

Additional file 21: Top 5 mutation effect prediction algorithm combinations ranked by either accuracy or composite score separately for subsets 1 and 2 using all 989 single nucleotide variants for which functional data are available and the corresponding best performing single and meta-predictors.

	Ranking	Mutation effect prediction algorithm combination	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Composite score (95% CI)
Subset 1	By accuracy	At least 1 of CHASM (breast), MutationTaster	95.46% (94.54%-96.51%)	99.88% (99.82%-100%)	68.61% (63.09%-74.73%)	95.07% (94.11%-96.13%)	98.98% (98.25%-100%)	3.6255 (3.5584-3.6982)
		At least 2 of CHASM (breast), CHASM (lung), MutationTaster, SIFT	95.16% (94.23%-96.21%)	99.07% (98.59%-99.48%)	71.47% (66%-77%)	95.47% (94.54%-96.48%)	92.69% (89.39%-96.05%)	3.5870 (3.5056-3.6697)
		At least 2 of CHASM (breast), CHASM (lung), Mutation Assessor, MutationTaster	95.08% (94.23%-96.05%)	98.49% (98.01%-99.12%)	74.36% (69.23%-79.78%)	95.89% (94.99%-96.91%)	89.04% (85.19%-93.33%)	3.5777 (3.4957-3.6589)
		At least 1 of CHASM (breast), CHASM (lung), MutationTaster	94.95% (93.93%-96.05%)	99.88% (99.82%-100%)	64.99% (59.3%-70.84%)	94.54% (93.49%-95.67%)	98.93% (98.11%-100%)	3.5834 (3.5144-3.6572)
		At least 1 of CHASM (lung), MutationTaster	94.95% (93.93%-96.05%)	99.88% (99.82%-100%)	64.99% (59.3%-70.84%)	94.54% (93.49%-95.67%)	98.93% (98.11%-100%)	3.5834 (3.5144-3.6572)
		FATHMM (cancer) [best single predictor]	91% (89.18%-92.62%)	97.88% (96.87%-98.82%)	49.29% (41.08%-57.24%)	92.13% (90.26%-93.72%)	79.31% (70.59%-87.66%)	3.1860 (3.0326-3.3292)
		CanDrA (lung) [best meta-predictor]	91.28% (89.54%-93.04%)	92.86% (91.05%-94.62%)	80.95% (73.64%-87.32%)	96.97% (95.75%-98.03%)	63.35% (56.1%-71.01%)	3.3413 (3.2103-3.4747)
	By composite score	At least 1 of CHASM (breast), MutationTaster	95.46% (94.54%-96.51%)	99.88% (99.82%-100%)	68.61% (63.09%-74.73%)	95.07% (94.11%-96.13%)	98.98% (98.25%-100%)	3.6255 (3.5584-3.6982)
		At least 2 of CHASM (breast), CHASM (lung), MutationTaster, SIFT	95.16% (94.23%-96.21%)	99.07% (98.59%-99.48%)	71.47% (66%-77%)	95.47% (94.54%-96.48%)	92.69% (89.39%-96.05%)	3.5870 (3.5056-3.6697)
		At least 1 of CHASM (breast), CHASM (lung), MutationTaster	94.95% (93.93%-96.05%)	99.88% (99.82%-100%)	64.99% (59.3%-70.84%)	94.54% (93.49%-95.67%)	98.93% (98.11%-100%)	3.5834 (3.5144-3.6572)
		At least 1 of CHASM (lung), MutationTaster	94.95% (93.93%-96.05%)	99.88% (99.82%-100%)	64.99% (59.3%-70.84%)	94.54% (93.49%-95.67%)	98.93% (98.11%-100%)	3.5834 (3.5144-3.6572)
		At least 2 of CHASM (breast), CHASM (lung), Mutation Assessor, MutationTaster	95.08% (94.23%-96.05%)	98.49% (98.01%-99.12%)	74.36% (69.23%-79.78%)	95.89% (94.99%-96.91%)	89.04% (85.19%-93.33%)	3.5777 (3.4957-3.6589)
		CHASM (lung) [best single predictor]	90.09% (88.27%-91.81%)	92.23% (90.4%-94.04%)	77.14% (69.93%-83.58%)	96.07% (94.74%-97.31%)	62.07% (54.72%-69.38%)	3.2751 (3.1418-3.3988)
		CanDrA (lung) [best meta-predictor]	91.28% (89.54%-93.04%)	92.86% (91.05%-94.62%)	80.95% (73.64%-87.32%)	96.97% (95.75%-98.03%)	63.35% (56.1%-71.01%)	3.3413 (3.2103-3.4747)
Subset 2	By accuracy	At least 1 of CHASM (breast), MutationTaster	95.43% (93.33%-97.27%)	99.88% (99.64%-100%)	68.5% (57.14%-79.55%)	95.05% (92.95%-96.98%)	98.93% (96.15%-100%)	3.6236 (3.4841-3.7573)
		At least 2 of CHASM (breast), CHASM (lung), MutationTaster, SIFT	95.11% (93.03%-96.97%)	99.03% (98.18%-100%)	71.35% (60%-82%)	95.44% (93.38%-97.29%)	92.42% (85.29%-100%)	3.5825 (3.4147-3.7387)
		At least 2 of CHASM (breast), CHASM (lung), Mutation Assessor, MutationTaster	94.98% (93.03%-96.67%)	98.42% (97.16%-99.33%)	74.13% (64%-84.62%)	95.84% (93.77%-97.61%)	88.58% (80%-96.02%)	3.5699 (3.4077-3.7313)
		At least 1 of CHASM (breast), CHASM (lung), MutationTaster	94.94% (92.73%-96.97%)	99.88% (99.64%-100%)	65.05% (53.19%-76.6%)	94.54% (92.26%-96.64%)	98.87% (96%-100%)	3.5834 (3.4389-3.7270)
		At least 1 of CHASM (lung), MutationTaster	94.94% (92.73%-96.97%)	99.88% (99.64%-100%)	65.05% (53.19%-76.6%)	94.54% (92.26%-96.64%)	98.87% (96%-100%)	3.5834 (3.4389-3.7270)
		FATHMM (cancer) [best single predictor]	91% (89.18%-92.62%)	97.88% (96.87%-98.82%)	49.29% (41.08%-57.24%)	92.13% (90.26%-93.72%)	79.31% (70.59%-87.66%)	3.1860 (3.0326-3.3292)
		CanDrA (lung) [best meta-predictor]	91.28% (89.54%-93.04%)	92.86% (91.05%-94.62%)	80.95% (73.64%-87.32%)	96.97% (95.75%-98.03%)	63.35% (56.1%-71.01%)	3.3413 (3.2103-3.4747)
	By composite score	At least 1 of CHASM (breast), MutationTaster	95.43% (93.33%-97.27%)	99.88% (99.64%-100%)	68.5% (57.14%-79.55%)	95.05% (92.95%-96.98%)	98.93% (96.15%-100%)	3.6236 (3.4841-3.7573)
		At least 1 of CHASM (breast), CHASM (lung), MutationTaster	94.94% (92.73%-96.97%)	99.88% (99.64%-100%)	65.05% (53.19%-76.6%)	94.54% (92.26%-96.64%)	98.87% (96%-100%)	3.5834 (3.4389-3.7270)
		At least 1 of CHASM (lung), MutationTaster	94.94% (92.73%-96.97%)	99.88% (99.64%-100%)	65.05% (53.19%-76.6%)	94.54% (92.26%-96.64%)	98.87% (96%-100%)	3.5834 (3.4389-3.7270)
		At least 2 of CHASM (breast), CHASM (lung), MutationTaster, SIFT	95.11% (93.03%-96.97%)	99.03% (98.18%-100%)	71.35% (60%-82%)	95.44% (93.38%-97.29%)	92.42% (85.29%-100%)	3.5825 (3.4147-3.7387)
		At least 2 of CHASM (breast), CHASM (lung), Mutation Assessor, MutationTaster	94.98% (93.03%-96.67%)	98.42% (97.16%-99.33%)	74.13% (64%-84.62%)	95.84% (93.77%-97.61%)	88.58% (80%-96.02%)	3.5699 (3.4077-3.7313)
		CHASM (lung) [best single predictor]	90.09% (88.27%-91.81%)	92.23% (90.4%-94.04%)	77.14% (69.93%-83.58%)	96.07% (94.74%-97.31%)	62.07% (54.72%-69.38%)	3.2751 (3.1418-3.3988)
		CanDrA (lung) [best meta-predictor]	91.28% (89.54%-93.04%)	92.86% (91.05%-94.62%)	80.95% (73.64%-87.32%)	96.97% (95.75%-98.03%)	63.35% (56.1%-71.01%)	3.3413 (3.2103-3.4747)