Evaluation of CDK12 Protein Expression as a Potential Novel Biomarker for DNA Damage Response Targeted Therapies in Breast Cancer

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Abstract:

Disruption of Cyclin Dependent Kinase 12 (*CDK12*) is known to lead to defects in DNA repair and sensitivity to platinum salts and poly(ADP-ribose) polymerase 1/2 inhibitors. However, *CDK12* has also been proposed as an oncogene in breast cancer. We therefore aimed to assess the frequency and distribution of CDK12 protein expression by immunohistochemistry (IHC) in independent cohorts of breast cancer and correlate this with outcome and genomic status. We found that 21% of primary unselected breast cancers were CDK12 high, and 10.5% were absent, by IHC. CDK12 positivity correlated with HER2 positivity but was not an independent predictor of breast cancer specific survival taking HER2 status into account, however absent CDK12 protein expression significantly correlated with a triple negative phenotype. Interestingly, CDK12 protein absence was associated with reduced expression of a number of DDR proteins including ATR, Ku70/Ku80, PARP1, DNA-PK and gamma-H2AX, suggesting a novel mechanism of CDK12 associated DDR dysregulation in breast cancer. Our data suggest that diagnostic IHC quantification of CDK12 in BC is feasible, with CDK12 absence possibly signifying defective DDR function. This may have important therapeutic implications, particularly for triple negative breast cancers.

Introduction

Breast cancer (BC) is a complex disease comprising a variety of molecular and clinically distinct subtypes. Substantial progress has been made in the management of BC mortality over the last 25 years, in part due to improved treatment modalities such as endocrine therapies, HER2-targeted therapy and combination chemotherapies (1-4). However, a proportion of sporadic primary BC remain difficult to treat. Hence, there is an urgent need for stratification and biomarker discovery within this cohort.

The CycK/CDK12 (Cyclin K/Cyclin dependent kinase 12) complex is involved in the regulation of RNA polymerase II (RNA pol II) and mRNA processing (5-7) and is known to protect normal cells from genomic instability by regulating the transcription of DNA damage response (DDR) genes (8). Moreover, CDK12 has been postulated as a tumor suppressor gene in high-grade serous ovarian cancer (HGSOC), where it is one of the only significantly recurrently mutated genes (9). Recurrent point mutations have been shown to abrogate the functional activity of CDK12, resulting in defects in multiple DNA repair pathways, leading to genomic instability, down-regulation of some homologous recombination (HR) genes such as BRCA1, FANCI or FANCD2 (10,11) and selective sensitivity to both platinum agents and poly (ADP-ribose) polymerase (PARP1/2) inhibitors (12,13). Indeed, recent data in HGSOC suggests that CDK12 inactivated tumors have a unique signature of genomic instability characterized by frequent mega-sized gains scattered over the genome, that is a result of numerous tandem duplications, indicative of gross defects in DNA repair (14). In addition, recent profiling studies have also identified *CDK12* mutations in primary and castration resistant prostate cancer that are mutually exclusive with other mutations in DNA repair genes (15,16), and akin to HGSOC, result in large tandem duplications (14). On the other hand, in BC, *CDK12* gene amplification often co-occurs with *ERBB2* amplification as both are co-located at locus Ch17q12 (17,18), and CDK12 overexpression has been correlated with indicators of aggressive disease, suggesting that CDK12 could act as a oncogenic driver and prognostic biomarker in BC as a result of this co-location (19).

We have previously shown that in BC, *CDK12* is recurrently targeted by both DNA rearrangements (13% of HER2-amplified BC) and recurrent point mutations (2.6% of unselected BC) (13) in a similar manner to HGSOC, and that loss of CDK12 in BC models confers sensitivity to PARP1/2 inhibitors *in vitro* through defects in HR (12,13). Loss of CDK12 in BC may therefore signify response to platinum salts and/or PARP1/2 inhibitors (12,13).

Here we sought to i) investigate the distribution and frequency of CDK12 protein expression in a large series of unselected and Herceptin treated HER2-positive BC, using immunohistochemistry (IHC) and examine any correlation with survival; ii) evaluate CDK12 protein and mRNA expression with genomic alterations and iii) assess whether CDK12 would constitute an oncogenic driver in *CDK12* amplified tumors.

Materials and Methods

Tissue Microarray Patient Cohorts

Unselected BC

Primary operable BC cases (n= 1,650) from the Nottingham Tenovus Primary Breast Carcinoma Series were utilized as previously described (20-22). Patients were under the age of 71 years (median, 55 years), diagnosed between 1986 and 1999, and treated uniformly in a single institution. Clinicopathological parameters for this series are summarized in Supplementary Table S1.

HER2-positive adjuvant trastuzumab series

The HER2-positive adjuvant trastuzumab series comprises 143 primary operable BC from patients presenting between 2003 and 2010 who received adjuvant trastuzumab (21). HER2 status was determined according to the American Society of Clinical Oncology (ASCO) guidelines as previously described (21). Clinicopathological parameters for this series are summarized in Supplementary Table S2.

METABRIC Nottingham Breast Cancers

This series comprised 282 primary BC from Nottingham, which form part of the METABRIC cohort (23), (Supplementary Table S3).

Tissue Microarray (TMA) Construction

Tumor samples were arrayed as previously described (22). Briefly, one core per tumor of 0.6 mm thickness was obtained from the most representative areas then re-embedded in microarray blocks.

CDK12 Immunohistochemistry

IHC was optimized in-house, using a standard Labelled Polymer technique, on 4µm sections of formalin-fixed paraffin embedded (FFPE) normal human tonsil; cell blocks containing the MCF7 breast cancer cell line known to express CDK12 transfected with a previously validated siRNA pool targeting CDK12 or non-targeting control and BT474 cells as a positive control (13) (Fig. 1). Cells were cultured as previously described (13) and authenticated by short tandem repeat (STR) typing using the StemElite Kit (Promega, UK). Briefly, slides were dewaxed in xylene and rehydrated through graded alcohols. Following heat-induced antigen retrieval in citrate buffer (pH 6.0), sections were incubated with a mouse anti-human CDK12 monoclonal antibody (1:5000 final dilution, Abcam clone 57311 that was raised against an immunogen peptide corresponding to amino acids 1281-1380 of Human CDK12) for one hour at room temperature. The staining was visualized using the Dako Flex Envision K8002

Kit (Dako), counterstained with Gills hematoxylin (Leica). Sections were then dehydrated and mounted.

TMAs were assessed for nuclear CDK12 protein expression in the malignant epithelium only, using a modified Allred score (14). Only technically sound cores containing >20% invasive tumor cells were included in the analysis. Cores were evaluated for both intensity (0 = no stain; 1 = mild; 2 = moderate; 3 = strong), and percentage of epithelial cells that stained positive (0 = absent; 1 = background; 2 = 1–25%; 3 = 26–50%; 4 = 51-75%; 5 = > 75%), Fig. 1. Scores were derived from a sum of the intensity and percentage of immunoreactive cells; an average score of 0 for each tumor was considered negative/absent, and a score of 7 or 8, high, and a score of 2-6 as intermediate expression. Scores of 1 were excluded from further analysis as these equated to background non-specific staining. IHC staining and dichotomization of the other biomarkers included in this study were as per previous publications (24-30). Scoring was performed blinded to the study endpoint.

Mining of public datasets

In order to corroborate our findings, we re-analysed publicly available data from The Cancer Genome Atlas (31,32) and METABRIC (23) datasets, to ascertain the frequency of *CDK12* copy number breakpoints, somatic mutations and methylation and correlate these with RNA expression levels. Low and high CDK12 gene expression were defined by using an optimal threshold for dichotomizing gene expression data as described (33). This was carried out by a stepwise analysis from 40 to 60 percentiles at an interval of 5. The cut-offs that displayed the highest prognostic significance with log-rank test were selected. In addition, analysis of published whole genome shRNA (34) and kinome wide siRNA (35) genetic perturbation screens was performed to correlate cell viability of breast cancer cell lines with and without *CDK12* amplification after CDK12 knockdown.

Assessment of Tandem Duplicator Phenotype

Affymetrix SNP6.0 copy number data of 224 METABRIC samples were preprocessed using PennCNV-affy package (affy: http://penncnv.openbioinformatics.org/en/latest/misc/credit/ and segmented absolute copy number and ploidy was established with ASCAT 2.1 (36). The two tandem duplication phenotypes were established as previously described in Watkins et al., 2016 (37).

Statistical Analysis

Retrospective statistical analysis was performed using SPSS 21.0 statistical software (SPSS Inc., Chicago, IL, USA), in compliance with reporting recommendations for tumor marker prognostic studies (REMARK) criteria (38). A chi-squared or Fisher's exact test of <0.05 was considered significant. Survival curves were analyzed by the method of Kaplan-Meier, with a p-value <0.05 being considered significant with a 10-year BC specific survival as the endpoint. Multivariate survival analysis was carried out using CDK12 expression status, node status, estrogen and progesterone receptor (ER/PR) status, HER2 status, age, tumor size and grade. A Student's *t*-test was employed to compare CDK12 expression of mined samples with genetic aberrations and normal controls. For comparisons, scores of 0 (absent) and high (7-8) were compared, given known correlations with high expression and amplification (19) and uncertainty regarding intermediate levels of expression. A p-value <0.05 (two-sided) was considered statistically significant. Differential gene expression analysis of CDK12 absent versus high tumors with gene expression known to be involved in DNA repair was performed using data from METABRIC using Limma with FDR (False Discovery Rate) multiple correction adjustment.

Results

Distribution of CDK12 expression and clinicopathological correlation

In the first instance, we assessed CDK12 protein expression by IHC in 696 unselected BC samples that met the inclusion criteria (described in methods; Fig. 1). Overall 73/696 tumors were absent/negative for CDK12 (10.5%) by IHC, and 146 had CDK12 high expression (21%; Fig. 1A, Supplementary Table S1). Breaking this down by subtype, in ER+ patients, 50/510 (9.8%) and 101/510 (19.8%) were CDK12 absent and high; in HER2+ patients 3/102 (2.9%) and 55/102 (53.9%) were CDK12 absent and high; and in TN patients, 21/123 (17%) and 17/123 (13.8%) were CDK12 absent and high respectively. Expression of CDK12 significantly correlated with HER2 expression; 96% of CDK12 absent tumors were HER2 negative and 95% of HER2 positive tumors had high CDK12 expression ($p < 0.001$, Chi-Square test). Interestingly, no significant correlation of CDK12 expression with ER or PR status was observed, but a greater proportion of CDK12 absent tumors showed a triple-negative phenotype (21/73, 29%) than CDK12 high tumors (17/143, 11.9%, $p = 0.002$, Chi-Square test, Supplementary Table S1). There was no association with CDK12 high expression and breast cancer specific survival in this cohort ($p = 0.354$, HR = 1.295, 95% CI= 0.75-2.24, Log Rank (Mantel-Cox), Fig. 2A, Supplementary Table S4).

These findings were validated in a subset of tumors from the METABRIC cohort of unselected BC, in which CDK12 was highly expressed in 63/250 tumors (25.2%) and absent in 89/250 tumors (35.6%), Fig. 1 Supplementary Table S3**.** Again, a significant correlation with HER2 status was observed, with 83/89 (93.3%) of CDK12 absent tumors being HER2 negative and 13/36 (36.1%) of HER2 amplified tumors being CDK12 high ($p < 0.0001$, Chi-Square test). CDK12 expression also conferred a significantly poorer BC specific survival ($p < 0.001$, HR = 3.161, 95% CI = 1.632-6.125, Log Rank (Mantel-Cox)) in this cohort in univariate analysis (Fig. 2B). This was also significant in multivariate comparisons when taking account for HER2 positivity ($p = 0.038$, HR = 2.26, 95% CI = 1.045-4.887, Supplementary Table S4). These associations were further corroborated at the mRNA level in a larger cohort of primary tumors (n=1961) from METABRIC, where high CDK12 expression was associated with a worse BC specific survival ($p < 0.001$, HR = 1.28, 95% CI = 1.17 -

1.41, Log Rank (Mantel-Cox), Fig. 2C), however this was not substantiated in multivariate analysis when taking HER2 into account (Supplementary Table S4).

We previously identified a proportion of HER2 amplified tumors harbour out-of-frame *CDK12* fusion genes. As CDK12 is known to map to the smallest region within the *HER2* amplicon (17,18) these fusions are the result of an amplification breakpoint in the *HER2* amplicon that converges on CDK12, disrupting its expression (13). We also found that tumor cells with loss of CDK12 due to the presence of a breakpoint in the *HER2* amplicon were sensitive to PARP1/2 inhibitors suggesting that a fraction of HER2 amplified patients with CDK12 fusions might also benefit from treatment with PARP1/2 inhibitors or platinum chemotherapy (13). To ascertain the frequency of CDK12 protein absence in HER2 amplified patients, and possible associations with outcome subsequent to anti-HER2 therapy, we assessed CDK12 protein expression in HER2 positive patients whom had been treated with Herceptin (21). Overall, 4/119 (3.4%) tumors were CDK12 absent and 71/119 (59.7%) tumors were CDK12 high (Fig. 1A). Lack of CDK12 expression did not improve survival in this cohort following Herceptin treatment (p= 0.586; HR= 22.636, 95% CI = 0-1718290, Log Rank (Mantel-Cox)), Fig. 2D).

In summary (Supplementary Table S1), overall, absence of CDK12 protein expression was seen in 10.5% of unselected BC; with a similar proportion of ER+ tumours showing absent CDK12 (9.8%). Interestingly, a higher frequency of absent CDK12 was seen in TNBC within this unselected cohort (17%); however, no association with BC specific survival was seen (p= 0.577, HR= 2, 95% CI = 1.8-3.4, Log Rank (Mantel-Cox)). As expected, in all three cohorts analysed, a lower proportion of HER2-positive tumours were CDK12 absent. Rather, most HER2 positive tumours were CDK12 high (protein and mRNA). Although high CDK12 expression was associated with a worse BC specific survival in these cohorts, this association was significant in the METABRIC dataset in multivariate analysis taking HER2 status into account, but not borne out in additional datasets.

Association of CDK12 expression and amplification

We subsequently investigated the associations of CDK12 mRNA expression with genomic status in primary BC from METABRIC (23) where there is copy number and gene expression data on the same tumor specimen. Of 1979 tumors with matched copy number and gene expression data available for CDK12, 208 (10.5%) harboured amplification encompassing the *CDK12* gene and a concurrent increase in its transcript expression, ($p < 0.0001$; Mann-Whitney U test; Fig. 3A). Of these, 99% (205/208) were also *HER2* amplified. There was a significant association with BC specific survival comparing *CDK12* amplified versus non-amplified tumors ($p < 0.0001$, Log Rank (Mantel-Cox), (HR = 0.45; 95% CI = 0.35 – 0.57), however, similarly to CDK12 protein expression this was lost in multivariate analysis taking HER2 status into account (Supplementary Table S4). Assessment of CDK12 protein expression by IHC in the METABRIC TMA, stratifying tumors as absent (0) versus highly expressed (7-8), however, revealed a significant association between *CDK12* amplification and increased CDK12 protein expression with 12/16 (75%) amplified and 42/120 (35%) non-amplified tumors showing high protein expression, $p = 0.0049$, Fishers exact-test, Fig. 3B).

Recent evidence has pointed to the role of *CDK12* as a potential oncogene, given that that its amplification is associated with increased protein expression and aggressive clinical characteristics (19) and that *CDK12* amplified tumors show significantly increased CDK12 protein activation (39). To seek any evidence of oncogenic addiction to the downstream consequences of activated CDK12, we mined publicly available genetic perturbation screens in BC cell line models using validated reagents (12,13), to ascertain if *CDK12* amplified cells were addicted to CDK12 expression and downstream signalling for their survival. Analysis of both genome-wide pooled shRNA screen data (34) and siRNA kinome screen data (35) failed to identify any association between *CDK12* amplification and sensitivity to shRNA or siRNA designed to target *CDK12* (Fig. 3C-D**)**.

Genetic mechanisms of absent CDK12 expression

Given our previous findings that disruption of *CDK12* can occur as a result of an amplification breakpoint in the *ERBB2* amplicon that converges on *CDK12*, disrupting its expression (13), we sought to confirm our findings in primary tumors from METABRIC (23). Of all cases that showed *CDK12* amplification, 14.4% (30/208) harboured a breakpoint in *CDK12* that was associated with a significant reduction in *CDK12* transcript levels (p< 0.0001, Mann Whitney U test; Fig. 4A). In *HER2* amplified patients, there was no significant difference in BC specific survival between patients with a breakpoint in *CDK12* and those without (p= 0.32, Log Rank (Mantel-Cox) HR= 0.9897, 95% CI= 0.5107-1.918).

To ascertain the frequency of absent CDK12 protein in tumors with copy number alterations in *CDK12*, we intersected the IHC data from a subset of the METABRIC cohort performed above with the available copy number data for *CDK12*. Of all *CDK12* amplified tumors, 14% (4/28) showed absent CDK12 protein expression and 33% (2/6) of tumors with a breakpoint in *CDK12* were CDK12 absent. This highlights that only a proportion of tumors with *CDK12* genomic breakpoints lead to loss of CDK12 protein expression.

In HGSOC*, CDK12* inactivating mutations have been reported to inactivate gene expression and consequently abrogate HR DNA repair pathways (10,11,14). Examination of DNA sequencing data from The Cancer Genome Atlas (TCGA) (32) identified *CDK12* mutations in 1.5% (20/1373) of unselected BC (Fig. 4B), (Supplementary Table S5 and S6)**.** These included 12 missense mutations, and 8 truncating mutations. Overall, 45% (9/20 (8 truncating and 1 missense) were predicted to disrupt protein function, and of these 25% (2/9) were seen in patients with triple-negative disease, whereas the remaining patients had ER+ or ER-/HER2+

disease. In contrast with recent data in HGSOC (11), predicted deleterious mutations did not correlate with reduced transcript expression, or with down-regulation of DNA damage response (DDR) genes, (Supplementary Table S7). CDK12 promoter methylation was a rare event seen in 1/696 (0.14%) of unselected BC (Supplementary Table S6). We next looked for other genomic alterations that would lead to absent CDK12 protein expression by interrogation of METABRIC cases with copy number and miRNA expression (23,40). This identified that heterozygous loss of CDK12 accounted for 7.1% (6/84) cases with absent CDK12 protein expression, however this was not enriched in the CDK12 absent group compared to the CDK12 high group ($p>0.999$, Fishers exact test). In addition, of the 14/162 miRNA's, that are known or predicted targets of CDK12, present in METABRIC (40) none showed correlation with CDK12 protein expression after multiple correction (Supplementary Table S8), suggesting there are additional mechanisms that lead to CDK12 protein loss.

Absent CDK12 protein expression is associated with reduced protein expression of genes involved in DNA repair

Although predicted deleterious mutations in *CDK12* did not correlate with reduced expression of DDR genes (see above), we assessed whether loss of CDK12 protein expression correlated with a reduction in the transcript expression of DNA repair proteins or biomarkers of DNA damage in the unselected series of BC cases (Table 1). Although no significant correlations were observed (after multiple testing correction) with DDR genes at the mRNA level (Supplementary Table S9), absent CDK12 protein was significantly correlated with reduced protein expression of ATR, APE1, nuclear and cytoplasmic SMC6, Ku70/Ku80, DNA-PK and γH2AX nuclear positivity. Absent CDK12 protein expression also significantly correlated with both cleaved PARP1 ($p= 0.003$, Chi-Square) and non-cleaved PARP1 ($p= 0.005$, Chi-Square) expression suggesting that PARP1 levels are higher in tumors with absent CDK12. Interestingly, absent CDK12 expression also correlated with a decreased expression of TP53 (p= 0.001; Chi-Square) and RB1 (p= 0.003, Chi-Square), however there was no significant correlation between absent CDK12 protein and *TP53* mutations in the METABRIC cohort of tumors (17.5% CDK12 absent and 26.4% CDK12 high tumours harbouring *TP53* mutations p= 0.2779, Fishers exact test).

Since absent CDK12 protein expression was seen in 17% of TNBC within our analysis, we assessed this subset of tumors for correlations with the expression of DNA repair proteins as above. Even within this relative small subset, some significant correlations were still seen with DDR genes at the protein level: ATR (p= 0.018, Chi-Square); Ku70/Ku80 (p= 0.01, Chi-Square); and loss or decrease in nuclear and cytoplasmic SMC6 (p= 0.045, Chi-Square; Table 1). Of note comparison of CDK12 absent (0) and intermediate (2-6) levels of expression together as one group versus high (7-8) failed to identify any significant associations with DNA repair genes both in unselected BC and TNBC (Supplementary Table S10). This suggests that functional loss of CDK12 is only observed in tumors with absent CDK12 protein expression in breast cancer and not low levels of CDK12 expression.

It has been shown that in HGSOC CDK12 mutations are consistently associated with a particular genomic instability pattern characterized by hundreds of tandem duplications of up to 10 megabases (Mb) in size, dubbed the ‘CDK12 TD-plus phenotype’ (14). Assessment of this pattern in both unselected and TNBC with absent CDK12 protein failed to identify any association with large numbers and sizes of tandem duplications (Fig. 4C-D). Together these results suggest that absent CDK12 protein in BC is associated with some defects in DNA repair related genes, however the resultant genomic scars are likely to be different to that seen in HGSOC (11).

Discussion

In this study, we were able to analyze, for the first time, the distribution of CDK12 protein in cohorts of primary BC. We show that high CDK12 expression is significantly correlated with HER2 status and that absent CDK12 is associated with a triple-negative phenotype and disruption of proteins involved in DNA repair.

The significant correlation of CDK12 with HER2 expression in these data is not surprising, since CDK12 is known to map to the smallest region within the HER2 amplicon (17,18). Therefore, although we observed significant correlations with CDK12 expression and patient survival, this significance was subsequently lost when HER2 positivity was taken into account. However, this association was substantiated in the METABRIC cohort at the protein level, suggesting investigation of additional cohorts are warranted. It has been postulated that CDK12 may act in an oncogenic manner, given observed associations with amplification and increased transcript and protein expression and subsequent phosphorylation (19,39). This may perhaps occur through its reported roles in transcription through phosphorylation of RNA Pol II and regulation of pre-mRNA processing (5,7). By analyzing published siRNA and shRNA cell viability screens, using validated reagents (12,13) we show here that amplified cells are not addicted to CDK12 for their survival. We concede the assay length (average 4-7 days) in these experiments, may be too short to detect a loss of viability to depletion of a cyclin dependent kinase and additional time may be required to reduce DNA repair protein expression and accumulate damage required to affect viability. Interestingly, a recent study has suggested that CDK12 does act in an oncogenic manner in HER2 amplified cells by promoting cell invasion via alternative splicing and subsequent down-regulation of the long isoform of DNAJB6 (41), suggestive of a mechanism by which CDK12 acts in an oncogenic manner to promote cell invasiveness. Of note, elevated levels of CDK12 in HER2 positive tumors have been a proposed reason why tumors arising in *BRCA1* carriers are usually ERBB2-negative, given elevated expression would oppose the defects in HR mediated by *BRCA1* loss (34).

We have shown previously that a proportion of HER2-positive tumors harbor inactivating (out-of-frame) fusion genes in *CDK12* that are due to a copy number breakpoint in the HER2 amplicon converging on *CDK12*, resulting in a significant decrease in both transcript and protein levels (13). Furthermore, cell lines with breakpoints in *CDK12* that result in loss of protein expression are sensitive to PARP1/2 inhibitor therapy, due to impaired HR mediated DNA repair (13). By assessing the distribution of CDK12 protein expression in CDK12 amplified breast cancers in the METABRIC cohort, we identified 14% that were CDK12 absent. Moreover, of the tumors with a breakpoint in CDK12, 33% had absent CDK12 protein expression. Whilst the numbers we were able to assess are small, this nevertheless suggests a proportion of HER2 positive patients show absent CDK12 protein as a result of both copy number breakpoints and additional mechanisms. Overall, our data suggest there may be a small proportion of HER2-positive patients that may benefit from treatment with DNA damage response targeted therapies such as PARP1/2 inhibitor therapy.

Recent data in HGSOC has shown that *CDK12* point mutations inactivate gene expression subsequently abrogating HR DNA repair pathways (10,11). Although in our study *CDK12* mutations did not themselves correlate with decreased expression of DNA repair genes (perhaps due to residual CDK12 activity, given some of these are not associated with loss of heterozygosity), we show that BC with absent CDK12 protein show down-regulation of a number of genes involved in functional HR DNA repair at the protein level, suggesting that absent CDK12 protein in BC may also be associated with HR defects. Although we were unable to assess all proteins known to be dysregulated in CDK12 mutant HGSOC such as RAD51, FANCI and FANCD2, it is reasonable to postulate that CDK12 may have other targets, including DNA repair proteins themselves, phosphorylation of which is required for protein stability. Lack of any observed associations at the mRNA level, may be due to small numbers in the study, however, our observed associations warrant further investigation in larger cohorts. Recent evidence in HGSOC points to a unique signature of genomic instability in *CDK12* mutated tumors that is indicative of gross defects in DNA repair characterized by tens to hundreds of large tandem duplications scattered throughout the genome, although this was not observed in *CDK12* mutated breast cancers (14). Consistent with this, we observed no correlation with large tandem duplications of neither all BC nor TNBC specifically. It is intriguing however that we observed absent CDK12 protein in 17% of TNBC from the unselected primary BC analyzed in this study. Of course, this could be a consequence of the small number of cases included, however CDK12 inactivation may play a role in a subset of TNBC's possibly through mechanisms distinct from those observed in HGSOC.

In conclusion, we have shown that a subset of HER2-positive patients show absent CDK12 protein expression and have shown an enrichment of absent CDK12 protein expression in TNBC. Moreover, we have provided evidence that absent CDK12 expression is associated with defects in DNA repair proteins. These results suggest that CDK12 IHC could potentially be useful, once validated in sufficiently powered studies, for stratification of patients for treatment with DDR targeted therapies.

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Figure Legends

Figure 1: Distribution of CDK12 protein expression in breast cancer

A, Modified CONSORT diagram depicting the distribution of CDK12 positive and negative breast cancers in each of the cohorts analysed. **B,** Representative micrographs of CDK12 protein expression in **i,** MCF7 cell line treated with non-targeting siRNA controls; **ii,** MCF7 cell line treated with previously validated siRNA against CDK12 (13); **iii.** BT474 CDK12 amplified cells all at x400 magnification; **iv,** tonsil positive control (x 200 magnification). **v-viii,** Representative images of staining intensity in primary breast cancers, where CDK12 expression was quantified using a modified Allred score, which assessed both intensity (highest score = 3) and percentage positivity (highest score = 5): **(v)** negative; **(vi)** 1+; (**vii)** 2+; and **(viii)** 3+; all images at 200x magnification. A score of 0 was considered absent and a score of 7 or 8, as high expression.

Figure 2: CDK12 positive breast cancer has a poorer survival in univariate analysis

Kaplan-Meier curves showing breast cancer specific survival for CDK12 high (7-8) versus negative (0) breast cancers asses by IHC in **A,** Nottingham unselected primary breast cancer series (n= 203); **B,** tumors from METABRIC (n= 140); **C,** Gene expression correlations of CDK12 low versus high from METABRIC (n= 1961) and **D,** HER2-positive tumors treated with Herceptin (n= 75).

Figure 3: CDK12 amplified cells are not dependent on CDK12 expression for their survival

A, Scatter dot plot depicting a significant association of *CDK12* transcript expression with gene amplification (n= 208) versus no amplification (n= 1769) (error bars represent median with the interquartile range). **B,** bar-chart depicting a significant increase of CDK12 protein expression as measured by IHC in *CDK12* amplified tumors (n= 16) compared to non-amplified (n= 103). **C-D,** Relative cell viability after *CDK12* silencing in *CDK12* amplified (Campbell, n= 8; Marcotte n= 14) versus non-amplified cell lines (Campbell, n= 19; Marcotte n= 40), showing no significant difference in cell survival from c) Marcotte et al (34) and d) Campbell at al (35).

Figure 4: CDK12 protein loss is associated with DNA repair defects in breast cancer

A, Box and whisker plot (min-max) showing a significant decrease in *CDK12* transcript levels in HER2-amplified tumors with breakpoints (n= 30) in *CDK12* compared with no breakpoints (n= 178) from METABRIC. **B,** Lollipop diagram depicting the distribution of *CDK12* mutations in breast cancer (red= frameshift and nonsense mutations, green= non-synonymous coding mutations). **C,** Scatter dot plot diagrams showing significant associations between CDK12 absent (n= 74) (IHC score 0) versus CDK12 high (n= 51) (IHC score 7-8) in unselected METABRIC tumors with large tandem duplication score, indicative of gross genomic defects. **D,** Scatter dot plot diagrams showing significant associations between CDK12 absent (n= 8) (IHC score 0) versus CDK12 high (n= 4) (IHC score 7-8) in TNBC from METABRIC, with large tandem duplication score, indicative of gross genomic defects.

Table 1: Association of CDK12 expression with DNA repair proteins in unselected and TNBC

	CDK12 Absent (0) *No. of cases (%)*	**CDK12 High (7/8)** *No. of cases (%)*	**p-value**
Unselected Series			
BRCA1 (n= 170)			0.249
Negative	27 (51.9)	50 (42.4)	
Positive	25 (48.1)	68 (57.6)	
PARP1 cleaved (n= 170)			0.003**
Negative	18 (30)	13 (11.8)	
Positive	42 (70)	97 (88.2)	
PARP1 non-cleaved (n= 175)			0.005**
Negative	36 (62.1)	46 (39.3)	
Positive	22 (37.9)	71 (60.7)	
ATR (n= 173)			<0.001**
Negative	46 (70.8)	45 (41.7)	
Positive	19 (29.2)	63 (58.3)	
APE1 (n= 89)			0.02*
Negative	10 (38.5)	10 (15.9)	
Positive	16 (61.5)	53 (84.1)	
Ku70/Ku80 (n= 153)			0.001**
Negative	18 (34.0)	11 (11.0)	
Positive	35 (66.0)	89 (89.0)	
DNA-PK (n= 156)			0.002**
Negative	17 (32.1)	12 (11.7)	
Positive	36 (67.9)	91 (88.3)	
SMC6 cytoplasmic (n= 166)			0.002**
Negative	30 (54.5)	33 (29.7)	
Positive	25 (45.5)	78 (70.3)	
SMC6 nuclear (n= 166)			< 0.001**
Negative	33 (60.0)	34 (30.6)	
Positive	22 (40.0)	77 (69.4)	
γH2AX (n= 150)			0.002**
Negative	24 (47.1)	22 (22.2)	
Positive	27 (52.9)	77 (77.8)	

TP53 (n= 209)			0.001**
Negative	56 (80.0)	80 (57.6)	
Positive	14 (20.0)	59 (42.4)	
CHEK1 cytoplasmic (n= 103)			0.321
Negative	29 (50.9)	44 (42.7)	
Positive	28 (49.1)	59 (57.3)	
CHEK1 nuclear (n= 161)			0.927
Negative	48 (84.2)	87 (83.7)	
Positive	9 (15.8)	17 (16.3)	
CHEK2 (n= 108)			0.345
Negative	31 (50.8)	63 (58.3)	
Positive	30 (49.2)	45 (41.7)	
Triple Negative Breast Cancer			
BRCA1 (n= 28)			0.430
Negative	10 (71.4)	8 (57.1)	
Positive	4 (28.6)	6 (42.9)	
PARP1 cleaved (n= 28)			0.378
Negative	8 (50.0)	4 (33.3)	
Positive	8 (50.0)	8 (66.7)	
PARP1 non-cleaved (n= 29)			0.103
Negative	11 (68.8)	5 (38.5)	
Positive	5 (31.2)	8 (61.5)	
ATR (n= 33)			0.018*
Negative	18 (90.0)	7 (53.8)	
Positive	2 (10.0)	6 (46.2)	
APE1 (n= 17)			0.453
Negative	2 (25.0)	1 (11.1)	
Positive	6 (75.0)	8 (88.9)	
Ku70/Ku80 (n= 27)			0.010*
Negative	8 (47.1)	0 (0.0)	
Positive	9 (52.9)	10 (100.0)	
DNA-PK (n= 31)			0.283
Negative	6 (37.5)	3 (25.0)	
Positive	10 (62.5)	12 (75.0)	
SMC6 cytoplasmic (n= 31)			0.018*
Negative	9 (60.0)	3 (23.1)	

Positive	6 (40.0)	13 (76.9)	
SMC6 nuclear (n= 31)			0.045*
Negative	11 (73.3)	6 (37.5)	
Positive	4 (26.7)	10 (62.5)	
γH2AX (n= 29)			0.089
Negative	9 (60.0)	4 (28.6)	
Positive	6 (40.0)	10 (71.4)	
TP53 (n= 36)			0.187
Negative	12 (63.2)	7 (41.2)	
Positive	7 (36.8)	10 (58.8)	
CHEK1 cytoplasmic (n= 27)			0.384
Negative	8 (47.1)	3 (30.0)	
Positive	9 (52.9)	7 (70.0)	
CHEK1 nuclear (n= 28)			0.068
Negative	17 (100.0)	9 (81.8)	
Positive	0 (0.0)	2 (18.2)	
CHEK2 (n= 32)			0.961
Negative	13 (68.4)	9 (69.2)	
Positive	6 (31.6)	4 (30.8)	

Supplementary Tables:

Supplementary Table S1: CDK12 expression in relation to clinicopathological parameters for the unselected TMA series

Supplementary Table S2: CDK12 expression in relation to clinicopathological parameters for the HER2-positive Herceptin treated series

Supplementary Table S3: CDK12 expression in relation to clinicopathological parameters for the METABRIC TMA series

Supplementary Table S4: Univariate and multivariate analysis of CDK12 in the TMA cohorts

Supplementary Table S5: CDK12 mutations in breast cancer. Taken from cBioportal (42,43).

Supplementary Table S6: Correlations of CDK12 mutations, methylation, gene expression and ERBB2 copy number in primary breast cancers from TCGA

Supplementary Table S7: Correlations of CDK12 mutations and gene expression of DNA repair genes in primary tumors from METABRIC. P values from heteroscedastic 2-tailed, t-test

Supplementary Table S8: Correlations of CDK12 protein expression, and miRNA expression in primary tumors from METABRIC. Wilcoxon rank P values are corrected for multiple testing.

Supplementary Table S9: Correlations of CDK12 protein expression and gene expression of DNA repair genes in primary tumors from METABRIC. Limma analysis corrected for multiple testing.

Supplementary Table S10: Association of CDK12 absent and intermediate (0, 2-6) versus high (7-8) expression with DNA repair proteins in unselected and TNBC. P values from Fishers exact test.

Figure 1

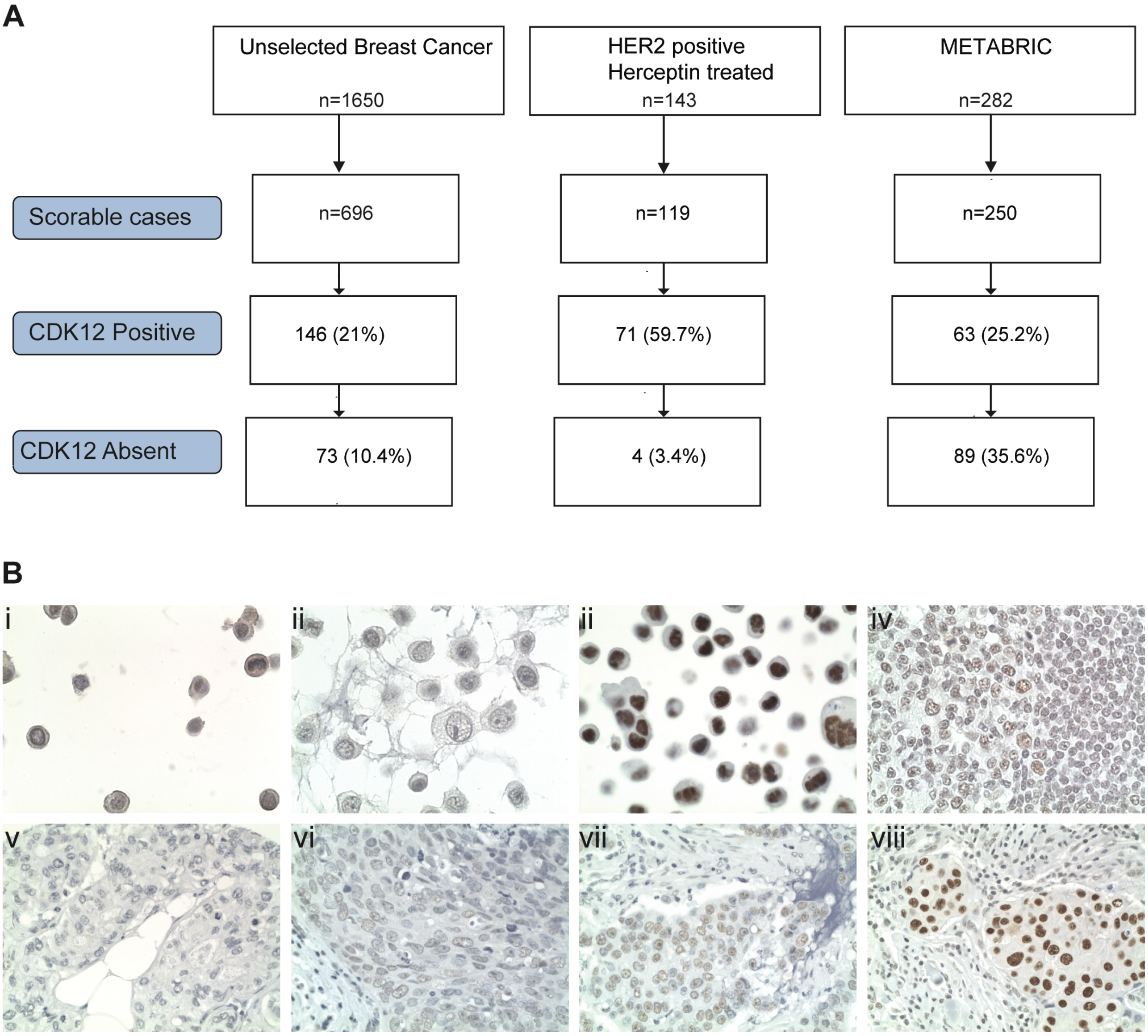
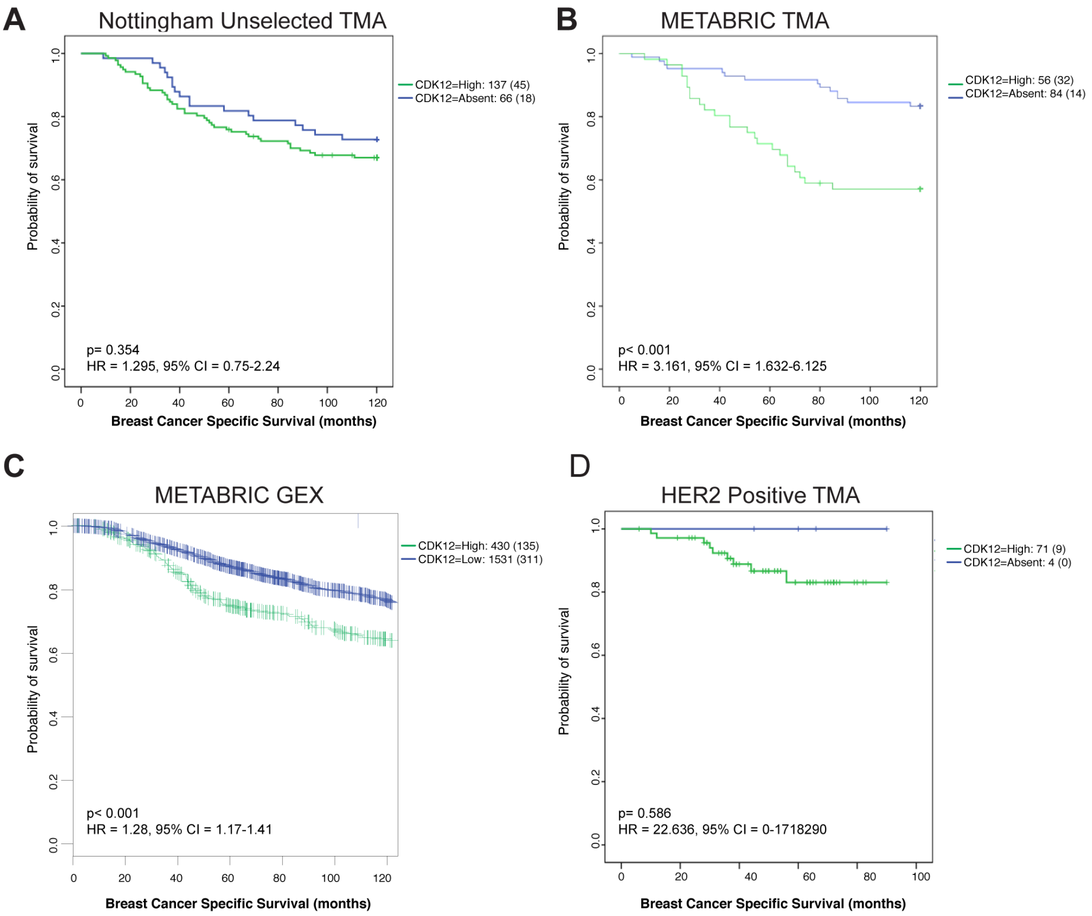
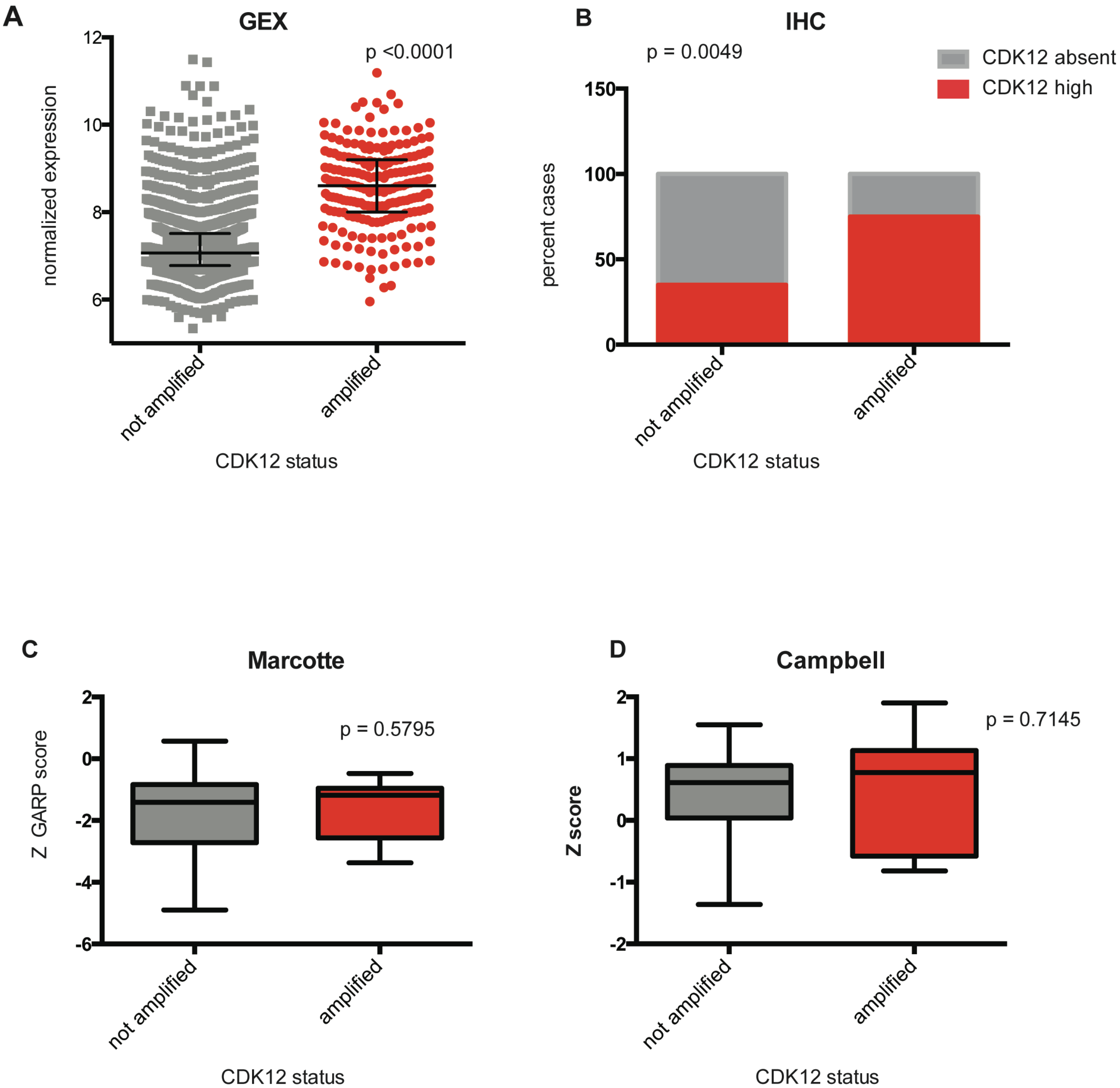

A
Unselected Breast Cancer
n=1650
HER2 positive
Herceptin treated
n=143
METABRIC
n=282
Scorable cases
n=696
n=119
n=250
CDK12 Positive
146 (21%)
71 (59.7%)
63 (25.2%)
CDK12 Absent
73 (10.4%)
4 (3.4%)
89 (35.6%)
B
i
ii
ii
iv
v
vi
vii
viii

Figure 2


A
Nottingham Unselected TMA
CDK12=High: 137 (45)
CDK12=Absent: 66 (18)
p= 0.354
HR = 1.295, 95% CI = 0.75-2.24
Probability of survival
Breast Cancer Specific Survival (months)
B
METABRIC TMA
CDK12=High: 56 (32)
CDK12=Absent: 84 (14)
p< 0.001
HR = 3.161, 95% CI = 1.632-6.125
Probability of survival
Breast Cancer Specific Survival (months)
C
METABRIC GEX
CDK12=High: 430 (135)
CDK12=Low: 1531 (311)
p< 0.001
HR = 1.28, 95% CI = 1.17-1.41
Probability of survival
Breast Cancer Specific Survival (months)
D
HER2 Positive TMA
CDK12=High: 71 (9)
CDK12=Absent: 4 (0)
p= 0.586
HR = 22.636, 95% CI = 0-1718290
Probability of survival
Breast Cancer Specific Survival (months)

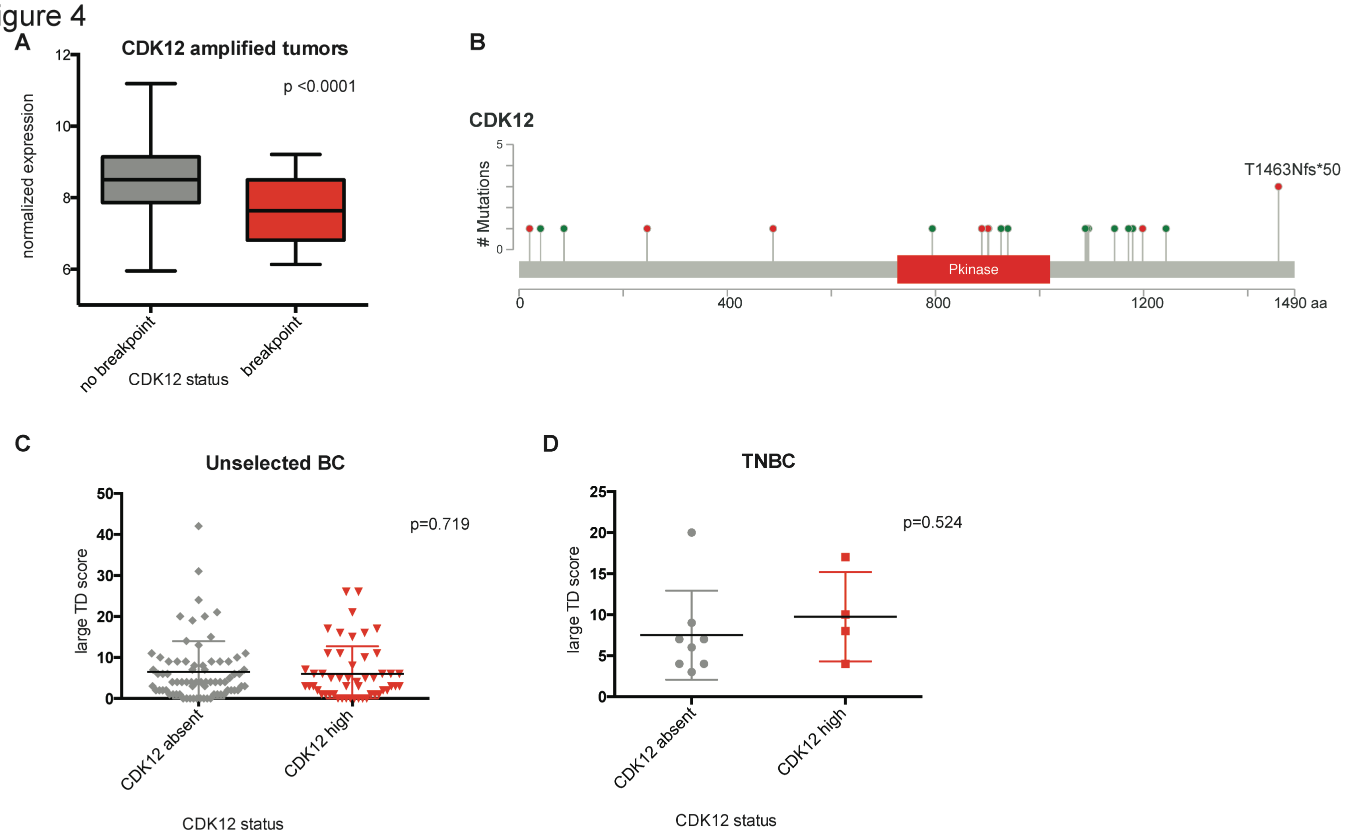
!

Figure 3



A
GEX
p <0.0001
normalized expression
12
10
8
6
not amplified
amplified
CDK12 status
B
IHC
p = 0.0049
CDK12 absent
CDK12 high
percent cases
150
100
50
0
not amplified
amplified
CDK12 status
C
Marcotte
p = 0.5795
Z GARP score
2
0
-2
-4
-6
not amplified
amplified
CDK12 status
D
Campbell
p = 0.7145
Z score
2
1
0
-1
-2
not amplified
amplified
CDK12 status

Figure 4



A
CDK12 amplified tumors
p <0.0001
normalized expression
12
10
8
6
no breakpoint
breakpoint
CDK12 status
B
CDK12
Mutations
5
0
T1463Nfs*50
Pkinase
0
400
800
1200
1490 aa
C
Unselected BC
p=0.719
large TD score
50
40
30
20
10
0
CDK12 absent
CDK12 high
CDK12 status
D
TNBC
p=0.524
large TD score
25
20
15
10
5
0
CDK12 absent
CDK12 high
CDK12 status

Supplementary Table S1

Parameter	Distribution	CDK12 Expression			p-value	
		Absent (0)	Intermediate (2-6)	High (7-8)	Absent vs High	Intermediate vs High
Age						
< 50 yrs	243 (34.9%)	28	164	51	0.619	0.903
≥ 50 yrs	453 (65.1%)	45	313	95		
Tumour Size						
< 2 cm	366 (48.3%)	34	235	61	0.500	0.113
≥ 2 cm	330 (51.7%)	39	242	85		
Grade						
1	92 (13.2%)	13	66	13	0.133	0.047
2	245 (35.2%)	23	177	45		
3	359 (51.6%)	37	234	88		
Tumour Type						
Ductal (inc mixed)	602 (86.5%)	64	409	129	0.560	0.621
Lobular	60 (8.6%)	4	43	13		
Medullary-like	14 (2.0%)	2	10	2		
Miscellaneous	4 (0.6%)	1	2	1		
Special type	16 (2.3%)	2	13	1		
Vascular Invasion						

Definite	246 (35.5%)	24	167	55	0.486	0.591
Negative/Probable	447 (64.5%)	49	307	91		
Lymph Node Stage						
1	423 (60.8%)	48	293	82	0.112	0.416
2	220 (31.6%)	23	148	49		
3	53 (7.6%)	2	36	15		
NPI Groups						
Good	191 (27.4%)	19	141	31	0.233	0.018
Moderate	392 (56.3%)	44	267	81		
Poor	113 (16.2%)	10	69	34		
ER Status						
Negative	180 (26.1%)	23	187	44	0.861	0.121
Positive	510 (73.9%)	50	359	101		
PR Status						
Negative	295 (43.5%)	33	187	75	0.314	0.012
Positive	383 (56.5%)	40	275	68		
HER2 Status						
Negative	571 (84.8%)	70	415	86		

Positive	102 (15.2%)	3	44	55	5.2 x 10^{-8}	1.8 x 10^{-16}
Triple Negative Status						
Non Triple Negative	559 (82.0%)	52	381	126	0.002	0.075
Triple Negative	123 (18.0%)	21	85	17		

Supplementary Table S2

Parameter	Distribution	CDK12 Expression			p-value	
		Absent (0)	Intermediate (2-6)	High (7-8)	Absent vs High	Intermediate (vs High
Age						
< 50 yrs	55 (46.2%)	2	20	33	0.891	0.915
≥ 50 yrs	64 (53.8%)	2	24	38		
Tumour Size						
< 2 cm	67 (57.3%)	3	24	40	0.481	0.890
≥ 2 cm	50 (42.7%)	1	19	30		
Grade						
1	3 (2.5%)	0	2	1	0.027	0.044
2	32 (26.9%)	3	16	13		
3	84 (70.6%)	1	26	57		
Vascular Invasion						
Definite	45 (37.8%)	2	20	23	0.467	0.159
Negative/Probable	74 (62.2%)	2	24	48		
Lymph Node Stage						
1	70 (59.8%)	2	26	42	0.887	0.875
2	40 (34.1%)	1	15	24		

3	7 (6.0%)	0	2	5	0.887	0.875
NPI Groups						
Good	9 (8.3%)	0	5	4	0.472	0.443
Moderate	69 (63.3%)	3	23	43		
Poor	31 (28.4%)	0	13	18		
ER Status						
Negative	55 (46.2%)	3	15	37	0.372	0.059
Positive	64 (53.8%)	1	29	34		
PR Status						
Negative	60 (60.6%)	3	18	39	0.209	0.147
Positive	39 (39.4%)	0	18	21		

Supplementary Table S3

Parameter	Distribution	CDK12 Expression			p-value	
		Absent (0)	Intermediate (2-6)	High (7-8)	Absent vs High	Intermediate vs High
Age						
< 50 yrs	79 (31.6)	31	27	21	0.848	0.434
≥ 50 yrs	171 (68.4)	58	71	42		
Tumour Size						
< 2 cm	99 (40)	41	36	22	0.152	0.778
≥ 2 cm	149 (60)	47	61	41		
Grade						
1	28 (11.3)	17	5	6	0.069	0.539
2	85 (34.4)	33	33	19		
3	134 (54.3)	37	59	38		
Tumour Type						
Ductal (inc mixed)	212 (86.2)	73	86	53	0.261	0.180
Lobular	18 (7.3)	7	7	4		
Medullary-like	5 (2.0)	0	3	2		

Special type	11 (4.5)	8	0	3		
Vascular Invasion						
Definite	101 (40.9)	31	37	33	0.035	0.086
Negative/Probable	146 (59.1)	57	59	30		
Stage						
1	127 (51.4)	52	47	28	0.178	0.446
2	94 (38.1)	29	36	29		
3	26 (10.5)	6	14	6		
NPI Groups						
Good	59 (24)	28	19	12	0.127	0.773
Moderate	123 (50)	42	51	30		
Poor	64 (26)	18	26	20		
ER Status						
Negative	63 (25.5)	13	34	16	0.102	0.183
Positive	184 (74.5)	75	62	47		
PR Status						

Negative	95 (40.3)	26	45	24	0.174	0.137
Positive	141 (59.7)	58	50	33		
HER2 Status						
Negative	200 (84.7)	83	75	42	0.001	0.623
Positive	36 (15.3)	4	19	13		
Triple Negative Status						
Non Triple Negative	201 (83.1)	76	73	52	0.626	0.036
Triple Negative	41 (16.9)	12	23	6		

Supplementary Table S4

Unselected series 0 v 7-8

	Patient statistics		Univariate Cox Regression analysis			Multivariate		
Variables	**No. of patients**	**Events (Censored)**	**Hazard Ratio (HR)**	**95% CI of HR**	**p-value**	**Hazard Ratio (HR)**	**95% CI of HR**	**p-value**
Grade	203	63 (140)	2.439	1.498-3.970	<0.001	2.222	1.313-3.761	0.003
Stage	203	63 (140)	2.175	1.534-3.084	<0.001	2.243	1.560-3.224	<0.001
Age	203	63 (140)	1.04	0.804-1.343	0.767	1.294	0.991-1.689	0.058
HER2	198	62 (136)	2.496	1.511-4.121	<0.001	2.012	1.123-3.605	0.019
CDK12	203	63 (140)	1.295	0.750-2.237	0.354	0.426	0.989-1.005	0.997

HER2 series 0 v 7-8

	Patient statistics		Univariate Cox Regression analysis			Multivariate		
Variables	**No. of patients**	**Events (Censored)**	**Hazard Ratio (HR)**	**95% CI of HR**	**p-value**	**Hazard Ratio (HR)**	**95% CI of HR**	**p-value**
Grade	74	9 (65)	1.219	0.281-5.288	0.792	0.593	0.132-3.175	0.593
Stage	73	9 (64)	2.526	1.093-5.838	0.03	2.377	1.030-5.486	0.043
Age	74	9 (65)	0.444	0.111-1.780	0.252	0.45	0.100-2.029	0.299
CDK12	74	9 (65)	22.636	0-1718290	0.586	1.186	0-1.03x1013	0.991

METABRIC IHC 0 v 7-8

	Patient statistics		Univariate Cox Regression analysis			Multivariate		
Variables	**No. of patients**	**Events (Censored)**	**Hazard Ratio (HR)**	**95% CI of HR**	**p-value**	**Hazard Ratio (HR)**	**95% CI of HR**	**p-value**
Grade	138	37 (101)	2.824	1.500-5.317	0.001	2.937	1.275-6.766	0.011
Stage	138	37 (101)	2.35	1.455-3.795	<0.001	1.503	0.844-2.678	0.166
Age	140	38 (102)	0.901	0.651-1.248	0.53	1.245	0.6-2.583	0.557
HER2	123	31 (92)	4.001	1.833-8.731	<0.001	2	0.883-4.530	0.097
CDK12	140	38 (102)	3.161	1.632-6.125	<0.001	2.26	1.045-4.887	0.038

METABRIC Gene Expression

	Patient statistics		Univariate Cox Regression analysis			Multivariate		
Variables	**No. of patients**	**Events (Censored)**	**Hazard Ratio (HR)**	**95% CI of HR**	**p-value**	**Hazard Ratio (HR)**	**95% CI of HR**	**p-value**
Grade	1878	434(1444)	1.81	1.54 - 2.14	<0.001	1.48	1.2-1.82	<0.001
Stage	1451	322(1129)	14.4	0 - Inf	<0.001	1.97	1.58-2.45	<0.001
Age	1964	446(1518)	1	0.99 - 1	<0.001	1	0.99-1	0.35
HER2	1963	446(1517)	2.13	1.7 - 2.67	<0.001	1.65	1.2-2.26	0.0018
CDK12	1961	446(1515)	1.28	1.17 - 1.41	<0.001	0.98	0.85-1.13	0.79

METABRIC Copy Number

	Patient statistics		Univariate Cox Regression analysis			Multivariate		
Variables	**No. of patients**	**Events (Censored)**	**Hazard Ratio (HR)**	**95% CI of HR**	**p-value**	**Hazard Ratio (HR)**	**95% CI of HR**	**p-value**
Grade	1391	313 (1006)	1.81	1.54 - 2.14	<0.0001	1.5	1.22-1.84	0.24
Stage	1391	314 (1006)	2.41	2.05 - 2.84	0	1.92	1.55-2.39	<0.0001
Age	1391	315 (1006)	1.05	0.87 - 1.26	0.64	1.15	0.91-1.45	0.24
HER2	1391	317 (1006)	2.13	1.7 - 2.67	<0.0001	1.85	1.17-2.93	0.0085
CDK12 amp	1391	318 (1006)	0.45	0.35 - 0.57	<0.0001	1.15	0.68-1.93	0.61

Supplementary Table S5

Sample ID	Cancer Study	AA change	Subtype	Type	Copy #	COSMIC	MS	VS	Mutation As	Center	Chr	Start Pos	End Pos	Ref	Var	Allele Freq	Allele Freq	Var Ref	Var Alt	Norm Ref	Norm Alt	BAM	#Mut in Sar
BR-V-060	Breast (Broad)	T794R	N/A	Missense	NA		S	U		Broad	chr17	37650909	37650909	C	-	NA	NA	NA	NA	NA	NA	IGV	53
PD4596a	Breast (Sanger)	E1198*	ER-/HER2+	Nonsense	NA	1	U	U		Sanger	chr17	37682401	37682401	G	-	NA	NA	NA	NA	NA	NA	IGV	131
SA065	Breast (BCCRC 2012	Y901*	TNBC	Nonsense	NA	1	U	U		BC	chr17	37667818	37667818	C	A	NA	NA	NA	NA	NA	NA	IGV	116
TCGA-A2-A0CU-01	Breast (TCGA 2015)	T1463Nfs*5(	ER+	FS ins	AMP		U	U		WashU	chr17	37687471	37687472	-	G	0.14	NA	37	6	34	0	IGV	45
TCGA-A2-A0CW-01	Breast (TCGA 2015)	V1094L	ER+	Missense	ShallowDel	1	U	U	Neutral	genome.wu	chr17	37681111	37681111	G	T	0.49	NA	31	30	98	0	IGV	55
TCGA-A7-A26G-01	Breast (TCGA 2015)	X889_splice	TNBC	Splice	ShallowDel		U	U		genome.wu	chr17	37666015	37666016	-	T	0.2	NA	69	17	90	0	IGV	48
TCGA-A8-A07E-01	Breast (TCGA 2015)	T1463Nfs*5(	ER+	FS ins	ShallowDel		U	U		WashU	chr17	37687471	37687472	-	G	0.11	NA	51	6	25	0	IGV	68
TCGA-AN-A046-01	Breast (TCGA 2015)	L926I	ER+	Missense	ShallowDel	1	U	U	Low	genome.wu	chr17	37671991	37671991	C	A	0.16	NA	225	44	305	0	IGV	4915
TCGA-AN-A0AK-01	Breast (TCGA 2015)	K41T	ER+	Missense	Diploid	1	U	U	Neutral	genome.wu	chr17	37618446	37618446	A	C	0.21	NA	49	13	50	0	IGV	1049
TCGA-BH-A0H9-01	Breast (TCGA 2015)	T1463Nfs*5(	ER+	FS ins	Diploid		U	U		WashU	chr17	37687471	37687472	-	G	0.13	NA	33	5	60	0	IGV	38
TCGA-BH-A0HB-01	Breast (TCGA 2015)	L21Afs*10	ER+	FS del	ShallowDel		U	U		WashU	chr17	37618384	37618385	TT	-	0.44	NA	20	16	53	0	IGV	30
TCGA-BH-A1FJ-01	Breast (TCGA 2015)	D86N	ER+	Missense	Gain	1	U	U	Neutral	genome.wu	chr17	37618580	37618580	G	A	0.44	NA	30	24	15	0	IGV	25
TCGA-BH-A204-01	Breast (TCGA 2015)	Q1088L	ER+	Missense	Gain		U	U	Neutral	unc.edu	chr17	37681094	37681094	A	T	0.43	NA	45	34	71	0	IGV	33
TCGA-BH-A204-01	Breast (TCGA 2015)	P1091L	ER+	Missense	Gain		U	U	Low	unc.edu	chr17	37681103	37681103	C	T	0.39	NA	45	29	80	0	IGV	33
TCGA-C8-A12W-01	Breast (TCGA 2015)	P1144S	ER+	Missense	Gain	1	U	U	Low	WashU	chr17	37682239	37682239	C	T	0.11	NA	131	17	27	0	IGV	37
TCGA-C8-A26Y-01	Breast (TCGA 2015)	R1243T	TNBC	Missense	Diploid		U	U	Neutral	unc.edu	chr17	37682537	37682537	G	C	0.25	NA	12	4	10	0	IGV	593
TCGA-E2-A1LG-01	Breast (TCGA 2015)	R902P	TNBC	Missense	Diploid	1	U	U	High	genome.wu	chr17	37667820	37667820	G	C	0.27	NA	73	27	88	0	IGV	104
TCGA-E9-A1NH-01	Breast (TCGA 2015)	N939S	ER+	Missense	ShallowDel	1	U	U	Neutral	genome.wu	chr17	37672031	37672031	A	G	0.2	NA	101	25	76	0	IGV	19
TCGA-EW-A1PD-01	Breast (TCGA 2015)	E488*	ER+	Nonsense	Gain	1	U	U		genome.wu	chr17	37627547	37627547	G	T	0.47	NA	27	24	35	0	IGV	63
TCGA-GM-A2DD-01	Breast (TCGA 2015)	Y246*	TNBC	Nonsense	ShallowDel	1	U	U		genome.wu	chr17	37619062	37619062	T	A	0.58	NA	5	7	22	0	IGV	45

Supplementary Table S6

Sample ID	CDK12_mutation	CDK12_copy number	CDK12_methylation	ERBB2_copy number	CDK12_RNAseq
TCGA-3C-AAAU-01	NaN	0	0.091569103351820	0	1586.1199
TCGA-3C-AALI-01	NaN	2	0.026121594341556	2	6572.5938
TCGA-3C-AALJ-01	NaN	2	0.050531196501768	2	2093.3817
TCGA-3C-AALK-01	NaN	2	0.036999623143159	2	2271.4108
TCGA-4H-AAAK-01	NaN	1	0.091240953888612	1	1330.6383
TCGA-5L-AAT0-01	NaN	0	0.050782629694884	0	864.6429
TCGA-5L-AAT1-01	NaN	0	0.073371920475317	0	929.9104
TCGA-5T-A9QA-01	NaN	1	0.074645609391082	1	1372.9079
TCGA-A1-A0SB-01	NaN	0	0.025026595936185	0	1920.4865
TCGA-A1-A0SD-01	NaN	0	NaN	0	1550.5748
TCGA-A1-A0SE-01	NaN	0	0.028610128720964	0	1787.9062
TCGA-A1-A0SF-01	NaN	0	0.020889252180827	0	1277.4995
TCGA-A1-A0SG-01	NaN	0	0.023712756533151	0	1687.3369
TCGA-A1-A0SH-01	NaN	1	0.030834703406590	1	1831.4049
TCGA-A1-A0SI-01	NaN	-1	0.033191012605481	-1	1208.3579
TCGA-A1-A0SJ-01	NaN	1	0.034731599419204	1	2605.9442
TCGA-A1-A0SK-01	NaN	-1	0.067622769887141	-1	1702.1746
TCGA-A1-A0SM-01	NaN	2	0.015693451772221	2	4276.1995
TCGA-A1-A0SN-01	NaN	2	0.024464414962343	2	2986.8505
TCGA-A1-A0SO-01	NaN	1	0.036464179078604	1	2411.5522
TCGA-A1-A0SP-01	NaN	-1	0.056877433867422	-1	1178.7669
TCGA-A1-A0SQ-01	NaN	0	0.015792499229414	0	1700.0504
TCGA-A2-A04N-01	NaN	0	NaN	0	1330.0317
TCGA-A2-A04P-01	NaN	-1	NaN	-1	701.7635
TCGA-A2-A04Q-01	NaN	0	NaN	0	1130.7366
TCGA-A2-A04R-01	NaN	0	0.031717540079808	0	1594.132
TCGA-A2-A04T-01	NaN	-1	NaN	-1	1311.6578
TCGA-A2-A04U-01	NaN	-1	NaN	-1	751.7859
TCGA-A2-A04V-01	NaN	0	NaN	0	1033.6117
TCGA-A2-A04W-01	NaN	2	NaN	2	5953.8025
TCGA-A2-A04X-01	NaN	2	NaN	2	5374.4255
TCGA-A2-A04Y-01	NaN	0	NaN	0	1496.8217
TCGA-A2-A0CK-01	NaN	0	0.031492867579318	0	855.3535
TCGA-A2-A0CL-01	NaN	0	NaN	0	1902.891
TCGA-A2-A0CM-01	NaN	-1	NaN	-1	1380.87
TCGA-A2-A0CO-01	NaN	0	0.031122551456698	0	1431.2272
TCGA-A2-A0CP-01	NaN	0	NaN	0	940.3485
TCGA-A2-A0CQ-01	NaN	0	NaN	0	902.1885
TCGA-A2-A0CR-01	NaN	-1	0.032671008849055	-1	409.7648
TCGA-A2-A0CS-01	NaN	0	NaN	0	1050.3
TCGA-A2-A0CT-01	NaN	1	0.020903068092735	1	2164.7157
TCGA-A2-A0CU-01	T1463Nfs*50	2	NaN	2	2662.4666
TCGA-A2-A0CV-01	NaN	-1	NaN	-1	936.085
TCGA-A2-A0CW-01	V1094L	-1	NaN	-1	1875.8442
TCGA-A2-A0CX-01	NaN	2	NaN	2	12330.9454
TCGA-A2-A0CY-01	NaN	NaN	NaN	NaN	620.6262
TCGA-A2-A0CZ-01	NaN	NaN	NaN	NaN	1182.381
TCGA-A2-A0D0-01	NaN	-1	NaN	-1	1352.9654
TCGA-A2-A0D1-01	NaN	2	NaN	2	1715.362
TCGA-A2-A0D2-01	NaN	0	NaN	0	1152.4672
TCGA-A2-A0D3-01	NaN	0	NaN	0	1709.4954
TCGA-A2-A0D4-01	NaN	1	NaN	1	1762.5555
TCGA-A2-A0EM-01	NaN	0	NaN	0	1571.0227
TCGA-A2-A0EN-01	NaN	0	0.037037241184150	0	1645.9302
TCGA-A2-A0EO-01	NaN	0	NaN	0	1298.4218
TCGA-A2-A0EP-01	NaN	0	0.044637997635909	0	899.6685
TCGA-A2-A0EQ-01	NaN	0	NaN	0	1573.886
TCGA-A2-A0ER-01	NaN	0	NaN	0	1765.3498
TCGA-A2-A0ES-01	NaN	0	NaN	0	1414.3215
TCGA-A2-A0ET-01	NaN	1	NaN	1	2218.3099
TCGA-A2-A0EU-01	NaN	1	0.034932769406692	1	1804.6816
TCGA-A2-A0EV-01	NaN	1	NaN	1	2445.614
TCGA-A2-A0EW-01	NaN	0	NaN	0	1506.5533
TCGA-A2-A0EX-01	NaN	0	NaN	0	1280.648
TCGA-A2-A0EY-01	NaN	2	NaN	2	9431.3941
TCGA-A2-A0ST-01	NaN	0	0.047320947960461	0	1754.6786
TCGA-A2-A0SU-01	NaN	0	0.033035793438026	0	1287.1287
TCGA-A2-A0SV-01	NaN	0	0.051130225872726	0	1337.3429
TCGA-A2-A0SW-01	NaN	-1	0.065519298603264	-1	1041.5376
TCGA-A2-A0SX-01	NaN	-1	0.035692626282128	-1	1702.6333
TCGA-A2-A0SY-01	NaN	2	0.027841304651720	2	2088.1533
TCGA-A2-A0T0-01	NaN	0	0.029187706414382	0	1497.3493
TCGA-A2-A0T1-01	NaN	2	0.014249446522097	2	4688.0764
TCGA-A2-A0T2-01	NaN	0	0.053970814036512	0	924.6545
TCGA-A2-A0T3-01	NaN	1	NaN	1	1976.0919
TCGA-A2-A0T4-01	NaN	0	0.036550810326881	0	1248.9019
TCGA-A2-A0T5-01	NaN	0	0.031305257701849	0	1112.0635
TCGA-A2-A0T6-01	NaN	0	0.041585151574306	0	1824.6675
TCGA-A2-A0T7-01	NaN	1	0.038401604941225	1	1957.1026
TCGA-A2-A0YC-01	NaN	1	0.024691103352004	1	2336.2756
TCGA-A2-A0YD-01	NaN	0	0.029960546560831	0	1726.0649
TCGA-A2-A0YE-01	NaN	1	0.032136985574797	1	2199.9366
TCGA-A2-A0YF-01	NaN	0	0.040747333376787	0	1605.4729
TCGA-A2-A0YG-01	NaN	2	0.033746899520777	2	16028.548
TCGA-A2-A0YH-01	NaN	0	0.033583074558562	0	1615.9645
TCGA-A2-A0YI-01	NaN	0	0.026549090060094	0	1866.4281
TCGA-A2-A0YJ-01	NaN	2	0.011388013520767	2	9921.8877
TCGA-A2-A0YK-01	NaN	-1	0.053637767927605	-1	1444.4932
TCGA-A2-A0YL-01	NaN	-1	0.032947965930642	-1	1222.3913
TCGA-A2-A0YM-01	NaN	1	0.027945235543066	1	2072.3817
TCGA-A2-A0YT-01	NaN	-1	0.039363549902104	-1	2222.6418
TCGA-A2-A1FV-01	NaN	0	0.024198626277152	0	2033.6301
TCGA-A2-A1FW-01	NaN	-1	0.057899814984713	-1	1603.7386
TCGA-A2-A1FX-01	NaN	1	0.026375149443731	1	1658.3847
TCGA-A2-A1FZ-01	NaN	0	0.032258395202042	0	1449.3173
TCGA-A2-A1G0-01	NaN	1	0.026367435721071	1	2167.9816
TCGA-A2-A1G1-01	NaN	1	0.014522200019939	1	31940.3477
TCGA-A2-A1G4-01	NaN	0	0.040967001702961	0	1904.7619
TCGA-A2-A1G6-01	NaN	0	0.032049242536854	0	1179.7865
TCGA-A2-A259-01	NaN	-1	0.062029912769000	-1	1633.331
TCGA-A2-A25A-01	NaN	-1	0.031449049174643	-1	1125.4529
TCGA-A2-A25B-01	NaN	-1	0.047448133999270	-1	1857.7889
TCGA-A2-A25C-01	NaN	0	0.023488305030056	0	2383.326
TCGA-A2-A25D-01	NaN	0	0.032643317187140	0	1292.46
TCGA-A2-A25E-01	NaN	1	0.022046327911031	1	3143.7107
TCGA-A2-A25F-01	NaN	0	0.0415785581712	0	2044.2956
TCGA-A2-A3KC-01	NaN	0	0.037897467252484	0	1489.7923
TCGA-A2-A3KD-01	NaN	0	0.032361918785276	0	1656.71
TCGA-A2-A3XS-01	NaN	0	0.035043709331436	0	748.851
TCGA-A2-A3XT-01	NaN	-1	0.036601136417650	-1	878.0577
TCGA-A2-A3XU-01	NaN	1	0.032911521376543	1	705.8333
TCGA-A2-A3XV-01	NaN	2	0.038913928958380	2	895.914
TCGA-A2-A3XW-01	NaN	0	0.038180192761590	0	660.8788
TCGA-A2-A3XX-01	NaN	1	0.036171654005367	1	1338.0173
TCGA-A2-A3XY-01	NaN	-1	0.035633660457222	-1	1063.619
TCGA-A2-A3XZ-01	NaN	2	0.01596599400169	2	4380.7719
TCGA-A2-A3Y0-01	NaN	-1	0.036314441907166	-1	945.9867
TCGA-A2-A4RW-01	NaN	0	0.045991721872376	0	1503.0266
TCGA-A2-A4RX-01	NaN	-1	0.044128475385474	-1	1445.4946
TCGA-A2-A4RY-01	NaN	0	0.063670618746925	0	1371.5551
TCGA-A2-A4S0-01	NaN	0	0.056074668403692	0	1204.1216
TCGA-A2-A4S1-01	NaN	-1	0.052056157470661	-1	494.3419
TCGA-A2-A4S2-01	NaN	0	0.063338214386271	0	1329.0656
TCGA-A2-A4S3-01	NaN	-1	0.059983351424173	-1	1248.5207
TCGA-A7-A0CD-01	NaN	1	NaN	1	2480.2211
TCGA-A7-A0CE-01	NaN	0	NaN	0	1473.6842
TCGA-A7-A0CG-01	NaN	-1	NaN	-1	1326.5306
TCGA-A7-A0CH-01	NaN	0	NaN	0	1648.1312
TCGA-A7-A0CJ-01	NaN	-1	NaN	-1	1158.9773
TCGA-A7-A0D9-01	NaN	-1	0.069539472395502	-1	1303.417
TCGA-A7-A0DA-01	NaN	-1	NaN	-1	1002.3427
TCGA-A7-A0DB-01	NaN	0	NaN	0	1259.8908
TCGA-A7-A0DC-01	NaN	1	NaN	1	NaN
TCGA-A7-A13D-01	NaN	2	0.036237215553073	2	2694.8309
TCGA-A7-A13E-01	NaN	0	0.034844245601844	0	1525.782
TCGA-A7-A13F-01	NaN	1	0.024074386835105	1	2008.8353
TCGA-A7-A13G-01	NaN	0	0.030553780943413	0	1702.8318
TCGA-A7-A13H-01	NaN	0	0.031843983758859	0	1271.8618
TCGA-A7-A26E-01	NaN	-1	0.139601525359712	-1	2058.6674
TCGA-A7-A26F-01	NaN	-1	0.044662412638964	-1	1898.6285
TCGA-A7-A26G-01	X889_splice	-1	0.030282666946496	-1	1887.5428
TCGA-A7-A26H-01	NaN	1	0.026537084617613	1	2683.2898
TCGA-A7-A26I-01	NaN	-1	0.033158204892657	-1	1498.2019
TCGA-A7-A26J-01	NaN	1	0.138067510277306	1	3186.5456
TCGA-A7-A2KD-01	NaN	2	0.017813215016052	2	13062.254
TCGA-A7-A3IY-01	NaN	0	0.040071170224667	0	789.7669
TCGA-A7-A3IZ-01	NaN	0	0.028930601066327	0	1596.6159
TCGA-A7-A3J0-01	NaN	1	0.04507346904651	1	1717.0152
TCGA-A7-A3J1-01	NaN	0	0.028894563562671	0	1729.301
TCGA-A7-A3RF-01	NaN	0	0.026876768581618	0	968.7899
TCGA-A7-A425-01	NaN	0	0.045674023229899	0	736.9932
TCGA-A7-A426-01	NaN	-1	0.032093718816814	-1	645.5907
TCGA-A7-A4SA-01	NaN	1	0.370712294349334	1	1413.8739
TCGA-A7-A4SB-01	NaN	1	0.039435782850982	1	1143.9455
TCGA-A7-A4SC-01	NaN	NaN	0.043668655826806	NaN	1762.2897
TCGA-A7-A4SD-01	NaN	-1	0.045436472357259	-1	1688.5572
TCGA-A7-A4SE-01	NaN	-1	0.036697185780769	-1	1284.0028
TCGA-A7-A4SF-01	NaN	2	0.024443622587763	2	3540.3509
TCGA-A7-A56D-01	NaN	2	NaN	-1	1447.9306
TCGA-A7-A5ZV-01	NaN	0	0.039186266639616	0	955.6401
TCGA-A7-A5ZW-01	NaN	0	0.038169084217388	0	945.617
TCGA-A7-A5ZX-01	NaN	0	0.050977643445290	0	777.4936
TCGA-A7-A6VV-01	NaN	-1	0.039156064243450	-1	1061.3388
TCGA-A7-A6VW-01	NaN	-1	0.054440255200304	-1	517.158
TCGA-A7-A6VX-01	NaN	-1	0.054549333030144	-1	932.6529
TCGA-A7-A6VY-01	NaN	-1	0.044823373070765	-1	756.1397
TCGA-A8-A06N-01	NaN	1	NaN	1	2717.0721
TCGA-A8-A06O-01	NaN	1	NaN	1	2437.6647
TCGA-A8-A06P-01	NaN	0	NaN	0	1582.9478
TCGA-A8-A06Q-01	NaN	-1	NaN	-1	1542.0226
TCGA-A8-A06R-01	NaN	-1	NaN	-1	939.0079
TCGA-A8-A06T-01	NaN	0	NaN	0	1775.9502
TCGA-A8-A06U-01	NaN	2	NaN	2	3300.6612
TCGA-A8-A06X-01	NaN	-1	NaN	-1	1046.1997
TCGA-A8-A06Y-01	NaN	0	NaN	0	1572.0054
TCGA-A8-A06Z-01	NaN	1	NaN	1	2117.662
TCGA-A8-A075-01	NaN	-1	0.065214328832061	-1	1792.7573
TCGA-A8-A076-01	NaN	2	NaN	2	4050.2392
TCGA-A8-A079-01	NaN	-1	NaN	-1	1362.4735
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TCGA-A8-A07E-01	T1463Nfs*50	-1	NaN	-1	1327.7937
TCGA-A8-A07F-01	NaN	0	NaN	0	2105.2007
TCGA-A8-A07G-01	NaN	1	NaN	1	1932.3489
TCGA-A8-A07I-01	NaN	2	NaN	2	7744.2399
TCGA-A8-A07J-01	NaN	0	NaN	0	1652.904
TCGA-A8-A07L-01	NaN	-1	NaN	-1	1480.8088
TCGA-A8-A07O-01	NaN	1	NaN	1	4180.323
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TCGA-A8-A07R-01	NaN	1	NaN	1	3437.575
TCGA-A8-A07S-01	NaN	0	NaN	0	1613.2541
TCGA-A8-A07U-01	NaN	0	NaN	0	1619.6987
TCGA-A8-A07W-01	NaN	1	NaN	1	2204.4967
TCGA-A8-A07Z-01	NaN	0	NaN	0	1301.4849
TCGA-A8-A081-01	NaN	1	NaN	1	3285.8257
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TCGA-A8-A086-01	NaN	1	NaN	1	1635.4403
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TCGA-A8-A08B-01	NaN	2	NaN	2	7024.735
TCGA-A8-A08C-01	NaN	0	NaN	0	1611.5814
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TCGA-A8-A08H-01	NaN	0	NaN	0	1493.2621
TCGA-A8-A08I-01	NaN	-1	NaN	-1	2180.5452
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TCGA-A8-A09C-01	NaN	1	NaN	1	1335.2369
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TCGA-A8-A09G-01	NaN	-1	NaN	-1	1532.9048
TCGA-A8-A09I-01	NaN	2	NaN	2	31539.4473
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TCGA-A8-A09M-01	NaN	1	NaN	1	1523.2506
TCGA-A8-A09N-01	NaN	1	NaN	1	1340.6066
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TCGA-A8-A09R-01	NaN	1	NaN	1	3140.6981
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TCGA-A8-A09X-01	NaN	1	NaN	1	1366.0354
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TCGA-AC-A23G-01	NaN	1	0.031433943263554	1	1238.3721
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TCGA-AC-A2B8-01	NaN	0	0.030297910808510	0	1813.807
TCGA-AC-A2BK-01	NaN	1	0.033016011343345	1	1581.7077
TCGA-AC-A2BM-01	NaN	-1	0.028517787035334	-1	1724.8107
TCGA-AC-A2FB-01	NaN	2	0.015454478162033	2	4129.0218
TCGA-AC-A2FE-01	NaN	0	0.023638705929816	0	1063.2011
TCGA-AC-A2FF-01	NaN	0	0.030378250448043	0	1643.1562
TCGA-AC-A2FG-01	NaN	0	0.035320664753946	0	1346.4628
TCGA-AC-A2FK-01	NaN	0	0.027746841920741	0	1766.1183
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TCGA-AC-A2FO-01	NaN	0	0.024348270479590	0	1622.9635
TCGA-AC-A2QH-01	NaN	-1	0.030063365613618	-1	1209.3982
TCGA-AC-A2QI-01	NaN	0	0.029393679468115	0	1202.8594
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TCGA-AC-A3HN-01	NaN	0	0.044774472869865	0	1431.5727
TCGA-AC-A3OD-01	NaN	0	0.039796311498834	0	1304.2609
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TCGA-AC-A3TM-01	NaN	0	0.033812728772485	0	470.7944
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TCGA-AC-A3W5-01	NaN	2	0.025733181567842	2	1107.3632
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TCGA-AC-A3W7-01	NaN	1	0.042989756429126	1	877.1352
TCGA-AC-A3YI-01	NaN	0	0.034316246667300	0	1220.4022
TCGA-AC-A3YJ-01	NaN	0	0.048541830454571	0	653.9431
TCGA-AC-A4ZE-01	NaN	0	0.052957480551536	0	1561.6646
TCGA-AC-A5EH-01	NaN	1	0.035441569714015	1	856.4948
TCGA-AC-A5EI-01	NaN	0	NaN	0	NaN
TCGA-AC-A5XS-01	NaN	0	0.030985487719740	0	828.7498
TCGA-AC-A5XU-01	NaN	0	0.037340160461103	0	1204.5101
TCGA-AC-A62V-01	NaN	0	0.034538894842546	0	486.7395
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TCGA-AC-A6IW-01	NaN	0	0.032052491856841	0	1069.0623
TCGA-AC-A6IX-01	NaN	0	0.040961015282944	0	826.9073
TCGA-AC-A6IX-06	NaN	NaN	0.031123684389551	NaN	831.3849
TCGA-AC-A6NO-01	NaN	1	0.038518415083906	1	1171.6093
TCGA-AC-A7VB-01	NaN	0	0.023622830693885	0	1823.2368
TCGA-AC-A7VC-01	NaN	0	0.027734731494281	0	723.036
TCGA-AC-A8OP-01	NaN	1	0.031825663541395	1	1711.4193
TCGA-AC-A8OQ-01	NaN	0	0.063110652592261	0	2032.5467
TCGA-AC-A8OR-01	NaN	0	0.086252632324361	0	1149.7036
TCGA-AC-A8OS-01	NaN	0	0.072918396872662	0	1097.4539
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TCGA-AN-A04C-01	NaN	2	NaN	2	4345.0966
TCGA-AN-A04D-01	NaN	0	NaN	0	1104.5206
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TCGA-AN-A0AL-01	NaN	1	NaN	1	841.3849
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TCGA-AN-A0XV-01	NaN	0	0.045171772667776	0	1406.5551
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TCGA-AO-A03O-01	NaN	0	NaN	0	2034.4978
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TCGA-AQ-A1H2-01	NaN	0	0.025732296111566	0	1398.6453
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TCGA-AQ-A54O-01	NaN	0	0.057601807128150	0	703.82
TCGA-AQ-A7U7-01	NaN	0	0.034075668370185	0	1451.9262
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TCGA-AR-A0U4-01	NaN	0	0.040949869967040	0	1295.7746
TCGA-AR-A1AH-01	NaN	1	NaN	1	1531.7191
TCGA-AR-A1AI-01	NaN	1	0.027672538868632	1	2501.0211
TCGA-AR-A1AJ-01	NaN	0	0.054616092938440	0	1939.2411
TCGA-AR-A1AK-01	NaN	0	0.041669913307839	0	2234.48
TCGA-AR-A1AL-01	NaN	0	0.038706598685010	0	2049.9561
TCGA-AR-A1AM-01	NaN	0	0.031651195456966	0	1286.8407
TCGA-AR-A1AN-01	NaN	0	0.043359008868834	0	1083.1109
TCGA-AR-A1AO-01	NaN	0	0.032271282725662	0	1228.0903
TCGA-AR-A1AP-01	NaN	1	0.035593370084100	1	1360.3239
TCGA-AR-A1AQ-01	NaN	0	0.033810305908580	0	1203.5124
TCGA-AR-A1AR-01	NaN	1	0.045828251374114	1	1518.784
TCGA-AR-A1AS-01	NaN	0	0.030316541787322	0	1416.4791
TCGA-AR-A1AT-01	NaN	1	0.029188210205257	1	5346.2934
TCGA-AR-A1AU-01	NaN	1	0.033654896557654	1	2038.3772
TCGA-AR-A1AV-01	NaN	1	0.049690344630770	1	2047.066
TCGA-AR-A1AW-01	NaN	1	0.031438170802752	1	2361.3318
TCGA-AR-A1AX-01	NaN	1	0.032138324480748	1	4576.1815
TCGA-AR-A1AY-01	NaN	1	0.043453610849314	1	1914.577
TCGA-AR-A24H-01	NaN	2	0.019484481786627	2	2912.2725
TCGA-AR-A24K-01	NaN	0	0.030908816755996	0	2238.6831
TCGA-AR-A24L-01	NaN	0	0.029780350088975	0	3193.2619
TCGA-AR-A24M-01	NaN	0	0.030739173611412	0	1778.0709
TCGA-AR-A24N-01	NaN	0	0.031848855936151	0	1774.0708
TCGA-AR-A24O-01	NaN	0	0.022750252502461	0	1773.2519
TCGA-AR-A24P-01	NaN	2	0.029271186392862	2	2753.3632
TCGA-AR-A24Q-01	NaN	0	0.033081851373799	0	1616.885
TCGA-AR-A24R-01	NaN	0	0.032358560234366	0	2541.006
TCGA-AR-A24S-01	NaN	2	0.028138354754258	2	2120.1336
TCGA-AR-A24T-01	NaN	0	0.021081771618222	0	1656.8162
TCGA-AR-A24U-01	NaN	2	0.046119388813419	2	15297.9001
TCGA-AR-A24V-01	NaN	1	0.019804727069195	1	2139.7899
TCGA-AR-A24W-01	NaN	0	0.026344679683880	0	1908.5567
TCGA-AR-A24X-01	NaN	0	0.028817340305998	0	1822.7542
TCGA-AR-A24Z-01	NaN	1	0.037492272254050	1	2645.9281
TCGA-AR-A250-01	NaN	2	0.023247870202734	2	4407.2848
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TCGA-AR-A252-01	NaN	1	0.037843770980522	1	1812.1481
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TCGA-B6-A0X5-01	NaN	0	0.030740186456786	0	1068.0065
TCGA-B6-A0X7-01	NaN	0	0.035984126590104	0	1140.7484
TCGA-B6-A1KC-01	NaN	0	0.022304270482270	0	1891.038
TCGA-B6-A1KF-01	NaN	2	0.013420417790326	2	10657.9851
TCGA-B6-A1KI-01	NaN	1	0.026695557987270	1	1312.7934
TCGA-B6-A1KN-01	NaN	2	0.031097607360162	2	30823.6666
TCGA-B6-A2IU-01	NaN	0	0.034002379152372	0	1171.8188
TCGA-B6-A3ZX-01	NaN	1	0.032909982397375	1	1680.4421
TCGA-B6-A400-01	NaN	0	0.031117281736589	0	801.054
TCGA-B6-A401-01	NaN	1	0.031689169927301	1	1150.8724
TCGA-B6-A402-01	NaN	0	0.033543311493343	0	1353.3007
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TCGA-BH-A0AZ-01	NaN	-1	0.026857215879920	-1	1193.1001
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TCGA-BH-A0BP-01	NaN	-1	NaN	-1	1000
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TCGA-BH-A0DD-01	NaN	2	0.020318735159955	2	6959.3838
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TCGA-BH-A0DK-01	NaN	-1	0.024863211720336	-1	993.2493
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TCGA-BH-A0DP-01	NaN	1	0.035403158985364	1	1503.1769
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TCGA-BH-A0H3-01	NaN	0	0.036116158902126	0	1565.6663
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TCGA-BH-A0HI-01	NaN	0	0.067647691784618	0	1148.1319
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TCGA-BH-A0HW-01	NaN	1	NaN	1	2821.6685
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TCGA-BH-A2L8-01	NaN	0	0.032222221560347	0	1057.4518
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TCGA-BH-A42U-01	NaN	0	0.023250461328606	0	607.2324
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TCGA-BH-AB28-01	NaN	0	0.061132770856496	0	1085.3397
TCGA-C8-A12K-01	NaN	1	NaN	1	933.6829
TCGA-C8-A12L-01	NaN	1	NaN	1	1756.2327
TCGA-C8-A12M-01	NaN	2	NaN	2	2377.456
TCGA-C8-A12N-01	NaN	0	NaN	0	1155.6989
TCGA-C8-A12O-01	NaN	1	NaN	1	2646.9817
TCGA-C8-A12P-01	NaN	2	NaN	2	8943.8288
TCGA-C8-A12Q-01	NaN	2	NaN	2	2748.5633
TCGA-C8-A12T-01	NaN	1	NaN	1	915.1314
TCGA-C8-A12U-01	NaN	1	NaN	1	1489.1869
TCGA-C8-A12V-01	NaN	1	NaN	1	1297.648
TCGA-C8-A12W-01	P1144S	1	NaN	1	2830.3841
TCGA-C8-A12X-01	NaN	0	NaN	0	1320.1439
TCGA-C8-A12Y-01	NaN	0	NaN	0	689.5885
TCGA-C8-A12Z-01	NaN	2	NaN	2	33677.689
TCGA-C8-A130-01	NaN	1	NaN	1	1496.7742
TCGA-C8-A131-01	NaN	1	NaN	1	773.3397
TCGA-C8-A132-01	NaN	2	NaN	2	6125.8687
TCGA-C8-A133-01	NaN	0	NaN	0	907.7953
TCGA-C8-A134-01	NaN	1	NaN	1	1240.3643
TCGA-C8-A135-01	NaN	2	NaN	2	2975.1152
TCGA-C8-A137-01	NaN	2	NaN	2	1252.257
TCGA-C8-A138-01	NaN	2	NaN	2	1673.0448
TCGA-C8-A1HE-01	NaN	0	0.037437456825519	0	1785.2502
TCGA-C8-A1HF-01	NaN	2	0.015669147106958	2	8566.9736
TCGA-C8-A1HG-01	NaN	0	0.032219793446941	0	1512.4633
TCGA-C8-A1HI-01	NaN	-1	0.043458379532391	-1	1129.1408
TCGA-C8-A1HJ-01	NaN	0	0.034925604892085	0	1119.9188
TCGA-C8-A1HK-01	NaN	1	0.032206779441784	1	1418.8547
TCGA-C8-A1HL-01	NaN	2	0.022151101698025	2	2734.1249
TCGA-C8-A1HM-01	NaN	1	0.046782574229157	1	1706.9129
TCGA-C8-A1HN-01	NaN	1	0.039559699672699	1	2433.0849
TCGA-C8-A1HO-01	NaN	-1	0.044381286162008	-1	1305.984
TCGA-C8-A26V-01	NaN	1	0.050139169067311	1	1116.0337
TCGA-C8-A26W-01	NaN	2	0.014148219200041	2	2665.4606
TCGA-C8-A26X-01	NaN	0	0.032848737938331	0	915.48
TCGA-C8-A26Y-01	R1243T	1	0.029043781545858	1	1466.116
TCGA-C8-A26Z-01	NaN	1	0.024822247801771	1	2065.289
TCGA-C8-A273-01	NaN	2	0.037494428572	2	916.1567
TCGA-C8-A274-01	NaN	0	0.026585447402101	0	1796.9852
TCGA-C8-A275-01	NaN	0	0.031838180732493	0	1116.7991
TCGA-C8-A278-01	NaN	2	0.017593834419522	2	8466.4488
TCGA-C8-A27A-01	NaN	2	0.025662188874697	2	3660.2405
TCGA-C8-A27B-01	NaN	0	0.040411405211661	0	1256.591
TCGA-C8-A3M7-01	NaN	0	0.042113210075631	0	933.399
TCGA-C8-A3M8-01	NaN	0	0.033411446138330	0	1525.8667
TCGA-C8-A8HP-01	NaN	2	0.024776824174389	2	3529.0901
TCGA-C8-A8HQ-01	NaN	0	0.035497652651566	0	1100.6897
TCGA-C8-A8HR-01	NaN	0	0.028904969020124	0	1260.2859
TCGA-C8-A9FZ-01	NaN	2	0.029917190322866	2	NaN
TCGA-D8-A13Y-01	NaN	1	NaN	1	1277.68
TCGA-D8-A13Z-01	NaN	1	NaN	1	2023.7517
TCGA-D8-A140-01	NaN	2	NaN	2	3632.6531
TCGA-D8-A141-01	NaN	0	NaN	0	1507.8285
TCGA-D8-A142-01	NaN	0	NaN	0	1286.587
TCGA-D8-A143-01	NaN	1	NaN	1	1956.9031
TCGA-D8-A145-01	NaN	1	NaN	1	1938.6602
TCGA-D8-A146-01	NaN	1	NaN	1	1325.0267
TCGA-D8-A147-01	NaN	1	NaN	1	3118.8055
TCGA-D8-A1J8-01	NaN	1	0.029114276032756	1	1718.9811
TCGA-D8-A1J9-01	NaN	2	0.008627141402211	2	11143.3804
TCGA-D8-A1JA-01	NaN	1	0.040488499491694	1	3264.8971
TCGA-D8-A1JB-01	NaN	1	0.031611323741661	1	1572.2448
TCGA-D8-A1JC-01	NaN	0	0.030140848215265	0	2195.7457
TCGA-D8-A1JD-01	NaN	0	0.019397008735784	0	2140.0424
TCGA-D8-A1JE-01	NaN	0	0.027494478029113	0	2285.5518
TCGA-D8-A1JF-01	NaN	1	0.025209715667441	1	2566.5628
TCGA-D8-A1JG-01	NaN	1	0.033711347027971	1	3426.9474
TCGA-D8-A1JH-01	NaN	1	0.015773052169801	1	1845.6637
TCGA-D8-A1JI-01	NaN	1	0.022162414502986	1	1591.3999
TCGA-D8-A1JJ-01	NaN	1	0.029786624133916	1	1657.4748
TCGA-D8-A1JK-01	NaN	1	0.028552247028970	1	991.0661
TCGA-D8-A1JL-01	NaN	1	0.030831989011299	1	2041.6794
TCGA-D8-A1JM-01	NaN	1	0.048167219065983	1	1598.3424
TCGA-D8-A1JN-01	NaN	1	0.042492143828418	1	1750.2029
TCGA-D8-A1JP-01	NaN	1	0.024737525469011	1	1319.8947
TCGA-D8-A1JS-01	NaN	2	0.031870949237319	2	645.2342
TCGA-D8-A1JT-01	NaN	1	0.040108125481522	1	1975.8785
TCGA-D8-A1JU-01	NaN	1	0.031091560424165	1	1145.2043
TCGA-D8-A1X5-01	NaN	1	0.026986774327683	1	2783.8988
TCGA-D8-A1X6-01	NaN	1	0.041432289196363	1	1166.4098
TCGA-D8-A1X7-01	NaN	0	0.020109962039808	0	1754.434
TCGA-D8-A1X8-01	NaN	0	0.025241533005604	0	1492.7986
TCGA-D8-A1X9-01	NaN	0	0.024741817820613	0	2718.3508
TCGA-D8-A1XA-01	NaN	2	0.025471591033065	2	2582.5558
TCGA-D8-A1XB-01	NaN	0	0.026209308872734	0	2077.7321
TCGA-D8-A1XC-01	NaN	0	0.043618050037086	0	1786.9796
TCGA-D8-A1XD-01	NaN	0	0.036600058447426	0	1994.0964
TCGA-D8-A1XF-01	NaN	0	0.020195553438405	0	2445.3569
TCGA-D8-A1XG-01	NaN	0	0.030663743782462	0	1906.8026
TCGA-D8-A1XJ-01	NaN	2	0.015477671841778	2	12873.0107
TCGA-D8-A1XK-01	NaN	0	0.031358890726928	0	1569.2078
TCGA-D8-A1XL-01	NaN	2	0.029062249795560	2	1195.8795
TCGA-D8-A1XM-01	NaN	1	0.027637518857905	1	2459.1245
TCGA-D8-A1XO-01	NaN	1	0.033362612498088	1	1857.9494
TCGA-D8-A1XQ-01	NaN	0	0.041571349696040	0	1156.0644
TCGA-D8-A1XR-01	NaN	0	0.030378663094453	0	1811.3632
TCGA-D8-A1XS-01	NaN	2	0.029750506224910	2	2812.2292
TCGA-D8-A1XT-01	NaN	2	0.012502819324202	2	14461.3739
TCGA-D8-A1XU-01	NaN	0	0.034846402790443	0	1640.8713
TCGA-D8-A1XV-01	NaN	0	0.028764086360534	0	1442.0402
TCGA-D8-A1XW-01	NaN	0	0.031444645205897	0	1301.3317
TCGA-D8-A1XY-01	NaN	0	0.033902010174465	0	2744.2168
TCGA-D8-A1XZ-01	NaN	0	0.041517322042637	0	1445.4724
TCGA-D8-A1Y0-01	NaN	0	0.028699783365181	0	2553.6197
TCGA-D8-A1Y1-01	NaN	0	0.035491936266988	0	1251.3828
TCGA-D8-A1Y2-01	NaN	1	0.029939619599771	1	1289.7826
TCGA-D8-A1Y3-01	NaN	0	0.030766358048833	0	1125.0493
TCGA-D8-A27E-01	NaN	0	0.027362601854733	0	1680.2246
TCGA-D8-A27F-01	NaN	0	0.030216059170669	0	1352.6841
TCGA-D8-A27G-01	NaN	2	0.016669742762714	2	1043.7035
TCGA-D8-A27H-01	NaN	2	0.014799554070487	2	1410.939
TCGA-D8-A27I-01	NaN	0	0.025918083831614	0	1614.6896
TCGA-D8-A27K-01	NaN	0	0.025276673234060	0	1813.4158
TCGA-D8-A27L-01	NaN	0	0.028316899329605	0	2028.4322
TCGA-D8-A27M-01	NaN	0	0.034445471816951	0	1703.202
TCGA-D8-A27N-01	NaN	0	0.029996395501088	0	2249.1033
TCGA-D8-A27P-01	NaN	0	0.030786253113556	0	1679.275
TCGA-D8-A27R-01	NaN	0	0.022916880187842	0	2700.9658
TCGA-D8-A27T-01	NaN	2	0.019095155160767	2	2437.6634
TCGA-D8-A27V-01	NaN	0	0.038685918105458	0	1129.6141
TCGA-D8-A27W-01	NaN	0	0.028854941949408	0	2825.2761
TCGA-D8-A3Z5-01	NaN	0	0.025637866463790	0	1091.7143
TCGA-D8-A3Z6-01	NaN	0	0.023177902552029	0	1034.7313
TCGA-D8-A4Z1-01	NaN	0	0.039062899884959	0	1167.1806
TCGA-D8-A73U-01	NaN	-1	0.041886889990504	-1	1027.4692
TCGA-D8-A73W-01	NaN	0	0.035085521003037	0	1655.9365
TCGA-D8-A73X-01	NaN	0	0.023928964769361	0	1150.5982
TCGA-E2-A105-01	NaN	2	0.023396900833886	2	2152.5641
TCGA-E2-A106-01	NaN	NaN	0.029133896026685	NaN	1724.7374
TCGA-E2-A107-01	NaN	1	0.029415937467270	1	1147.1074
TCGA-E2-A108-01	NaN	0	0.026728597646037	0	1282.4589
TCGA-E2-A109-01	NaN	1	0.022257423385062	1	2199.5381
TCGA-E2-A10A-01	NaN	0	NaN	0	1666.8647
TCGA-E2-A10B-01	NaN	0	0.058692322308575	0	1998.862
TCGA-E2-A10C-01	NaN	1	0.030374682910930	1	811.1323
TCGA-E2-A10E-01	NaN	0	0.033206543517576	0	1263.3887
TCGA-E2-A10F-01	NaN	0	0.032040979035924	0	1704.4773
TCGA-E2-A14N-01	NaN	0	0.034413467142214	0	1489.8353
TCGA-E2-A14O-01	NaN	1	NaN	1	1103.006
TCGA-E2-A14P-01	NaN	2	NaN	2	3634.3612
TCGA-E2-A14Q-01	NaN	-1	NaN	-1	896.4487
TCGA-E2-A14R-01	NaN	-1	NaN	-1	902.4418
TCGA-E2-A14S-01	NaN	0	NaN	0	1279.7018
TCGA-E2-A14T-01	NaN	1	NaN	1	1992.1067
TCGA-E2-A14U-01	NaN	0	0.030403633952259	0	1050.5649
TCGA-E2-A14V-01	NaN	2	NaN	2	18683.4775
TCGA-E2-A14W-01	NaN	1	NaN	1	1799.2333
TCGA-E2-A14X-01	NaN	-1	NaN	-1	1359.0464
TCGA-E2-A14Y-01	NaN	2	NaN	2	12617.7872
TCGA-E2-A14Z-01	NaN	-1	NaN	-1	1010.7623
TCGA-E2-A150-01	NaN	-1	NaN	-1	1074.0591
TCGA-E2-A152-01	NaN	2	NaN	2	1683.5856
TCGA-E2-A153-01	NaN	1	NaN	1	1523.9155
TCGA-E2-A154-01	NaN	0	NaN	0	2015.4076
TCGA-E2-A155-01	NaN	0	NaN	0	2319.4229
TCGA-E2-A156-01	NaN	0	NaN	0	1669.7775
TCGA-E2-A158-01	NaN	-1	NaN	-1	926.7415
TCGA-E2-A159-01	NaN	-1	NaN	-1	1233.3244
TCGA-E2-A15A-01	NaN	1	NaN	1	2270.815
TCGA-E2-A15A-06	NaN	NaN	NaN	NaN	1726.0211
TCGA-E2-A15C-01	NaN	0	NaN	0	2182.4
TCGA-E2-A15D-01	NaN	0	NaN	0	1362.5219
TCGA-E2-A15E-01	NaN	2	NaN	2	2549.5951
TCGA-E2-A15E-06	NaN	NaN	NaN	NaN	3055.7439
TCGA-E2-A15F-01	NaN	0	NaN	0	2250.3433
TCGA-E2-A15G-01	NaN	-1	NaN	-1	1473.7705
TCGA-E2-A15H-01	NaN	2	NaN	2	6106.2374
TCGA-E2-A15I-01	NaN	0	0.039266406650055	0	1799.0856
TCGA-E2-A15J-01	NaN	0	0.033690540241879	0	1406.3604
TCGA-E2-A15K-01	NaN	0	0.027799429760624	0	1443.3069
TCGA-E2-A15K-06	NaN	NaN	0.047397260330796	NaN	1487.7063
TCGA-E2-A15L-01	NaN	0	NaN	0	1391.8175
TCGA-E2-A15M-01	NaN	-1	NaN	-1	3665.0165
TCGA-E2-A15O-01	NaN	0	NaN	0	2320.7994
TCGA-E2-A15P-01	NaN	0	NaN	0	2231.135
TCGA-E2-A15R-01	NaN	0	NaN	0	2194.469
TCGA-E2-A15S-01	NaN	0	NaN	0	2051.7613
TCGA-E2-A15T-01	NaN	1	NaN	1	2942.828
TCGA-E2-A1AZ-01	NaN	-1	0.035874118943400	-1	1906.2266
TCGA-E2-A1B0-01	NaN	2	0.012393332945682	2	15432.603
TCGA-E2-A1B1-01	NaN	2	0.025374025316499	2	3033.9893
TCGA-E2-A1B4-01	NaN	0	0.038042300632714	0	702.6634
TCGA-E2-A1B5-01	NaN	-1	0.076193680237788	-1	693.1285
TCGA-E2-A1B6-01	NaN	0	0.042460798580646	0	716.4212
TCGA-E2-A1BC-01	NaN	0	0.033174871534045	0	2021.4797
TCGA-E2-A1BD-01	NaN	0	0.030406703874894	0	922.9995
TCGA-E2-A1IE-01	NaN	0	0.024258426325185	0	1580.8159
TCGA-E2-A1IF-01	NaN	0	0.027064814784324	0	630.2376
TCGA-E2-A1IG-01	NaN	1	0.018829387611194	1	2190.8242
TCGA-E2-A1IH-01	NaN	1	0.025550335472777	1	1347.2234
TCGA-E2-A1II-01	NaN	-1	0.029237220475598	-1	1481.7518
TCGA-E2-A1IJ-01	NaN	1	0.025697561865877	1	1323.0572
TCGA-E2-A1IK-01	NaN	0	0.027344756845503	0	988.3333
TCGA-E2-A1IL-01	NaN	0	0.027329400837987	0	2144.2164
TCGA-E2-A1IN-01	NaN	0	0.031627775481277	0	1284.4687
TCGA-E2-A1IO-01	NaN	0	0.028467484791487	0	2174.6425
TCGA-E2-A1IU-01	NaN	0	0.029480647630232	0	1654.2652
TCGA-E2-A1L6-01	NaN	0	0.059571345813736	0	1331.6712
TCGA-E2-A1L7-01	NaN	-1	0.025465856658207	-1	1264.5881
TCGA-E2-A1L8-01	NaN	0	0.039840683344137	0	1541.8502
TCGA-E2-A1L9-01	NaN	0	0.030664125339399	0	1126.381
TCGA-E2-A1LA-01	NaN	1	0.019916008447775	1	1076.1015
TCGA-E2-A1LB-01	NaN	2	0.015846210374506	2	1476.3563
TCGA-E2-A1LE-01	NaN	2	0.022468445126804	2	768.4987
TCGA-E2-A1LG-01	R902P	0	0.025484235671364	0	1300.6757
TCGA-E2-A1LH-01	NaN	0	0.032114021927623	0	701.5242
TCGA-E2-A1LI-01	NaN	0	0.024935253396276	0	1195.9135
TCGA-E2-A1LK-01	NaN	1	0.022094297835180	1	987.1848
TCGA-E2-A1LL-01	NaN	-1	0.027767740154498	-1	1244.8539
TCGA-E2-A1LS-01	NaN	NaN	0.082051824863105	NaN	787.2873
TCGA-E2-A2P5-01	NaN	-1	0.025975208593921	-1	685.9688
TCGA-E2-A2P6-01	NaN	0	0.022450789313631	0	736.5657
TCGA-E2-A3DX-01	NaN	0	0.025852913506243	0	1785.8174
TCGA-E2-A56Z-01	NaN	1	0.034917195443346	1	974.3012
TCGA-E2-A570-01	NaN	0	0.038278316501499	0	791.8673
TCGA-E2-A572-01	NaN	NaN	0.032381477658129	NaN	511.8081
TCGA-E2-A573-01	NaN	-1	0.042466093734147	-1	876.7023
TCGA-E2-A574-01	NaN	1	0.035827561235888	1	775.5331
TCGA-E2-A576-01	NaN	0	0.024532614389015	0	663.1531
TCGA-E2-A9RU-01	NaN	-1	0.102930263460485	-1	784.4987
TCGA-E9-A1N3-01	NaN	0	0.028864415143765	0	1777.5283
TCGA-E9-A1N4-01	NaN	0	0.028971233340321	0	1720.8933
TCGA-E9-A1N5-01	NaN	-1	0.031816451892453	-1	1240.7342
TCGA-E9-A1N6-01	NaN	2	0.010981823953562	2	3825.1781
TCGA-E9-A1N8-01	NaN	-1	0.028863961853231	-1	1533.5838
TCGA-E9-A1N9-01	NaN	0	0.027628572823984	0	1907.793
TCGA-E9-A1NA-01	NaN	-1	0.031268782263057	-1	780.7669
TCGA-E9-A1NC-01	NaN	-1	0.030977463583648	-1	514.4801
TCGA-E9-A1ND-01	NaN	-1	0.026101076723894	-1	1142.4231
TCGA-E9-A1NE-01	NaN	0	0.025889068094564	0	2325.4572
TCGA-E9-A1NF-01	NaN	-1	0.039982865004786	-1	875.4822
TCGA-E9-A1NG-01	NaN	0	0.034360783170992	0	1391.9001
TCGA-E9-A1NH-01	N939S	-1	0.027240425037439	-1	1231.6637
TCGA-E9-A1NI-01	NaN	0	0.024423237843866	0	1437.9562
TCGA-E9-A1QZ-01	NaN	1	0.026773326278411	1	1982.0871
TCGA-E9-A1R0-01	NaN	0	0.033305134894940	0	1429.8054
TCGA-E9-A1R2-01	NaN	1	0.082915313475018	1	2160.9936
TCGA-E9-A1R3-01	NaN	0	0.030093157939802	0	1664.5792
TCGA-E9-A1R4-01	NaN	1	0.024434798785462	1	1979.1199
TCGA-E9-A1R5-01	NaN	1	0.023826936949918	1	2174.3337
TCGA-E9-A1R6-01	NaN	1	0.022319589622807	1	1986.3575
TCGA-E9-A1R7-01	NaN	1	0.023963470350245	1	3579.1696
TCGA-E9-A1RA-01	NaN	-1	0.025845556438655	-1	1258.9454
TCGA-E9-A1RB-01	NaN	-1	0.030890931516995	-1	1400.6243
TCGA-E9-A1RC-01	NaN	0	0.050365216435974	0	2282.9861
TCGA-E9-A1RD-01	NaN	0	0.044133792818637	0	1484.2735
TCGA-E9-A1RE-01	NaN	1	0.023692410341751	1	2609.9767
TCGA-E9-A1RF-01	NaN	1	0.027328796818607	1	1734.2599
TCGA-E9-A1RG-01	NaN	0	0.027181732301893	0	767.5601
TCGA-E9-A1RH-01	NaN	1	0.031358823939151	1	3095.3929
TCGA-E9-A1RI-01	NaN	1	0.023252370455604	1	2378.7172
TCGA-E9-A226-01	NaN	-1	0.043087963057042	-1	1411.2877
TCGA-E9-A227-01	NaN	0	0.033436039347614	0	1062.7353
TCGA-E9-A228-01	NaN	2	0.019946692958635	2	4362.4577
TCGA-E9-A229-01	NaN	0	0.031239634891120	0	1923.3095
TCGA-E9-A22A-01	NaN	-1	0.037656546054093	-1	1166.6667
TCGA-E9-A22B-01	NaN	1	0.033481960594684	1	1580.048
TCGA-E9-A22D-01	NaN	2	0.022824224294734	2	2200.3094
TCGA-E9-A22E-01	NaN	-1	0.046606920541324	-1	965.9304
TCGA-E9-A22G-01	NaN	-1	0.048907085341858	-1	872.2693
TCGA-E9-A22H-01	NaN	0	0.032314922658360	0	2018.5337
TCGA-E9-A243-01	NaN	0	0.042409678229148	0	1796.0327
TCGA-E9-A244-01	NaN	-1	0.022252384390036	-1	871.9373
TCGA-E9-A245-01	NaN	0	0.030096921497585	0	1097.3888
TCGA-E9-A247-01	NaN	0	0.023851771905861	0	1171.2298
TCGA-E9-A248-01	NaN	0	0.017814682897376	0	2189.0579
TCGA-E9-A249-01	NaN	0	0.021701269763488	0	1664.403
TCGA-E9-A24A-01	NaN	0	0.030160206949908	0	1638.8722
TCGA-E9-A295-01	NaN	1	0.022042371316389	1	1085.597
TCGA-E9-A2JS-01	NaN	1	0.022690522349477	1	2074.1124
TCGA-E9-A2JT-01	NaN	0	0.030955467106354	0	1734.4193
TCGA-E9-A3HO-01	NaN	0	0.040677660457734	0	824.0235
TCGA-E9-A3Q9-01	NaN	0	0.025454173920530	0	1068.6847
TCGA-E9-A3QA-01	NaN	-1	0.034487982072737	-1	893.0798
TCGA-E9-A3X8-01	NaN	-1	0.035796986996852	-1	397.8563
TCGA-E9-A54X-01	NaN	0	0.061984919882996	0	805.3625
TCGA-E9-A54Y-01	NaN	1	0.039707932330459	1	698.4597
TCGA-E9-A5FK-01	NaN	0	NaN	0	547.031
TCGA-E9-A5FL-01	NaN	1	NaN	1	812.0155
TCGA-E9-A5UO-01	NaN	1	0.030632117019200	1	1604.3243
TCGA-E9-A5UP-01	NaN	1	0.036564029204937	1	2257.1885
TCGA-E9-A6HE-01	NaN	0	0.037847571985007	0	562.5
TCGA-EW-A1IW-01	NaN	2	0.016250610227335	2	5858.9779
TCGA-EW-A1IX-01	NaN	0	0.031307762525971	0	1904.7253
TCGA-EW-A1IY-01	NaN	0	0.061029866117203	0	1742.1952
TCGA-EW-A1IZ-01	NaN	0	0.025551139234969	0	1035.5959
TCGA-EW-A1J1-01	NaN	0	0.025043846645131	0	1888.3542
TCGA-EW-A1J2-01	NaN	1	0.023155651131434	1	2165.0869
TCGA-EW-A1J3-01	NaN	2	0.031955987675273	2	5559.0999
TCGA-EW-A1J5-01	NaN	1	0.027169310390144	1	2642.8947
TCGA-EW-A1J6-01	NaN	1	0.020917249267794	1	929.4761
TCGA-EW-A1OV-01	NaN	-1	0.023678397650562	0	1245.7806
TCGA-EW-A1OW-01	NaN	0	0.019710486113306	0	1916.7367
TCGA-EW-A1OX-01	NaN	0	0.024064579827471	0	1746.7007
TCGA-EW-A1OY-01	NaN	1	0.019430978009908	1	1525.5814
TCGA-EW-A1OZ-01	NaN	2	0.013765808518918	2	9637.3825
TCGA-EW-A1P0-01	NaN	0	0.021971734311312	0	1347.185
TCGA-EW-A1P1-01	NaN	0	0.041955939763775	0	1485.2941
TCGA-EW-A1P3-01	NaN	1	0.019832459287558	1	1156.0758
TCGA-EW-A1P4-01	NaN	-1	0.034274061147486	-1	1707.2893
TCGA-EW-A1P5-01	NaN	1	0.022258172272252	1	1803.7499
TCGA-EW-A1P6-01	NaN	0	0.022870412904238	0	1493.8484
TCGA-EW-A1P7-01	NaN	0	0.020432179151710	0	1764.0728
TCGA-EW-A1P8-01	NaN	-1	0.025795880762033	-1	790.3226
TCGA-EW-A1PA-01	NaN	-1	0.030132732764439	-1	1282.0454
TCGA-EW-A1PB-01	NaN	0	0.026790036787023	0	951.7017
TCGA-EW-A1PC-01	NaN	1	0.026344685598936	1	2154.0452
TCGA-EW-A1PD-01	E488*	1	0.021314343259922	1	1629.189
TCGA-EW-A1PE-01	NaN	0	0.021767332217527	0	2055.4717
TCGA-EW-A1PF-01	NaN	-1	0.028677535628783	-1	1465.6351
TCGA-EW-A1PG-01	NaN	0	0.023681259247382	0	1791.1602
TCGA-EW-A1PH-01	NaN	1	0.024004674125293	1	1866.7147
TCGA-EW-A2FR-01	NaN	2	0.023900692064412	2	2064.787
TCGA-EW-A2FS-01	NaN	1	0.034699105905263	1	1087.1339
TCGA-EW-A2FV-01	NaN	-1	0.024366623304477	-1	1449.2919
TCGA-EW-A2FW-01	NaN	0	0.029111844927611	0	1402.6796
TCGA-EW-A3E8-01	NaN	0	0.035654278565338	0	1036.2314
TCGA-EW-A3U0-01	NaN	0	0.032908673942148	0	1386.267
TCGA-EW-A423-01	NaN	1	0.035372662636213	1	747.3503
TCGA-EW-A424-01	NaN	0	0.031928468384712	0	998.644
TCGA-EW-A6S9-01	NaN	2	0.015671880718556	2	6281.4532
TCGA-EW-A6SA-01	NaN	-1	0.036436198308413	-1	1078.6063
TCGA-EW-A6SB-01	NaN	-1	0.023243449501529	-1	659.1479
TCGA-EW-A6SC-01	NaN	0	0.028487111481006	0	1540.3023
TCGA-EW-A6SD-01	NaN	2	0.018047117911853	2	12483.0837
TCGA-GI-A2C8-01	NaN	-1	0.034698851173899	-1	1149.5984
TCGA-GI-A2C9-01	NaN	-1	0.057821770254584	-1	1240.9417
TCGA-GM-A2D9-01	NaN	0	0.031507691292426	0	738.9732
TCGA-GM-A2DA-01	NaN	-1	0.045151129175882	2	665.5809
TCGA-GM-A2DB-01	NaN	-1	0.035821722402782	-1	635.3468
TCGA-GM-A2DC-01	NaN	1	0.023169759824513	1	1070.1682
TCGA-GM-A2DD-01	Y246*	-1	0.031587140359359	-1	493.9122
TCGA-GM-A2DF-01	NaN	0	0.043447598436562	0	621.988
TCGA-GM-A2DH-01	NaN	0	0.026236063185274	0	1850.0652
TCGA-GM-A2DI-01	NaN	-1	0.035382625879564	-1	1752.3734
TCGA-GM-A2DK-01	NaN	1	0.023538797748988	1	1128.7671
TCGA-GM-A2DL-01	NaN	-1	0.039455264528194	-1	624.8292
TCGA-GM-A2DM-01	NaN	0	0.048873425777737	0	1376.5552
TCGA-GM-A2DN-01	NaN	0	0.028630222988967	0	1075.5881
TCGA-GM-A2DO-01	NaN	0	0.022947699260372	0	904.5276
TCGA-GM-A3NW-01	NaN	0	0.030022752323300	0	785.6615
TCGA-GM-A3NY-01	NaN	0	0.031197917392281	0	823.5702
TCGA-GM-A3XG-01	NaN	0	0.023905707054691	0	629.1316
TCGA-GM-A3XL-01	NaN	-1	0.053723920841472	-1	1058.8439
TCGA-GM-A3XN-01	NaN	0	0.040640085541938	0	954.9326
TCGA-GM-A4E0-01	NaN	0	0.065459376262022	0	670.419
TCGA-GM-A5PV-01	NaN	0	0.033337967587602	0	777.6457
TCGA-GM-A5PX-01	NaN	0	0.051363893807766	0	640.0938
TCGA-HN-A2NL-01	NaN	-1	0.030196165425360	-1	758.5796
TCGA-HN-A2OB-01	NaN	0	NaN	0	1244.1547
TCGA-JL-A3YW-01	NaN	0	0.034983069584173	1	1271.9741
TCGA-JL-A3YX-01	NaN	0	0.038865858928975	0	972.747
TCGA-LD-A66U-01	NaN	0	0.036928528358247	0	534.4569
TCGA-LD-A74U-01	NaN	-1	0.054569608089699	-1	932.7886
TCGA-LD-A7W5-01	NaN	-1	0.041822757744844	-1	975.3126
TCGA-LD-A7W6-01	NaN	0	0.032570683778758	0	1216.0937
TCGA-LD-A9QF-01	NaN	2	0.040516261591491	2	5553.5977
TCGA-LL-A440-01	NaN	0	0.028867619138364	0	1333.7778
TCGA-LL-A441-01	NaN	0	0.035920014224482	0	1400.2991
TCGA-LL-A442-01	NaN	0	0.036817074410704	0	1442.3377
TCGA-LL-A50Y-01	NaN	0	0.038115297843860	0	514.0033
TCGA-LL-A5YL-01	NaN	0	0.038998921781050	0	686.6747
TCGA-LL-A5YM-01	NaN	1	0.027641403779542	1	719.3988
TCGA-LL-A5YN-01	NaN	2	0.025956104212607	2	1198.5371
TCGA-LL-A5YO-01	NaN	-1	0.044466971530044	-1	851.9895
TCGA-LL-A5YP-01	NaN	0	0.035667642208791	0	873.8698
TCGA-LL-A6FP-01	NaN	-1	0.034789721961404	-1	424.3952
TCGA-LL-A6FQ-01	NaN	0	0.033855636964179	0	528.4974
TCGA-LL-A6FR-01	NaN	0	0.037964112191759	0	562.9768
TCGA-LL-A73Y-01	NaN	0	0.037917508056433	0	1192.0385
TCGA-LL-A73Z-01	NaN	-1	0.029995955656029	-1	719.0083
TCGA-LL-A740-01	NaN	0	0.027836303076150	0	1499.3944
TCGA-LL-A7SZ-01	NaN	-1	0.039904998387215	-1	482.23
TCGA-LL-A7T0-01	NaN	1	0.028481593577320	1	1321.0923
TCGA-LL-A8F5-01	NaN	-1	0.043022064275307	-1	485.8342
TCGA-LL-A9Q3-01	NaN	0	0.082822703970490	0	538.3655
TCGA-LQ-A4E4-01	NaN	-1	0.053753592926783	-1	1031.8546
TCGA-MS-A51U-01	NaN	1	0.033741721685920	1	1669.2749
TCGA-OK-A5Q2-01	NaN	0	NaN	0	1060.8596
TCGA-OL-A5D6-01	NaN	-1	NaN	0	859.5592
TCGA-OL-A5D7-01	NaN	-1	NaN	-1	1051.7262
TCGA-OL-A5D8-01	NaN	0	NaN	0	925.9719
TCGA-OL-A5DA-01	NaN	0	NaN	0	867.1276
TCGA-OL-A5RU-01	NaN	0	0.053602096378737	0	1120.9503
TCGA-OL-A5RV-01	NaN	0	0.042197742217254	0	1392.1874
TCGA-OL-A5RW-01	NaN	0	0.050101098016061	0	610.2461
TCGA-OL-A5RX-01	NaN	0	0.043770977221581	0	1081.6855
TCGA-OL-A5RY-01	NaN	0	0.035040490866888	2	728.8481
TCGA-OL-A5RZ-01	NaN	1	0.063362016789804	1	19041.9437
TCGA-OL-A5S0-01	NaN	2	0.017836436096051	2	1325.0539
TCGA-OL-A66H-01	NaN	0	0.033478756060454	0	889.4912
TCGA-OL-A66I-01	NaN	-1	0.030184325758362	-1	726.1346
TCGA-OL-A66J-01	NaN	0	0.030331531185386	0	740.4236
TCGA-OL-A66K-01	NaN	1	0.054124124036947	1	1382.6546
TCGA-OL-A66L-01	NaN	0	0.026310625246693	0	448.7712
TCGA-OL-A66N-01	NaN	0	0.026334651980839	0	474.3403
TCGA-OL-A66O-01	NaN	-1	0.032893504954010	-1	478.4463
TCGA-OL-A66P-01	NaN	0	0.037018563881187	0	535.9712
TCGA-OL-A6VO-01	NaN	1	0.029377971786845	1	1478.8449
TCGA-OL-A6VQ-01	NaN	0	0.072723239145483	0	1467.7806
TCGA-OL-A6VR-01	NaN	0	0.049911923495616	0	1129.6015
TCGA-OL-A97C-01	NaN	0	0.045769065850566	0	1426.0635
TCGA-PE-A5DC-01	NaN	0	NaN	0	1228.0288
TCGA-PE-A5DD-01	NaN	-1	NaN	-1	746.5209
TCGA-PE-A5DE-01	NaN	-1	NaN	-1	859.427
TCGA-PL-A8LV-01	NaN	0	0.032066023980760	0	859.6251
TCGA-PL-A8LX-01	NaN	0	0.046860904883900	0	988.9841
TCGA-PL-A8LY-01	NaN	0	0.045689845134534	0	785.4406
TCGA-PL-A8LZ-01	NaN	0	0.039917868845160	0	1248.2118
TCGA-S3-A6ZF-01	NaN	0	0.026800377130988	0	1627.1353
TCGA-S3-A6ZG-01	NaN	1	0.0268632646926	1	1992.0604
TCGA-S3-A6ZH-01	NaN	1	0.024436720599321	1	1658.4521
TCGA-S3-AA0Z-01	NaN	0	0.086064199205912	0	1966.4269
TCGA-S3-AA10-01	NaN	1	0.108419510273614	1	1845.1723
TCGA-S3-AA11-01	NaN	0	0.041392405088065	0	1173.7006
TCGA-S3-AA12-01	NaN	0	0.039252491441076	0	1166.1022
TCGA-S3-AA14-01	NaN	2	0.038150389783948	2	3540.5561
TCGA-S3-AA15-01	NaN	0	0.077472227367621	0	1075.3341
TCGA-S3-AA17-01	NaN	0	0.024862583627594	0	1773.3926
TCGA-UL-AAZ6-01	NaN	2	0.025357855003496	2	7851.1217
TCGA-UU-A93S-01	NaN	-1	0.076554775599849	2	520.2605
TCGA-V7-A7HQ-01	NaN	0	0.026224548180173	0	574.5764
TCGA-W8-A86G-01	NaN	0	0.045403532403137	0	700.9967
TCGA-WT-AB41-01	NaN	0	0.051517467141702	0	619.0852
TCGA-WT-AB44-01	NaN	-1	0.087866633549528	-1	530.2382
TCGA-XX-A899-01	NaN	0	0.022957985081176	0	1281.4961
TCGA-XX-A89A-01	NaN	-1	0.051836745147773	-1	962.2107
TCGA-Z7-A8R5-01	NaN	0	0.058190970472666	0	551.9219
TCGA-Z7-A8R6-01	NaN	0	0.042546454118872	0	1134.7542

Supplementary Table S7

Gene	DK12 all mutations vs expression of DDR gen	K12 predicted inactivating mutations vs expression of DDR genes		
ATM	0.851524955958678	0.941673879595891		
ATR	0.813568345997468	0.700173082174884		
BRCA1	0.0662678121883283	0.646553641618561		
BRCA2	0.11370901357789	0.548969280873147		
CDK12	0.844024709502402	0.0962412122000874		
CHEK1	0.302047709219828	0.564938257261009		
FANCI	0.150505180110187	0.903503241395654		
MDC1	0.574996745191518	0.00293749285617183		
NEK9	0.0295990718958163	0.33276012954725		
PALB2	0.873133873542608	0.544834312419397		
PTEN	0.18556820318073	0.348993303095084		
RAD51D	0.39029775028547	0.892421357346923		
TERF2	0.579374811250409	0.202610644088523		

Supplementary Table S8

miRNA	P	P.adjusted		
hsa.miR.765	0.0385394204238962	0.443897436084014		
hsa.miR.548c.5p	0.0853676130598789	0.443897436084014		
hsa.miR.4311	0.0951208791608602	0.443897436084014		
hsa.miR.421	0.399708833986005	0.913594449918169		
hsa.miR.548n	0.432271991141654	0.913594449918169		
hsa.miR.3125	0.455353372712088	0.913594449918169		
hsa.miR.2110	0.561053425922274	0.913594449918169		
hsa.miR.4270	0.641965087156667	0.913594449918169		
hsa.miR.193a.3p	0.733129507762471	0.913594449918169		
hsa.miR.548d.5p	0.768372466069205	0.913594449918169		
hsa.miR.548q	0.798144405638823	0.913594449918169		
hsa.miR.519b.3p	0.802132718286832	0.913594449918169		
hsa.miR.519c.3p	0.862578824686899	0.913594449918169		
hsa.miR.548c.3p	0.913594449918169	0.913594449918169		

Supplementary Table S9

ProbeId	Quality_sc	Symbol	Symbol_0	Cytoband	Ensembl_g	Genomic_lo	UCSC_genc	CpG_island	SNPs	miRNAs	Exons	chromosom	start_posit	end_positic	logFC	AveExpr	t	P.Value	adj.P.Val	B
ILMN_17131	Perfect	SMARCA5	SMARCA5	4q31.21c	ENSG00000	chr4:14468	chr4:144680012:144680061:+				21 X 21 21	4	144680012	144680061	0.64897611	0.03542311	3.81828388	0.00013458	0.03997096	0.85386316
ILMN_17211	Perfect	USP10	USP10	16q24.1a	ENSG00000	chr16:8337	chr16:83370108:83370157:+				14 11 X 13	16	83370108	83370157	0.60293138	0.01959130	3.54737737	0.00038952	0.05784035	-0.0793464
ILMN_16877	Perfect	RAD17	RAD17	5q13.2a	ENSG00000	chr5:68745	chr5:68745789:68745838:+				5 X 5 5 5 5	5	68745789	68745838	0.54876301	0.15438503	3.26493745	0.00112530	0.12510006	-1.0025443
ILMN_17557	Perfect	RIF1	RIF1	2q23.3b-q2	ENSG00000	chr2:15203	chr2:152030638:152030687:+				30 X 29 30	2	152030638	152030687	0.53166678	0.09695682	3.12808840	0.00176071	0.13072395	-1.3883565
ILMN_22231	Perfect****	SMARCA5	SMARCA5	4q31.21c	ENSG00000	chr4:14469	chr4:144690689:144693752:+				23-24 X 23-	4	144690689	144693752	0.51719152	-0.0223862	3.04292256	0.00234416	0.13256457	-1.6341498
ILMN_16831	Perfect	FANCC	FANCC	9q22.32b	ENSG00000	chr9:96901	chr9:96901275:96901324		rs56199232(39)		1 X X X 1 X	9	96901275	96901324	-0.4943388	0.01765518	-2.9084675	0.00363401	0.13256457	-1.8924669
ILMN_17410	Perfect	XRCC6	XRCC6	22q13.2a	ENSG00000	chr22:4038	chr22:40387281:40387330		rs61754572(15)		12 10 11 11	22	40387281	40387330	-0.4839191	-0.0148408	-2.8471628	0.00441328	0.13256457	-1.7340346
ILMN_17945	Perfect	SHFM1	SHFM1	7q21.3c	ENSG00000	chr7:96177	chr7:96177135:96177184				X X 6 8 8 X	7	96177135	96177184	-0.4828745	-0.0836943	-2.8410159	0.00449924	0.13256457	-1.8975596
ILMN_17422	Perfect	CCNH	CCNH	5q14.3d	ENSG00000	chr5:86736	chr5:86736432:86736481:-				5 5 X 5 5 5	5	86736432	86736481	-0.4521806	0.05962951	-2.8340009	0.00459918	0.13256457	-2.0837404
ILMN_17357	Perfect	ERCC3	ERCC3	2q14.3d	ENSG00000	chr2:12773	chr2:127731657:127731706:-				1 X 1 X 1 1	2	127731657	127731706	0.46926278	0.05947869	2.76993141	0.00576625	0.13256457	-2.1146478
ILMN_16538	Perfect	ATRIP	ATRIP	3p21.31e	ENSG00000	chr3:48481	chr3:48481919:48481968:+				X X X X X X	3	48481919	48481968	0.46651717	0.03770308	2.74509841	0.00621983	0.13256457	-2.4403408
ILMN_17207	Perfect	UBA1	UBE1	Xp11.3a	ENSG00000	chrX:46935	chrX:46935223:46935272				1 X 1 X	23	46935223	46935272	0.45925818	0.00759520	2.70207251	0.00707146	0.13256457	-2.5499507
ILMN_18068	Perfect	MCM3	MCM3	6p12.2a	ENSG00000	chr6:52237	chr6:52237346:52237395:-				1 X 1 1 1	6	52237346	52237395	-0.4522107	-0.0087419	-2.6782304	0.00746409	0.13256457	-2.6019799
ILMN_18126	Perfect	NEIL1	NEIL1	15q24.2a	ENSG00000	chr15:7343	chr15:73434144:73434193:+				X X 9 X 8 8	15	73434144	73434193	-0.4543936	0.05493231	-2.6758015	0.00745806	0.13256457	-2.6160234
ILMN_21316	Perfect	CLK2	CLK2	1q22a	ENSG00000	chr1:15549	chr1:155499603:155499652:-				1 X 1 1 1 1	1	155499603	155499652	-0.4524184	0.03011722	-2.6619306	0.00777432	0.13256457	-2.6305627
ILMN_18804	Perfect	PTEN	PTEN	10q23.31a		chr10:8971	chr10:89718328:89718377:+				9 X 9 X 9	10	89718328	89718377	0.44231086	0.01105909	2.63785350	0.00834643	0.13256457	-2.7103294
ILMN_17966	Perfect	PARP3	PARP3	3p21.31e		chr3:51957	chr3:51957563:51957612:+				11 11 X X X	3	51957563	51957612	-0.4479334	0.04675695	-2.6543092	0.00904603	0.13256457	-2.7162835
ILMN_18064	Perfect	UBE1	UBE1	Xp11.3a	ENSG00000	chrX:46959	chrX:46959131:46959180:+				26 26 10 X	23	46959131	46959180	0.44202674	0.07826955	2.62917806	0.00920700	0.13256457	-2.8013844
ILMN_23636	Perfect	RBBP8	RBBP8	18q11.2b	ENSG00000	chr18:1885	chr18:18856131:18856180:+				17 16 18 18	18	18856131	18856180	-0.4403943	-0.0610729	-2.6214796	0.00907582	0.13256457	-2.8247069
ILMN_16972	Perfect	RECQL	RECQL	12p12.1e	ENSG00000	chr12:2151	chr12:21519061:21519110:-				X X X X X X	12	21519061	21519110	-0.4349612	0.06398323	-2.5884233	0.00993773	0.13256457	-2.9196988
ILMN_17704	Perfect	ATRIP	ATRIP	3p21.31e	ENSG00000	chr3:48481	chr3:48481908:48481957:+				12 13 X X X	3	48481908	48481957	-0.4391503	0.04688818	-2.5837611	0.00977634	0.13256457	-2.8424205
ILMN_17985	Perfect	HLTF	HLTF	3q24f	ENSG00000	chr3:15023	chr3:150231956:150232005:-				1 X 1 1 1 1	3	150231956	150232005	0.43889138	0.06718686	2.58223972	0.00981959	0.13256457	-2.8461010
ILMN_17416	Perfect	UNG	UNG	12q24.11a	ENSG00000	chr12:1080	chr12:108020880:108020929:+				1 X 1 1 1 X	12	108020880	108020929	0.43127796	0.04009494	2.53744261	0.01107812	0.14042223	-2.9533625
ILMN_22776	Perfect	ERCC1	ERCC1	19q13.32a	ENSG00000	chr19:5060	chr19:50604721:50604822:-				X X 1 X X X	19	50604721	50604822	-0.4253182	0.06094265	-2.5028136	0.01239977	0.14360011	-3.0360108
ILMN_21823	Perfect	SMC3	SMC3	10q25.2a	ENSG00000	chr10:1123	chr10:112353997:112354046:+				29 X 29 29	10	112353997	112354046	0.41841175	-0.0186852	2.46310158	0.01368695	0.14880275	-3.1306209
ILMN_17929	Perfect	ESCO2	ESCO2	8p21.1e	ENSG00000	chr8:27717	chr8:27717895:27717944:+				X X X X X X	8	27717895	27717944	0.40963682	-0.0677536	2.41011901	0.01595172	0.16221778	-3.2479723
ILMN_23730	Perfect	LIG4	LIG4	13q33.3b	ENSG00000	chr13:1076	chr13:107657907:107657956:-				1 X 1 1 X X	13	107657907	107657956	-0.3995497	0.00165862	-2.3502710	0.01877393	0.20413237	-3.3801148
ILMN_20694	Perfect	XRCC4	XRCC4	5q14.2b	ENSG00000	chr5:82590	chr5:82590178:82590227:+				5 X 5 X 6	5	82590178	82590227	-0.3819253	-0.0932956	-2.2471360	0.02415264	0.24055462	-3.4706088
ILMN_17501	Perfect	EME1	EME1	17q21.33b	ENSG00000	chr17:4581	chr17:45813455:45813504:+				9 9 9 2 8	17	45813455	45813504	-0.3783340	-5.36E-05	-2.2264315	0.02627108	0.25401480	-3.4469317
ILMN_21709	Perfect	MPG	MPG	16p13.3f	ENSG00000	chr16:7554	chr16:75547:75596:+				4 4 5 X X	16	75547	75596	-0.3776622	0.01766289	-2.2191975	0.02666013	0.25401480	-3.4939087
ILMN_22574	Perfect	RAD51	RAD51	15q15.1b	ENSG00000	chr15:3879	chr15:38798304:38798353:+				6 5 X 6 6 6	15	38798304	38798353	0.37590147	0.07803491	2.21163337	0.02699740	0.25401480	-3.5110980
ILMN_17432	Perfect	ORC5L	ORC5L	7q22.1g-q2	ENSG00000	chr7:10355	chr7:103554164:103554213:-				1 1 X 1 1 1	7	103554164	103554213	-0.3744549	-0.0148827	-2.2031247	0.02755011	0.25401480	-3.6956668
ILMN_17558	Perfect	FEN1	FEN1	11q12.2b	ENSG00000	chr11:6132	chr11:61320359:61320408:+				X 1 2 X 1	11	61320359	61320408	0.37100056	0.09613962	2.18286633	0.02905614	0.25401480	-3.7362551
ILMN_22034	Perfect	MSH2	MSH2	2p21a	ENSG00000	chr2:47656	chr2:47656147:47656196:+		rs63750179		15 16 15-16	2	47656147	47656196	-0.3703097	0.03676631	-2.1827017	0.02907719	0.25401480	-3.7445478
ILMN_22536	Perfect	PRKDC	PRKDC	8q11.21a-q	ENSG00000	chr8:48855	chr8:48855729:48855778:-				X X X X 8 8	8	48855729	48855778	0.36946209	0.02960776	2.17033144	0.02993443	0.25401480	-3.7699474
ILMN_21629	Perfect	CLK2	CLK2	1q22a	ENSG00000	chr1:15549	chr1:155499380:155499429:-				1 X 1 1 1 1	1	155499380	155499429	-0.3665834	0.08372171	-2.1568123	0.03102612	0.25596553	-3.7989905
ILMN_17888	Perfect****	MLH1	MLH1	3p22.2b	ENSG00000	chr3:37065	chr3:37065502:37065551		rs63750...		7 7	3	37065502	37065551	-0.3592909	-0.0337630	-2.1138366	0.03468050	0.27113253	-3.8748347
ILMN_16856	Perfect	PCNA	PCNA	20p12.3c	ENSG00000	chr20:5055	chr20:5055200:5055249:-				X X 1 X X	20	5055200	5055249	0.35782807	0.04380317	2.10760139	0.03516736	0.27113253	-3.9162206
ILMN_17024	Perfect	TOP3A	TOP3A	17p11.2f	ENSG00000	chr17:1811	chr17:18118488:18118537:-				X X 17 17	17	18118488	18118537	0.35779397	0.07557575	2.09020047	0.03644376	0.27113253	-3.9417008
ILMN_21923	Perfect	ERCC4	ERCC4	16p13.12a	ENSG00000	chr16:1394	chr16:13949958:13950007:+		rs9896633(16)		11 11 11 X	16	13949958	13950007	0.35512739	0.10090213	2.09891480	0.03583855	0.27113253	-3.9199098
ILMN_17011	Perfect	PTEN	PTEN	10q23.31a	ENSG00000	chr10:8971	chr10:89716566:89716615:+				X X X	10	89716566	89716615	-0.3551362	-0.0399413	-2.0660735	0.03828880	0.27788880	-3.9820040
ILMN_16761	Perfect	DNMT3A	DNMT3A	2p23.3c	ENSG00000	chr2:25358	chr2:25358150:25358199:-				1 X 1 1 1 1	2	25358150	25358199	-0.3580799	-0.3503200	-2.0616027	0.03861255	0.27788880	-3.9777540
ILMN_17400	Perfect	MSH3	MSH3	5q14.1b	ENSG00000	chr5:79949	chr5:79949202:79949251:+				6 X X X X	5	79949202	79949251	0.34821915	0.07649447	2.04876506	0.04094919	0.27915595	-4.0151395
[illegible]																				
ILMN_17210	Perfect	DUT	DUT	15q21.1d	ENSG00000	chr15:4641	chr15:4641	chr15:46410477:46411943			1 1 1 X X X	15	46411003	46411052	0.05206079	0.10471933	0.30630230	0.75937605	0.88260274	-5.9206898
ILMN_16778	Perfect****	PMS2	PMS2	7p22.1b	ENSG00000	chr7:60151	chr7:60121	chr7:6014922:6015781			X 14-15 14-	7	6015154	6015185	-0.0514727	0.11028323	-0.3028428	0.76201119	0.88260274	-5.9216754
ILMN_22335	Perfect	POLD3	POLD3	11q13.4c	ENSG00000	chr11:7403	chr11:74031191:74031240:+				12 12 12 4	11	74031191	74031240	0.05142183	0.06987953	0.30254295	0.76223974	0.88260274	-5.9217603
ILMN_17066	Perfect	OGG1	OGG1	3p25.3c	ENSG00000	chr3:97676	chr3:9767666:9767715:+				X X X X X X	3	9767666	9767715	0.05139283	0.04251806	0.30237232	0.76236979	0.88260274	-5.9218085
ILMN_17094	Perfect	MRE11A	MRE11A	11q21b	ENSG00000	chr11:9381	chr11:93818650:93818699:-				5 X 5 5 5 5	11	93818650	93818699	-0.0510887	0.06628227	-0.3005834	0.76373368	0.88260274	-5.9223130
ILMN_17022	Perfect	POLI	POLI	18q21.2c	ENSG00000	chr18:5007	chr18:50074751:50074800:+				10 X X 10 10	18	50074751	50074800	0.04889324	0.12868277	0.28766588	0.77360397	0.89054410	-5.9258668
ILMN_17457	Perfect	POLL	POLL	10q24.32a	ENSG00000	chr10:1033	chr10:103328873:103328922:-				1 1 1 1 X 1	10	103328873	103328922	-0.0455123	0.13572002	-0.2677742	0.78887441	0.90302304	-5.9310340
ILMN_16523	Perfect	ERCC1	ERCC1	19q13.32a	ENSG00000	chr19:5061	chr19:5061	chr19:50618501:50619031			8 X 8	19	50618483	50618532	0.04514797	0.18067256	0.26563038	0.79052522	0.90302304	-5.9315688
ILMN_17058	Perfect	NAP1L1	NAP1L1	12q21.2a	ENSG00000	chr12:7472	chr12:74728257:74728306:-				X 1 1 X X 1	12	74728257	74728306	0.04339260	-0.0097575	0.25530262	0.79849066	0.90655212	-5.9340849
ILMN_17936	Perfect	UBE2N	UBE2N	12q22b	ENSG00000	chr12:9232	chr12:92326395:92326444:-				1 X 1 X X	12	92326395	92326444	-0.0431222	-0.0930116	-0.2537119	0.79971938	0.90655212	-5.9344636
ILMN_21019	Perfect	POLG	POLG	15q26.1a	ENSG00000	chr15:8766	chr15:87661727:876627		rs62640038(10)		X X X 2-3 3-	15	87662776	87662780	-0.0412953	0.08025288	-0.2429631	0.80803517	0.91249599	-5.9369604
ILMN_23795	Perfect	CDC14B	CDC14B	9q22.33a	ENSG00000	chr9:98302715:98302764:-					1 1 1 1 1 1	9	98302715	98302764	-0.0391220	-0.0056616	-0.2301768	0.81795552	0.91605974	-5.9397897
ILMN_17575	Perfect	MPG	MPG	16p13.3f	ENSG00000	chr16:6707	chr16:67071:67120:+				1 X	16	67071	67120	-0.0387892	0.02048847	-0.2282187	0.81947735	0.91605974	-5.9402095
ILMN_16827	Perfect****	FANCA	FANCA	16q24.3b	ENSG00000	chr16:8839	chr16:88393520:883971		rs34354932(19) rs55660		3-4 35-36 2-	16	88397168	88397189	0.03857794	-0.0674005	0.22697530	0.82044408	0.91605974	-5.9404742
ILMN_20832	Perfect	MNAT1	MNAT1	14q23.1c	ENSG00000	chr14:6050	chr14:60504811:60504860:+				8 7 X 8 X X	14	60504811	60504860	0.03713232	0.03659561	0.21846989	0.82706410	0.91999266	-5.9422461
ILMN_21147	Perfect	NEIL3	NEIL3	4q34.3a	ENSG00000	chr4:17852	chr4:178520545:178520594:+				10 X 10 10	4	178520545	178520594	-0.0357300	0.09102706	-0.2102195	0.83349739	0.92368927	-5.9439002
ILMN_16605	Perfect	LIG3	LIG3	17q12a	ENSG00000	chr17:3035	chr17:30356015:30356064:+				20 20 X	17	30356015	30356064	0.03360891	-0.0071604	0.19773976	0.84324966	0.92784525	-5.9462813
ILMN_17515	Perfect	RAD23A	RAD23A	19p13.13c	ENSG00000	chr19:1292	chr19:12925269:129253		rs1803719(10) rs455002		9 8 9 9 9 9	19	12925269	12925318	0.03339770	-0.0588998	0.19649707	0.84422209	0.92784525	-5.9465104
ILMN_16931	Perfect	MLH3	MLH3	14q24.3b	ENSG00000	chr14:7455	chr14:74553065:745531		rs61980781(46) rs61980		1 1 X X 1 X	14	74553065	74553114	-0.0328771	-0.0192960	-0.1934343	0.84661974	0.92784525	-5.9470689
ILMN_22772	Perfect	ATR	ATR	3q23d	ENSG00000	chr3:14365	chr3:143650820:143650		rs13062411(26)		1 1 X 1 1 1	3	143650820	143650869	0.03121207	0.01263906	0.18363781	0.85429850	0.93281859	-5.9487965
ILMN_17290	Perfect****	MSH6	MSH6	2p16.3d	ENSG00000	chr2:47887	chr2:47887292:4788746		rs61748086(13)		9-10 X 9-10	2	47887292	47887294	0.02817617	-0.0196425	0.16577593	0.86833411	0.94467117	-5.9517154
ILMN_16698	Perfect	CHAF1A	CHAF1A	19p13.3d	ENSG00000	chr19:4394	chr19:4394296:4394345:+				15 X	19	4394296	4394345	-0.0246223	-0.0403954	-0.1448666	0.88481690	0.95432221	-5.9547531
ILMN_17227	Perfect	UNG	UNG	12q24.11a	ENSG00000	chr12:1080	chr12:1080	chr12:108019647:108020814			1 X 1 1 1 1	12	108020498	108020547	-0.0243607	0.08837564	-0.1433275	0.88603218	0.95432221	-5.9549606
ILMN_17579	Perfect	INO80D	FLJ20309	2q33.3b	ENSG00000	chr2:20657	chr2:206577075:206577124:-				1 X 1	2	206577075	206577124	-0.0241858	0.02897497	-0.1422985	0.88684488	0.95432221	-5.9550980
ILMN_18103	Perfect	ATR	ATR	3q23d	ENSG00000	chr3:14376	chr3:143764412:143764461:-				44 X 44 44	3	143764412	143764461	0.02163828	0.04453274	0.12730995	0.89869570	0.96358348	-5.9569879
ILMN_23173	Perfect	APTX	APTX	9p13.3e	ENSG00000	chr9:32962	chr9:32962785:32962834:-				1 1 1 1 1 1	9	32962785	32962834	-0.0189828	0.04409947	-0.1116868	0.91107227	0.96911189	-5.9587342
ILMN_17190	Perfect	EXO1	EXO1	1q43e	ENSG00000	chr1:24007	chr1:240079091:240079140:+				3 X 3	1	240079091	240079140	0.01847587	0.01836791	0.10870377	0.91343798	0.96911189	-5.9590417
ILMN_17087	Perfect	RAD50	RAD50	5q31.1b	ENSG00000	chr5:13193	chr5:131939457:131939506:+				3 X 3 3 3 3	5	131939457	131939506	0.01843241	0.03623840	0.10844802	0.91364084	0.96911189	-5.9590676
ILMN_17136	Perfect	ATM	ATM	11q22.3c	ENSG00000	chr11:1075	chr11:1075	chr11:107598421:107599179			1 1 1	11	107598979	107599028	-0.0172592	-0.0483040	-0.1015458	0.91911764	0.97145174	-5.9597455
ILMN_23095	Perfect	RDM1	RDM1	17q12b	ENSG00000	chr17:3127	chr17:31273789:31275766:-				3-4 1-2 1-2	17	31275721	31275766	0.01653797	-0.1351928	0.09730204	0.92248701	0.97155547	-5.9601402
ILMN_17540	Perfect****	FANCL	FANCL	2p16.1b	ENSG00000	chr2:58244	chr2:58243699:58244107:-				5-6 5-6 X X	2	58244073	58244107	0.01504227	0.03113155	0.08850199	0.92947813	0.97545938	-5.9609049
ILMN_17204	Perfect****	HELQ	HEL308	4q21.23a	ENSG00000	chr4:84561740:84561746:-,chr4:84558341:84558383:-					3-4 X X 3-4	4	84561740	84561746	-0.0136936	-0.0090309	-0.0805670	0.93578665	0.97862195	-5.9615323
ILMN_20434	Perfect	FANCE	FANCE	6p21.31c	ENSG00000	chr6:35542	chr6:35542731:35542780:+				10 X 10 X 10	6	35542731	35542780	-0.0113662	-0.1072261	-0.0668740	0.94668230	0.98654261	-5.9624765
ILMN_16533	Perfect	RECQL5	RECQL5	17q25.1c	ENSG00000	chr17:7115	chr17:71158861:71158910:-				2 13 1 X X X	17	71158861	71158910	0.00926941	0.08923823	0.05453709	0.95650752	0.99329627	-5.9631770
ILMN_16802	Perfect	GEN1	GEN1	2p24.2b	ENSG00000	chr2:17826	chr2:17826349:17826398:+				X 14 X 13 13	2	17826349	17826398	-0.0070083	0.03305587	-0.0412341	0.96710940	0.99337009	-5.9637728
ILMN_18083	Perfect****	PMS2	PMS2CL	7p22.1a	ENSG00000	chr7:59794	chr7:6757590:6757639:+				1 X 6 6 X 1	7	5979465	5979514	0.00646767	-0.0223678	0.03805292	0.96964567	0.99337009	-5.9638908
ILMN_16786	Perfect	USP1	USP1	1p31.3d	ENSG00000	chr1:62674	chr1:62674	chr1:62674239:62676255			1 X	1	62674750	62674799	-0.0064604	-0.0174499	-0.0380105	0.96967946	0.99337009	-5.9638923
ILMN_17678	Perfect	POLB	POLB	8p11.21a	ENSG00000	chr8:42348	chr8:42348293:42348342:+				14 13 14 X	8	42348293	42348342	-0.0064012	0.18002218	-0.0376620	0.96995733	0.99337009	-5.9639046
ILMN_17046	Perfect	OBFC2B	OBFC2B	12q13.2c	ENSG00000	chr12:5490	chr12:54909410:54909459:+				X X 7 7 7 6	12	54909410	54909459	-0.0048998	-0.0491623	-0.0288286	0.97700139	0.99645814	-5.9641793
ILMN_18158	Perfect****	ERCC2	ERCC2	19q13.32a	ENSG00000	chr19:5054	chr19:50546809:50547345:-				X 1-2 1-2 1-	19	50547307	50547345	0.00432847	-0.0371263	0.02546679	0.97968275	0.99645814	-5.9642647
ILMN_17695	Perfect	PRKDC	PRKDC	8q11.21a-q	ENSG00000	chr8:48848	chr8:48848325:48848374:-				X X X X X 1	8	48848325	48848374	0.00358899	-0.0003825	0.02111604	0.98315318	0.99657507	-5.9643595
ILMN_17394	Perfect	GTF2H5	GTF2H5	6q25.3d	ENSG00000	chr6:15853	chr6:158533002:158533051:+				X X 3 2 2 3	6	158533002	158533051	-0.0023473	0.03282262	-0.0138109	0.98898084	0.99849761	-5.9644788
ILMN_22600	Perfect	APTX	APTX	9p13.3e	ENSG00000	chr9:32979	chr9:32979915:32979964:-				7 4 7 X 7 7	9	32979915	32979964	0.00175240	0.03512973	0.01031035	0.99177372	0.99849761	-5.9645183
ILMN_17921	Perfect****	ERCC8	ERCC8	5q12.1b	ENSG00000	chr5:60236	chr5:60235282:6023640		rs1644460(17)		X X X X X X	5	60236376	60236406	-0.0003427	0.13341004	-0.0020167	0.99839085	0.99935901	-5.9645661
ILMN_17711	Perfect	EME2	EME2	16p13.3e	ENSG00000	chr16:1766	chr16:1766167:1766216:+				8 X 8 X	16	1766167	1766216	-0.0001365	-0.0256301	-0.0008033	0.99935901	0.99935901	-5.9645677

	CDK12 absent and intermediate (0, 2-6) *No. of cases (%)*	**CDK12 Positive (7/8)** *No. of cases (%)*	**p-value**
Unselected Series			
BRCA1 (n = 544)			0.7537
Negative	189 (44.3)	50 (42.4)	
Positive	238 (55.7)	68 (57.6)	
PARP1 cleaved (n = 520)			0.2981
Negative	66 (16.1)	13 (11.8)	
Positive	344 (83.9)	97 (89.2)	
PARP1 non-cleaved (n = 541)			0.3436
Negative	189 (44.6)	46 (39.3)	
Positive	235 (55.4)	71 (60.7)	
ATR (n = 553)			0.0413
Negative	236 (53.0)	45 (41.7)	
Positive	209 (47.0)	63 (58.3)	
APE1 (n = 275)			0.8505
Negative	38 (17.9)	10 (15.8)	
Positive	174 (82.1)	53 (84.1)	
Ku70/Ku80 (n = 446)			0.2654
Negative	56 (16.2)	11 (11.0)	

Supplementary Table S10

	CDK12 absent and intermediate (0, 2-6)	CDK12 Positive (7/8)	p-value
	No. of cases (%)	No. of cases (%)	
Unselected Series			
BRCA1 (n = 544)			
Negative	189 (44.3)	50 (42.4)	0.7537
Positive	238 (55.7)	68 (57.6)	
PARP1 cleaved (n = 520)			
Negative	66 (16.1)	13 (11.8)	0.2981
Positive	344 (83.9)	97 (89.2)	
PARP1 non-cleaved (n = 541)			
Negative	189 (44.6)	46 (39.3)	0.3436
Positive	235 (55.4)	71 (60.7)	
ATR (n = 553)			
Negative	236 (53.0)	45 (41.7)	0.0413
Positive	209 (47.0)	63 (58.3)	
APE1 (n = 275)			
Negative	38 (17.9)	10 (15.8)	0.8505
Positive	174 (82.1)	53 (84.1)	
Ku70/Ku80 (n = 446)			
Negative	56 (16.2)	11 (11.0)	0.2654
Positive	290 (83.8)	89 (89.0)	
DNsA PK (n = 494)			
Negative	72 (18.4)	12 (11.7)	0.1394
Positive	319 (81.6)	91 (88.3)	
SMC6 cytoplasmic (n = 525)			
Negative	142 (34.2)	33 (29.7)	0.4275
Positive	272 (65.7)	78 (70.3)	
SMC6 nuclear (n = 525)			
Negative	154 (37.2)	34 (30.6)	0.2209
Positive	260 (49.5)	77 (69.4)	
GammaH2AX (n = 473)			
Negative	107 (28.6)	22 (22.2)	0.2532
Positive	267 (71.3)	77 (77.8)	
TP53 (n = 572)			
Negative	290 (66.9)	80 (57.6)	0.0524
Positive	143 (33.0)	59 (42.4)	
CHEK1 cytoplasmic (n = 473)			
Negative	169 (45.7)	44 (42.7)	0.6546
Positive	201 (54.3)	59 (57.3)	
CHEK1 nuclear (n = 643)			
Negative	475 (88.1)	87 (83.7)	0.20006
Positive	64 (11.8)	17 (16.3)	
CHEK2 (n = 514)			
Negative	202 (49.7)	63 (58.3)	0.1294
Positive	204 (50.2)	45 (41.7)	
Triple Negative Breast Cancer			
BRCA1 (n = 102)			
Negative	64 (72.2)	8 (57.1)	0.3425
Positive	24 (27.8)	6 (42.9)	
PARP1 cleaved (n = 99)			
Negative	19 (21.8)	4 (33.3)	0.4658
Positive	68 (79.2)	8 (66.7)	
PARP1 non-cleaved (n = 102)			
Negative	36 (40.4)	5 (38.5)	1
Positive	53 (59.6)	8 (61.5)	
ATR (n = 108)			
Negative	50 (52.6)	7 (53.8)	1
Positive	45 (47.4)	6 (46.2)	
APE1 (n = 46)			
Negative	4 (25.0)	1 (11.1)	1
Positive	33 (75.0)	8 (88.9)	
Ku70/Ku80 (n = 82)			
Negative	17 (23.6)	0 (0.0)	0.1119
Positive	55 (76.4)	10 (100.0)	
DNsA PK (n = 98)			
Negative	15 (18.1)	3 (25.0)	1
Positive	68 (81.9)	12 (75.0)	
SMC6 cytoplasmic (n = 31)			
Negative	38 (40.0)	3 (23.1)	0.1606
Positive	57 (60.0)	13 (76.9)	
SMC6 nuclear (n = 101)			
Negative	43 (50.6)	6 (37.5)	0.4183
Positive	42 (49.4)	10 (62.5)	
GammaH2AX (n = 95)			
Negative	30 (37.0)	4 (28.6)	0.7639
Positive	51 (63.0)	10 (71.4)	
TP53 (n = 102)			
Negative	38 (63.2)	7 (41.2)	0.7912
Positive	64 (36.8)	10 (58.8)	
CHEK1 cytoplasmic (n = 85)			
Negative	28 (37.3)	3 (30.0)	0.7403
Positive	47 (62.7)	7 (70.0)	
CHEK1 nuclear (n = 86)			
Negative	71 (82.6)	9 (81.8)	0.1679
Positive	4 (11.4)	2 (18.2)	
CHEK2 (n = 32)			
Negative	62 (68.4)	9 (69.2)	0.7638
Positive	41 (31.6)	4 (30.8)	

Positive	290 (83.8)	89 (89.0)	
DNsA PK (n = 494)			0.1394
Negative	72 (18.4)	12 (11.7)	
Positive	319 (81.6)	91 (88.3)	
SMC6 cytoplasmic (n = 525)			0.4275
Negative	142 (34.2)	33 (29.7)	
Positive	272 (65.7)	78 (70.3)	
SMC6 nuclear (n = 525)			0.2209
Negative	154 (37.2)	34 (30.6)	
Positive	260 (49.5)	77 (69.4)	
GammaH2AX (n = 473)			0.2532
Negative	107 (28.6)	22 (22.2)	
Positive	267 (71.3)	77 (77.8)	
TP53 (n = 572)			0.0524
Negative	290 (66.9)	80 (57.6)	
Positive	143 (33.0)	59 (42.4)	
CHEK1 cytoplasmic (n = 473)			0.6546
Negative	169 (45.7)	44 (42.7)	
Positive	201 (54.3)	59 (57.3)	
CHEK1 nuclear (n = 643)			0.20006
Negative	475 (88.1)	87 (83.7)	

Positive	64 (11.8)	17 (16.3)	
CHEK2 (n = 514)			0.1294
Negative	202 (49.7)	63 (58.3)	
Positive	204 (50.2)	45 (41.7)	
Triple Negative Breast Cancer			
BRCA1 (n = 102)			0.3425
Negative	64 (72.2)	8 (57.1)	
Positive	24 (27.8)	6 (42.9)	
PARP1 cleaved (n = 99)			0.4658
Negative	19 (21.8)	4 (33.3)	
Positive	68 (79.2)	8 (66.7)	
PARP1 non-cleaved (n = 102)			1.000
Negative	36 (40.4)	5 (38.5)	
Positive	53 (59.6)	8 (61.5)	
ATR (n = 108)			1.000
Negative	50 (52.6)	7 (53.8)	
Positive	45 (47.4)	6 (46.2)	
APE1 (n = 46)			1.000
Negative	4 (25.0)	1 (11.1)	
Positive	33 (75.0)	8 (88.9)	
Ku70/Ku80 (n = 82)			0.1119

Negative	17 (23.6)	0 (0.0)	
Positive	55 (76.4)	10 (100.0)	
DNsA PK (n = 98)			1.000
Negative	15 (18.1)	3 (25.0)	
Positive	68 (81.9)	12 (75.0)	
SMC6 cytoplasmic (n = 31)			0.1606
Negative	38 (40.0)	3 (23.1)	
Positive	57 (60.0)	13 (76.9)	
SMC6 nuclear (n = 101)			0.4183
Negative	43 (50.6)	6 (37.5)	
Positive	42 (49.4)	10 (62.5)	
GammaH2AX (n = 95)			0.7639
Negative	30 (37.0)	4 (28.6)	
Positive	51 (63.0)	10 (71.4)	
TP53 (n = 102)			0.7912
Negative	38 (63.2)	7 (41.2)	
Positive	64 (36.8)	10 (58.8)	
CHEK1 cytoplasmic (n = 85)			0.7403
Negative	28 (37.3)	3 (30.0)	
Positive	47 (62.7)	7 (70.0)	
CHEK1 nuclear (n = 86)			0.1679

Negative	71 (82.6)	9 (81.8)	
Positive	4 (11.4)	2 (18.2)	
CHEK2 (n = 32)			0.7638
Negative	62 (68.4)	9 (69.2)	
Positive	41 (31.6)	4 (30.8)	