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Real-World Landscape of Genomic Medicine in Breast Cancer Revealed by the C-CAT Database: Reappraisal of Drug Accessibility and Clinical Utility in 6,307 Patients

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Abstract

Background

Comprehensive genomic profiling (CGP) has advanced precision oncology in breast cancer, yet its real-world contribution to treatment selection in Japan remains unclear.

Methods

We analyzed 6,307 Japanese patients with breast cancer who underwent CGP in the nationwide Center for Cancer Genomics and Advanced Therapeutics (C-CAT) database. Drug accessibility to Pharmaceuticals and Medical Devices Agency (PMDA)-approved therapies was assessed using two criteria, excluding biomarkers identifiable by prior companion diagnostics: Criterion I reflecting phase III breast cancer trials, and Criterion II reflecting phase I/II basket or tumor-agnostic trials. Evidence levels at testing were compared with those reassessed using evidence available as of October 2025.

Results

At least one genomic alteration was detected in 97.6% of cases; *TP53* (53.9%), *PIK3CA* (37.7%) were most frequent. Re-evaluation increased Evidence Level A assignments from 3,757 to 5,874. Nevertheless, biomarkers linked to PMDA-approved therapies were limited to ten categories: *PIK3CA/AKT1/PTEN* alterations, *ERBB2* amplification, *BRCA1/2* mutations, *NTRK* fusions, *BRAF* V600 mutation, and TMB-H/MSI-H. Drug accessibility was 30.8% under Criterion I, driven exclusively by eligibility for capivasertib. Under Criterion II, the accessibility was 19.5%, comprising *ERBB2* amplification (4.7%), somatic *BRCA1/2* mutations (3.4%), *NTRK* fusions (0.1%), *BRAF* V600 mutation (0.2%), and non-overlapping TMB-H/MSI-H (11.1%). The prevalence of somatic *BRCA1/2* mutations in germline *BRCA1/2* noncarriers were identified in 3.4%, representing the first large-scale estimate in Japanese breast cancer.

Conclusion

Despite high detection rates, translation into PMDA-approved therapies remains limited, underscoring the need to optimize testing timing, expand trial access, harmonize molecular tumor boards practice, and consider breast cancer–specific mini-panels.

Introduction

Recent advances in molecular oncology have transformed the clinical management of cancer, positioning precision oncology—therapeutic decision-making based on tumor genomic alterations—at the center of contemporary practice[1]. Improvements in next-generation sequencing (NGS) technologies now enable comprehensive profiling of somatic mutations, gene fusions, and copy-number alterations, thereby facilitating the identification of actionable targets and prediction of therapeutic sensitivity[2]. Accordingly, cancer classification is shifting from morphology-based taxonomy to molecular subtyping, and the traditional “one-size-fits-all” approach is increasingly outdated.

In Japan, comprehensive genomic profiling (CGP) testing was incorporated into the national health insurance system in 2019, leading to the nationwide establishment of a clinical genomic medicine infrastructure centered on designated core hospitals[3]. This system has expanded CGP from a technology largely restricted to research settings to a standardized component of routine oncology practice[4]. Simultaneously, liquid biopsy—analysis of circulating tumor DNA (ctDNA)—is increasingly recognized for its clinical utility in elucidating mechanisms of acquired resistance and enabling early detection of minimal residual disease (MRD)[5, 6]. MRD-guided prediction of recurrence and monitoring of treatment response may further refine adjuvant therapy selection[7].

Artificial intelligence (AI) has also accelerated the interpretation of genomic and multi-omic data. AI-based models integrate large-scale omics datasets, support automated inference of the clinical significance of genomic alterations, and assist in predicting therapeutic sensitivity[8]. Large language models (LLMs), capable of surveying synthesizing rapidly expanding literature and real-world evidence, may further support evidence-based treatment recommendations. Collectively, these tools allow large-scale clinical CGP datasets to be analyzed more comprehensively and dynamically[9].

Despite these advances, several challenges continue to limit the clinical impact of precision oncology. First, only a minority of NGS-identified alterations represent truly actionable mutations with established therapeutic implications[10]. Many alterations remain variants of uncertain significance (VUS). Second, therapeutic response to identical genomic alterations may differ by tumor type, and intertumoral heterogeneity contributes to therapeutic resistance[11]. To overcome these gaps, integrated multi-omic approaches—incorporating transcriptomic or

methylation data—are being explored; however, such methods may be irrelevant or impractical in real-world setting, and their clinical value remains uncertain[12].

To comprehensively evaluate the present state of precision oncology in breast cancer, we analyzed genomic and clinical data from 6,307 Japanese patients registered in the national Center for Cancer Genomics and Advanced Therapeutics (C-CAT) database. We summarized the trajectory of cancer genomic medicine over the past six years and quantified drug accessibility rates. To evaluate clinical needs, we defined two criteria of drug accessibility[13]:

Criterion I:

The proportion of patients who, through CGP (but not companion diagnostics [CDx]), were first linked to PMDA-approved drugs supported by evidence from a phase III breast cancer trial.

Criterion II:

The proportion of patients who, through CGP (but not CDx), were first linked to PMDA-approved drugs supported by evidence from phase I/II basket or tumor-agnostic trials.

Criterion I reflects the expectations of general clinicians who rely on conventional trial-based evidence; Criterion II represents the perspectives of genomic-medicine specialists who incorporate tumor-agnostic approvals. Both criteria were used to quantify drug accessibility and evaluate clinical utility.

We additionally compared the Evidence Levels (ELs) assigned in the original C-CAT Expert Panel reports (EP-EL in C-CAT) with those updated using a simulated expert panel review based on evidence available as of October 2025 (EP-EL in SIM). This process enabled us to evaluate whether accumulated evidence increased drug accessibility and to identify unresolved challenges and future directions.

Materials and Methods

Study design and patients

We conducted a retrospective analysis of clinical and genomic data from patients with breast cancer who underwent CGP testing between June 2019 and December 2024. Clinical and genomic information was collected from all patients who received any CGP assay. Data elements included CGP results (oncogenic alterations, tumor mutational burden [TMB]), patient characteristics (age, sex, Eastern Cooperative Oncology Group Performance Status [ECOG-PS], estrogen receptor [ER] status, HER2 status), assay type, specimen origin, and cancer-predisposing alterations identified via prior CDx testing (e.g., *BRCA1/2*). The counts of oncogenic alterations were defined as those categorized as “Oncogenic” or “Predisposing” in the C-CAT database.

Target alterations were extracted from variants classified as “Oncogenic”, “Likely Oncogenic”, “Pathogenic”, or “Likely Pathogenic”. TMB-high (TMB-H) was defined as ≥ 10 muts/Mb for tissue-based assays and ≥ 14 muts/Mb for liquid biopsy assays. Microsatellite instability-high (MSI-H) was counted only for assays reporting MSI (GenMine TOP® does not report MSI). HER2 positivity was defined as immunohistochemistry (IHC) 3 + or in situ hybridization (ISH)-positive.

For capivasertib eligibility, *PIK3CA, AKT1, PTEN* mutations, and *PTEN* deletions were identified in ER-positive, HER2-negative breast cancer. Somatic *BRCA1/2* mutations (*sBRCA1/2*m) were assessed across all assays; germline *BRCA1/2* mutations (*gBRCA1/2*m) were assessed only in assays capable of paired germline analysis (OncoGuide™ NCC Oncopanel [NOP], GenMine TOP®). Here, we use the term ‘mutation’ to describe a deleterious sequence variant, and the term ‘carrier’ to describe an individual with a germline mutation.

The Center for Cancer Genomics and Advanced Therapeutics (C-CAT) database

This study used the national C-CAT database maintained by the Ministry of Health, Labour and Welfare. C-CAT collects CGP results and clinical information from all insured CGP assays in Japan[4]. Since June 2019, FoundationOne® CDx (F1CDx) (Foundation Medicine Inc., Cambridge, MA, USA) and OncoGuideTM NCC Oncopanel (NOP) (Sysmex Co., Ltd., Kobe, Japan) have been started; FoundationOne® Liquid CDx (F1Liquid) (Foundation Medicine Inc., Cambridge, MA, USA) was added in 2021, and Guardant360® CDx (Guardant Health Inc., Palo Alto, CA, USA) and GenMine TOP® (Konica Minolta, Inc., Toyo, Japan) were approved in 2023. All assays were included in this analysis.

Under Japanese insurance, CGP testing is permitted for patients with advanced solid tumors who have completed or are expected to complete standard therapy. By December 2024, approximately 7,000 patients with breast cancer had undergone CGP testing, of whom 99.7%

consented to secondary use of their data[14].

In C-CAT, test results are interpreted and clinical annotations of genomic alterations are determined using the Cancer Knowledge Database (CKDB) and commercial tools (e.g., QIAGEN Clinical Insight, JAX-CKB). Evidence Levels (ELs) are defined from A to R (supplementary Table 1), and secondary germline findings reviewed by expert panels (molecular tumor boards [MTBs]). Some missing clinical and treatment data were noted in the dataset.

Assessment of drug accessibility rates in clinical practice

Drug accessibility was evaluated by extracting actionable alterations annotated as "Predictive" in C-CAT. For the top 100 most frequent alterations, we listed drugs matched to each alteration together with their EP-ELs as assigned in the original C-CAT reports. We then calculated the number of drugs classified as Evidence Level A (EL-A; EP-EL in C-CAT). Subsequently, we conducted an expert panel simulation in which C-CAT reports were re-evaluated by expert panel members from multiple designated core hospitals, using evidence available as of October 2025. We then recalculated the numbers of drugs classified as EL-A (EP-EL in SIM). Drug accessibility rates were calculated according to Criterion I and Criterion II defined above.

The protocol was approved by the institutional review board of Kyoto Prefectural University of Medicine (ERB-C-2860) and the C-CAT Review Committee (AP20241127-01E). The requirement for informed consent was waived due to the retrospective nature of the study.

Statistical analyses

All statistical analyses were performed using R statistical software version 4.3.2. The oncoprint visualizations (Fig. 1) were created using the GenVisR package.

Results

Clinical and genomic characteristics

In the C-CAT database, a total of 6,307 patients with breast cancer with analyzable data were included. The median age was 56 years (range, 22–91), and 99.4% were female (n = 6,269). ECOG-PS of 0–1 was observed in 92.3% (n = 5,823). ER positivity was 63.9% (Table 1). F1CDx was the most frequently used assay (71.3%), followed by F1Liquid (17.5%), NOP (8.3%), GenMineTOP® (1.6%), and Guardant360® (1.3%). Figure 1 presents an oncoprint of genomic alterations identified by CGP testing in 6,307 Japanese patients with breast cancer, integrating small variants, deletions, amplifications, and rearrangements, together with MSI, TMB, and ER and HER2 status extracted from clinical data. The most frequently altered genes were *TP53* (53.9%), *PIK3CA* (37.7%), *MYC* (17.9%), *CCND1* (15.8%), and *GATA3* (14.7%), followed by *ESR1*, which ranked tenth with a mutation frequency of 11.8%. The frequency of alterations outside the top ten genes was only a few percent. Overall, at least one genomic alteration was detected in 6,156 of 6,307 patients (97.6%) (Table 2). The median TMB was 4.0 muts/Mb, and TMB-H was observed in 11.1% of cases. MSI-H was identified in 0.4% of the cohort (Table 2).

Table 1
Patient and Clinical Characteristics in C-CAT Database.

Variable	Classification	N = 6307 (%)
Sex	Female	6269 (99.4)
	Male	38 (0.6)
Median age, range		56 (22–91)
Age group, years	-29	42 (0.7)
	30–39	363 (5.8)
	40–49	1282 (20.3)
	50–59	2071 (32.8)
	60–69	1591 (25.2)
	70–79	872 (13.8)
	80-	86 (1.4)
Alcohol	Yes	270 (4.3)
	None	5257 (83.3)
	Unknown	780 (12.4)
Smoking	Yes	1190 (18.9)
	None	4621 (73.3)
	Unknown	496 (7.8)
Estrogen receptor status	Positive	4031 (63.9)
	Negative	1918 (30.4)
	Unknown/Uninspected	358 (5.7)
Progesteron receptor status	Positive	2969 (47.1)
	Negative	2947 (46.7)
	Unknown/Uninspected	391 (6.2)
HER2	Positive	624 (9.9)
	Negative	5328 (84.5)
	Unknown/Uninspected	355 (5.6)
gBRCA1	Positive	144 (2.3)
	Negative	3655 (57.9)
	Unknown/Uninspected	2508 (39.8)
gBRCA2	Positive	264 (4.2)
	Negative	3515 (55.7)
	Unknown/Uninspected	2528 (40.1)
ECOG-PS	0	3738 (59.3)
	1	2085 (33.0)
	2≦	212 (3.4)
C-CAT: Center for Cancer Genomics and Advanced Therapeutics		
ECOG-PS: Eastern Cooperative Oncology Group Performance Status		
CGP: Comprehensive genomic profiling		

Variable	Classification	N = 6307 (%)
	Unknown	272 (4.3)
Type of CGP test	FoundationOne® CDx	4496 (71.3)
	FoundationOne® Liquid CDx	1104 (17.5)
	OncoGuide™ NCC Oncopanel System	522 (8.3)
	Guardant360® CDx	85 (1.3)
	GenMineTOP® CDx	100 (1.6)
Specimens submitted for gene panel testing	Primary lesion	2682 (42.5)
	Metastatic lesion	2430 (38.5)
	Liquid biopsy	1189 (18.9)
	Unknown	6 (0.1)
C-CAT: Center for Cancer Genomics and Advanced Therapeutics		
ECOG-PS: Eastern Cooperative Oncology Group Performance Status		
CGP: Comprehensive genomic profiling		

Table 2
Genomic Characteristics in CGP Tests.

Variable	Classification	N = 6307 (%)
mutation	Yes	6156 (97.6)
	No	151 (2.4)
TMB (Muts/Mb)	Low (tissue < 10, liquid < 14)	5523 (87.6)
	High (≥ 10 tissue, ≥ 14 liquid)	698 (11.1)
	Unknown	86 (1.3)
Median TMB, range		4 (0-258.9)
MSI-status※	High	28 (0.4)
	Stable	4379 (69.4)
	Equivocal	24 (0.4)
	High not detected	1097 (17.4)
	Cannot be determined	360 (5.7)
	Unknown	419 (6.7)
※ GenMineTOP is included in Unknown.		
CGP: Comprehensive genomic profiling		
TMB: tumor mutation burden		
Muts/Mb: mutations-per-megabase		
MSI: microsatellite instability		

The TOP100 Genomic Alterations, Evidence Levels at the Time of CGP Testing (EP-EL in C-CAT) and the Reassessed Evidence Levels (EP-EL in SIM), and Drugs Recommended by Expert Panels and Drug Accessibility Rates

Table 3 summarizes the 100 most frequent genomic alterations identified in Japanese patients with advanced or metastatic breast cancer, along with the evidence levels assigned by the expert panels at the time of CGP testing (EP-EL in C-CAT), as documented in the C-CAT reports. The proportion of alterations classified as evidence level A (EL-A) at the time of CGP testing is also shown. Furthermore, using the

expert panel simulation incorporating updated evidence as of October 2025 (EP-EL in SIM), we reassessed evidence levels and corresponding therapeutic recommendations. Based on these data, Criteria I and II were calculated to assess drug accessibility and clinical applicability, and the results are presented in Table 3.

Table 3

Top 100 Genomic Alteration: Evidence Levels at the Time of CGP Tests (EP-EL in C-CAT) and the reassessed Evidence Levels (EP-EL in SIM), and Drugs Recommended by Expert Panels and Drug Accessibility Rates.

No.	Gene	(%)	EP in C-CAT		EP in SIM				The proportion first linked to PMDA-approved drugs with phase III trial evidence for breast cancer through CGP tests but not prior CDx (Criterion 1) (%)	The proportion first linked to PMDA-approved drugs including based on phase I and II trial evidence through CGP tests but not prior CDx (Criterion 2) (%)
			EL※	EL-A (N)	EL※	EL-A (N)	Drugs recommended by the EP (including FDA-approval)	Drugs recommended by the EP (PMDA-approval only)		
1	*TP53*	53.9	C, E	-	-	-	-	-	0	0
2	*PIK3CA*	37.7	A, B, C, D, E	2192	A_alpelisib A_capivasertib	2377	alpelisib, fulvestrant, alpelisib + fulvestrant	If mutation, A_capivasertib + fulvestrant	23.2 (ER+HER2−)	0
3	*MYC*	17.9	-	-	-	-	-	-	0	0
4	*CCND1*	15.8	C, E	-	-	-	-	-	0	0
5	*GATA3*	14.7	-	-	-	-	-	-	0	0
6	*FGF19*	14.3	-	-	If co-amplification FGF3/4/19, D_FGFRinhibitor	-	-	-	0	0
7	*PTEN*	13.4	A, B, C, E	296	If loss and truncation, A_capivasertib C_everolimus	809	-	C_everolimus If mutation and deletion, A_capivasertib + fulvestrant	6.3 (ER+HER2−)	0
8	*ERBB2*	13.1	A, B, C, D, E	620	If amplification, A_trastuzumab A_pertuzumab A_lapatinib A_T-DM1 A_T-DXd A_tucatinib A_neratinib If mutation, C_neratinib C_T-DXd	851	anit-HER2 drugs	If amplification, A_trastuzumab A_pertuzumab A_lapatinib A_T-DM1 A_T-DXd	0	4.7 (changed from HER2 − based on IHC/ISH to HER2 + through CGP testing)
9	*FGFR1*	12.4	B, C, D, E	-	D_pemigatinib D_futibatinib D_erdafitinib D_infigratinib	-	-	-	0	0

No.	Gene	(%)	EP in C-CAT		EP in SIM				The proportion first linked to PMDA-approved drugs with phase III trial evidence for breast cancer through CGP tests but not prior CDx (Criterion 1) (%)	The proportion first linked to PMDA-approved drugs including based on phase I and II trial evidence through CGP tests but not prior CDx (Criterion 2) (%)
			EL※	EL-A (N)	EL※	EL-A (N)	Drugs recommended by the EP (including FDA-approval)	Drugs recommended by the EP (PMDA-approval only)		
10	*ESR1*	11.8	A, B, C, E	405	A_elasestrant B_fulvestrant	686	elacestrant	B_fulvestrant	0	0
11	*RB1*	9.0	-	-	-	-	-	-	0	0
12	*AKT1*	8.4	A, B	191	A_capivasertib	459	-	If mutation, A_capivasertib + fulvestrant	4.5 (ER+HER2−)	0
13	*BRCA2*	7.3	A, B, C	30	A_olaparib A_talazoparib A_niraparib C_rucaparib	459	olaparib, talazoparib	A_olaparib A_talazoparib	0	2.2 (g*BRCA2*− s*BRCA2+*)
14	*CDKN2A*	6.6	E	-	-	-	-	-	0	0
15	*MDM4*	6.4	-	-	-	-	-	-	0	0
16	*NF1*	6.2	C, E	-	C_MEKinhibitor	-	-	-	0	0
17	*CDH1*	6.0	-	-	-	-	-	-	0	0
18	*RAD21*	5.8	-	-	-	-	-	-	0	0
19	*ARID1A*	5.5	E	-	-	-	-	-	0	0
20	*IKBKE*	5.2	-	-	-	-	-	-	0	0
21	*ZNF703*	5.0	-	-	-	-	-	-	0	0
22	*DDR2*	5.0	-	-	-	-	-	-	0	0
23	*MCL1*	5.0	-	-	-	-	-	-	0	0
24	*AURKA*	4.9	-	-	-	-	-	-	0	0
25	*STK11*	4.9	-	-		-	-	-	0	0
26	*CDKN2B*	4.4	-	-	-	-	-	-	0	0
27	*MDM2*	4.1	C	-	-	-	-	-	0	0
28	*KRAS*	4.1	C, D, E	-	If G12C, C_sotorasib	-	-	-	0	0
29	*MAP3K1*	4.1	-	-	-	-	-	-	0	0
30	*AKT3*	3.9	-	-	-	-	-	-	0	0
31	*MAP2K4*	3.7	-	-	-	-	-	-	0	0
32	*DNMT3A*	3.6	C	-	-	-	-	-	0	0

No.	Gene	(%)	EP in C-CAT		EP in SIM				The proportion first linked to PMDA-approved drugs with phase III trial evidence for breast cancer through CGP tests but not prior CDx (Criterion 1) (%)	The proportion first linked to PMDA-approved drugs including based on phase I and II trial evidence through CGP tests but not prior CDx (Criterion 2) (%)
			EL※	EL-A (N)	EL※	EL-A (N)	Drugs recommended by the EP (including FDA-approval)	Drugs recommended by the EP (PMDA-approval only)		
33	*BRCA1*	3.4	A, B, C	14	A_olaparib A_talazoparib A_niraparib C_rucaparib	216	olaparib, talazoparib	A_olaparib A_talazoparib	0	1.3 (g*BRCA1*–s*BRCA1+*)
34	*GNAS*	3.2	-	-	-	-	-	-	0	0
35	*KDM5A*	3.0	-	-	-	-	-	-	0	0
36	*ZNF217*	3.0	-	-	-	-	-	-	0	0
37	*NTRK1*	2.7	C	-	If fusion, A_entrectinib A_larotrectinib If amplification, D_TRKinhibitor	4	-	If fusion, A_entrectinib A_larotrectinib	0	0.05
38	*ATM*	2.6	C, E	-	C_olaparib C_talazoparib C_niraparib C_rucaparib	-	-	-	0	0
39	*FGFR2*	2.5	C, D, E	-	If fusion, C_pemigatinib C_futibatinib D_erdafitinib D_infigratinib If mutation, D_pemigatinib D_futibatinib C_erdafitinib D_infigratinib If not fusion and mutation, D_pemigatinib D_futibatinib D_erdafitinib	-	-	-	0	0

No.	Gene	(%)	EP in C-CAT		EP in SIM				The proportion first linked to PMDA-approved drugs with phase III trial evidence for breast cancer through CGP tests but not prior CDx (Criterion 1) (%)	The proportion first linked to PMDA-approved drugs including based on phase I and II trial evidence through CGP tests but not prior CDx (Criterion 2) (%)
			EL※	EL-A (N)	EL※	EL-A (N)	Drugs recommended by the EP (including FDA-approval)	Drugs recommended by the EP (PMDA-approval only)		
					D_infigratinib					
40	*CHEK2*	2	C	-	C_olaparib C_talazoparib C_niraparib C_rucaparib	-	-	-	0	0
41	*EGFR*	2.2	C, D, E	-	If mutation (not exon20ins), C_gefitinib C_elrotinib C_afatinib C_osimertinib If mutation (exon20ins), C_osimertinib If amplification, C_afatinib D_EGFRinhibitor	-	-	-	0	0
42	*MUTYH*	2.2	-	-	-	-	-	-	0	0
43	*CCNE1*	2.2	E	-	-	-	-	-	0	0
44	*SF3B1*	2.1	-	-	-	-	-	-	0	0
45	*TBX3*	2.1	-	-	-	-	-	-	0	0
46	*CCND2*	2.1	E	-	-	-	-	-	0	0
47	*SPEN*	2.1	-	-	-	-	-	-	0	0
48	*MSH6*	2.1	-	-	-	-	-	-	0	0
49	*EMSY*	2.1	-	-	-	-	-	-	0	0
50	*CDK4*	2.0	C	-	C_CDK4/6inhibitor	-	-	-	0	0
51	*TET2*	2.0	-	-	-	-	-	-	0	0
52	*SMAD4*	2.0	-	-	-	-	-	-	0	0
53	*JAK2*	1.7	-	-	-	-	-	-	0	0
54	*VEGFA*	1.7	-	-	-	-	-	-	0	0
55	*PALB2*	1.6	C	-	C_olaparib C_talazoparib	-	-	-	0	0

No.	Gene	(%)	EP in C-CAT		EP in SIM				The proportion first linked to PMDA-approved drugs with phase III trial evidence for breast cancer through CGP tests but not prior CDx (Criterion 1) (%)	The proportion first linked to PMDA-approved drugs including based on phase I and II trial evidence through CGP tests but not prior CDx (Criterion 2) (%)
			EL※	EL-A (N)	EL※	EL-A (N)	Drugs recommended by the EP (including FDA-approval)	Drugs recommended by the EP (PMDA-approval only)		
					C_niraparib C_rucaparib					
56	*KMT2D*	1.6	-	-	-	-	-	-	0	0
57	*ERBB3*	1.5	-	-	-	-	-	-	0	0
58	*CDKN1B*	1.5	-	-	-	-	-	-	0	0
59	*CREBBP*	1.5	-	-	-	-	-	-	0	0
60	*RICTOR*	1.5	-	-	-	-	-	-	0	0
61	*BCL2L1*	1.5	-	-	-	-	-	-	0	0
62	*ASXL1*	1.5	-	-	-	-	-	-	0	0
63	*SRC*	1.5	-	-	-	-	-	-	0	0
64	*CCND3*	1.5	-	-	-	-	-	-	0	0
65	*BRAF*	1.4	A, C, D, E	9	If V600, A_dabrafenib + trametinib A_dabrafenib A_trametinib If classII, C_MEKinhibitor	If V600, 13	dabrafenib + trametinib dimethyl sulfoxide	If V600, A_dabrafenib + trametinib A_dabrafenib A_trametinib	0	0.2
66	*RAC1*	1.4	-	-	-	-	-	-	0	0
67	*CDK12*	1.6	C, D	-	C_olaparib C_talazoparib C_niraparib C_rucaparib If loss of function, C_immune checkpoint inhibitor	-	-	-	0	0
68	*NOTCH1*	1.3	-	-	-	-	-	-	0	0
69	*SMO*	1.3	E	-	-	-	-	-	0	0
70	*NKX2-1*	1.3	-	-	-	-	-	-	0	0
71	*KIT*	1.3	C, D	-	If mutation_Exson 17,	-	-	-	0	0

No.	Gene	(%)	EP in C-CAT		EP in SIM				The proportion first linked to PMDA-approved drugs with phase III trial evidence for breast cancer through CGP tests but not prior CDx (Criterion 1) (%)	The proportion first linked to PMDA-approved drugs including based on phase I and II trial evidence through CGP tests but not prior CDx (Criterion 2) (%)
			EL※	EL-A (N)	EL※	EL-A (N)	Drugs recommended by the EP (including FDA-approval)	Drugs recommended by the EP (PMDA-approval only)		
					R_imatinib R_sunitinib C_dasatinib C_avapritinib C_ponatinib If mutation_Exson 11, C_imatinib C_dasatinib C_ponatinib If amplification, C_imatinib C_dasatinib C_ponatinib					
72	*CARD11*	1.2	-	-	-	-	-	-	0	0
73	*RAF1*	1.2	-	-	-	-	-	-	0	0
74	*FGFR4*	1.2	D	-	-	-	-	-	0	0
75	*TERT*	1.2	-	-	-	-	-	-	0	0
76	*BCL6*	1.2	-	-	-	-	-	-	0	0
77	*EZH2*	1.2	-	-	-	-	-	-	0	0
78	*HARS*	1.1	-	-	-	-	-	-	0	0
79	*NOTCH3*	1.1	-	-	-	-	-	-	0	0
80	*PIK3R1*	1.1	-	-	-	-	-	-	0	0
81	*ROS1*	1.1	-	-	If fusion, C_crizotinib C_entrectinib C_lorlatinib	-	-	-	0	0
82	*KDM6A*	1.0	-	-	-	-	-	-	0	0
83	*CDK6*	1.0	-	-	-	-	-	-	0	0
84	*JAK1*	1.0	-	-	-	-	-	-	0	0
85	*PIK3CB*	1.0	-	-	-	-	-	-	0	0

No.	Gene	(%)	EP in C-CAT		EP in SIM				The proportion first linked to PMDA-approved drugs with phase III trial evidence for breast cancer through CGP tests but not prior CDx (Criterion 1) (%)	The proportion first linked to PMDA-approved drugs including based on phase I and II trial evidence through CGP tests but not prior CDx (Criterion 2) (%)
			EL※	EL-A (N)	EL※	EL-A (N)	Drugs recommended by the EP (including FDA-approval)	Drugs recommended by the EP (PMDA-approval only)		
86	*MTAP*	1.0	-	-	-	-	-	-	0	0
87	*NOTCH2*	1.0	-	-	-	-	-	-	0	0
88	*APC*	1.0	E	-	-	-	-	-	0	0
89	*SETD2*	1.0	-	-	-	-	-	-	0	0
90	*TSC1*	1.0	C, D	-	-	-	-	-	0	0
91	*AKT2*	1.0	-	-	-	-	-	-	0	0
92	*BRD4*	1.0	-	-	-	-	-	-	0	0
93	*MYCN*	0.9	-	-	-	-	-	-	0	0
94	*CBFB*	0.9	-	-	-	-	-	-	0	0
95	*MEN1*	0.9	-	-	-	-	-	-	0	0
96	*TSC1*	0.9	-	-	-	-	-	-	0	0
97	*AR*	0.9	-	-	-	-	-	-	0	0
98	*RNF43*	0.9	-	-	-	-	-	-	0	0
99	*SOX9*	0.9	-	-	-	-	-	-	0	0
100	*FLT3*	0.8	C	-	C_gilteritinib	-	-	-	0	0

C-CAT: Center for Cancer Genomics and Advanced Therapeutics

CGP: Comprehensive genomic profiling

EP: Expert panel

EL: Evidence level

EL-A: Evidence level-A

SIM: Simulation

N: number of patients

PMDA: Pharmaceuticals and Medical Devices Agency

CDx: Companion diagnostics

ER+: Estrogen receptor-positive

HER2−: HER2-negative

HER2+: HER2-positive

gBRCA−sBRCA+: germline breast cancer susceptibility gene-negative and somatic breast cancer susceptibility gene-positive

※Exclusion of EL-R

Compared with EP-EL in C-CAT, the number of EL-A assignments increased substantially after re-evaluation using EP-EL in SIM, rising from 3,757 to 5,874. Among variants assigned as EL-A under EP-EL in SIM, the corresponding PMDA-approved agents included: anti-HER2 therapies for *ERBB2* amplification, PARP inhibitors for *BRCA1/2* mutations, capivasertib plus fulvestrant for *PIK3CA/AKT1/PTEN* alterations, entrectinib and larotrectinib for *NTRK* fusions, and dabrafenib plus trametinib for *BRAF* mutations. After excluding biomarkers already evaluable by pre-CGP CDx, clinically actionable alterations firstly identified by CGP were: *ERBB2* amplification in HER2-negative breast cancer (4.3%), s*BRCA1/2*m carriers in *gBRCA1/2*m noncarriers (3.4%), *PIK3CA/AKT1/PTEN* alterations in ER-positive/HER2-negative breast cancer (non-overlapping; 30.8%), *NTRK* fusions (0.1%), and *BRAF*V600 mutations (0.2%).

According to Criterion I, only *PIK3CA/AKT1/PTEN* alterations (30.8%) fulfilled the requirement of linking to PMDA-approved therapies supported by phase III trial evidence in breast cancer. According to Criterion II, which included PMDA-approved drugs supported by phase I/II basket trial or tumor-agnostic evidence, the drug accessibility rate comprised *ERBB2* amplification (4.7%), *sBRCA1/2* mutations (3.4%), *NTRK* fusions (0.1%), *BRAF*V600 mutations (0.2%), and non-overlapping TMB-H/MSI-H (11.1%). The overall Criterion II accessibility rate was 19.5% (Tables 3 and 4). When grouped by biomarkers, only ten actionable categories remained clinically relevant:

Table 4
Summary of Evidence Level A in the Expert Panel Simulation.

Biomarkers	**Drugs recommended by the EP (PMDA-approval only)**	**Criterion 1 (%) phase III evidence**	**Criterion 2 (%) phase I/II evidence**
PIK3CA/AKT1/PTEN alterations	capivasertib	30.8 (ER+HER2−)	
TMB-high/MSI-high	pembrolizumab		11.1
ERBB2 amplification	anti-HER2 therapy		4.7 (HER2−)
sBRCA1/2 mutation	olaparib		3.4 (*gBRCA1/2*−)
BRAF V600 mutation	dabrafenib + trametinib		0.2
NTRK fusions	entrectinib, larotrectinib		0.1
total		30.8	19.5
EP: Expert panel			
ER+: Estrogen receptor-positive			
HER2−: HER2-negative			

sBRCA: somatic breast cancer susceptibility gene

gBRCA−: germline breast cancer susceptibility gene-negative

PIK3CA, AKT1, PTEN, ERBB2, BRCA1, BRCA2, NTRK, BRAF, TMB, and MSI.

Prevalence and Concordance of Germline and Somatic BRCA1/2 Mutations

Germline *BRCA1/2* mutations previously assessed by CDx (e.g., BRACAnalysis®) were identified in 144 patients (2.3%) for *gBRCA1*m carriers and 264 patients (4.2%) for *gBRCA2*m carriers. Approximately 40% of patients had an unknown or untested germline *BRCA1/2*m status at the time of CGP testing (Table 1). After excluding cases with unknown g*BRCA1/2* test results, the prevalence was 3.8% for *gBRCA1*m carriers (144/3799) and 7.0% for *gBRCA2*m carriers (264/3779). Among patients with *gBRCA1*m carriers (n = 144), *sBRCA1*m were detected by CGP in 106 patients (73.6%). Similarly, among patients with *gBRCA2*m carriers (n = 264), *sBRCA2*m were detected in 246 (93.2%). In contrast, among CDx-confirmed germline mutation noncarriers, *sBRCA1*m was detected by CGP in 49 of 3,655 patients (1.3%) who were *gBRCA1*m noncarriers, and *sBRCA2*m was detected in 77 of 3,515 patients (2.2%) who were *gBRCA2*m noncarriers (Table 3). After excluding overlap, 116 patients (3.4%) who were *gBRCA1/2*m noncarriers by CDx were found to harbor *sBRCA1/2*m by CGP testing. Notably, among cases classified as g*BRCA1/2*m noncarriers by CDx, none were reclassified as germline carriers based on CGP testing. determined to be g*BRCA1/2*m carriers based on CGP testing.

Discordance between HER2 positivity by IHC/ISH and ERBB2 amplification by CGP testing

Discordance between HER2 status assessed by conventional IHC/ISH and *ERBB2* amplification detected by CGP testing was observed (Fig. 3). When stratified by HER2 IHC score, the positivity rate of *ERBB2* amplification by CGP testing was highest in IHC 3 + tumors (61.7%), followed by IHC 2+ (12.8%) and IHC 1+ (5.5%). Importantly, *ERBB2* amplification was not identified in a substantial proportion of tumors even among those classified as IHC 3+. Similarly, concordance between HER2 positivity by ISH and *ERBB2* amplification detected by CGP testing was limited, with *ERBB2* amplification identified in only 39.2% of HER2 ISH–positive tumors. Notably, *ERBB2* amplification was also detected in 4.7% of tumors classified as HER2-negative by IHC/ISH (Tables 3 and 4).

Discussion

The present study demonstrates that genomic medicine for breast cancer in Japan has steadily advanced through coordinated improvements in technology, regulatory frameworks, and clinical infrastructure. The approval of CGP testing, introduction of tumor–normal paired sequencing, and alignment with global standards for CDx and tumor-agnostic drug approvals have significantly expanded therapeutic opportunities. Among these developments, regulatory approval of a CDx for *PIK3CA/AKT1/PTEN* alterations represents a major milestone in precision oncology for breast cancer[15]. Accumulated data from the C-CAT have demonstrated a comparable prevalence of *PIK3CA/AKT1/PTEN* alterations in the domestic population[13, 16]. In our cohort, CGP testing firstly enabled access to at least one PMDA-approved drug in 50.3% of patients when Criteria I and II were combined. This represents a substantial increase compared with our previous report of 37.9%[13], primarily attributable to an increased number of cases classified as EL-A and the regulatory approval of additional targeted therapies, including capivasertib for *PIK3CA/AKT1/PTEN* alterations and olaparib for *sBRCA1/2* mutations. Notably, *sBRCA1/2* mutations were identified in 3.4% of patients without *gBRCA1/2* mutations. In a nationwide analysis of 7,051 Japanese patients with breast cancer, the prevalence of *gBRCA1* and *gBRCA2* mutations carriers has been reported to be 1.9% and 3.2%, respectively[17]; however, the prevalence of *sBRCA1/2*m in this population had not previously been well characterized. To our knowledge, the present study is the first to demonstrate that 3.4% of Japanese patients with breast cancer who are *gBRCA1/2* noncarriers harbor *sBRCA1/2* mutations (1.3% in *sBRCA1*m and 2.2% in *sBRCA2*m). These findings are generally consistent with prior reports, including a Scandinavian cohort of 273 breast cancer cases showing an *sBRCA*m prevalence of 3.0%[18], a meta-analysis (3.4% for *sBRCA1*m and 2.7% for *sBRCA2*m)[19], and a study across Western and Asia-Pacific populations (1.6% *sBRCA1*m and 4.7% *sBRCA2*m)[20]. Collectively, these data suggest that ethnic differences in the prevalence of *sBRCA1/2*m prevalence may be limited. Taken together, these real-world insights derived from CGP testing using the C-CAT database contribute substantially to the refinement of therapeutic targets and the optimization of patient selection in precision oncology for breast cancer.

Despite these advances, significant limitations persist. According to Criterion I—the conventional standard requiring breast cancer-specific phase III evidence—only *PIK3CA/AKT1/PTEN* alterations (30.8%) were linked to actionable therapies. In practical terms, it is not an overstatement to suggest that, to date, CGP testing in breast cancer has largely been performed to identify candidates for capivasertib. Consequently, with the broader clinical implementation of the CDx (e.g., OncoGuide™OncoScreen™Plus CDx), it will be necessary to re-evaluate the incremental value of broad CGP beyond targeted CDx testing. Moreover, although Criterion II expanded the actionable population to 19.5%, most supporting evidence derives from tumor-agnostic phase I/II trials, and breast cancer was not always represented in these studies, warranting caution in clinical interpretation. The discordance between HER2 positivity assessed by conventional diagnostics and *ERBB2* amplification detected by CGP testing should also be interpreted in this context. Although HER2 positivity by IHC or ISH has traditionally been considered concordant with *ERBB2* amplification, our analysis demonstrated discordance. Specifically, *ERBB2* amplification detected by CGP testing was observed in only 61.7% of HER2 IHC–positive tumors, and in merely 39.2% of HER2 ISH–positive tumors. This result was consistent with previous reports[21]. Furthermore, while *ERBB2* amplification was detected in a small subset of HER2-negative tumors, the low frequency and uncertainty regarding its clinical significance further underscore the currently limited role of CGP in guiding HER2-targeted therapeutic decisions. Despite the fact that 97.6% of the 6,307 cases harbored at least one genomic alteration, only 10 genomic or molecular biomarkers (*PIK3CA, AKT1, PTEN, ERBB2, BRCA1, BRCA2, NTRK, BRAF*, TMB, MSI) were clinically relevant for drug accessibility. From a practical and cost-effectiveness perspective, the development of a low-cost, high-efficiency, breast cancer–specific targeted gene panel focusing on this limited set of biomarkers may be warranted for real-world implementation. Thus, insights derived from large-scale CGP analyses using the C-CAT database provide an important foundation for optimizing precision oncology in the future.

Nevertheless, several major gaps persist in real-world clinical implementation. The rate of conversion from alteration detection to actual treatment access remains low. A domestic report has suggested that only approximately 10% of patients undergo genotype-matched treatment after CGP testing[10, 21]. CGP testing is often performed at an advanced stage of disease, frequently after the exhaustion of standard therapies; as a result, a subset of patients are unable to receive subsequent genotype-matched treatments because of disease progression or deterioration in performance status[22]. And, substantial variability exists in the operation of MTBs and in access to

recommended treatments across institutions. For example, inter-institutional differences have been reported in MTB processes, including the quality and timeliness of genomic interpretation and reporting[23]. Persistent challenges remain in the management of genetic counseling, secondary findings, presumed germline pathogenic variants (PGPVs), and the establishment of robust follow-up systems. In our cohort, *sBRCA1/2*m were detected in 3.4% of patients who were negative for *gBRCA1/2*m (after excluding overlap). These findings underscore the need to further define optimal clinical handling and follow-up frameworks for such results, including appropriate counseling, confirmatory testing when indicated, and longitudinal management strategies. In addition, the C-CAT database currently lacks comprehensive clinical outcome data, limiting the ability to fully assess the real-world effectiveness of CGP-guided therapies. Taken together, genomic medicine in breast cancer appears to be transitioning from a phase focused primarily on "testing to detect alterations" to a phase in which the key objective is to "translate detected alterations into actionable treatment and supportive care." However, at present, the field has not yet reached a stage of broad dissemination and routine, scalable implementation in clinical practice. Looking ahead over the next 5–10 years, the following directions for improvement will be very important.

First, the timing of CGP testing warrants reconsideration. In breast cancer, CGP testing should ideally be performed not only at the time of recurrence or metastasis but also at an appropriate earlier stage, when expanding therapeutic options is most clinically meaningful[22, 24]. Recently, a companion diagnostic assay targeting *PIK3CA/AKT1/PTEN* alterations for capivasertib has been implemented in clinical practice, demonstrating a high overall concordance rate of 95.7% with F1CDx[25]. As demonstrated in the present study, the proportion of patients eligible for approved therapies based on conventional criteria—namely, drugs supported by phase III trials in breast cancer (Criterion I)—was limited to alterations in these three genes, accounting for only 30.8% of cases. Given the availability of companion diagnostics for these three genes, it seems appropriate to re-evaluate both the optimal timing and clinical significance of comprehensive CGP testing. As discussed above, the development and implementation of a cost-effective, breast cancer–specific targeted gene mini-panel incorporating these three genes along with additional clinically relevant alterations may represent a practical and valuable alternative in real-world settings. Strategic integration of such targeted panels with CGP testing, performed at an appropriate time point, may further expand therapeutic sequencing options for patients.

Second, improving access to matched therapies and securing sufficient clinical trial opportunities are critical. To streamline the transition from mutation detection to access to approved or investigational therapies, the establishment of a nationwide collaborative MTB network, reduction of inter-institutional and regional disparities, and strengthening of support systems for clinical trial enrollment are required[10]. In addition, the cost-effectiveness and accessibility of off-label treatments and non-reimbursed drugs should be carefully evaluated to ensure equitable access to precision oncology[26].

Third, the clinical implementation of next-generation technologies and assays requires both robust evidence generation and regulatory preparedness. Circulating tumor DNA–based monitoring (liquid biopsy), as well as RNA sequencing and methylation analyses, hold promise for early detection and the identification of emerging drug resistance. However, their adoption into routine clinical practice requires high-level evidence demonstrating analytical validity, reproducibility, clinical utility, and cost-effectiveness. Similarly, while AI-based interpretation support systems are promising, their clinical validity, fairness, and explainability must be rigorously evaluated alongside appropriate regulatory frameworks[8, 12].

Fourth, workforce development and operational standardization within multidisciplinary and nationwide frameworks remain ongoing challenges. In March 2022, the Japanese Ministry of Health, Labour and Welfare announced that simplification of expert panel processes may be feasible by limiting reported results to high-evidence-level genomic alterations. However, such alterations account for less than 10% of all detected variants. Moreover, annotation of not only somatic variants but also germline variants and presumed germline pathogenic variants (PGPVs) relies on expertise informed by global databases, population-specific genomic data, and individual and family histories, making this process labor-intensive and technically demanding. Consequently, substantial human resources are still required at individual institutions, particularly at core hospitals[27]. Despite ongoing efforts to expand panel testing capacity, variability in expertise, experience, and institutional resources among MTB members continues to result in heterogeneity in discussion quality, posing a barrier to equitable genomic medicine delivery[23]. Additionally, balancing process simplification with workforce training remains challenging under constraints related to cost-effectiveness and healthcare labor reforms.

Fifth, enhanced data utilization and clinical outcome assessment are essential. The C-CAT system was established to centrally collect, manage, and appropriately utilize genomic data for cancer genomic medicine in Japan[3, 4]. However, the complexity of clinical data entry and the high proportion of missing data—particularly for subsequent treatments and survival outcomes—limit its current utility[13]. Standardized methodologies and metrics are needed to longitudinally evaluate the real-world impact of genomic medicine, including mutation detection rates, matched therapy rates, clinical trial enrollment, survival outcomes, and quality of life.

Finally, patient and family education, ethical considerations, and follow-up systems must be strengthened. A substantial proportion of reported genomic alterations are variants of uncertain significance (VUS), posing interpretational challenges even for experts[23].

Communicating these findings without causing unrealistic expectations or undue anxiety is difficult. Comprehensive support frameworks encompassing pre-test informed consent, disclosure of secondary findings, genetic counseling, family testing and support, and post-test follow-up are therefore essential. Reduced patient satisfaction and increased psychological burden have been reported among patients who undergo CGP testing without receiving matched therapies, underscoring the importance of ethical communication and psychological support in routine implementation[27, 28].

In summary, genomic medicine for breast cancer in Japan is progressing toward integration into routine clinical practice. In the short term, the above-mentioned improvement directions will be prioritized, and in the medium to long term, the key will be to build a system to quantify the effects of individualized treatment that combines C-CAT, a nationwide data infrastructure, and AI. However, the clinical impact of CGP remains limited by low rates of drug accessibility and the narrow range of biomarkers linked to approved therapies. Even with updated 2025 evidence, high-level evidence–based treatment opportunities remain concentrated in a small subset of genomic alterations.

From the perspectives of cost-effectiveness, resource allocation, and real-world feasibility, CGP may currently be most appropriate for use within research-intensive cancer centers rather than universal deployment across all clinical settings. Continued national-level discussion and policy development will be essential to define the optimal role of CGP testing in Japanese breast cancer care.

Abbreviations

CGP
comprehensive genomic profiling
C-CAT
Center for Cancer Genomics and Advanced Therapeutics
CDx
Companion diagnostics
RCT
randomized controlled trial
p□ RCT
Phase □ Randomized controlled trial
HER2
human epidermal growth factor receptor type2
FDA
Food and Drug Administration
PMDA
Pharmaceuticals and Medical Devices Agency
EP
Expert panel
EL
Evidence level
SIM
simulation
ER
estrogen receptor
TMB-H
tumor mutation burden-high
MSI-H
Microsatellite instability-high.

Declarations

Ethics statement

Approval of the research protocol by the Ethics Review Committee of Kyoto Prefectural University of Medicine (ERB-C-2860) and by the review board of C-CAT (AP20241127-01E).

Consent for publication

Not applicable.

Conflict of interest

Midori Morita has received research funding from Murata outside the submitted work. **Koichi Takayama** received grants from Chugai Pharmaceutical and Ono Pharmaceutical, and personal fees from AstraZeneca, Chugai Pharmaceutical, MSD, Eli Lilly, Boehringer Ingelheim, and Daiichi-Sankyo. **Yasuto Naoi** has received research funding from Eisai, Shimazu, Murata, ONO, Daiichi-Sankyo and AstraZeneca, as well as honoraria from Eisai, AstraZeneca, Pfizer, Eli Lilly, Daiichi-Sankyo and Chugai outside the submitted work; he holds joint patents with Sysmex including Curebest™ 95GC Breast (JP.5725274.B2). The other authors declare no conflicts of interest.

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Author Contributions

M Morita and Y Naoi contributed to the planning and design of the study. M Morita and R Tsunashima analyzed the data. T Yoshinami and M Nishida added annotation of the data. All authors approved the final version of the manuscript.

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Figures

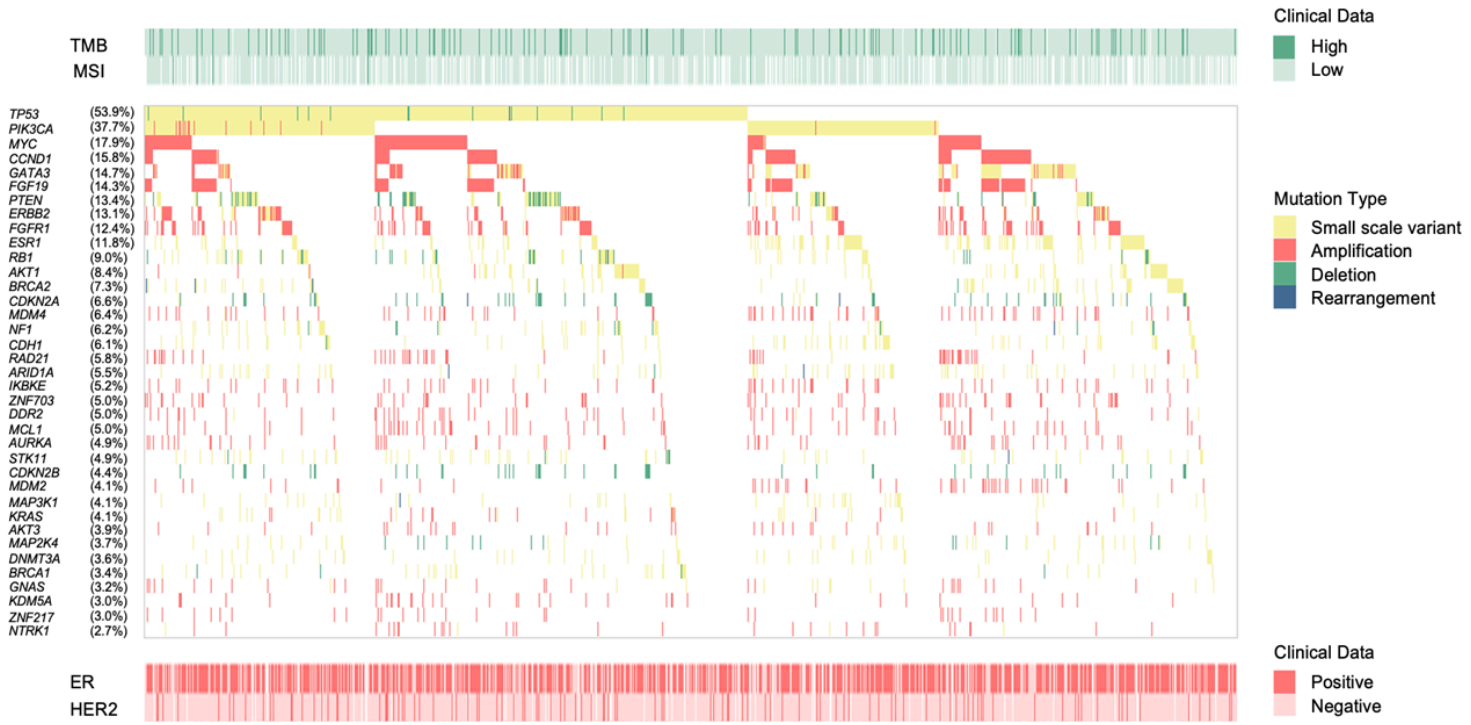


Figure 1

Overview of the most frequent genomic alterations in C-CAT data.

The top 37 mutation frequencies were extracted. TMB-high defined as ≥10 muts/Mb for tissue-based assays and ≥14 muts/Mb for liquid biopsy assays.



Figure 2

Inclusion of capivasertib adaptation between *PIK3CA*, *AKT1* and *PTEN* alterations in ER-positive HER2-negative breast cancer.

The venn diagram shows the overlap between *PIK3CA*, *AKT1* and *PTEN* alterations in ER-positive HER2-negative breast cancer. It is 30.8% of all patients (1943/6307), accounting for 53.7% of ER-positive HER2-negative breast cancer (1943/3617).

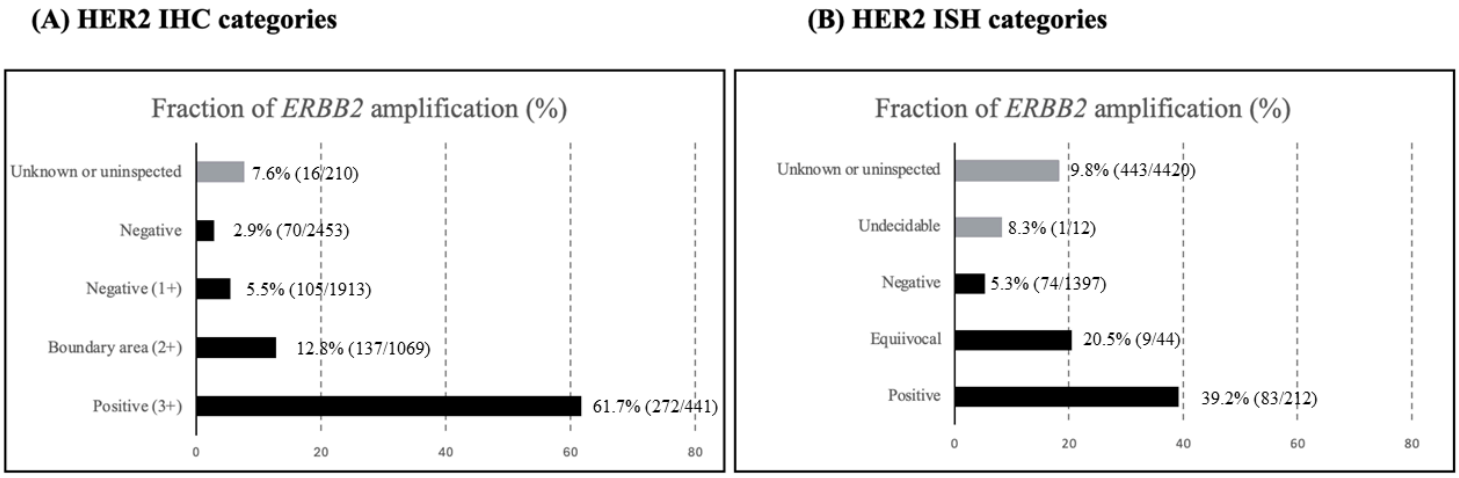


Figure 3

***ERBB2* amplification positivity rates stratified by HER2 testing categories. (A) HER2 IHC categories. (B) HER2 ISH categories**.

Bars represent descriptive percentages derived from the study dataset. Numbers shown represent percentage of *ERBB2* amplification with corresponding numerator and denominator (n/N).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 20260128MoritaCCATTableS1.docx