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1 Table of Contents

2	SUPPLEMENTARY METHODS.....	2
3	INCLUSION AND EXCLUSION CRITERIA	2
4	EXTRACTION	2
5	PROBAST	4
6	SUPPLEMENTARY FIGURES	10
7	SUPPLEMENTARY TABLES	11
8	SEARCH.....	11
9	EXTRACTION	12
10	SAMPLES.....	15
11	SOFTWARE	18
12	BIAS.....	19
13	MODELS	20
14	PREDICTORS.....	26
15	HYPERPARAMETER SEARCH	29
16	REFERENCES.....	32
17		
18		

19 Supplementary Methods

20

21 Inclusion and Exclusion Criteria

22 Studies which combined genetics and non-genetic data (such as from neuroimaging) were
23 included if they developed or validated a model using only genetic data. Models were only
24 considered for inclusion if they contained two or more genetic predictors from more than
25 one locus. Psychiatric disorders were limited to those with demonstrated heritability and for
26 which large association studies have been undertaken; neurological conditions with
27 psychiatric comorbidities were excluded. A machine learning or statistical learning method
28 was required to be used as the prediction model, with models only using ML for quality
29 control or predictor selection not considered. Changes were made to the registered
30 protocol (registration number CRD42019128820) to further restrict the review's scope, and
31 to clarify inclusion and search criteria before completing database searches.

32

33 Extraction

34 Events per candidate predictor were extracted for all models. Candidate predictors include
35 all predictors considered for inclusion in a model by their association with the outcome.
36 Predictors removed due to association only with other predictors were not counted. As
37 coding of variables is not supplied by most authors, categorical predictors that may be
38 converted to multiple indicator variables by methods are considered only as a single
39 candidate predictor. Similarly, where methods consider additional parameters in the model,
40 such as hidden layers in deep neural networks, only the number of actual predictors is used,
41 not including all possible additional parameters estimated in the model. EPV should

42 therefore be considered an upper bound. Where authors were ambiguous in their reporting
43 of sample size or number of predictors, bounds of the highest and lowest possible EPV are
44 given.

45

46 Where models were fit and internally evaluated before external validation in a single study,
47 we extracted information for both internal and external validation. Internal validation is
48 taken to be any form of evaluation on a subset of the same sample used for training,
49 including splitting samples between training and test sets, bootstrapping and *k*-fold cross
50 validation. Apparent validation, where training and testing are both done on the whole
51 sample, is also recorded under internal validation for the purpose of this review. This is part
52 of model development. External validation is understood as evaluation on an independent
53 dataset, which differs in temporal, geographic or other aspects, and is not simply a splitting-
54 off from the original sample. If multiple models were presented with subsampled predictors
55 or participants, only main models presented in the text were extracted; if such a distinction
56 was unclear, all models were selected for review. Where AUC was only available graphically
57 it was extracted from the figure using Plot Digitizer [1], and accuracy was calculated from
58 the confusion matrix if not provided in-text.

59

60 Model discrimination was extracted independently by two authors (MBS, KC). AUC
61 extracted were the same for both authors, except for 3 of 77 models from a single study;
62 consensus was reached after reviewing the text. Studies often included many models;
63 logistic regression models were only extracted where they received the same predictors as
64 ML methods, in order to keep models comparable.

65

66 PROBAST

67 Risk of bias (ROB) was assessed using the prediction model risk of bias assessment tool
68 (PROBAST). Where information was unavailable within a study, any references or links given
69 to descriptions of datasets or methods were examined. Questions remained unchanged;
70 however, recommendations for assessing studies using genetics and machine learning were
71 added to adapt the tool and keep consistency in answers across models and reviewers.
72 These are detailed below. No studies dictated if a model was intended for prognostic or
73 diagnostic use. For the purpose of assessing ROB, models are assumed to be diagnostic;
74 changing intended model use to prognostic does not alter the final ROB assessments for
75 models. Where databases or publications were referenced for a study, these were assessed
76 for information relevant to ROB. As large genetic datasets may change composition over
77 iterations as smaller studies are added, additional publications that may describe an
78 iteration of a publicly available dataset, but which were not referenced in the included
79 study, were not examined.

80

81 Questions in PROBAST are formatted such that answering “Yes” indicates low risk of bias,
82 and answered “no” indicates high risk of bias. Normally, if any questions within a domain
83 are rated “no” or “probably no” (N/PN), then the rating is considered to be “high” ROB for
84 that domain. In the absence of any N/PN responses, if any questions are reported as “no
85 information” (NI), then the domain is taken to have “unclear” ROB. If instead all questions
86 were answered as “yes” or “probably yes” (Y/PY), then the domain is rated as “low” ROB.
87 Select situations where questions are rated NI or N/PN were allowed to be rated “low” ROB
88 overall. For predictors, if question 2.2 (“Were predictor assessments made without
89 knowledge of outcome data?”) was rated as NI or Y/PY, overall rating for ROB of predictors

90 was allowed to be “low”. Knowledge of the outcome can enable careful design of cases and
91 controls across arrays and batches, and exclusion by a more stringent threshold of Hardy-
92 Weinberg equilibrium in controls. These may allow for reduced ROB for predictors, rather
93 than increased. For outcome, question 3.5 (“Was the outcome determined without
94 knowledge of predictor information?”), if NI or Y/PY, was allowed to be rated “low” ROB for
95 outcome overall if it was considered that genotypes or other predictors would have been
96 extremely unlikely to influence the outcome of standard assessments, or that outcomes
97 were likely to have been assessed prior to genotyping. For question 4.1 (“Were there a
98 reasonable number of participants with the outcome?”), events per candidate predictors
99 were assessed against recommendations using machine learning methods with default
100 hyperparameters, and therefore represent the worst-case scenario. If EPV was determined to
101 be near to the cut-off, and all other modelling procedures indicated low ROB, including
102 appropriate regularisation and handling of predictors, analysis was allowed to be rated
103 “low” overall. In practice, this situation did not occur.

104

105 PROBAST requires a ROB assessment of each evaluation of each distinct model [2].

106 Development and validation are therefore both assessed for each model and contribute

107 separately to overall counts. Restricting counts to development-only does not appreciably

108 change results. ROB was assessed for all studies by one author (MBS), with the exception of

109 a single publication on which MBS and VEP are co-authors [3]. Here two authors, MBS and

110 KC, independently assessed ROB, the latter being uninvolved in the original study.

111 Differences were overcome through consensus. A third colleague not included in the

112 original study was designated as arbiter should disagreements be unable to be resolved.

113 This situation did not occur.

114

115 *1.1 Were appropriate data sources used, e.g. cohort, RCT, or nested case-control study data?*

116 Studies may be made of multiple smaller studies, some of which are cohorts or where cases
117 are from cohorts but controls are from elsewhere. If cases and controls are sampled from
118 different sources to give a roughly balanced (equal events and non-events) combined
119 sample, denote the combined sample as case-control. If absolute risk cannot be estimated
120 from the combined sample, rate as N/PN.

121

122 *1.2 Were all inclusions and exclusions of participants appropriate?*

123 If the target population for the prediction model is undefined, rate as NI, as this cannot be
124 assessed.

125

126 *2.1 Were predictors defined and assessed in a similar way for all participants?*

127 If genotypes measured on different arrays and there has been no effort to demonstrate
128 similarity across arrays or lack of batch effects, rate N/PN. If genotypes from different arrays
129 have been imputed to the same panel of reference genomes to infer untyped or missing
130 variants, rate Y/PY.

131

132 *3.1 Was the outcome determined appropriately?*

133 Consensus best-estimate diagnosis using medical records and structured interview is
134 considered appropriate. Use of only a structured interview is also considered appropriate,
135 but use of only interviews with family members and records is rated N/PN. Routine care
136 registry data are appropriate only if studies confirming comparability with standard

137 diagnostic methods are available. If method is appropriate only for cases, rate 3.1 as Y and
138 3.4 as N.

139

140 *3.2 Was a prespecified or standard outcome definition used?*

141 Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification
142 of Diseases (ICD)-based outcomes are accepted.

143

144 *3.4 Was the outcome defined and determined in a similar way for all participants?*

145 If the same assessments tool was used for all participants, rate Y/PY. If cases were assessed
146 differently to controls, rate N/PN.

147

148 *3.6 Was the time interval between predictor assessment and outcome determination*
149 *appropriate?*

150 If predictors are genetics-only, rate Y/PY. If predictors include gene-expression data sampled
151 after diagnosis or onset, rate N/PN.

152

153 *4.1 Were there a reasonable number of participants with the outcome?*

154 No recommendations are available for assessing events per variable (EPV) in machine
155 learning models. To our knowledge, only one paper has attempted to assess EPV needed for
156 machine learning models across multiple datasets [4], which we use here as a guide in lieu
157 of a more rigorous alternative. For the purpose of assessing ROB in this review, support
158 vector machines are required to have greater than 200 EPV. Neural networks require at
159 least 200 EPV, but a cut-off of at least 500 EPV should be imposed as architecture can vary
160 greatly. Random forests are also required to have greater than 500 EPV. For other machine

161 learning methods not specified above, 200 EPV is taken as the minimum requirement.
162 Everything below these cut-offs is rated as N/PN. It should be noted that the models these
163 estimates are based on were run using default (hyper)parameters [4] on non-genetic data.
164 Final assessment of ROB for “analysis” should therefore take into account regularisation and
165 model architecture, as models with an EPV of less than 200 may still be rated as “low” ROB
166 for the domain. However, given that all models had multiple aspects of analysis which
167 introduced ROB, changing these thresholds would not affect the final rating for the ‘analysis’
168 domain in any models.

169

170 *4.4 Were participants with missing data handled appropriately?*

171 For imputation using a genetics-specific application or server, such as IMPUTE2, rate Y/PY.
172 For imputation in the sample using other methods, rate N/PN. For complete-case analysis,
173 rate N/PN.

174

175 *4.5 Was selection of predictors based on univariable analysis avoided?*

176 If any plink-based univariable tests for association in the current dataset were used, rate
177 N/PN. If information from an external published GWAS was used to select predictors, rate
178 Y/PY.

179

180 *4.8 Were model overfitting, underfitting, and optimism in model performance accounted for?*

181 If nested cross-validation was used, rate Y/PY, assuming other standard procedures were
182 followed. If any method of repeated cross-validation on the whole dataset where both
183 tuning and evaluation of models were done in the same *k*-fold cross-validation loop was
184 used, or where test data were observed during tuning of hyperparameters, rate N/PN.

185

186 *4.9 Do predictors and their assigned weights in the final model correspond to the results from*
187 *the reported multivariable analysis?*

188 If no model coefficients or assigned weights clearly reported, rate NI, as this cannot be
189 assessed.

190

191 Supplementary Figures

192 **Figure S1:** PRISMA flow diagram. Where a publication met multiple exclusion criteria, it is
193 counted only under the first reason in the list.

194
195 **Figure S2:** within-study risk of bias and applicability assessed by PROBAST. Colours indicate
196 low, high or unclear risk of bias or applicability.

197
198 **Figure S3:** discrimination (AUC) for machine learning, logistic regression and polygenic risk
199 scores. Internal validation (split-sample) and partly-external validation (with sample overlap)
200 are reported for the same models in a single study [5]. ¹Median AUC for internal validation
201 (model development). ²Median AUC for external validation (independent replication).
202 Annotated scores are the median AUC for each model and study. Pirooznia et al. (bipolar
203 disorder) and Vivian-Griffiths et al. (schizophrenia) show SNP-only models for LR and ML [3,
204 6], while Chen et al. (schizophrenia) used multiple schizophrenia-associated trait polygenic
205 risk scores as predictors [5]. PRS model performance was extracted from a figure when
206 unreported in-text [3]. AUC is shown only for 5 of the 9 reported logistic regression models;
207 a fourth study compared ML and LR but did not report discrimination [7]. AUC was not
208 available for a logistic regression which was reported as attempted but not completed for
209 one study [6]. AUC: area under the receiver operating characteristic curve, ML: machine
210 learning, LR: logistic regression, PRS: polygenic risk scores.

211

212

213 [Supplementary Tables](#)

214 Where percentages are reported in any table, they are taken from the total number of
215 models, 77, and rounded to the nearest integer unless stated otherwise. Some aspects of
216 methodology differed between models within studies. Where this occurs, studies are
217 counted under each category that has been met unless stated otherwise, and total counts
218 may not sum to 13.

219 [Search](#)

1. (schizophreni* or schizoaffective or schizotyp* or anxiety or depressi* or autis* or adhd or anorexi* or bullimi* or psychos?s or psychotic or manic or mania or hypomani* or tourette* or obsessive compulsive disorder or ocd).ti,ab. or (exp SCHIZOPHRENIA/ or Bipolar Disorder/ or exp ANXIETY DISORDERS/ or exp Autism Spectrum Disorder/ or exp Depressive Disorder/ or Attention Deficit Disorder with Hyperactivity/ or Anorexia Nervosa/ or Bulimia Nervosa/ or exp Obsessive-Compulsive Disorder/ or Tourette Syndrome/)
 2. (machine learning or statistical learning or pattern analysis or pattern recognition or ensemble or bayesian network* or relevance vector machine* or support vector machine* or decision tree* or classification tree* or regression tree* or elastic net or bagging or gradient boosting or neural network or perceptron or nearest neighbo?r or gaussian process* or ridge or lasso or regulari#ed regression or penali#ed regression or naive bayes or (deep adj3 learning) or (boosted adj2 trees) or (deep adj2 network) or (random adj2 forest) or (supervised adj2 learning)).ti,ab. or exp Machine Learning/
 3. (rare variant* or rare variation or copy number variant* or copy number variation* or dna variant* or polygenic or genetic* or polymorphism* or genotype* or genome* or genomic* or exome*).ti,ab. or exp Polymorphism, Genetic/
-

4. 1 and 2 and 3
5. limit 4 to english language
6. limit 5 to journal article
7. remove duplicates from 6

220

221 **Table S1:** example literature search from Medline (Ovid).

222

223

224 **Extraction**

Domain	Item
<i>Background</i>	Reference
	Disorder
	Study design
	Publication number
	Model type (diagnostic/prognostic)
<i>Participants</i>	Recruitment method
	Study setting
	Retrospective or Prospective?
	Number of Centres
	Inclusion/Exclusion criteria
	Sample description
	Study Dates
	Dataset names or identifiers
<i>Sample size</i>	Total number of observations before QC
	Total number of observations after QC
	Case:control ratio in final dataset
	Number of cases in training set/fold
	Events Per Variable in the training set/fold

<i>Outcome</i>	<p>Definition of outcome</p> <p>Measurement</p> <p>Same for all patients?</p> <p>Type of outcome (single/combined)</p> <p>Were assessors blinded to knowledge of predictors?</p> <p>Predictors in outcome?</p>
<i>Predictors</i>	<p>Genotyping/sequencing method</p> <p>Imputation method and reference</p> <p>Types of genetic data</p> <p>Method of choice of variants to genotype/sequence</p> <p>Genetic Predictor QC</p> <p>Number of candidate predictors</p> <p>Number predictors in final model</p> <p>Coding of genetic data</p> <p>Risk allele definition for coding at a single locus</p> <p>Knowledge/annotation information included?</p> <p>Knowledge/annotation inclusion method</p> <p>Was measurement of predictors blinded to outcome/other predictors?</p> <p>Any other handling of predictors</p> <p>Was leakage handled appropriately?</p>
<i>Participant QC</i>	<p>Genetic sample QC</p> <p>Method for accounting for genetic ancestry</p> <p>Method of accounting for plate/batch/site effects</p> <p>Method for accounting for relatedness</p>
<i>Missing Data</i>	<p>Number participants with any missing value^{1,2}</p> <p>Number of participants with missing data for each predictor¹</p> <p>Handling of missing data</p> <p>Modelling method/representation</p>

<i>Model</i>	Model implementation (programming language)
<i>Development</i>	Model modifications
	Predictor selection types used
	Method for selection of predictors prior to modelling (filter)
	Method for selection of predictors during modelling (wrapper)
	Method for selection of predictors as part of model (embedded)
	Hyperparameter search method
	Tuned Hyperparameters
	Class imbalance method ¹
<i>Model</i>	Discrimination measures reported
<i>Performance</i>	Calibration measures reported
	Classification measures reported
	Other measures reported
	A-priori decision threshold cut-off used for classification?
<i>Model Evaluation</i>	Method for testing model performance internally
	Method for testing model performance externally
	Model adjusted or updated after poor validation? ³
<i>Results</i>	Model AUC
	Model Accuracy, sensitivity and specificity
	Model calibration ¹
	Comparison of distribution of predictors ¹
	Data/code available (link)
<i>Extra</i>	Resources
	Notes

225

226

227 **Table S2:** extraction form, modified from the checklist for critical appraisal and data extraction for systematic reviews of

228 prediction modelling studies (CHARMS) checklist [8]. Items which overlap heavily with prediction model risk of bias

229 assessment tool (PROBAST) signalling questions, such as participant information, are reported in risk of bias summaries.

230 AUC: area under the receiver operating characteristic curve, QC: quality control. ¹Not reported in any publications.
 231 ²Number of participants excluded above a threshold of missingness was reported in many studies. ³No for all publications.

232

233 [Samples](#)

234 [Datasets](#)

235 Titles and descriptions of studies making up a dataset are recorded as given in the extracted
 236 publication. Where references are supplied, these were given in the text, or clear from an online
 237 repository, such as the database of Genotypes and Phenotypes (dbGaP) [9]. Where datasets appear
 238 to overlap, this has been noted.

239

Study	Disorder	Dataset
Yang et al. (2010)	Schizophrenia	No name/reference given
Ghafouri-Fard et al. (2010)	Autism	No name/reference given
Aguiar-Pulido et al. (2010;2013)	Schizophrenia	External sample ^a
Wang et al. (2018)	Schizophrenia	PsychENCODE ^b
	Bipolar disorder	PsychENCODE ^b
	Autism	PsychENCODE ^b
Pirooznia et al. (2012)	Bipolar disorder	BGSC ^{c††} (DEV), WTCCC ^{d*} (VAL)
Lakshman et al. (2017)	Bipolar disorder	Not clearly reported ^e
Acikel et al. (2016)	Bipolar disorder	Whole-Genome Association
		Study of Bipolar Disorder ^{f††}
Li et al. (2014)	Bipolar disorder	Whole-Genome Association
		Study of Bipolar Disorder ^{f††}
	Schizophrenia	Genome-Wide Association Study of Schizophrenia ^{g†}

Guo et al. (2016)	Anorexia	GCAN ^h , WTCCC ^{d*} , CHOP ⁱ , PFCG ^j
Trakadis et al. (2019)	Schizophrenia	Sweden-Schizophrenia Population-Based Case-Control Exome Sequencing ^{k**}
Engchuan et al. (2015)	Autism	AGP ^l
Chen et al. (2018)	Schizophrenia	MGS ^{m†} , SSCCS ^{n**} (DEV), CATIE ^{o†} (VAL)
Vivian-Griffiths et al. (2019)	Schizophrenia	CLOZUK ^{p*}

240

241 **Table S3:** sample overlap between studies. **a:** Galician sample described elsewhere [10]. **b:** PsychENCODE, made up of 8/9

242 studies, where only 6 are listed in the supplementary as having genotype data - study 1 (BrainGVEX, consisting of the

243 Banner Sun Mental Research Institute, BSHRI [11], and Stanley Medical Research Institute, SMRI); study 2 (BrainSpan), no

244 genotype data; study 3 (CommonMind [12]); study 4 (Yale-ASD); no genotype data; study 5 (UCLA-ASD [13]); study 6

245 (BipSeq); study 7 (CMC_HBCC); study 8 (LIBD_szControl + BipSeq); study 9 (not reported). Information and data also

246 available through an online repository [14]. **c:** Bipolar Genome Studies Consortium (BGSC) [15], made up of the Genetic

247 Association Information Network European American (GAIN) [16], and the Translational Genomics Research Institute

248 (TGRI) samples. Controls obtained through Knowledge Networks (KN) [17], and recruitment described elsewhere [18, 19].

249 **d:** Wellcome Trust Case Control Consortium (WTCCC). Bipolar Disorder cases are described in methods, with further

250 information provided elsewhere [20, 21]. Controls include the 1958 British Birth Cohort (58BC) [22] and the UK Blood

251 Service (UKBS) [23]. **e:** part of the Critical Assessment of Genome Interpretation (CAGI)-4 challenge. Lakshman et al. [24]

252 reference Daneshjou et al. [25], from which a third reference [26] gives information on an exome dataset with only bipolar

253 cases recruited for a suicide study, but not controls. **f:** Whole-Genome Association Study of Bipolar Disorder, dbGaP study

254 accession "phs000017.v3.p1". References on dbGaP provide further details on sample recruitment [18, 27]. Acikel et al.

255 acquired Bipolar Disorder Only (BDO) participants [28]; Li et al. report using the Bipolar and Related Disorders (BARD)

256 subset [29]. Controls, obtained through KN, are described under "Clinical Procedures" of the relevant dbGaP entry, and by

257 other studies [17]. **g:** Genome-Wide Association Study of Schizophrenia, dbGaP study accession "phs000021.v3.p2". Cases

258 described on dbGaP, controls obtained through KN. **h:** the Genetic Consortium for Anorexia Nervosa (GCAN). **i:** Price

259 Foundation Collaborative Group and the Children's Hospital of Philadelphia (CHOP). Methodological details for Guo et al.

260 are also referenced to a previous study [30]. **j:** the Price Foundation Collaborative Group (PFCG). **k:** Sweden-Schizophrenia

261 Population-Based Case-Control Exome Sequencing, dbGaP study accession "phs000473.v1.p1". Described in more detail

262 elsewhere [31]. **l**: Autism Genome Project (AGP); three references supplied for methodology and participants [32–34]. **m**:
 263 Molecular Genetics of Schizophrenia (MGS) [35], with controls from KN. **n**: Swedish Schizophrenia Case Control Study
 264 (SSCCS) [36]. **o**: Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) [37, 38], with controls from KN.
 265 Imputation for Chen et al. is also given elsewhere [39]. **p**: CLOZUK [40]; controls from 58BC and UKBS. *Includes controls
 266 from the 1958 British Birth Cohort and the UK Blood Service. †Includes controls from Knowledge Networks. ‡Publications
 267 do not all give the same dataset name or description, but do include a common reference for recruitment or inclusion
 268 criteria. **Studies refer to a Swedish population-based sample with the same outcome definition, but no clear statement
 269 or reference describing sample overlap.

270

271 *Handling of Missing Data*

Method	Studies	Models
Reported	7	43 (56%)
Exclusion (complete-case analysis)	1	1
Code missingness as category in predictor	1	12
Imputation after excluding high missingness	5	30
Imputation using genetics server/application	3	16
Imputation in-sample from binomial distribution ^a	2	14
Unclear/unreported	6	34 (44%)
Only exclusion for high missingness reported ^b	4	28
Not reported	2	6

272

273 **Table S4:** missingness. Handling of missing data differed between the development and validation set for Pirooznia et al.
 274 (2012), where imputation is only reported for external validation [6]; these models are counted under the method
 275 reported in model development, “only exclusion for high missingness”. ^aA study [3] reported using unspecified imputation
 276 prior to quality control filters, before a second in-sample imputation and is recorded once as in-sample. ^bIncludes high
 277 missingness filters for samples, predictors or both, with method for handling remaining missingness not reported.

278

Language/Implementation/Method	Studies	Models
R	4	11 (14%)
glmnet (LASSO)	1	1
randomForest (RF)	2	2
party (CIF)	1	1
e1071 (SVM, NB)	2	2
gbm (GBM)	1	1
XGBoost (Histogram-based GBM)	1	1
kNN (<i>k</i> -NN)	1	1
MDR (MDR)	1	2
Python	4	16 (21%)
scikit-learn	3	12
SVM	1	8
Data handling	1	1
Unspecified	1	3
Keras (NN) ^a	2	4
Tensorflow (NN)	1	4
Java (WEKA) ^b	2	28 (36%)
Matlab	2	11 (14%)
Matlab (NN)	2	10
libSVM (SVM)	1	1
Not reported	3	11

280

281 **Table S5:** software and packages used in machine learning. ^aBackend to Keras not specified. ^bMethods used in WEKA:

282 neural networks (linear, perceptron and radial basis function), evolutionary computation, multifactor dimensionality

283 reduction, Bayesian networks, naïve Bayes, support vector machine, decision tables, decision tree-naïve Bayes, best-first
 284 tree, AdaBoost. LASSO: least absolute shrinkage and selection operator, RF: random forest, CIF: conditional inference
 285 forest, GBM: gradient boosting machine, XGBoost, eXtreme Gradient Boosting, *k*-NN: *k*-nearest neighbours, MDR:
 286 multifactor dimensionality reduction, SVM: support vector machine, NN: neural network, NB: naïve Bayes.

287

288 Bias

289 *Method of accounting for ancestry*

Method	Studies	Models
Population substructure identified in current study but not accounted for	2	14 (18%)
Visualised by PCs for subsample after restricting to European	1	9
Table of ancestry for European American and African American^a	1	5
Unclear ^b	9	50 (65%)
Population structure identified in dataset reference(s)	7	42
Exclusion of non-European ancestry through PCs/MDS	5	35
Visualised but observations not excluded	3	11
Reported as European/ Caucasian -only, no details given	2	8
Not reported in publication or reference	2	13 (17%)

290

291 **Table S6:** methodology for accounting for population structure. Where development or validation sets are made-up of

292 multiple datasets with separate ancestry filters, these are counted separately. ^aMethod of establishing ancestry not

293 specified. ^bAncestry not clearly specified in current study. PCs: principal components, MDS: multi-dimensional scaling.

294

295 Models

296 *Model Performance Measures*

Reported measures	Studies	Models
Discrimination	8	45 (58%)
AUC	8	45
ROC plot	4	7
Classification	9	41 (53%)
Accuracy	8	39
Sensitivity/Recall/Hit-rate/TPR	6	16
Specificity/TNR	4	10
<i>F</i> ₁ -score (<i>F</i> -measure)	3	12
Precision/PPV	3	12
Confusion matrix	3	3
Other	5	29 (38%)
Variance explained on liability scale	1	9
<i>p</i> -value*	1	4
% correctly classified cases, averaged over repeats	1	4
Nagelkerke's pseudo-R ²	1	4
<i>t</i> -test comparisons between models	1	8

297

298 **Table S7:** model performance. *The *p*-value "indicates that XGBoost algorithm is performing better than a random
299 predictor simply predicting the majority class" [41]. ROC: receiver operating characteristic, AUC: area under the ROC curve,
300 TRP: true positive rate, TNR: true negative rate, PPV: positive predictive value. As many studies reported multiple
301 measures, percentages do not combine to 100.

302

303 *Decision threshold cut-off*

Method for choosing cut-off	Studies	Models
<i>a-priori</i>	1	9 (22%)
Unclear	3	6 (15%)
Unreported	5	26 (63%)

304

305 **Table S8:** method for choosing decision threshold when reporting classification metrics. Studies which were unclear either
 306 reported a general outline of how classification works for a given method, without stating this was used in the current
 307 implementation, or reported the use of 0.5 as the threshold but not how the number was chosen. Percentages are taken
 308 from the total number of models which reported classification measures, 41, and rounded to the nearest integer. Number
 309 of studies does not sum to 13 as not all studies reported classification metrics.

310

311 *Validation*

312

Method	Studies	Models
<i>Internal validation</i>		
Cross-validation	8	44 (57%)
3-fold	1	4
4-fold	1	8
5-fold	2	8
10-fold	3	22
LOOCV	1	2
Split-sample	5	16 (21%)
34% train ^a	1	3
40% train ^b	1	3
70% train	1	4
80% train	1	2

90% train	1	4
Apparent	1	1 (1%)
Not reported ^c	1	16 (21%)
<i>External Validation</i>		
External (temporal, geographic) ^c	1	16 (21%)
Partly external ^d	1	4 (5%)
Not performed	11	57 (74%)

313

314

Table S9: validation. Percentages are given with respect to 77, the total number of models. Methodology for internal

315

validation differed between models in a study [31], which is counted in cross-validation (CV), split-sample and apparent.

316

^aApproximately equal three-way split between predictor selection, train and test, with 10-fold CV performed in the training

317

fold for hyperparameter tuning. ^b40% train, 10% test, 50% final test. ^cNo performance measures reported for internal

318

validation, but discrimination for fully external validation reported [25]. ^dControl sample used in development and

319

validation partially overlaps. LOOCV: Leave-one-out cross validation.

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321

Study	Method	Data	Modifications n/N	p/P	Imbalance	EPV	Risk allele	Sensitivity	Specificity	Validation
a	AB	SNP	Y 20/40	150/367	1	0.0054	NR	0.7175	0.76	CV
a	SVM	SNP	N 20/40	367/367	1	0.0054	NR	0.4	0.4	CV
b	NN	SNP	Y 487/942	15/15	0.93	32.5	NR	0.8275	0.6395	CV
c	NN	SNP	N 260/614	40-48/40-48*	1.36	5.42-6.5*	NR	NR	NR	CV
c	NN	SNP	N 260/614	40-48/40-48*	1.36	5.42-6.5*	NR	NR	NR	CV
c	EC	SNP	N 260/614	40-48/40-48*	1.36	5.42-6.5*	NR	NR	NR	CV
c	NN	SNP	N 260/614	40-48/40-48*	1.36	5.42-6.5*	NR	NR	NR	CV
c	MDR	SNP	N 260/614	40-48/40-48*	1.36	5.42-6.5*	NR	NR	NR	CV
c	BN	SNP	N 260/614	40-48/40-48*	1.36	5.42-6.5*	NR	NR	NR	CV
c	NB	SNP	N 260/614	40-48/40-48*	1.36	5.42-6.5*	NR	NR	NR	CV
c	SVM	SNP	N 260/614	40-48/40-48*	1.36	5.42-6.5*	NR	NR	NR	CV
c	DTb	SNP	N 260/614	40-48/40-48*	1.36	5.42-6.5*	NR	NR	NR	CV
c	DTNB	SNP	N 260/614	40-48/40-48*	1.36	5.42-6.5*	NR	NR	NR	CV
c	BFT	SNP	N 260/614	40-48/40-48*	1.36	5.42-6.5*	NR	NR	NR	CV
c	AB	SNP	N 260/614	40-48/40-48*	1.36	5.42-6.5*	NR	NR	NR	CV
d	NN	SNP/GE	N 355/710	NCR/NR	1	n/a	NR	NR	NR	CV
d	NN	SNP/GE	Y 355/710	NCR/NR	1	n/a	NR	NR	NR	CV
d	NN	SNP/GE	Y 355/710	NCR/NR	1	n/a	NR	NR	NR	CV
d	NN	SNP/GE	N 94/188	NCR/NR	1	n/a	NR	NR	NR	CV
d	NN	SNP/GE	Y 94/188	NCR/NR	1	n/a	NR	NR	NR	CV
d	NN	SNP/GE	Y 94/188	NCR/NR	1	n/a	NR	NR	NR	CV
d	NN	SNP/GE	N 31/62	NCR/NR	1	n/a	NR	NR	NR	CV
d	NN	SNP/GE	Y 31/62	NCR/NR	1	n/a	NR	NR	NR	CV
d	NN	SNP/GE	Y 31/62	NCR/NR	1	n/a	NR	NR	NR	CV
e	SVM	SNP	N 2191/3625	3514/NCR	0.65	n/a	NR	NR	NR	Ext
e	SVM	SNP	N 2191/3625	14632/NCR	0.65	n/a	NR	NR	NR	Ext
e	SVM	SNP	N 2191/3625	1252/NCR	0.65	n/a	NR	NR	NR	Ext
e	SVM	SNP	N 2191/3625	5366/NCR	0.65	n/a	NR	NR	NR	Ext
e	NN	SNP	N 2191/3625	3514/NCR	0.65	n/a	NR	NR	NR	Ext
e	NN	SNP	N 2191/3625	14632/NCR	0.65	n/a	NR	NR	NR	Ext

e	NN	SNP	N	2191/3625	1252/NCR	0.65	n/a	NR	NR	NR	Ext
e	NN	SNP	N	2191/3625	5366/NCR	0.65	n/a	NR	NR	NR	Ext
e	RF	SNP	N	2191/3625	3514/NCR	0.65	n/a	NR	NR	NR	Ext
e	RF	SNP	N	2191/3625	14632/NCR	0.65	n/a	NR	NR	NR	Ext
e	RF	SNP	N	2191/3625	1252/NCR	0.65	n/a	NR	NR	NR	Ext
e	RF	SNP	N	2191/3625	5366/NCR	0.65	n/a	NR	NR	NR	Ext
e	BN	SNP	N	2191/3625	3514/NCR	0.65	n/a	NR	NR	NR	Ext
e	BN	SNP	N	2191/3625	14632/NCR	0.65	n/a	NR	NR	NR	Ext
e	BN	SNP	N	2191/3625	1252/NCR	0.65	n/a	NR	NR	NR	Ext
e	BN	SNP	N	2191/3625	5366/NCR	0.65	n/a	NR	NR	NR	Ext
f	NN	Exome	Y	200/400	~1000/>500000*	1	<0.0004*	Ref/alt	0.64	NR	Split
f	RF	Exome	N	200/400	~1000/>500000*	1	<0.0004*	Ref/alt	0.55	NR	Split
f	DT	Exome	N	200/400	~1000/>500000*	1	<0.0004*	Ref/alt	0.54	NR	Split
g	RF	SNP	N	604/2371	693/761830	2.93	0.00079	NR	0.998	NR	App.
g	NB	SNP	N	483/1414	693/761830	1.93	0.00063	NR	0.734	NR	Split
g	k-NN	SNP	N	483/1414	693/761830	1.93	0.00063	NR	0.954	NR	Split
g	MDR	SNP	N	604/2371	693/761830	2.93	0.00079	NR	0.664	NR	CV
g	MDR	SNP	N	604/2371	693/761830	2.93	0.00079	NR	0.883	NR	CV
h	Ridge	SNP	N	653/1158	298604/298604	0.77	0.0022	NR	NR	NR	CV
h	SVM	SNP	N	653/1158	98604/298604	0.77	0.0022	NR	NR	NR	CV
h	LASSO	SNP	N	653/1158	98604/298604	0.77	0.0022	NR	NR	NR	CV
h	Ridge	SNP	N	1170/2068	98604/298604	0.77	0.0039	NR	NR	NR	CV
h	SVM	SNP	N	1170/2068	98604/298604	0.77	0.0039	NR	NR	NR	CV
h	LASSO	SNP	N	1170/2068	98604/298604	0.77	0.0039	NR	NR	NR	CV
i	LASSO	SNP	N	1341/4402	1486/317481*	2.28	>=0.0042*	NR	0.11	0.97	Split ⁺
i	SVM	SNP	N	1341/4402	1486/317481*	2.28	>=0.0042*	NR	NR	NR	Split ⁺
i	GBM	SNP	N	1341/4402	1486/317481*	2.28	>=0.0042*	NR	NR	NR	Split ⁺
j	LASSO	Exome	N	1782*/3564	1155/17138	1	0.1*	NR	0.720	0.773	Split
j	SVM	Exome	N	1782*/3564	1155/17138	1	0.1*	NR	0.708	0.706	Split
j	RF	Exome	N	1782*/3564	1155/17138	1	0.1*	NR	0.820	0.813	Split
j	GBM	Exome	N	1782*/3564	1155/17138	1	0.1*	NR	0.849	0.866	Split
k	CIF	CNV	N	1570/3486	21/21	1.22	74.6	NR	NR	NR	CV
k	RF	CNV	N	1570/3486	21/21	1.22	74.6	NR	NR	NR	CV
k	SVM	CNV	N	1570/3486	21/21	1.22	74.6	NR	NR	NR	CV
k	NN	CNV	N	1570/3486	21/21	1.22	74.6	NR	NR	NR	CV

I	NN	PRS	N	5018/10859	19/116	1.16	43.26	NR	NR	NR	Split/ Ext.
I	NN	PRS	N	5018/10859	116/116	1.16	43.26	NR	NR	NR	Split/ Ext.
I	NN	PRS	N	5018/10859	14/29-32*	1.16	156.81-173.03*	NR	NR	NR	Split/ Ext.
I	NN	PRS	N	5018/10859	26/29-32*	1.16	156.81-173.03*	NR	NR	NR	Split/ Ext.
m	SVM	SNP	N	3446/7731	125/125	1.24	27.57	Ref	NR	NR	CV
m	SVM	SNP	N	5554/11853	125/125	1.13	44.43	Ref	NR	NR	CV
m	SVM	SNP	N	3446/7731	4998/4998	1.24	0.69	Ref	NR	NR	CV
m	SVM	SNP	N	5554/11853	4998/4998	1.13	1.11	Ref	NR	NR	CV
m	SVM	SNP	N	3446/7731	125/125	1.24	27.57	Ref	NR	NR	CV
m	SVM	SNP	N	5554/11853	125/125	1.13	44.43	Ref	NR	NR	CV
m	SVM	SNP	N	3446/7731	4998/4998	1.24	0.69	Ref	NR	NR	CV
m	SVM	SNP	N	5554/11853	4998/4998	1.13	1.11	Ref	NR	NR	CV

323

324 **Table S10:** overview of prediction models. n: number of cases used in model development in final model, N: number of
325 total observations in model development in final model, p: number of predictors in final model, P: number of candidate
326 predictors, EPV: events per candidate variable/predictor, NR: not reported, NCR: not clearly reported, Ref: risk allele coded
327 as reference allele, Alt: coded as alternative allele, SNP: single nucleotide polymorphism, CNV: copy number variant, PRS:
328 polygenic risk score, GE: gene expression, AB: AdaBoost, SVM: support vector machine, NN: neural network, EC:
329 evolutionary computation, MDR: multifactor dimensionality reduction, BN: Bayesian networks, NB: naïve Bayes, DTb:
330 decision tables, DTNB: decision table naïve Bayes, BFT: best-first tree (BFTree), RF: random forest, DT: decision tree, *k*-NN:
331 *k*-nearest neighbours, LASSO: least absolute shrinkage and selection operator, GBM: gradient boosting machine, CIF:
332 conditional inference forests, CV: cross-validation, n/a: not applicable. *Study used a roughly equal 3-way split for predictor
333 selection, training and testing, where 10-fold CV was used in the training fold [42]. Splits were repeated, but reported AUCs
334 in the main text are for only one of the repeats; the study is recorded here as split-sample. *Number reported is unclear;
335 upper and lower bounds, or an approximation given by the authors in the text are used. Where insufficient information is
336 provided to give a reasonable approximation for predictors, NCR or NR is recorded. Imbalance refers to class imbalance,
337 given here as number of controls divided by number of cases in model development. Modification refers to whether a
338 classifier was used “out-of-the-box”, N, or was modified in some way, Y. Validation is *k*-fold CV, split-sample (Split),
339 apparent (App.) or external (Ext.). A single study reported internal validation (split-sample) and external validation (but
340 with partial sample overlap) [5]. Studies: a (Yang et al., 2010) [43], b (Ghafouri-Fard et al., 2019) [44], c (Aguar-Pulido et al.,

341 2010;2013) [45, 46], d (Wang et al., 2018) [7], e (Pirooznia et al., 2012) [6], f (Laksshman et al., 2017) [24], g (Acikel et al.,
 342 2016) [28], h (Li et al., 2014) [29], i (Guo et al., 2016) [42], j (Trakadis et al., 2019) [41], k (Engchuan et al., 2015) [47], l
 343 (Chen et al., 2018) [5], m (Vivian-Griffiths et al., 2019) [3].

344

345 Predictors

346 *Coding of predictors*

Coding	Studies	Models
Reported	6	35 (45%)
Continuous (weighted average of additive SNPs; PRS)	1	4
Counts of genes per gene set (CNV)	1	4
Counts of variants per gene (Exome)	1	4
Additive model (0, 1, 2), missing coded as 3 (SNP)	1	12
Z-transformation of additive model (0, 1, 2; SNP)	1	8
One-hot encoded (SNP)	1	3
Unclear/unreported	7	42 (55%)
Unclear ^a	2	3
Not reported	5	39

347

348 **Table S11:** coding of predictors. ^aCoding implied through description as 'ordinal' or through an abstract description of the
 349 type of classifier, but not clear.

350

351 *Information in predictors*

Method	Studies	Models
Additional knowledge used	9	49 (64%)
Predictors	8	43
Array not genome-wide	3	15

Predictors only from brain-expressed genes	1	8
Selection by p -value cut-off from external GWAS	1	8
Annotation of gene and variant-type	1	4
Annotation of gene and gene set	1	4
Choice of phenotypes and weights from GWAS for SZ-PRS	1	4
Modelling	1	6
Non-zero matrix weights in cRBM determined from GE data	1	6
Unclear/unreported	6	28 (36%)
Not clear	1	3
Not reported	5	25

352

353 **Table S12:** explicit use of additional knowledge in selecting or weighting of predictors and modelling. Implicit knowledge,
354 such as choice of a linear machine learning method, or additive encoding of genotyping data, are not included. GE: gene
355 expression, cBRM: conditional restricted Boltzmann machine.

356

357 *Predictor selection*

Type	Studies	Models
Filter	8	48 (62%)
Association test in external dataset, clumping	1	8
Association test in current dataset, clumping	1	8
Association test in current dataset for brain-expressed genes only, clumping	1	8
Association test in split of current dataset, p -value cut-off	1	3
Pruning, association test in current dataset, p -value cut-off	1	5
Embedded (LASSO/RF/GBM combined) ^a	1	4
Embedded (LASSO) with p -value cut-off	1	2

Forward sequential feature selection (FSFS) ^b	1	1
Correlation with outcome or intermediate phenotype	1	9
Embedded	8	20 (26%)
Regression (LASSO)	3	4
Tree-based	7	13
RF (including CIF)	4	8
Boosting (GBM, AdaBoost)	3	3
DT	2	2
Other	2	3
DTb	1	1
DTNB	1	1
Feature-selective AdaBoost ^c	1	1
Unclear ^d	1	3 (4%)
None reported	6	18 (23%)

358

359

Table S13: predictor selection technique. ^aTrakadis et al. (2019) report predictors being selected “in combination of”

360

embedded methods, but do not state how such methods were combined [41]. ^bFSFS is a wrapper on an embedded

361

method, used as a filter. ^cYang et al. (2010) modified AdaBoost to include univariable predictor selection within each

362

iteration before training each weak learner [43]; as the modification is within each iteration it is listed as “embedded”

363

here. This is counted once under feature-selective AdaBoost, and is not counted under ‘Boosting’. ^dLakshman et al. (2017)

364

report using “L1-based feature selection” but no indication about what method the L1-norm was applied to [24]. LASSO:

365

least absolute shrinkage and selection operator, RF: random forest, GBM: gradient-boosting machine, DTNB: decision

366

table-naïve Bayes, DTb: decision table, DT: decision tree, CIF: conditional inference forest. Several models exploited both

367

filter and embedded methods; these are counted in both sections.

368

Leakage handled appropriately?	Studies	Models
Yes/Probably Yes	7	44 (57%)
No/Probably No	7	32 (42%)
Predictor selection performed prior to cross-validation	2	7
Predictor transformed prior to cross-validation ^a	4	22
Prior knowledge in predictors generated from test set	1	4
DEV and VAL sets overlap	1	4
HP chosen by test-set/split performance	4	22
GRN from whole dataset used to set NN architecture	1	6
Unclear ^b	1	1 (1%)

369

370 **Table S14:** handling of information “leaks” during training. Where studies have multiple reasons for suspected leakage,
371 each of these is counted separately. If predictors were reduced to a set number before cross-validation was described, or a
372 transformation was not reported as having been done within a pipeline or for each fold of cross-validation, this is recorded
373 as ‘probably no’. ^aTransform includes anything that summarises information from the test set, such the mean of the whole
374 sample in a z-transformation. ^bPredictor handling implied, as scikit-learn is listed for pre-processing and preparation, but
375 no pre-processing steps are given [44]. DEV: development, VAL: validation, HP: hyperparameter, GRN: gene regulatory
376 network, NN: neural network.

377

378 [Hyperparameter search](#)

379

Search method for hyperparameters	Studies	Models
Search method reported	4	15 (19%)
Grid	1	1
Random	1	8
Manual	2	12
Bias variance decomposition	1	2
Default hyperparameters	1	16 (21%)

Search method unclear/unreported	9	46 (60%)
Not clearly reported ^a	2	8
Not reported	7	38

380

381

Table S15: hyperparameter search technique. ^aMethods reported clearly for other models in publications, but not made clear that the same methods apply to extracted models. One publication [3] used both manual and random elements for search, and is counted in both categories. Manual tuning by Chen et al. (2019) is implied through reported values which were attempted for hyperparameters, but not explicitly stated [5]. Hyperparameters searched systematically using a given set of values are denoted as grid search. If authors report attempting various hyperparameter choices but give no indication of systematic search or value choices, this is recorded as manual. Two studies (12 models) reported hyperparameters that were tuned but gave no indication of how this was done [7, 24]. A study (1 model) reported search methodology, but not what hyperparameters were tuned [43].

389

Method	Studies	Models
Reported	6	26 (34%)
SVM (RBF)		
C	2	9
Gamma	2	9
AdaBoost ^a		
Iterations	1	1
Neural Networks		
Epochs	2	12
Optimiser	1	4
Activation function	1	4
Layers	1	4
LASSO		
Lambda	1	1

Unclear/unreported	9	51 (66%)
Not clearly reported	2	5
Not reported	8	46

390

391

Table S16: hyperparameters tuned during model training. ^aFeature-selective AdaBoost [43]. Manual experiments with

392

different hyperparameters are presented by Engchuan et al. (2015) in the supplementary: these are included as “not

393

reported”, as they appear to be post-hoc experiments rather than a search as part of learning [47]. Several studies report

394

either hyperparameter search method, or the hyperparameters that were tuned, but not both (see Table S15). A study (16

395

models) used the default hyperparameters (Table S15) and is counted here under ‘not reported’ [6].

396

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