

## Supplementary Online Content

Peiffer DS, Zhao F, Chen N, et al. Clinicopathologic characteristics and prognosis of ERBB2-low breast cancer among patients in the National Cancer Database. *JAMA Oncol*. Published online February 23, 2023. doi:10.1001/jamaoncol.2022.7476

**eFigure 1.** CONSORT Diagram for Included Patients

**eFigure 2.** ERBB2-Low Status by ER Expression and PR Expression

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**eTable 1.** Baseline Patient Demographics and Clinicopathologic Characteristics per ERBB2 Immunohistochemistry Results

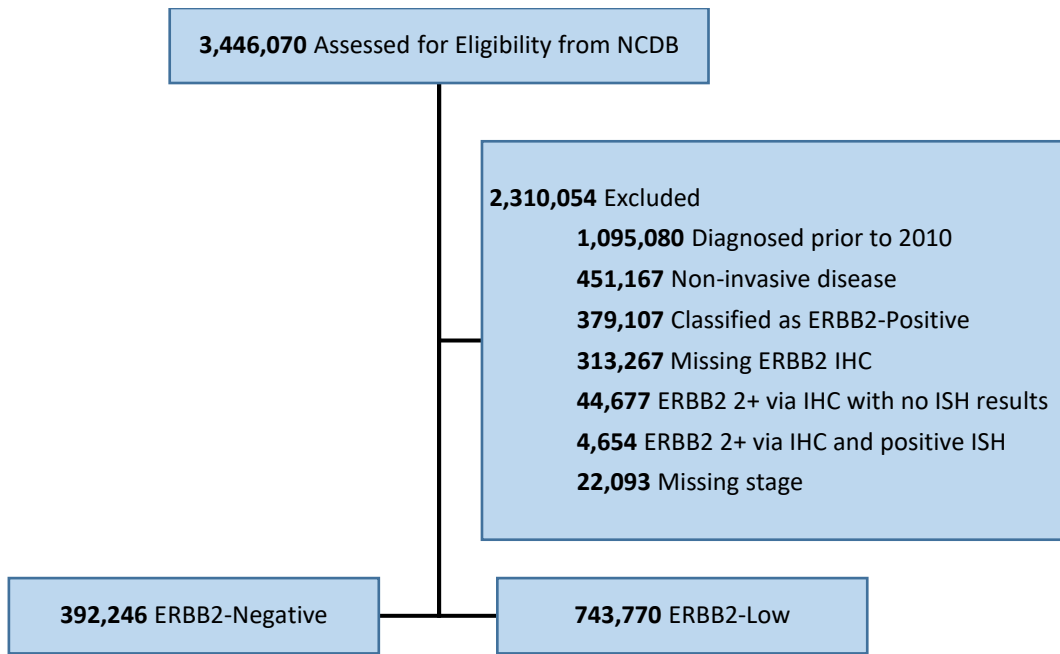
**eTable 2.** Sites of Metastatic Disease in ERBB2-Negative Versus ERBB2-Low cancers

**eTable 3.** Baseline Patient Demographics and Clinicopathologic Characteristics of Patients Treated With Neoadjuvant Chemotherapy

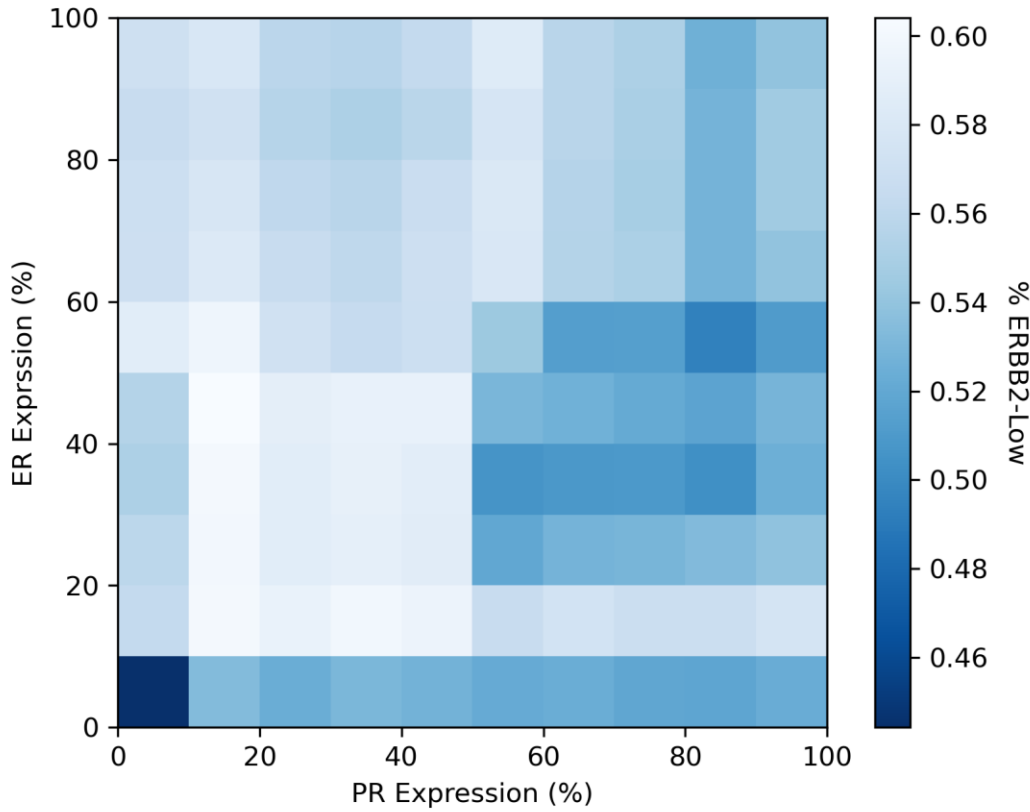
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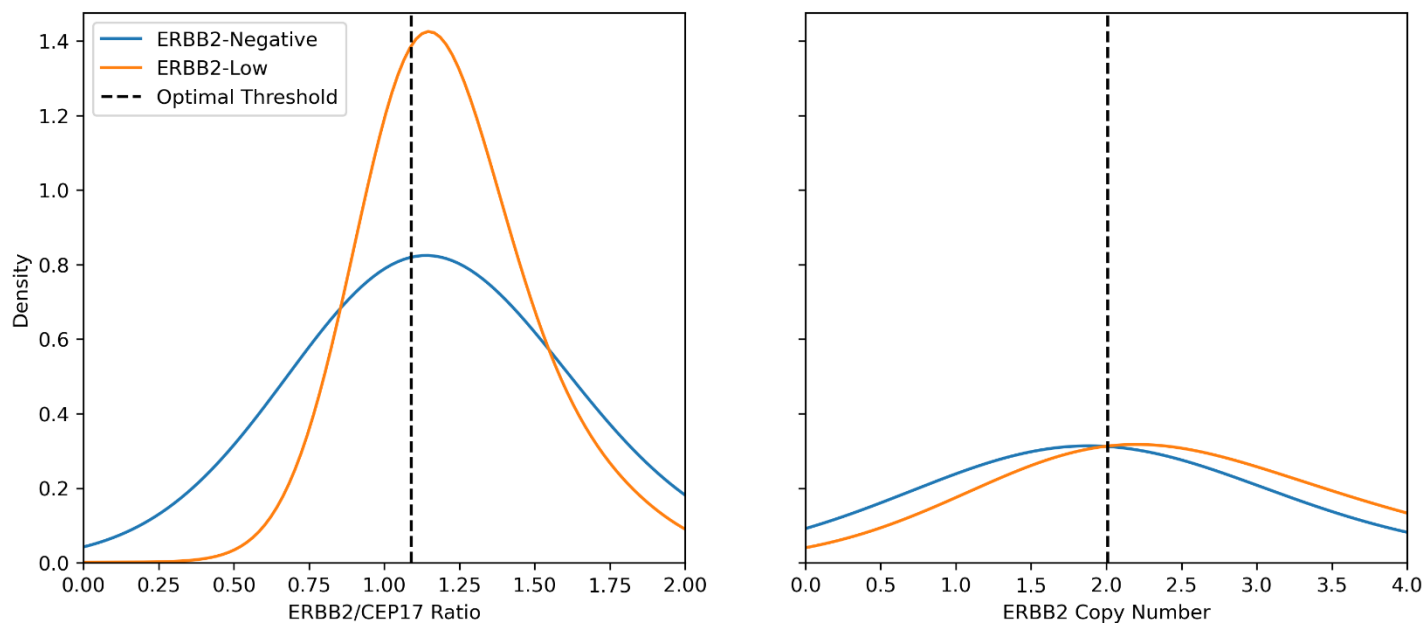
This supplementary material has been provided by the authors to give readers additional information about their work.



**eFigure 1. CONSORT Diagram for Included Patients.** Abbreviations: NCDB = National Cancer Database. ERBB2 = erb-b2 receptor tyrosine kinase 2. IHC = Immunohistochemistry. ISH = in situ hybridization.



**eFigure 2. ERBB2-Low Status by ER Expression and PR Expression.** Results from 274,716 patients with percentage ER and PR expression available. Patients with weak ER expression demonstrate a decrease in rates of ERBB2-low disease when PR expression is strong (bottom right) as opposed to weak (bottom left). Abbreviations: ERBB2 = erb-b2 receptor tyrosine kinase 2. ER = estrogen receptor. PR = progesterone receptor.



**eFigure 3. Density Plots of ERBB2/CEP17 Ratio and ERBB2 Copy Number for ERBB2-Low and ERBB2-Negative Cancers.** A total of  $n = 74,035$  patients had dual probe ERBB2/CEP17 ratio results (**left**), and a threshold ratio of 1.09 optimized Youden's index, achieving a sensitivity of 77% and specificity of 37% for ERBB2-low disease. Similarly,  $n = 99,541$  had ERBB2 copy number results (**right**), and a threshold of 2.01 had a sensitivity of 61% and specificity of 58% for identifying ERBB2-low disease. Abbreviations: ERBB2 = erb-b2 receptor tyrosine kinase 2.

**eTable 1. Baseline Patient Demographics and Clinicopathologic Characteristics per ERBB2 Immunohistochemistry Results.** P-values are listed for a chi-squared test for categorical variables and a two-sided t-test for continuous variables. Abbreviations: ERBB2 = erb-b2 receptor tyrosine kinase 2. SD = standard deviation. ER = estrogen receptor. PR = progesterone receptor.

		Overall	ERBB2 0	ERBB2 1+	ERBB2 2+	P-Value
<b>n</b>		1136016	392246	548293	195477	
<b>Age, n (%)</b>	<b>&lt; 40</b>	46482 (4.1)	17581 (4.5)	20620 (3.8)	8281 (4.2)	<0.001
	<b>40 - 49</b>	158040 (13.9)	55541 (14.2)	74976 (13.7)	27523 (14.1)	
	<b>50 - 59</b>	255811 (22.5)	88438 (22.5)	123304 (22.5)	44069 (22.5)	
	<b>60 - 69</b>	326651 (28.8)	111515 (28.4)	159406 (29.1)	55730 (28.5)	
	<b>70 - 79</b>	237176 (20.9)	81558 (20.8)	115678 (21.1)	39940 (20.4)	
	<b>≥ 80</b>	111856 (9.8)	37613 (9.6)	54309 (9.9)	19934 (10.2)	
<b>Sex, n (%)</b>	<b>Female</b>	1125645 (99.1)	389318 (99.3)	543013 (99.0)	193314 (98.9)	<0.001
	<b>Male</b>	10371 (0.9)	2928 (0.7)	5280 (1.0)	2163 (1.1)	
<b>Race / Ethnicity, n (%)</b>	<b>Asian</b>	41619 (3.7)	14112 (3.6)	19473 (3.6)	8034 (4.1)	<0.001
	<b>Hispanic</b>	62985 (5.6)	24536 (6.3)	27978 (5.1)	10471 (5.4)	
	<b>Native American</b>	3242 (0.3)	972 (0.2)	1634 (0.3)	636 (0.3)	
	<b>Non-Hispanic Black</b>	126977 (11.3)	47194 (12.1)	58236 (10.7)	21547 (11.1)	
	<b>Non-Hispanic White</b>	886131 (78.6)	299961 (77.1)	433984 (79.8)	152186 (78.5)	
	<b>Other</b>	5737 (0.5)	2217 (0.6)	2614 (0.5)	906 (0.5)	
<b>Facility Type, n (%)</b>	<b>Academic / Research</b>	333794 (30.6)	127586 (34.1)	150347 (28.5)	55861 (29.8)	<0.001
	<b>Community Cancer Program</b>	78218 (7.2)	26174 (7.0)	39368 (7.5)	12676 (6.8)	
	<b>Comprehensive Community Cancer Program</b>	450549 (41.4)	146217 (39.0)	225667 (42.8)	78665 (42.0)	
	<b>Integrated Network Cancer Program</b>	226973 (20.8)	74688 (19.9)	112291 (21.3)	39994 (21.4)	
<b>Charlson/Deyo Score, n (%)</b>	<b>0</b>	931623 (82.0)	322257 (82.2)	449731 (82.0)	159635 (81.7)	<0.001
	<b>≥ 1</b>	204393 (18.0)	69989 (17.8)	98562 (18.0)	35842 (18.3)	
<b>Grade, n (%)</b>	<b>1</b>	284050 (26.1)	91339 (24.4)	151338 (28.8)	41373 (22.0)	<0.001
	<b>2</b>	514099 (47.3)	167171 (44.6)	250798 (47.8)	96130 (51.2)	
	<b>3</b>	289022 (26.6)	115949 (31.0)	122660 (23.4)	50413 (26.8)	
<b>Histologic Subtype, n (%)</b>	<b>Ductal</b>	883090 (77.7)	296283 (75.5)	427789 (78.0)	159018 (81.3)	<0.001
	<b>Ductal and Lobular</b>	60000 (5.3)	20430 (5.2)	29711 (5.4)	9859 (5.0)	
	<b>Inflammatory</b>	1758 (0.2)	677 (0.2)	760 (0.1)	321 (0.2)	
	<b>Lobular</b>	132380 (11.7)	48657 (12.4)	64483 (11.8)	19240 (9.8)	
	<b>Medullary</b>	1461 (0.1)	734 (0.2)	571 (0.1)	156 (0.1)	
	<b>Metaplastic</b>	6236 (0.5)	3989 (1.0)	1789 (0.3)	458 (0.2)	
	<b>Mucinous</b>	22457 (2.0)	10410 (2.7)	9695 (1.8)	2352 (1.2)	
	<b>Others</b>	18347 (1.6)	7706 (2.0)	7839 (1.4)	2802 (1.4)	
	<b>Paget Disease</b>	610 (0.1)	181 (0.0)	288 (0.1)	141 (0.1)	
	<b>Papillary</b>	3049 (0.3)	1057 (0.3)	1551 (0.3)	441 (0.2)	
	<b>Sarcoma</b>	230 (0.0)	156 (0.0)	60 (0.0)	14 (0.0)	
	<b>Tubular</b>	6398 (0.6)	1966 (0.5)	3757 (0.7)	675 (0.3)	
<b>T Stage, n (%)</b>	<b>0</b>	2924 (0.3)	1165 (0.3)	1346 (0.3)	413 (0.2)	<0.001
	<b>1</b>	677942 (65.2)	230180 (64.3)	336525 (66.9)	111237 (62.5)	
	<b>2</b>	284172 (27.3)	99427 (27.8)	131739 (26.2)	53006 (29.8)	
	<b>3</b>	52152 (5.0)	19408 (5.4)	23600 (4.7)	9144 (5.1)	
	<b>4</b>	21914 (2.1)	7857 (2.2)	9803 (1.9)	4254 (2.4)	
<b>N Stage, n (%)</b>	<b>0</b>	723240 (72.2)	251448 (72.8)	351896 (72.6)	119896 (69.8)	<0.001
	<b>1</b>	216005 (21.6)	72358 (21.0)	103481 (21.3)	40166 (23.4)	
	<b>2</b>	40267 (4.0)	13564 (3.9)	19078 (3.9)	7625 (4.4)	
	<b>3</b>	22208 (2.2)	7812 (2.3)	10252 (2.1)	4144 (2.4)	
<b>Stage Group, n (%)</b>	<b>I</b>	678389 (59.7)	230618 (58.8)	335842 (61.3)	111929 (57.3)	<0.001
	<b>II</b>	309228 (27.2)	107907 (27.5)	144990 (26.4)	56331 (28.8)	
	<b>III</b>	98683 (8.7)	35646 (9.1)	44789 (8.2)	18248 (9.3)	
	<b>IV</b>	49716 (4.4)	18075 (4.6)	22672 (4.1)	8969 (4.6)	
<b>Bone Mets at Diagnosis, n (%)</b>	<b>No</b>	1097880 (97.7)	378662 (97.7)	530617 (97.7)	188601 (97.5)	<0.001
	<b>Yes</b>	26141 (2.3)	8899 (2.3)	12389 (2.3)	4853 (2.5)	
<b>Brain Mets at Diagnosis, n (%)</b>	<b>No</b>	1121087 (99.8)	386395 (99.7)	541719 (99.8)	192973 (99.8)	<0.001
	<b>Yes</b>	2575 (0.2)	1024 (0.3)	1143 (0.2)	408 (0.2)	
<b>Liver Mets at Diagnosis, n (%)</b>	<b>No</b>	1116283 (99.3)	384631 (99.3)	539588 (99.4)	192064 (99.3)	<0.001
	<b>Yes</b>	7463 (0.7)	2849 (0.7)	3291 (0.6)	1323 (0.7)	
<b>Lung Mets at Diagnosis, n (%)</b>	<b>No</b>	1112823 (99.0)	383552 (99.0)	537906 (99.1)	191365 (99.0)	<0.001
	<b>Yes</b>	10790 (1.0)	3882 (1.0)	4918 (0.9)	1990 (1.0)	
<b>ERBB2/CEP17 Ratio, mean (SD)</b>		1.3 (1.3)	1.3 (2.2)	1.3 (1.6)	1.3 (0.6)	0.001
<b>ERBB2 Copies, mean (SD)</b>		2.7 (4.2)	2.4 (4.7)	2.6 (4.5)	2.9 (3.7)	<0.001
<b>Receptor Status, n (%)</b>	<b>ER+PR+</b>	856039 (75.8)	269903 (69.2)	434346 (79.7)	151790 (78.2)	<0.001
	<b>ER+PR-</b>	109383 (9.7)	38144 (9.8)	50464 (9.3)	20775 (10.7)	

	<b>ER-PR+</b>	9559 (0.8)	4201 (1.1)	4001 (0.7)	1357 (0.7)	
	<b>ER-PR-</b>	153818 (13.6)	77693 (19.9)	55901 (10.3)	20224 (10.4)	
<b>ER (% Positive), mean (SD)</b>		78.1 (35.2)	70.8 (40.2)	82.7 (30.8)	82.0 (31.9)	<0.001
<b>PR (% Positive), mean (SD)</b>		53.9 (40.8)	49.8 (42.2)	57.9 (39.6)	52.4 (39.9)	<0.001
<b>Ki67 (% Positive), mean (SD)</b>		24.6 (26.8)	27.6 (30.1)	22.3 (25.2)	24.1 (22.4)	<0.001
<b>OncotypeDx Score, n (%)</b>	<b>High (26+)</b>	35287 (12.5)	10734 (12.4)	16594 (11.7)	7959 (14.7)	<0.001
	<b>Intermediate (11 - 25)</b>	176469 (62.5)	53496 (61.6)	88775 (62.7)	34198 (63.3)	
	<b>Low (0 - 10)</b>	70673 (25.0)	22675 (26.1)	36127 (25.5)	11871 (22.0)	
<b>Chemotherapy, n (%)</b>	<b>Chemotherapy</b>	386952 (34.5)	144168 (37.2)	172816 (31.9)	69968 (36.2)	<0.001
	<b>No Chemo</b>	735429 (65.5)	243244 (62.8)	368948 (68.1)	123237 (63.8)	
<b>Hormonal Therapy, n (%)</b>	<b>Hormonal Therapy</b>	813107 (73.3)	258075 (67.4)	407531 (76.1)	147501 (77.2)	<0.001
	<b>No Hormonal Therapy</b>	296554 (26.7)	124931 (32.6)	127954 (23.9)	43669 (22.8)	

**eTable 2. Sites of Metastatic Disease in ERBB2-Negative Versus ERBB2-Low cancers.** Adjusted odds ratio is listed for a multivariable logistic regression including age, sex, comorbidity score, facility type, race / ethnicity, grade, histologic subtype, and quantitative receptor status for prediction of presence of metastasis at diagnosis for indicated site among patients with Stage IV disease. Imputation was used for missing values. Abbreviations: ERBB2 = erb-b2 receptor tyrosine kinase 2.

<b>Metastatic Site</b>	<b>n ERBB2-Negative</b>	<b>n ERBB2-Low</b>	<b>Adjusted OR (95% CI)</b>	<b>p</b>
Brain	13,248	24,114	0.88 (0.81 - 0.96)	0.002
Lung	13,263	24,050	1.00 (0.95 – 1.05)	0.93
Liver	13,309	24,137	0.95 (0.90 – 1.00)	0.06
Bone	13,390	24,331	1.02 (0.97 – 1.07)	0.35

**eTable 3. Baseline Patient Demographics and Clinicopathologic Characteristics of Patients Treated With Neoadjuvant Chemotherapy.** P-values are listed for a chi-squared test for categorical variables and a two-sided t-test for continuous variables. Abbreviations: ERBB2 = erb-b2 receptor tyrosine kinase 2. SD = standard deviation. ER = estrogen receptor. PR = progesterone receptor.

		Missing	Overall	ERBB2-Negative	ERBB2-Low	p-Value
n			109588	44019	65569	
Age, n (%)	< 40	0	15665 (14.3)	6716 (15.3)	8949 (13.6)	<0.001
	40 - 49		26946 (24.6)	11098 (25.2)	15848 (24.2)	
	50 - 59		31534 (28.8)	12487 (28.4)	19047 (29.0)	
	60 - 69		24871 (22.7)	9622 (21.9)	15249 (23.3)	
	70 - 79		9314 (8.5)	3601 (8.2)	5713 (8.7)	
	≥ 80		1258 (1.1)	495 (1.1)	763 (1.2)	
Sex, n (%)	Female	0	109003 (99.5)	43829 (99.6)	65174 (99.4)	<0.001
	Male		585 (0.5)	190 (0.4)	395 (0.6)	
Race / Ethnicity, n (%)	Asian	874	4531 (4.2)	1721 (3.9)	2810 (4.3)	<0.001
	Hispanic		9532 (8.8)	4126 (9.4)	5406 (8.3)	
	Native American		390 (0.4)	126 (0.3)	264 (0.4)	
	Non-Hispanic Black		20292 (18.7)	8649 (19.8)	11643 (17.9)	
	Non-Hispanic White		73274 (67.4)	28752 (65.8)	44522 (68.5)	
	Other		695 (0.6)	302 (0.7)	393 (0.6)	
Facility Type, n (%)	Academic / Research	15665	32507 (34.6)	13672 (36.7)	18835 (33.3)	<0.001
	Community Cancer Program		5519 (5.9)	2201 (5.9)	3318 (5.9)	
	Comprehensive Community Cancer Program		35597 (37.9)	13514 (36.2)	22083 (39.0)	
	Integrated Network Cancer Program		20300 (21.6)	7916 (21.2)	12384 (21.9)	
Charlson/Deyo Score, n (%)	0	0	94226 (86.0)	37855 (86.0)	56371 (86.0)	0.914
	≥ 1		15362 (14.0)	6164 (14.0)	9198 (14.0)	
Grade, n (%)	1	5645	6051 (5.8)	1929 (4.6)	4122 (6.6)	<0.001
	2		34191 (32.9)	11269 (27.0)	22922 (36.9)	
	3		63701 (61.3)	28599 (68.4)	35102 (56.5)	
Histologic Subtype, n (%)	Ductal	0	93344 (85.2)	37657 (85.5)	55687 (84.9)	<0.001
	Ductal and Lobular Inflammatory		3765 (3.4)	1343 (3.1)	2422 (3.7)	
	Lobular		821 (0.7)	331 (0.8)	490 (0.7)	
	Medullary		7512 (6.9)	2651 (6.0)	4861 (7.4)	
	Medullary		135 (0.1)	72 (0.2)	63 (0.1)	
	Metaplastic		1264 (1.2)	763 (1.7)	501 (0.8)	
	Mucinous		409 (0.4)	128 (0.3)	281 (0.4)	
	Others		2137 (2.0)	1004 (2.3)	1133 (1.7)	
	Paget Disease		41 (0.0)	12 (0.0)	29 (0.0)	
	Papillary		99 (0.1)	25 (0.1)	74 (0.1)	
	Sarcoma		30 (0.0)	20 (0.0)	10 (0.0)	
	Tubular		31 (0.0)	13 (0.0)	18 (0.0)	
	T Stage, n (%)	0	1601	442 (0.4)	200 (0.5)	242 (0.4)
1			20535 (19.0)	8527 (19.7)	12008 (18.6)	
2			54626 (50.6)	22248 (51.3)	32378 (50.1)	
3			20562 (19.0)	7913 (18.3)	12649 (19.6)	
4			11822 (10.9)	4468 (10.3)	7354 (11.4)	
N Stage, n (%)	0	1510	45746 (42.3)	19833 (45.7)	25913 (40.1)	<0.001
	1		49153 (45.5)	18424 (42.4)	30729 (47.5)	
	2		7614 (7.0)	3028 (7.0)	4586 (7.1)	
Stage Group, n (%)	3		5565 (5.1)	2138 (4.9)	3427 (5.3)	
	I	0	13853 (12.6)	5858 (13.3)	7995 (12.2)	<0.001
	II		60115 (54.9)	24001 (54.5)	36114 (55.1)	
	III		35620 (32.5)	14160 (32.2)	21460 (32.7)	
ERBB2/CEP17 Ratio, mean (SD)		73933	1.3 (1.3)	1.3 (2.2)	1.3 (1.0)	0.569
ERBB2 Copies, mean (SD)		99407	2.8 (3.7)	2.5 (4.1)	2.9 (3.5)	<0.001
Receptor Status, n (%)	ER+PR+	570	46742 (42.9)	13851 (31.6)	32891 (50.4)	<0.001
	ER+PR-		12498 (11.5)	4448 (10.2)	8050 (12.3)	
	ER-PR+		2636 (2.4)	1145 (2.6)	1491 (2.3)	
	ER-PR-		47142 (43.2)	24361 (55.6)	22781 (34.9)	
ER (% Positive), mean (SD)		77646	39.4 (45.1)	27.9 (41.5)	49.0 (45.7)	<0.001
PR (% Positive), mean (SD)		77649	24.0 (36.6)	17.2 (32.7)	29.7 (38.6)	<0.001
Ki67 (% Positive), mean (SD)		92957	49.8 (34.8)	55.0 (37.8)	45.5 (31.5)	<0.001
OncotypeDx Score, n (%)	High (26+)	107025	1100 (42.9)	327 (44.2)	773 (42.4)	0.140
	Intermediate (11 - 25)		1243 (48.5)	339 (45.9)	904 (49.6)	
	Low (0 - 10)		220 (8.6)	73 (9.9)	147 (8.1)	
Hormonal Therapy, n (%)	Hormonal Therapy	1510	55228 (51.1)	17173 (39.6)	38055 (58.9)	<0.001
	No Hormonal Therapy		52850 (48.9)	26242 (60.4)	26608 (41.1)	
Pathologic Response	Residual Disease	2026	80599 (80.8)	30316 (76.4)	50283 (83.7)	<0.001
	Pathologic Complete Response		19184 (19.2)	9372 (23.6)	9812 (16.3)	



**eTable 4. Overall Survival Versus ERBB2 Immunohistochemistry Results, by Cancer Subtype and Stage.**

Adjusted hazard ratio is listed for a multivariable Cox proportional hazards model including age, sex comorbidity score, facility type, race / ethnicity, grade, histologic subtype, and quantitative estrogen and progesterone receptor status in the hormone receptor positive model, with imputation used for missing values. Abbreviations: ERBB2 = erb-b2 receptor tyrosine kinase 2. HR = hazard ratio. CI = confidence interval.

<b>Triple Negative Breast Cancer</b>							
<b>Stage</b>	<b>n ERBB2 0</b>	<b>n ERBB2 1+</b>	<b>n ERBB2 2+</b>	<b>Adjusted HR, ERBB2 1+ (95% CI)</b>	<b>p</b>	<b>Adjusted HR, ERBB2 2+ (95% CI)</b>	<b>p</b>
1	22662	17152	6185	1.02 (0.98 - 1.06)	0.40	0.98 (0.93 - 1.04)	0.54
2	23467	17911	6358	0.97 (0.94 - 1.0)	0.03	0.89 (0.85 - 0.93)	< 0.001
3	8021	6281	2436	0.96 (0.92 - 1.00)	0.06	0.86 (0.81 - 0.91)	< 0.001
4	3067	2237	791	0.94 (0.89 - 0.98)	0.009	0.87 (0.81 - 0.93)	< 0.001
<b>Hormone Receptor Positive</b>							
1	154377	246550	80685	1.01 (0.99 - 1.02)	0.27	1.00 (0.99 - 1.02)	0.78
2	63386	103504	40215	1.0 (0.98 - 1.02)	0.87	0.98 (0.96 - 1.01)	0.16
3	17998	28893	11637	0.98 (0.96 - 1.01)	0.21	0.96 (0.93 - 0.99)	0.01
4	8040	12726	5141	0.98 (0.96 - 1.01)	0.20	0.93 (0.90 - 0.97)	< 0.001

**eTable 5. Sensitivity and Specificity for Prediction of ERBB2-Low Status Using Select Cutoffs for ERBB2**

**ISH Results.** Results are computed using n = 74,035 patients had dual probe ERBB2/CEP17 ratio results and n = 99,541 who had ERBB2 copy number results. Abbreviations: ERBB2 = erb-b2 receptor tyrosine kinase 2. ISH = in situ hybridization.

ERBB2 Copy Number			ERBB2/CEP17 Ratio		
Cutoff	Sensitivity (%)	Specificity (%)	Cutoff	Sensitivity (%)	Specificity (%)
1	98.8	4.1	1	98.7	3.3
1.15	92.1	18.9	1.05	79.2	33.8
1.3	89	23	1.1	76	37.4
1.45	85.7	27.3	1.15	52.6	58.6
1.6	84.1	29.6	1.2	50.2	61.2
1.75	79.3	37	1.25	34.1	74.5
1.9	74.7	42.6	1.3	32.4	76.1
2.05	61.1	58.2	1.35	22.6	83.7
2.2	55.4	63.5	1.4	21.6	84.5
2.35	46.7	71.8	1.45	15.5	88.6
2.5	43.1	75.1	1.5	14.9	89.1
2.65	36.8	80.5	1.55	10.8	91.8
2.8	34.1	82.4	1.6	10.3	92.1
2.95	29	86.1	1.65	7.4	93.9
3.1	26.7	87.6	1.7	7.1	94.2
3.25	22.6	89.8	1.75	4.7	95.5
3.4	20.8	90.7	1.8	4.5	95.7
3.55	16.9	92.4	1.85	2.6	97.1
3.7	15	93.3	1.9	2.5	97.2
3.85	11.2	94.6	1.95	1.6	97.9
4	9.6	95.4	2	1.5	98