S1. EGFR Pareto Frontier

Table S1: All RESISTOR resistance mutation predictions for EGFR with erlotinib. "Pos" is the position of the residue. "WT AA" is the wildtype identity of the amino acid. "Mut AA" is the resistance mutation. "Sig Prob" is the mutational signature probability for the mutation from "WT AA" to "Mut AA" in lung adenocarcinoma. "ATP WT" and "ATP Mut" are the K^* scores of the endogenous ligand with the wildtype and mutant residues, respectively. "Drug WT" and "Drug Mut" are the K^* scores of erlotinib with the wildtype and mutant residues, respectively. "Count" is number of resistance mutations at the position. "Rank" is the Pareto rank of the mutation. Note: K^* scores are in $\log_{10}$ units where possible and 0 where there is predicted to be no binding. The complete set of inputs used for the Pareto ranking can be found in Data S1.

Pos	WT AA	Mut AA	Sig Prob	ATP WT	ATP Mut	Drug WT	Drug Mut	Count	Rank
718	LEU	PHE	0.000247	19.05	17.16	25.26	0	8	1
718	LEU	HIP	0.00042	19.05	18.86	25.26	-62.44	8	1
718	LEU	HIE	0.00042	19.05	18.92	25.26	-61.9	8	1
723	PHE	VAL	0.000316	19.06	19.14	25.20	0	5	1
723	PHE	LEU	0.00827	19.06	19.05	25.20	0	5	1
726	VAL	PHE	0.000509	19.04	19.71	25.24	0	2	1
743	ALA	ASP	0.0109	19.14	13.51	25.22	0	4	1
790	THR	LYS	0.00738	19.14	19.54	25.17	22.01	4	1
790	THR	MET	0.00602	19.14	19.79	25.17	23.89	4	1
791	GLN	PRO	0.0023	19.12	19.22	25.19	0	3	1
791	GLN	LYS	0.0163	19.12	19.1	25.19	0	3	1
796	GLY	TRP	2.06E-05	18.99	19.13	25.42	0	12	1
796	GLY	LEU	4.41E-05	18.99	19.55	25.42	-25.46	12	1
796	GLY	GLU	0.000154	18.99	18.88	25.42	1.16	12	1
796	GLY	PHE	0.000176	18.99	19.48	25.42	4.68	12	1
796	GLY	ARG	0.00286	18.99	19.54	25.42	9.36	12	1
796	GLY	ASP	0.00532	18.99	19.15	25.42	18.29	12	1
796	GLY	CYS	0.00384	18.99	19.28	25.42	21.71	12	1
796	GLY	SER	0.00643	18.99	19.23	25.42	22.24	12	1
718	LEU	GLY	8.49E-06	19.05	18.15	25.26	0	8	2
718	LEU	TRP	1.75E-05	19.05	17.96	25.26	0	8	2
718	LEU	HID	0.00042	19.05	18.9	25.26	-60.92	8	2
718	LEU	ARG	0.00238	19.05	19.41	25.26	22.5	8	2
726	VAL	TRP	4.82E-05	19.04	19.51	25.24	0	2	2
745	LYS	ILE	0.000243	18.98	19.05	25.18	0	5	2
745	LYS	MET	0.00516	18.98	18.97	25.18	0	5	2
790	THR	ARG	0.00139	19.14	19.32	25.17	11.4	4	2
791	GLN	GLY	1.81E-05	19.12	19.06	25.19	0	3	2
796	GLY	TYR	4.34E-05	18.99	19.48	25.42	-13.32	12	2
796	GLY	ASN	5.25E-05	18.99	19.36	25.42	21	12	2
796	GLY	HIE	1.88E-05	18.99	19.55	25.42	23.68	12	2
800	ASP	GLY	0.00153	19.06	19.13	25.21	0	1	2
718	LEU	LYS	0.00027	19.05	19.22	25.26	22.98	8	3
723	PHE	ASP	8.41E-07	19.06	18.98	25.20	0	5	3
745	LYS	HIE	6.76E-05	18.98	18.85	25.18	0	5	3
745	LYS	THR	0.00126	18.98	18.71	25.18	0	5	3
790	THR	ASN	0.000219	19.14	19.16	25.17	21.87	4	3
793	MET	ASN	0.000104	19.04	18.93	25.16	0	1	3

Pos	WT AA	Mut AA	Sig Prob	ATP WT	ATP Mut	Drug WT	Drug Mut	Count	Rank
796	GLY	THR	3.45E-05	18.99	19.28	25.42	16.88	12	3
844	LEU	TRP	1.9E-05	18.99	19.02	25.45	-17.34	4	3
844	LEU	HID	0.00042	18.99	18.8	25.45	22.65	4	3
844	LEU	HIE	0.00042	18.99	18.74	25.45	22.63	4	3
854	THR	ASN	0.000262	19.01	19.09	25.43	21.08	1	3
723	PHE	ALA	5.72E-07	19.06	18.98	25.20	0	5	4
723	PHE	GLY	5.92E-07	19.06	18.91	25.20	0	5	4
743	ALA	CYS	7.34E-05	19.14	14.53	25.22	0	4	4
743	ALA	GLU	7.74E-05	19.14	4.17	25.22	0	4	4
745	LYS	HID	6.76E-05	18.98	18.81	25.18	0	5	4
844	LEU	HIP	0.00042	18.99	18.57	25.45	22.42	4	4
743	ALA	ARG	1.73E-05	19.14	6.55	25.22	0	4	5

Table S2: All RESISTOR resistance mutation predictions for EGFR with gefitinib. "Pos" is the position of the residue. "WT AA" is the wildtype identity of the amino acid. "Mut AA" is the resistance mutation. "Sig Prob" is the mutational signature probability for the mutation from "WT AA" to "Mut AA" in lung adenocarcinoma. "ATP WT" and "ATP Mut" are the K^* scores of the endogenous ligand with the wildtype and mutant residues, respectively. "Drug WT" and "Drug Mut" are the K^* scores of gefitinib with the wildtype and mutant residues, respectively. "Count" is number of resistance mutations at the position. "Rank" is the Pareto rank of the mutation. Note: K^* scores are in $\log_{10}$ units where possible and 0 where there is predicted to be no binding. The complete set of inputs used for the Pareto ranking can be found in Data S2.

Pos	WT AA	Mut AA	Sig Prob	ATP WT	ATP Mut	Drug WT	Drug Mut	Count	Rank
718	LEU	PHE	0.000247	19.05	17.16	26.94	-23.15	7	1
718	LEU	TRP	1.75E-05	19.05	17.96	26.94	1.76	7	1
718	LEU	HIP	0.00042	19.05	18.86	26.94	4.5	7	1
718	LEU	HID	0.00042	19.05	18.9	26.94	4.92	7	1
718	LEU	HIE	0.00042	19.05	18.92	26.94	4.99	7	1
718	LEU	ARG	0.00238	19.05	19.41	26.94	23.69	7	1
743	ALA	GLU	7.74E-05	19.14	4.17	26.93	-49.27	2	1
777	LEU	HID	0.000281	19.05	19.04	26.86	0	1	1
790	THR	ARG	0.00139	19.14	19.32	26.95	12.73	4	1
790	THR	LYS	0.00738	19.14	19.54	26.95	23.21	4	1
790	THR	MET	0.00602	19.14	19.79	26.95	25.06	4	1
796	GLY	LEU	4.41E-05	18.99	19.55	26.88	22.57	1	1
844	LEU	TRP	1.9E-05	18.99	19.02	26.97	-28.99	4	1
718	LEU	LYS	0.00027	19.05	19.22	26.94	24.45	7	2
726	VAL	PHE	0.000509	19.04	19.71	26.94	25.26	1	2
743	ALA	ARG	1.73E-05	19.14	6.55	26.93	-4.31	2	2
745	LYS	ILE	0.000243	18.98	19.05	26.88	16.99	1	2
790	THR	ASN	0.000219	19.14	19.16	26.95	23.52	4	2
844	LEU	HIP	0.00042	18.99	18.57	26.97	23.69	4	2
844	LEU	HID	0.00042	18.99	18.8	26.97	23.97	4	2
844	LEU	HIE	0.00042	18.99	18.74	26.97	23.94	4	2
854	THR	ASN	0.000262	19.01	19.09	26.98	20.61	1	2

Table S3: All RESISTOR resistance mutation predictions for EGFR with osimertinib. "Pos" is the position of the residue. "WT AA" is the wildtype identity of the amino acid. "Mut AA" is the resistance mutation. "Sig Prob" is the mutational signature probability for the mutation from "WT AA" to "Mut AA" in lung adenocarcinoma. "ATP WT" and "ATP Mut" are the K^* scores of the endogenous ligand with the wildtype and mutant residues, respectively. "Drug WT" and "Drug Mut" are the K^* scores of osimertinib with the wildtype and mutant residues, respectively. "Count" is number of resistance mutations at the position. "Rank" is the Pareto rank of the mutation. Note: K^* scores are in $\log_{10}$ units where possible and 0 where there is predicted to be no binding. The complete set of inputs used for the Pareto ranking can be found in Data S3.

Pos	WT AA	Mut AA	Sig Prob	ATP WT	ATP Mut	Drug WT	Drug Mut	Count	Rank
718	LEU	TRP	1.75E-05	19.05	17.96	27.51	0	9	1
718	LEU	PHE	0.000247	19.05	17.16	27.51	0	9	1
718	LEU	HIP	0.00042	19.05	18.86	27.51	-38.77	9	1
718	LEU	HIE	0.00042	19.05	18.92	27.51	-38.57	9	1
718	LEU	MET	0.0108	19.05	19.44	27.51	25.52	9	1
719	GLY	VAL	0.017	19.05	14.7	27.50	20.75	2	1
726	VAL	TRP	4.82E-05	19.04	19.51	27.48	0	3	1
743	ALA	ASP	0.0109	19.14	13.51	27.43	17.5	3	1
796	GLY	TRP	2.06E-05	18.99	19.13	27.38	-97.39	14	1
796	GLY	TYR	4.34E-05	18.99	19.48	27.38	-61.59	14	1
796	GLY	PHE	0.000176	18.99	19.48	27.38	-41.78	14	1
796	GLY	LEU	4.41E-05	18.99	19.55	27.38	-3.75	14	1
796	GLY	ARG	0.00286	18.99	19.54	27.38	10.61	14	1
796	GLY	ASP	0.00532	18.99	19.15	27.38	14.96	14	1
796	GLY	CYS	0.00384	18.99	19.28	27.38	21.85	14	1
796	GLY	SER	0.00643	18.99	19.23	27.38	24.76	14	1
718	LEU	HID	0.00042	19.05	18.9	27.51	-37.61	9	2
718	LEU	ARG	0.00238	19.05	19.41	27.51	20.16	9	2
723	PHE	ILE	0.00209	19.06	19.5	27.45	25.68	1	2
792	LEU	HIP	0.00486	19.03	18.88	27.47	24.98	3	2
792	LEU	HIE	0.00486	19.03	18.93	27.47	25.07	3	2
792	LEU	HID	0.00486	19.03	18.98	27.47	25.15	3	2
796	GLY	GLU	0.000154	18.99	18.88	27.38	2.49	14	2
796	GLY	HIE	1.88E-05	18.99	19.55	27.38	11.32	14	2
796	GLY	ASN	5.25E-05	18.99	19.36	27.38	18.38	14	2
718	LEU	LYS	0.00027	19.05	19.22	27.51	24.7	9	3
719	GLY	THR	4.02E-05	19.05	17.76	27.50	20.4	2	3
726	VAL	ARG	2.32E-05	19.04	17.68	27.48	21.62	3	3
726	VAL	LYS	5.39E-05	19.04	17.07	27.48	21.87	3	3
743	ALA	GLU	7.74E-05	19.14	4.17	27.43	0.47	3	3
796	GLY	HID	1.88E-05	18.99	19.49	27.38	11.69	14	3
796	GLY	THR	3.45E-05	18.99	19.28	27.38	22.43	14	3
844	LEU	TRP	1.9E-05	18.99	19.02	27.56	22.12	1	3
796	GLY	HIP	1.88E-05	18.99	19.46	27.38	12.09	14	4
718	LEU	GLY	8.49E-06	19.05	18.15	27.51	24.02	9	5
743	ALA	ARG	1.73E-05	19.14	6.55	27.43	12.58	3	5

S2. BRAF Pareto Frontier

Table S4: All RESISTOR resistance mutation predictions for BRAF with dabrafenib. "Pos" is the position of the residue. "WT AA" is the wildtype identity of the amino acid. "Mut AA" is the resistance mutation. "Sig Prob" is the mutational signature probability for the mutation from "WT AA" to "Mut AA" in melanoma. "ATP WT" and "ATP Mut" are the K^* scores of the endogenous ligand with the wildtype and mutant residues, respectively. "Drug WT" and "Drug Mut" are the K^* scores of dabrafenib with the wildtype and mutant residues, respectively. "Count" is number of resistance mutations at the position. "Rank" is the Pareto rank of the mutation. Note: K^* scores are in $\log_{10}$ units where possible and 0 where there is predicted to be no binding. The complete set of inputs used for the Pareto ranking can be found in Data S4.

Pos	WT AA	Mut AA	Sig Prob	ATP WT	ATP Mut	Drug WT	Drug Mut	Count	Rank
466	GLY	ARG	5.84E-02	18.80	10.53	37.16	-167.92	11	1
466	GLY	LYS	2.38E-02	18.80	11.79	37.16	-52.4	11	1
466	GLY	GLU	2.19E-01	18.80	12.89	37.16	21.32	11	1
471	VAL	LEU	4.43E-04	18.65	19.67	37.26	25.1	6	1
508	THR	ARG	2.95E-04	18.59	18.59	37.23	-118.81	4	1
535	SER	PRO	1.30E-03	18.72	18.65	37.26	0	1	1
593	GLY	PHE	1.99E-06	18.66	20.07	37.17	0	16	1
593	GLY	TYR	3.58E-05	18.66	19.86	37.17	0	16	1
593	GLY	ARG	7.80E-04	18.66	16.17	37.17	0	16	1
593	GLY	GLU	2.76E-04	18.66	18.73	37.17	-60.32	16	1
593	GLY	ASN	1.34E-03	18.66	19.16	37.17	-39.82	16	1
593	GLY	ASP	1.63E-02	18.66	18.89	37.17	-29.79	16	1
593	GLY	CYS	1.66E-03	18.66	19.06	37.17	17.46	16	1
593	GLY	VAL	9.35E-04	18.66	19.18	37.17	28.45	16	1
593	GLY	ILE	4.55E-05	18.66	19.8	37.17	30.24	16	1
593	GLY	SER	6.09E-02	18.66	18.83	37.17	34.27	16	1
466	GLY	GLN	7.24E-05	18.80	12.55	37.16	11.37	11	2
466	GLY	ASP	7.51E-04	18.80	17.06	37.16	18.64	11	2
466	GLY	VAL	2.51E-03	18.80	13.44	37.16	29.23	11	2
467	SER	PRO	7.37E-04	18.62	18.85	37.15	30.42	1	2
481	ALA	LYS	2.74E-04	18.58	17.32	36.98	-4.22	8	2
481	ALA	LEU	7.06E-05	18.58	18.68	36.98	9.97	8	2
481	ALA	GLU	1.21E-03	18.58	17.92	36.98	22.11	8	2
505	LEU	ARG	8.61E-04	18.59	18.58	36.85	16.53	5	2
508	THR	LYS	9.16E-04	18.59	18.59	37.23	27.22	4	2
514	LEU	ARG	5.22E-05	18.57	17.18	37.10	21.32	12	2
514	LEU	ILE	1.65E-03	18.57	18.4	37.10	32.55	12	2
529	THR	PHE	3.77E-05	18.58	15.91	36.99	-125.31	11	2
529	THR	MET	1.74E-05	18.58	18.65	36.99	-8.16	11	2
529	THR	ASN	9.96E-04	18.58	18.55	36.99	34.54	11	2
593	GLY	HIE	1.66E-05	18.66	19.58	37.17	0	16	2
593	GLY	THR	2.67E-05	18.66	19.06	37.17	27.33	16	2
464	GLY	GLN	7.24E-05	18.58	2.95	37.09	11.05	1	3
466	GLY	THR	5.47E-05	18.80	14.85	37.16	29.21	11	3
481	ALA	ILE	5.14E-05	18.58	14.2	36.98	21.38	8	3
481	ALA	VAL	1.46E-03	18.58	17.77	36.98	33.45	8	3
505	LEU	SER	2.78E-05	18.59	18.58	36.85	35.02	5	3
514	LEU	PRO	1.21E-03	18.57	18.12	37.10	33.34	12	3

Pos	WT AA	Mut AA	Sig Prob	ATP WT	ATP Mut	Drug WT	Drug Mut	Count	Rank
527	ILE	LEU	6.37E-05	18.60	18.61	37.30	33.5	1	3
593	GLY	HIP	1.66E-05	18.66	19.56	37.17	0	16	3
514	LEU	SER	2.27E-04	18.57	18.1	37.10	34.19	12	4
593	GLY	HID	1.66E-05	18.66	19.55	37.17	0	16	4
471	VAL	MET	8.44E-06	18.65	18.96	37.26	27.83	6	5
481	ALA	ARG	1.53E-05	18.58	17.02	36.98	-15.13	8	5
481	ALA	ASP	4.39E-06	18.58	19.21	36.98	31.9	8	5
508	THR	GLU	1.05E-05	18.59	18.59	37.23	35	4	5
514	LEU	PHE	1.53E-05	18.57	18.19	37.10	0	12	5
578	LYS	TYR	5.24E-06	18.55	18.39	37.11	-143.76	1	5
593	GLY	TRP	4.78E-06	18.66	18.83	37.17	0	16	5
593	GLY	LEU	3.87E-07	18.66	19.35	37.17	-85.52	16	5
466	GLY	PRO	1.77E-07	18.80	18.27	37.16	0	11	6
466	GLY	TRP	2.10E-06	18.80	13.1	37.16	0	11	6
466	GLY	LEU	4.82E-06	18.80	9.74	37.16	-39.41	11	6
466	GLY	CYS	3.82E-06	18.80	17.62	37.16	27.45	11	6
469	GLY	PRO	1.77E-07	18.60	18.75	37.10	0	1	6
471	VAL	PRO	5.74E-07	18.65	17.88	37.26	0	6	6
471	VAL	ARG	3.03E-07	18.65	18.99	37.26	23.05	6	6
471	VAL	GLU	9.01E-07	18.65	18.82	37.26	31.61	6	6
481	ALA	GLN	1.80E-06	18.58	18.37	36.98	15.47	8	6
508	THR	GLN	2.51E-06	18.59	18.59	37.23	33.59	4	6
513	ILE	ARG	1.06E-06	18.57	18.57	37.09	-30.17	2	6
513	ILE	TYR	2.73E-06	18.57	18.57	37.09	27.86	2	6
514	LEU	HIP	3.37E-07	18.57	17.68	37.10	25.98	12	6
514	LEU	HID	3.37E-07	18.57	17.72	37.10	26.06	12	6
514	LEU	LYS	1.68E-06	18.57	17.37	37.10	32.25	12	6
514	LEU	MET	2.51E-06	18.57	18.42	37.10	33.68	12	6
528	VAL	ARG	5.57E-07	18.57	18.61	37.01	-72.34	1	6
529	THR	TYR	1.12E-06	18.58	18.58	36.99	-10.9	11	6
529	THR	ARG	4.98E-07	18.58	18.6	36.99	-4.95	11	6
529	THR	LYS	1.74E-06	18.58	18.57	36.99	4.7	11	6
529	THR	LEU	3.10E-06	18.58	18.56	36.99	26.71	11	6
532	CYS	HID	4.44E-06	18.49	14.39	37.09	26.54	7	6
532	CYS	HIP	4.44E-06	18.49	14.51	37.09	26.79	7	6
532	CYS	HIE	4.44E-06	18.49	12.48	37.09	25.2	7	6
532	CYS	ILE	1.16E-06	18.49	18.82	37.09	34.28	7	6
532	CYS	VAL	2.11E-06	18.49	18.7	37.09	34.77	7	6
471	VAL	HID	6.58E-07	18.65	17.61	37.26	33.79	6	7
505	LEU	GLY	6.90E-08	18.59	18.58	36.85	34.62	5	7
505	LEU	GLN	1.84E-06	18.59	18.6	36.85	34.82	5	7
514	LEU	HIE	3.37E-07	18.57	17.72	37.10	27.35	12	7
514	LEU	GLY	3.88E-08	18.57	18.03	37.10	33.68	12	7
514	LEU	ALA	9.24E-07	18.57	18.09	37.10	34.25	12	7
529	THR	HID	6.68E-08	18.58	18.58	36.99	-10.11	11	7
529	THR	HIE	6.68E-08	18.58	18.58	36.99	-4.75	11	7
529	THR	ASP	2.37E-06	18.58	18.51	36.99	34.7	11	7

Pos	WT AA	Mut AA	Sig Prob	ATP WT	ATP Mut	Drug WT	Drug Mut	Count	Rank
531	TRP	PRO	5.44E-07	18.51	16.76	37.07	0	1	7
505	LEU	ALA	5.28E-07	18.59	18.58	36.85	35	5	8
529	THR	HIP	6.68E-08	18.58	18.58	36.99	-6.63	11	8

Table S5: All RESISTOR resistance mutation predictions for BRAF with vemurafenib. "Pos" is the position of the residue. "WT AA" is the wildtype identity of the amino acid. "Mut AA" is the resistance mutation. "Sig Prob" is the mutational signature probability for the mutation from "WT AA" to "Mut AA" in melanoma. "ATP WT" and "ATP Mut" are the K^* scores of the endogenous ligand with the wildtype and mutant residues, respectively. "Drug WT" and "Drug Mut" are the K^* scores of vemurafenib with the wildtype and mutant residues, respectively. "Count" is number of resistance mutations at the position. "Rank" is the Pareto rank of the mutation. Note: K^* scores are in $\log_{10}$ units where possible and 0 where there is predicted to be no binding. The complete set of inputs used for the Pareto ranking can be found in Data S5.

Pos	WT AA	Mut AA	Sig Prob	ATP WT	ATP Mut	Drug WT	Drug Mut	Count	Rank
471	VAL	LEU	0.000443	18.65	19.67	33.41	29.39	4	1
481	ALA	THR	0.0177	18.58	18.99	33.27	30.69	9	1
529	THR	ILE	0.0202	18.58	18.57	33.45	29.33	10	1
535	SER	PRO	0.0013	18.72	18.65	33.65	0	1	1
593	GLY	PHE	1.99E-06	18.66	20.07	33.47	0	16	1
593	GLY	TYR	3.58E-05	18.66	19.86	33.47	0	16	1
593	GLY	ARG	0.00078	18.66	16.17	33.47	-231.93	16	1
593	GLY	ASN	0.00134	18.66	19.16	33.47	-103.95	16	1
593	GLY	ASP	0.0163	18.66	18.89	33.47	-26.78	16	1
593	GLY	CYS	0.00166	18.66	19.06	33.47	19.89	16	1
593	GLY	VAL	0.000935	18.66	19.18	33.47	21.09	16	1
593	GLY	ILE	4.55E-05	18.66	19.8	33.47	23.08	16	1
593	GLY	SER	0.0609	18.66	18.83	33.47	31.33	16	1
463	ILE	TYR	2.55E-05	18.60	15.94	33.42	-124.43	4	2
481	ALA	GLU	0.00121	18.58	17.92	33.27	11.12	9	2
481	ALA	VAL	0.00146	18.58	17.77	33.27	28.52	9	2
505	LEU	PHE	0.00544	18.59	18.58	33.45	27.01	3	2
505	LEU	ARG	0.000861	18.59	18.58	33.45	27.41	3	2
508	THR	ARG	0.000295	18.59	18.59	33.45	12.91	2	2
508	THR	LYS	0.000916	18.59	18.59	33.45	21.18	2	2
514	LEU	ILE	0.00165	18.57	18.4	33.43	30.08	11	2
532	CYS	ARG	0.000812	18.49	13.04	33.28	-10.66	9	2
593	GLY	HIE	1.66E-05	18.66	19.58	33.47	0	16	2
593	GLY	GLU	0.000276	18.66	18.73	33.47	-12.82	16	2
593	GLY	THR	2.67E-05	18.66	19.06	33.47	20.72	16	2
481	ALA	LEU	7.06E-05	18.58	18.68	33.27	18.19	9	3
481	ALA	LYS	0.000274	18.58	17.32	33.27	18.46	9	3
514	LEU	ARG	5.22E-05	18.57	17.18	33.43	22.28	11	3
514	LEU	GLN	8.77E-05	18.57	17.02	33.43	27.9	11	3
514	LEU	SER	0.000227	18.57	18.1	33.43	30.81	11	3
529	THR	MET	1.74E-05	18.58	18.65	33.45	-8.52	10	3
529	THR	PHE	3.77E-05	18.58	15.91	33.45	5.09	10	3
593	GLY	HIP	1.66E-05	18.66	19.56	33.47	0	16	3
481	ALA	ILE	5.14E-05	18.58	14.2	33.27	24.57	9	4

Pos	WT AA	Mut AA	Sig Prob	ATP WT	ATP Mut	Drug WT	Drug Mut	Count	Rank
593	GLY	HID	1.66E-05	18.66	19.55	33.47	0	16	4
471	VAL	MET	8.44E-06	18.65	18.96	33.41	31.15	4	5
481	ALA	ARG	1.53E-05	18.58	17.02	33.27	19.55	9	5
481	ALA	ASP	4.39E-06	18.58	19.21	33.27	24.15	9	5
514	LEU	PHE	1.53E-05	18.57	18.19	33.43	0	11	5
593	GLY	TRP	4.78E-06	18.66	18.83	33.47	0	16	5
593	GLY	LEU	3.87E-07	18.66	19.35	33.47	-237.44	16	5
463	ILE	HIE	5.14E-06	18.60	18.06	33.42	30.11	4	6
463	ILE	HID	5.14E-06	18.60	18.08	33.42	30.75	4	6
466	GLY	PRO	1.77E-07	18.80	18.27	33.48	0	1	6
471	VAL	PRO	5.74E-07	18.65	17.88	33.41	0	4	6
471	VAL	GLU	9.01E-07	18.65	18.82	33.41	31.34	4	6
481	ALA	GLN	1.8E-06	18.58	18.37	33.27	-15.45	9	6
514	LEU	HIP	3.37E-07	18.57	17.68	33.43	25.66	11	6
514	LEU	HID	3.37E-07	18.57	17.72	33.43	25.78	11	6
514	LEU	GLY	3.88E-08	18.57	18.03	33.43	30.29	11	6
514	LEU	ALA	9.24E-07	18.57	18.09	33.43	30.82	11	6
516	PHE	ARG	4.47E-06	18.59	18.58	33.51	29.7	1	6
529	THR	TYR	1.12E-06	18.58	18.58	33.45	-114.94	10	6
529	THR	ARG	4.98E-07	18.58	18.6	33.45	-34.39	10	6
529	THR	LYS	1.74E-06	18.58	18.57	33.45	-7.92	10	6
529	THR	LEU	3.1E-06	18.58	18.56	33.45	28.04	10	6
532	CYS	HIP	4.44E-06	18.49	14.51	33.28	-0.94	9	6
532	CYS	HIE	4.44E-06	18.49	12.48	33.28	-2.8	9	6
532	CYS	ILE	1.16E-06	18.49	18.82	33.28	27.39	9	6
532	CYS	VAL	2.11E-06	18.49	18.7	33.28	29.58	9	6
463	ILE	HIP	5.14E-06	18.60	17.51	33.42	30.23	4	7
505	LEU	MET	3.58E-07	18.59	18.6	33.45	25.88	3	7
514	LEU	HIE	3.37E-07	18.57	17.72	33.43	25.91	11	7
529	THR	HIE	6.68E-08	18.58	18.58	33.45	10.11	10	7
531	TRP	PRO	5.44E-07	18.51	16.76	33.25	0	1	7
532	CYS	HID	4.44E-06	18.49	14.39	33.28	-0.66	9	7
532	CYS	THR	2.67E-07	18.49	18.32	33.28	30.91	9	7
514	LEU	GLU	5.81E-08	18.57	17.36	33.43	28	11	8
529	THR	HIP	6.68E-08	18.58	18.58	33.45	10.86	10	8
529	THR	HID	6.68E-08	18.58	18.58	33.45	11.36	10	8

Table S6: All RESISTOR resistance mutation predictions for BRAF with encorafenib. "Pos" is the position of the residue. "WT AA" is the wildtype identity of the amino acid. "Mut AA" is the resistance mutation. "Sig Prob" is the mutational signature probability for the mutation from "WT AA" to "Mut AA" in melanoma. "ATP WT" and "ATP Mut" are the K^* scores of the endogenous ligand with the wildtype and mutant residues, respectively. "Drug WT" and "Drug Mut" are the K^* scores of encorafenib with the wildtype and mutant residues, respectively. "Count" is number of resistance mutations at the position. "Rank" is the Pareto rank of the mutation. Note: K^* scores are in $\log_{10}$ units where possible and 0 where there is predicted to be no binding. The complete set of inputs used for the Pareto ranking can be found in Data S6.

Pos	WT AA	Mut AA	Sig Prob	ATP WT	ATP Mut	Drug WT	Drug Mut	Count	Rank
471	VAL	LEU	0.000443	18.65	19.67	38.16	28.68	10	1
481	ALA	LEU	7.06E-05	18.58	18.68	38.13	-24.05	8	1
481	ALA	GLU	0.00121	18.58	17.92	38.13	10.6	8	1
529	THR	ILE	0.0202	18.58	18.57	38.12	31.23	12	1
532	CYS	ARG	0.000812	18.49	13.04	38.06	-19.78	9	1
535	SER	PRO	0.0013	18.72	18.65	38.18	0	1	1
593	GLY	TYR	3.58E-05	18.66	19.86	38.09	0	17	1
593	GLY	ARG	0.00078	18.66	16.17	38.09	-2.33	17	1
593	GLY	ILE	4.55E-05	18.66	19.8	38.09	2.23	17	1
593	GLY	VAL	0.000935	18.66	19.18	38.09	7.05	17	1
593	GLY	ASN	0.00134	18.66	19.16	38.09	28.19	17	1
593	GLY	ASP	0.0163	18.66	18.89	38.09	28.87	17	1
593	GLY	PHE	1.99E-06	18.66	20.07	38.09	30.05	17	1
593	GLY	CYS	0.00166	18.66	19.06	38.09	34.56	17	1
593	GLY	SER	0.0609	18.66	18.83	38.09	35.04	17	1
471	VAL	PHE	0.000785	18.65	16.37	38.16	26	10	2
481	ALA	LYS	0.000274	18.58	17.32	38.13	7.23	8	2
514	LEU	ARG	5.22E-05	18.57	17.18	38.14	20.73	10	2
529	THR	MET	1.74E-05	18.58	18.65	38.12	-18.87	12	2
529	THR	PHE	3.77E-05	18.58	15.91	38.12	0.72	12	2
529	THR	ASN	0.000996	18.58	18.55	38.12	33.77	12	2
536	SER	ASN	0.0137	18.63	18.53	38.02	34.35	3	2
583	PHE	TYR	0.00408	18.60	18.68	38.10	29.81	9	2
593	GLY	HIE	1.66E-05	18.66	19.58	38.09	0	17	2
593	GLY	GLU	0.000276	18.66	18.73	38.09	22.97	17	2
593	GLY	THR	2.67E-05	18.66	19.06	38.09	24.19	17	2
593	GLY	ALA	0.000254	18.66	18.8	38.09	35.61	17	2
463	ILE	TYR	2.55E-05	18.60	15.94	38.08	9.07	3	3
481	ALA	ILE	5.14E-05	18.58	14.2	38.13	30.63	8	3
481	ALA	VAL	0.00146	18.58	17.77	38.13	34.23	8	3
505	LEU	HIP	0.00146	18.59	18.59	38.08	35.98	2	3
514	LEU	GLN	8.77E-05	18.57	17.02	38.14	31.64	10	3
536	SER	ASP	5.03E-05	18.63	18.21	38.02	33.54	3	3
583	PHE	VAL	0.000214	18.60	17.05	38.10	33.2	9	3
583	PHE	ILE	0.00316	18.60	17.45	38.10	34.49	9	3
583	PHE	SER	0.00262	18.60	16.86	38.10	34.31	9	3
593	GLY	HIP	1.66E-05	18.66	19.56	38.09	0	17	3
505	LEU	HID	0.00146	18.59	18.59	38.08	36.08	2	4
593	GLY	HID	1.66E-05	18.66	19.55	38.09	0	17	4

Pos	WT AA	Mut AA	Sig Prob	ATP WT	ATP Mut	Drug WT	Drug Mut	Count	Rank
471	VAL	PRO	5.74E-07	18.65	17.88	38.16	0	10	5
471	VAL	ARG	3.03E-07	18.65	18.99	38.16	18.89	10	5
471	VAL	MET	8.44E-06	18.65	18.96	38.16	21.35	10	5
481	ALA	GLN	1.8E-06	18.58	18.37	38.13	-7.07	8	5
481	ALA	ARG	1.53E-05	18.58	17.02	38.13	1.87	8	5
481	ALA	ASP	4.39E-06	18.58	19.21	38.13	30.87	8	5
514	LEU	PHE	1.53E-05	18.57	18.19	38.14	-25.54	10	5
529	THR	ARG	4.98E-07	18.58	18.6	38.12	-6.65	12	5
532	CYS	HIP	4.44E-06	18.49	14.51	38.06	-40.5	9	5
532	CYS	HIE	4.44E-06	18.49	12.48	38.06	-40.74	9	5
533	GLU	PRO	3.22E-07	18.58	18.63	38.12	0	1	5
593	GLY	LEU	3.87E-07	18.66	19.35	38.09	19.61	17	5
593	GLY	TRP	4.78E-06	18.66	18.83	38.09	19.1	17	5
463	ILE	HIE	5.14E-06	18.60	18.06	38.08	35.28	3	6
471	VAL	GLU	9.01E-07	18.65	18.82	38.16	35.77	10	6
529	THR	TYR	1.12E-06	18.58	18.58	38.12	19.14	12	6
529	THR	LYS	1.74E-06	18.58	18.57	38.12	20.27	12	6
529	THR	HIE	6.68E-08	18.58	18.58	38.12	21.51	12	6
529	THR	LEU	3.1E-06	18.58	18.56	38.12	22.42	12	6
531	TRP	PRO	5.44E-07	18.51	16.76	38.04	0	1	6
532	CYS	HID	4.44E-06	18.49	14.39	38.06	-40.35	9	6
532	CYS	ILE	1.16E-06	18.49	18.82	38.06	30.25	9	6
532	CYS	VAL	2.11E-06	18.49	18.7	38.06	30.4	9	6
583	PHE	ARG	5.91E-06	18.60	17.17	38.10	32.32	9	6
583	PHE	THR	1.13E-05	18.60	16.91	38.10	32.78	9	6
583	PHE	MET	5.94E-06	18.60	18.39	38.10	35.48	9	6
463	ILE	HID	5.14E-06	18.60	18.08	38.08	35.51	3	7
471	VAL	HIP	6.58E-07	18.65	17.42	38.16	30.52	10	7
471	VAL	HID	6.58E-07	18.65	17.61	38.16	31.08	10	7
471	VAL	TYR	1.33E-06	18.65	16.37	38.16	31.46	10	7
514	LEU	HIP	3.37E-07	18.57	17.68	38.14	31.73	10	7
514	LEU	HID	3.37E-07	18.57	17.72	38.14	31.87	10	7
514	LEU	LYS	1.68E-06	18.57	17.37	38.14	33.97	10	7
514	LEU	MET	2.51E-06	18.57	18.42	38.14	35.5	10	7
529	THR	HID	6.68E-08	18.58	18.58	38.12	20.75	12	7
529	THR	ASP	2.37E-06	18.58	18.51	38.12	34.9	12	7
536	SER	LEU	5.47E-07	18.63	17.44	38.02	30.59	3	7
583	PHE	TRP	9.45E-07	18.60	13.08	38.10	24.17	9	7
583	PHE	GLY	1.52E-06	18.60	16.63	38.10	33.81	9	7
471	VAL	HIE	6.58E-07	18.65	17.28	38.16	30.93	10	8
514	LEU	HIE	3.37E-07	18.57	17.72	38.14	32.04	10	8
529	THR	HIP	6.68E-08	18.58	18.58	38.12	20.97	12	8
532	CYS	THR	2.67E-07	18.49	18.32	38.06	35.12	9	8
514	LEU	GLU	5.81E-08	18.57	17.36	38.14	32.45	10	9
514	LEU	GLY	3.88E-08	18.57	18.03	38.14	35.47	10	9

Table S7: All RESISTOR resistance mutation predictions for BRAF with PLX8394. "Pos" is the position of the residue. "WT AA" is the wildtype identity of the amino acid. "Mut AA" is the resistance mutation. "Sig Prob" is the mutational signature probability for the mutation from "WT AA" to "Mut AA" in melanoma. "ATP WT" and "ATP Mut" are the K^* scores of the endogenous ligand with the wildtype and mutant residues, respectively. "Drug WT" and "Drug Mut" are the K^* scores of PLX8394 with the wildtype and mutant residues, respectively. "Count" is number of resistance mutations at the position. "Rank" is the Pareto rank of the mutation. Note: K^* scores are in $\log_{10}$ units where possible and 0 where there is predicted to be no binding. The complete set of inputs used for the Pareto ranking can be found in Data S7.

Pos	WT AA	Mut AA	Sig Prob	ATP WT	ATP Mut	Drug WT	Drug Mut	Count	Rank
471	VAL	LEU	0.000443	18.645	19.67	31.624	29.38	3	1
513	ILE	PHE	0.00146	18.569	18.57	31.663	0	1	1
529	THR	ILE	0.0202	18.583	18.57	32.196	12.61	14	1
535	SER	PRO	0.0013	18.717	18.65	31.813	0	5	1
535	SER	LEU	0.00156	18.717	19.09	31.813	24.04	5	1
593	GLY	PHE	1.99E-06	18.659	20.07	31.991	0	16	1
593	GLY	TYR	3.58E-05	18.659	19.86	31.991	0	16	1
593	GLY	ARG	0.00078	18.659	16.17	31.991	-248.98	16	1
593	GLY	GLU	0.000276	18.659	18.73	31.991	-61.35	16	1
593	GLY	ASN	0.00134	18.659	19.16	31.991	-56.56	16	1
593	GLY	ASP	0.0163	18.659	18.89	31.991	-29.16	16	1
593	GLY	VAL	0.000935	18.659	19.18	31.991	6.66	16	1
593	GLY	CYS	0.00166	18.659	19.06	31.991	12.77	16	1
593	GLY	ILE	4.55E-05	18.659	19.8	31.991	22.76	16	1
593	GLY	SER	0.0609	18.659	18.83	31.991	28.13	16	1
463	ILE	TYR	2.55E-05	18.596	15.94	31.621	-260.1	5	2
481	ALA	LEU	7.06E-05	18.575	18.68	32.195	2.47	8	2
481	ALA	LYS	0.000274	18.575	17.32	32.195	3.05	8	2
481	ALA	GLU	0.00121	18.575	17.92	32.195	12.04	8	2
505	LEU	ARG	0.000861	18.589	18.58	31.429	24.96	4	2
508	THR	ARG	0.000295	18.594	18.59	31.461	-115.96	2	2
508	THR	LYS	0.000916	18.594	18.59	31.461	12.12	2	2
514	LEU	ILE	0.00165	18.57	18.4	31.667	21.52	10	2
514	LEU	ARG	5.22E-05	18.57	17.18	31.667	21.09	10	2
529	THR	PHE	3.77E-05	18.583	15.91	32.196	-106.19	14	2
529	THR	MET	1.74E-05	18.583	18.65	32.196	-28.68	14	2
529	THR	VAL	4.99E-05	18.583	18.72	32.196	28.05	14	2
529	THR	ASN	0.000996	18.583	18.55	32.196	27.98	14	2
532	CYS	ARG	0.000812	18.49	13.04	31.578	-0.71	9	2
535	SER	ILE	0.000391	18.717	19.02	31.813	28.17	5	2
535	SER	TYR	0.00262	18.717	18.68	31.813	29.19	5	2
593	GLY	HIE	1.66E-05	18.659	19.58	31.991	0	16	2
593	GLY	THR	2.67E-05	18.659	19.06	31.991	6.63	16	2
471	VAL	PHE	0.000785	18.645	16.37	31.624	27.32	3	3
481	ALA	ILE	5.14E-05	18.575	14.2	32.195	16.28	8	3
481	ALA	VAL	0.00146	18.575	17.77	32.195	27.92	8	3
514	LEU	VAL	0.000522	18.57	18.3	31.667	27.8	10	3
514	LEU	PRO	0.00121	18.57	18.12	31.667	29.31	10	3
593	GLY	HIP	1.66E-05	18.659	19.56	31.991	0	16	3

Pos	WT AA	Mut AA	Sig Prob	ATP WT	ATP Mut	Drug WT	Drug Mut	Count	Rank
593	GLY	HID	1.66E-05	18.659	19.55	31.991	0	16	4
471	VAL	MET	8.44E-06	18.645	18.96	31.624	30.12	3	5
481	ALA	ARG	1.53E-05	18.575	17.02	32.195	-7	8	5
481	ALA	ASP	4.39E-06	18.575	19.21	32.195	26.65	8	5
505	LEU	TYR	8.68E-06	18.589	18.59	31.429	13.95	4	5
514	LEU	PHE	1.53E-05	18.57	18.19	31.667	0	10	5
535	SER	ARG	1.91E-06	18.717	18.84	31.813	26.28	5	5
593	GLY	TRP	4.78E-06	18.659	18.83	31.991	0	16	5
593	GLY	LEU	3.87E-07	18.659	19.35	31.991	-172.14	16	5
463	ILE	HIE	5.14E-06	18.596	18.06	31.621	14.78	5	6
463	ILE	HIP	5.14E-06	18.596	17.51	31.621	14.5	5	6
463	ILE	HID	5.14E-06	18.596	18.08	31.621	23.91	5	6
481	ALA	GLN	1.8E-06	18.575	18.37	32.195	-57.06	8	6
516	PHE	THR	3.77E-06	18.593	18.56	32.276	29.08	1	6
528	VAL	ARG	5.57E-07	18.569	18.61	32.223	21.75	1	6
529	THR	TYR	1.12E-06	18.583	18.58	32.196	0	14	6
529	THR	ARG	4.98E-07	18.583	18.6	32.196	-73.94	14	6
529	THR	LEU	3.1E-06	18.583	18.56	32.196	-40.25	14	6
529	THR	LYS	1.74E-06	18.583	18.57	32.196	-16.49	14	6
532	CYS	HIP	4.44E-06	18.49	14.51	31.578	10.43	9	6
532	CYS	HIE	4.44E-06	18.49	12.48	31.578	8.45	9	6
532	CYS	ILE	1.16E-06	18.49	18.82	31.578	28.7	9	6
532	CYS	VAL	2.11E-06	18.49	18.7	31.578	29	9	6
505	LEU	MET	3.58E-07	18.589	18.6	31.429	28.4	4	7
505	LEU	GLN	1.84E-06	18.589	18.6	31.429	29.15	4	7
514	LEU	HIP	3.37E-07	18.57	17.68	31.667	24.27	10	7
514	LEU	HIE	3.37E-07	18.57	17.72	31.667	24.93	10	7
514	LEU	HID	3.37E-07	18.57	17.72	31.667	25.66	10	7
529	THR	HIP	6.68E-08	18.583	18.58	32.196	-75.31	14	7
529	THR	HID	6.68E-08	18.583	18.58	32.196	-74.57	14	7
529	THR	HIE	6.68E-08	18.583	18.58	32.196	-73.8	14	7
529	THR	ASP	2.37E-06	18.583	18.51	32.196	27.31	14	7
529	THR	CYS	1.13E-07	18.583	18.53	32.196	29.46	14	7
531	TRP	PRO	5.44E-07	18.512	16.76	31.57	0	1	7
532	CYS	HID	4.44E-06	18.49	14.39	31.578	10.57	9	7
514	LEU	GLU	5.81E-08	18.57	17.36	31.667	26.07	10	8
514	LEU	LYS	1.68E-06	18.57	17.37	31.667	28.06	10	8

S3. Predictive Contributions of the Individual Parameters

RESISTOR optimizes four criteria, K^* positive design, K^* negative design, mutational probability, and hotspot cardinality. To further investigate the contributions of each criterion, we ran a computational ablation study on EGFR resistance to osimertinib. We first describe the contributions of the structure- and sequence-based criteria to pruning the mutational sequence space. We then describe how we omitted each of the four objectives, one-at-a-time, and recomputed each mutant's Pareto rank using the three remaining objectives. To disambiguate between RESISTOR with four criteria and the results of this computational ablation study, we denote the later as *3-RANK*. We compared RESISTOR and 3-RANK's results to see whether using 3-RANK could improve the predictions.

Note that 3-RANK is, by nature, an imperfect comparison to RESISTOR because an ablation study should remove each criterion from both the pruning and the ranking steps. As described above, RESISTOR consists of two components, *viz.*, a pruning and a Pareto-ranking step. We considered an ablation study where each of the criteria is removed from both the pruning and ranking steps. However, by applying the cut-off c (described in Section 2.4), we combine positive and negative design in a nonlinear fashion, and it is therefore not possible to remove them individually. In addition, the residue hotspot cardinality is a result of the pruning, and can thus not be ablated from the pruning. To account for these limitations, we describe below first the magnitude of the effect of each of the three pruning criteria (the ratio of positive to negative design, loss of wildtype clonal fitness, and mutational probability) on the pruning step, and then describe how each of the criteria, when ablated solely from the ranking step, affects the ranking step (assuming full RESISTOR pruning has already occurred).

There were two structure-based pruning criteria, namely the resistance cut-off and loss of wildtype clonal fitness via ablated endogenous ligand binding as described in Section 2.4. These two criteria prune the largest proportion of sequences, accounting for the removal of $86.24 \pm 3.20\%$ of mutants in the EGFR and BRAF case studies. Removing all mutations with a mutational signature-derived probability of zero removes an additional $3.58 \pm 0.87\%$ of mutants. However, we have applied consecutive filtering steps here, and if we look at each parameter in this particular EGFR dataset individually, the cut-off c alone prunes $51.03 \pm 5.97\%$ of mutants, ablated endogenous ligand binding prunes $37.20 \pm 6.18\%$ of mutants, and mutations with a mutational probability of zero alone prunes $19.21 \pm 0.70\%$ of mutants. This shows that the structure based criteria prune the overwhelming majority of the candidate sequences. In this particular EGFR:osimertinib case, after pruning there remain 36 out of the original 357 candidate sequences that we then ranked using Pareto optimization.

In Table 1, we list RESISTOR's correct predictions for EGFR. There are five correct predictions for resistance mutations in EGFR when treated with osimertinib: L792H, G796R, G796D, G796C, and G796S. RESISTOR predicted L792H to be in the second Pareto rank and the four mutations at position 796 to be on the Pareto frontier. In comparing the RESISTOR ranks to the 3-RANK results, we found that omitting an objective with 3-RANK never improved the predictive accuracy (see Table S8 for the full results).

Being clinically confirmed resistance mutations, ideally 5 of the mutants should be on the Pareto fronter, i.e., have a Pareto rank of 1. 3-RANK that omits the K^* score of the EGFR:wildtype ligand complex changed G796C's Pareto rank from 1 to 2, and increased the ranks to 3 and 4 respectively of the HIE and HIP protonation states of L792H. 3-RANK that omits the K^* score of the EGFR:osimertinib complex reduced G796D's Pareto rank from 1 to 2, and reduced the HIP, HIE, and HID 792H protonation states from a Pareto rank of 2 to 5, 4, and 3, respectively. The largest reduction in rank accuracy is when 3-RANK omits mutational probabilities. In this case, L796R, L796D, L796C, and L796S have their Pareto ranks reduced from 1 to 2, 5, 6, and 8. The L792H mutation, in all protonation states, has its Pareto rank reduced from 2 to 9. On the other hand, when 3-RANK omits hotspot cardinality the Pareto ranks of the clinically confirmed resistance mutants remain the same RESISTOR. This is not too surprising, as hotspot cardinality is a count of the number of amino acids at a particular location that are predicted by K^* positive and negative design,

as well mutational probability, to confer resistance. It is thus dependent on the other three criteria, and in essence boosts locations that are predicted to be critical for drug or endogenous ligand binding. This indicates that in the future it might be possible to omit hotspot cardinality with only a minor drop in predictive accuracy.

In summary, positive design, negative design, and mutational probability all affect the pruning step, with the structural components most aggressively pruning the candidate resistance mutations. In the ranking step, the omission of positive design, negative design, or mutational probability in the Pareto optimization all negatively impact the accuracy of the results. Hotspot cardinality has a smaller effect on the predicted rankings than the other three criteria.

Table S8: Pareto ranks of computational Pareto objective ablation study on EGFR:osimertinib. Every mutation in this table is predicted to confer resistance. "Pos" is the position of the residue. "WT AA" is the wildtype identity of the amino acid. "Mut AA" is the resistance mutation. "Rank" is the RESISTOR-computed Pareto rank. "w/o (+) Design" is the Pareto rank of the mutation when the K^* score of the wildtype ligand (ATP) is omitted from the Pareto optimization. "w/o (-) Design" is the Pareto rank of the mutation when the K^* score of the drug (osimertinib) is omitted from the Pareto optimization. "w/o Probs" is the Pareto rank of the mutation when the mutational probability is omitted from the Pareto optimization. "w/o Count" is the Pareto rank of the mutation when the hotspot cardinality is omitted from the Pareto optimization.

Pos	WT AA	Mut AA	Rank	w/o (+) Design	w/o (-) Design	w/o Probs	w/o Count
718	leu	TRP	1	2	6	1	2
718	leu	PHE	1	1	6	2	1
718	leu	HIP	1	1	5	3	1
718	leu	HIE	1	2	3	3	1
718	leu	MET	1	1	1	5	1
719	gly	VAL	1	1	1	7	1
726	val	TRP	1	2	2	1	1
743	ala	ASP	1	1	1	6	1
796	gly	TRP	1	1	5	1	2
796	gly	TYR	1	1	2	1	2
796	gly	PHE	1	1	2	2	1
796	gly	LEU	1	2	1	1	1
796	gly	ARG	1	1	1	2	1
796	gly	ASP	1	1	2	5	1
796	gly	CYS	1	2	1	6	1
796	gly	SER	1	1	1	8	1
718	leu	HID	2	3	4	4	2
718	leu	ARG	2	2	2	5	2
723	phe	ILE	2	5	2	3	2
792	leu	HIP	2	2	5	9	2
792	leu	HIE	2	3	4	9	2
792	leu	HID	2	4	3	9	2
796	gly	GLU	2	2	3	3	3
796	gly	HIE	2	3	2	2	2
796	gly	ASN	2	3	3	5	2
718	leu	LYS	3	4	3	8	3
719	gly	THR	3	5	6	6	4
726	val	ARG	3	5	6	6	5
726	val	LYS	3	5	7	7	4
743	ala	GLU	3	4	7	5	3

Pos	WT AA	Mut AA	Rank	w/o (+) Design	w/o (-) Design	w/o Probs	w/o Count
796	gly	HID	3	4	3	3	3
796	gly	THR	3	4	4	7	3
844	leu	TRP	3	6	6	7	3
796	gly	HIP	4	5	4	4	4
718	leu	GLY	5	6	6	8	5
743	ala	ARG	5	6	8	5	5