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Supplemental Data

ClinPred: Prediction Tool to Identify Disease-Relevant Nonsynonymous Single-Nucleotide Variants

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Supplemental figures

Figure S1

Figure S1: The performance of our models was compared against their constituting features and other available tools in ClinVarTest and MouseVariSNP. Analysis is based on the raw scores and was calculated for 5-fold cross validation.

Figure S2

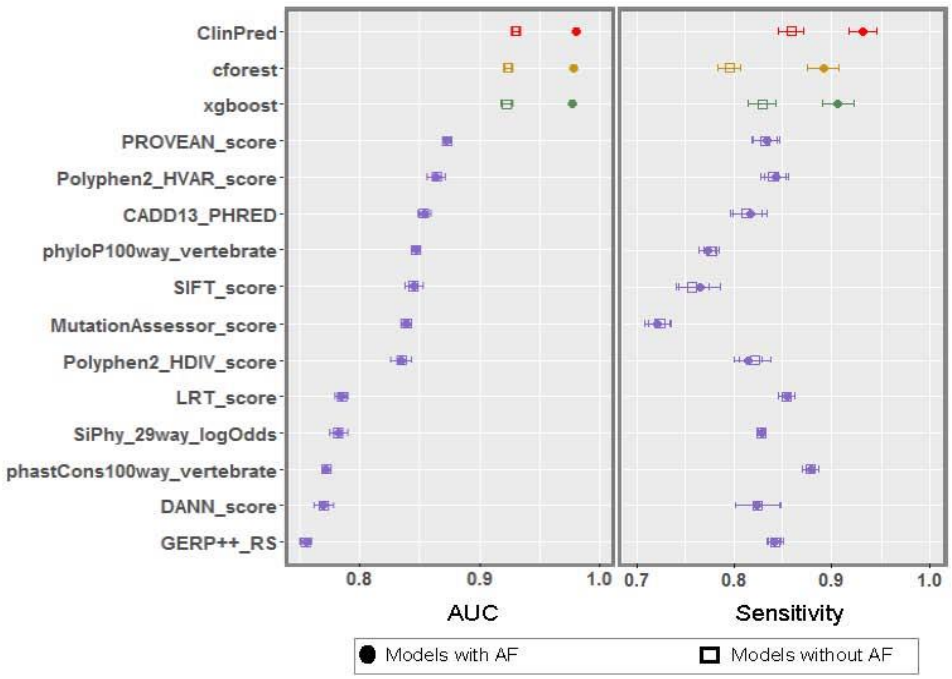

Figure S2: AF boost sensitivity and AUC score when applied as a feature in our models. We show mean AUC, mean sensitivity and error bars for 5-fold cross validation.

Figure S3

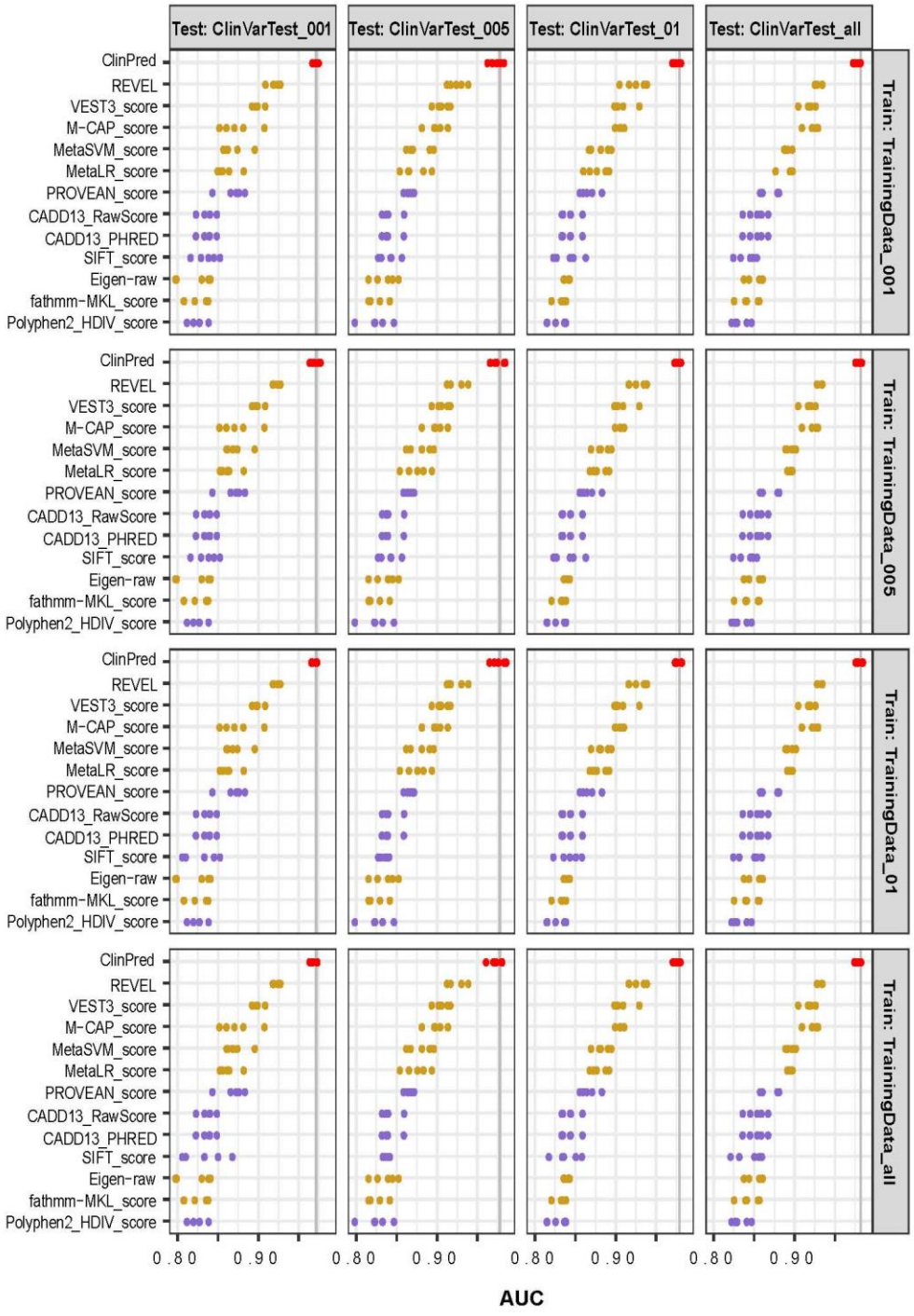

Figure S3: The performance of ClinPred was compared to recently developed and commonly used tools. We trained on our training data and tested our models on ClinVarTest using various AF cutoffs: whole data set regardless of AF, AF less than 0.01, less than 0.005 and less than 0.001. In all conditions, ClinPred was superior to other tools, achieving highest AUC score. Analysis is based on the raw scores and was calculated for 5-fold cross validation.

Figure S4

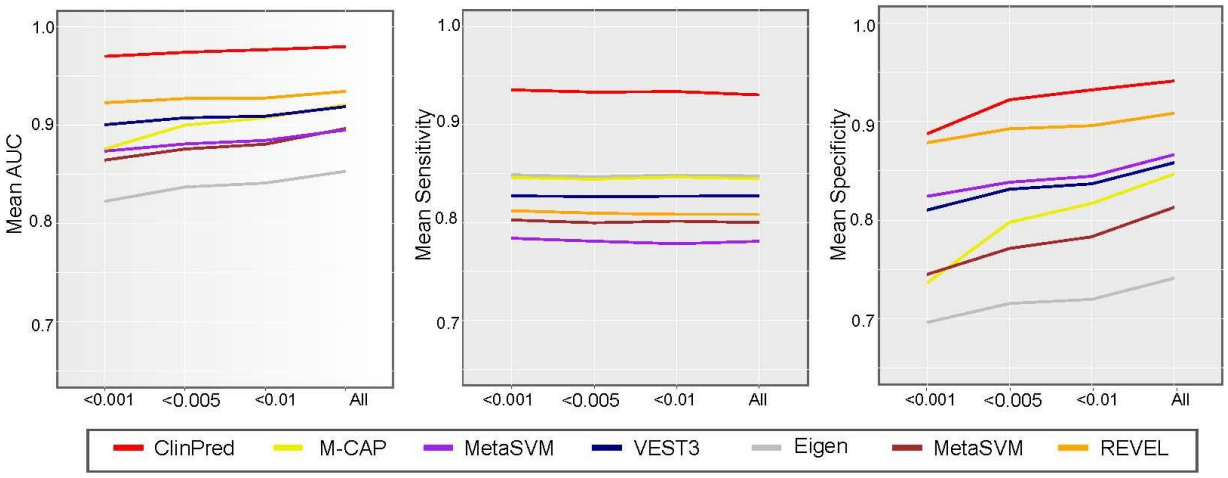

Figure S4: Performance of ClinPred was compared to recently developed ensemble tools. Models were trained on the training data and tested on ClinVarTest using various AF cutoffs: all data set regardless of AF, AF less than 0.01, less than 0.005 and less than 0.001. In all conditions, ClinPred was superior to other tools.

Figure S5

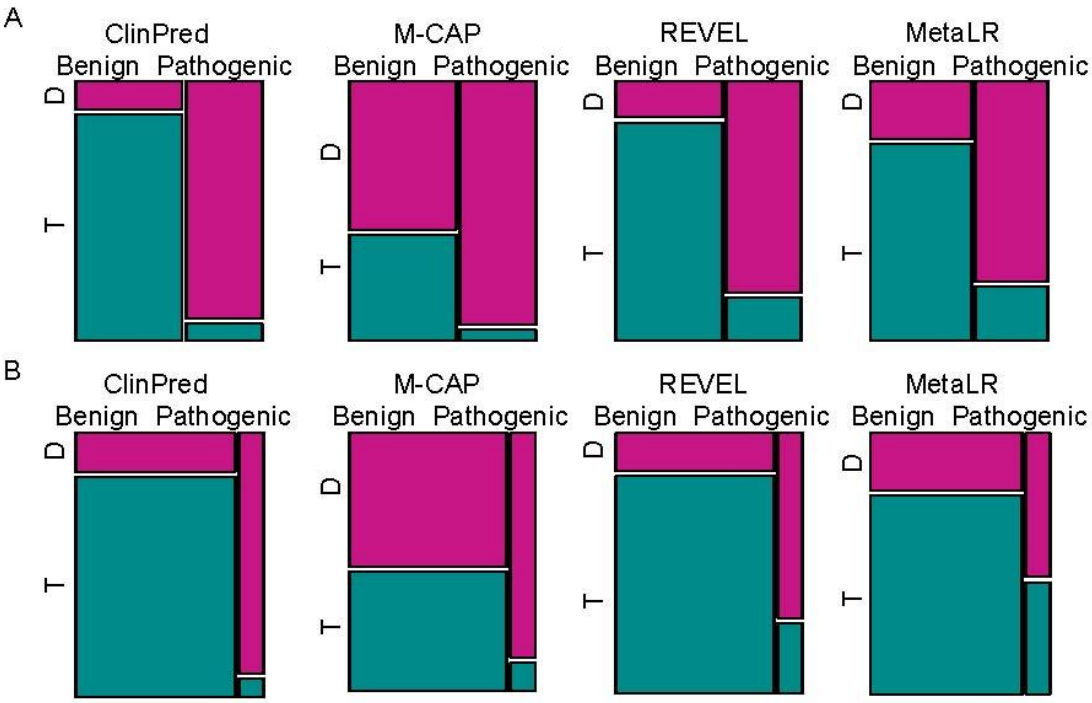

Figure S5: Comparison of ClinPred with categorical predictions available from M-CAP, REVEL, and MetaLR. REVEL and ClinPred scores lower than 0.5 are defined as tolerant and greater than 0.5 as damaging. We show proportions of benign and pathogenic variants that were classified as Tolerated (T, Green) and Damaging (D, Pink). ClinPred had the best performance in finding as many pathogenic variants possible while minimizing the number of benign variants that are predicted as damaging both in ClinVarTest with AF<0.01 (A) and MouseVariSNP with AF<0.01 (B).

Figure S6

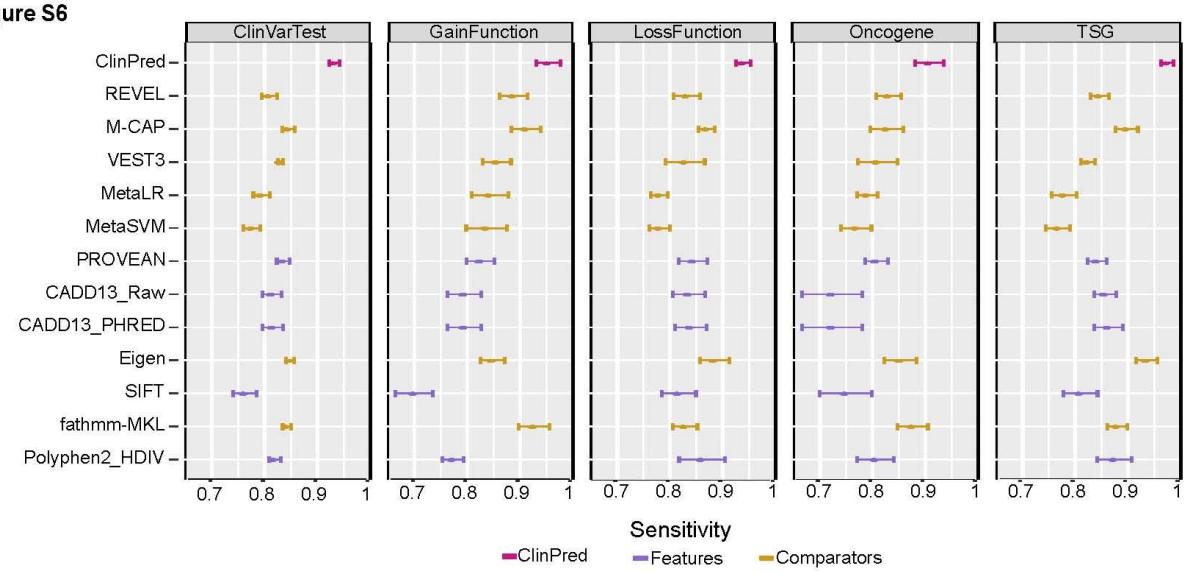

Figure S6: ClinPred performance remained robust across distinct datasets based on different genetic models and pathogenic mechanisms. We show mean sensitivity and error bars for 5-fold cross validation in all test datasets.

Figure S7

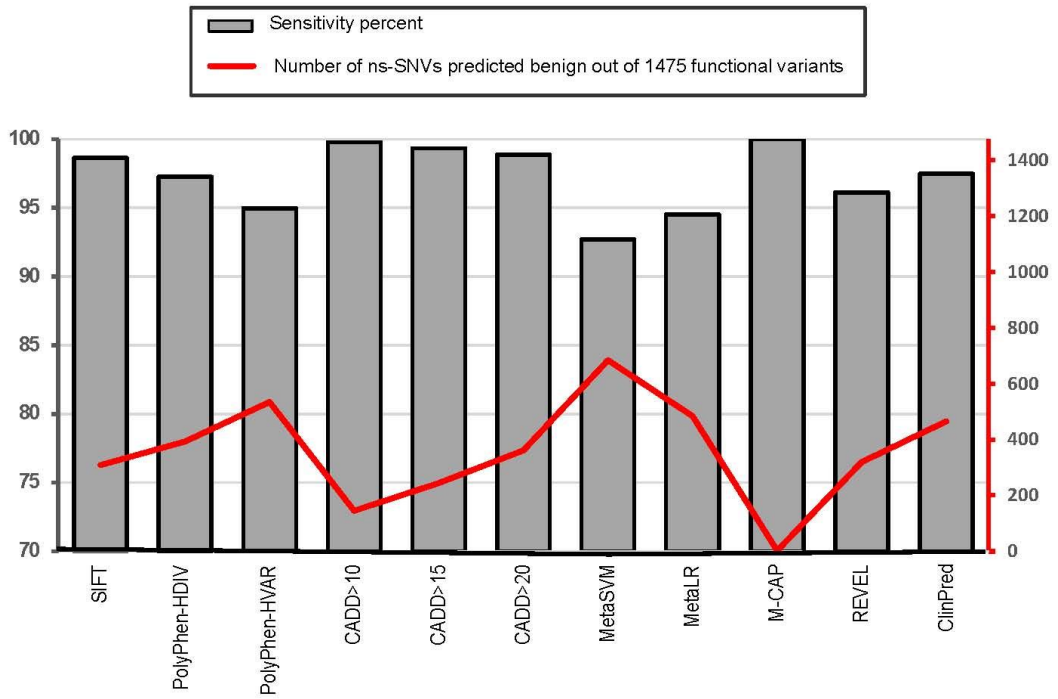

Figure S7: Illustration of performance of ClinPred as compared to other tools for functional assays scores of BRCA1 variants from Database of Functional Classifications of BRCA1. We show sensitivity of each tool to detect loss of function variants in comparison to number of nonsynonymous variants predicted as benign among 1464 functional variants in this database.

Supplemental tables

Table S1: Description of datasets

Data		Total variants	Benign	Pathogenic
Training data		11082	7059	4023
Test data	ClinVar Test	5759	4169	1590
	MouseVariSNP	1897	1680	217
	DoCM	1189	0	1189
	LossFunction	1066	776	290
	GainFunction	293	160	133
	Oncogene	354	242	112
	TSG	635	475	160

Table S2: Overview of performance of ClinPred in comparison to raw scores of other tools in ClinVarTest

model	sensitivity	specificity	FPR	accuracy	precision	error.percent	F1 score	MCC
ClinPred	0.94	0.94	0.06	0.94	0.86	6.04	0.90	0.85
xgboost	0.91	0.95	0.05	0.94	0.87	6.42	0.89	0.84
cforest	0.89	0.97	0.03	0.95	0.91	5.49	0.90	0.86
VEST3_score	0.83	0.84	0.16	0.84	0.66	16.48	0.73	0.62
MetaSVM_score	0.78	0.85	0.15	0.83	0.67	16.84	0.72	0.60
MetaLR_score	0.80	0.80	0.20	0.80	0.60	20.18	0.69	0.55
M-CAP_score	0.84	0.36	0.64	0.50	0.34	50.36	0.48	0.20
fathmm-MKL_score	0.84	0.69	0.31	0.73	0.51	26.53	0.64	0.48
Eigen-raw	0.76	0.74	0.26	0.74	0.53	25.58	0.62	0.45
REVEL	0.82	0.89	0.11	0.87	0.74	13.20	0.77	0.68

FPR: False positive rate
MCC: Matthews correlation coefficient

Table S3: Overview of performance of ClinPred in comparison to raw scores of other models in MouseVariSNP test

model	sensitivity	specificity	FPR	accuracy	precision	error.percent	F1 score	MCC
ClinPred	0.93	0.88	0.12	0.89	0.50	11.44	0.65	0.63
xgboost	0.91	0.89	0.11	0.89	0.51	11.02	0.65	0.63
cforest	0.88	0.92	0.08	0.92	0.60	8.07	0.72	0.69
VEST3_score	0.86	0.78	0.22	0.79	0.34	20.98	0.48	0.45
MetaSVM_score	0.58	0.81	0.19	0.79	0.29	21.24	0.38	0.30
MetaLR_score	0.58	0.75	0.25	0.73	0.23	26.73	0.33	0.23
M-CAP_score	0.66	0.61	0.39	0.62	0.18	37.95	0.29	0.18
fathmm-MKL_score	0.75	0.68	0.32	0.69	0.23	31.15	0.36	0.28
Eigen-raw	0.76	0.73	0.27	0.73	0.27	26.67	0.40	0.34
REVEL	0.71	0.87	0.13	0.86	0.42	14.50	0.53	0.47

FPR: False positive rate
MCC: Matthews correlation coefficient

Table S4: Overview of performance of ClinPred in comparison to categorical scores of other tools in MouseVariSNP test.

	Sensitivity %	Specificity %	FPR	Accuracy	Precision	Error Percent	F1 Score	MCC
ClinPred	92.63	88.04	0.12	0.89	0.50	11.44	0.65	0.63
xgboost	91.24	88.69	0.11	0.89	0.51	11.02	0.65	0.63
cforest	88.48	92.38	0.08	0.92	0.60	8.07	0.72	0.69
REVEL	71.43	86.65	0.13	0.85	0.41	15.09	0.52	0.46
M-CAP	88.73	47.20	0.53	0.53	0.21	47.16	0.34	0.25
MetaLR	56.28	79.25	0.21	0.77	0.26	23.36	0.35	0.26
Fathmm_mkl	91.16	38.92	0.61	0.45	0.16	55.15	0.27	0.20

FPR: False positive rate
MCC: Matthews correlation coefficient

Table S5: Overview of performance of ClinPred in comparison to categorical scores of other tools in DoCM test.

	NA/Pathogenic	TPR sensitivity	FNR
cforest	0	0.89	0.10
xgboost	0	0.91	0.08
ClinPred	0	0.94	0.05
REVEL	0	0.83	0.16
M-CAP	12	0.95	0.04
MetaLR	0	0.67	0.32
Fathmm_mkl	0	0.97	0.02

NA/pathogenic: Number of pathogenic variants with missing data
TPR: True positive rate
FNR: False negative rate