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Abstract

In many applications, it is of interest to identify a parsimonious set of features, or panel, from multiple candidates that achieves a desired level of performance in predicting a response. This task is often complicated in practice by missing data arising from the sampling design or other random mechanisms. Most recent work on variable selection in missing data contexts relies in some part on a finite-dimensional statistical model, e.g., a generalized or penalized linear model. In cases where this model is misspecified, the selected variables may not all be truly scientifically relevant and can result in panels with suboptimal classification performance. To address this limitation, we propose a nonparametric variable selection algorithm combined with multiple imputation to develop flexible panels in the presence of missing-at-random data. We outline strategies based on the proposed algorithm that achieve control of commonly used error rates. Through simulations, we show that our proposal has good operating characteristics and results in panels with higher classification and variable selection performance compared to several existing penalized regression approaches in cases where a generalized linear model is misspecified. Finally, we use the proposed method to develop biomarker panels for separating pancreatic cysts with differing malignancy potential in a setting where complicated missingness in the biomarkers arose due to limited specimen volumes.

Keywords: variable selection; missing data; machine learning; nonparametric statistics; multiple imputation; variable importance.

1 Introduction

Missing data present a common challenge in many scientific domains. This challenge is compounded if a goal of the analysis is to identify a parsimonious set of features that are related
to the response, a notion that has been referred to as variable selection. Many existing approaches to variable selection in missing-data contexts rely in some part on a finite-dimensional statistical model, including generalized linear models (see, e.g., Little and Schluchter, 1985; Long and Johnson, 2015; Liu et al., 2019). While variable selection based on generalized linear models has been shown to perform well in many cases, recovering the true set of important variables and selecting few unimportant variables, model misspecification or correlated features may impact the performance of these methods (Bang and Robins, 2005). This motivates the consideration of approaches to variable selection with missing data that are more robust to model misspecification. These approaches should incorporate flexible algorithms, ensuring that complex relationships between the features and the outcome can be captured reliably.

Traditional approaches to variable selection with missing data can be broadly categorized into two groups. In the first, variable selection methods valid with fully-observed data are adapted to the missing-data paradigm using either likelihood-based methods (see, e.g., Little and Schluchter, 1985) or inverse probability weighting methods (see, e.g., Tsiatis, 2007; Bang and Robins, 2005; Johnson et al., 2008; Wolfson, 2011). These approaches, while useful in many contexts, often are tailored to a specific data-generating distribution or missing data process or can only be used with estimating functions for regression parameters. Additionally, inverse probability weighting is challenging in cases with non-monotone missing data (see, e.g., Sun and Tchetgen Tchetgen, 2018), limiting its more widespread adoption. The second group of approaches is based on multiple imputation (MI; Rubin, 1987), and is widely used (see, e.g., Long and Johnson, 2015; Liu et al., 2019). Among the advantages of MI over other approaches are that imputation is easily done with existing software and the imputation process is disentangled from the variable selection procedure. The imputation process must be specified with care, because methods that rely too heavily on modelling assumptions may still be subject to bias in cases with misspecification. Multiple imputation by chained equations (see, e.g., van Buuren, 2018) allows flexible imputation models to be used in an effort to reduce the risk of misspecification. Once an imputation procedure has been specified, variable selection methods developed for fully-observed data can be used on the imputed datasets.
Methods for variable selection valid with fully-observed data include the lasso (Tibshirani, 1996) and smoothly clipped absolute deviation (Fan and Li, 2001) and extensions thereof (see, e.g., Meinshausen and Bühlmann, 2010). The knockoff procedure (Barber and Candès, 2015) has seen recent focus, including towards making the procedure more robust to model misspecification (see, e.g., Candès et al., 2018), but often some level of assumptions are necessary for valid error control or inference (see, e.g., Barber et al., 2020). Other methods have been proposed that generate pseudo-variables for variable selection (see, e.g., Wu et al., 2007; Boos et al., 2009), similar to knockoffs. Stability selection (Meinshausen and Bühlmann, 2010; Shah and Samworth, 2013) has also been shown to provide error control for lasso-based procedures. However, as noted above, in some contexts model misspecification may result in poor performance of these procedures (see, e.g., Leng et al., 2006), motivating the consideration of alternatives that are not based upon generalized linear models. Additionally, if multiple imputation is used in settings with missing data, the results from these variable selection methods must be combined after being applied to each imputed dataset separately (Peterson, 2021). Often, variables that are selected in some proportion of the imputed datasets are designated in the final set (see, e.g. Heymans et al., 2007; Long and Johnson, 2015).

In this article, we propose an approach to more flexible variable selection in contexts with missing data. Our proposed approach to variable selection is based upon an algorithm-agnostic definition of intrinsic variable importance (Williamson et al., 2021). Intrinsic importance quantifies the population-level prediction potential of features. Importantly, though recent theoretical developments have led to a procedure for doing inference on intrinsic importance (Williamson and Feng, 2020; Williamson et al., 2021), making inference on this importance in general missing-data cases and using the importance as part of a variable selection procedure have not been studied. To allow for flexible modeling of the missing data process, we propose that missing data be imputed using multiple imputation by chained equations. Our proposed intrinsic approach to variable selection builds on the Shapley population variable importance measure (Williamson and Feng, 2020) and formally incorporates variability in the imputation process into the variable selection procedure using Rubin’s rules (Rubin, 1987), circumventing
the need for post-hoc combination of multiple selected variable sets. This approach results in a single set of variables explicitly selected based on estimated population importance. We provide theoretical results guaranteeing control over several commonly-used error rates, including the generalized family-wise error rate and the false discovery rate.

The remainder of this paper is organized as follows. In Section 2, we discuss the connection between intrinsic variable importance and selection and a procedure for selecting an initial set of variables in cases with fully-observed or missing data. In Section 2.4, we describe an approach to augmenting this initial set and provide theoretical results guaranteeing control over variable selection error rates. We provide numerical experiments illustrating the use of our proposed approach and detailing its operating characteristics in Section 3. Finally, we select possible important biomarkers for pancreatic cancer early detection in Section 4, and provide concluding remarks in Section 5. All technical details and results from additional simulation studies can be found in the Supplementary Material.

2 Intrinsic variable selection

2.1 Data structure and notation

Suppose that observations $Z_1, \ldots, Z_n$ are drawn independently from data-generating distribution $P_0$ known only to belong to a rich class of distributions $\mathcal{M}$. Suppose further that $Z_i := (Y_i, X_i)$, where $X_i := (X_{i1}, \ldots, X_{ip}) \in \mathcal{X} \subseteq \mathbb{R}^p$ is a vector of covariates and $Y_i \in \mathbb{R}$ is the outcome of interest. We refer to the vector $Z := (Y, X)$ as the complete-data unit or the ideal-data unit in cases with no missing data and with missing data, respectively.

Let $\Delta_i := (\Delta_{i0}, \ldots, \Delta_{ip}) \in \{0, 1\}^{p+1}$ denote a pattern of missing data for the outcome and covariates, where $\Delta_{i0} = 1$ implies that the outcome is observed and $\Delta_{ij} = 1$ implies that covariate $X_j$ is observed for $j = 1, \ldots, p$. We denote the observed data by $O_1, \ldots, O_n$, where $O_i := (\Delta_i, \Delta_{i0}Y_i, \Delta_{i1}X_{i1}, \ldots, \Delta_{ip}X_{ip})$, and denote the observed data unit by $O := (\Delta, \Delta_{0}Y, \Delta_{1}X_{1}, \ldots, \Delta_{p}X_{p})$. We denote the observed-data distribution, which includes the
missing-data mechanism, by $Q_0$.

For each index set $s \subseteq \{1, \ldots, p\}$, we consider the class of functions $\mathcal{F}_s := \{f \in \mathcal{F} : f(u) = f(v) \text{ for all } u, v \in \mathcal{X} \text{ satisfying } u_s = v_s\}$, where $\mathcal{F}$ is a large class of functions. We also consider a scientifically meaningful predictiveness measure $V(f, P)$, where larger values of $V$ are assumed to be better; examples of $V$ include $R^2$ and classification accuracy (see, e.g., Williamson et al., 2021). For each $s \subseteq \{1, \ldots, p\}$, we define the predictiveness-maximizing function $f_{0,s} \in \arg\max_{f \in \mathcal{F}_s} V(f, P_0)$.

### 2.2 Estimating intrinsic variable importance in missing-data settings

To circumvent the need to rely on potentially restrictive parametric modelling assumptions, we can consider an approach to variable selection that is based on intrinsic variable importance. We propose to perform intrinsic variable selection using the Shapley population variable importance measure (SPVIM; Williamson and Feng, 2020), which we denote by $\psi_0 := \{\psi_{0,j}\}_{j=1}^p$. The ideal-data SPVIM for feature $X_j$ is

$$\psi_{0,j} := \sum_{s \in \{1, \ldots, p\} \setminus \{j\}} \binom{p - 1}{|s| - 1}^{-1} \frac{1}{p} \{V(f_{0,s\cup j}, P_0) - V(f_{0,s}, P_0)\},$$

and quantifies the increase in population prediction potential, as measured by $V$, of including $X_j$ in each possible subset of the remaining features $\{1, \ldots, p\} \setminus \{j\}$. This definition provides a useful dichotomy: if $\psi_{0,j} > 0$, feature $X_j$ has some utility in predicting the outcome in combination with at least one subset of the remaining features; if $\psi_{0,j} = 0$, then feature $X_j$ does not improve population prediction potential if added to any subset of the remaining features. This key fact suggests that estimators of the SPVIM may be used to screen out variables with no intrinsic utility. More formally, for each $j \in \{1, \ldots, p\}$, we define the null hypothesis $H_{0,j} : \psi_{0,j} = 0$. We
can then define the following sets of variables:

\[ S_0 \equiv S_0(P_0) := \{ j \in \{1, \ldots, p \} : \psi_{0,j} > 0 \} \]  
\[ S_0^c \equiv S_0^c(P_0) := \{ j \in \{1, \ldots, p \} : \psi_{0,j} = 0 \}. \]

We will refer to \( S_0 \) as the active set and \( S_0^c \) as the null set. The goal of a variable selection procedure can be recast into identifying \( S_0 \) while ignoring \( S_0^c \); these sets and the true ideal-data SPVIM values are all defined relative to the underlying population \( P_0 \).

Prior to considering missing-data settings, we provide a brief overview of the ideal-data estimation procedure detailed more fully in Williamson and Feng (2020). There, the authors describe the efficient influence function (EIF; see, e.g., Pfanzagl, 1982) of the ideal-data SPVIM and propose an estimator \( \psi_{c,n} := \{ \psi_{c,n,j} \}_{j=1}^p \) for each SPVIM based on \( K \)-fold cross-fitting that is asymptotically efficient in complete-data settings. Since obtaining an estimator \( f_{n,s} \) of \( f_{0,s} \) for each \( s \subseteq \{1, \ldots, p \} \) is generally computationally prohibitive, this estimation procedure is based on sampling a fraction \( c \) of all possible subsets of \( \{1, \ldots, p \} \). Under regularity conditions, \( n^{1/2}(\psi_{c,n} - \psi_0) \sim N_p(0, \Sigma_0) \), where \( \Sigma_0 = E_0[\phi_0(O)\phi_0(O)^\top] \) and \( \phi_0(o) \) is the vector of EIF values for each \( j \). We provide the exact conditions (A1)–(A7) in the Supplementary Materials, but briefly describe them here. The conditions ensure that: estimation of \( f_{0,s} \) only contributes to the higher-order behavior of \( \psi_{c,n} \), and this contribution is asymptotically negligible; \( \psi_{c,n} \) is a consistent estimator of \( \psi_0 \); and \( \Sigma_0 \) is based on the EIF. These conditions hold for many common choices of the predictiveness measure \( V \) and estimators of \( f_{0,s} \) (Williamson et al., 2021).

However, in many cases, including our analysis in Section 4, we do not observe the ideal data unit \( Z \) but instead observe \( O \), where data on covariates, the outcome, or some subset of these are missing. In these cases, a strategy for properly handling these missing data is necessary to perform variable selection and establish control of error rates. Our goal remains to do variable selection based on the ideal-data intrinsic importance described above.

One strategy involves defining an observed-data intrinsic variable importance measure based on \( O \) that identifies the ideal-data intrinsic importance under assumptions on the missing-data
process, such as the positivity assumption (Bang and Robins, 2005). However, this strategy is inherently tied to the measure $V$ under consideration, and the assumptions must be carefully specified. For each combination of $V$ and missing-data process, a different EIF must be analytically derived. Additionally, in many cases with non-monotone patterns of missing data, the positivity assumption may not hold.

A second strategy involves multiple imputation. Imputation is an appealing approach to estimation of and inference on the ideal-data intrinsic variable importance both due to the availability of easy-to-use software and the ability to flexibly model both monotone and non-monotone missing data patterns. We adopt an MI approach in this article due to this potential for flexibility. Once an imputation model is determined, $M$ imputed datasets $\tilde{Z}_1, \ldots, \tilde{Z}_M$ are created. This imputation model must be sufficiently flexible to reduce the risk of model misspecification.

We will use MI to do inference on the ideal-data intrinsic importance using Rubin’s rules (Rubin, 1987). Suppose that for each of the $M$ imputed datasets, we have computed SPVIM estimator $\psi_{m,c,n}$ of $\psi_0$ and its corresponding variance estimator $\sigma_{m,n}^2$. Define $\psi_{M,c,n} := M^{-1} \sum_{m=1}^{M} \psi_{m,c,n}$, $\sigma_{M,n}^2 := M^{-1} \sum_{m=1}^{M} \sigma_{m,n}^2$, $\tau_{M,n}^2 := (M - 1)^{-1} \sum_{m=1}^{M} (\psi_{m,c,n} - \psi_{M,c,n})^2$, and $\omega_{M,n}^2 := \sigma_{M,n}^2 + (M + 1)M^{-1} \tau_{M,n}^2$. Before stating a formal result, we first introduce a regularity condition for the use of Rubin’s rules. Below, all expectations are with respect to the full data.

\( (A8) \) (consistency of imputations)

(A8a) $\lim_{M \to \infty} E(\psi_{M,c,n} | Z) = \psi_{c,n}$;

(A8b) $\lim_{M \to \infty} E(\sigma_{M,n}^2 | Z) = \sigma_n^2$;

(A8c) $\lim_{M \to \infty} E(\tau_{M,n}^2 | Z) = \lim_{M \to \infty} \text{var}(\psi_{M,c,n} | Z)$.

These conditions are commonly referred to as the essential conditions for proper MI (see, e.g., Rubin, 1996), and in turn provide conditions for the approximate asymptotic normality of appropriately centered and scaled version of $\psi_{M,c,n}$. The missing data must be missing completely at random or missing at random (Rubin, 1987). The following result describes the asymptotic distribution of the imputation-based estimator $\psi_{M,c,n}$. 

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Lemma 1. Provided that conditions (A1)–(A8) hold and the data are missing at random, then
\( n^{1/2}(\psi_{M,c,n} - \psi_0) \) is approximately asymptotically normally distributed with consistent variance estimator \( \omega_{M,n}^2 \).

We can thus use the imputation-based estimator \( \psi_{M,c,n} \) and its variance estimator \( \omega_{M,n}^2 \) to make inference on \( \psi_0 \). We adopt a two-stage strategy towards variable selection: first, select an initial set of variables using a procedure with possibly strict multiple-testing control; and second, augment this set of variables while maintaining control of generalized error rates. We describe these stages in the following sections.

2.3 Selecting an initial set of variables

Suppose that conditions (A1)–(A8) hold. Let \( \omega_{M,n,j}^2 \) denote the \( j \)th component of the diagonal of the estimated covariance matrix based on the estimated EIF and imputation variance; if the data are fully observed, then there is only a single dataset and no imputation component to the variance. Based on the estimated variance and importance, we can define test statistics \( T_{M,n,j} := \omega_{M,n,j}^{-1}(\psi_{M,c,n,j} - \psi_{0,j}) \). The test statistics \( T_{M,n} := (T_{M,n,1}, \ldots, T_{M,n,p}) \) follow a multivariate normal distribution under the joint null hypothesis, which we denote \( P_0 \).

Armed with these test statistics, we select an initial set of variables. For a given \( \alpha \in (0,1) \) and possibly random cutoff functions \( c_j(t, P_0, \alpha) \), we define adjusted p-values \( \tilde{p}_{M,n,j} := \inf \{ \alpha \in [0,1] : T_{M,n,j} > c_j(T_{M,n}, P_0, \alpha) \} \) (see, e.g., Dudoit and van der Laan, 2008), resulting in

\[
S_{M,n}(\alpha) = \{ j \in \{1, \ldots, p\} : \tilde{p}_{M,n,j} \leq \alpha \}.
\]

The procedure for determining the adjusted p-values will determine how and whether any multiple-testing control is achieved in determining \( S_{M,n}(\alpha) \). Below, we will provide an example of the adjusted p-values using a Holm procedure (Holm, 1979). We define \( R_{M,n}(\alpha) := |S_{M,n}(\alpha)| \) to be the number of rejected null hypotheses after this initial variable selection step. In settings with complete data, where multiple imputation is not necessary, we refer to these objects as \( S_n(\alpha) \) and \( R_n(\alpha) \), respectively.
An ideal selection procedure will result in $S_{M,n}(\alpha) \to_P S_0$ and $R_{M,n}(\alpha) \to_P |S_0|$ as $n \to \infty$ and $M \to \infty$ while maintaining control of the number of falsely selected variables. In other words, we want to minimize the number of type I errors $V_{M,n}(\alpha) := |S_{M,n}(\alpha) \cap S_0|$ while maximizing the number of selected truly important variables $|S_{M,n}(\alpha) \cap S_0|$. However, many procedures, including the Holm procedure, provide control over the familywise error rate, which may be too strict in some settings. In the next section, we describe a procedure for augmenting the set $S_{M,n}(\alpha)$, obtained using the estimated intrinsic importance values, to provide control over possibly less strict error rates.

### 2.4 Augmenting the initial set to ensure error rate control and persistence

Before detailing our full procedure and providing our main results, we introduce some additional notation. First, we define three commonly used error rates. For a given integer $k \geq 0$, the generalized family-wise error rate, of at least $k + 1$ type I errors, is defined as $gFWER(k) := \Pr_{P_0}(V_{M,n}(\alpha) \geq k + 1) = 1 - F_{V_{M,n}(\alpha)}(k + 1)$, where $F_{V_{M,n}(\alpha)}$ is the cdf of $V_{M,n}$ and $gFWER(0)$ is the family-wise error rate. The proportion of false positives among the rejected variables at level $q \in (0, 1)$ is defined as $PFP(q) := \Pr_{P_0}(V_{M,n}(\alpha)/R_{M,n}(\alpha) > q)$. Finally, we define the false discovery rate to be $FDR := E_{P_0}(V_{M,n}(\alpha)/R_{M,n}(\alpha))$.

Next, we define the collection of sets of functions $C_n := \bigcup_{s \subseteq \{1, \ldots, p\} : |s| = k_n} \mathcal{F}_s$ for $k_n \leq p$ and let $f_* \in \text{argmax}_{f \in C_n} V(f, P_0)$ denote the predictiveness-maximizing function over all function classes that make use of $k_n$ variables. We say that a variable selection procedure $S_n$ that selects $k_n$ variables is persistent (see, e.g., Greenshtein and Ritov, 2004) if $V(f_{n,S_n}, P_0) - V(f_*, P_0) \to_P 0$, where $f_{n,S_n}$ is an estimator of $f_{0,S_n}$, the predictiveness-maximizing function that uses the variables selected by $S_n$. In other words, a persistent procedure ensures that the true predictiveness of the empirical prediction function using the selected variables converges to the true predictiveness of the best possible prediction function making use of the same number of variables. Our definition of persistence can be seen as a nonparametric generalization of
Greenshtein and Ritov (2004).

Based on a chosen multiple-testing control procedure, under conditions (A1)–(A8) we obtain \( S_{M,n}(\alpha) \) as described in Equation (3). To provide control over the error rates defined above, we propose to augment \( S_{M,n}(\alpha) \). For an integer \( k \in \{0, \ldots, p - R_{M,n}(\alpha)\} \), we define the augmentation set

\[
A_{M,n} : (\alpha, k) \in (0, 1) \times \{0, \ldots, p - R_{M,n}(\alpha)\} \mapsto \begin{cases} \emptyset & k = 0, \\
\{s \subseteq S_{M,n}^c(\alpha) : \tilde{p}_{M,n,\ell} \leq \tilde{p}_{M,n}(k) \text{ for all } \ell \in s\} & k > 0,
\end{cases}
\]

\( (4) \)

where \( a_{(j)} \) denotes the \( j \)th order statistic of a vector \( a \). This results in an augmented set of selected variables \( S_{M,n}^+(k, \alpha) = S_{M,n}(\alpha) \cup A_{M,n}(k, \alpha) \), augmented number of selected variables \( R_{M,n}^+(k, \alpha) = |S_{M,n}^+(k, \alpha)| \), and augmented number of type I errors \( V_{M,n}^+(k, \alpha) = |S_{M,n}^+(k, \alpha) \cap S_0^c| \).

Finally, we define the following set of conditions:

(B1) \textit{(finite-sample familywise error rate control)} \( P_{P_0}(V_{M,n}(\alpha) > 0) = \alpha_n \) for all \( n \);

(B2) \textit{(asymptotic familywise error rate control)} \( \limsup_{n \to \infty} P_{P_0}(V_{M,n}(\alpha) > 0) = \alpha^* \leq \alpha \);

(B3) \textit{(perfect asymptotic power)} \( \lim_{n \to \infty} P_{P_0}(S_0 \subseteq S_{M,n}(\alpha)) = 1 \);

(B4) \textit{(limited number of initial rejections)} \( \lim_{n \to \infty} P_{P_0}(S_{M,n}(\alpha) \leq p - k) = 1 \).

\textbf{Theorem 1.} If conditions (A1)–(A8) and (B1)–(B2) hold, then for any \( k \geq 0 \) and \( q \in (0, 1) \), \( S_{M,n}^+(k, \alpha) \) provides finite-sample control of \( gFWER(k) \) and \( PFP(q) \) at level \( \alpha_n \):

\[
P_{P_0}(V_{M,n}^+(k, \alpha) > k) = \alpha_n, \quad P_{P_0}(V_{M,n}^+(k, \alpha)/R_{M,n}^+(k, \alpha) > q) = \alpha_n
\]

for all \( n \). If additionally (B3)–(B4) hold, then \( S_{M,n}^+(k, \alpha) \) provides asymptotic control of these...
quantities and the FDR, that is,

\[
\limsup_{n \to \infty} Pr_{P_0}(V_{M,n}(k, \alpha) > k) \leq \alpha, \quad \limsup_{n \to \infty} Pr_{P_0}(V_{M,n}(k, \alpha)/R_{M,n}(k, \alpha) > q) \leq \alpha, \\
\limsup_{n \to \infty} E_{P_0}(V_{M,n}(k, \alpha)/R_{M,n}(k, \alpha)) \leq q(1 - \alpha) + \alpha.
\]

In complete-data settings, these results hold without reliance on condition (A8).

This result implies that the user can specify a tolerable threshold for the tail probability of a number of false discoveries, which can result in an augmented set of variables \(S_{M,n}^+(\alpha)\) with increased power over the potentially strict initial procedure \(S_{M,n}(\alpha)\) while still providing error control. This holds in finite samples and asymptotically, so long as the initial procedure \(S_{M,n}(\alpha)\) has high asymptotic power.

Conditions (B1)–(B4) describe the initial variable selection procedure \(S_{M,n}(\alpha)\). While a number of procedures satisfy these conditions under (A1)–(A8), we consider here a Holm-based procedure for simplicity. Based on the p-values \(\{p_{M,n,j}\}_{j=1}^p\) from the individual, unadjusted null hypothesis tests, we can construct Holm-adjusted p-values

\[
\tilde{p}_{M,n,(j)} := \max_{\ell \in \{1, \ldots, j\}} \{\min\{p_{M,n,\ell}(p - \ell + 1), 1\}\}. \quad (5)
\]

For \(\alpha \in (0, 1)\), we set \(S_{M,n}(\alpha) = \{j \in \{1, \ldots, p\} : \tilde{p}_{M,n,j} < \alpha\}\), which guarantees control of the familywise error rate. Next, to control the gFWER, select \(k \in \{0, \ldots, p - R_{M,n}(\alpha)\}\); to control the PFP among the selected variables, select \(q \in (0, 1)\) and set \(k = \max\{j \in \{0, \ldots, p - R_{M,n}(\alpha)\} : j\{j + R_{M,n}(\alpha)\}^{-1} \leq q\}\). Define \(A_{M,n}(k, \alpha)\) as in Equation (4), and augment the initial set to obtain \(S_{M,n}^+(k, \alpha)\). Other procedures may satisfy (B1)–(B4) and could result in increased power (see, e.g., Dudoit and van der Laan, 2008). The general procedure based on any familywise error rate-controlling initial selection step is summarized in Algorithm 1.

The next result describes that under a subset of the conditions of the previous theorem and in complete-data settings, the algorithm described in Algorithm 1 is persistent.

**Lemma 2.** If conditions (A1), (A2), (A5) and (A6) hold for all \(s \subseteq \{1, \ldots, p\}\) and conditions
Algorithm 1  Intrinsic variable selection with error rate control

1: Obtain estimator $\hat{\psi}_{M,c,n}$ of $\psi_0$ using multiple imputation in settings with missing data, and 
   its corresponding variance estimator $\hat{\omega}_{M,n}^2$;
2: For a given $\alpha \in (0, 1)$, compute unadjusted p-values $p_{M,n,j}$ for each hypothesis test $H_{0,j}$;
3: Compute adjusted p-values $\tilde{p}_{M,n,j}$ according to the desired familywise error rate-controlling 
   procedure, e.g., Holm adjusted p-values as in Equation (5);
4: Set $S_{M,n}(\alpha) = \{j \in \{1, \ldots, p\} : \tilde{p}_{M,n,j} < \alpha\}$ as in Equation (3);
5: For a given $k \in \{0, \ldots, p - R_{M,n}(\alpha)\}$, obtain $A_{M,n}(k, \alpha)$ as in Equation (4);
6: Set $S_{M,n}^+(k, \alpha) = S_{M,n}(\alpha) \cup A_{M,n}(k, \alpha)$.

(A7) and (B3) hold, then the procedure described in Algorithm 1 is persistent:

$$ V(f_{n,S_n^+(k,\alpha)}, P_0) - V(f_*, P_0) \to_P 0. $$

This result implies that $S_{n}^+(k, \alpha)$, the result of Algorithm 1 in complete-data settings, returns 
a set of features that has predictiveness converging to the best possible predictiveness among all 
procedures that select $R_{n}^+(k, \alpha)$ variables. In missing-data settings, if condition (A8) is satisfied, 
then this result holds when averaged across the imputed datasets and as $M \to \infty$.

3  Numerical experiments

3.1 Experimental setup

We provide several experiments that are designed to describe the operating characteristics of 
our proposed intrinsic importance-based variable selection procedure, and compare these pro-
cedures with other well-established algorithms. In all cases, our simulated dataset consisted of 
independent replicates of $(X, Y)$, where $X = (X_1, \ldots, X_p)$ and $Y$ followed a Bernoulli distri-
bution with success probability $\Phi(\beta_{00} + f(\beta_0, x))$ conditional on $X = x$, where $\Phi$ denotes the 
cumulative distribution function of the standard normal distribution. Under this specification, 
$Y$ followed a probit model.

In Scenario 1, we vary $p \in \{30, 500\}$, set $f(\beta_0, x) = x\beta_0$, and specify $\beta_{00} = 0.5$ and $\beta_0 = 
(-1, 1, -0.5, 0.5, 1/3, -1/3, 0_{p-6})^\top$, where $0_k$ denotes a zero-vector of dimension $k$. We consider
$X \sim MVN(0, I_p)$, where $I_p$ is the $p \times p$ identity matrix. In this scenario, procedures that are based on a generalized linear model are correctly specified.

In Scenario 2, we set $p = 6$, add correlation between variables, and specify

$$f(\beta_0, x) = 2[\beta_{0,1} \sin \left( \frac{\pi}{4} x_1 \right) + \beta_{0,2} x_2 x_3 + \beta_{0,3} \tanh(x_3) + \beta_{0,4} \cos \left( \frac{\pi}{4} x_4 \right) + \beta_{0,5} x_5 x_1 - \beta_{0,6} \tanh(x_6)],$$

where \( \tanh \) denotes the hyperbolic tangent. In this scenario, $\beta_{00} = 0.5$, $\beta_0 = (0, 1, 0, 0, 0, 1)^T$, and $X \sim MVN(0, \Sigma)$, where $\Sigma_{i,j} = \rho_{|i-j|}$ for $i, j$ not in the active set, and $\Sigma_{i,j} = I_p + \rho_2(J_p - I_p)$ for $i, j$ in the active set, where $J_p$ is a $p \times p$ matrix of ones. We set $\rho_1 = 0.3$ and $\rho_2 = 0.95$. In this scenario, procedures that are based on a generalized linear model are misspecified.

We first generate complete $(X, Y)$ and then generate missing data using amputation (van Buuren, 2018). The outcome and certain features always have complete data, i.e., $\delta_j = 1$ for $j \in \{0, 1, 3, 5\}$. The missing data are missing at random. We specify a monotone missing pattern for $(X_2, X_4, X_6)$, where observing $X_2$ implies that both $X_4$ and $X_6$ are observed. When $p = 500$, 40 noise features can be missing; when $p = 30$, 3 noise features can be missing; the remaining noise features are fully observed. In all scenarios, we consider fully observed data and a maximum of 20% or 40% missing data within each column.

For each sample size $n \in \{200, 500, 1500, 3000\}$, we generated 1000 replicates from each combination of data-generating mechanism, number of features, and proportion of missing data. We additionally generated an independent test dataset following the same distribution but with no missing data and with sample size 10,000. We used MI with $M = 10$ and predictive mean matching to impute any missing feature information.

In cases with missing data, we considered three procedures for performing variable selection: the stability-selection based algorithms considered in Long and Johnson (2015) with 100 bootstrap replicates, which we refer to as lasso + SS (LJ) and lasso + SS (BI-BL), denoting stability selection within bootstrap imputation and bootstrap imputation with bolasso (Bach, 2008), respectively; and intrinsic selection with gFWER, PFP, and FDR control, using AUC to define intrinsic importance. In the latter case, we used a Super Learner to estimate intrin-
sic importance. In cases with complete data, we used the lasso, lasso with stability selection, lasso with knockoffs, and intrinsic selection to perform variable selection. We attempted to use error-rate control tuning parameters that would provide similar theoretical control over the various error rates across algorithms. The values of the specific algorithms used in the Super Learner, the tuning parameters used in each procedure for error rate control, and the specific R implementations of each algorithm are provided in the Supplementary Material.

After performing variable selection, we estimated the prediction performance of the selected variables by fitting a regression of the outcome on these variables. In cases with missing data, we fit this regression on each of the imputed datasets. We used a probit regression in the case of variables selected by the lasso-based methods and used the Super Learner in all other cases. We then computed the test-set AUC based on the independent sample; in missing-data settings, we averaged the performance on this test set across the prediction functions trained on each imputed dataset. We additionally computed the sensitivity and specificity of the selected set of variables. Finally, we evaluated the average test-set AUC based of the selected variables and the average sensitivity and specificity of each procedure over the 1000 samples.

3.2 Primary empirical results

In Figure 1, we display the results of the experiment conducted under Scenario 1; the features are multivariate normal and the outcome-feature relationship follows a linear model. We only show results for the case with 40% missing data; the results for 20% missing data are similar and are presented in the Supplementary Material. In this scenario, the lasso-based estimators are correctly specified. We observe that for both feature-space dimensions $p \in \{30, 500\}$, all estimators have increasing test-set AUC regardless of the proportion of missing data. In this experiment, the Long and Johnson (2015) lasso and intrinsic variable selection with gFWER control tend to have the highest test-set AUC. The PFP and FDR-controlling intrinsic selection procedures tend to have lower AUC, particularly at smaller sample sizes, reflecting the fact that these procedures provide stricter control of specificity at the cost of sensitivity in these
Figure 1: Test-set area under the receiver operating characteristic curve (AUC) (panel A) and empirical variable selection sensitivity (panel B) and specificity (panel C) vs \( n \) for each estimator and missing data proportion, in Scenario 1 (a linear model for the outcome and multivariate normal features). The dotted line in panel A shows the true (optimal) test-set AUC. The methods compared are: lasso + SS (LJ), the stability-selection within bootstrap imputation algorithm of (Long and Johnson, 2015); lasso + SS (BI-BL), the bootstrap imputation with bolasso algorithm of (Long and Johnson, 2015); SPVIM + gFWER, intrinsic selection to control the generalized familywise error rate; SPVIM + PFP, intrinsic selection to control the proportion of false positives among the rejected variables; and SPVIM + FDR, intrinsic selection to control the false discovery rate.

scenarios. A different choice of tuning parameters might lead to a more favorable tradeoff between these two error rates. In Figure 1, we observe that empirical sensitivity increases towards one for all algorithms regardless of the feature-space dimension, though the PFP- and FDR-controlling intrinsic selection approaches have low sensitivity in the \( p = 500 \) case. Worryingly, the specificity of the BI-BL lasso is near zero for all cases.

In Figure 2, we display the results of the experiment conducted under Scenario 2; the features are correlated multivariate normal and the outcome-feature relationship is nonlinear. We observe test-set AUC near the optimal value for the gFWER-controlling intrinsic selection procedure, while test-set AUC is much lower for the lasso-based procedures. We again observe lower test-set AUC for the PFP and FDR-controlling intrinsic procedures. We observe poor empirical sensitivity for the stability-selection within bootstrap imputation procedure, while we observe high sensitivity for the gFWER-controlling intrinsic procedure. Empirical specificity
Figure 2: Test-set area under the receiver operating characteristic curve (AUC) (panel A) and empirical variable selection sensitivity (panel B) and specificity (panel C) vs $n$ for each estimator, in Scenario 2 (a nonlinear model for the outcome and correlated multivariate normal features). The dotted line in panel A shows the true (optimal) test-set AUC. The methods compared are: lasso + SS (LJ), the stability-selection within bootstrap imputation algorithm of (Long and Johnson, 2015); lasso + SS (BI-BL), the bootstrap imputation with bolasso algorithm of (Long and Johnson, 2015); SPVIM + gFWER, intrinsic selection to control the generalized familywise error rate; SPVIM + PFP, intrinsic selection to control the proportion of false positives among the rejected variables; and SPVIM + FDR, intrinsic selection to control the false discovery rate.

also tends to be high for this intrinsic procedure; among lasso-based estimators, the stability-selection within bootstrap imputation procedure has the highest empirical specificity, which tends to be lower than specificity for the gFWER-controlling intrinsic procedure.

This simulation study suggests that the intrinsic variable selection procedures proposed here have good practical performance, as suggested by theory. As is the case with other procedures, we observed a tradeoff between sensitivity and specificity for our proposed procedures. In Scenario 2, where procedures based on a generalized linear model were misspecified, we observed poor variable selection and prediction performance when using lasso-based estimators, whereas our proposed methods protected against this model misspecification.
3.3 Additional empirical results

In the Supplementary Material, we present the 20% missing data case for Scenarios 1 and 2, observing similar results to those presented in Figures 1 and 2. We also consider the complete-data case, observing that our proposed intrinsic selection procedure has similar performance to the lasso with stability selection and knockoffs under Scenario 1, and improved performance under Scenario 2. We also consider six additional scenarios scrutinizing the effect of intermediate departures from the linear outcome regression and independent normal feature distribution. While a nonlinear outcome regression resulted in decreased test-set prediction performance and decreased probability of selecting some important variables for the lasso-based procedures, a nonnormal feature distribution had a minimal effect on the performance of these procedures. When the variables were equally weakly important, we observed poor performance of lasso-based estimators in cases with correlated predictors. Our intrinsic selection procedure maintained good overall performance in all scenarios, reflecting its robustness to model misspecification.

4 Developing a biomarker panel for pancreatic cancer early detection

Pancreatic ductal adenocarcinoma is the fourth-leading cause of cancer death in the United States. There is increasing focus on identifying pancreatic cancer at an early stage when treatment should be most effective. Mucinous cysts are one potential precursor lesion to pancreatic ductal adenocarcinoma and might be identified using routine imaging. However, imaging can be prohibitively expensive and current radiographic tests have limited ability to differentiate between benign and pre-malignant cystic neoplasms (Brugge et al., 2004). This has spurred development of fluid biomarkers that can be assayed using pancreatic cyst fluid, which is routinely collected during clinical care.

We consider specimens from 321 participants with confirmed surgical pathology diagnosis from the Pancreatic Cyst Biomarker Validation Study (Liu et al., 2020), designed to evaluate
multiple cystic fluid biomarkers at several research institutes across the United States. The 21 candidate biomarkers are described further in the Supplementary Material. A main objective of the study is to develop biomarkers or biomarker panels that can be used to separate pancreatic cysts with differential malignant potentials. A major complication in achieving this objective is limited available cystic fluid volume from each study participant. The study statistical team randomly assigned available specimens to validation sites, such that each biomarker was only measured in a subset of the total study participants. This results in a highly non-monotone pattern of missingness in the biomarker data. Here the missing at random assumption holds since the probability of measuring a biomarker from an individual depends on that individual’s specimen volume based on the specimen allocation scheme. Our goal here is to develop biomarker panels to separate mucinous cysts from non-mucinous cysts. In the Supplementary Material, we present an analysis focused on malignancy potential.

We use the same procedures that we evaluated in the previous section. We assessed the prediction performance of each procedure through repeating an imputation-within-cross-validation procedure 100 times. We used MI with $M = 10$ in all cases, and used an outer layer of five-fold cross-validation to assess prediction performance. We obtained a final set of biomarkers selected by each procedure using Algorithm 1 on the full imputed datasets. More details on the approaches to estimating prediction performance and obtaining the final panel are provided in the Supplementary Material.

We present the results of our analysis in Figure 3. The PFP- and FDR-controlling intrinsic selection procedures did not select any variables on average, suggesting that the tuning parameters we selected were too conservative. The gFWER-controlling intrinsic selection procedure had high predictiveness, as measured by cross-validated AUC (CV-AUC), and was the top-performing algorithm with an average estimated CV-AUC of 0.946 and 95% confidence interval of [0.89, 1]. Performance was worse for the lasso-based estimators, with an average estimated CV-AUC of 0.541 [0.385, 0.697] and 0.539 [0.383, 0.695] for the bootstrap imputation with bolasso and stability selection within bootstrap imputation lasso, respectively. In the Supplementary Material, we display the final set of biomarkers selected by each procedure. Among
Figure 3: Cross-validated area under the receiver operating characteristic curve (CV-AUC) for predicting whether a cyst is mucinous averaged over 100 replicates of the imputation-within-cross-validated procedure for each variable selection algorithm. Prediction performance for lasso-based methods is based on logistic regression on the selected variables, while performance for Super Learner-based methods is based on a Super Learner. Error bars denote 95% confidence intervals based on the average variance over the 100 replications. The methods compared are: lasso + SS (LJ), the stability-selection within bootstrap imputation algorithm of (Long and Johnson, 2015); lasso + SS (BI-BL), the bootstrap imputation with bolasso algorithm of (Long and Johnson, 2015); SPVIM + gFWER, intrinsic selection to control the generalized familywise error rate; SPVIM + PFP, intrinsic selection to control the proportion of false positives among the rejected variables; and SPVIM + FDR, intrinsic selection to control the false discovery rate.

The three procedures that selected variables, several biomarkers were selected by all procedures. These include biomarkers related to amphiregulin, glucose, fluorescent protease activity, and protein expression. Amphiregulin has been found to be elevated in adenocarcinoma cells (Tun et al., 2012).

5 Discussion

We have proposed a variable selection procedure that is robust to model misspecification and is valid in settings with missing data, providing an alternative to existing, model-based approaches. We proved that our intrinsic selection procedure is persistent in complete-data set-
tings and that error rate control can be achieved through the use of a tuning parameter, and identified conditions under which Rubin’s rules can be used with intrinsic selection to formally incorporate imputation variance in settings with missing data. We found in simulated examples that our proposal had high sensitivity and specificity and good overall prediction performance. Importantly, in settings with missing data where a simple linear outcome regression model is correctly specified, our proposals have similar operating characteristics to the lasso-based procedures proposed in Long and Johnson (2015). In these settings with complete data, our proposals have similar operating characteristics to the lasso, lasso with stability selection, and lasso with knockoffs, all of which are commonly used. In settings with a nonlinear relationship, weakly important features, and correlated features, we observed that our proposals maintained high sensitivity and specificity, while the performance of the lasso-based procedures suffered, as suggested by theory (see, e.g., Leng et al., 2006).

In settings with missing data, many variable selection procedures require post-hoc harmonization of many selected sets resulting from multiply imputed datasets. A benefit of our proposed intrinsic selection procedure is that Rubin’s rules can be used to obtain a single set of point and variance estimates accounting for the across-imputation variance, resulting in a single set of selected variables. In cases where the imputation mechanism is misspecified and incongenial with the analytic approach, it may be necessary to update the variance estimator (Robins and Wang, 2000); however, the form of this estimator is complex. This idea is being pursued in ongoing research.

Software and supplementary materials

The proposed methods are implemented in the R package flevr, freely available on GitHub. Supplementary Materials, including all technical proofs and code to reproduce all numerical experiments and data analyses, are available on GitHub at https://github.com/bdwilliamson/flevr_supplementary.
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6 Proofs of theorems

6.1 Regularity conditions

This section is a review of the formal regularity conditions required to specify the distribution of the SPVIM values (Williamson and Feng, 2020). We define the linear space \( \mathcal{R} := \{ c(P_1 - P_2) : c \in \mathbb{R}, P_1, P_2 \in \mathcal{M} \} \) of finite signed measures generated by \( \mathcal{M} \). For any \( R \in \mathcal{R} \), we consider the supremum norm \( \| R \|_\infty := \max_{z \in \mathbb{R}} |c| F_1(z) - F_2(z) | \), where \( F_1 \) and \( F_2 \) are the distribution functions corresponding to \( P_1 \) and \( P_2 \), respectively, and we have used the representation \( R = c(P_1 - P_2) \).

For distribution \( P_0, \epsilon = P_0 + \epsilon h \) with \( \epsilon \in \mathbb{R} \) and \( h \in \mathcal{R} \), we define \( f_{0,\epsilon,s} = f_{P_0,\epsilon,s} \) to be the oracle prediction function with respect to each subset \( s \in \{1, \ldots, p\} \). Let \( \hat{V}(f, P_0; h) \) denote the Gâteaux derivative of \( P \mapsto V(f, P) \) at \( P_0 \) in the direction \( h \in \mathcal{R} \). The Gâteaux derivatives for several common choices of \( V \) are provided in Williamson et al. (2021). Next, we define the random function \( g_{n,s} : z \mapsto \hat{V}(f_{n,s}, P_0; \delta z - P_0) - \hat{V}(f_{0,s}, P_0; \delta z - P_0) \), where \( \delta z \) is the degenerate distribution on \( \{z\} \). For each \( s \subseteq \{1, \ldots, p\} \), we require the following conditions to hold:

(A1) (optimality) there is some \( C > 0 \) such that for each sequence \( f_1, f_2, \ldots \in \mathcal{F}_s \) with \( \| f_j - f_{0,s} \|_{\mathcal{F}_s} \to 0 \), there is a \( J \) such that for all \( j > J \), \( |V(f_j, P_0) - V(f_{0,s}, P_0)| \leq C \| f_j - f_{0,s} \|_{\mathcal{F}_s}^2 \);

(A2) there is some \( \delta > 0 \) such that for each sequence \( \epsilon_1, \epsilon_2, \ldots \in \mathbb{R} \) and \( h, h_1, h_2, \ldots \in \mathcal{R} \) satisfying that \( \epsilon_j \to 0 \) and \( \| h_j - h \|_\infty \to 0 \), it holds that

\[
\sup_{f \in \mathcal{F}_s : \| f - f_{0,s} \|_{\mathcal{F}_s} < \delta} \left| \frac{V(f, P_0 + \epsilon_j h_j) - V(f, P_0)}{\epsilon_j} - \hat{V}(f, P_0; h_j) \right| \to 0;
\]

(A3) \( \| f_{0,\epsilon,s} - f_{0,s} \|_{\mathcal{F}_s} = o(\epsilon) \) for each \( h \in \mathcal{R} \);

(A4) \( f \mapsto \hat{V}(f, P_0; h) \) is continuous at \( f_{0,s} \) relative to \( \mathcal{F}_s \) for each \( h \in \mathcal{R} \);

(A5) \( \| f_{n,s} - f_{0,s} \|_{\mathcal{F}_s} = o_P(n^{-1/4}) \);
(A6) \( E_{P_0}[\int \{g_{n,s}(z)\}^2 dP_0(z)] = o_P(1); \)

(A7) for \( \gamma > 0 \) and sequence \( \gamma_1, \gamma_2, \ldots \in \mathbb{R}^+ \) satisfying that \( |\gamma_j - \gamma| \to 0, c = \gamma_n n. \)

In settings with missing data, a modified version of (A5) and (A6) must hold for on average over the imputed datasets:

(A5) (in missing data settings) \( M^{-1} \sum_{m=1}^{M} ||f_{m,n,s} - f_{0,s}||_{F_s} = o_P(n^{-1/4}); \)

(A6) (in missing data settings) \( M^{-1} \sum_{m=1}^{M} E_{P_0}[\int \{g_{m,n,s}(z)\}^2 dP_0(z)] = o_P(1), \)

where \( f_{m,n,s} \) is a prediction function estimated using the \( m \)th imputed dataset, and \( g_{m,n,s} \) is defined as above but replacing all instances of \( f_{n,s} \) with \( f_{m,n,s} \), and replacing the ideal-data unit \( z \) with the observed-data unit \( o. \)

6.2 Proof of Lemma 1

The result follows under conditions (A1)–(A8) and an application of results in Chapter 4 of Rubin (1987). Using this result, we can write that

\[
\sqrt{n}(\psi_{M,c,n} - \psi_0) \to_d W \sim N(0, \sigma^2),
\]

where a consistent estimator of \( \sigma^2 \) is given by \( \sigma^2_{M,n} + \frac{m+1}{m} r_{M,n}^2 \). Recall that (A8) requires consistency of the imputation-based estimators as \( M \to \infty. \)

6.3 Proof of Theorem 1

Before proving the theorem, we state and prove a lemma that will be useful.

**Lemma S3.** For any \( \alpha \in (0,1) \), \( k \in \{0, \ldots, p - R_n(\alpha)\} \) and \( q \in (0,1) \), if conditions (A1)–(A6) hold for each \( s \subseteq \{1, \ldots, p\} \) and (A7) holds, then the procedure \( S_n(\alpha) \) satisfies the following: (a) when based on Holm-adjusted p-values, FWER \( \leq \alpha \) both in finite samples and asymptotically; and (b) when based on a step-down maxT or minP procedure, FWER \( \leq \alpha \) asymptotically.
Proof. Under the collection of conditions (A1)–(A7), \( \sqrt{n}(\psi_{c,n} - \psi_0) \rightarrow_d Z \sim N(0, \Sigma_0) \) by Theorem 1 in Williamson and Feng (2020), where \( \Sigma_0 = E_0\{\phi_0(O)\phi_0(O)^\top\} \) and \( \phi_0 \) is the vector of efficient influence function values provided in Williamson and Feng (2020) for each \( j \). Therefore, the centered and scaled test statistics \( T_n \) follow a multivariate Gaussian distribution.

Thus, by Proposition 3.8 in Dudoit and van der Laan (2008), when \( S_n(\alpha) \) is based on Holm-adjusted p-values the procedure has finite-sample and asymptotic control of the FWER. When \( S_n(\alpha) \) is based on a step-down maxT or minP procedure, the procedure has asymptotic control of the FWER as a result of Theorems 5.2 and 5.7 in Dudoit and van der Laan (2008), respectively.

Under conditions (A1)–(A7) and (B1)–(B2), an application of Lemma S3 and Theorem 6.3 in Dudoit and van der Laan (2008) to the procedure \( S_n^+(k, \alpha) \) yields that

\[
\Pr_{P_0}(V_n^+(k, \alpha) > k) = \alpha_n \text{ and } \Pr_{P_0}(V_n^+(k, \alpha)/R_n^+(k, \alpha) > q) = \alpha_n \text{ for all } n, 
\]

i.e., the gFWER(\( k \)) and PFP(\( q \)) are controlled in finite samples at level \( \alpha_n \).

If additionally conditions (B3)–(B4) hold, then an application of Lemma S3 and Theorem 6.5 in Dudoit and van der Laan (2008) to the procedure \( S_n^+(k, \alpha) \) yields that

\[
\limsup_{n \to \infty} \Pr_{P_0}(V_n^+(k, \alpha) > k) \leq \alpha \text{ and } \limsup_{n \to \infty} \Pr_{P_0}(V_n^+(k, \alpha)/R_n^+(k, \alpha) > q) \leq \alpha, 
\]

i.e., the gFWER(\( k \)) and PFP(\( q \)) are controlled asymptotically at level \( \alpha \).

Finally, under the above conditions, an application of Lemma S3 and Theorem 6.6 in Dudoit and van der Laan (2008) to the procedure \( S_n^+(k, \alpha) \) yields that the FDR is controlled asymptotically.

In missing-data settings, we simply require that condition (A8) additionally hold, and modify the above displays to use \( S_{M,n}^+(\alpha), V_{M,n}^+(\alpha), \) and \( R_{M,n}^+(\alpha) \) in place of \( S_n^+(\alpha), V_n^+(\alpha), \) and \( R_n^+(\alpha) \).
6.4 Proof of Lemma 2

Suppose that we are in a complete-data setting. Without loss of generality, suppose that we use
Holm-adjusted p-values to construct the initial set of selected variables and that the augmented
set is chosen so as to control the gFWER\(^k\). For a fixed sample size \(n\) and constant \(k_n\), this
results in selected set \(S_n := S_n^+(k_n, \alpha)\), where \(|S_n| = k_n\). The claim of persistence is equivalent
to showing that

\[
V(f_{n,S_n}, P_0) - V(f_*, P_0) \rightarrow_P 0.
\]

We can decompose the left-hand side of the above expression into two terms:

\[
V(f_{n,S_n}, P_0) - V(f_*, P_0) = \{V(f_{n,S_n}, P_0) - V(f_{0,S_n}, P_0)\} - \{V(f_{0,S_n}, P_0) - V(f_*, P_0)\}. \tag{S6}
\]

The first term in (S6) is the contribution to the limiting behavior of \(V(f_{n,S_n}, P_0) - V(f_*, P_0)\)
from estimating \(f_0\) for a fixed \(S_n\); by condition (A1),

\[
|V(f_{n,S_n}, P_0) - V(f_{0,S_n}, P_0)| \leq C\|f_{n,S_n} - f_{0,S_n}\|^2_{\mathcal{F}_{S_n}} \rightarrow_P 0.
\]

The second term in (S6) is the contribution to the limiting behavior of \(V(f_{n,S_n}, P_0) - V(f_*, P_0)\)
from selecting \(S_n\) compared to the population-optimal set. To study this term, recall
that for a fixed \(p\), we have under conditions (A1), (A2), (A5), (A6), and (A7) that \(\psi_{c,n,j} \rightarrow_P \psi_{0,j}\)
for each \(j \in \{1, \ldots, p\}\). Thus, for each \(j \in S_0\), the p-value \(p_{n,j}\) associated with testing the null hypothesis \(H_{0,j} : \psi_{0,j} = 0\) converges to 0. This implies that as \(n \rightarrow \infty\), \(S_n(\alpha) \rightarrow_P S_0\).
Moreover, by condition (B3), \(S_0 \subseteq S_n^+(k_n, \alpha)\) as \(n \rightarrow \infty\). By definition, \(\psi_{0,j} > 0\) if and only
if \(V(f_{0,s \cup \{j\}}, P_0) - V(f_{0,s}, P_0) > 0\) for some \(s \subseteq \{1, \ldots, p\}\). This implies that for \(j \in S_0^c\),
\(V(f_{0,s \cup \{j\}}, P_0) - V(f_{0,s}, P_0) = 0\) for all \(s \subseteq \{1, \ldots, p\}\). In particular, for \(j \in S_0^c\),

\[
V(f_{0,S_0 \cup \{j\}}, P_0) - V(f_{0,S_0}, P_0) = 0.
\]
This implies that \( S^+_n(k_n, \alpha) \rightarrow_p S_0 \), which further implies that \( \{V(f_{0,n}, P_0) - V(f_*, P_0)\} \rightarrow_p 0 \), proving the claim with

\[
V(f_{n,n}, P_0) - V(f_*, P_0) = o_P(n^{-1/2}).
\]

In a setting with missing data, we consider the imputation-based analogue of the above result. Suppose that we have a selected set \( S_{M,n} := S^+_M(\alpha) \). Then

\[
\frac{1}{M} \sum_{m=1}^M V(f_{m,n,S_{M,n}}, P_0) - V(f_*, P_0) = \frac{1}{M} \sum_{m=1}^M \{V(f_{m,n,S_{M,n}}, P_0) - V(f_{0,S_{M,n}})\} - \{V(f_{0,S_{M,n}} - V(f_*, P_0))\}.
\]

Under conditions (A1), (A2), and (A5)–(A8), the same logic applies to the second term in the above display as applied to the second term in Equation (S6), so \( \{V(f_{0,S_{M,n}}, P_0) - V(f_*, P_0)\} \rightarrow_p 0 \). For the first term in the display, an application of (A1) to each of the \( m \) terms in the average yields the desired convergence in probability.

7 Additional numerical experiments

7.1 Replicating all numerical experiments

All numerical experiments presented here and in the main manuscript can be replicated using code available on GitHub.

In all cases, our simulated dataset consisted of independent replicates of \((X, Y)\), where \( X = (X_1, \ldots, X_p) \) and \( Y \) followed a Bernoulli distribution with success probability \( \Phi\{\beta_{00} + f(\beta_0, x)\} \) conditional on \( X = x \), where \( \Phi \) denotes the cumulative distribution function of the standard normal distribution. Under this specification, \( Y \) followed a probit model. A summary of the eight scenarios is provided in Table S1.

In Scenarios 3–5, we investigate the effect of departures from a multivariate normal feature distribution and a linear outcome regression model under a similar setup to Scenario 1. We set \( \beta_{00} = 0.5 \) and \( \beta_0 = (-1, 1, -0.5, 0.5, 1/3, -1/3, 0, \ldots, 0\)\)\top, where \( 0_k \) denotes a zero-vector of
| Scenario | Outcome regression | Feature distribution | Importance | $p$ |
|----------|--------------------|----------------------|------------|-----|
| 1        | Linear             | Independent normal   | Mix        | $\{30,500\}$ |
| 2        | Nonlinear          | Correlated normal    | Weak       | 6   |
| 3        | Linear             | Independent nonnormal| Mix        | $\{30,500\}$ |
| 4        | Nonlinear          | Independent normal   | Mix        | $\{30,500\}$ |
| 5        | Nonlinear          | Independent nonnormal| Mix        | $\{30,500\}$ |
| 6        | Linear             | Independent normal   | Weak       | 6   |
| 7        | Linear             | Correlated normal    | Weak       | 6   |
| 8        | Nonlinear          | Independent normal   | Weak       | 6   |

Table S1: Summary of the eight data-generating scenarios considered in the numerical experiments.

dimension $k$. We vary $p \in \{30,500\}$. In Scenario 3, we set $f(\beta_0, x) = x\beta_0$, but in contrast to Scenario 1, $X$ follows a nonnormal feature distribution specified by

$$X_1 \sim N(0.5, 1); \quad X_2 \sim Binomial(0.5); \quad X_3 \sim Weibull(1.75, 1.9); \quad X_4 \sim Lognormal(0.5, 0.5);$$

$$X_5 \sim Binomial(0.5); \quad X_6 \sim N(0.25, 1); \quad (X_7, \ldots, X_p) \sim MVN(0, I_{p-6}). \quad (S7)$$

In Scenarios 4 and 5, the outcome regression follows the same nonlinear specification as in Scenario 2. Specifically, using a centering and scaling function $c_j$ for each variable,

$$f(\beta_0, x) = 2[\beta_{0,1}f_1\{c_1(x_1)\} + \beta_{0,2}f_2\{c_2(x_2), c_3(x_3)\} + \beta_{0,3}f_3\{c_3(x_3)\}$$

$$+ \beta_{0,4}f_4\{c_4(x_4)\} + \beta_{0,5}f_5\{c_5(x_5), c_1(x_1)\} + \beta_{0,6}f_5\{c_6(x_6)\}], \quad (S8)$$

$$f_1(x) = \sin\left(\frac{\pi}{4}x\right), \quad f_2(x, y) = xy, \quad f_3(x) = \tanh(x),$$

$$f_4(x) = \cos\left(\frac{\pi}{4}x\right), \quad f_5(x) = -\tanh(x),$$

where $\tanh$ denotes the hyperbolic tangent. In Scenario 4, $X \sim MVN(0, I_p)$, while in Scenario 5, $X$ follows the distribution specified in Equation (S7). In these scenarios, only the first six features truly influence the outcome; some of the features are strongly important, while others are more weakly important.

In the final scenarios, we investigate the effect of correlated features and departures from a linear outcome regression model in a setting where the features are equally, and weakly,
important; these settings are similar to Scenario 2. In these cases, we set $p = 6$, $\beta_{00} = 0.5$, $\beta_0 = (0, 1, 0, 0, 0, 1) \top$, and $X \sim MVN(0, \Sigma)$, where $\Sigma_{i,j} = \rho_{i-j}^{|i-j|}$ for $i, j$ not in the active set, and $\Sigma_{i,j} = I_p + \rho_2(J_p - I_p)$ for $i, j$ in the active set, where $J_p$ is a $p \times p$ matrix of ones. In Scenarios 6 and 7 we set $f(\beta_0, x) = x\beta_0$, while in Scenario 8 $f$ is specified as in Equation (S8).

In Scenarios 6 and 8 we set $\rho_1 = \rho_2 = 0$, while in Scenario 7 we set $\rho_1 = 0.3$ and $\rho_2 = 0.95$.

### 7.2 Tuning parameters for variable selection

The tuning parameters that specify each variable selection procedure are as follows. For the intrinsic selection algorithm, we determined $k$ and $q$ for error control using a target specificity at $n = 3000$ of 75% for $p = 6$, 85% for $p = 30$, and 95% for $p = 500$. For target specificity denoted by $s_p$ and $s_0 = \sum_{j=1}^{p} I(\beta_{0j} > 0)$, we set $k = \lceil(1 - s_p)(p - s_0)\rceil$, where $\lceil \cdot \rceil$ denotes the ceiling; and set $q = k\{p^{-1}(p - s_0)(n/200)^{1/2} + k\}^{-1}$. The exact values of $k$ (for $gFWER(k)$ control) and $q$ (for $PFP(q)$ control) are provided in Table S2. For stability selection, we specified stability selection threshold equal to 0.9 and target per-comparison type I error rate of 0.04. For the lasso with knockoffs, we set target FDR equal to 0.2.

For cases with missing data, the methods compared are: stability selection within bootstrap imputation, lasso + SS (LJ); bootstrap imputation with bolasso, lasso + SS (BI-BL); SPVIM + gFWER, intrinsic selection to control the generalized familywise error rate; SPVIM + PFP, intrinsic selection to control the proportion of false positives among the rejected variables; and SPVIM + FDR, intrinsic selection to control the false discovery rate.

For cases with complete data the methods compared are: lasso; lasso + SS, lasso with stability selection; lasso + KF, lasso with knockoffs; SPVIM + gFWER, intrinsic selection to control the generalized familywise error rate; SPVIM + PFP, intrinsic selection to control the proportion of false positives among the rejected variables; and SPVIM + FDR, intrinsic selection to control the false discovery rate.
Table S2: Values of: the number of variables selected in each bootstrap run of stability selection (SS\textsubscript{q}), target specificity for \textit{gFWER}(k) and \textit{PFP}(q) control, and \textit{k} and \textit{q} used for \textit{gFWER} and \textit{PFP} control, respectively, in the numerical experiments.

| n   | p   | SS\textsubscript{q} | Target specificity | k   | q   |
|-----|-----|----------------------|---------------------|-----|-----|
| 200 | 30  | 23                   | 0.762               | 6   | 0.882 |
| 500 | 30  | 23                   | 0.774               | 6   | 0.826 |
| 1500| 30  | 23                   | 0.809               | 5   | 0.695 |
| 3000| 30  | 23                   | 0.854               | 4   | 0.564 |
| 200 | 500 | 91                   | 0.812               | 94  | 0.990 |
| 500 | 500 | 91                   | 0.824               | 88  | 0.983 |
| 1500| 500 | 91                   | 0.861               | 69  | 0.962 |
| 3000| 500 | 91                   | 0.904               | 48  | 0.926 |

7.3 Super Learner specification

The specific candidate learners and their corresponding tuning parameters for our Super Learner library are provided in Tables S3 (Scenarios 1, 3–5) and S4 (Scenarios 2, 6–8). In both cases, we used a wide variety of algorithms, each with several tuning parameter values, in an effort to be robust to model misspecification. It is possible that with a different library of learners, different results could be obtained.

For the internal library in our intrinsic selection procedure in Scenarios 1 and 3–5, we first pre-screened variables based on their univariate rank correlation with the outcome, and then fit boosted trees with maximum depth equal to three and shrinkage equal to 0.1. In Scenarios 2 and 6–8, we again first pre-screened variables based on their univariate rank correlation with the outcome, and then fit a logistic regression or boosted trees with maximum depth equal to four, shrinkage equal to 0.1, and number of rounds equal to 100. Recall that within the intrinsic selection procedure, we estimate the optimal prediction function for each subset \textit{s} of the \textit{p} features. The univariate rank correlation screen operated as follows: if |\textit{s}| \leq 2, we did no screening; if 2 < |\textit{s}| < 100, we picked the top two variables ranked by univariate correlation with the outcome; and if |\textit{s}| \geq 100, we picked the top ten variables ranked by univariate correlation with the outcome. This screening substantially reduced the computation time for the intrinsic selection procedure, and reflects the type of aggressive screen that is used in some cases (Neidich et al., 2019). Also, the univariate comparisons of each feature to the null model
| Candidate Learner               | R Implementation | Tuning Parameter and possible values | Tuning parameter description |
|--------------------------------|------------------|-------------------------------------|-----------------------------|
| Random forests                 | ranger           | mtry ∈ \{1/2, 1, 2\} \sqrt{p} †   | Number of variables to possibly split at in each node |
|                                | (Wright and Ziegler, 2017) |                                      |                             |
| Gradient boosted trees         | xgboost          | max.depth ∈ \{1, 3\}               | Maximum tree depth          |
|                                | (Chen et al., 2019) |                                      |                             |
| Support vector machines        | ksvm             |                                     |                             |
|                                | (Karatzoglou et al., 2004) |                                      |                             |
| Lasso                          | glmnet           | λ chosen via 10-fold CV             | †\: p denotes the total number of predictors |
|                                | (Friedman et al., 2010) |                                      |                             |

Table S3: Candidate learners in the Super Learner ensemble for Scenarios 1 and 3–5 along with their R implementation, tuning parameter values, and description of the tuning parameters. All tuning parameters besides those listed here are set to their default values. In particular, the random forests are grown with 500 trees, a minimum node size of 5 for continuous outcomes and 1 for binary outcomes, and a subsampling fraction of 1; the boosted trees are grown with a maximum of 1000 trees, shrinkage rate of 0.1, and a minimum of 10 observations per node; and the SVMs are fit with radial basis kernel, cost of constraints violation equal to 1, upper bound on training error (\(\nu\)) equal to 0.2, \(\epsilon\) equal to 0.1, and three-fold cross-validation with a sigmoid for calculating class probabilities.

(with no features) are given high weight in the intrinsic importance measure, so screening should not have much impact on the final intrinsic importance estimate.

### 7.4 Additional results from Scenarios 1 and 2 with missing data

In the main manuscript, we presented results with a maximum of 40% missing data in some variables in Scenarios 1 and 2. In Figure S1 we present results in an intermediate setting with a maximum of 20% missing data in some variables; the results in this setting tend to be similar to the results with maximum 40% missing data.

In Figure S2 we present results in an intermediate setting with a maximum of 20% missing data in some variables, which again tend to be similar to the results with maximum 40% missing data.

In Figures S3–S4, we display the empirical selection probability for each active-set variable under each selection algorithm in Scenario 1. All active-set variables are selected with high
| Candidate Learner       | R Implementation | Tuning Parameter and possible values | Tuning parameter description |
|------------------------|------------------|-------------------------------------|------------------------------|
| Random forests         | ranger           | min.node.size \(\in\) \{1, 20, 50, 100, 250, 500\} | Minimum node size            |
| Gradient boosted       | xgboost          | shrinkage \(\in\) \{1 \times 10^{-2}, 1 \times 10^{-1}\} | Shrinkage                    |
| trees                  |                  | ntrees \(\in\) \{100, 1000\}          | Number of trees              |
| Support vector machines| ksvm             |                                     |                              |
| Lasso                  | glmnet           | \(\lambda\) chosen via 10-fold CV    | \(\ell_1\) regularization parameter |

Table S4: Candidate learners in the Super Learner ensemble for Scenarios 2 and 6–8 along with their R implementation, tuning parameter values, and description of the tuning parameters. All tuning parameters besides those listed here are set to their default values. In particular, the random forests are grown with 500 trees and a subsampling fraction of 1; the boosted trees are grown with a minimum of 10 observations per node; and the SVMs are fit with radial basis kernel, cost of constraints violation equal to 1, upper bound on training error (\(\nu\)) equal to 0.2, \(\epsilon\) equal to 0.1, and three-fold cross-validation with a sigmoid for calculating class probabilities.

Figure S1: Test-set AUC (panel A) and empirical variable selection sensitivity (panel B) and specificity (panel C) vs \(n\) for each estimator and missing data proportion equal to 0.2, in Scenario 1 (a linear model for the outcome and multivariate normal features). The dotted line in panel A shows the true (optimal) test-set AUC.
Figure S2: Test-set AUC (panel A) and empirical variable selection sensitivity (panel B) and specificity (panel C) vs \( n \) for each estimator and missing data proportion equal to 0.2, in Scenario 2 (a nonlinear model for the outcome and correlated multivariate normal features). The dotted line in panel A shows the true (optimal) test-set AUC.

probability by all procedures, with the exception of SPVIM + FDR and SPVIM + PFP. In small samples, all estimators besides lasso + SS (BI-BL) sometimes fail to select variables 5 and 6, the variables with smallest intrinsic importance; these variables are selected with low probability by SPVIM + PFP and SPVIM + FDR at all sample sizes considered here. In the higher dimensional case, SPVIM + gFWER selects these variables in cases where lasso + SS (LJ) does not. This reflects the low true importance of these variables combined with tuning parameters that provide strict PFP and FDR control. As the proportion of missing data increases, the selection probabilities tend to decrease slightly.

In Figures S5–S6, we display the empirical selection probability for each active-set variable under each selection algorithm in Scenario 2. In this scenario, as expected, the selection probability is low for lasso + SS (LJ) and high for SPVIM + gFWER (as reflected in the empirical sensitivity presented in the main manuscript). Variables 2 and 3, which are highly correlated and include an interaction term not modelled by the lasso, have the lowest selection probability for lasso + SS (LJ), as expected (though lasso + SS (BI-BL) has perfect sensitivity, it also has zero specificity).
Figure S3: Empirical selection probability for each active-set variable vs $n$ for each estimator and dimension with missing data proportion equal to 0.2, in Scenario 1 (a linear model for the outcome and multivariate normal features).

Figure S4: Empirical selection probability for each active-set variable vs $n$ for each estimator and dimension with missing data proportion equal to 0.4, in Scenario 1 (a linear model for the outcome and multivariate normal features).

Figure S5: Empirical selection probability for each active-set variable vs $n$ for each estimator, in Scenario 2 (a nonlinear model for the outcome and correlated multivariate normal features).
7.5 Results from Scenarios 3–8 with missing data

In Scenario 3, we generate features from a nonnormal joint distribution and the outcome is a linear combination of these features. We display the results of this experiment in Figure S7. We observe similar performance in this scenario to the performance we observed in Scenario 1: test-set AUC increases towards the optimal value with increasing sample size for all estimators, though slowest for SPVIM + FDR and SPVIM + PFP; empirical sensitivity and specificity tend to both increase, with the exception of the lasso + SS (BI-BL) algorithm, which has near-zero specificity at all sample sizes considered here.

In Scenario 4, we generate features from a multivariate normal distribution and the outcome is a nonlinear combination of these features. In this case, lasso-based methods follow a misspecified mean model. We display the results of this experiment in Figure S8. We observe that test-set AUC tends to increase quickly towards the optimal AUC with increasing sample size for the SPVIM + gFWER procedure, but increases more slowly for lasso-based procedures; empirical sensitivity and specificity tend to both increase, with the exception of the lasso + SS (BI-BL) algorithm, which again has near-zero specificity at all sample sizes considered here. In this case, among the algorithms with non-zero specificity, SPVIM + gFWER has the highest sensitivity at all sample sizes considered here.

In Figure S9, we display the results of the experiment conducted under Scenario 5, in which

Figure S6: Empirical selection probability for each active-set variable vs $n$ for each estimator, in Scenario 2 (a nonlinear model for the outcome and correlated multivariate normal features).
Figure S7: Test-set AUC (panel A) and empirical variable selection sensitivity (panel B) and specificity (panel C) vs $n$ for each estimator and missing data proportion, in Scenario 3 (a linear model for the outcome and nonnormal features). The dotted line in panel A shows the true (optimal) test-set AUC.

Figure S8: Test-set AUC (panel A) and empirical variable selection sensitivity (panel B) and specificity (panel C) vs $n$ for each estimator and missing data proportion, in Scenario 4 (a nonlinear model for the outcome and normal features). The dotted line in panel A shows the true (optimal) test-set AUC.
Figure S9: Test-set AUC (panel A) and empirical variable selection sensitivity (panel B) and specificity (panel C) vs $n$ for each estimator and missing data proportion, in Scenario 5 (a nonlinear model for the outcome and nonnormal features). The dotted line in panel A shows the true (optimal) test-set AUC.

The features are nonnormal and the outcome-feature relationship is nonlinear. In this case, the lasso-based methods are misspecified. In panel A, we observe that lasso-based methods have test-set AUC increasing slowly with $n$, while SPVIM + gFWER has test-set AUC approaching the optimal value more quickly. In panels B and C, we see that sensitivity tends to be lower than in Scenario 1 for all procedures, though still increasing towards one; and that specificity trends are similar to those in Scenario 1. In all cases considered here, SPVIM + gFWER has higher empirical sensitivity than lasso + SS (LJ), and often has comparable specificity, particularly in the lower-dimensional setting.

In Scenarios 6–8, the features are more weakly important. We present the results of the experiments under these scenarios in Figures S10–S12. In Scenario 7, we observe reduced variable selection performance for the lasso-based procedures compared to Scenario 6. In Scenario 8, we observe similar trends to Scenario 2, though performance for the lasso-based methods tends to be better than the performance we observed in Scenario 2, reflecting that this scenario does not involve correlation among the features. These experiments suggest that correlation makes variable selection more difficult, particularly in combination with a misspecified outcome regression model.
Figure S10: Test-set AUC (panel A) and empirical variable selection sensitivity (panel B) and specificity (panel C) vs \( n \) for each estimator and missing data proportion, in Scenario 6 (a weak linear model for the outcome and normal features). The dotted line in panel A shows the true (optimal) test-set AUC.

Figure S11: Test-set AUC (panel A) and empirical variable selection sensitivity (panel B) and specificity (panel C) vs \( n \) for each estimator and missing data proportion, in Scenario 7 (a weak nonlinear model for the outcome and correlated normal features). The dotted line in panel A shows the true (optimal) test-set AUC.
In Figures S13–S24, we display the empirical selection probability for each active-set variable under each selection algorithm in Scenarios 3–8. We observe similar performance in Scenario 3 as in Scenario 1. In Scenarios 3 and 4, we observe that most procedures select variables 1, 2, 3, 4, and 6 with high probability as sample size increases. However, in the higher-dimensional case lasso-based procedures select variable 5 with lower probability than our proposed intrinsic selection procedure. Variable 5 is moderately important (its coefficient is 1, compared to a maximum coefficient of 2), but the function relating this variable to the outcome is highly nonlinear over its support. In Scenario 6–8, we observe similar patterns to Scenario 5: variables 2 and 3 tend to be selected infrequently by the lasso-based procedures, but with high frequency by the intrinsic selection procedure.

7.6 Results with completely-observed data

Here, we consider Scenarios 1–8 with completely-observed data. We compare our intrinsic selection algorithm to the lasso, the lasso with stability selection, and the lasso with knockoffs; these latter three algorithms are often used in variable selection analyses with fully-observed data. In Figures S25–S32, we present the results of these experiments. The results tend to be
Figure S13: Empirical selection probability for each active-set variable vs \( n \) for each estimator and dimension with missing data proportion equal to 0.2, in Scenario 3 (a linear model for the outcome and nonnormal features).

Figure S14: Empirical selection probability for each active-set variable vs \( n \) for each estimator and dimension with missing data proportion equal to 0.4, in Scenario 3 (a linear model for the outcome and nonnormal features).

Figure S15: Empirical selection probability for each active-set variable vs \( n \) for each estimator and dimension with missing data proportion equal to 0.2, in Scenario 4 (a nonlinear model for the outcome and multivariate normal features).
Figure S16: Empirical selection probability for each active-set variable vs $n$ for each estimator and dimension with missing data proportion equal to 0.4, in Scenario 4 (a nonlinear model for the outcome and multivariate normal features).

Figure S17: Empirical selection probability for each active-set variable vs $n$ for each estimator and dimension with missing data proportion equal to 0.2, in Scenario 5 (a nonlinear model for the outcome and nonnormal features).

Figure S18: Empirical selection probability for each active-set variable vs $n$ for each estimator and dimension with missing data proportion equal to 0.4, in Scenario 5 (a nonlinear model for the outcome and nonnormal features).
Figure S19: Empirical selection probability for each active-set variable vs $n$ for each estimator, in Scenario 6 (a weak linear model for the outcome and normal features).

Figure S20: Empirical selection probability for each active-set variable vs $n$ for each estimator, in Scenario 6 (a weak linear model for the outcome and normal features).

Figure S21: Empirical selection probability for each active-set variable vs $n$ for each estimator, in Scenario 7 (a weak linear model for the outcome and correlated normal features).
Figure S22: Empirical selection probability for each active-set variable vs $n$ for each estimator, in Scenario 7 (a weak linear model for the outcome and correlated normal features).

Figure S23: Empirical selection probability for each active-set variable vs $n$ for each estimator, in Scenario 8 (a weak nonlinear model for the outcome and normal features).

Figure S24: Empirical selection probability for each active-set variable vs $n$ for each estimator, in Scenario 8 (a weak nonlinear model for the outcome and normal features).
Figure S25: Test-set AUC (panel A) and empirical variable selection sensitivity (panel B) and specificity (panel C) vs $n$ for each estimator and missing data proportion equal to 0, in Scenario 1 (a linear model for the outcome and multivariate normal features). The dotted line in panel A shows the true (optimal) test-set AUC.

similar to the results with missing data: when a linear outcome regression model is correctly specified, our intrinsic procedure tends to perform as well as the lasso-based procedures; when the linear outcome regression model is misspecified, our gFWER-controlling procedure tends to perform better than the lasso-based procedures. In settings with more weakly important variables, our intrinsic procedures continue to perform well. We present the proportion of replications where each variable was selected in Figures S33–S40, again observing similar trends to the missing-data cases.

7.7 Summary of results from Scenarios 1–8

Taken together, these results suggest that (a) as the missing data proportion increases, performance of all procedures tends to degrade; (b) the outcome distribution (linear vs nonlinear) appears to have a larger effect on test-set AUC than the covariate distribution (normal vs non-normal); (c) weakly important variables are less likely to be selected by lasso-based procedures than strongly important variables; and (d) correlation causes further degradation in performance for lasso-based methods. Variable selection performance (sensitivity and specificity) is similar asymptotically across Scenarios 1 and 3–5. This last finding is surprising, since the
Figure S26: Test-set AUC (panel A) and empirical variable selection sensitivity (panel B) and specificity (panel C) vs $n$ for each estimator and missing data proportion equal to 0, in Scenario 2 (a nonlinear model for the outcome and correlated multivariate normal features), when the data are completely observed. The dotted line in panel A shows the true (optimal) test-set AUC.

Figure S27: Test-set AUC (panel A) and empirical variable selection sensitivity (panel B) and specificity (panel C) vs $n$ for each estimator and missing data proportion, in Scenario 3 (a linear model for the outcome and nonnormal features), when the data are completely observed. The dotted line in panel A shows the true (optimal) test-set AUC.
Figure S28: Test-set AUC (panel A) and empirical variable selection sensitivity (panel B) and specificity (panel C) vs $n$ for each estimator and missing data proportion, in Scenario 4 (a nonlinear model for the outcome and normal features), when the data are completely observed. The dotted line in panel A shows the true (optimal) test-set AUC.

Figure S29: Test-set AUC (panel A) and empirical variable selection sensitivity (panel B) and specificity (panel C) vs $n$ for each estimator and missing data proportion, in Scenario 5 (a nonlinear model for the outcome and nonnormal features), when the data are completely observed. The dotted line in panel A shows the true (optimal) test-set AUC.
Figure S30: Test-set AUC (panel A) and empirical variable selection sensitivity (panel B) and specificity (panel C) vs $n$ for each estimator and missing data proportion, in Scenario 6 (a weak linear model for the outcome and normal features), when the data are completely observed. The dotted line in panel A shows the true (optimal) test-set AUC.

Figure S31: Test-set AUC (panel A) and empirical variable selection sensitivity (panel B) and specificity (panel C) vs $n$ for each estimator and missing data proportion, in Scenario 7 (a weak nonlinear model for the outcome and correlated normal features), when the data are completely observed. The dotted line in panel A shows the true (optimal) test-set AUC.
Figure S32: Test-set AUC (panel A) and empirical variable selection sensitivity (panel B) and specificity (panel C) vs $n$ for each estimator and missing data proportion, in Scenario 8 (a weak nonlinear model for the outcome and normal features), when the data are completely observed. The dotted line in panel A shows the true (optimal) test-set AUC.

Figure S33: Empirical selection probability for each active-set variable vs $n$ for each estimator and dimension with missing data proportion equal to 0, in Scenario 1 (a linear model for the outcome and multivariate normal features), when the data are completely observed.
Figure S34: Empirical selection probability for each active-set variable vs $n$ for each estimator, in Scenario 2 (a nonlinear model for the outcome and correlated multivariate normal features), when the data are completely observed.

Figure S35: Empirical selection probability for each active-set variable vs $n$ for each estimator and dimension with missing data proportion equal to 0, in Scenario 3 (a linear model for the outcome and nonnormal features), when the data are completely observed.

Figure S36: Empirical selection probability for each active-set variable vs $n$ for each estimator and dimension with missing data proportion equal to 0, in Scenario 4 (a nonlinear model for the outcome and multivariate normal features), when the data are completely observed.
Figure S37: Empirical selection probability for each active-set variable vs $n$ for each estimator and dimension with missing data proportion equal to 0, in Scenario 5 (a nonlinear model for the outcome and nonnormal features), when the data are completely observed.

Figure S38: Empirical selection probability for each active-set variable vs $n$ for each estimator, in Scenario 6 (a weak linear model for the outcome and normal features), when the data are completely observed.

Figure S39: Empirical selection probability for each active-set variable vs $n$ for each estimator, in Scenario 7 (a weak linear model for the outcome and correlated normal features), when the data are completely observed.
variable selection performance of the lasso is not guaranteed in misspecified settings. However, as we saw in Scenarios 2, 7, and 8, in adversarial cases the lasso-based estimators can have poor variable selection performance, as suggested by theory. Additionally, in the plots describing empirical selection probability for lasso-based estimators, we saw that while lasso-based procedures may have good overall selection performance, some important variables may still be missed, even in the non-adversarial settings. In contrast, our intrinsic variable selection procedure is more robust to model misspecification. Finally, we saw that our proposal performs comparably to commonly used variable selection procedures in settings both with and without missing data when lasso-based estimators are correctly specified.

8 Additional details for the pancreatic cancer analysis

We had two overall objectives:

1. separate mucinous cysts from non-mucinous cysts, where a mucinous cyst is thought to have some malignant potential; and

2. separate cysts with high malignant potential from cysts with low or no malignant potential.
Table S5: All biomarkers of interest for the pancreatic cancer analysis.

| Biomarker                        | Description                                                                                                                                 |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| CEA                              | Carcinoembryonic antigen. Serum levels may be elevated in some types of cancer (e.g., colorectal cancer, pancreatic cancer).              |
| CEA mucinous call                | Binary indicator of whether CEA > 192.                                                                                                      |
| ACTB                             | Actin Beta (Hata et al., 2017)                                                                                                                |
| Molecules score                  | Methylated DNA levels of selected genes (Hata et al., 2017)                                                                                        |
| Molecules neoplasia call         | Binary indicator of whether molecules score > 25                                                                                              |
| Telomerase score                 | Telomerase activity measured using telomere repeat amplification protocol (Hata et al., 2016)                                                   |
| Telomerase neoplasia call        | Binary indicator of whether telomerase score > 730                                                                                           |
| AREG score                       | Amphiregulin (AREG) overexpression (Tun et al., 2012)                                                                                         |
| AREG mucinous call               | Binary indicator of whether AREG score > 112                                                                                                 |
| Glucose score                    | Glucometer glucose level (Zikos et al., 2015)                                                                                                 |
| Glucose mucinous call            | Binary indicator of whether glucose score < 50                                                                                               |
| Combined mucinous call           | Binary indicator of whether AREG score > 112 and glucose score < 50                                                                         |
| Fluorescence score               | Fluorescent protease activity (Ivry et al., 2017)                                                                                            |
| Fluorescence mucinous call       | Binary indicator of whether fluorescence score > 1.23                                                                                         |
| DNA mucinous call                | Presence of mutations in a DNA sequencing panel (Singhi et al., 2018)                                                                           |
| DNA neoplasia call (v1)          | Binary indicator of methylated DNA levels of selected genes being above a threshold (Majumder et al., 2019)                                    |
| DNA neoplasia call (v2)          | Binary indicator of methylated DNA levels of selected genes being above a threshold (Majumder et al., 2019)                                    |
| MUC3AC score                     | Expression of protein Mucin 3AC                                                                                                               |
| MUC5AC score                     | Expression of protein Mucin 5AC (Cao et al., 2013)                                                                                            |
| Ab score                         | Monoclonal antibody reactivity (Das et al., 2014)                                                                                            |
| Ab neoplasia call                | Binary indicator of whether Ab score > 0.104                                                                                                 |

To meet these objectives, we want to assess both individual biomarkers and panels of biomarkers, both using continuous markers and binary calls.

8.1 Data preprocessing

To create analysis data from the raw data, we selected the following variables: participant ID, institution, the entire set of continuous biomarkers and binary calls (listed in Table S5). The proportion of missing data in the biomarkers ranged from a minimum of 24.5% to a maximum of 68.3%; the median proportion of missing data was 31%.
8.2 Imputing missing data

Our analyses are all based on multiple imputation via chained equations (MICE, implemented in the R package mice; van Buuren, 2007; van Buuren and Groothuis-Oudshoorn, 2010). For \( i = 1, \ldots, n \) and \( j = 1, \ldots, r \) (where \( n = 321 \) is the sample size and \( r = 21 \) denotes the total number of biomarkers), we denote the \( i \)th measurement of biomarker \( j \) by \( X_{i,j} \) and the outcome of interest by \( Y_i \). We used the following model to impute missing biomarker values:

\[
X_{i,j,\text{mis}} \sim Y_i + X_{i,j,\text{obs}} + \text{Institution}_i.
\]

These models allow us to relate observed biomarker values (and the institution at which each specimen was collected) to the unobserved biomarker values. All imputations were performed using a maximum of 20 iterations and predictive mean matching (PMM; van Buuren and Groothuis-Oudshoorn, 2010) to create 10 fully-imputed datasets. In some cases, the PMM algorithm failed to converge; in these cases, we used tree-based imputation.

8.3 Variable selection procedures

We use the same variable selection procedures as in the main manuscript: stability selection within bootstrap imputation (denoted by lasso + SS (LJ)) or bootstrap imputation with bolasso for variable selection (denoted by lasso + SS (BI-BL)), with final predictions made using logistic regression; and intrinsic selection designed to control the gFWER, PFP, and FDR, both with and without using Rubin’s Rules via Lemma 1 (denoted SPVIM + \{gFWER, PFP, FDR\}, respectively), with final predictions made using the Super Learner.

8.4 Assessing prediction performance

Assessing prediction performance is complicated by both the imputation step and the initial variable selection step. To address this, we performed imputation within cross-fitting within Monte-Carlo sampling; this provides an unbiased assessment of the entire procedure, from
imputation to variable selection to prediction. More specifically, for each of 100 replicates and each outcome, we performed the procedure outlined in Algorithm 2.

**Algorithm 2** Imputation and pooled variable selection within cross-fitting and Monte-Carlo sampling

1: for $b = 1, \ldots, 50$ do
2: generate a random vector $B_n \in \{1, \ldots, 5\}^n$ by sampling uniformly from $\{1, \ldots, 5\}$ with replacement, and for each $v \in \{1, \ldots, 5\}$, denote by $D_v$ the data with index in $\{i : B_n,i = v\}$;
3: for $v = 1, \ldots, 5$ do
4: if using a bootstrap imputation-based procedure, create 100 bootstrap datasets based on the data in $\bigcup_{j \neq v} D_j$ and a single imputed dataset for each;
5: create 10 imputed datasets $\{Z_{k,-v}\}_{k=1}^{10}$ based on the data in $\bigcup_{j \neq v} D_j$ using MICE;
6: create 10 imputed datasets $\{Z_{k,v}\}_{k=1}^{10}$ based on the data in $D_v$ using MICE;
7: apply the chosen variable selection procedure on the training data, resulting in a final set of selected variables $S_v$;
8: for $k = 1, \ldots, 10$ do
9: train the chosen prediction algorithm on the training data $Z_{k,-v}$ using only variables in $S_v$;
10: obtain $\text{AUC}_{k,v}$ and its associated variance $\text{var(}\text{AUC}\text{)}_{k,v}$ by predicting on the withheld test data $Z_{k,v}$ and measure prediction performance using AUC;
11: end for
12: combine the AUCs and associated variance estimators into $\text{AUC}_v$ and $\text{var(}\text{AUC}\text{)}_v$ using Rubin’s rules;
13: end for
14: compute $\text{CV-}\text{AUC}_b = \frac{1}{5} \sum_{v=1}^{5} \text{AUC}_v$ and $\text{var(}\text{CV-}\text{AUC}\text{)}_b = \frac{1}{5} \sum_{v=1}^{5} \text{var(}\text{AUC}\text{)}_v$;
15: end for
16: compute overall performance by averaging over the Monte-Carlo iterations.

8.5 Obtaining a final set of selected biomarkers

We obtain a final set of selected biomarkers by applying the variable selection procedure to the full set of observations for each imputed dataset.

8.6 Super Learner specification

As in the simulations, we used a different specification for the internal Super Learner in the intrinsic selection procedure (max. depth 4 boosted trees (all tuning parameter values in Table S6) with pre-screening via univariate rank correlation with the outcome) and all other Super
| Candidate Learner       | R Implementation | Tuning Parameter and possible values | Tuning parameter description |
|------------------------|------------------|-------------------------------------|------------------------------|
| Random forests         | ranger           | max.depth ∈ {1, 10, 20, 30, 100, ∞} | Maximum tree depth           |
| Gradient boosted trees | xgboost          | max.depth = {4}                      |                               |
|                        |                  | nrounds ∈ {100, 500, 2000}          | Number of tree depth         |
| Elastic net            | glmnet           | mixing parameter α ∈ {0, 1/4, 1/2, 3/4, 1} | Trade-off between ℓ₁ and ℓ₂ regularization† |

Table S6: Candidate learners in the Super Learner ensemble for the pancreatic cyst data analysis along with their R implementation, tuning parameter values, and description of the tuning parameters. All tuning parameters besides those listed here are set to their default values. In particular, the random forests are grown with mtry = \(\sqrt{p}\)†, a minimum node size of 5 for continuous outcomes and 1 for binary outcomes, and a subsampling fraction of 1; the boosted trees are grown with shrinkage rate of 0.1 and a minimum of 10 observations per node; and the ℓ₁ tuning parameter for the elastic net is determined via 10-fold cross-validation.

†: \(p\) denotes the total number of predictors.

Learners (Table S6). In all cases, the final Super Learner fit for prediction performance of the selected set of variables used the candidate learners in Table S6.

9 Additional results from the pancreatic cyst analysis

In the main manuscript, we performed an analysis with goal of predicting whether a cyst was mucinous, using Algorithm 2 to assess prediction performance. In Table S7, we present the biomarkers selected using each procedure. Here, we show results using this same algorithm for the outcome of whether a cyst has high malignancy potential.

We present the results of our analysis in Figure S41 and Table S8. In Figure S41, we see that the PFP- and FDR-controlling intrinsic selection procedures again select no variables, on average, as we saw in the analysis of the mucinous outcome in the main manuscript. Prediction performance is also poor for the lasso-based estimators. Compared to the mucinous outcome, we observe reduced prediction performance for the gFWER-controlling intrinsic selection procedure, with an estimated cross-validated AUC of 0.803 (95% confidence interval [0.67, 0.936]). In Table S8, we display the final set of biomarkers selected by each procedure. Several biomarkers
Figure S41: Cross-validated area under the receiver operating characteristic curve (CV-AUC) for predicting whether a cyst has high malignancy potential averaged over 100 replicates of the imputation-within-cross-validated procedure (Algorithm 2) for each variable selection algorithm. Prediction performance for lasso-based methods is based on logistic regression on the selected variables, while performance for Super Learner-based methods is based on a Super Learner. Error bars denote 95% confidence intervals based on the average variance over the 100 replications.

are selected across all two or more procedures that selected any variables on the full dataset. An antibody score was selected across all three procedures. Variables appearing in two or more procedures included an ACTB score, four neoplasia calls (binary variables), a glucose score, a combined amphiregulin- and glucose-based mucinous call, a fluorescence score and its associated mucinous call, and an antibody-based neoplasia call. Selection across the majority of procedures suggests that these variables may useful for predicting whether a cyst has high malignancy potential.
Table S7: Biomarkers selected by each selection procedure for predicting whether a cyst is mucinous on the full imputed dataset. Full definitions of each variable are provided in the Supplementary Material.

| Biomarker                        | lasso + SS (LJ) | lasso + SS (BI-BL) | SPVIM + gFWER | Number of procedures |
|----------------------------------|-----------------|--------------------|---------------|---------------------|
| CEA                              | No              | Yes                | No            | 1                   |
| CEA mucinous call                | No              | Yes                | No            | 1                   |
| ACTB                             | No              | Yes                | No            | 1                   |
| Molecules (M) score              | No              | Yes                | No            | 1                   |
| M neoplasia call                 | No              | Yes                | Yes           | 2                   |
| Telomerase (T) score             | No              | Yes                | No            | 1                   |
| T neoplasia call                 | No              | Yes                | No            | 1                   |
| AREG (A) score                   | Yes             | Yes                | Yes           | 3                   |
| A mucinous call                  | No              | Yes                | No            | 1                   |
| Glucose (G) score                | No              | Yes                | Yes           | 2                   |
| G mucinous call                  | Yes             | Yes                | Yes           | 3                   |
| A and G mucinous call            | Yes             | Yes                | Yes           | 3                   |
| Fluorescence (F) score           | Yes             | Yes                | Yes           | 3                   |
| F mucinous call                  | No              | Yes                | Yes           | 2                   |
| DNA mucinous call                | No              | Yes                | No            | 1                   |
| DNA neoplasia call (v1)          | No              | Yes                | No            | 1                   |
| DNA neoplasia call (v2)          | No              | Yes                | Yes           | 2                   |
| MUC3AC score                     | Yes             | Yes                | Yes           | 3                   |
| MUC5AC score                     | No              | Yes                | No            | 1                   |
| Ab score                         | No              | Yes                | No            | 1                   |
| Ab neoplasia call                | No              | Yes                | Yes           | 2                   |
Table S8: Biomarkers selected by each selection procedure for predicting whether a cyst has high malignancy potential on the full imputed dataset. Full definitions of each variable are provided in Table S5.

| Biomarker                      | lasso + SS (LJ) | lasso + SS (BI-BL) | SPVIM + gFWER | Number of procedures |
|--------------------------------|-----------------|--------------------|---------------|---------------------|
| CEA                            | No              | Yes                | No            | 1                   |
| CEA mucinous call              | No              | Yes                | No            | 1                   |
| ACTB                           | No              | Yes                | Yes           | 2                   |
| M molecules (M) score          | No              | Yes                | No            | 1                   |
| M neoplasia call               | No              | Yes                | Yes           | 2                   |
| Telomerase (T) score           | No              | Yes                | No            | 1                   |
| T neoplasia call               | Yes             | Yes                | No            | 2                   |
| AREG (A) score                 | No              | Yes                | No            | 1                   |
| A mucinous call                | No              | Yes                | No            | 1                   |
| Glucose (G) score              | No              | Yes                | Yes           | 2                   |
| G mucinous call                | No              | Yes                | No            | 1                   |
| A and G mucinous call          | No              | Yes                | Yes           | 2                   |
| Fluorescence (F) score         | No              | Yes                | Yes           | 2                   |
| F mucinous call                | No              | Yes                | Yes           | 2                   |
| DNA mucinous call              | No              | Yes                | No            | 1                   |
| DNA neoplasia call (v1)        | No              | Yes                | Yes           | 2                   |
| DNA neoplasia call (v2)        | No              | Yes                | Yes           | 2                   |
| MUC3AC score                   | No              | Yes                | No            | 1                   |
| MUC5AC score                   | No              | Yes                | No            | 1                   |
| Ab score                       | Yes             | Yes                | Yes           | 3                   |
| Ab neoplasia call              | No              | Yes                | Yes           | 2                   |