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1 Original article

2 Assessment of structural chromosomal instability phenotypes as  
3 biomarkers of carboplatin response in the TNT trial

4

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29

## 30 Abstract

31

### 32 **Background**

33

34 In the TNT trial (NCT00532727) germline *BRCA1/2* mutations were present in 28% of  
35 carboplatin responders. We assessed quantitative measures of structural chromosomal  
36 instability (CIN) to identify a wider patient subgroup within TNT with preferential benefit  
37 from carboplatin over docetaxel.

38

### 39 **Patients and methods**

40

41 Copy number aberrations (CNAs) were established from 135 FFPE primary carcinomas using  
42 Illumina OmniExpress SNP-arrays. Seven published (allelic imbalanced CNA, AiCNA; allelic  
43 balanced CNA, AbCNA; copy number neutral loss of heterozygosity, CnLOH; number of  
44 telomeric allelic imbalances, NtAI; *BRCA1*-like status; percentage of genome altered, PGA;  
45 homologous recombination deficiency, HRD scores) and two novel (Shannon index, SI; high-  
46 level amplifications, HLAMP) CIN-measurements were derived. HLAMP was defined based  
47 on the presence of at least 1 of the top 5% amplified cytobands located on 1q, 8q and 10p.  
48 Continuous CIN-measurements were divided into tertiles. All nine CIN-measurements were  
49 used to analyse objective response rate (ORR) and progression free survival (PFS).

50

### 51 **Results**

52

53 Patients with tumours without HLAMP had a numerically higher ORR and significantly longer  
54 PFS in the carboplatin(C) than in the docetaxel(D) arm (56%(C) versus 29%(D),  
55  $P_{HLAMP,quiet}=0.085$ ; 6.1 months(C) vs 4.1 months(D),  $P_{interaction/HLAMP}=0.047$ ). In the carboplatin  
56 arm, patients with tumours showing intermediate telomeric NtAI and AiCNA had higher ORR  
57 (54%(C) versus 20%(D),  $P_{NtAI,intermediate}=0.03$ ; 62%(C) versus 33%(D),  $P_{AiCNA,intermediate}=0.076$ ).  
58 Patients with high AiCNA and PGA had shorter PFS in the carboplatin arm (3.4 months (high)  
59 versus 5.7 months (low/intermediate); and 3.8 months (high) versus 5.6 months  
60 (low/intermediate), respectively;  $P_{interaction/AiCNA}=0.027$ ,  $P_{adj.interaction/AiCNA}=0.125$  and  
61  $P_{interaction/PGA}=0.053$ ,  $P_{adj.interaction/PGA}=0.176$ ), whilst no difference was observed in the  
62 docetaxel arm.

63

### 64 **Conclusions**

65

66 Patients with tumours lacking HLAMP and demonstrating intermediate CIN-measurements  
67 formed a subgroup benefitting from carboplatin relative to docetaxel treatment within the  
68 TNT trial. This suggests a complex and paradoxical relationship between the extent of  
69 genomic instability in primary tumours and treatment response in the metastatic setting.

70

71 **Keywords:** metastatic triple negative breast cancer, carboplatin, genomic instability, allelic  
72 imbalance

73

74

## 75 Highlights

76

77 • Patients with intermediate levels of allelic imbalanced CNAs show a better response  
78 rate to carboplatin in TNT

79 • The lack of amplifications on 1q, 8q and 10p is associated with a superior carboplatin  
80 response in TNT

81 • The relation between chromosomal instability in primary tumours and carboplatin  
82 response in advanced settings is non-linear

## 83 Introduction

84

85 The TNT trial (NCT00532727), a phase III, open label, randomised clinical trial compared  
86 carboplatin (C) to docetaxel (D) in patients with recurrent locally advanced or metastatic  
87 triple negative breast cancer (TNBC) or with recurrent locally advanced or metastatic  
88 disease in germline *BRCA1/2* mutation carriers irrespective of ER/PR/HER2 status. TNT trial  
89 patients with germline *BRCA1/2* mutations had a significantly better objective response rate  
90 (ORR) to carboplatin and showed improved progression free survival (PFS) with this agent<sup>1</sup>.  
91 As some TNBC patients without known germline defects of *BRCA1/2* benefit from platinum-  
92 based chemotherapy, biomarkers that better predict treatment response for this subgroup  
93 of patients are urgently required<sup>2,3</sup>.

94

95 Most TNBCs display highly aberrant genomes as a consequence of defects in DNA Damage  
96 Response (DDR) pathways. In ~35% of TNBCs, this increased genomic instability can be  
97 explained by functional inactivation of *BRCA1/2*<sup>3</sup>, leading to homologous recombination  
98 deficiency (HRD)<sup>4</sup>. Using a range of platforms, including array comparative genomic  
99 hybridisation (aCGH)<sup>5</sup>, SNP arrays<sup>6-9</sup>, targeted sequencing panels<sup>10-12</sup> and whole genome  
100 sequencing<sup>3,10,12,13</sup>, measures of unique patterns of chromosomal instability (CIN) have  
101 been developed to identify “*BRCAness*”<sup>14</sup> and HRD, which potentially identify sensitivity to  
102 DDR-targeting drugs compared to other standards of care. Such measures are sometimes  
103 referred to as “genomic scars” and include mutational and rearrangement signatures. In the  
104 neoadjuvant setting, these “genomic scars” have been shown to carry clinically relevant  
105 information for platinum-based chemotherapy response in TNBC patients<sup>2,9,11</sup>. However,  
106 their value for patients with advanced disease is still debatable. High levels of HRD were  
107 associated with platinum response in the single agent platinum TBCR009 study<sup>15</sup>, whilst the  
108 Myriad HRD score<sup>2</sup> was not specifically associated with improved carboplatin ORR or PFS  
109 compared to docetaxel in the TNT trial<sup>1</sup>.

110

111 Here, we have quantitatively assessed a suite of nine CIN-measurements based on genome  
112 profiles of primary tumours from the TNT trial to identify a wider patient subgroup  
113 benefitting from carboplatin over docetaxel. We compared their prevalence to the patient’s  
114 pathogenic germline and somatic *BRCA1/2* mutation and *BRCA1* promoter methylation  
115 status. Then, we asked whether a primary tumour’s degree of genomic instability has  
116 predictive value with regards to treatment response of the metastatic disease, and whether  
117 prediction was selective of carboplatin response. As a result, biomarker defined subgroups  
118 of patients for whom platinum-based treatment may be selectively beneficial in the  
119 metastatic setting were deciphered.

## 120 Patients and methods

121

122 We analysed genome-wide allele specific copy number profiles from 135 TNT trial patients  
123 (NCT00532727)<sup>1</sup> using Illumina HumanOmniExpress 24 SNP-arrays. The cohort included 131  
124 (97%) TNBC cases and 4 ER+ *BRCA1/2* mutation carriers. Cases were categorised as: (i)  
125 germline or somatic *BRCA1/2* mutation carriers without *BRCA1* promoter methylation  
126 ( $n=20$ ); (ii) *BRCA1* methylated cases without *BRCA1/2* mutations ( $n=19$ ); (iii) *BRCA1/2* wild-  
127 type cases ( $n=75$ ). Germline and somatic *BRCA1/2* mutated cases were grouped together, as  
128 no statistically significant different chromosomal instability patterns were observed.  
129 Samples with ambiguous *BRCA1/2* deficiency status ( $n=21$ ) were excluded when the  
130 associations of CIN-measurements with *BRCA1/2* mutation and *BRCA1* methylation status  
131 were examined.

132

133 The majority of the analysed *BRCA1/2* mutated and *BRCA1* promoter methylated cases were  
134 associated with LOH 19/20 (95%) of the *BRCA1/2* mutated cases, 17/19 (89.5%) of the  
135 *BRCA1* methylated cases. Three cases without LOH associated had moderate to low tumour  
136 purity (60%, 49% and 27%), however Myriad scores >42, thus indicating HR deficiency. Two  
137 cases with *BRCA1* methylation without LOH exhibited only a moderate *BRCA1* methylation  
138 level, yet above the 10% threshold<sup>1</sup>.

139

140 The clinical baseline characteristics of the whole TNT trial ( $n=376$ ) was comparable to the  
141 subset of patients with primary tumours ( $n=196$ ), and the study cohort ( $n=135$ ) (**Figure 1**,  
142 **supplementary Table S1**, available at Annals of Oncology online (for details see  
143 supplementary materials)).

144

145 The copy number aberrations (CNAs) identified were used to derive the assessed  
146 quantitative measurements of CIN. Allelic imbalanced CNA (AiCNA), allelic balanced CNA  
147 (AbCNA), copy number neutral loss of heterozygosity (CnLOH) and number of telomeric  
148 allelic imbalances (NtAI) were calculated as previously described<sup>9</sup>. Percentage of genome  
149 altered (PGA) and Shannon diversity index<sup>16</sup> (SI) were quantified based on the copy number  
150 (CN) profiles. Based on the observed unimodal distributions of the continuous CIN-  
151 measurements, equally-sized tertiles (low, intermediate, high) were established. The  
152 *BRCA1*-like classifier<sup>17</sup> was used to identify tumours with similar CN profiles to *BRCA1*  
153 mutation carriers. We composed a novel score termed high-level amplifications (HLAMP),  
154 which was defined based on the presence of at least 1 of the top 5% of recurrently amplified  
155 genomic regions (cytobands) in this cohort. These cytobands were located on 1q, 8q and  
156 10p chromosomal arms (including 1q21.1-24.1, 1q42.2-44, 8q11.21-24.3 and 10p15.3-14).  
157 The cohort was divided into three HLAMP groups: (i) samples lacking these amplifications  
158 were referred to as quiet; (ii) those with <50% amplified cytobands as low; (iii) >=50%  
159 amplified cytobands as high HLAMP, which was chosen based on the observed distribution  
160 of the HLAMP score. Cut-off points for all continuous CIN-measurements and the HLAMP  
161 score were determined blinded to the patient outcome. The Myriad HRD score was used to  
162 divide the cohort into HR deficient and HR proficient subgroups, as defined in the previous  
163 report on the TNT trial<sup>1</sup>.

164

165 Illumina TruSight Cancer v2 targeted sequencing panel<sup>18</sup> was used to identify pathogenic  
166 germline variants of 97 genes associated with predisposition to cancer.

167

168 The association of CIN-measurements with ORR and PFS was assessed using logistic  
169 regression and restricted mean survival analysis, respectively. Detailed procedures are  
170 provided in the **supplementary material**, available at Annals of Oncology online. In the  
171 reporting process the REMARK guidelines were followed where applicable (**supplementary**  
172 **Table S2**).

## 173 Results

174

### 175 **Association between CIN features, *BRCA1/2* mutation and *BRCA1* promoter methylation**

176

177 Of 376 patients randomised in the TNT trial, genome profiles of primary tumours from 135  
178 patients were suitable for chromosomal instability assessment (see CONSORT diagram in  
179 **Figure 1**). Many of these tumours displayed highly aberrant genomes (**Figure 2A**),  
180 comparable to those in previously published series of TNBCs, such as the Guy's Hospital  
181 King's College London<sup>9</sup> and METABRIC<sup>19</sup> cohorts, when considering only those patients who,  
182 as in the TNT trial, developed metastases (**supplementary material, supplementary Figure**  
183 **S1**, available at Annals of Oncology online). As the majority of the samples were TNBCs,  
184 characteristic CNAs including gains on 1q, 3q, 8q, 10p or 12p and losses on 4q, 5q or 8p  
185 chromosomal arms were seen<sup>20</sup> (**Figure 2A**).

186

187 We first established nine different CIN-measurements to capture the consequences of  
188 diverse defects in DDR mechanisms that could lead to excessive genomic instability in TNBCs  
189 (**Figure 2B**). These included our three previously published "scores of chromosomal  
190 instability scarring" (SCINS) measures, namely AiCNA, AbCNA and CnLOH<sup>9</sup>. We also  
191 quantified the percentage of genome altered (PGA) measure<sup>21</sup>, a general proxy for the total  
192 amount of CNA across the whole genome; NtAI<sup>6</sup>, that was shown to be indicative of DDR  
193 deficiency and platinum sensitivity in TNBC patients; and the aCGH-based *BRCA1*-like  
194 classifier (*BRCA1*-like)<sup>5</sup>, that was shown to predict benefit from high-dose platinum-based  
195 chemotherapy. To measure the heterogeneity of the aberrant CN states, we introduced the  
196 Shannon diversity index (SI)<sup>16</sup>. In addition, a novel score termed HLAMP was derived from  
197 the observed amplifications in the CN profiles within the TNT cohort. The distribution of the  
198 novel HLAMP score was confirmed in the SCAN-B<sup>3</sup>, a TNBC cohort, and the TNBC subset of  
199 the METABRIC<sup>19</sup> dataset. For both independent studies, tumours were selected when  
200 patients who, as necessary for TNT trial eligibility, developed relapse or distant metastasis  
201 (**supplementary material, supplementary Figure S2**). To complete this compendium of CIN-  
202 measurements, the Myriad HRD score, as reported in the TNT study<sup>1</sup>, was also included.

203

204 Then, we ensured that the characteristics of the CIN-measurements of the ER+ *BRCA1/2*  
205 mutation carriers were consistent with the rest of the TNT study cohort (**supplementary**  
206 **Figure S3, supplementary Table S3**).

207

208 Next, the extent of each of the nine CIN-measurements were compared between those TNT  
209 trial cases with pathogenic germline or somatic *BRCA1/2* mutations, *BRCA1* methylated and  
210 *BRCA1/2* wild-type cancers. Continuous CIN-measurements, such as NtAI, AiCNA, AbCNA,  
211 CnLOH and PGA scores displayed similar distributions across all three subgroups (**Figure 2C**).  
212 In alignment with our previous study<sup>1</sup>, HR deficient cases were clearly associated with the  
213 presence of *BRCA1/2* mutation and *BRCA1* promoter methylation (Kruskal-Wallis rank sum  
214 test  $P=1.61e-17$ ) (**Figure 2C, supplementary Table S4**, available at Annals of Oncology  
215 online). The majority of tumours (76%, 103/135) were classified as *BRCA1*-like<sup>17</sup>, including  
216 80% (16/20) of *BRCA1/2* mutated and 73% (14/19) of *BRCA1* methylated cases. In 55%  
217 (11/20) of germline and somatic *BRCA1/2* mutation carriers, tumours were categorised as  
218 quiet HLAMP, whilst 35% (7/20) and 10% (2/20) were grouped into the low and high HLAMP  
219 groups respectively. Conversely, tumours with *BRCA1* promoter methylation were most



220 prominent in the low HLAMP subgroup (68%, 13/19), and were present at a significantly  
221 lesser extent in the quiet (3/19) and high (4/19) HLAMP categories (Fisher's exact  
222  $P_{adj}=0.029$ , **Figure 2C, supplementary Table S4**, available at Annals of Oncology online).

223

### 224 **Association of germline variants in additional DDR related cancer predisposition genes** 225 **with CIN features**

226

227 Pathogenic germline variants in DDR genes<sup>18</sup> increase the risk of developing cancer and  
228 were identified in peripheral blood leukocyte DNA in 8/135 patients, not including *BRCA1/2*  
229 (**supplementary Table S5**, available at Annals of Oncology online). The majority (62.5%, 5/8)  
230 of these cases were part of the low HLAMP group, and were completely absent in the high  
231 group (**Figure 2B**). Moreover, tumours of patients with germline variants in DDR genes had  
232 high Shannon diversity score (62.5%, 5/8) and were more often classified as being *BRCA1*-  
233 like (75%, 6/8) or HR deficient (62.5%, 5/8), but small numbers limit conclusive  
234 interpretation of these data (**Figure 2B**).

235

### 236 **CIN measures as biomarkers for chemotherapy response**

237

238 Next we asked whether any of the nine established CIN-measurements carried prognostic or  
239 predictive value within the TNT trial.

240

241 Subgroup analyses indicated that patients with tumours of the intermediate NtAI subgroup  
242 had a significantly better response to carboplatin than docetaxel (ORR: 13/24 (54%) vs 4/20  
243 (20%)  $P_{NtAI,intermediate} = 0.03$ ) (**Figure 3A, supplementary Table S6**), and patients with tumours  
244 of the intermediate AiCNA subgroup also appeared to have better response to carboplatin  
245 than docetaxel (ORR: 13/21 (62%) vs 8/24 (33%)  $P_{AiCNA,intermediate} = 0.076$ ) (**Figure 3B,**  
246 **supplementary Table S6**). For both, a trend for interaction between treatment group and  
247 AiCNA ( $P_{interaction/AiCNA} = 0.060$ ) and NtAI ( $P_{interaction/NtAI} = 0.083$ ) was observed, which  
248 remained evident after adjustment for clinical covariates (for details see **supplementary**  
249 **material**), including *BRCA1/2* mutation status ( $P_{adj.interaction/AiCNA} = 0.024$ ,  $P_{adj.interaction/NtAI} =$   
250  $0.016$ ). Whilst no significant interactions were found between treatment and any of the  
251 other tested CIN-measurements, a numerically higher ORR was observed in the carboplatin  
252 arm in the intermediate CnLOH group (ORR: 12/25 (48%) (C) vs 3/20 (15%) (D),  
253  $P_{CnLOH,medium}=0.027$ ) and in the quiet HLAMP group (ORR: 14/25 (56%) (C) vs 7/24 (29%) (D),  
254  $P_{HLAMP,quiet}=0.085$ ) (**Figure 3C, supplementary Table S6**).

255

256 Patients with carcinomas in the quiet HLAMP group had an improved PFS with carboplatin  
257 versus docetaxel; and this association remained significant following adjustment for clinical  
258 variables including *BRCA1/2* mutation (restricted mean PFS 6.1 months (C) versus 4.1  
259 months (D),  $P_{interaction/HLAMP}=0.047$  and  $P_{adj.interaction/HLAMP}=0.033$ ; **Figure 3D**). Trends for  
260 interaction of treatment with AiCNA ( $P_{interaction/AiCNA}=0.027$ ) and with PGA  
261 ( $P_{interaction/PGA}=0.053$ ) were observed, showing the shortest PFS in cases with the highest PGA  
262 scores and in the high AiCNA subgroup in the carboplatin arm. However, these interactions  
263 were lost after adjustment for clinical covariates ( $P_{adj.interaction/AiCNA}=0.125$ ,  
264  $P_{adj.interaction/PGA}=0.176$ ) (**Figures 3E, 3F**). Sixty-seven of 135 primary tumours showed low to  
265 intermediate CIN burden based on AiCNA and PGA scores. Within this subgroup carboplatin

266 responders were more prevalent (64%, 18/28) in comparison to docetaxel responders (39%,  
267 9/23) (**supplementary Figure S4**).

268

269 Lastly, we excluded the 4 ER+ *BRCA1/2* mutation carriers from the outcome analyses, which  
270 showed that the results and derived conclusions remained essentially unaffected,  
271 supporting the plausibility of the inclusion the ER+ cases (**supplementary Table S7**).

272

## 273 Discussion

274

275 The FDA approved olaparib and talazoparib in 2018 for patients with confirmed germline  
276 *BRCA1/2* mutation<sup>22, 23</sup>, including those with TNBC, providing one of the first targeted  
277 therapy options for a subset of TNBC patients. However, the majority of TNBC patients lack  
278 germline *BRCA1/2* mutations, and are treated with either standard-of-care chemotherapy or  
279 in some circumstances with immunotherapy<sup>24</sup>. By exploring the highly aberrant genomes of  
280 TNBC, several “genomic scars” caused by disruptions of DDR mechanisms, have been  
281 developed and carry some predictive value for treatment responses to chemotherapy in the  
282 neoadjuvant setting. However, the specificity of the prediction of platinum response, which  
283 is distinct from more generic chemotherapy response, is unclear in this setting<sup>2, 5-7, 9, 25</sup>.

284

285 The randomised controlled TNT trial provides the opportunity to dissect genomic features  
286 and differentiate response to mechanistically highly distinct carboplatin and docetaxel  
287 treatments in metastatic or locally advanced TNBC. Indeed, we identified intermediate  
288 levels of allelic imbalanced CNAs, as measured by AiCNA, that focuses on genomic segments  
289 larger than 8 Mbp<sup>9</sup>, and telomeric NtAI<sup>6</sup> as being differentially associated with improved  
290 ORR in the carboplatin arm. Moreover, we noticed that in the TBCRC009 trial<sup>15</sup>, in which  
291 metastatic TNBC patients were treated with platinum monotherapy, the highest levels of  
292 tumour response were observed in cases with medium levels of the “genomic scar” assays  
293 developed by Myriad that measure large LOH events (HRD-LOH)<sup>7</sup> and large-scale state  
294 transition events (HRD-LST)<sup>8</sup>, both of which have been associated with HR deficiency. Our  
295 analyses of the TNT trial allow the testing of the specific interaction of these measures with  
296 platinum, as opposed to mechanistically distinct docetaxel, chemotherapy, and suggest that  
297 an intermediate CIN phenotype may represent a selective biomarker for platinum-based  
298 treatment response (as opposed to taxanes) in TNBC. Furthermore, AiCNA, and PGA, as well  
299 as the HLAMP scores, were associated with differential carboplatin effect as defined by PFS.  
300 As HLAMP was developed by analysis within this dataset this result must be regarded as  
301 hypothesis-generating.

302

303 Response to carboplatin, a DNA cross-linking agent, is related to the cell’s failure to  
304 successfully repair and survive the induced DNA damage. This prompted us to examine the  
305 utility of CIN-measurements as predictors of carboplatin response, as they can provide  
306 genomic evidence of disruption of DDR mechanisms reflected in acquired genome damage.  
307 In contrast, the cytotoxic effect of docetaxel is mediated by the stabilisation of normally  
308 dynamic microtubule assembly during mitotic cell division leading to cell death. In  
309 agreement with our observations it was, therefore, not anticipated that “genomic scars” of  
310 DNA repair deficiency should be selectively associated with docetaxel response.

311

312 Limitations of this study include the low resolution of the SNP-array platform that was used  
313 and the potential confounding factor of selecting a certain biological subset of TNBC.  
314 Although the ideal tissue resource for a predictive biomarker study of patients with  
315 metastatic/advanced breast carcinoma would be a set of metastatic biopsies, these were  
316 not regularly collected at the time of conduct of the TNT trial. There may, therefore, have  
317 been selection of DDR related resistance by DNA damage inducing adjuvant therapy  
318 between primary diagnosis and trial entry with advanced disease, hence the biology of  
319 these recurrent tumours may not be adequately represented by archival primary invasive

320 cancer tissues. Nevertheless, the copy number landscape of these archival primary tumours  
321 in the TNT trial did display distinctive CNAs, including known amplifications and losses, that  
322 are characteristic of TNBCs occurring in patients who develop metastatic disease.

323

324 In summary, the somatic genome profiles of these series of TNT trial cases provide an  
325 opportunity to explore the molecular features of TNBC and their association with treatment  
326 response of metastases to two single agent chemotherapies with highly distinct  
327 mechanisms of action. The finding that intermediate levels of allelic imbalanced CNAs  
328 determined by AiCNA and NtAI are selectively predictive of carboplatin responses offers a  
329 potential approach to find specific associations to platinum response. Moreover, we found a  
330 signal that requires validation in other TNBC cohorts that patients with tumours displaying  
331 intermediate CIN scores, as well as those with tumours lacking high level amplifications  
332 (HLAMP), have differential prediction of response. If our findings are substantiated they may  
333 potentially facilitate the prediction of a wider subgroup of TNBC patients who might be  
334 selected for platinum-based chemotherapy and support the potential integration of  
335 “genomic scars” as a decision tool in clinical practice.

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337

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349

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354

## 355 Disclosure

356

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366

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368

369

## 370 References

371

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Figure 1.

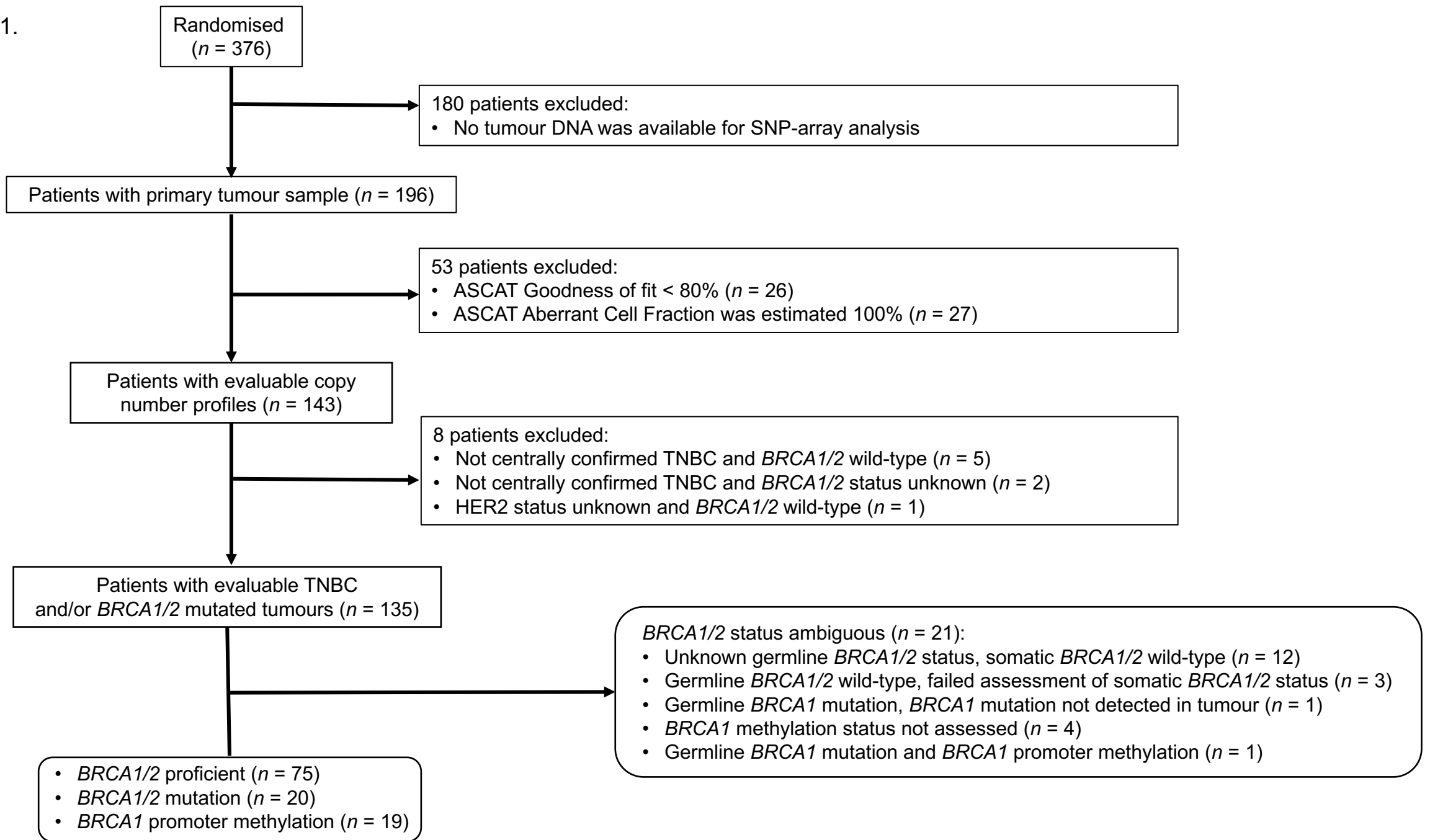




Figure 2.

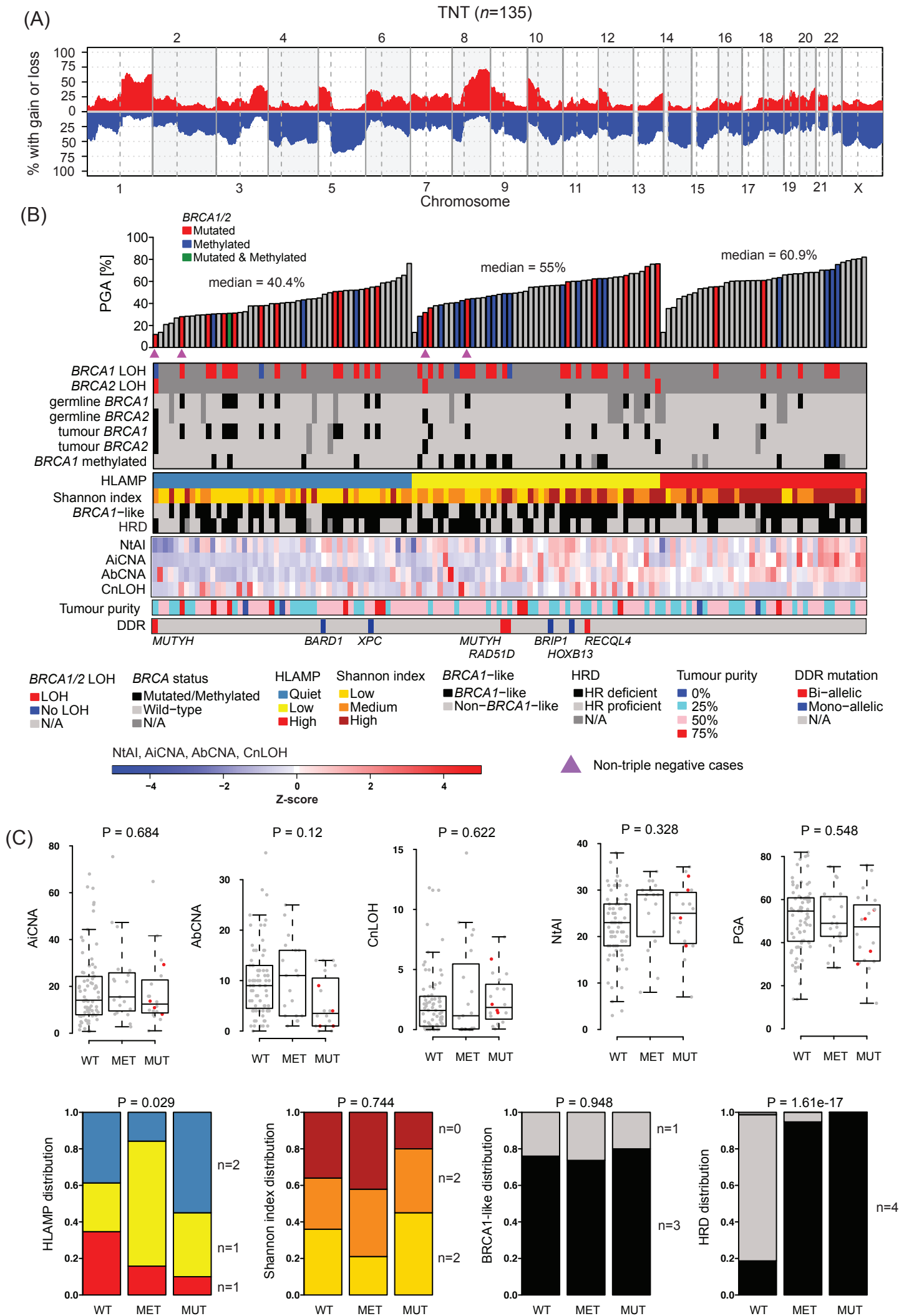
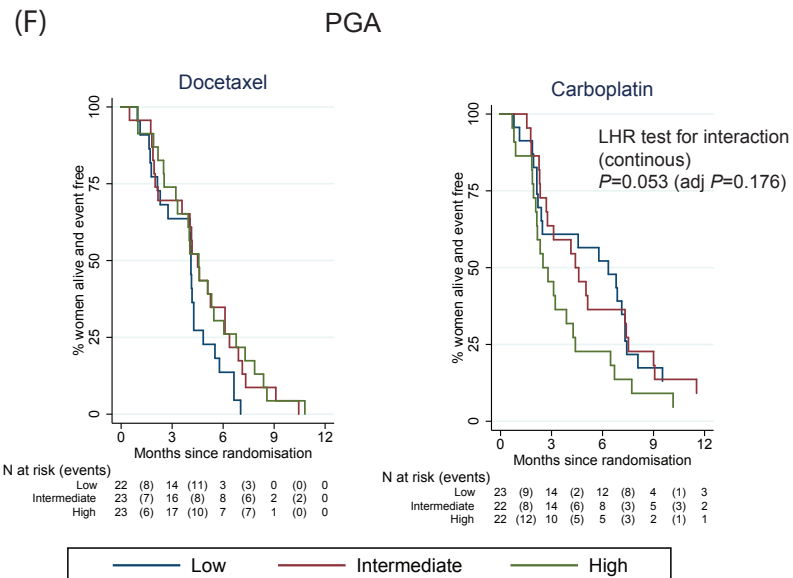
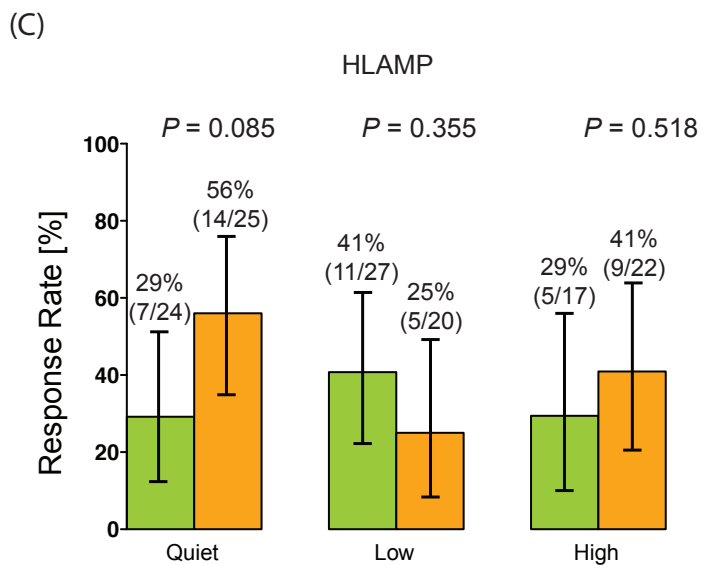
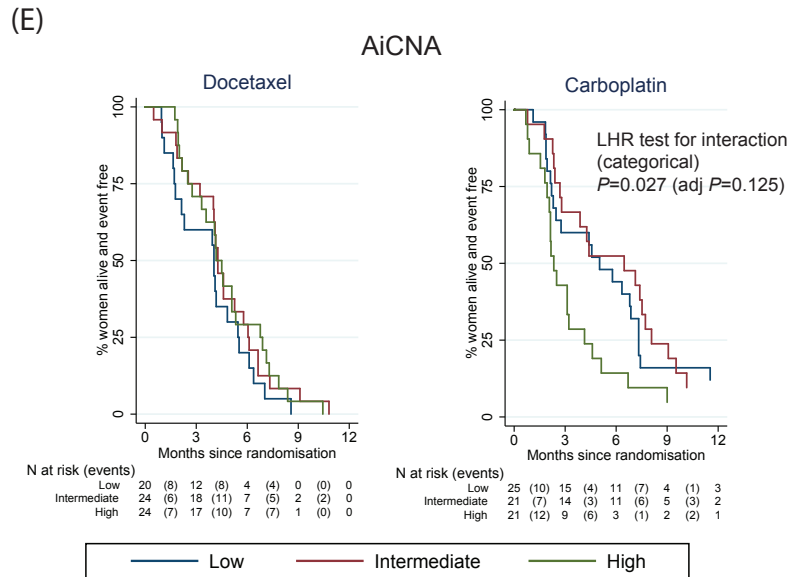
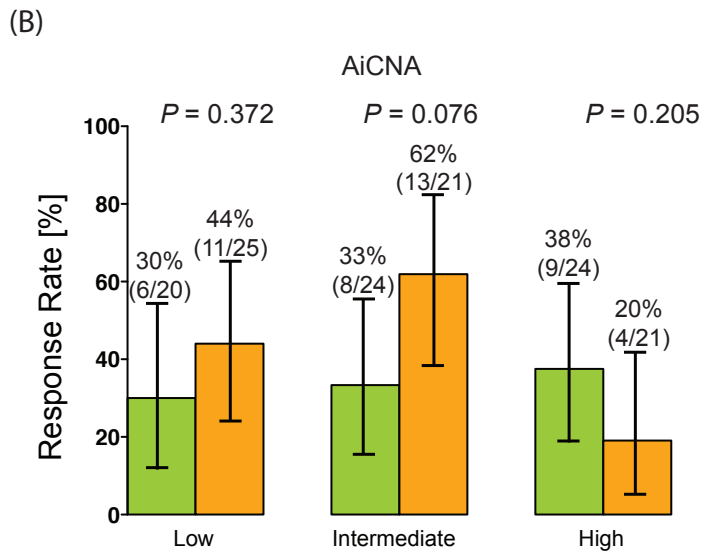
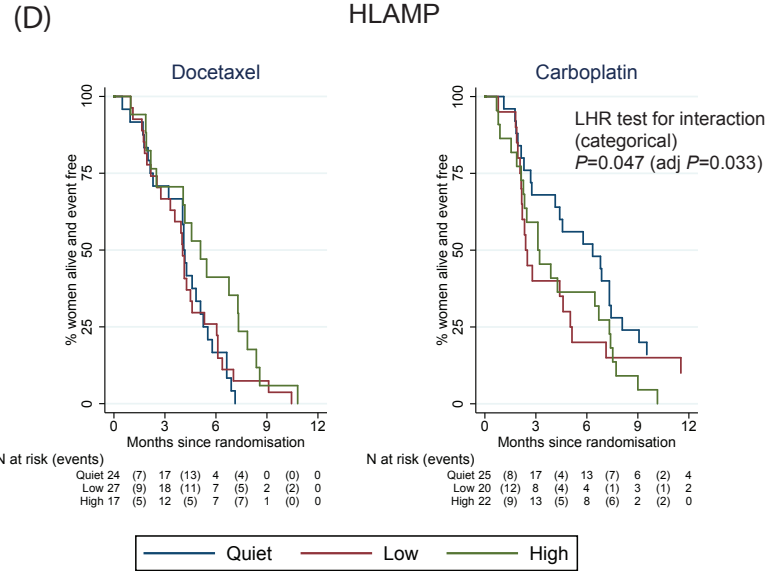
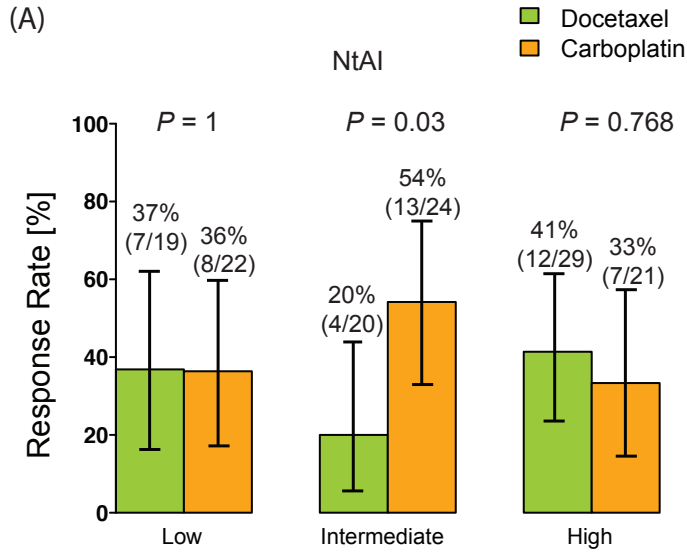


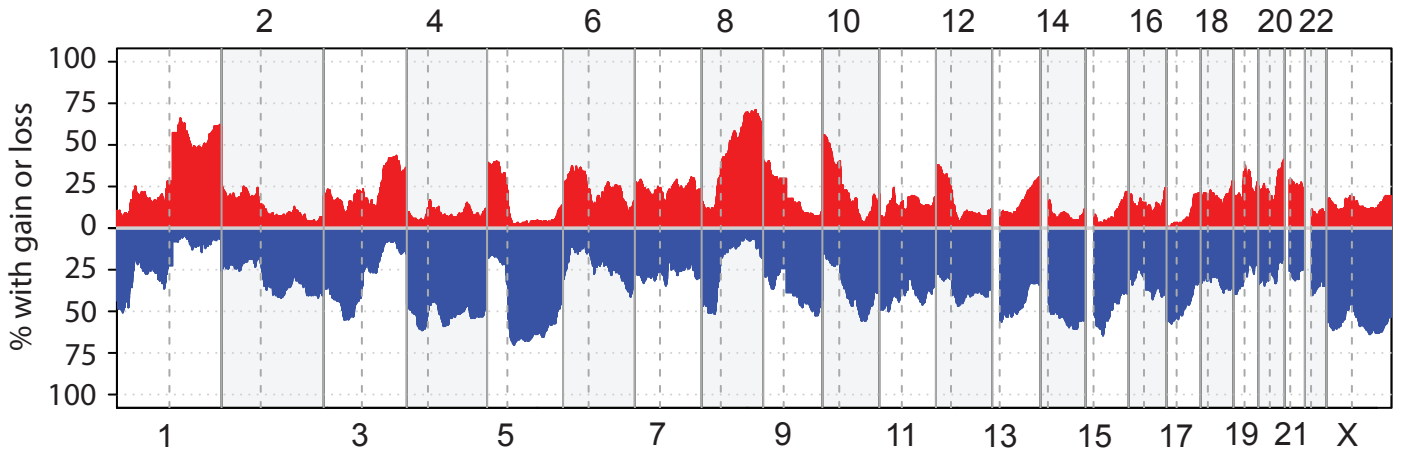
Figure 3.



Supplementary Figure S1.

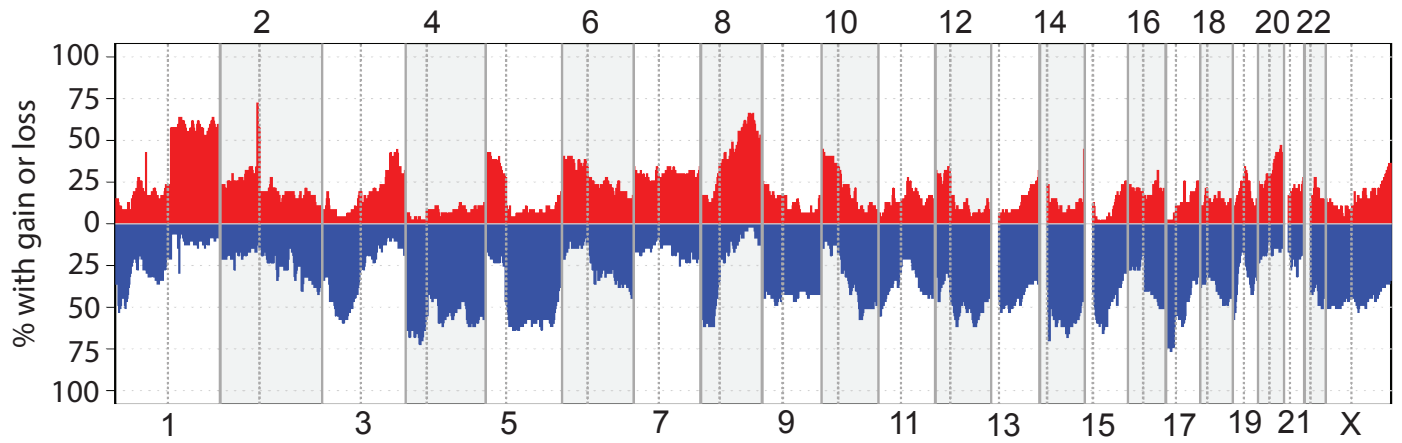
(A)

TNT cohort - unknown BRCA1/2 status at trial entry ( $n=124$ )



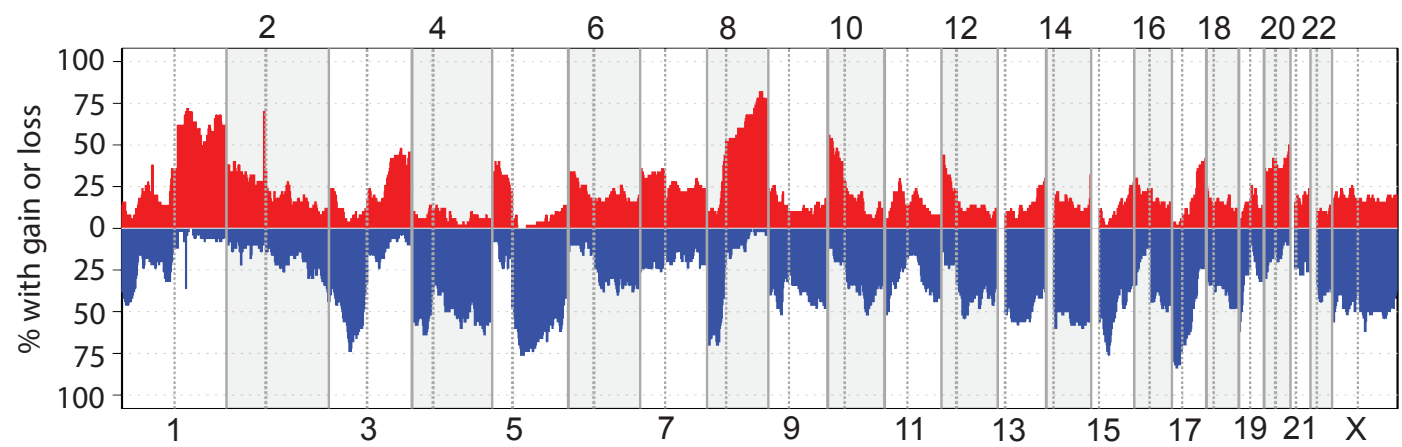
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KCL cohort ( $n=47$ )

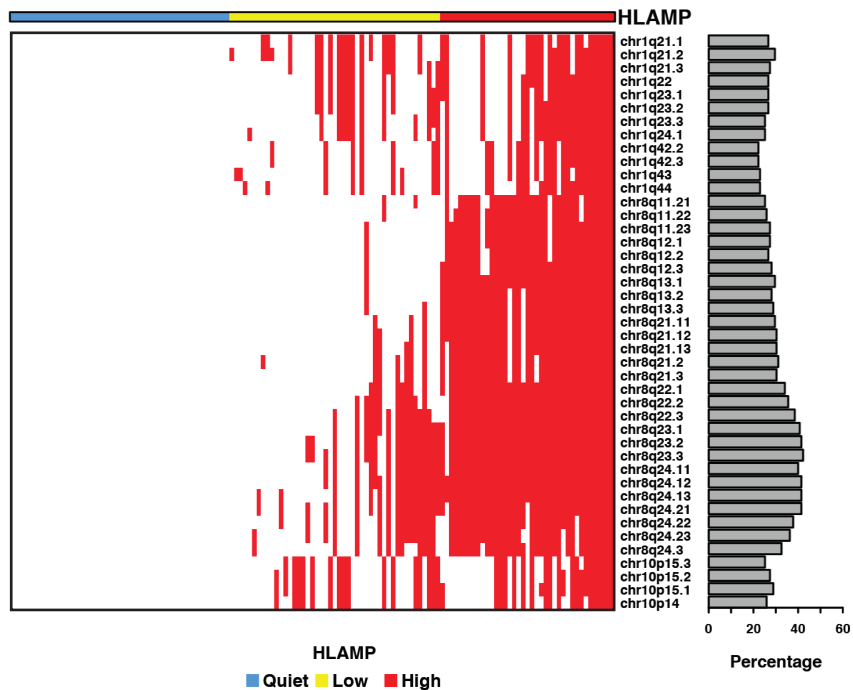


(C)

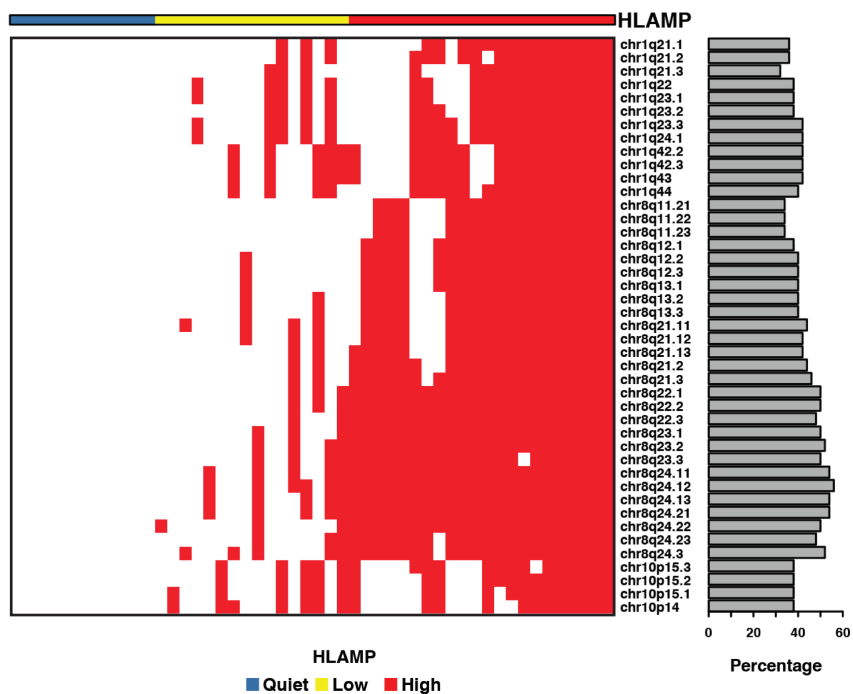
METABRIC cohort ( $n=50$ )



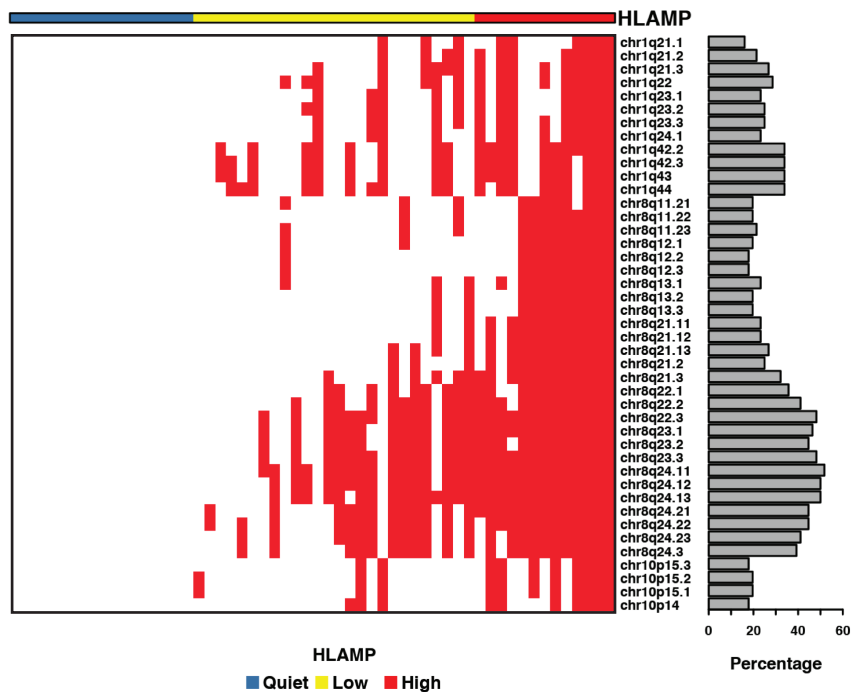
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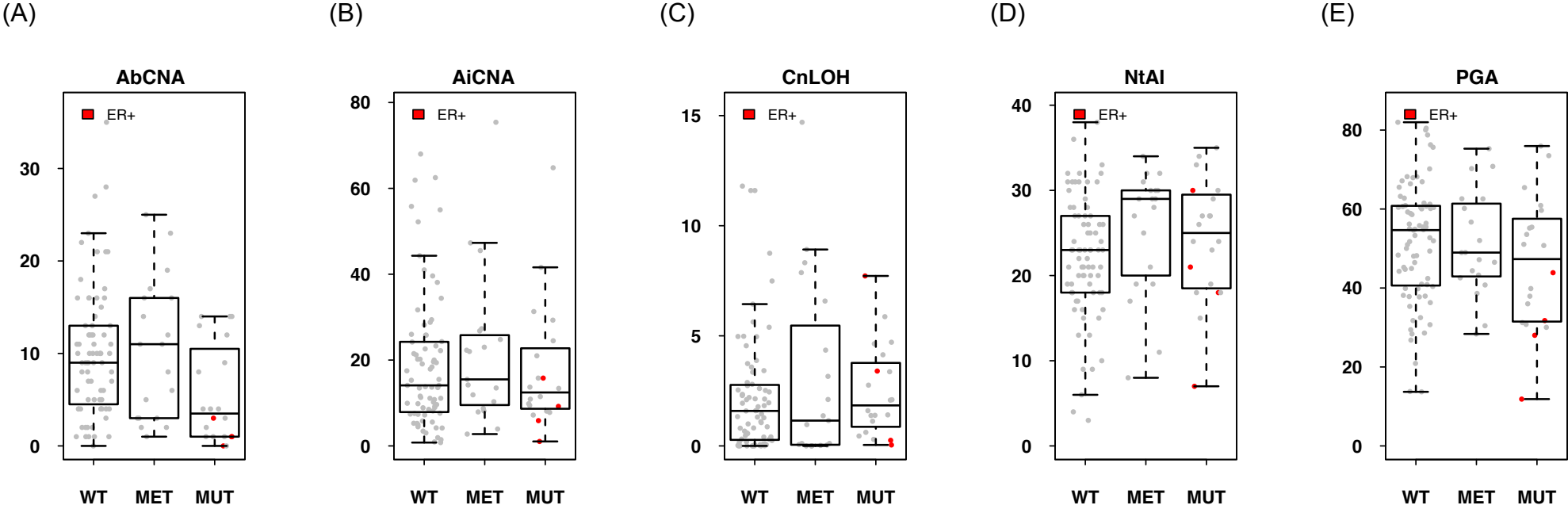
(B) METABRIC (n=50)



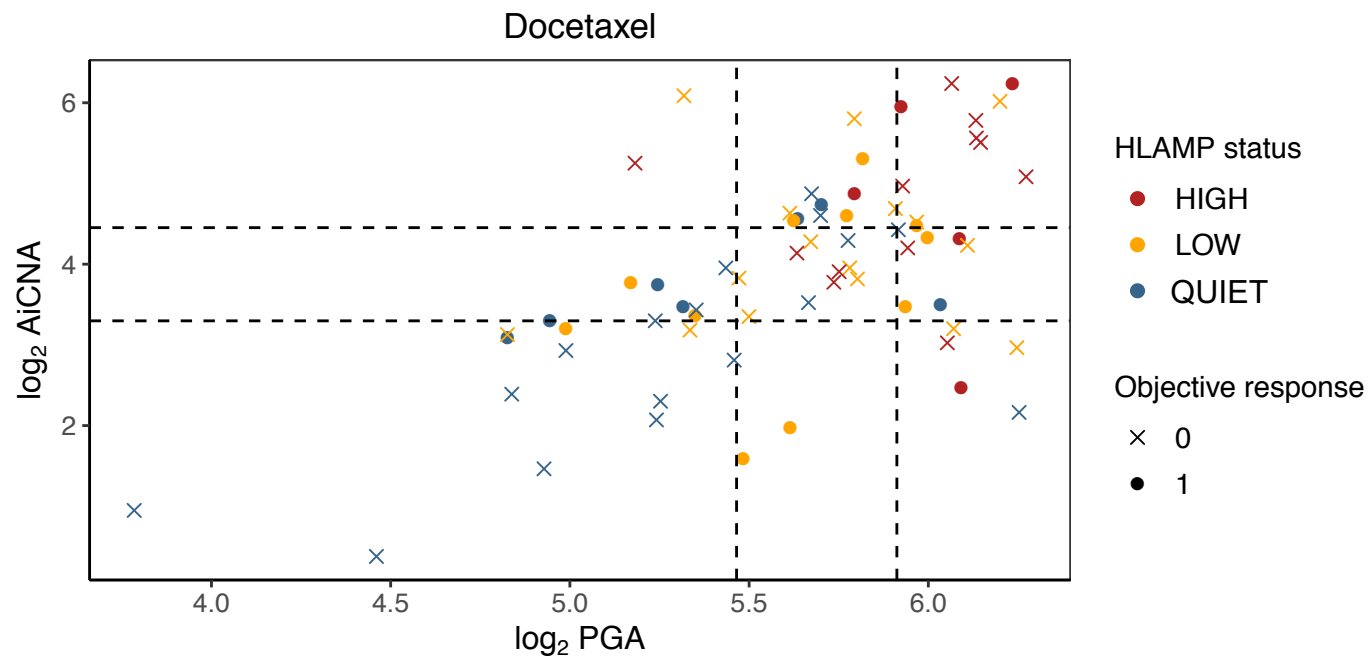
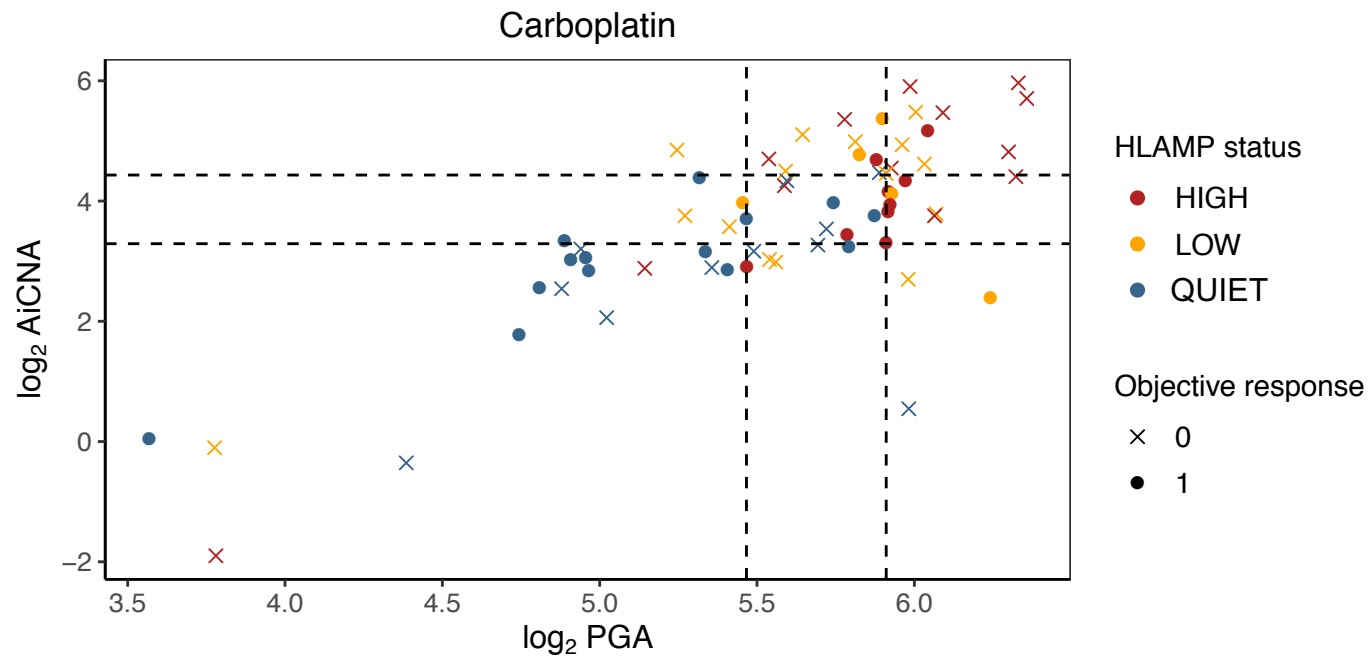
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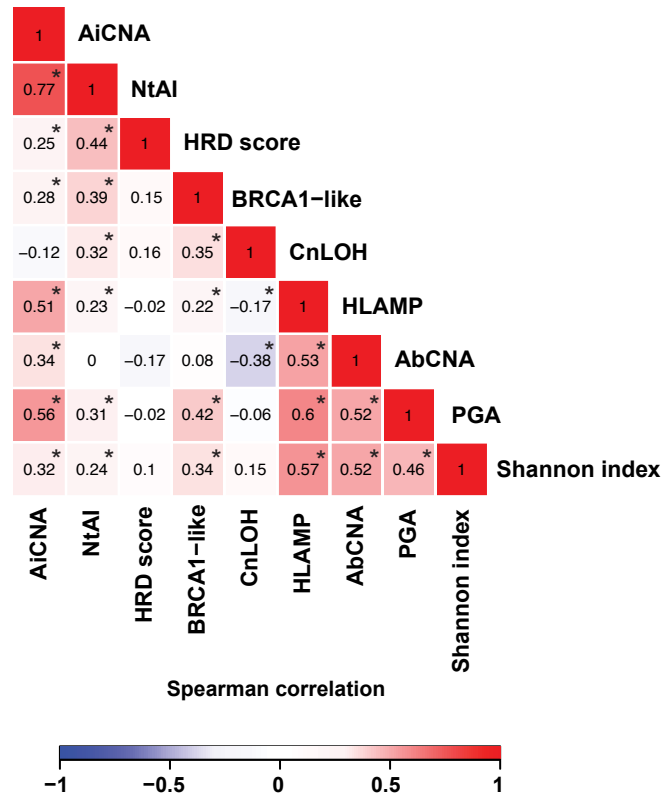
Supplementary Figure S3.



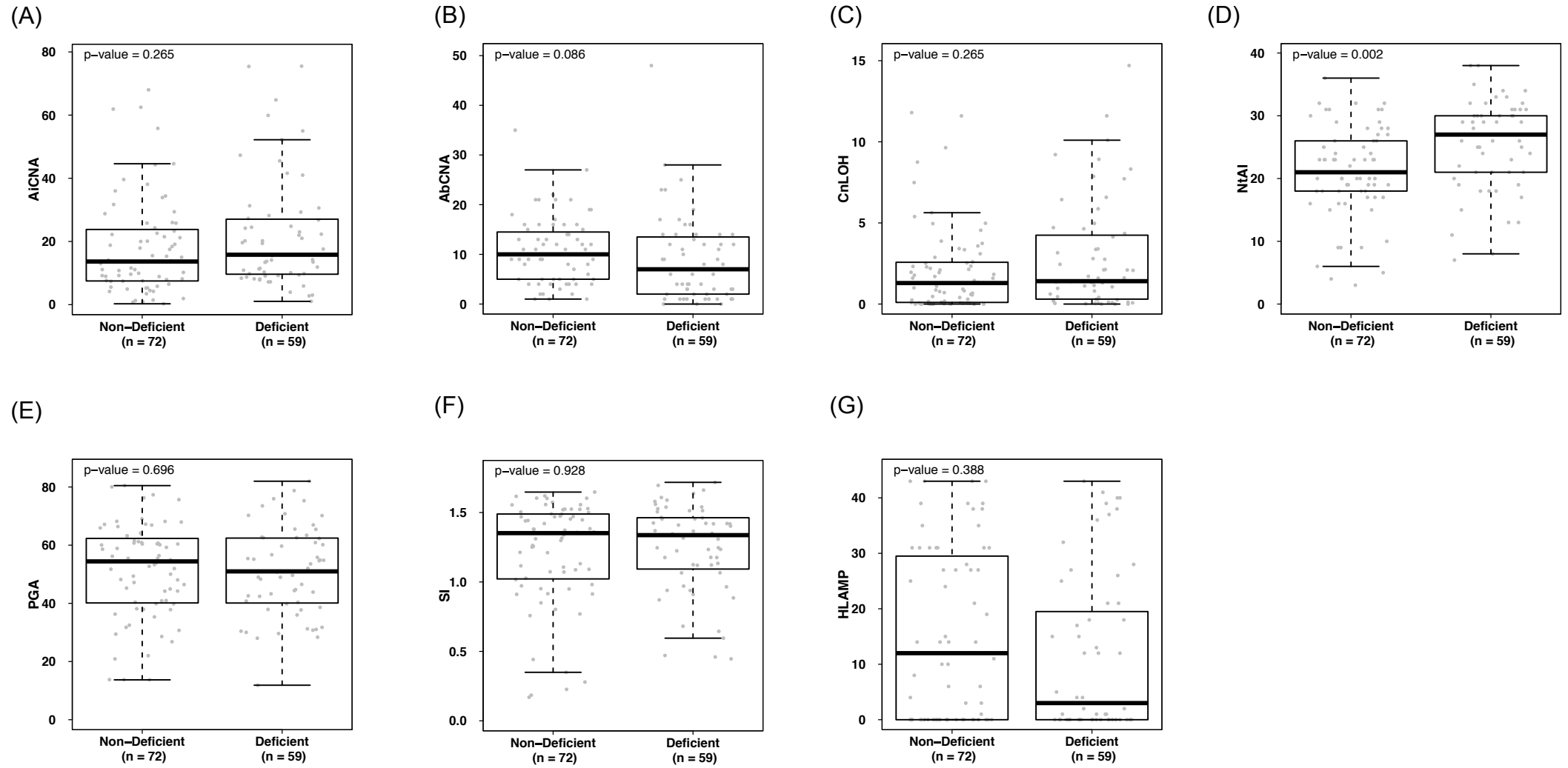
Supplementary Figure S4.



Supplementary Figure S5.



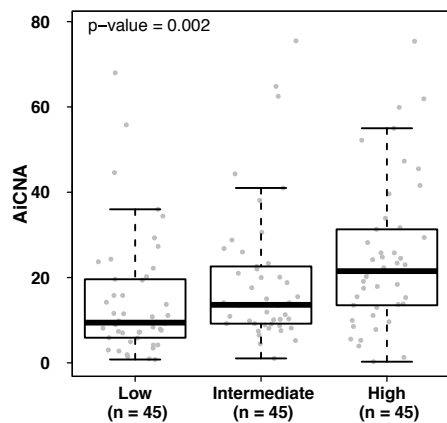
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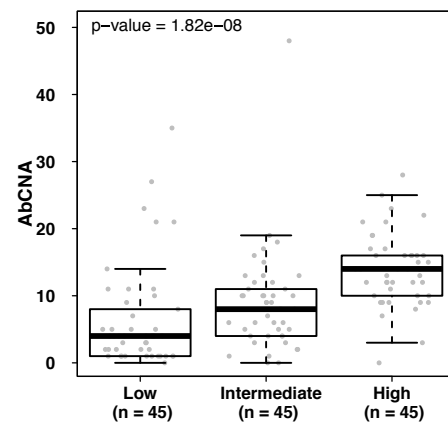


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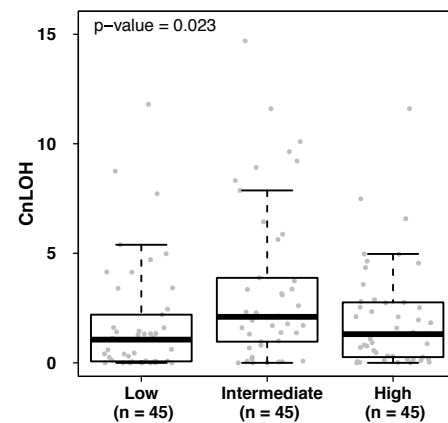
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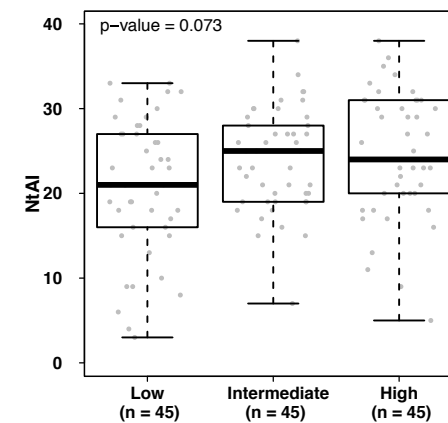
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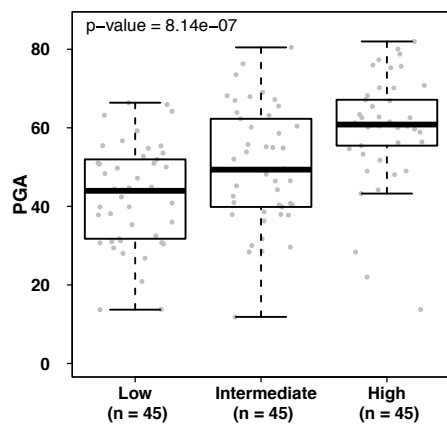
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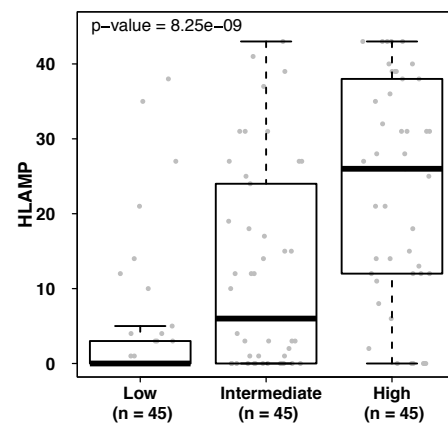
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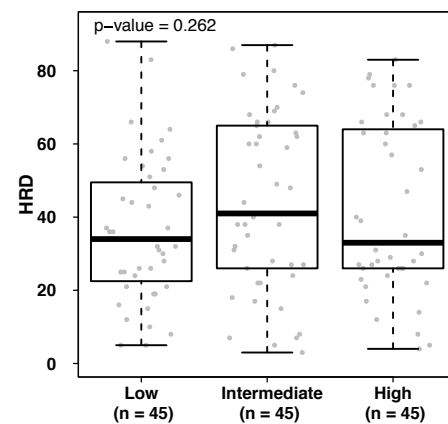
(E)



(F)

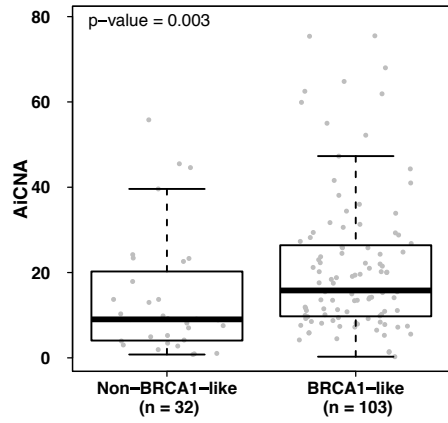


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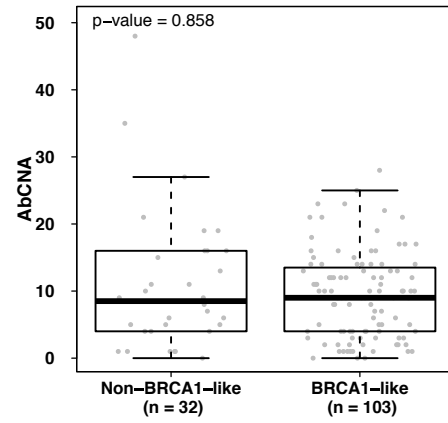


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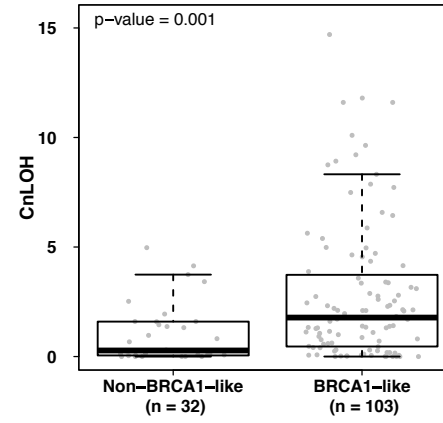
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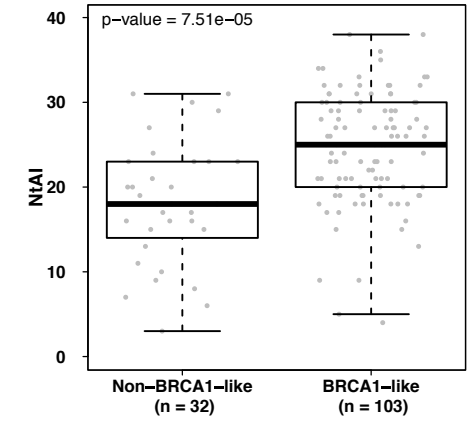
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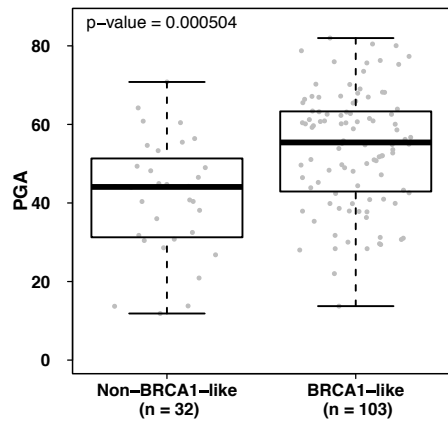
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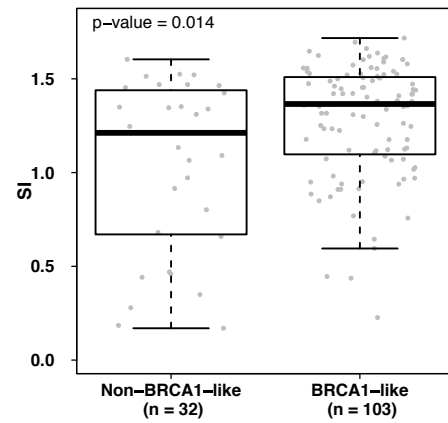
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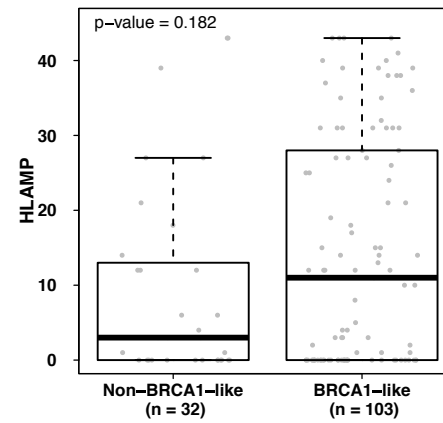
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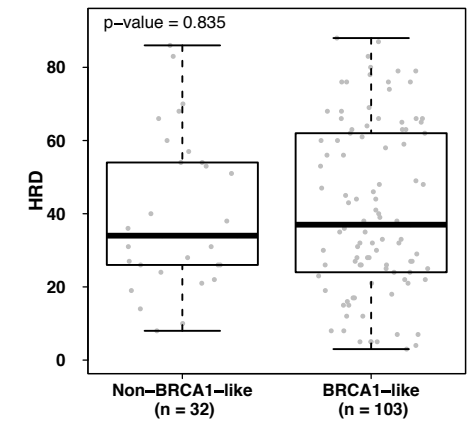
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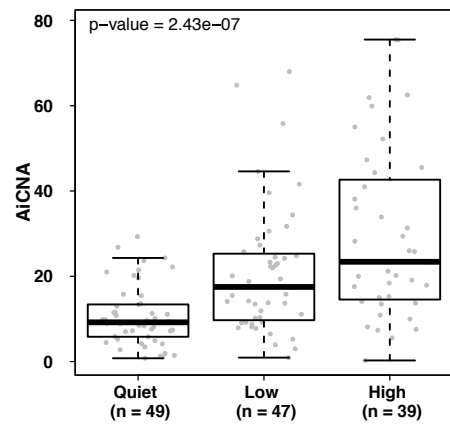


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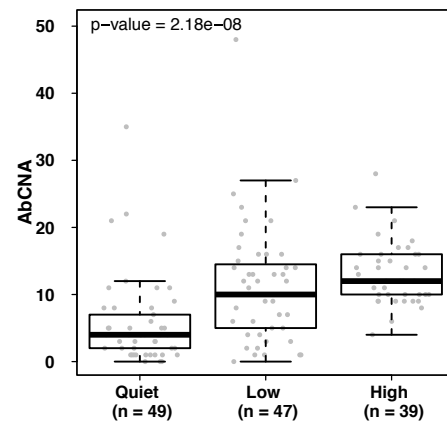


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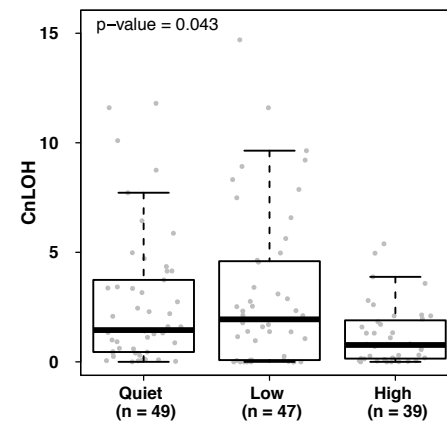
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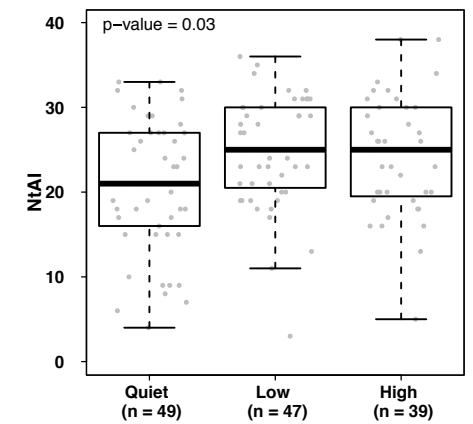
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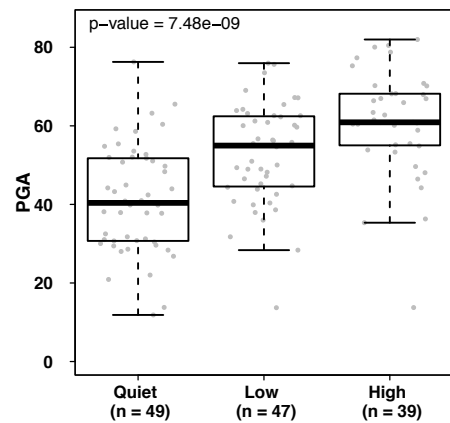
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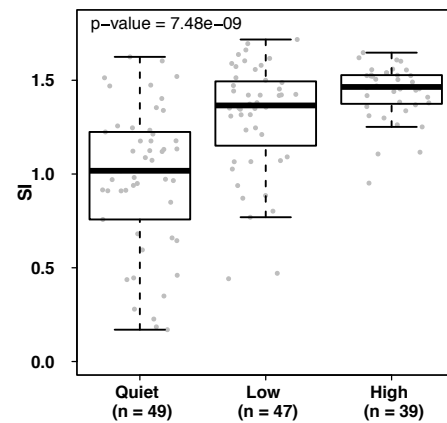
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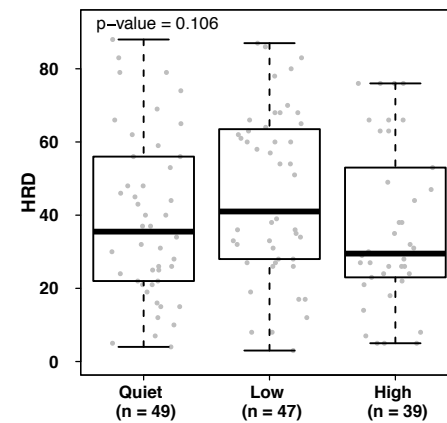
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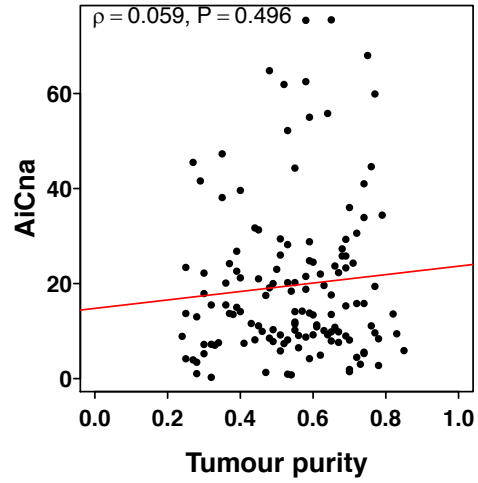


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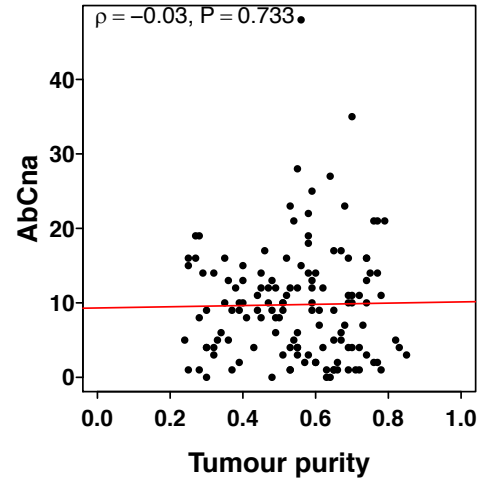


Supplementary Figure S10.

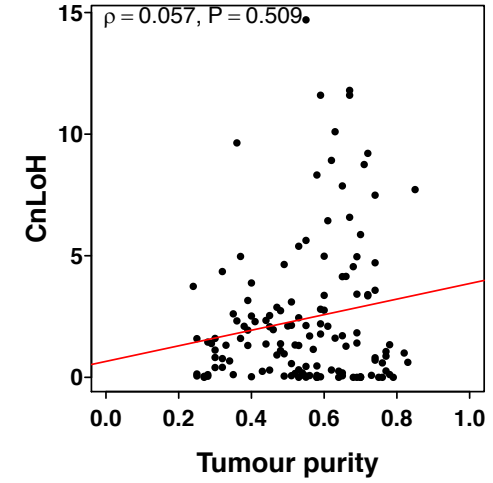
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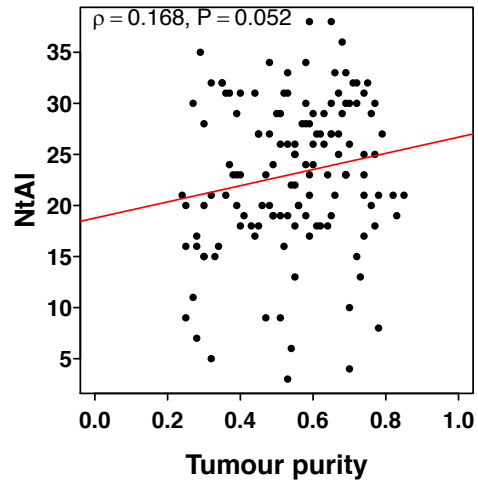
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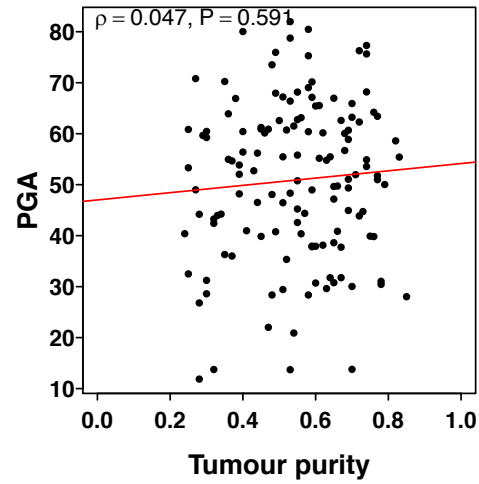
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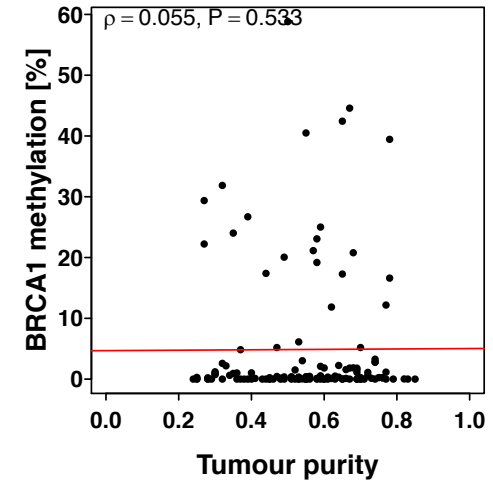
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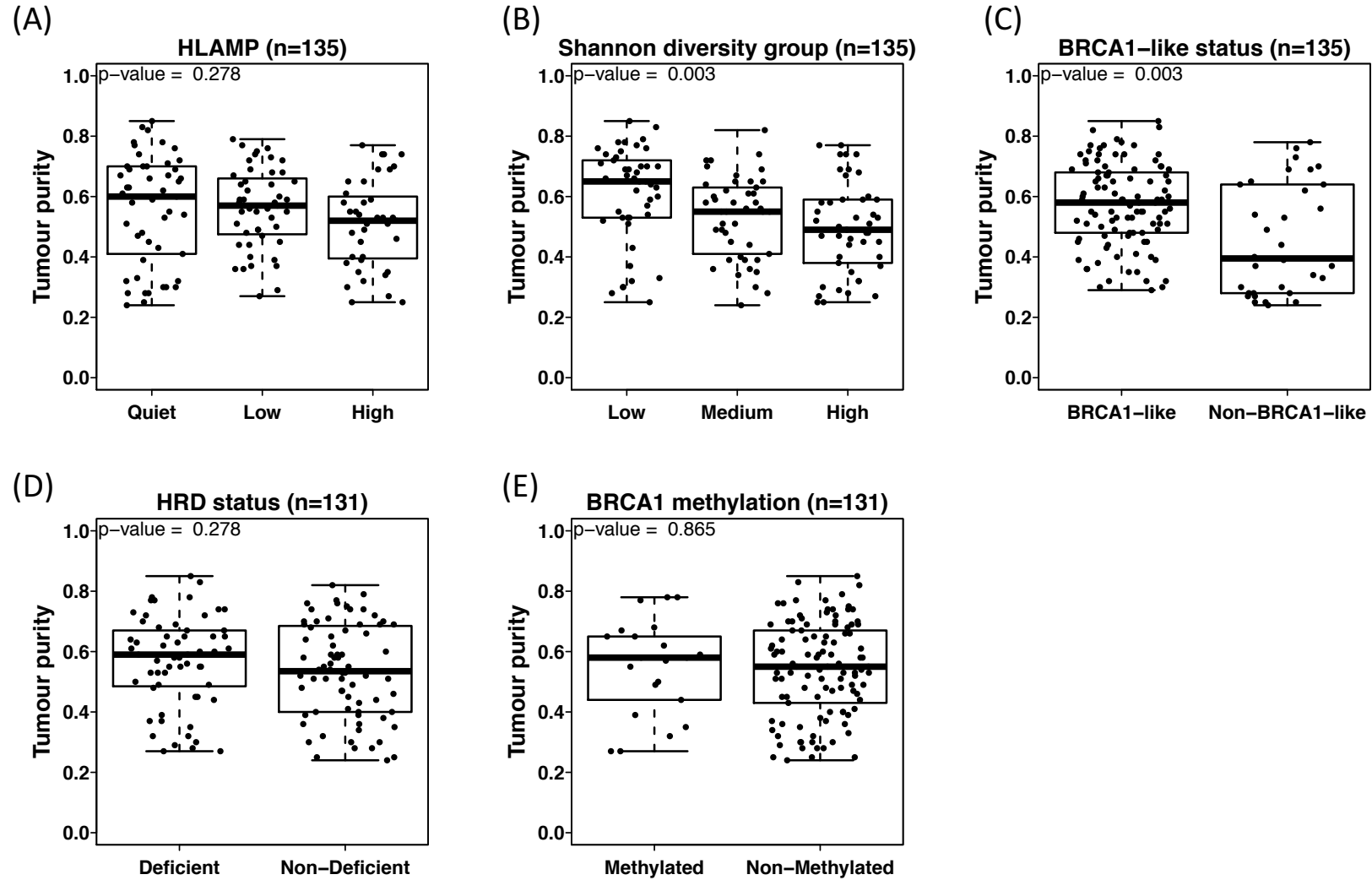
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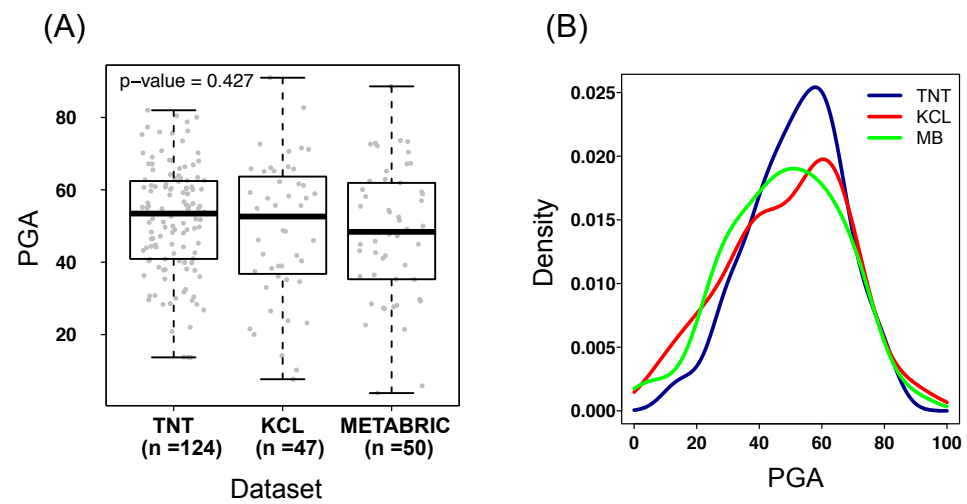


(F)



Supplementary Figure S11.





## 1 Supplementary Figure Legends

### 3 **Supplementary Figure S1**

4 The frequency of copy number gains and losses across the whole genome of primary  
5 tissue samples of the **(A)** patients without known germline *BRCA1/2* mutation status  
6 at trial entry in the TNT cohort ( $n=124$ ), **(B)** KCL subset ( $n=47$ ), **(B)** METABRIC subset  
7 ( $n=50$ ) with reported relapse. The complete KCL and METABRIC breast cancer  
8 cohorts were manually curated to include only triple negative samples that were  
9 reported to have been developed local or metastatic recurrences.

### 11 **Supplementary Figure S2**

12 The distribution of the amplified HLAMP regions across the (A) TNT cohort ( $n=135$ ),  
13 (B) METABRIC TNBC subset with reported relapse ( $n=50$ ), (C) SCAN-B metastatic  
14 subset ( $n=56$ ). Each column represents a sample. The presence of an amplification is  
15 shown in red. The amplification frequencies of the HLAMP cytobands are displayed  
16 as bar plots next to each corresponding heatmap. The HLAMP subgroups are  
17 indicated on top (quiet = blue, low = yellow, high = red).

### 19 **Supplementary Figure S3**

20 Comparison of the distribution of the CIN-measurements (A) AiCNA, (B) AbCNA, (C)  
21 CnLOH, (D) NtAI and (E) PGA among the *BRCA1/2* deficiency subgroups (WT = wild-  
22 type, MET = *BRCA1* methylated, MUT = *BRCA1/2* mutated) are displayed. The ER+  
23 cases are coloured in red.

### 25 **Supplementary Figure S4**

26 Schematic display of AiCNA, PGA and HLAMP status that provided evidence of  
27 interaction with treatment response in the carboplatin and docetaxel arms for each  
28 case. PGA and AiCNA are presented on  $\log_2$  scale, and vertical and horizontal lines  
29 show the boundaries between the subgroups at the tertiles of the CIN-  
30 measurements. HLAMP status is colour coded as red = high, yellow = low and blue =  
31 quiet HLAMP group. Solid circle = reported objective response, cross = no objective  
32 response.

### 34 **Supplementary Figure S5**

35 Correlation matrix showing the Spearman correlation coefficients among the CIN-  
36 measurements for the primary tumour samples ( $n=135$ ). *BRCA1*-like values represent  
37 the probability score from the *BRCA1*-like classification. Colour coding indicates the  
38 strength of the correlation. Asterisks show if the p-value associated with the  
39 Spearman correlation was  $P < 0.05$ .

### 41 **Supplementary Figure S6**

42 Comparison of the distribution of the CIN-measurements among the homologous  
43 recombination deficiency (HRD) subgroups, **(A)** AiCNA, **(B)** AbCNA, **(C)** CnLOH, **(D)**  
44 NtAI, **(E)** PGA, **(F)** SI, **(G)** HLAMP. P-values of Wilcoxon tests are shown. The p-values  
45 were corrected for multiple comparisons by the Benjamini-Hochberg method.

47 **Supplementary Figure S7**

48 Comparison of the distribution of the CIN-measurements among the Shannon index  
49 (SI) subgroups, **(A)** AiCNA, **(B)** AbCNA, **(C)** CnLOH, **(D)** NtAI, **(E)** PGA, **(F)** HLAMP, **(G)**  
50 HRD scores. P-values of Kruskal-Wallis rank sum tests are shown. The p-values were  
51 corrected for multiple comparisons by the Benjamini-Hochberg method.

52

53 **Supplementary Figure S8**

54 Comparison of the distribution of the CIN-measurements among the *BRCA1*-like  
55 subgroups, **(A)** AiCNA, **(B)** AbCNA, **(C)** CnLOH, **(D)** NtAI, **(E)** PGA, **(F)** SI, **(G)** HLAMP, **(H)**  
56 HRD scores. P-values of Wilcoxon tests are shown. The p-values were corrected for  
57 multiple comparisons by the Benjamini-Hochberg method.

58

59 **Supplementary Figure S9**

60 Comparison of the distribution of the CIN-measurements among the HLAMP groups,  
61 **(A)** AiCNA, **(B)** AbCNA, **(C)** CnLOH, **(D)** NtAI, **(E)** PGA, **(F)** SI, **(G)** HRD scores. P-values  
62 of Kruskal-Wallis rank sum test are shown. The p-values were corrected for multiple  
63 comparisons by the Benjamini-Hochberg method.

64

65 **Supplementary Figure S10**

66 Scatterplots showing the associations between with tumour purity (by ASCAT  
67 algorithm) and (A) AiCNA, (B) AbCNA, (C) CnLOH, (D) NtAI, (E) PGA as continuous  
68 variables, and (F) the percentage of *BRCA1* promoter methylation in the TNT study  
69 cohort (n=135). Spearman correlation coefficient ( $\rho$ ) and associated p-values (P)  
70 are shown in the top left corner. Fitted line of linear regression is indicated in red.

71

72 **Supplementary Figure S11**

73 Boxplots showing the associations between with tumour purity (by ASCAT algorithm)  
74 and (A) HLAMP, (B) Shannon diversity groups as categorical variables, (C) *BRCA1*-like  
75 status, (D) HRD status, and (E) the *BRCA1* promoter methylation status in the TNT  
76 study cohort (n=135). In the cases of HRD and *BRCA1* methylation status data is  
77 available for n=131 patients. P-values of Kruskal-Wallis rank sum tests are shown in  
78 the top left corner. The p-values were adjusted for multiple comparisons with the  
79 Benjamini-Hochberg method.

80

81 **Supplementary Figure S12**

82 Comparison of the distribution of PGA between the reduced TNT cohort (n=124)  
83 (including patients without known *BRCA1/2* mutation status at trial entry) and the  
84 KCL and METABRIC triple negative metastatic subsets on **(A)** boxplots and **(B)** density  
85 plots. P-value of Kruskal-Wallis rank sum test is shown.

86

87

88 PGA = percentage genome altered, AbCNA = allelic balanced CNA, AiCNA = allelic  
89 imbalanced CNA, NtAI = number of telomeric allelic imbalances, HRD score =  
90 homologous recombination deficiency score, CnLOH = copy number neutral loss of  
91 heterozygosity, HLAMP = high-level amplifications, *BRCA1*-like = probability score for  
92 *BRCA1*-like classification, SI = Shannon index, KCL = King's College London, MB =  
93 METABRIC.



**Supplementary Table S1.** Clinical baseline characteristics of (A) TNT trial cohort ( $n=376$ ), (B) patients with available DNA ( $n=196$ ) and (C) TNT study cohort ( $n=135$ ).

(A)

	TNT trial cohort ( $n=376$ )					
	Carboplatin		Docetaxel		Total	
	No.	%	No.	%	No.	%
<b>Age group [years]</b>						
<35	14	7.4	21	11.2	35	9.3
35-40	47	25	39	20.7	86	22.9
40-45	63	33.5	67	35.6	130	34.6
45-50	64	34	61	32.4	125	33.2
<b>Ethnic Origin</b>						
Any other ethnic group	1	0.5	2	1.1	3	0.8
Asian or Asian British: Bangladesh	2	1.1	0	0	2	0.5
Asian or Asian British: Indian	3	1.6	0	0	3	0.8
Asian or Asian British: Pakistani	1	0.5	2	1.1	3	0.8
Black or Black British: African	6	3.2	3	1.6	9	2.4
Black or Black British: Caribbean	4	2.1	6	3.2	10	2.7
Mixed: White and Black Caribbean	0	0	1	0.5	1	0.3
Not stated	5	2.7	2	1.1	7	1.9

Other Asian Background	2	1.1	1	0.5	3	0.8
Other Black Background	3	1.6	1	0.5	4	1.1
Other White background	4	2.1	6	3.2	10	2.7
White: British	154	81.9	161	85.6	315	83.8
White: Irish	1	0.5	2	1.1	3	0.8
Missing	2	1.1	1	0.5	3	0.8
<b>Carcinoma Type</b>						
Recurrent locally advanced	20	10.6	19	10.1	39	10.4
Metastatic	168	89.4	169	89.9	337	89.6
<b>ECOG performance status</b>						
0-1	174	92.6	176	93.6	350	93.1
2	14	7.4	12	6.4	26	6.9
<b>Previous taxane chemotherapy</b>						
Yes	65	34.6	61	32.4	126	33.5
No	123	65.4	127	67.6	250	66.5
<b>Liver or lung metastases</b>						
Yes	98	52.1	100	53.2	198	52.7
No	90	47.9	88	46.8	178	47.3
<b>Time since diagnosis to initial relapse [years]</b>						
0-1 from	31	16.5	41	21.8	72	19.1
1-3 years	100	53.2	89	47.3	189	50.3
3-5 years	41	21.8	33	17.6	74	19.7
>5 years	16	8.5	25	13.3	41	10.9
<b>Visceral disease present at baseline</b>						
No	52	27.7	52	27.7	104	27.7
Yes	136	72.3	136	72.3	272	72.3

<b>Germline <i>BRCA1/2</i> mutational status*</b>						
No mutation	128	68.1	145	77.1	273	72.6
BRCA1 mut	16	8.5	15	8	31	8.2
BRCA2 mut	9	4.8	3	1.6	12	3.2
Unknown	35	18.6	25	13.3	60	16
<b>Tumour <i>BRCA1/2</i> mutational status*</b>						
Negative	90	47.9	90	47.9	180	47.9
Positive	18	9.6	14	7.4	32	8.5
Uncertain	1	0.5	6	3.2	7	1.9
Untested	79	42	78	41.5	157	41.8
<b><i>BRCA1</i> methylation*</b>						
Non-methylated	93	49.5	86	45.7	179	47.6
Methylated	14	7.4	19	10.1	33	8.8
Unknown	81	43.1	83	44.1	164	43.6
<b>Surgery of primary disease</b>						
Yes	166	88.3	163	86.7	329	87.5
No	18	9.6	22	11.7	40	10.6
Missing	4	2.1	3	1.6	7	1.9
<b>Axillary lymph node surgery performed</b>						
Yes	166	88.3	158	84	324	86.2
No	20	10.6	24	12.8	44	11.7
Missing	2	1.1	6	3.2	8	2.1
<b>Number of lymph nodes involved</b>						
N-	96	51.1	95	50.5	191	50.8
1-3N+	53	28.2	51	27.1	104	27.7
>=4N+	39	20.7	42	22.3	81	21.5

<b>Side of primary tumour</b>						
Left	108	57.4	111	59	219	58.2
Right	78	41.5	74	39.4	152	40.4
Missing	2	1.1	3	1.6	5	1.3
<b>Vascular invasion</b>						
Yes	80	42.6	69	36.7	149	39.6
No	76	40.4	83	44.1	159	42.3
Not reported	28	14.9	30	16	58	15.4
Missing	4	2.1	6	3.2	10	2.7
<b>Tumour grade</b>						
1	0	0	2	1.1	2	0.5
2	28	14.9	29	15.4	57	15.2
3	151	80.3	150	79.8	301	80.1
Not known	6	3.2	4	2.1	10	2.7
Missing	3	1.6	3	1.6	6	1.6
<b>Pathological invasive tumour size</b>						
<2cm	42	22.3	40	21.3	82	21.8
2-5cm	100	53.2	108	57.4	208	55.3
>5cm	26	13.8	17	9	43	11.4
Missing	20	10.6	23	12.2	43	11.4
<b>Histological Type</b>						
Infiltrating ductal	158	84	161	85.6	319	84.8
Infiltrating lobular	4	2.1	5	2.7	9	2.4
Mixed ductal & lobular	3	1.6	3	1.6	6	1.6
Other	18	9.6	14	7.4	32	8.5
Missing	5	2.7	5	2.7	10	2.7
<b>Anthracycline chemotherapy for</b>						

<b>metastatic/locally advanced disease</b>						
Yes	16	8.5	20	10.6	36	9.6
No	172	91.5	166	88.3	338	89.9
Missing	0	0	2	1.1	2	0.5

(B)

	<b>TNT cohort – DNA available (n=196)</b>					
	<b>Carboplatin</b>		<b>Docetaxel</b>		<b>Total</b>	
	<b>No.</b>	<b>%</b>	<b>No.</b>	<b>%</b>	<b>No.</b>	<b>%</b>
<b>Age group [years]</b>						
<35	8	8.3	13	13	21	10.7
35-40	25	26	22	22	47	24
40-45	34	35.4	38	38	72	36.7
45-50	29	30.2	27	27	56	28.6
<b>Ethnic Origin</b>						
Any other ethnic group	1	1	0	0	1	0.5
Asian or Asian British:						
Bangladesh	2	2.1	0	0	2	1
Asian or Asian British:						
Indian	2	2.1	0	0	2	1
Asian or Asian British:						
Pakistani	0	0	1	1	1	0.5
Black or Black British:						
African	3	3.1	2	2	5	2.6
Black or Black British:						
Caribbean	3	3.1	5	5	8	4.1

Mixed: White and Black						
Caribbean	0	0	1	1	1	0.5
Not stated	2	2.1	1	1	3	1.5
Other Asian Background	1	1	0	0	1	0.5
Other Black Background	1	1	0	0	1	0.5
Other White background	2	2.1	2	2	4	2
White: British	79	82.3	86	86	165	84.2
White: Irish	0	0	2	2	2	1
Missing	0	0	0	0	0	0
<b>Carcinoma Type</b>						
Recurrent locally advanced	7	7.3	11	11	18	9.2
Metastatic	89	92.7	89	89	178	90.8
<b>ECOG performance status</b>						
0-1	88	91.7	92	92	180	91.8
2	8	8.3	8	8	16	8.2
<b>Previous taxane chemotherapy</b>						
Yes	39	40.6	37	37	76	38.8
No	57	59.4	63	63	120	61.2
<b>Liver or lung metastases</b>						
Yes	58	60.4	54	54	112	57.1
No	38	39.6	46	46	84	42.9
<b>Time since diagnosis to initial relapse [years]</b>						
0-1 from	8	8.3	19	19	27	13.8
1-3 years	60	62.5	51	51	111	56.6
3-5 years	22	22.9	19	19	41	20.9
>5 years	6	6.3	11	11	17	8.7
<b>Visceral disease present at baseline</b>						

No	21	21.9	26	26	47	24
Yes	75	78.1	74	74	149	76
<b>Germline <i>BRCA1/2</i> mutational status*</b>						
No mutation	73	76	82	82	155	79.1
BRCA1 mut	10	10.4	8	8	18	9.2
BRCA2 mut	2	2.1	1	1	3	1.5
Unknown	11	11.5	9	9	20	10.2
<b>Tumour <i>BRCA1/2</i> mutational status*</b>						
Negative	79	82.3	81	81	160	81.6
Positive	16	16.7	14	14	30	15.3
Uncertain	1	1	5	5	6	3.1
Untested	0	0	0	0	0	0
<b><i>BRCA1</i> methylation*</b>						
Non-methylated	83	86.5	76	76	159	81.1
Methylated	11	11.5	19	19	30	15.3
Unknown	2	2.1	5	5	7	3.6
<b>Surgery of primary disease</b>						
Yes	95	99	98	98	193	98.5
No	0	0	2	2	2	1
Missing	1	1	0	0	1	0.5
<b>Axillary lymph node surgery performed</b>						
Yes	96	100	95	95	191	97.4
No	0	0	5	5	5	2.6
Missing	0	0	0	0	0	0
<b>Number of lymph nodes involved</b>						
N-	46	47.9	40	40	86	43.9

1-3N+	27	28.1	29	29	56	28.6
>=4N+	23	24	31	31	54	27.6
<b>Side of primary tumour</b>						
Left	54	56.3	65	65	119	60.7
Right	42	43.8	35	35	77	39.3
Missing	0	0	0	0	0	0
<b>Vascular invasion</b>						
Yes	52	54.2	48	48	100	51
No	40	41.7	42	42	82	41.8
Not reported	4	4.2	10	10	14	7.1
Missing	0	0	0	0	0	0
<b>Tumour grade</b>						
1	0	0	1	1	1	0.5
2	10	10.4	11	11	21	10.7
3	86	89.6	87	87	173	88.3
Not known	0	0	1	1	1	0.5
Missing	0	0	0	0	0	0
<b>Pathological invasive tumour size</b>						
<2cm	18	18.8	18	18	36	18.4
2-5cm	62	64.6	70	70	132	67.3
>5cm	15	15.6	8	8	23	11.7
Missing	1	1	4	4	5	2.6
<b>Histological Type</b>						
Infiltrating ductal	84	87.5	89	89	173	88.3
Infiltrating lobular	2	2.1	2	2	4	2
Mixed ductal & lobular	1	1	1	1	2	1
Other	9	9.4	8	8	17	8.7
Missing	0	0	0	0	0	0



<b>Anthracycline chemotherapy for metastatic/locally advanced disease</b>						
Yes	4	4.2	7	7	11	5.6
No	92	95.8	92	92	184	93.9
Missing	0	0	1	1	1	0.5

(C)

	<b>TNT study cohort (n=135)</b>					
	<b>Carboplatin</b>		<b>Docetaxel</b>		<b>Total</b>	
	<b>No.</b>	<b>%</b>	<b>No.</b>	<b>%</b>	<b>No.</b>	<b>%</b>
<b>Age group [years]</b>						
<35	7	10.4	8	11.8	15	11.1
35-40	20	29.9	15	22.1	35	25.9
40-45	23	34.3	26	38.2	49	36.3
45-50	17	25.4	19	27.9	36	26.7
<b>Ethnic Origin</b>						
Any other ethnic group	1	1.5	0	0	1	0.7
Asian or Asian British: Bangladesh	1	1.5	0	0	1	0.7
Asian or Asian British: Indian	2	3	0	0	2	1.5
Asian or Asian British: Pakistani	0	0	0	0	0	0

Black or Black British:						
African	1	1.5	2	2.9	3	2.2
Black or Black British:						
Caribbean	2	3	5	7.4	7	5.2
Mixed: White and Black						
Caribbean	0	0	0	0	0	0
Not stated	2	3	1	1.5	3	2.2
Other Asian Background	1	1.5	0	0	1	0.7
Other Black Background	1	1.5	0	0	1	0.7
Other White background	2	3	2	2.9	4	3
White: British	54	80.6	58	85.3	112	83
White: Irish	0	0	0	0	0	0
Missing	0	0	0	0	0	0
<b>Carcinoma Type</b>						
Recurrent locally advanced	4	6	7	10.3	11	8.1
Metastatic	63	94	61	89.7	124	91.9
<b>ECOG performance status</b>						
0-1	61	91	61	89.7	122	90.4
2	6	9	7	10.3	13	9.6
<b>Previous taxane chemotherapy</b>						
Yes	26	38.8	25	36.8	51	37.8
No	41	61.2	43	63.2	84	62.2
<b>Liver or lung metastases</b>						
Yes	39	58.2	37	54.4	76	56.3
No	28	41.8	31	45.6	59	43.7
<b>Time since diagnosis to initial relapse [years]</b>						
0-1 from	6	9	13	19.1	19	14.1
1-3 years	40	59.7	35	51.5	75	55.6

3-5 years	16	23.9	14	20.6	30	22.2
>5 years	5	7.5	6	8.8	11	8.1
<b>Visceral disease present at baseline</b>						
No	17	25.4	18	26.5	35	25.9
Yes	50	74.6	50	73.5	100	74.1
<b>Germline <i>BRCA1/2</i> mutational status*</b>						
No mutation	50	74.6	55	80.9	105	77.8
<i>BRCA1</i> mut	9	13.4	5	7.4	14	10.4
<i>BRCA2</i> mut	1	1.5	1	1.5	2	1.5
Unknown	7	10.4	7	10.3	14	10.4
<b>Tumour <i>BRCA1/2</i> mutational status*</b>						
Negative	53	79.1	57	83.8	110	81.5
Positive	13	19.4	9	13.2	22	16.3
Uncertain	1	1.5	2	2.9	3	2.2
Untested	0	0	0	0	0	0
<b><i>BRCA1</i> methylation*</b>						
Non-methylated	58	86.6	51	75	109	80.7
Methylated	8	11.9	13	19.1	21	15.6
Unknown	1	1.5	4	5.9	5	3.7
<b>Surgery of primary disease</b>						
Yes	67	100	67	98.5	134	99.3
No	0	0	1	1.5	1	0.7
Missing	0	0	0	0	0	0
<b>Axillary lymph node surgery performed</b>						
Yes	67	100	65	95.6	132	97.8
No	0	0	3	4.4	3	2.2

Missing	0	0	0	0	0	0
<b>Number of lymph nodes involved</b>						
N-	33	49.3	25	36.8	58	43
1-3N+	16	23.9	20	29.4	36	26.7
>=4N+	18	26.9	23	33.8	41	30.4
<b>Side of primary tumour</b>						
Left	40	59.7	43	63.2	83	61.5
Right	27	40.3	25	36.8	52	38.5
Missing	0	0	0	0	0	0
<b>Vascular invasion</b>						
Yes	35	52.2	33	48.5	68	50.4
No	29	43.3	29	42.6	58	43
Not reported	3	4.5	6	8.8	9	6.7
Missing	0	0	0	0	0	0
<b>Tumour grade</b>						
1	0	0	1	1.5	1	0.7
2	9	13.4	6	8.8	15	11.1
3	58	86.6	61	89.7	119	88.1
Not known	0	0	0	0	0	0
Missing	0	0	0	0	0	0
<b>Pathological invasive tumour size</b>						
<2cm	12	17.9	11	16.2	23	17
2-5cm	43	64.2	50	73.5	93	68.9
>5cm	11	16.4	6	8.8	17	12.6
Missing	1	1.5	1	1.5	2	1.5
<b>Histological Type</b>						
Infiltrating ductal	57	85.1	59	86.8	116	85.9
Infiltrating lobular	2	3	0	0	2	1.5

Mixed ductal & lobular	0	0	1	1.5	1	0.7
Other	8	11.9	8	11.8	16	11.9
Missing	0	0	0	0	0	0
<b>Anthracycline chemotherapy for metastatic/locally advanced disease</b>						
Yes	2	3	5	7.4	7	5.2
No	65	97	62	91.2	127	94.1
Missing	0	0	1	1.5	1	0.7

\*When *BRCA1/2* mutational status was determined, in order to completely separate the effect of *BRCA1/2* mutation and *BRCA1* promoter methylation, only samples with either mutation or methylation were included. Out of the 22 *BRCA1/2* mutation carriers and 21 *BRCA1* promoter methylated cases, 1 sample was excluded because of being both mutated and methylated, 1 *BRCA1* methylated sample with unknown *BRCA1/2* status and 1 *BRCA1/2* mutated sample with unknown *BRCA1* methylation status were excluded, resulting in 20 *BRCA1/2* mutated and 19 *BRCA1* promoter methylated cases.

**Supplementary Table S2.** The REMARK checklist as published by McShane *et al.*, British journal of cancer. 2005;93(4):387-91 and the application for the guidelines in this manuscript.

REMARK checklist item	Description	TNT manuscript
<b>Introduction</b>		
1	State the marker examined, study objectives and pre-specified hypotheses.	✓ Introduction
<b>Materials and Methods</b>		
<b>Patients</b>		
2	Describe the characteristics (eg disease stage or co-morbidities) of study patients, including their source and inclusion and exclusion criteria	✓ In original TNT publication
3	Describe treatments received and how chosen (eg randomized or rule-based).	✓ In original TNT publication
<b>Specimen characteristics</b>		
4	Describe the type of biological material used (incl. control samples) and methods for preservation.	✓ In original TNT publication
<b>Assay methods</b>		
5	Specify the assay method used and provide (or reference) a detailed protocol, incl. specific reagents or kits used, quality control procedures, reproducibility assessment, quantitation methods, and scoring and reporting protocols. Specify whether and how assays were performed blinded to the study endpoint.	✓ In original TNT publication
<b>Study design</b>		
6	State the method of case selection, including whether prospective or retrospective and whether stratification or matching (eg by stage of disease or age) was used. Specify the time period from which cases were taken, the end of the follow-up period, and the median-follow-up time.	✓ Materials and Methods
7	Precisely define all clinical endpoints examined.	✓ Materials and Methods
8	List all candidate variables initially examined or considered for inclusion in models.	✓ Materials and Methods
9	Give rationale for sample size; if the study was designed to detect a specified effect size, give the target power and effect size.	✓ Sample size was defined by number of available samples
<b>Statistical analysis methods</b>		
10	Specify all statistical methods, including details of any variable selection procedures and other model-building issues, how model assumptions were verified, and how missing data were handled.	✓ Materials and Methods
11	Clarify how marker values were handled in the analyses; if relevant, describe methods used for cutpoint determination.	✓ Materials and Methods

Results		
Data		
12	Describe the flow of patients through the study, including the number of patients included in each stage of the analysis (a diagram may be helpful) and reasons for dropout. Specifically, both overall and for each subgroup extensively examined report the number of patients and the number of events.	✓ CONSORT diagram
13	Report distributions of basic demographic characteristics (at least age and sex), standard (disease-specific) prognostic variables, and tumor marker, including number of missing values.	✓ Supplementary Table S1
Analysis and interpretation		
14	Show the relation of the marker to standard prognostic variables	
15	Present univariable analysis showing the relation between the marker and outcome, with the estimated effect (eg hazard ratio and survival probability). Preferably provide similar analyses for all other variables being analyzed. For the effect of a tumor marker on a time-to-event outcome, a Kaplan-Meier plot is recommended.	
16	For key multivariable analyses, report estimated effects (eg hazard ratio) with confidence intervals for the marker and, at least for the final model, all other variables in the model.	
17	Among reported results, provide estimated effects with confidence intervals from an analysis in which the marker and standard prognostic variables are included, regardless of their statistical significance.	
18	If done, report results of further investigations, such as checking assumptions, sensitivity analysis, and internal validation.	✓ Supplementary material
Discussion		
19	Interpret the results in the context of the pre-specified hypotheses and other relevant studies; include a discussion of limitations of the study.	✓ Discussion
20	Discuss implications for further research and clinical value.	✓ Discussion

**Supplementary Table S3.** *BRCA1/2* mutation, *BRCA1* promoter methylation and all CIN measurement values for the ER+ cases ( $n=4$ ).

CIN measurements	TNT72	TNT147	TNT227	TNT232
<b>Germline BRCA1 mutation*</b>	0	1	1	0
<b>Germline BRCA2 mutation*</b>	1	0	0	1
<b>Tumour BRCA1 mutation*</b>	1	1	1	0
<b>Tumour BRCA2 mutation*</b>	1	0	0	1
<b>BRCA1 methylation</b>	Non-methylated	Non-methylated	Non-methylated	Non-methylated
<b>AiCNA**</b>	1.04 (Low)	5.89 (Low)	15.8 (Medium)	9.21 (Low)
<b>AbCNA**</b>	1 (Low)	3 (Low)	1 (Low)	0 (Low)
<b>CnLOH**</b>	0.04 (Low)	7.72 (High)	3.4 (High)	0.25 (Low)
<b>NtAI**</b>	7 (Low)	21 (Medium)	30 (High)	18 (Low)
<b>PGA**</b>	11.85 (Low)	28.02 (Low)	43.87 (Low)	31.75 (Low)
<b>HLAMP</b>	Quiet	Quiet	Low	Low
<b>Shannon diversity</b>	Medium	Low	Low	Medium
<b>BRCA1-like</b>	Not BRCA1-like	BRCA1-like	BRCA1-like	Not BRCA1-like
<b>HRD</b>	HR deficient	HR deficient	HR deficient	HR deficient

\*0 = No mutation

1 = Mutation

\*\*The continuous CIN measurements were divided into tertiles (Low, Medium, High) and this information was added next to each CIN value to demonstrate the level of CIN for each sample in comparison to the whole TNT study cohort ( $n=135$ ).



**Supplementary Table S4.** (A) P-values of Fisher's exact tests of the associations between the tested CIN-measurements (as categorical) and *BRCA1/2* deficiency status (B) P-values of Wilcoxon and Kruskal-Wallis rank sum tests of the associations between the tested CIN-measurements (as continuous) and *BRCA1/2* deficiency status.

(A)

CIN measurements (categorical)	BRCA1/2 deficiency*	HLAMP	Shannon diversity	BRCA1-like	HRD
HLAMP	0.029	N/A	2.48E-07	0.207	0.609
PGA	0.744	6.43E-09	3.33E-06	0.009	0.778
Shannon diversity	0.744	1.86E-07	N/A	0.419	0.773
NtAI	0.086	0.198	0.343	0.003	0.006
AiCNA	0.744	1.36E-05	0.006	0.004	0.773
AbCNA	0.047	6.43E-09	2.28E-10	0.82	0.021
CnLOH	0.744	0.089	0.184	0.025	0.773
BRCA1-like	0.948	0.177	0.366	N/A	0.773
HRD	1.61E-17	0.228	0.605	0.676	N/A

(B)

CIN measurements (continuous)	BRCA1/2 deficiency*	HLAMP	Shannon diversity	BRCA1-like	HRD
PGA	0.548	7.48E-09	8.14E-07	5.04E-04	0.696
Shannon diversity	0.543	7.48E-09	N/A	0.014	0.928
NtAI	0.328	0.03	0.073	7.51E-05	0.002
AiCNA	0.684	2.43E-07	0.002	0.003	0.265
AbCNA	0.12	2.18E-08	1.82E-08	0.858	0.086
CnLOH	0.622	0.043	0.023	0.001	0.265

P-values were adjusted for multiple comparisons with the Benjamini-Hochberg method.

\* The assessment of *BRCA1/2* deficiency included the comparison of three groups: the *BRCA1/2* wild-type ( $n=75$ ), the *BRCA1/2* mutated ( $n=20$ ) and the *BRCA1* promoter methylated ( $n=19$ ) cases.

**Supplementary Table S5.** Characteristics of identified pathogenic germline variants in cancer predisposition associated genes.

Patient	Chr.	Start	End	Ref	Alt	Variant type	Exonic function	Gene	Annotation Transcript	Nucleotide change	AA change	Clinical sign.
TNT267	2	215595140	215595140	G	A	exonic	stopgain	BARD1	NM_001282549	exon4:c.C457T	p.Q153X	Pathogenic/ Likely pathogenic
TNT115	17	59861775	59861775	-	A	exonic	frameshift insertion	BRIP1	NM_032043	exon11:c.1483dupT	p.S495fs	Pathogenic
TNT8	17	46805705	46805705	C	T	exonic	nonsynonymous SNV	HOXB13	NM_006361	exon1:c.G251A	p.G84E	Pathogenic/ Likely pathogenic, risk factor
TNT72	1	45799121	45799121	G	T	exonic	stopgain	MUTYH	NM_001128425	exon3:c.C312A	p.Y104X	Pathogenic
TNT237	1	45797228	45797228	C	T	exonic	nonsynonymous SNV	MUTYH	NM_001128425	exon13:c.G1187A	p.G396D	Pathogenic
TNT167	17	56787218	56787218	A	G	splicing	-	RAD51C	NM_058216	exon5:c.706-2A>G	-	Pathogenic/ Likely pathogenic
TNT134	8	145739070	145739070	T	-	exonic	frameshift deletion	RECQL4	NM_004260	exon13:c.2085delA	p.K695fs	Pathogenic
TNT75	3	14200382	14200382	G	T	exonic	nonsynonymous SNV	XPC	NM_004628	exon9:c.C1001A	p.P334H	Pathogenic

**Supplementary Table S6.** Odds ratios, associated 95% confidence intervals and p-values for interaction from the evaluation of ORR between the treatment arms among the patient subgroups of (A) NtAI, (B) AiCNA and (C) HLAMP.

(A) NtAI

Treatment	NtAI tertile	N	Odds ratio	95% CI	<i>P</i> <sub>interaction</sub>
Docetaxel	1 <sup>st</sup>	19	1	-	0.083
	2 <sup>nd</sup>	20	0.43	0.10 – 1.81	
	3 <sup>rd</sup>	29	1.21	0.37 – 3.98	
Carboplatin	1 <sup>st</sup>	22	0.98	0.27 – 3.50	
	2 <sup>nd</sup>	24	2.03	0.59 – 6.93	
	3 <sup>rd</sup>	21	0.86	0.23 – 3.15	

(B) AiCNA

Treatment	AiCNA tertile	N	Odds ratio	95% CI	<i>P</i> <sub>interaction</sub>
Docetaxel	1 <sup>st</sup>	20	1	-	0.060
	2 <sup>nd</sup>	24	1.17	0.32 – 4.19	
	3 <sup>rd</sup>	24	1.40	0.40 – 4.96	
Carboplatin	1 <sup>st</sup>	25	1.83	0.53 – 6.34	
	2 <sup>nd</sup>	21	3.79	1.03 – 13.91	
	3 <sup>rd</sup>	21	0.55	0.13 – 2.34	

(C) HLAMP

<b>Treatment</b>	<b>HLAMP tertile</b>	<b>N</b>	<b>Odds ratio</b>	<b>95% CI</b>	<b><i>P</i><sub>interaction</sub></b>
Docetaxel	Quiet	24	1	-	0.098
	Low	27	1.67	0.52 – 5.37	
	High	17	1.01	0.26 – 3.96	
Carboplatin	Quiet	25	3.09	0.95 – 10.08	
	Low	20	0.81	0.21 – 3.10	
	High	22	1.68	0.49 – 5.72	

*P*-values for interaction tests are based on a logistic regression model of response, with terms for CIN-measurement status, treatment arm and interaction.

**Supplementary Table S7.** Comparison of the results of Objective Response Rate (ORR) and Progression Free Survival analysis in the TNT study cohort (n=135) and the TNT ER- subset (n=131). (A) Associations between the CIN-measurements and ORR in the TNT study cohort, (B) in the ER- subset. (C) Non-adjusted and adjusted interaction p-values of logistic regression analysis of the association between the CIN-measurements and ORR, (D) PFS.

(A)

TNT study cohort (n=135)									
CIN measurement	Subgroup	ORR	Carboplatin		Docetaxel		Total		Fisher's exact p
			No.	%	No.	%	No.	%	
NtAI	intermediate	No	11	45.83	16	80.00	27	61.36	0.030
		Yes	13	54.17	4	20.00	17	38.64	
AiCNA	intermediate	No	8	38.10	16	66.67	24	53.33	0.076
		Yes	13	61.90	8	33.33	21	46.67	
CnLOH	intermediate	No	13	52.00	17	85.00	30	66.67	0.027
		Yes	12	48.00	3	15.00	15	33.33	
HLAMP	quiet	No	11	44.00	17	70.83	28	57.14	0.085
		Yes	14	56.00	7	29.17	21	42.86	

(B)

TNT ER- subset (n=131)									
CIN measurement	Subgroup	ORR	Carboplatin		Docetaxel		Total		Fisher's exact p
			No.	%	No.	%	No.	%	
NtAI	intermediate	No	11	47.83	16	80.00	27	62.79	0.056
		Yes	12	52.17	4	20.00	16	37.21	
AiCNA	intermediate	No	8	60.00	16	66.67	24	54.55	0.128
		Yes	12	40.00	8	33.33	20	45.45	
CnLOH	intermediate	No	13	52.00	17	85.00	30	66.67	0.027
		Yes	12	48.00	3	15.00	15	33.33	
HLAMP	quiet	No	11	47.83	17	70.83	28	59.57	0.142
		Yes	12	52.17	7	29.17	19	40.43	

(C)

Objective Response Rate (ORR)				
CIN measurement	TNT study cohort (n=135)		TNT ER- subset (n=131)	
	P <sub>interaction</sub>	P <sub>adj,interaction</sub>	P <sub>interaction</sub>	P <sub>adj,interaction</sub>
NtAI	0.083	0.016	0.083	0.018
AiCNA	0.060	0.024	0.075	0.022

(D)

Progression Free Survival (PFS)				
CIN measurement	TNT study cohort (n=135)		TNT ER- subset (n=131)	
	P <sub>interaction</sub>	P <sub>adj,interaction</sub>	P <sub>interaction</sub>	P <sub>adj,interaction</sub>
HLAMP	0.047	0.033	0.081	0.033
AiCNA	0.027	0.125	0.034	0.106
PGA	0.053	0.176	0.123	0.218





**Supplementary Table S8.** P-values of the Spearman correlations between CIN-measurements.

<b>CIN measurements</b>	<b>AiCna</b>	<b>NtAI</b>	<b>HRD score</b>	<b>BRCA1-like</b>	<b>CnLoH</b>	<b>HLAMP</b>	<b>AbCna</b>	<b>PGA</b>	<b>Shannon index</b>
AiCna	N/A	0.00E+00	0.004	0.001	0.163	1.98E-10	6.41E-05	2.32E-12	1.90E-04
NtAI	0.00E+00	N/A	1.35E-07	3.64E-06	1.31E-04	0.009	0.958	3.02E-04	0.006
HRD score	0.004	1.35E-07	N/A	0.098	0.077	0.844	0.057	0.83	0.234
BRCA1-like	0.001	3.64E-06	0.098	N/A	3.09E-05	0.01	0.37	5.53E-07	4.68E-05
CnLoH	0.163	1.31E-04	0.077	3.09E-05	N/A	0.048	5.19E-06	0.507	0.084
HLAMP	1.98E-10	0.009	0.844	0.01	0.048	N/A	4.90E-11	1.35E-14	8.02E-13
AbCna	6.41E-05	0.958	0.057	0.37	5.19E-06	4.90E-11	N/A	1.37E-10	1.49E-10
PGA	2.32E-12	3.02E-04	0.83	5.53E-07	0.507	1.35E-14	1.37E-10	N/A	2.01E-08
Shannon index	1.90E-04	0.006	0.234	4.68E-05	0.084	8.02E-13	1.49E-10	2.01E-08	N/A

The corresponding Spearman correlation coefficients are shown on supplementary Figure S5.

**Supplementary Table S9.** Objective Response Rate (ORR) within the *BRCA1/2* mutated subgroup.

Objective response	Treatment arm				Total	
	Carboplatin		Docetaxel		Total	
	No.	%	No.	%	No.	%
<b>No</b>	2	15.38	5	55.56	7	31.82
<b>Yes</b>	11	84.62	4	44.44	15	68.18
<b>Total</b>	13	100	9	100	22	100