Predicting outcomes for patients with mixed ductal/lobular carcinoma of the breast based on circulating tumor DNA positivity patterns

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Background

- Invasive lobular carcinoma (ILC) exhibits distinct histopathologic characteristics and prognoses compared to invasive ductal breast carcinoma (IDC).
- Mixed IDC/ILC is an uncommon subtype of ILC, accounting for ~2.7 % of all invasive breast cancers in this cohort, or about one-fifth (21%) of the incidence of pure lobular carcinoma.
- Mixed IDC/ILC poses unique clinical challenges due to its mixed histology and heterogeneous expression of hormone receptors and HER2.
- We describe the development of a quantitative model to classify mixed IDC/ILC tumors based on genomic features and molecular recurrence patterns.

Methods

- This study included a cohort of 11,507 patients with early-stage breast cancer (eBC) and available results from personalized, tumor-informed ctDNA testing (Signatera™, Natera, Inc.), identified using Natera's proprietary real-world database, which is linked to the Forian claims database.
- Histological subtype determination were made according to pathologist's report. Hormone receptor status, HER2 status, and the date of relapse were inferred from the claims codes associated with interventions and secondary neoplasms.
- A quantitative model was trained using an ensemble learning strategy consisting of random forest classifiers and logistic regression models to classify tumors, including mixed IDC/ILC tumors based on genomic features of known IDC and ILC cases as either "ductal-like", "lobular-like", or "ambiguous". The model was independently validated on a class-balanced cohort of cases with known histological subtype.
- We compared patterns of genomic alterations, ctDNA positivity, and tumor recurrence between tumors with known ductal or lobular histology and those predicted to be ductal-like and lobular-like by the balanced genomic classifier.

Table 1. Patient Cohort and Clinical Characteristics

Characteristic, n (%)	Ductal; n=9678	Lobular; n=1513	Mixed; n=316
Age, years, median (range)	58 (21-89)	65 (32-89)	60 (30-87)
Sex			
Female	9602 (99.2%)	1512 (99.9%)	315 (99.7%)
Male	76 (0.8%)	1 (0.1%)	1 (0.3%)
Tumor Stage			
I	3426 (35.4%)	509 (33.6%)	112 (35.4%)
II	2839 (29.3%)	396 (26.2%)	87 (27.5%)
III	1755 (18.1%)	345 (22.8%)	63 (19.9%)
IV	579 (6%)	125 (8.3%)	20 (6.3%)
Not reported	1079 (11.1%)	138 (9.1%)	34 (10.8%)
Receptor Subtype			
HR+/HER2-	2737 (28.3%)	686 (45.3%)	226 (71.5%)
HR-/HER2+	672 (6.9%)	27 (1.8%)	47 (14.9%)
HR+/HER2+	327 (3.4%)	26 (1.7%)	7 (2.2%)
TNBC	866 (8.9%)	54 (3.6%)	14 (4.4%)
Not reported	5076 (52.4%)	720 (47.6%)	22 (7%)
LN status			
Positive	3567 (36.9%)	693 (45.8%)	150 (47.5%)
Negative	6111 (63.1%)	820 (54.2%)	166 (52.5%)
ctDNA dynamics			
Persistently Negative	7975 (82.4%)	1168 (77.2%)	262 (82.9%)
Persistently Positive	609 (6.3%)	190 (12.6%)	26 (8.2%)
Positive to Negative	471 (4.9%)	56 (3.7%)	7 (2.2%)
Negative to Positive	237 (2.4%)	41 (2.7%)	5 (1.6%)
Mixed	386 (4%)	58 (3.8%)	16 (5.1%)
Relapse status			
Relapsed	1212 (12.5%)	218 (14.4%)	44 (13.9%)
No relapse	8466 (87.5%)	1295 (85.6%)	272 (86.1%)
Median follow-up (months)	35.5	41.9	42.8
Median ctDNA tests per patient	3	3	3

Figure 1. Genomic features of invasive ductal and lobular breast carcinoma

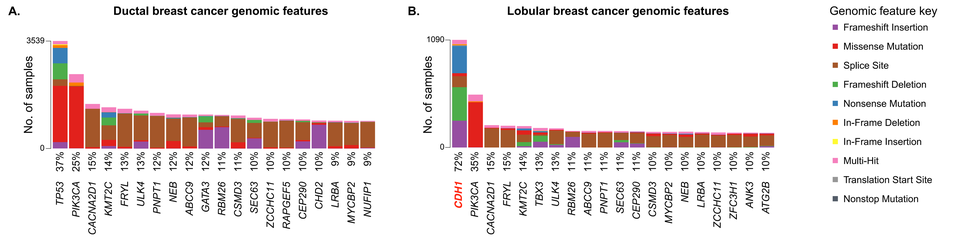


Figure 1. Mutational landscape of eBC with confirmed ductal or lobular histology. A) invasive ductal breast carcinoma (n=9678), **B)** invasive lobular breast carcinoma (n=1513)

Figure 2. Genomic classifier development and performance

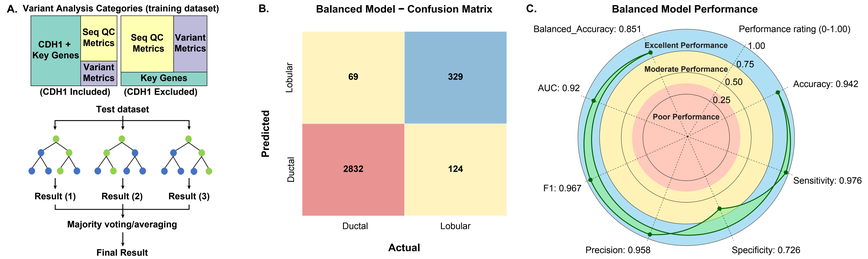


Figure 2. Development and performance of genomic classifier. A) Workflow for the development of the genomic classifier. Patients with eBC of known ductal or lobular histology were separated into two class-balanced cohorts; 70% in the training cohort (6774 ductal, 1059 lobular) and 30% in the test cohort (2904 ductal, 455 lobular). Feature importance analysis consistently identified CDH1 as the most discriminative genomic feature, consistent with its well-established role as a defining marker of lobular carcinoma through E-cadherin loss. To evaluate the contribution of additional genetic determinants, we retrained the model after excluding CDH1. **B)** Confusion matrix demonstrating performance of the balanced model, indicating the accuracy of the model in correctly identifying the histology of known cases in the test cohort. **C)** Performance metrics of the balanced model in the test cohort. Green area indicates the overall consistency of the balanced model, showcasing an accuracy of 0.942 and an AUC of 0.92.

Conclusions

- In phenotypically diverse disease types, such as mixed IDC/ILC, genomic features and molecular relapse patterns can help predict the clinical trajectory of the disease and discriminate between "ductal-like" vs. "lobular-like" phenotypes.
- Breast cancer subtype-specific molecular architecture can be defined in the genomic space, and is preserved within ctDNA-derived temporal trajectories.
- Upon further refinement and validation, the model can potentially inform prognosis among patients with mixed IDC/ILC.

Acknowledgments and Disclosures

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Figure 3. Classification of mixed ductal/lobular cases

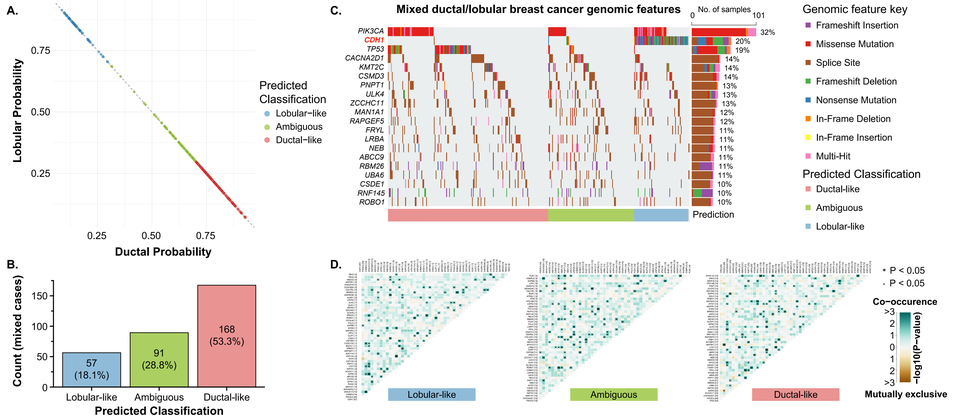


Figure 3. Classification of mixed ductal/lobular cases. A) Mixed ductal/lobular cases were classified as "ductal-like", "lobular-like", or "ambiguous" based on probabilistic proximity to either the ductal or lobular genomic signatures. Samples with posterior probabilities greater than 0.6 were categorized as lobular-like, while those below 0.4 were assigned as ductal-like. Cases falling within the intermediate 0.4–0.6 confidence interval were classified as ambiguous, representing tumors with genomic profiles lying between canonical ductal and lobular boundaries, the most plausible candidates for true mixed (50:50) histology at the molecular level. **B)** Counts and proportion of mixed ductal/lobular cases (n=316) classified as "ductal-like" (n=169), "lobular-like" (n=57), or "ambiguous" (n=90) by the genomic classifier. **C)** Genomic features of mixed cases according to prediction classification. **D)** Top most frequently co-occurring mutations and/or mutually exclusive mutations in mixed cases, by predicted classification.

Figure 4. Genomic classification of mixed cases predicts molecular and recurrence behavior

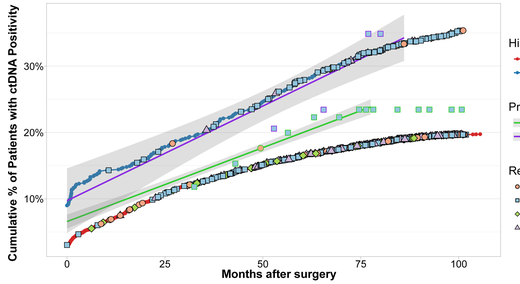


Figure 4. Patterns of molecular recurrence and clinical relapse in Ductal, Lobular, and mixed ductal/lobular carcinoma.

Cumulative incidence of ctDNA-positivity (molecular recurrence) in patients with confirmed ductal and lobular carcinoma, and mixed ductal/lobular, classified according to the genomic prediction classifier. Disease recurrence events are indicated according to receptor subtype. Cases classified as lobular-like (purple line) exhibit ctDNA positivity and disease recurrence patterns most similar to cases with histologically-confirmed invasive lobular carcinoma (blue line); cases classified as ductal-like (green line) exhibit ctDNA positivity and disease recurrence patterns most similar to cases with histologically-confirmed invasive ductal carcinoma (red).

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