Development of multiple AI pipelines that predict NAC response of breast cancer using H&E-stained tissues

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Supplementary Tables S1–S10

Table S1. JBCS histopathological criteria for the assessment of therapeutic response in breast cancer (2007 version)

Grade		Definitions
0: No response		Almost no change in cancer cells after treatment.
1: Slight response	1a	Mild response. Mild changes in cancer cells regardless of the extent, and/or marked changes in less than one-third of cancer cells.
	1b	Moderate response. Marked changes in one-third or more but less than two-thirds of cancer cells.
2: Marked response	2a	High grade changes. Marked changes in two-thirds or more of tumor cells with apparent remaining cancer cells.
	2b	Extremely high grade. Marked changes approaching a complete response with only a few remaining cancer cells.
3: Complete response		Necrosis and/or disappearance of all tumor cells, and/or the replacement of cancer cells by granulation and/or fibrosis.

Table S2. Number of ROIs for the CNN, SVM and RF models

	Training	Test	Total
CNN Model			
ROIs of Cancer area	530,173	169,533	699,709
ROIs of Non-cancer area	76,585	82,572	159,157
Total ROIs	606,758	252,105	858,863
SVM & RF Models			
Selected ROIs of Cancer area	3,366	1,545	4,911
Nuclei	1,563,586	952,770	2,516,356

Table S3. The prediction result for each ROI by CNN model

A: Training cases (CNN) Accuracy: 98.8% (95% CI: 98.8–98.8%)

κ = 0.98

		Prediction						
		RG0	RG1	RG2	RG3	Total ROIs of cancer area	ROIs of non-cancer area	Total ROIs
Truth	RG0	101,748	119	156	254	102,277	14,787	117,064
	RG1	797	148,993	718	2,081	152,589	27,831	180,420
	RG2	143	214	99,383	958	100,698	16,136	116,834
	RG3	190	402	362	173,655	173,609	17,831	191,440
	Total	102,878	149,728	100,619	176,948	530,173	76,585	606,758

B: Test cases (CNN) Accuracy: 88.8% (95% CI: 88.7–89.0%)

κ =0.85

		Prediction						
		RG0	RG1	RG2	RG3	Total ROIs of cancer area	ROIs of non-cancer area	Total ROIs
Truth	RG0	36,283	391	914	1,856	39,444	11,685	51,129
	RG1	1,817	31,897	2,072	5,470	41,256	32,012	73,268
	RG2	349	1,617	22,729	2,601	27,296	14,719	42,015
	RG3	363	894	628	59,652	61,537	24,156	85,693
	Total	38,812	34,799	26,343	69,579	169,533	82,572	252,105

Table S4. The prediction result for each ROI by the SVM model, trained by RG information only

A: Training Cases (SVM, RG only) **Accuracy: 87.6% (95% CI: 86.4–88.7%)**

κ = 0.83

		Prediction				
		RG0	**RG1**	**RG2**	**RG3**	**Total**
Truth	**RG0**	399	43	2	8	452
	RG1	14	1043	35	75	1167
	RG2	11	59	606	38	714
	RG3	6	93	34	900	1033
	Total	430	1238	677	1021	3366

B: Test Cases (SVM, RG only) **Accuracy: 72.6% (95% CI: 70.3–74.8%)**

κ = 0.60

		Prediction				
		RG0	**RG1**	**RG2**	**RG3**	**Total**
Truth	**RG0**	87	44	17	24	172
	RG1	29	550	12	57	648
	RG2	16	75	142	44	277
	RG3	10	73	23	342	448
	Total	142	742	194	467	1545

Table S5. The prediction result for each ROI by the SVM model, trained by RG and subtype information

A: Training Cases (SVM, RG + Subtype)

RG prediction accuracy: 89.4% (95% CI: 88.3–90.4%)

κ = 0.88

			Prediction														
			RG0	RG0	RG0	RG1	RG1	RG1	RG1	RG2	RG2	RG2	RG2	RG3	RG3	RG3	RG3	Total
			TN	H+	H+ HER2+	TN	H+	HER2+	H+ HER2+	TN	H+	HER2+	H+ HER2+	TN	H+	HER2+	H+ HER2+	
Truth	RG0	TN	73	0	0	0	4	0	2	0	0	0	1	0	0	1	0	81
	RG0	H+	0	290	0	0	28	0	3	1	5	0	0	0	0	4	5	336
	RG0	H+ HER2+	0	0	28	0	7	0	0	0	0	0	0	0	0	0	0	35
	RG1	TN	0	1	0	141	7	0	0	0	1	0	0	1	0	0	2	153
	RG1	H+	0	4	0	0	687	0	0	0	0	0	0	0	5	0	3	699
	RG1	HER2+	0	0	0	0	8	34	1	0	2	0	0	0	0	0	4	49
	RG1	H+ HER2+	0	0	0	0	46	0	212	0	2	0	1	0	2	2	1	266
	RG2	TN	0	0	0	1	18	0	2	108	2	0	1	0	1	6	1	140
	RG2	H+	0	5	0	0	18	0	1	0	227	0	0	0	0	0	1	252
	RG2	HER2+	0	0	0	0	5	0	0	0	3	91	0	0	0	2	3	104
	RG2	H+ HER2+	0	0	0	1	22	0	1	0	1	0	185	0	5	3	0	218
	RG3	TN	0	1	0	0	17	0	0	0	3	0	0	145	2	0	1	169
	RG3	H+	1	2	0	0	19	1	0	0	1	1	0	0	257	0	0	282
	RG3	HER2+	0	0	0	0	11	0	2	0	2	0	1	0	3	249	6	274
	RG3	H+ HER2+	0	0	0	0	19	0	1	0	1	0	1	0	0	5	281	308
	Total		74	303	28	143	916	35	225	109	250	92	190	146	275	272	308	3,366

B: Test Cases (SVM, RG + Subtype)

RG prediction accuracy: 63.7% (95% CI: 61.2–66.1%)

κ = 0.58

			Prediction														
			RG0 TN	RG0 H+	RG0 H+ HER2+	RG1 TN	RG1 H+	RG1 HER2+	RG1 H+ HER2+	RG2 TN	RG2 H+	RG2 HER2+	RG2 H+ HER2+	RG3 TN	RG3 H+	RG3 HER2+	RG3 H+ HER2+	Total
Truth	RG0	TN	11	1	0	1	0	0	0	1	0	0	0	1	0	0	0	15
	RG0	H+	0	69	0	4	21	1	8	0	20	0	2	5	2	15	10	157
	RG0	H+ HER2+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	RG1	TN	0	0	1	53	10	0	0	2	1	0	1	1	4	1	2	76
	RG1	H+	1	12	0	6	372	1	12	4	8	0	5	5	16	10	7	459
	RG1	HER2+	0	0	0	0	4	14	0	0	0	1	0	0	0	0	1	20
	RG1	H+ HER2+	3	4	0	2	16	2	48	3	0	0	0	0	0	3	12	93
	RG2	TN	0	0	0	0	21	0	0	42	0	1	1	0	6	9	9	89
	RG2	H+	0	0	0	2	3	0	0	2	32	5	0	0	0	3	6	53
	RG2	HER2+	0	0	0	1	11	0	2	1	4	30	1	2	0	3	16	71
	RG2	H+ HER2+	1	1	0	3	13	0	1	2	5	0	25	3	6	2	2	64
	RG3	TN	0	1	0	0	20	0	0	0	4	1	0	90	15	4	0	135
	RG3	H+	1	5	0	0	20	3	0	0	0	0	2	0	35	3	0	69
	RG3	HER2+	1	0	0	3	3	0	1	4	0	0	4	1	0	61	0	78
	RG3	H+ HER2+	0	1	0	6	20	3	0	4	2	0	1	1	0	26	102	166
	Total		18	94	1	81	534	24	72	65	76	38	42	109	84	140	167	1,545

Note: In the test cases, there was no case of (RG0, H+ HER2+).

Table S6. The prediction result for each ROI by the RF model, trained by RG and subtype information

A: Training Cases (RF, RG + Subtype) **Accuracy: 100% (95% CI: 99.9–100%)**

κ = 1

			Prediction														
			RG0	RG0	RG0	RG1	RG1	RG1	RG1	RG2	RG2	RG2	RG2	RG3	RG3	RG3	RG3	Total
			TN	H+	H+ HER2+	TN	H+	HER2+	H+ HER2+	TN	H+	HER2+	H+ HER2+	TN	H+	HER2+	H+ HER2+	
Truth	RG0	TN	81	0	0	0	0	0	0	0	0	0	0	0	0	0	0	81
	RG0	H+	0	336	0	0	0	0	0	0	0	0	0	0	0	0	0	336
	RG0	H+ HER2+	0	0	35	0	0	0	0	0	0	0	0	0	0	0	0	35
	RG1	TN	0	0	0	153	0	0	0	0	0	0	0	0	0	0	0	153
	RG1	H+	0	0	0	0	699	0	0	0	0	0	0	0	0	0	0	699
	RG1	HER2+	0	0	0	0	0	49	0	0	0	0	0	0	0	0	0	49
	RG1	H+ HER2+	0	0	0	0	0	0	266	0	0	0	0	0	0	0	0	266
	RG2	TN	0	0	0	0	0	0	0	140	0	0	0	0	0	0	0	140
	RG2	H+	0	0	0	0	0	0	0	0	252	0	0	0	0	0	0	252
	RG2	HER2+	0	0	0	0	0	0	0	0	0	104	0	0	0	0	0	104
	RG2	H+ HER2+	0	0	0	0	0	0	0	0	0	0	218	0	0	0	0	218
	RG3	TN	0	0	0	0	0	0	0	0	0	0	0	169	0	0	0	169
	RG3	H+	0	0	0	0	0	0	0	0	0	0	0	0	282	0	0	282
	RG3	HER2+	0	0	0	0	0	0	0	0	0	0	0	0	0	274	0	274
	RG3	H+ HER2+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	308	308
	Total		81	336	35	153	699	49	266	140	252	104	218	169	282	274	308	3,366

B: Test Cases (RF, RG + Subtype)

Accuracy: 72.3% (95% CI: 70.0–74.5%)

κ = 0.66

			Prediction														
			RG0 TN	RG0 H+	RG0 H+ HER2+	RG1 TN	RG1 H+	RG1 HER2+	RG1 H+ HER2+	RG2 TN	RG2 H+	RG2 HER2+	RG2 H+ HER2+	RG3 TN	RG3 H+	RG3 HER2+	RG3 H+ HER2+	Total
Truth	RG0	TN	10	1	0	0	2	0	1	0	1	0	0	0	0	0	0	15
	RG0	H+	0	97	0	1	49	0	0	0	7	0	1	1	1	0	0	157
	RG0	H+ HER2+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	RG1	TN	0	0	0	58	15	0	0	0	0	0	0	0	3	0	0	76
	RG1	H+	0	2	0	0	436	0	1	2	7	1	1	0	7	1	1	459
	RG1	HER2+	0	0	0	0	8	8	1	0	1	0	2	0	0	0	0	20
	RG1	H+ HER2+	0	3	0	1	26	0	57	0	0	0	0	0	0	2	4	93
	RG2	TN	0	1	0	0	27	0	2	47	0	0	0	0	3	4	5	89
	RG2	H+	0	1	0	0	8	0	0	0	40	2	0	0	1	0	1	53
	RG2	HER2+	0	4	0	0	14	0	1	0	5	33	0	1	0	2	11	71
	RG2	H+ HER2+	0	0	0	0	25	0	0	0	1	0	32	0	3	2	1	64
	RG3	TN	0	0	0	0	40	0	0	0	3	0	0	85	2	1	4	135
	RG3	H+	0	1	0	0	31	0	0	0	1	0	0	0	33	0	3	69
	RG3	HER2+	2	0	0	0	14	0	0	0	0	0	7	0	1	53	1	78
	RG3	H+ HER2+	0	1	0	4	32	0	0	0	0	0	0	0	0	1	128	166
	Total		12	111	0	64	727	8	63	49	66	36	43	87	54	66	159	1,545

Note: In the test cases, there was no case of (RG0, H+ HER2+).

Table S7. CNN, SVM and RF model analysis summarized into case-based results on training cases

A: Training Cases (CNN)

Accuracy: 95.2%
(95% CI: 91.3–97.7%)
κ = 0.93

		Prediction				
		RG0	RG1	RG2	RG3	Total
Truth	RG0	30	0	0	0	30
	RG1	4	64	0	1	69
	RG2	0	2	47	0	49
	RG3	1	2	0	56	59
	Total	35	68	47	57	207

B: Training Cases (SVM, RG only)

Accuracy: 96.1%
(95% CI: 92.5–98.3%)
κ = 0.95

		Prediction				
		RG0	RG1	RG2	RG3	Total
Truth	RG0	29	1	0	0	30
	RG1	0	69	0	0	69
	RG2	0	3	44	2	49
	RG3	0	1	1	57	59
	Total	29	74	45	59	207

C: Training Cases (SVM RG + Subtype)

Accuracy: 100%
(95% CI: 98.2–100%)
κ = 1.00

		Prediction				
		RG0	RG1	RG2	RG3	Total
Truth	RG0	30	0	0	0	30
	RG1	0	69	0	0	69
	RG2	0	0	49	0	49
	RG3	0	0	0	59	59
	Total	30	69	49	59	207

D: Training Cases (RF, RG + Subtype)

Accuracy: 100%
(95% CI: 98.2–100%)
κ = 1.00
Out-of-Bag (OOB) error rate: 17.76%

		Prediction				
		RG0	RG1	RG2	RG3	Total
Truth	RG0	30	0	0	0	30
	RG1	0	69	0	0	69
	RG2	0	0	49	0	49
	RG3	0	0	0	59	59
	Total	30	69	49	59	207

Note: **A.** CNN model analysis result on training cases. **B.** SVM model analysis (only RG information was used) result on training cases. **C.** SVM model analysis (RG and subtype information was used) result on training cases. **D.** Random Forest model analysis (RG and subtype information was used) result on training cases.

Table S8. Test case results of the pipeline system and majority voting method

Case Information				CNN		SVM			RF	Pipeline System Result	Majority Voting Result
Case #	Response Grade	RCB Class	Subtype	LH (△)	DL result	Subtype Prediction	Subtype LH	SVM result	RF result		
1	1	3	H+	12.0	1	H+	0.61	1	1	1	1
2	0	2	H+	19.1	0	H+	0.90	0	0	0	0
3	1	1	H+	10.8	1	H+	0.77	1	1	1	1
4	2	1	HER2+	1.2	2	HER2+	0.44	2	2	2	2
5	3	0	H+ HER2+	17.3	3	H+ HER2+	0.34	3	3	3	3
6	1	2	H+	9.9	1	H+	0.56	1	2	1	1
7	3	0	HER2+	21.1	3	HER2+	0.38	3	3	3	3
8	2	2	TN	0.1	2	TN	0.47	3	2	2	2
9	1	2	TN	5.4	3	TN	0.48	1	1	1	1
10	2	1	TN	8.1	2	TN	0.73	2	2	2	2
11	1	2	H+	5.7	1	H+	0.89	1	1	1	1
12	1	2	H+	9.3	1	H+	0.88	1	1	1	1
13	3	0	H+ HER2+	1.8	0	H+	0.38	3	3	3	3
14	1	3	H+	1.3	1	H+	0.56	1	1	1	1
15	3	0	H+ HER2+	15.9	3	H+ HER2+	0.90	3	3	3	3
16	2	1	H+ HER2+	12.4	2	H+	0.39	2	2	2	2
17	3	0	TN	9.8	3	H+	0.75	1	3	3	3
18	3	0	TN	13.9	3	H+	0.42	3	3	3	3
19	1	1	H+	6.4	1	H+	0.50	1	1	1	1
20	2	2	HER2+	4.1	2	HER2+	0.48	2	2	2	2
21	3	0	H+	19.2	3	H+	0.72	3	3	3	3
22	1	2	TN	0.6	3	TN	0.34	3	1	1	3
23	2	1	H+ HER2+	7.7	2	H+	0.48	2	2	2	2
24	1	2	TN	10.8	1	H+	0.61	1	1	1	1
25	1	2	H+	0.4	1	H+	0.82	3	1	3	1
26	3	0	H+ HER2+	3.8	3	H+	0.47	3	3	3	3
27	2	2	H+	8.9	2	H+	0.59	2	2	2	2
28	1	2	H+ HER2+	6.7	1	H+	0.55	1	1	1	1
29	2	2	HER2+	0.2	3	H+	0.50	1	2	2	Unable

											to reach final resutl
30	3	0	HER2+	13.4	3	HER2+	0.76	3	3	3	3
31	2	2	TN	5.7	2	H+	0.87	1	2	2	2
32	3	0	TN	12.2	3	TN	0.90	3	3	3	3
33	1	2	H+ HER2+	13.7	1	H+	0.74	1	1	1	1
34	3	2	TN	6.0	3	H+	0.80	3	3	3	3
35	0	3	TN	5.4	0	TN	0.52	0	0	0	0
36	1	2	HER2+	16.4	1	HER2+	0.47	1	2	1	1
37	2	2	H+ HER2+	8.8	0	H+	0.64	1	2	2	Unable to reach final resutl
38	0	3	H+	17.3	0	H+	0.69	0	0	0	0
39	0	3	H+	3.8	3	H+	0.71	2	0	2	Unable to reach final resutl
40	1	2	H+	6.3	1	H+	0.76	1	1	1	1
41	0	3	H+	17.3	0	H+	0.89	0	0	0	0
42	3	0	H+	5.9	3	H+	0.81	3	3	3	3
43	1	2	H+ HER2+	13.7	1	TN	0.45	1	1	1	1
44	2	1	H+	11.8	2	H+	0.42	2	2	2	2
45	3	0	H+ HER2+	14.4	3	HER2+	0.65	3	3	3	3
46	0	3	H+	9.9	0	H+	0.83	0	0	0	0
47	2	2	HER2+	5.5	2	H+ HER2+	0.60	3	3	3	3
48	1	2	H+	2.2	2	H+	0.58	1	1	1	1
49	1	2	H+	4.6	1	H+	0.91	1	1	1	1
50	0	3	H+	6.8	0	H+ HER2+	0.66	3	1	1	Unable to reach final resutl
51	2	2	TN	10.1	2	TN	0.59	2	2	2	2
52	1	3	H+	6.6	3	H+	0.71	1	1	1	1
53	3	0	TN	21.5	3	TN	0.79	3	3	3	3
54	2	2	H+	11.0	2	H+	0.60	2	2	2	2
55	1	2	H+	6.6	1	H+	0.87	1	1	1	1

56	0	3	H+	15.0	0	H+	0.36	3	0	0	0
57	1	2	H+	9.8	1	H+	0.65	1	1	1	1
58	3	0	H+	12.1	3	H+	0.49	3	3	3	3
59	1	2	H+	5.1	1	H+	0.81	1	1	1	1
60	2	2	H+ HER2+	14.6	2	TN	0.39	2	2	2	2
61	1	2	H+ HER2+	10.3	1	H+ HER2+	0.63	1	1	1	1
62	0	2	H+	12.5	0	H+	0.48	0	0	0	0
63	3	0	HER2+	16.4	3	HER2+	0.72	3	3	3	3
64	0	2	H+	3.7	0	H+	0.64	2	0	2	0
65	3	0	HER2+	16.6	3	HER2+	0.78	3	3	3	3
66	3	0	H+ HER2+	15.4	3	H+ HER2+	0.72	3	3	3	3
67	2	1	HER2+	10.1	2	HER2+	0.88	2	2	2	2
68	3	0	TN	13.9	3	TN	0.47	3	3	3	3
69	1	2	H+	3.3	1	H+	0.90	1	1	1	1
70	3	0	H+	7.3	3	H+	0.75	3	3	3	3
71	3	0	TN	12.9	3	TN	0.84	3	3	3	3
72	1		TN	2.6	1	TN	0.91	1	1	1	1
73	3	0	H+ HER2+	14.4	3	H+ HER2+	0.85	3	3	3	3
74	2	1	TN	5.6	2	H+	0.57	1	2	2	2
75	3	0	H+ HER2+	7.7	3	TN	0.49	1	3	3	3
76	2	2	H+ HER2+	9.7	2	H+ HER2+	0.73	2	2	2	2
77	1	2	H+ HER2+	4.3	1	H+ HER2+	0.78	1	1	1	1
78	1	2	H+	14.2	1	H+	0.89	1	1	1	1
79	1	2	H+ HER2+	7.3	1	H+ HER2+	0.39	1	1	1	1
80	3	0	H+ HER2+	12.0	3	H+ HER2+	0.80	3	3	3	3
81	1	2	H+	2.0	3	H+	0.69	1	1	1	1
82	3	0	TN	8.3	3	TN	0.75	3	3	3	3
83	1	3	H+	1.9	1	H+	0.70	1	1	1	1
84	1	3	H+	6.6	1	H+	0.53	1	1	1	1
85	1	2	H+	2.5	3	H+	0.46	1	1	1	1
86	3	0	H+ HER2+	15.2	3	H+	0.61	1	3	3	3
87	1	3	H+	7.8	1	H+	0.79	1	1	1	1

88	1	2	H+	3.8	1	H+	0.87	1	1	1	1
89	1	3	TN	4.2	3	TN	0.82	1	1	1	1
90	1	2	HER2+	8.0	1	HER2+	0.52	1	1	1	1
91	1	2	H+	4.2	1	H+	0.65	1	1	1	1
92	1	2	H+	6.0	3	H+	0.83	1	1	1	1
93	1	2	H+	2.3	3	H+	0.88	1	1	1	1
94	1	2	H+	5.7	1	H+	0.87	1	1	1	1
95	2	2	TN	0.2	2	TN	0.29	3	2	2	2
96	2	2	HER2+	1.0	2	H+	0.46	2	2	2	2
97	1	2	H+	0.2	3	H+	0.50	1	1	1	1
98	1	1	H+	3.6	1	H+	0.87	1	1	1	1
99	3	0	H+ HER2+	7.4	3	H+ HER2+	0.73	3	3	3	3
100	1	2	TN	4.8	1	TN	0.71	1	1	1	1
101	2	2	H+	7.3	2	H+	0.80	2	2	2	2
102	3	1	HER2+	15.2	3	HER2+	0.54	3	3	3	3
103	1	2	H+	8.7	1	H+	0.72	1	1	1	1

Note: Yellow fill shows the discrepant cases.

Table S9. Detailed analysis results of CNN heat map example cases

Case information		ROI count				Likelihood			
Case #	Response Grade	RG0	RG1	RG2	RG3	RG0	RG1	RG2	RG3
62	0	2,646	31	107	272	16.921	0.000	4.401	4.350
12	1	36	1,860	107	314	0.000	15.655	2.898	6.329
10	2	6	360	1,511	331	0.000	8.936	17.123	8.982
15	3	3	22	30	2,468	0.000	7.856	8.164	24.058

Table S10. Detailed analysis results of SVM heat map example cases

Case information		ROI count				Likelihood			
Case #	Response Grade	RG0	RG1	RG2	RG3	RG0	RG1	RG2	RG3
41	0	14	0	0	1	0.48	0.23	0.19	0.10
83	1	2	22	2	0	0.03	0.72	0.05	0.20
10	2	3	0	18	0	0.01	0.13	0.82	0.03
65	3	1	3	0	14	0.07	0.11	0.04	0.78