Short Communication Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.4597261830-058

Gene Expression Comparison of Pleomorphic Lobular Carcinoma In-Situ with Classical Lobular Carcinoma In-Situ and High-Grade Ductal Carcinoma In-Situ

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ARTICLE INFO

Received:
15 January 2026
Revised:
8 March 2026
Accepted:
8 March 2026

Keywords:
breast neoplasms, molecular biology, pathology, molecular, breast carcinoma in situ, gene expression

ABSTRACT

Background: Pleomorphic lobular carcinoma in situ (PLCIS) shares histologic features with both classical lobular carcinoma in situ (cLCIS) and high-grade ductal carcinoma in-situ (hgDCIS), leading to ambiguity on optimal clinical management. Retrospective gene expression profiling and analysis were used to explore the biological behavior of PLCIS relative to cLCIS and hgDCIS.

Methods: This is a retrospective study. Overall, 16 PLCIS specimens, 10 cLCIS specimens, and 9 hgDCIS cases were included; gene expression using a 725 cancer-related gene expression assay was measured.

Results: PLCIS gene expression profile had greater overlap with cLCIS than hgDCIS. E2F target genes were upregulated in PLCIS compared to cLCIS, while glycolysis genes and interferon-α genes were upregulated in hgDCIS relative to PLCIS.

Conclusion: Although gene set analysis suggests PLICS could have more aggressive behavior than cLCIS, gene expression profiling suggests it has closer biological behavior to cLCIS than to hgDCIS. Long-term clinical outcome studies are still needed to determine prognosis and optimal management.

INTRODUCTION

Pleomorphic lobular carcinoma in situ (PLCIS) is a lobular neoplasm variant with worrying histologic features including high nuclear grade, necrosis, and increased mitoses, features also seen in high-grade ductal carcinoma in situ (hgDCIS). Optimal management of PLCIS is unclear. Classic lobular carcinoma in situ (cLCIS) is considered an incidental risk factor that does not necessitate additional interventions;[1] however, the literature suggests that PLCIS may be a non-obligate precursor to invasive carcinoma.[2,3] The National Health Service and European Society for Medical Oncology advocate for PLCIS to be treated with complete excision followed by adjuvant hormone therapy and/or radiation, similar to management of hgDCIS.[1] The National Comprehensive Cancer Network, while more conservative, still recommends complete surgical excision of PLCIS with negative margins;[1] however, there is a lack of uniform approach among general surgeons as some approach PLCIS in the same way as they deal with cLCIS.[4] To explore the biological behavior of PLCIS, which has implications for its malignant potential, we looked at gene expression to compare PLCIS's expression profile to those of cLCIS and hgDCIS, entities which were chosen for comparison due to overlaps in histologic features and surgical recommendations.

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METHODS

Patient sample selection

This is a retrospective study. Samples from patients with either a diagnosis of PLCIS, cLCIS, or hgDCIS from 2015 to 2024 were identified in the Cedars-Sinai Medical Center pathology database. To reduce biologically confounding variables of potentially unsampled adjacent breast tissue, only excision specimens were selected from patients who did not carry a diagnosis of invasive carcinoma, either historical or current on either side. For cLCIS and PLCIS samples, cases were selected who had no concurrent atypical ductal hyperplasia or ductal carcinoma in situ (DCIS) of any grade present in the excision specimen. For cLCIS samples, cases where cLCIS was the sole neoplastic process present in the specimen were selected. Due to high concurrence of cLCIS with PLCIS, PLCIS cases often had a background of cLCIS; however, only blocks that were predominantly PLCIS with good margins from neighboring cLCIS, which were conducive for macrodissection, were selected. Cases underwent re-review by an expert breast pathologist to confirm the qualifying diagnosis and to select appropriate representative formalin fixed paraffin embedded (FFPE) tissue blocks without any additional confounding pathology (i.e., usual ductal hyperplasia, pseudoangiomatous stromal hyperplasia, etc.). Representative histologic images of the disease entities are shown in Figure 1. A summary of basic clinical details is provided in Table 1.

RNA extraction and gene expression analysis

Regions composed predominantly of the qualifying diagnosis were identified for macrodissection to reduce the gene expression noise of normal background breast tissue.

Table 1. Summary of Patient Demographics

Diagnosis	No.[a]	Age, median (IQR)	Caucasian, No. (%)	Black, No. (%)	Asian, No. (%)	Other, No. (%)	Unknown, No. (%)
cLCIS	10	44 (41.25–46.75)	7 (70)	1 (10)	0 (0)	1 (10)	1 (10)
hgDCIS	9	66 (49–73)	7 (77.8)	0 (0)	1 (11.1)	1 (11.1)	0 (0)
PLCIS	16	58.5 (48.5–69)	9 (56.3)	2 (12.5)	4 (25.0)	1 (6.3)	0 (0)
Total	35	53 (45–68)	23 (65.7)	3 (8.6)	5 (14.3)	3 (8.6)	1 (2.9)

[a]All participants were female

cLCIS, classic lobular carcinoma in situ; hgDCIS, high-grade ductal carcinoma in situ; PLCIS, pleomorphic lobular carcinoma in situ; IQR, interquartile range.

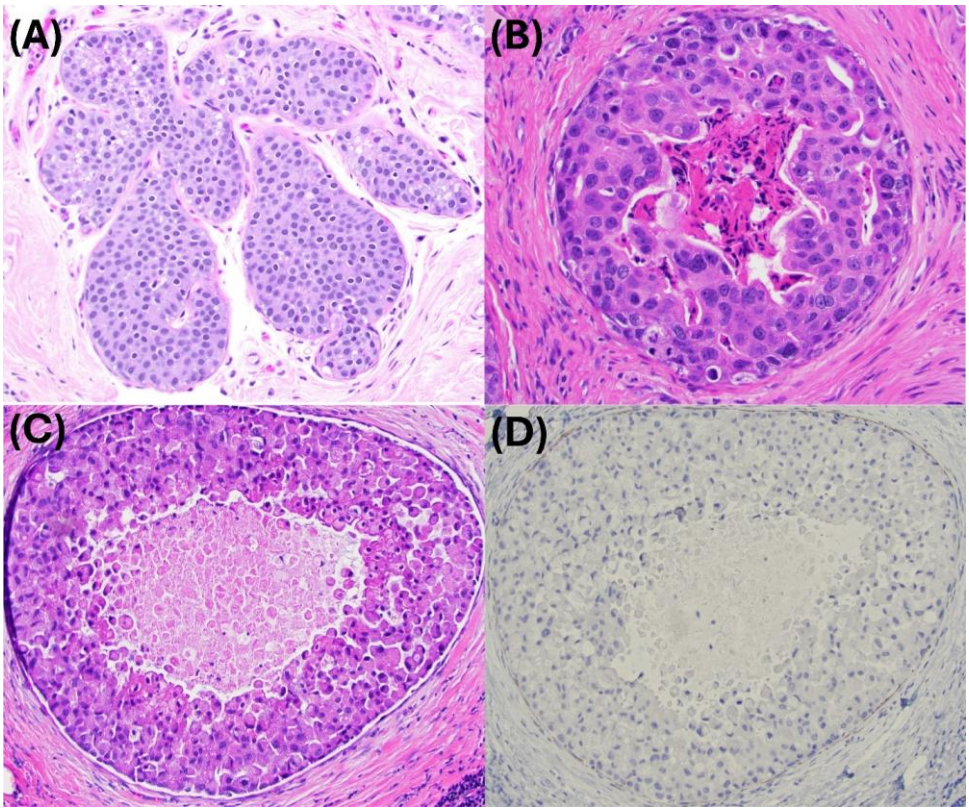

Figure 1. Representative histologic images of the different entities. (A) cLCIS, 100x H&E (B) hgDCIS with necrosis, 200x H&E (C) PLCIS with central necrosis, 100x H&E (D) PLCIS with central necrosis, 100x eCadherin IHC

RNA was extracted with the Rneasy FFPE kit (Qiagen, Hwereen, Germany) and expression of 725 tumor-related genes (NanoString PanCancer 360 panel) was measured using the nCounter platform (Nanostring Technologies, Seattle, WA, USA). All samples passed NanoString platform-specific quality control metrics, including binding density, positive control linearity, and imaging quality parameters.

Differential gene expression

The raw expression values which were log2-transformed, were converted to pseudo-counts by raising 2 to the power of the raw values (2^raw) to generate pseudo-count data suitable for statistical modeling. Genes with low expression across all conditions (without pseudo-counts > 1 in more than 3 samples) were filtered out for further analysis. Pseudo-counts were normalized using the Trimmed Mean of M-values (TMM) method to adjust for library size differences between the samples. Given the limited sample size and standardized sample collection and processing procedures, no significant batch effects were identified. Therefore, only the biological classification (disease state) was included as a factor in the statistical model, with no additional covariates considered.

Differential expression analysis was performed using the *edgeR* package (https://bioconductor.org/packages/release/bioc/html/edgeR.html).[5] All validated samples were incorporated into a single generalized linear model with disease state as the main factor. Differential expression was assessed using likelihood ratio tests for pairwise disease contrasts (PLCIS vs cLCIS, PLCIS vs hgDCIS), as well as a joint likelihood ratio test to evaluate the overall disease effect across all 3 groups simultaneously. *P* values were adjusted using the Benjamini-Hochberg method to control the false discovery rate (FDR). For downstream analyses, the significance threshold was set at absolute fold-change ≥1.5 and adjusted *P* value <0.01.

Gene set enrichment analysis

Gene Set Enrichment Analysis (GSEA) was performed using the Hallmark gene set collection from the Human Molecular Signatures Database to compare PLCIS against both LCIS and DCIS.[6–9] Significance was defined as nominal *P* value <0.05. To account for multiple hypothesis testing, FDR was additionally calculated off the normalized enrichment score (NES) for significant gene sets (as determined by nominal *P* value) to determine the probability of false positive results.

RESULTS

There were initially 329 cases of PLCIS and 2603 cases of cLCIS identified within the in-house pathology database in the period of 2015 to 2024. Of these, 192 PLCIS cases and 501 cases of cLCIS cases were from core needle biopsies and excluded. Of the remaining 137 PLCIS cases and 2102 cLCIS cases, 121 PLCIS cases and 2085 cLCIS cases were excluded due to either contemporary or historical invasive carcinoma or concurrent DCIS within the specimen. Of the remaining 17 cLCIS cases, 7 were excluded due to concurrent PLCIS within the specimen. In total, there were 16 cases of PLCIS and 10 cases of cLCIS after implementation of the inclusion and exclusion criteria outlined above, all of whom were included within this study. A large number of qualifying hgDCIS cases were identified after implementation of inclusion and exclusion criteria, from whom 9 cases were chosen to match the number of eligible PLCIS and cLCIS cases. In total, there were 16 cases of PLCIS, 10 cases of cLCIS, and 9 cases of hgDCIS who were included for gene expression analysis.

A total of 3 differentially expressed genes (DEGs) were identified between PLCIS and cLCIS (1 upregulated and 2 downregulated in PLCIS). A total of 63 DEGs were identified between PLCIS and hgDCIS (43 upregulated and 20 downregulated in PLCIS). Volcano plots showing pair-wise comparisons of DEGs between PLCIS against cLCIS and hgDCIS are shown in Figures 2A–B, respectively.

Based on nominal *P* values, gene set analysis between PLCIS-cLCIS showed that PLCIS was significantly enriched in the E2F transcription factor target gene expression *(P* = 0.028) while cLCIS had enrichment in the apical junction complex (*P* = 0.037) set of genes; corresponding FDR values were 6.8% for E2F transcription factors and 76.8% for apical junction complex genes, indicating a high likelihood that the difference in apical junction complex was a false positive. Gene set analysis between PLCIS-hgDCIS showed hgDCIS was enriched for glycolysis pathway (*P* = 0.030) and interferon-α response (*P* = 0.017) while no gene sets were enriched in PLCIS; corresponding FDR values were 27.7% for glycolysis and 0.9% for the interferon-α response.

Of note, when the familywise-error rate (FWER) correction method was used to correct the *P* values of the 4 significant gene sets listed, only the interferon-α response remained significant (*P* = 0.009) while the E2F transcription factor target gene set had borderline significance (*P* = 0.068); however, it has been noted that FWER is a conservative correction method.[9] Heat maps from gene set analysis are shown in Figures 2C–D.

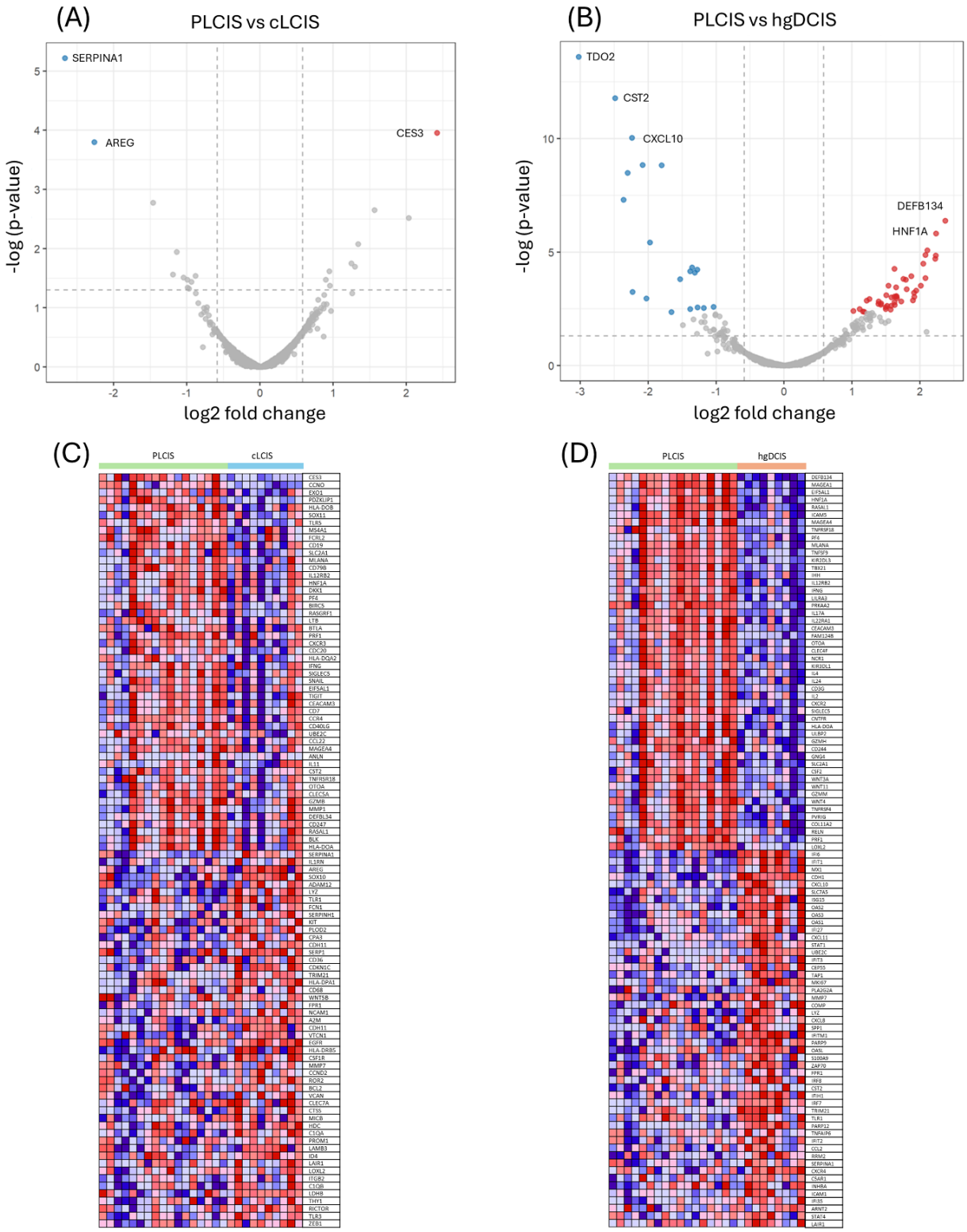

Figure 2. Differential Gene Expression Profiles Among PLCIS, cLCIS, and hgDCIS. Gene expression profiles showing that hgDCIS–PLCIS has more differentially expressed genes compared with cLCIS–PLCIS. Volcano plots for pairwise comparisons of A, PLCIS vs cLCIS, and B, PLCIS vs hgDCIS. Heatmaps showing the top 50 genes for each disease state during pairwise gene set analyses of C, PLCIS vs cLCIS, and D, PLCIS vs hgDCIS.
cLCIS, classic lobular carcinoma in situ; hgDCIS, high-grade ductal carcinoma in situ; PLCIS, pleomorphic lobular carcinoma in situ.

DISCUSSION

There is a much more distinctive differential gene expression profile between PLCIS and hgDCIS than with cLCIS, suggesting that the differences in biological behavior are more pronounced between hgDCIS and PLCIS. This might be intuitively

expected due to a shared lobular phenotype and studies showing a stepwise molecular progression from cLCIS to PLCIS;[3] however, it is unexpected to find that only few genes have differential expression between cLCIS and PLCIS which could suggest a closer biological behavior than would be expected based on morphology.

Gene set analysis can give a more nuanced insight into biological behavior. Although the apical junction gene set represents adherents and tight junctions which are characteristically lost in cancer, it is difficult to draw any conclusions from this finding given the high probability that it is a false positive result.[6,10] Because of this, the primary difference between cLCIS and PLCIS is upregulation of E2F transcription factor targets in PLCIS. E2F transcription factors are primarily associated with cellular proliferation due to their regulation of DNA replication and checkpoint control genes and are frequently upregulated in cancer.[11–13] Increased proliferation due to upregulation of the E2F transcription factor targets could explain the characteristic necrosis which is one of the distinguishing features between cLCIS and PLCIS. Previous studies have linked increased E2F target gene expression in breast cancer with worse prognosis, including decreased survival rates and heightened mortality risk.[14]

Between PLCIS and hgDCIS, the primary DEGs sets were upregulation of glycolysis genes and interferon-α response genes in hgDCIS. Aerobic glycolysis is a key process in cancer cells; not only is it responsible for the majority of energy production in cancer, but it also influences other aspects of tumor development and progression, such as immune suppression and modulation of the tumor microenvironment.[15,16] Although the differences in glycolysis gene set expression had a relatively high chance of being a false positive finding at 27.7%, previous studies exploring gene expression between invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC) similarly found an increased expression of glycolysis-related genes in IDC relative to ILC, which does provide some reassurance that this could be a real finding;[17] however, upregulation of glycolysis in the fully malignant IDC does also limit the inferences which can be made about malignant progression of in-situ lesions, as this could instead just be a biological feature associated with the ductal phenotype. The exact role of interferon-α in cancer biology is still not entirely known. Interferon-α has classically been associated with antitumoral properties, being a driver of apoptosis and modulator of the immune microenvironment;[18,19] however, interferon-α has been shown to have procancer effects on cells, such as the ability to activate the NF-κB pathway, promote angiogenesis, and induce cell survival.[20–22]

Importantly, there is a noticeable lack of differences in TGF-β, hedgehog, notch, Wnt/β-catenin, or PI3K-AKT-mTOR signaling pathway which are key signaling pathways in breast cancer biology.[23,24] The significance of this finding is hard to determine, especially since mutational profiles are not available for the samples used in this study. Given that gain-of-function mutations in PIK3CA are ubiquitous throughout breast neoplasms, including both DCIS and LCIS, and are an early event implicated in tumor initiation, it is possible that a high prevalence of activating PIK3CA mutations in the study samples could be upregulating the PI3K pathways at comparable rates.[25,26] It is interesting to note, however, that a gene expression study between IDC and ILC found lower mTOR activity and increased AKT and PI3K activity in ILC, which is suggestive of a unique mTOR regulation pathway in ILC.[17] The absence of such findings in our study could be due either to absence of this regulation pathway in the in-situ lesions or because such a granular pathway might not be represented in the gene set collection used in analyses and the resultant counterintuitive changes in mTOR, AKT, and PI3K expression could be confounding the analysis of the broader PI3K-AKT-mTOR pathway; a separate ILC-IDC gene expression study using GSEA analysis with the same Hallmark gene set collection used in this study likewise did not find any differences in the PI3K-AKT-mTOR signaling pathway which supports the latter interpretation.[27] The lack of gene-gene interaction analysis has been a criticism of GSEA and could explain why it may not be able to discern such a specific interaction.[28]

It is important to note that although gene set analysis can provide vague insights into biological behavior, the main purpose of GSEA is the generation of hypotheses and so it is difficult to use these findings to extrapolate firm conclusions about biological behavior.[9] Additional nuances can be introduced by placing the findings of this study within the context of similar lobular and ductal breast cancer gene expression studies, but even this exploration is limited due to the lack of literature analyzing gene expression in specifically pleomorphic lobular variants. Furthermore, this study was limited by a relatively small sample size due to stringent inclusion/exclusion criteria as well as a relatively low number of genes analyzed, which are all factors likely contributing to the highly variable FDRs.[29] Findings with low FDR, primarily the differences in E2F transcription factor and interferon-α gene expressions, are expected to be relatively stable while the reliability of other findings are questionable and

could be further resolved by increasing the sample size.

While this study provides a general hierarchy of disease severity and disease overlap, it does highlight the challenges associated with using gene expression data to reach conclusions about biological behavior or clinical significance. As such, larger cohort studies interrogating long-term clinical outcomes of PLCIS are needed to determine prognosis and optimal management.

CONCLUSION

PLCIS gene expression profile had greater overlap with cLCIS than with hgDCIS. Gene set analysis showed increased expression of E2F transcription factor targets in PLCIS relative to cLCIS and increased expression of glycolysis genes and interferon-α genes in hgDCIS as compared to PLCIS. These findings suggest that PLCIS behaves more similarly to cLCIS than hgDCIS and may be more aggressive than cLCIS, but not as aggressive as hgDCIS. Due to limitations translating gene expression studies to clinical outcomes, large cohort studies evaluating long-term clinical outcomes of PLCIS are still needed to definitively determine prognosis and optimal management.

ETHICAL CONSIDERATIONS

All experiments were performed in accordance with the relevant guidelines and regulations of the Cedars-Sinai Medical Center Institutional Review Board committee (IRB#Pro00050065). As determined by the Institutional Review Board, this study is not subject to the informed consent requirements.

DATA AVAILABILITY

The corresponding author can be contacted directly for access to the data.

CONFLICT OF INTERESTS

There are no conflicts of interest to be declared by the authors.

FUNDING

All sources of funds supporting the completion of this manuscript are under the auspices of Cedars-Sinai Medical Center. Funding for the project was provided by breast research grants from Armando Giuliano provided by the Fashion Footwear Charitable Foundation of New York, Inc.

ACKNOWLEDGMENTS

None.

AI DISCLOSURE

No generative AI was used in either the writing of the manuscript or production of the figures.

AUTHOR CONTRIBUTION

ML: Conceptualization, Methodology, Investigation, Writing – Original Draft, Writing – Review & Editing, Visualization; XL: Conceptualization, Methodology, Investigation, Writing – Review & Editing; KY: Formal Analysis, Writing – Original Draft, Writing – Review & Editing, Visualization; HN: Methodology, Writing – Review & Editing; EV: Methodology, Writing – Review & Editing; AG: Writing – Review & Editing, Supervision, Funding Acquisition; FD: Conceptualization, Methodology, Writing – Review & Editing, Visualization.

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How to Cite This Article

Leong M, Li X, Ying K, Nguyen H, Vail E, Giuliano A, et al. Gene Expression Comparison of Pleomorphic Lobular Carcinoma In-Situ with Classical Lobular Carcinoma In-Situ and High-Grade Ductal Carcinoma In-Situ. Arch Breast Cancer. 2026; 13(2):243-9.
Available from: https://www.archbreastcancer.com/index.php/abc/article/view/1274