**Clinical Cancer Research**

# Homologous Recombination Deficiency (HRD) Score Predicts Response to Platinum-Containing Neoadjuvant Chemotherapy in Patients with Triple-Negative Breast Cancer

Melinda L. Telli[1], Kirsten M. Timms[2], Julia Reid[2], Bryan Hennessy[3], Gordon B. Mills[3], Kristin C. Jensen[1], Zoltan Szallasi[4,5,6], William T. Barry[6,7], Eric P. Winer[6,7], Nadine M. Tung[6,8], Steven J. Isakoff[6,9], Paula D. Ryan[9], April Greene-Colozzi[7], Alexander Gutin[2], Zaina Sangale[2], Diana Iliev[2], Chris Neff[2], Victor Abkevich[2], Joshua T. Jones[2], Jerry S. Lanchbury[2], Anne-Renee Hartman[2], Judy E. Garber[6,7], James M. Ford[1], Daniel P. Silver[6,7], and Andrea L. Richardson[6,7,10]

## Abstract

**Purpose:** *BRCA1/2*-mutated and some sporadic triple-negative breast cancers (TNBC) have DNA repair defects and are sensitive to DNA-damaging therapeutics. Recently, three independent DNA-based measures of genomic instability were developed on the basis of loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST).

**Experimental Design:** We assessed a combined homologous recombination deficiency (HRD) score, an unweighted sum of LOH, TAI, and LST scores, in three neoadjuvant TNBC trials of platinum-containing therapy. We then tested the association of HR deficiency, defined as HRD score $\geq 42$ or *BRCA1/2* mutation, with response to platinum-based therapy.

**Results:** In a trial of neoadjuvant platinum, gemcitabine, and iniparib, HR deficiency predicted residual cancer burden score of 0 or I (RCB 0/I) and pathologic complete response (pCR;

OR = 4.96, $P = 0.0036$; OR = 6.52, $P = 0.0058$). HR deficiency remained a significant predictor of RCB 0/I when adjusted for clinical variables (OR = 5.86, $P = 0.012$). In two other trials of neoadjuvant cisplatin therapy, HR deficiency predicted RCB 0/I and pCR (OR = 10.18, $P = 0.0011$; OR = 17.00, $P = 0.0066$). In a multivariable model of RCB 0/I, HR deficiency retained significance when clinical variables were included (OR = 12.08, $P = 0.0017$). When restricted to *BRCA1/2* nonmutated tumors, response was higher in patients with high HRD scores: RCB 0/I $P = 0.062$, pCR $P = 0.063$ in the neoadjuvant platinum, gemcitabine, and iniparib trial; RCB 0/I $P = 0.0039$, pCR $P = 0.018$ in the neoadjuvant cisplatin trials.

**Conclusions:** HR deficiency identifies TNBC tumors, including *BRCA1/2* nonmutated tumors more likely to respond to platinum-containing therapy. *Clin Cancer Res; 22(15); 3764–73. ©2016 AACR.*

## Introduction

Triple-negative breast cancers (TNBC) lack expression of estrogen and progesterone receptors and overexpression or amplification of the HER2/neu oncogene, and are therefore not amenable to therapy directed at these targets. Sporadic (*BRCA1*

and *BRCA2* germline wild-type) TNBCs share many characteristics with *BRCA1* mutation–associated cancers, including a basal-like gene expression profile, frequent p53 mutations, and a high burden of genomic aberrations such as loss of heterozygosity (1–7). *BRCA1* or *BRCA2* (*BRCA1/2*)-mutated cancers have defects in several aspects of DNA repair including homologous recombination deficiency (HRD; refs. 1, 8). *BRCA1/2* mutation–associated cancers have been shown to have increased sensitivity to DNA crosslinking agents such as platinum salts (9). A number of studies have suggested that some sporadic TNBC may bear substantial similarities to *BRCA1/2*-mutated cancers, including harboring DNA repair defects that might predispose to platinum sensitivity (1, 10, 11). Confirming this concept, two neoadjuvant clinical trials have demonstrated that a subset of sporadic, non-*BRCA1/2*–mutated TNBC are sensitive to single-agent platinum chemotherapy (12, 13). Furthermore, several recent randomized trials have shown improvement in pathologic response with the addition of platinum to standard-of-care neoadjuvant regimens for TNBC but at the cost of increased toxicity (14–16). A predictive biomarker for platinum sensitivity would be helpful to personalize the use of platinum agents, restricting their use to those who would benefit while avoiding unnecessary toxicity for those who would not.

[1]Stanford University School of Medicine, Stanford, California. [2]Myriad Genetics Inc., Salt Lake City, Utah. [3]University of Texas MD Anderson Cancer Center, Houston, Texas. [4]Denmark Technical University, Lyngby, Denmark. [5]Children's Hospital Boston, Boston, Massachusetts. [6]Harvard Medical School, Boston, Massachusetts. [7]Dana-Farber Cancer Institute, Boston, Massachusetts. [8]Beth Israel Deaconess Medical Center, Boston, Massachusetts. [9]Massachusetts General Hospital, Boston, Massachusetts. [10]Brigham and Women's Hospital, Boston, Massachusetts.

**Corresponding Author:** Daniel P. Silver, Dana-Farber Cancer Institute, 450 Brookline Ave, SM 868B, Boston, MA 02215. Phone: 617-582-8485; Fax: 617-632-4381; E-mail: Daniel_Silver@DFCI.Harvard.Edu

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## Translational Relevance

Clinical trials in TNBC have shown sensitivity to platinum agents and an increase in pathologic response with the addition of platinum to standard neoadjuvant chemotherapy. Not all patients benefit, however, and adding a platinum agent to standard combination chemotherapy increases the toxicity of treatment. A test that is performed on a pretreatment biopsy that determines the likelihood of response to platinum agents would be useful to identify patients who are most likely to benefit from that treatment, and spare others the added toxicity. Here we show that HR deficiency, defined as HRD score $\geq 42$ and/or BRCA1/2 mutation, predicts the likelihood of response to neoadjuvant platinum-containing therapy.

Recently, three independent DNA-based measures of genomic instability reflecting underlying tumor homologous recombination DNA repair deficiency have been developed on the basis of loss of heterozygosity (LOH; ref. 17), telomeric allelic imbalance (TAI; ref. 18), and large-scale state transitions (LST; ref. 19). Although each individual metric is significantly associated with BRCA1/2 status, the combination of the three scores performed best at distinguishing homologous recombination deficient from nondeficient tumors (20, 21). We have previously shown that the homologous recombination deficiency loss of heterozygosity (HRD-LOH) score is significantly associated with favorable response to neoadjuvant platinum-based therapy in a phase II trial of gemcitabine, carboplatin, and iniparib (PrECOG 0105; ref. 22). In addition, in a pooled analysis of two other platinum-based neoadjuvant studies, we showed that the number of regions of TAI, predicted for favorable pathologic response in TNBC, and was also associated with platinum sensitivity in ovarian cancer (18).

In this study, we set out to evaluate the combined homologous recombination deficiency score (HRD score), defined as the unweighted numeric sum of LOH, TAI, and LST and test the predictive power of the HRD score threshold. The HRD score threshold was predefined by analyzing HRD scores in a training cohort of 497 breast and 561 ovarian chemotherapy-naive tumors with known BRCA1/2 status, and identifying a cutoff with 95% sensitivity to detect those tumors with BRCA1/2 mutations or BRCA1 promoter methylation. HR deficiency, defined as HRD score $\geq 42$ and/or tumor BRCA1/2 mutation, was tested for its ability to identify which tumors responded to neoadjuvant platinum-containing chemotherapy in patients with TNBC.

The PrECOG 0105 study included 93 stage I–IIIA (T $\geq 1$ cm) triple-negative and/or BRCA1/2 mutation–associated breast cancer patients, treated with either 4 or 6 cycles of carboplatin, gemcitabine, and iniparib in the neoadjuvant setting. The two cisplatinum neoadjuvant studies (Cisplatin-1 and Cisplatin-2) enrolled 79 TNBC patients with stage II or III disease. Cisplatin-1 utilized 4 cycles of cisplatin monotherapy in 28 patients (12), whereas Cisplatin-2 added bevacizumab to the same cisplatin backbone in 51 patients (13). As the response rates for the Cisplatin-1 and Cisplatin-2 trials were similar, these trials were pooled for further analysis. In the current study, the PrECOG 0105 cohort and the pooled Cisplatin-1 and Cisplatin-2 trials were analyzed to determine the association of HR deficiency with pathologic response.

## Materials and Methods

### Training set used to establish HRD score threshold

A training set completely independent of Cisplatin-1 (NCT00148694), Cisplatin-2 (NCT00580333), and the PrECOG 0105 (NCT00813956) study cases was assembled using four publicly available or previously published cohorts (497 breast and 561 ovarian cases; refs. 20, 23–25) that included 78 breast and 190 ovarian cancers lacking a functional copy of either BRCA1 or BRCA2 (i.e. BRCA1/2 deficient) based on mutation and methylation data (Supplementary Table S1). Assay methods and sample acquisition for these studies have been previously published (20, 23–25). Specifically, tumors selected as BRCA1/2 deficient had either (i) one deleterious mutation in BRCA1 or BRCA2, with LOH in the wild-type copy (ii) two deleterious mutations in the same gene, or (iii) promoter methylation of BRCA1 with LOH in the wild-type copy. This cohort was used to define a threshold for the HRD score intended to reflect HR-deficient versus HR nondeficient status. The threshold selected was the 5th percentile of HRD scores in tumors lacking a functional copy of BRCA1 or BRCA2 (BRCA1/2 deficient; Supplementary Table S2).

### Description of the clinical studies

PrECOG 0105 was a single-arm phase II study that enrolled stage I–IIIA (T $\geq 1$ cm) triple-negative (ER/PR $\leq 5\%$, HER2-negative) or BRCA1/2 germline mutation–associated breast cancer patients. Patients received gemcitabine 1,000 mg/m$^2$ i.v. on days 1 and 8, carboplatin AUC 2 intravenoulsy on days 1 and 8, and iniparib 5.6 mg/kg i.v. on days 1, 4, 8, and 11 every 21 days. Thirteen patients received 4 cycles of preoperative therapy before the study was amended to enroll 80 patients on the six-cycle regimen. All patients in the four-cycle group completed treatment, although one did not go to surgery as scheduled due to an intercurrent illness. Of the 80 patients in the six-cycle group, 11 discontinued treatment prematurely: five experienced progressive disease, five discontinued due to unacceptable toxicity, and one discontinued due to a protocol violation (patient lost to follow-up and never had surgery). Patients with progression of disease were defined as nonresponders. Patients who discontinued therapy due to toxicity prior to completion of four cycles were excluded (3/5). Patients without pathologic response data were excluded from this analysis.

The two neoadjuvant cisplatin trials enrolled a total of 79 patients with stage II or III TNBC who had tumors greater than 1.5 cm in size, negative for estrogen and progesterone receptors as defined by being less than 1% nuclear staining by IHC, and HER2/Neu 0 or 1+ by IHC, or HER2 nonamplified by FISH (archival core biopsy blocks were available from 70 patients). In Cisplatin-1, patients received cisplatin 75 mg/m$^2$ every 3 weeks for 4 cycles; in Cisplatin-2, patients received the same cisplatin regimen with the addition of bevacizumab 15 mg/kg on day 1 for the first three cycles. For the combined cisplatin trials, one patient did not complete the course of chemotherapy due to progression and was classified as a nonresponder; 4 discontinued study therapy due to toxicity, were classified as missing response, and were excluded from analysis.

### Determination of pathologic response

Pathologic response was assessed centrally in all three trials using the residual cancer burden (RCB) index (26). This index has

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been validated as an independent prognostic marker of distant relapse-free survival in patients with breast cancer treated with neoadjuvant chemotherapy (RCB 0, complete pathologic response; RCB I, minimal residual disease; RCB II, moderate residual disease; and RCB III, extensive residual disease). For this analysis, two dichotomous measures of tumor response were used, RCB 0/I yes versus no and pathologic complete response (pCR) yes versus no. pCR was defined as RCB score 0 and requires no residual invasive or metastatic carcinoma in breast or lymph nodes. "RCB 0/I yes" includes pathologic response classes of pCR or RCB-I; "RCB 0/1 no" includes pathologic responses classes RCB-II or RCB-III.

### Tissue processing

For each patient sample, five to ten 5-μm tissue sections from a pretreatment tumor core biopsy were sent to Myriad Genetics, Inc. and processed in the research laboratory according to the CLIA protocol. DNA extraction from formalin-fixed paraffin-embedded (FFPE) or frozen tumors is described in the Supplementary Materials. For PrECOG 0105, 3 samples could not be processed due to insufficient tumor tissue, leaving 90 sufficient for processing. For the two neoadjuvant cisplatin clinical trials, 17 of 79 patient samples had exhausted tumor blocks or insufficient tumor tissue, thus DNA was extracted from 62 samples.

### Molecular analyses

DNA was analyzed using the recently described next-generation sequencing–based assay to generate genome-wide SNP profiles from which the three components of the HRD score are calculated (20). A custom enrichment panel was developed, which targets 54,091 single-nucleotide polymorphisms (SNP) distributed across the complete human genome. The panel also includes an additional 685 probes targeting the complete coding region of BRCA1 and BRCA2. A detailed description of the panel design and development and the assay process is provided in Timms and colleagues (20).

MIP SNP arrays have been previously described in detail (27). For PrECOG 0105, MIP SNP array data had previously been generated on 55 samples from this study. In 31 samples with HRD scores from both arrays and sequencing, the Pearson correlation was 0.94. The sequencing-based HRD assay was used for molecular data for 60 of the 70 samples in the analysis set and a whole genome MIP array was used to generate data for the remaining 10 where sequencing data were not available (3 with insufficient tissue and 7 where sequencing failed). The sequencing-based HRD assay was used for all of the cisplatin trial cohort samples.

To determine BRCA1/2 mutation status, variant and large rearrangement detection was performed on sequence from BRCA1 and BRCA2. Complete descriptions of the sequence alignment and mutation detection methods are provided in Timms and colleagues (20). Mutations identified were only included in the analysis if classified as deleterious or suspected deleterious based on previously described criteria (28).

To calculate the HRD score for samples analyzed by custom hybridization sequencing assay, reads covering SNP positions were used to generate allelic imbalance profiles as described by Timms and colleagues (20). HRD score was defined as the unweighted sum of LOH, TAI, and LST scores: HRD = LOH + TAI + LST. Details of the individual LOH, TAI, and LST scores, as well as the combined HRD score, are described in the Supplementary Material.

HR deficiency status was determined on the basis of the combination of the dichotomized HRD score using the predefined HRD threshold and tumor BRCA1/2 status (scored as mutated if deleterious or suspected deleterious mutations in BRCA1/2 were present; nonmutated if otherwise, including variants of uncertain significance). HR deficiency was defined as high HRD score (above the HRD threshold, $\geq 42$) and/or mutated tumor BRCA1/2. HR nondeficiency was defined as low HRD score (below the HRD threshold, $< 42$) and nonmutated or failed tumor BRCA1/2 mutation analysis. HR status could not be determined if HRD score analysis failed and tumor BRCA1/2 analysis was negative or failed.

### Analysis cohorts

The PrECOG 0105 trial cohort consisted of 93 patients. Excluding those with insufficient tumor for processing and/or who did not complete at least four cycles of treatment left 86 samples. Eighty-three of 86 (97%) samples generated tumor BRCA1/2 mutation data, and HRD score analysis was successful for 68 of 86 (79%) tumors, which provided 70 of 86 (81%) samples with HR deficiency status and clinical response data for statistical analysis. Of the 90 tumors submitted for molecular assay, 52 were HR deficient including one missing response (58%), 21 were HR nondeficient (23%), and 17 were undetermined (19%; Supplementary Fig. S1A).

The combined cisplatin trials cohort consisted of 79 patients, of which 17 had insufficient tumor for processing. Fifty-three of 62 (85%) passed BRCA1/2 mutation screening, HRD score analysis was successful for 51 of 62 (82%), and HR deficiency status was determined for 53 of 62 (85%). Of the 62 tumors subjected to molecular assay, 31 were HR deficient including 2 missing response (50%), 22 were nondeficient including 1 missing response (35%), and 9 were undetermined (15%; Supplementary Fig. S1B). After removing the three samples with missing response data, there were 50 samples evaluable for statistical analysis of HR deficiency and response. The combined cisplatin cohort was not used in the development of the HRD score, HRD threshold, or any of the individual components of the HRD score (LOH, TAI, LST), but were the first two cohorts in which TAI was tested. As such, this cohort offers an independent test of the HRD score threshold and the HR deficiency predictor.

### Statistical analysis

For the PrECOG 0105 cohort, statistical analysis was performed on the set of 70 samples with HR deficiency status and response or on nested subsets (68 had HRD scores; 68 had BRCA1/2 mutation screening of which 22/68 had BRCA1/2 mutations identified; 66 had HRD scores and BRCA1/2 mutation screening of which 46/66 were BRCA1/2 wild-type). For the cisplatin trials cohort, analysis was performed on the set of 50 samples with HR deficiency status and response, or on nested subsets (48 had HRD scores; 47 had BRCA1/2 mutation screening of which 9/47 had BRCA1/2 mutations identified; 45 had HRD scores and BRCA1/2 mutation screening of which 38/45 were BRCA1/2 wild-type).

Statistical analysis for both cohorts was conducted according to the statistical analysis plan that was prespecified for the cisplatin trials cohort. The primary endpoint was RCB 0/I with a secondary endpoint of pCR. The primary objective was to test the association of HR deficiency. The secondary objectives were to test

individually the association of quantitative HRD score and tumor *BRCA1/2* status with RCB 0/I. A subgroup analysis of dichotomous HRD score was conducted in *BRCA1/2* wild-type. Each analysis was then repeated with the secondary endpoint of pCR.

Logistic regression was used to test association with binary response in univariate and multivariable models, and to test association of clinical variables and HRD score with *BRCA1/2* mutation. We report the OR for the interquartile range (IQR) of numerical variables, or for each category relative to the reference, with a 95% confidence interval. The *P* value for each covariate was calculated from the change in the likelihood deviance between the full and an appropriate reduced model, with and without the covariate of interest.

HR deficiency was modeled as a predictor of response with logistic regression methods. Standard maximum likelihood statistics were used to test RCB 0/I; Firth's penalized likelihood was used to adjust for small sample bias and produce confidence intervals in models of pCR with no events in the HR nondeficient category.

Statistical inference was conducted within the R software environment (29). Statistical significance was set at the 5% level. All *P* values and confidence intervals are two-sided with no adjustment for multiple testing.

## Results

### Establishing a threshold for the combined HRD score

The training set to determine a threshold for the combined HRD score was assembled from 4 cohorts [497 breast and 561 ovarian cases (20, 23–25)], and included 78 breast and 190 ovarian tumors with *BRCA1/2* deficiency based on tumor mutation screening and promoter methylation analysis. These four cohorts used for training the HRD threshold are completely independent from and have no overlap with PrECOG 0105 and the cisplatin cohorts analyzed below. The distribution of HRD scores in the training set is shown in Fig. 1 and has an apparent bimodal distribution with a nadir between 40 and 45. The HRD

threshold was selected to have a high sensitivity for detecting HR deficiency in breast and ovarian cancer. It was assumed that the loss of *BRCA1/2* function results in HR deficiency, and that the distribution of HRD scores in *BRCA1/2*-deficient samples would represent the distribution of scores in HR-deficient samples due to any underlying mechanism. To obtain a sensitivity of at least 95%, the threshold was set at the 5th percentile of the HRD scores in this training set of known *BRCA1/2*-deficient tumors. The 5th percentile of HRD scores was 42 in the combined breast and ovarian training set, consequently high HRD was defined as HRD scores ≥42. The 5th percentile was 41.9 for *BRCA1/2*-deficient breast tumors and 42.9 for *BRCA1/2*-deficient ovarian tumors.
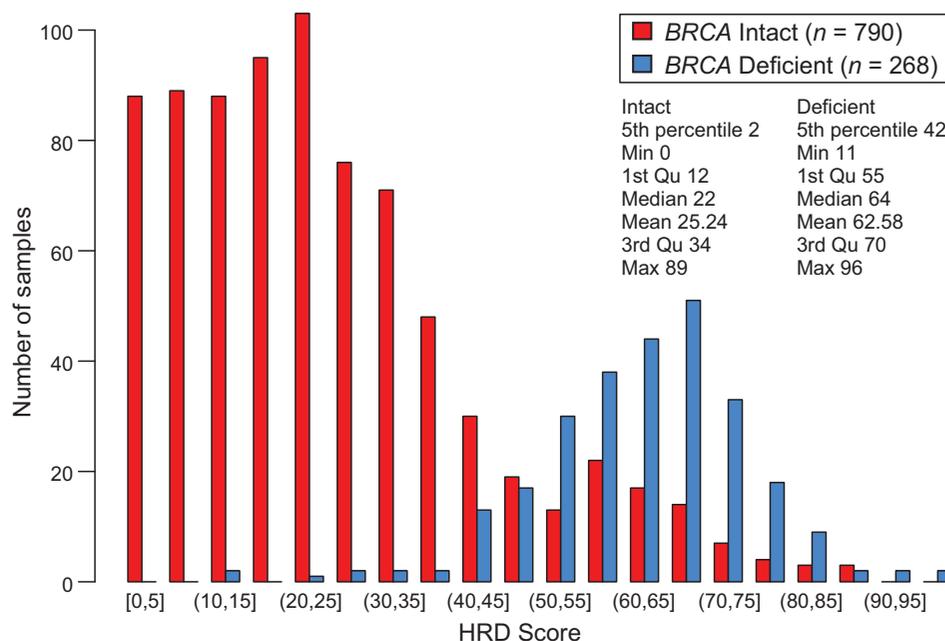
### HRD scores in the clinical trial cohorts

The PrECOG 0105 patient demographic and clinical data of the patients with evaluable HR status are shown in Supplementary Table S3A. Overall pCR rate in this HR subset of PrECOG 0105 was 23/70 = 33% (31/88 = 35% in the entire study for combined 4 + 6 cycle groups) and the RCB 0/I rate was 40/70 = 57% (51/88 = 58% in the entire study for combined 4 + 6 cycle groups). In the HR-evaluable subset of this cohort, 11 (16%) received 4 cycles of therapy and 59 (84%), 6 cycles. The patient demographic and clinical data of the patients with evaluable HR deficiency is shown for the combined cisplatin trials cohort in Supplementary Table S3B. The frequency of pCR was 18% in the original combined trials (14/79) and 16% in those patients with evaluable HR deficiency status (8/50). The frequency of RCB 0/I was 37% in the original combined trials (29/79) and 34% in those patients with evaluable HR deficiency status (17/50).

The distributions of HRD scores for the two cohorts are shown in Supplementary Fig. S2A and B. The distributions of HRD scores were similar to that seen in the training set, and appear somewhat bimodal in the PrECOG 0105 study and clearly bimodal in the cisplatin trials cohort. Forty-eight of 68 (71%) tumors had a high HRD score (≥42) in the PrECOG 0105 HRD cohort, whereas in the cisplatin trials HRD cohort, 26 of 48 (54%) had a high HRD



**Figure 1.**
HRD score distribution in the combined breast and ovarian training set. *BRCA*-deficient tumors include those with a *BRCA1/2* mutation and/or *BRCA1* methylation.

Legend:
BRCA Intact (*n* = 790)
BRCA Deficient (*n* = 268)

| | Intact | Deficient |
| --- | --- | --- |
| 5th percentile | 2 | 42 |
| Min | 0 | 11 |
| 1st Qu | 12 | 55 |
| Median | 22 | 64 |
| Mean | 25.24 | 62.58 |
| 3rd Qu | 34 | 70 |
| Max | 89 | 96 |

Y-axis: Number of samples
X-axis: HRD Score — [0,5] (10,15] (20,25] (30,35] (40,45] (50,55] (60,65] (70,75] (80,85] (90,95]

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score. The higher frequency of high HRD scores in the PrECOG 0105 cohort is consistent with the higher proportion of *BRCA1/2*-mutated tumors in that cohort (22/68, 32%) compared with the cisplatin trials cohort (9/47, 19%).

### Association of HR deficiency status with response to platinum-based chemotherapy

HR deficiency was significantly associated with both RCB 0/I and pCR in both the PrECOG 0105 and cisplatin trials cohorts (Table 1). In the PrECOG 0105 cohort, RCB 0/I rates in HR-deficient tumors ($n = 50$) were 68.0%, compared with 30.0% in HR nondeficient tumors [$n = 20$; OR $= 4.96$ (1.61–15.3), $P = 0.0036$]. pCR rates were 42.0% in HR-deficient and 10.0% in HR nondeficient tumors [OR $= 6.52$ (1.36–31.2), $P = 0.0058$]. In the cisplatin trials cohort, RCB 0/I rates in HR-deficient tumors ($n = 29$) were 51.7%, compared with 9.5% in HR nondeficient tumors [$n = 21$; OR $= 10.18$ (2.00–51.89), $P = 0.0011$]. pCR rates were 27.5% in HR-deficient and 0% in HR nondeficient tumors [OR $= 17.00$ (1.91–2249), $P = 0.0066$].

### Association of HRD score with response to platinum-based chemotherapy

The distributions of all passing HRD scores by RCB response class for each cohort ($N = 68$ and $N = 48$) are shown as box plots in Fig. 2. In the PrECOG 0105 cohort ($N = 68$), quantitative HRD score (IQR $= 28$) was significantly associated with RCB 0/I [OR $= 2.63$ (1.26–5.48), $P = 0.0061$], but not pCR [OR $= 1.85$ (0.88–3.88), $P = 0.093$]. The dichotomous HRD score (high/low) was significantly associated with both RCB 0/I [OR $= 4.67$ (1.51–14.4), $P = 0.0053$] and pCR [OR $= 6.43$ (1.34–30.9), $P = 0.0065$] in this cohort (Supplementary Table S4A). In the cisplatin trials cohort ($N = 48$), quantitative HRD was significantly associated with both RCB 0/I [OR $= 10.5$ (2.3–48.6), $P = 3.1 \times 10^{-4}$] and pCR [OR $= 117$ (2.9–4764), $P = 7.0 \times 10^{-5}$], as was the dichotomous HRD score for RCB 0/I [OR $= 10.0$ (1.93–51.8), $P = 0.0014$] and pCR [OR $= 17.3$ (1.90–2300), $P = 0.0071$; Supplementary Table S4B]. To assess the performance of the HRD score to place patients into response categories in the combined PrECOG 0105 and cisplatin cohorts, ROC curves of the HRD score predicting RCB 0/I and pCR are shown in Supplementary Fig. S3A and S3B. The AUC values were 0.761

for RCB 0/I and 0.747 for pCR, and the sensitivity at the predefined threshold of 42 is 85% for RCB 0/I and 93% for pCR, consistent with the expectation of 95% sensitivity to detect homologous recombination deficiency.

### BRCA1/2 mutations and association with high HRD score and with response to platinum-based chemotherapy

*BRCA1/2* mutation data were available for 66 tumors with passing HRD scores in PrECOG 0105. *BRCA1* mutations were identified in 15 tumors, *BRCA2* mutations were identified in 4 tumors, and one tumor carried both a *BRCA1* and a *BRCA2* mutation. In the cisplatin trials cohort, *BRCA1/2* mutation data were available for 45 tumors with passing HRD scores. Six tumors had a *BRCA1* mutation, and one had a *BRCA2* mutation. In the PrECOG 0105 cohort, which is enriched for *BRCA1/2* mutation carriers, *BRCA1/2* mutation status was significantly associated with high HRD scores ($P = 4.0 \times 10^{-5}$). 100% of *BRCA1/2*-mutant tumors ($n = 20$) had high HRD scores, compared with 59% of *BRCA1/2* wild-type tumors ($n = 46$). Although the cisplatin trials cohort had fewer *BRCA1/2* tumor mutations, the mean HRD score was significantly higher in the *BRCA1/2*-mutated compared with nonmutated tumors (63.1 vs. 45.3; $P = 0.015$). All but one of the *BRCA1/2*-mutated tumors had HRD score $\geq 42$ (6/7 $=$ 86%) compared with 19 of 38 (50%) of *BRCA1/2* wild-type tumors (Fisher exact test $P = 0.11$).

*BRCA1/2* tumor mutation status as a binary variable (yes/no) was a significant predictor of response in the PrECOG 0105 cohort, but was not significant in the cisplatin trials cohort (Table 2A). In the PrECOG 0105 study, RCB 0/I rate in *BRCA1/2*-mutant tumors ($n = 20$) was 75.0% compared with 48.0% in the *BRCA1/2* wild-type tumors [$n = 48$; OR $= 3.27$ (1.02–10.5), $P = 0.037$]. pCR rates were 50.0% in mutant and 24.0% in *BRCA1/2* wild-type tumors, which was also statistically significant [OR $= 3.18$ (1.05–9.63), $P = 0.040$]. However, in the cisplatin trials cohort with fewer *BRCA1/2*-mutated tumors, *BRCA1/2* mutation status alone was not significantly associated with RCB 0/I rate (42.9% vs. 31.6%; $P = 0.57$) or pCR rate (28.6% vs. 13.2%; $P = 0.33$).

Figure 3 shows the relative response rates in the two cohorts in tumors stratified by HR deficiency status, HRD score, or *BRCA1/2* mutation status. In the PrECOG 0105 cohort, *BRCA1/2* mutation

**Table 1.** HR deficiency status and association with response to platinum-containing therapy

**PrECOG 0105 (N = 70)**

| Responder | Deficient number (% response) | Nondeficient number (% response) | OR (95% CI) Reference = nondeficient | Logistic P |
|---|---|---|---|---|
| RCB 0/I = No | 16 | 14 | | |
| RCB 0/I = Yes | 34 (68%) | 6 (30%) | 4.96 (1.61–15.3) | 0.0036 |
| pCR = No | 29 | 18 | | |
| pCR = Yes | 21 (42%) | 2 (10%) | 6.52 (1.36–31.2) | 0.0058 |

**Cisplatin Trials Cohort (N = 50)**

| Responder | Deficient number (% response) | Nondeficient number (% response) | OR (95% CI) Reference = nondeficient | Logistic P |
|---|---|---|---|---|
| RCB 0/I = No | 14 | 19 | | |
| RCB 0/I = Yes | 15 (51.7%) | 2 (9.5%) | 10.18 (2.00–51.89) | 0.0011 |
| pCR = No | 21 | 21 | | |
| pCR = Yes | 8 (27.5%) | 0 (0%) | 17.00 (1.91–2,249)[a] | 0.0066[a] |

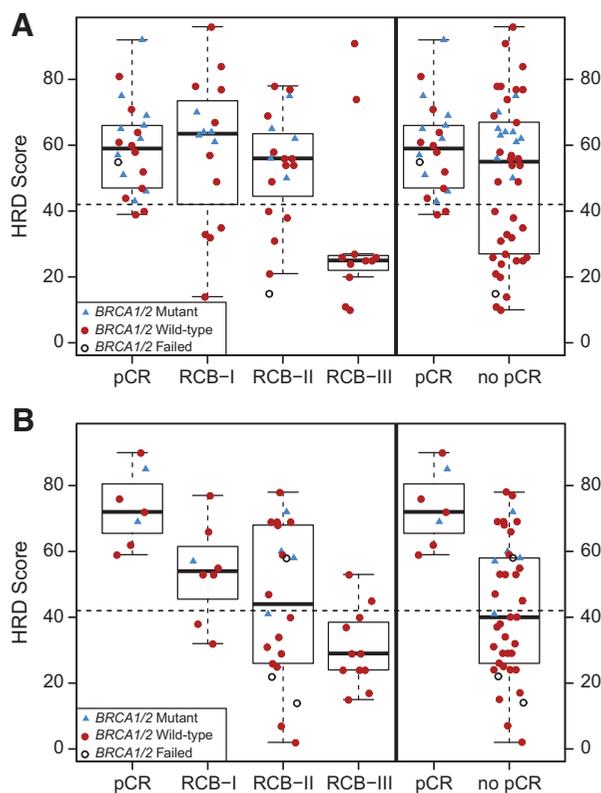[a]Based on Firth's penalized profile likelihood.

**Figure 2.**
Box plot of HRD score versus RCB class for all patients with HRD scores PrECOG 0105 ($n = 68$; **A**) and Cisplatin trials cohort ($n = 48$; **B**). Box outlines the 25th and 75th percentiles; solid line is the median; whiskers extend to the most extreme data point that is no more than 1.5 times the IQR. Red dots, *BRCA1/2* wild-type; blue triangles, *BRCA1/2*-mutant; black circles, failed mutation screening.

status provided the highest positive predictive value (PPV) of both RCB 0/I and pCR, while its negative predictive value (NPV) is lower compared with HRD score or HR deficiency status; however, these differences were not statistically significant. In the cisplatin trials cohort, *BRCA1/2* mutation status, HRD score, and HR deficiency provided similar PPVs for RCB 0/I (43%, 52%, and 52%, respectively) and for pCR (29%, 28%, and 28%, respectively). In this cohort, *BRCA1/2* mutation status also gave a lower NPV than either HRD score or HR deficiency for RCB 0/I (68%, 90%, and 90%, respectively) and for pCR (87%, 100%, and 100%, respectively).

### Association of HRD score with response to platinum-based chemotherapy in BRCA1/2 wild-type tumors

When analysis was confined to *BRCA1/2* wild-type tumors, response was higher in patients with high HRD scores in PrECOG 0105 ($n = 46$), where RCB 0/I rates were 59.0% in HRD high and 32.0% in HRD low ($P = 0.062$) and pCR was 33.0% in HRD high and 11.0% in HRD low ($P = 0.063$; Table 2B). In the cisplatin trials cohort, high HRD score was significantly associated with both higher RCB 0/I and pCR rates. RCB 0/I rate was 52.6% in HRD high and 10.5% in HRD low [OR = 9.44 (1.69–52.7), $P = 0.0039$]; pCR was 26.3% in HRD high and 0% in HRD low [OR = 14.79 (1.49–2001), $P = 0.018$].

### Association of clinical variables with response and HR deficiency status

For the PrECOG 0105 cohort, available clinical variables included clinical stage, tumor grade, age at diagnosis, and number of cycles of chemotherapy; for the cisplatin trials cohort, the clinical variables included use of bevacizumab, tumor size, nodal status, and age at diagnosis. To check for possible confounding, clinical variables were tested first for association with *BRCA1/2* mutation status, but were not significant [PrECOG 0105: grade: $P = 0.38$; stage: $P = 0.71$ (4 levels; I, IIA, IIB, IIIA), 0.60 (3 levels; I, II, III); chemotherapy cycles: $P = 0.11$; and age at diagnosis: $P = 0.12$]. Cisplatin trials: use of bevacizumab: $P = 0.73$; nodal status: $P = 0.23$; tumor size: $P = 0.90$; age at diagnosis: $P = 0.53$.

Univariate associations with response and HR deficiency were then tested (Supplementary Table S5). In the PrECOG 0105 cohort (Supplementary Table S5a), tumor grade, stage, and number of cycles of chemotherapy were not statistically significantly associated with RCB 0/I or HR deficiency status. Younger age at diagnosis was associated with HR deficiency status ($P = 2.0 \times 10^{-4}$) and was also associated with improved response ($P = 0.031$). However, this association was confounded by *BRCA1/2* mutations being more common in younger patients. When mutation status was taken into account, age was no longer a significant predictor of response ($P = 0.11$). In univariate analysis of the cisplatin trials cohort (Supplementary Table S5b), only age at diagnosis was associated with HR deficiency status ($P = 0.037$). No other clinical variables were associated with either RCB 0/I or HR deficiency status.

### HR deficiency status adjusted by clinical covariates

Multivariable logistic regression was used to determine whether HR deficiency status was a significant predictor of RCB 0/I and pCR after adjustment by clinical covariates (Table 3). In the PrECOG 0105 cohort, HR deficiency status ($P = 0.012$) and disease stage ($P = 0.0042$) were independent predictors of RCB 0/I in multivariable analysis. The interaction between HR deficiency status and stage was not significant when added to the full model ($P = 0.43$). In multivariable models of pCR neither HR deficiency status nor clinical variables reached statistical significance (Table 3A). In the cisplatin trials cohort, only HR deficiency status ($P = 0.0017$) was a significant predictor of RCB 0/I after adjustment for use of bevacizumab, tumor size, baseline nodal status, and age at diagnosis (Table 3B). In multivariable models of pCR, both HR deficiency ($P = 0.0063$) and age at diagnosis ($P = 0.026$) were independent predictors of pCR. Interaction between HR deficiency and age was not significant ($P = 1.0$).

To estimate the clinical utility of HRD status, logistic regression analysis of 3 models for predicting RCB 0/I and pCR were performed in the combined PrECOG 0105 and cisplatin cohorts (Supplementary Table S6). In each model, cohort was included as a covariate to adjust for possible confounding. The first model included patient stage; the second included stage and tumor *BRCA1/2* (t*BRCA1/2*) mutation status; the third included stage, t*BRCA1/2* mutation status, and dichotomous HRD score. For each of these models, a ROC curve was computed (Supplementary Fig. S4A and S4B). For RCB 0/I, the dichotomous HRD score remained significant after adjustment for cohort, clinical stage, and t*BRCA1/2* mutation status ($P = 8.3 \times 10^{-5}$). AUC was increased from 0.710 to 0.788 by adding dichotomous HRD score to clinical stage and t*BRCA1/2* adjusted for cohort ($P = 0.014$). For pCR, dichotomous HRD score remained significant

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**Table 2.** *BRCA1/2* mutation status (whole cohorts) or HRD score (*BRCA1/2* wild-type subset) and associations with response

**A. *BRCA1/2* mutation status**

**PrECOG 0105 Cohort (*N* = 66)**

| Responder | Mutant number (% response) | Nonmutant number (% response) | OR (95% CI) Reference = nonmutant | Logistic *P* |
|---|---|---|---|---|
| RCB 0/I = no | 5 | 24 | | |
| RCB 0/I = yes | 15 (75%) | 22 (48%) | 3.27 (1.02–10.5) | 0.037 |
| pCR = no | 10 | 35 | | |
| pCR = yes | 10 (50%) | 11 (24%) | 3.18 (1.05–9.63) | 0.040 |

**Cisplatin Trials Cohort (*N* = 45)**

| Responder | Mutant number (% response) | Nonmutant number (% response) | OR (95% CI) Reference = nonmutant | Logistic *P* |
|---|---|---|---|---|
| RCB 0/I = no | 4 | 26 | | |
| RCB 0/I = yes | 3 (42.9%) | 12 (31.6%) | 1.62 (0.31–8.43) | 0.57 |
| pCR = no | 5 | 33 | | |
| pCR = yes | 2 (28.6%) | 5 (13.2%) | 2.64 (0.40–17.5) | 0.33 |

**B. HRD Score ≥42 (high vs. low), subset of *BRCA1/2* wild-type tumors**

**PrECOG 0105 Cohort (*N* = 46)**

| Responder | HRD high number (% response) | HRD low number (% response) | OR (95% CI) Reference = low HRD score | Logistic *P* |
|---|---|---|---|---|
| RCB 0/I = no | 11 | 13 | | |
| RCB 0/I = yes | 16 (59%) | 6 (32%) | 3.15 (0.92–10.8) | 0.062 |
| pCR = no | 18 | 17 | | |
| pCR = yes | 9 (33%) | 2 (11%) | 4.25 (0.80–22.6) | 0.063 |

**Cisplatin Trials Cohort (*N* = 38)**

| Responder | HRD high number (% response) | HRD low number (% response) | OR (95% CI) Reference = low HRD score | Logistic *P* |
|---|---|---|---|---|
| RCB 0/I = no | 9 | 17 | | |
| RCB 0/I = yes | 10 (52.6%) | 2 (10.5%) | 9.44 (1.69–52.7) | 0.0039 |
| pCR = no | 14 | 19 | | |
| pCR = yes | 5 (26.3%) | 0 (0%) | 14.79 (1.49–201) | 0.018 |

after adjustment for cohort, clinical stage, and t*BRCA1/2* mutation status ($P = 0.0011$). AUC was increased from 0.694 to 0.762 by adding dichotomous HRD score to clinical stage and t*BRCA1/2* adjusted for cohort ($P = 0.037$).

## Discussion

In this study, the HRD score (the sum of three metrics of chromosomal level aberration: LOH, TAI, and LST), and the
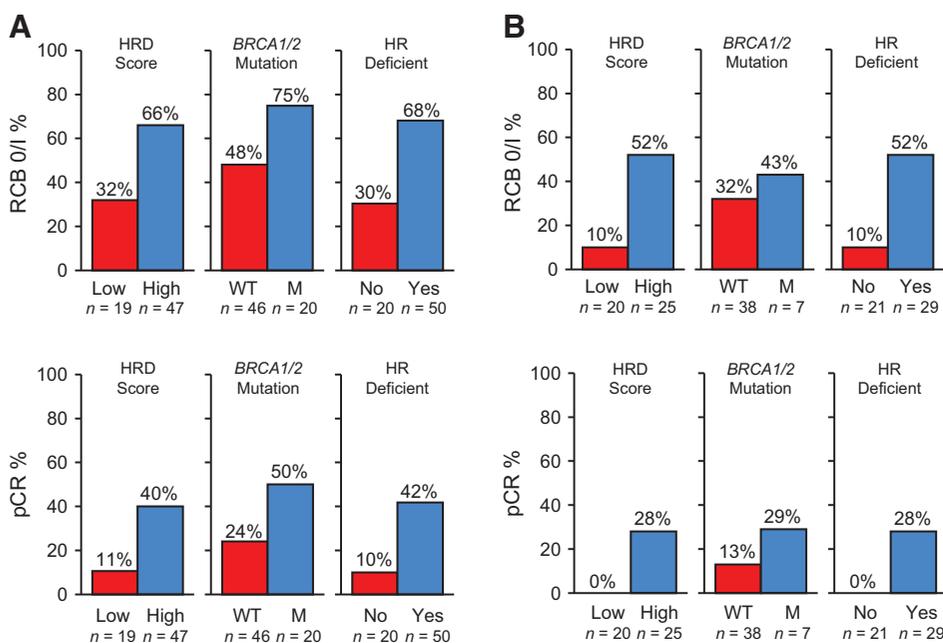


**Figure 3.**
Relative response rates for PrECOG 0105 (**A**) and in the cisplatin cohort (**B**) stratified by HRD score, *BRCA1/2* mutation status, and HR deficiency status. WT, wild-type; M, mutant.

**Table 3.** Multivariable models of RCB 0/I and pCR

**A. PrECOG 0105 Cohort (N = 70)**

| Variable | Levels | Number of patients (%) | % RCB 0/I | OR (95% CI) | P | % pCR | OR (95% CI) | P |
|---|---|---|---|---|---|---|---|---|
| HR deficiency status | Nondeficient | 20 (29%) | 30 | Reference | | 10 | | |
| | Deficient | 50 (71%) | 68 | 5.86 (1.33–25.7) | 0.012 | 42 | 4.06 (0.67–24.6) | 0.098 |
| Tumor grade | II | 17 (24%) | 53 | Reference | | 12 | | |
| | III | 53 (76%) | 58 | 0.69 (0.18–2.69) | 0.59 | 40 | 4.58 (0.83–25.3) | 0.055 |
| Clinical stage | I | 9 (13%) | 89 | Reference | | 44 | | |
| | II | 51 (73%) | 57 | 0.05 (0.00–0.58) | | 33 | 0.26 (0.04–1.56) | |
| | III | 10 (14%) | 30 | 0.02 (0.00–0.35) | 0.0042 | 20 | 0.20 (0.02–2.20) | 0.29 |
| Chemotherapy cycles | 4 cycles | 11 (16%) | 55 | Reference | | 18 | | |
| | 6 cycles | 59 (84%) | 58 | 0.93 (0.19–4.60) | 0.93 | 36 | 3.48 (0.58–21.1) | 0.15 |
| Age at diagnosis (yrs) | | | | OR per IQR = 14 0.51 (0.23–1.13) | 0.087 | | OR per IQR = 14 0.47 (0.19–1.15) | 0.085 |

**B. Cisplatin Trials Cohort (N = 50)**

| Variable | Levels | Number of patients (%) | % RCB 0/I | OR (95% CI) | P | % pCR | OR[a] (95% CI) | P |
|---|---|---|---|---|---|---|---|---|
| HR deficiency status | Nondeficient | 21 (42%) | 10 | Reference | | 0 | | |
| | Deficient | 29 (58%) | 52 | 12.1 (1.97–74.0) | 0.0017 | 28 | 8.42 (0.93–1697) | 0.014 |
| Treatment | Cisplatin | 18 (36%) | 28 | Reference | | 17 | | |
| | Cisplatin + bevacizumab | 32 (64%) | 38 | 2.27 (0.51–10.0) | 0.27 | 16 | 1.20 (0.22–8.53) | 0.62 |
| Tumor size (cm) | | | 34 | OR per IQR = 1.3 1.48 (0.39–5.56) | 0.56 | 16 | OR per IQR = 1.3 2.97 (0.64–0.90) | 0.11 |
| Baseline nodal status | Negative | 27 (54%) | 26 | Reference | | 11 | Reference | |
| | Positive | 23 (46%) | 43 | 1.85 (0.08–38.4) | 0.71 | 22 | 5.62 (0.16–273) | 0.26 |
| Clinical stage | IIA | 25 (50%) | 24 | Reference | | 8 | Reference | |
| | IIB | 21 (42%) | 43 | 1.29 (0.04–44.7) | | 29 | 0.49 (0.01–24.3) | |
| | IIIA | 4 (8%) | 50 | 1.30 (0.00–1076) | 0.99 | 0 | 0.03 (0.00–53.9) | 0.28 |
| Age at diagnosis (yrs) | | | 34 | OR per IQR = 14 0.68 (0.22–2.15) | 0.51 | 16 | OR per IQR = 14 0.47 (0.08–2.30) | 0.47 |

[a]Confidence intervals fit by profile likelihood.

concept of HR deficiency (defined as HRD score $\geq$ 42 and/or *BRCA1* or *BRCA2* mutation) were evaluated as predictors of response to neoadjuvant platinum-based therapy in two different clinical cohorts. The PrECOG 0105 study was enriched for *BRCA1* and *BRCA2* mutation carriers, and this cohort received multiagent cytotoxic chemotherapy with gemcitabine, carboplatin, and the investigational agent iniparib. In contrast, the two cisplatin trials were not enriched for *BRCA1* and *BRCA2* mutation carriers, and employed only one cytotoxic chemotherapy, cisplatin, given either alone or in combination with bevacizumab.

This analysis makes several practical points. First, the HRD score and mutation analysis necessary to determine HR deficiency can be performed on formalin-fixed paraffin-embedded material from limited core-needle biopsy specimens. Second, the cut-off threshold of an HRD score of greater than or equal to 42, which was predefined in an independent set of breast and ovarian cancers, performs as expected in the two experimental cohorts. This cutoff correctly identified all 20 *BRCA1*- or *BRCA2*-mutated samples in the PrECOG 0105 cohort, and 6 of 7 *BRCA1*- or

*BRCA2*-mutated samples in the cisplatin trials cohort. Thus, overall this cutoff correctly identified 26 of 27 mutated samples, a detection rate of 96.3%, consistent with the 95% sensitivity for which the cutoff was chosen.

The dichotomized HRD score itself was significantly associated with both RCB 0/I and pCR in both cohorts. Furthermore, HR deficiency successfully predicted RCB 0/I and pCR in a highly significant manner in both cohorts. Finally, multivariable models showed that these predictions remained significant after taking into account clinical variables. The distribution of HRD scores in the training set used to establish the HRD score cutoff and in the two neoadjuvant cohorts analyzed here is bimodal, with fewer tumors with scores around the cut-off point. The ability to predict response independently of clinical variables, with few tumors in an equivocal range, is an attractive aspect of a clinically useful test.

The current understanding of the determinants of chemotherapy responsiveness is insufficient to predict *a priori* to which specific chemotherapeutic agents HR deficiency might predict response. Retrospective analyses of the GeparSixto and other

experiences using cytotoxic chemotherapies suggests that HR deficiency may also predict responses to topoisomerase inhibitors such as the anthracyclines and alkylating agents (30, 31). This study and others suggest that HR deficiency may identify the patients who would benefit from treatment with DNA-damaging agents such as platinum.

In summary, in this analysis, HRD status provides significant improvement over clinical variables or *BRCA1/2* mutation status in identifying tumors with an increased likelihood of response to platinum-based neoadjuvant therapy among patients with TNBC. Clinical use of the HRD test has the potential to identify sporadic TNBC patients likely to respond to DNA-damaging therapy beyond those currently identified by germline *BRCA1/2* mutation screening. The clinical trials described here do not include a nonplatinum comparator arm. Additional studies, including retrospective analysis of larger clinical trials with a control arm or prospective clinical trials, will further define and clarify the clinical utility of the HR deficiency assay and ultimately determine the range of chemotherapies for which HR deficiency may predict response.

## Disclosure of Potential Conflicts of Interest

## Authors' Contributions

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# Clinical Cancer Research

# Homologous Recombination Deficiency (HRD) Score Predicts Response to Platinum-Containing Neoadjuvant Chemotherapy in Patients with Triple-Negative Breast Cancer

Melinda L. Telli, Kirsten M. Timms, Julia Reid, et al.

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