Automated prediction of response to neoadjuvant chemotherapy from digitized H&E slides of pre-treatment biopsies of germline BRCA carriers with HER2-negative breast cancer (TBCRC 031)

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Abstract # 605

BACKGROUND

- The TBCRC031 (INFORM), a randomized phase II trial of neoadjuvant cisplatin (C) vs doxorubicin-cyclophosphamide (AC) in germline BRCA mutation carriers with HER2-negative breast cancer, showed no difference in response rates between the two arms [1].
- A systematic and direct computational measurement of cell cycle deregulation (CCD) and its interaction with tumor immune microenvironment (TIME) from the pretreatment core needle biopsies (CNB) could potentially be useful in automated prediction of the neoadjuvant chemotherapy (NAC) response [2,3], achieving residual cancer burden 0/1 (RCB 0,1) at surgery.
- The current study examines if quantification of the immune, proliferative, and key cell cycle deregulation signatures from digital images of H&E-stained pre-treatment CNB could distinguish patients with a good response to NAC (RCB 0,1) from those with a poor response (RCB 2,3).

METHODS

- CNBs (n = 92 with RCB scores available) scanned at 40x on a Hamamatsu Nanozoomer scanner were evaluated using the 4D Q-Plasia OncoReader (***QPOR™***) generated image-based signatures (Figure 1). 96% (88/92) of the CNBs could be analyzed successfully.
- ***QPOR™*** is a statistical physics and tumor biology-based hard-coded algorithm that quantifies CCD and TIME dynamics as continuous biomarkers from digitized H&E CNB whole slide images (WSI) alone.
- ***QPOR™*** biomarkers used in the study:
  - **IHI**: complex immune response signature based on the intra-slide spatial heterogeneity of immune infiltrates.
  - **CmbI**: combined **IHI**, proliferative (**PI**), and cell cycle G1S deregulation (**G1SI**) signatures based on the hypotheses and prediction-logic described in Figure-2. **CmbI-Tree** and **CmbI** are categorical and continuous signatures respectively.
- All the biomarkers were validated out of sample both as i) continuous scales, and ii) dichotomized at median value to predict RCB 0,1 vs. RCB 2,3 status.
- Receiver operator characteristic (ROC) curves with area under the curve (AUC) measures and odds ratios (OR) per unit increase with 95% confidence intervals (CI) were used to assess the predictive performance of each continuous biomarker.
- Accuracy, specificity, sensitivity, positive and negative predictive values (PPV, NPV), and OR with 95% CI were used to assess the predictive performance of the dichotomized biomarkers.
- The analysis is repeated for each therapy arms (C and AC), the TNBC and the BRCA-1 sub-cohorts, using two different image formats (ndpi 40x and tiff 40x).
- Other ***QPOR™*** indices were analyzed using AUC-ROC to test further reduction of false positive (FP) and false negative (FN) rates. Pathology review was done on FP and FN cases to determine if they were associated with any specific features.

RESULTS

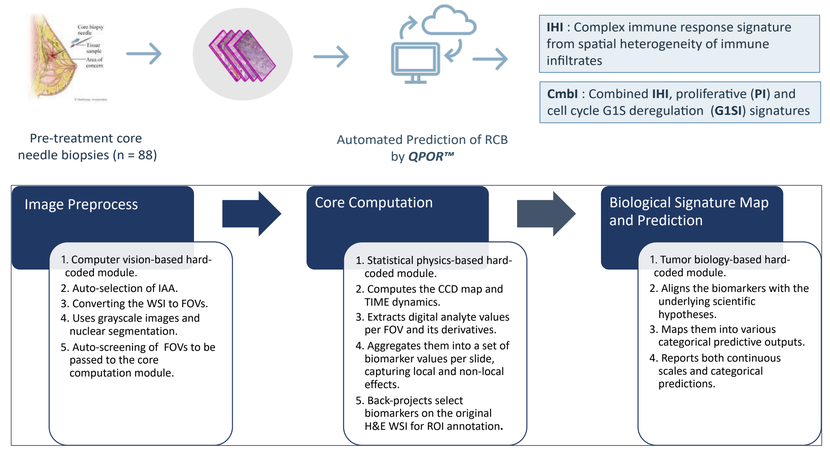

Figure 1: Study design and **QPOR** workflow following image upload; IAA = Initial Analyzable Area, FOV = Field of View, ROI = Region of Interest, CCD = Cell Cycle Deregulation, TIME = Tumor Immune Micro-Environment

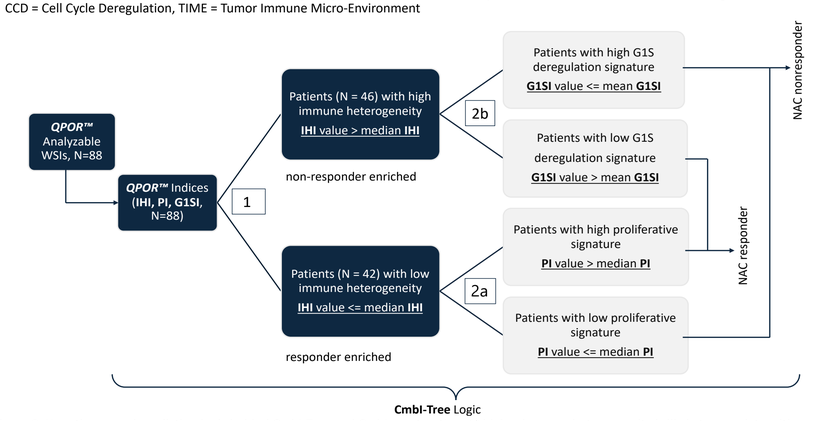

Figure 2: Hypotheses and prediction logic behind CmbI-Tree and CmbI construction: 1) higher immune heterogeneity is likely to associate with poor chemotherapy response; 2a) lower proliferative status is likely to associate with poor chemotherapy response, particularly for patients with low immune heterogeneity; 2b) higher G1S deregulation is likely to associate with poor chemotherapy response, which is likely more significant in patients with high immune heterogeneity. Assigning projected %confidence weights for each arm and then aggregating produces the continuous CmbI value. CmbI >= 0 predicts responders (median cut-off =0).

• Low **IHI** was predictive of NAC response in the overall population (Table 1) and showed better prediction of response compared to pathologist identified % sTILs (the latter had nonsignificant Wilcoxon test p-values). • High **CmbI** was significantly predictive of NAC response in the full cohort with higher accuracy, as well as in the AC, C, and TNBC sub-cohorts and predicted response better than IHI alone (Table 1, 2). • CmbI was predictive of NAC response across different image filetypes (ndpi, tiff, svs) and in BRCA proficient TNBC cohort. • Most of the FP and FN cases (> 90%) were found to be associated with specific features (*e.g.,* prominent necrosis).

Table 1: Combined signature (CmbI*) is superior to immune heterogeneity signature (IHI*) to predict neoadjuvant chemotherapy response (RCB 0,1)

Subgroup	Biomarker	AUC (95% CI)	OR (95% CI)	P value (Wilcoxon test)
All (N = 88)	**IHI**	0.65 (0.53, 0.77)	0.58 (0.33, 0.95)	0.016
All (N = 88)	**CmbI**	0.80 (0.71, 0.90)	1.23 (1.13, 1.36)	3.3e-07
AC (N = 43)	**IHI**	0.62 (0.45, 0.80)	0.68 (0.31,1.36)	0.18
AC (N = 43)	**CmbI**	0.83 (0.71, 0.96)	1.26 (1.11, 1.47)	1e-04
C (N = 45)	**IHI**	0.68 (0.51, 0.84)	0.48 (0.2, 0.99)	0.047
C (N = 45)	**CmbI**	0.77 (0.63, 0.91)	1.21 (1.07, 1.39)	0.0015
TNBC (N = 54)	**IHI**	0.64 (0.48, 0.80)	0.60 (0.31, 1.08)	0.086
TNBC (N = 54)	**CmbI**	0.85 (0.75, 0.95)	1.32 (1.16, 1.57)	4.3e-06

*All biomarkers were evaluated as continuous scales. High CmbI, and low IHI predicted NAC response (RCB 0,1) as continuous biomarkers. The unit increase/decrease of IHI, and CmbI is in a scale of 100, and 0.1, respectively.

Table 2: Performance of dichotomized CmbI to predict response (RCB 0,1) to neoadjuvant chemotherapy**

Biomarker	TP: RCB 0, 1	TN: RCB 2, 3	FP	FN	Accuracy	Sensitivity	Specificity	PPV	NPV	OR (95% CI)
CmbI	29	41	6	12	80%	71%	87%	83%	77%	15.56 (5.52, 50.96)

**The dichotomized CmbI predicted NAC response (RCB 0,1) according to the rule explained Figure 2.

CONCLUSIONS

- **Low immune heterogeneity (IHI), high proliferative (PI), and high cell cycle deregulation measured by low G1S length (G1SI) signature indices generated by the computational algorithm (*QPOR™*) individually, and much more strongly in combination (CmbI), are predictive of NAC response in germline BRCA mutation carriers with HER2-negative breast cancers.**
- **The combined index (CmbI) demonstrated superior predictive performance in the overall population, in each therapy arm and in the TNBC sub-cohort.**

References: 1. Tung, N. et al. J Clin Oncol 2020;
2. Williams, G. H. J Pathol. 2012;
3. Tisled, C. et al. Frontiers in Oncol 2022.

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