Exploring homologous recombination deficiency thresholds for predicting response to platinum-based treatment in triple negative breast cancer

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Abstract # 525

BACKGROUND

- Homologous recombination deficiency (HRD) status can be used to identify patients who are eligible for treatment with DNA damaging agents.
- Studies have previously examined the association between HRD status and outcomes in patients with triple negative breast cancer (TNBC) using a 3-biomarker Genomic Instability Score (GIS).
- These studies have used a threshold of ≥42, set as the 5th percentile for *BRCA* deficient tumors. Evidence suggests that a GIS threshold of ≥33, set as the 1st percentile for *BRCA* deficient tumors, may be more appropriate.
- Here, we conducted an exploratory analysis evaluating the ability of ≥33 and ≥42 GIS thresholds to predict response to platinum-based treatment in patients with TNBC.

METHODS

- Patients across 5 cohorts (TBCRC030[1], TBCRC008[2], NCT01372579[3], PrECOG 0105[4], combined cisplatin cohort[4]) were included in this analysis if they had a primary TNBC diagnosis, received neoadjuvant platinum-based treatment, had a valid GIS, and had known pathologic complete response (pCR) status.
- GIS was determined by a combination of loss of heterozygosity, telomeric-allelic imbalance, and large-scale state transitions.[4,5]
- *BRCA* mutation status was defined by loss of function resulting from a pathogenic variant in *BRCA1* or *BRCA2*.
- Logistic regression models were fit with binary threshold status predicting pCR status.
- Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated by comparing binary threshold status and binary pCR status.

RESULTS

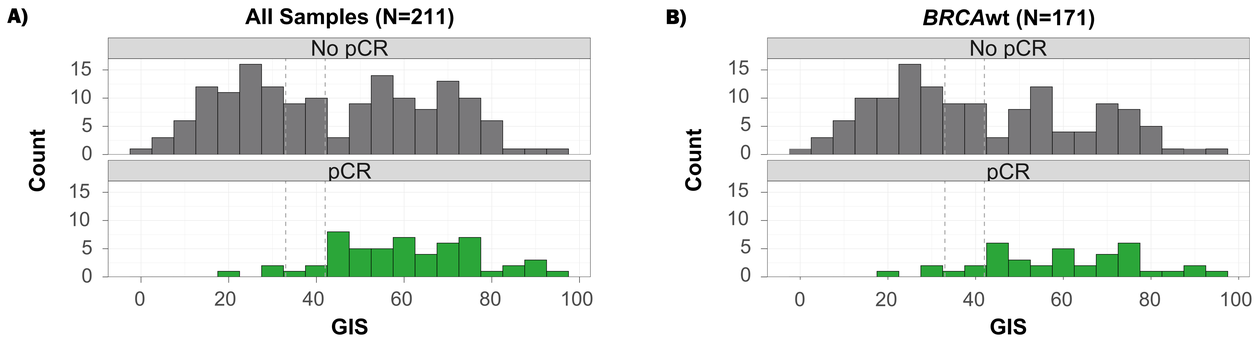
- A total of 211 tumors (171 *BRCA*wt; 35 *BRCA*m; 5 unknown) were included (Figure 1).
  - pCR to platinum-based treatment occurred in 55 cases (26%; 39 *BRCA*wt; 15 *BRCA*m; 1 unknown).
- The pre-specified threshold of GIS ≥33 is a significant predictor of pCR status in the full cohort and in *BRCA*wt samples only (Table 1).
- A threshold at GIS ≥33 results in a higher odds ratio than a threshold GIS ≥42 (Table 1, Figure 2).
- Sensitivity, specificity, PPV, and NPV were comparable between the ≥33 and ≥42 GIS thresholds, with the ≥33 threshold producing higher sensitivity values, but lower specificity (Figure 3).
- This was true when thresholds were applied to all samples and to *BRCA*wt samples only (Figure 3).
- Among patients who achieved pCR in response to platinum-based treatment, 5.5% of patients in the full cohort and 7.7% of those in the *BRCA*wt cohort had a GIS between 33-41.

Table 1. Results of logistic regression models fit with binary threshold status predicting pCR status

	Univariable Models		Bivariable Models[a]	
	OR (95% CI)	P-value	OR (95% CI)	P-value
All (N=211)				
GIS ≥33	11.1 (3.9, 47.1)	2.2×10^{-7}	3.6 (0.6, 21.0)	0.15
GIS ≥42	8.2 (3.5, 22.3)	5.6×10^{-8}	3.6 (1.1, 15.8)	0.03
***BRCA*wt (N=171)**				
GIS ≥33	9.4 (3.2, 40.4)	5.6×10^{-6}	3.6 (0.6, 21.3)	0.15
GIS ≥42	7.0 (2.9, 19.6)	3.0×10^{-6}	3.0 (0.9, 13.7)	0.07

[a]Bivariable models fit with binary GIS ≥33 status and binary GIS ≥42 status predicting pCR

Figure 1. Distribution of GIS by pCR status in (A) the full cohort, and (B) *BRCA*wt samples only



Dashed vertical lines denote the pre-defined thresholds at GIS=33 and GIS=42

Figure 2. Odds ratios from models with threshold status predicting pCR in both the full and *BRCA*wt cohorts

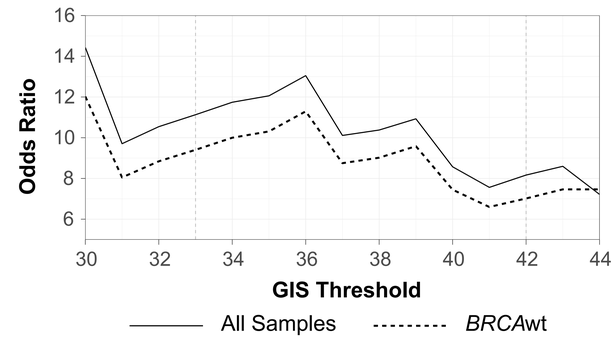
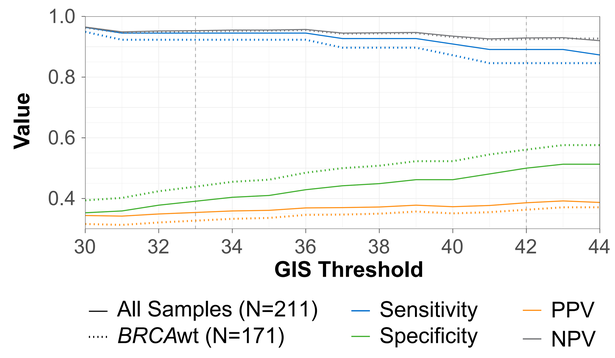


Figure 3. Sensitivity, specificity, and predictive values for pCR to platinum-based treatment by GIS threshold



CONCLUSIONS

- To increase detection of patients likely to benefit from treatment while maintaining good PPV, a GIS of ≥33 (1st percentile of *BRCA* deficient tumors) may be the most appropriate threshold to predict response to platinum-based treatment in patients with TNBC; however, a prospective trial will be needed to confirm these findings.
- Additional studies will be important to determine whether this threshold may be appropriate to determine eligibility for other DNA-damaging agents such as PARP inhibitors.

REFERENCES: 1) Ann Oncol. 2020 2) J Nucl Med. 2015 3) Breast Cancer Res Treat. 2015 4) Clin Cancer Res. 2016 5) Breast Cancer Res Treat. 2014

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