

Lobular Breast Cancer Statement

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1. What is known about lobular breast cancer

Invasive lobular carcinoma (ILC) is the second most common breast-cancer histology, accounting for roughly 10% to 15% of cases, and is distinct from the more common invasive breast carcinoma of no special type (NST), historically called invasive ductal carcinoma (IDC) or ductal breast cancer. In New Zealand (NZ), ILC is also more likely to be multifocal and can occur in both breasts.

Biologically, the defining feature of ILC is loss of the E-cadherin cell to cell adhesion protein, usually through alteration of the CDH1 tumour suppressor gene. A major molecular study identified CDH1 loss as the hallmark molecular lesion and found enrichment of PTEN, TBX3, and FOXA1 genes in ILC. Separate pathology work reports that E-cadherin immunostaining is lost in about 90% of ILC. This is why lobular cancer is not simply “another ER-positive breast cancer”; it has a distinct adhesion defect and a distinct downstream signalling landscape.

That biology changes the way the cancer looks and behaves. Lobular cancer cells tend to grow in single-file or single-layer patterns rather than forming a clear mass, which is one reason ILC can be harder to detect on standard imaging. This diffuse, less mass-forming growth also helps explain why lobular disease may be undermeasured by standard radiology and why patients often describe thickening or subtle change rather than a discrete lump.

ILC also differs in where it spreads. In a 2025 JAMA Network Open cohort of 9,714 patients with metastatic breast cancer, metastatic ILC had fewer visceral metastases and more bone-only metastases than metastatic invasive ductal carcinoma / invasive breast carcinoma of no special type (IDC/NST). Bone, meninges, bone marrow, peritoneum, and uterus were more prevalent in metastatic ILC, and the authors also noted the recognised tendency of lobular cancer to involve the peritoneum, gastrointestinal tract, and ovary.

These growth and spread patterns have practical consequences for research. A 2021 study reported in *npj Breast Cancer* found that most stage IV breast-cancer trials required measurable disease, and that metastatic ILC patients were significantly underrepresented in clinical-trial enrolment at the authors’ institution. That is a serious issue, because it means the evidence base for treatment efficacy is partly built in populations that do not fully reflect how lobular cancer presents.

The research community increasingly recognises this. An international 2024 survey with 1,774 participants from 66 countries found that patients and advocates prioritised better imaging and earlier detection, while clinicians and researchers prioritised endocrine resistance, novel drugs, and genomic predictors of response. The same survey found that only 11% of respondents thought enough ILC models existed, and 52% felt ILC was poorly represented in public genomic datasets.

In summary, ILC is a distinct clinicobiologic entity: it has different cell adhesion, a different growth pattern, different metastatic behaviour from other cancers, and probably different mechanisms of treatment resistance. It remains problematic that detection and treatment systems have only partly caught up.

2. How treatment for lobular breast cancer differs from other breast cancers

Today, patients with ILC are still treated mostly according to stage and receptor biology ER, PR, HER2, menopausal status, germline status, and prior therapy, rather than by a wholly separate lobular-specific algorithm. That is sensible in the short term because many effective drugs work across breast-cancer subtypes, but it also means lobular patients are often managed with evidence generated mainly in non-lobular populations. Current standard frameworks in official breast-cancer guidance are overwhelmingly receptor- and stage-based.

For early-stage disease, the backbone remains surgery, with nodal staging as appropriate, and radiotherapy when indicated. National Cancer Institute (USA) notes that whole-breast radiotherapy after breast-conserving

surgery reduces recurrence and breast-cancer death. For hormone-receptor-positive disease, endocrine therapy is a major pillar. Chemotherapy is added based on stage, biology, genomic-risk tools, and patient factors. HER2-positive disease gets anti-HER2 therapy. Selected triple-negative disease may receive immunotherapy-based treatment.

Where ILC differs is that classic lobular cancer is often less chemosensitive than IDC/NST cancer, especially in the neoadjuvant setting. A meta-analysis cited by recent literature found that ILC is much less likely to achieve pathologic complete response with neoadjuvant chemotherapy, and more recent trial analyses continue to report lower response rates than IDC/NST disease. That does not mean chemotherapy never helps; it means clinicians should be cautious about assuming it will work in lobular cancer in the same way it does in IDC/NST cancer.

Endocrine therapy is especially important in ILC. In the BIG 1-98 analysis, letrozole was more effective than tamoxifen for patients with lobular carcinoma, which helped establish aromatase inhibition as particularly important in postmenopausal ER-positive lobular disease. Therefore, in classic ILC, endocrine therapy is not just “one option among many”; it is often the central systemic strategy.

Recent ESMO Breast Cancer commentary reinforces this direction of travel: advances in molecular profiling are strengthening the view that ILC is biologically distinct from other ER-positive breast cancers, particularly through CDH1/E-cadherin loss, FOXA1/PTEN/TBX3 enrichment, differences in the oestrogen receptor axis, late recurrence risk, lower chemotherapy responsiveness, and the need for more ILC-specific trials. The practical implication is not that all ILC already has a separate standard treatment algorithm, but that treatment research and trial design increasingly need to account for lobular biology.

For advanced ER-positive / HER2-negative disease, which is the most common lobular phenotype, recent NZ consensus guidance states that a CDK4/6 inhibitor plus endocrine therapy is the standard of care that should be offered. The CDK4/6 inhibitor can be paired with an aromatase inhibitor or fulvestrant. Later-line treatment options include everolimus, not funded in NZ for breast cancer; alpelisib for PIK3CA-mutated disease, not funded in NZ; elacestrant for ESR1-mutant disease where known, neither registered nor funded in NZ; and capivasertib, not registered or funded in NZ, with fulvestrant for selected AKT-pathway altered disease where approved. In later lines, antibody-drug conjugates such as sacituzumab govitecan, currently on Pharmac’s Options for Investment list, also enter the picture.

For advanced HER2-positive lobular breast cancer, treatment generally follows the HER2-positive advanced breast-cancer pathway rather than a lobular-specific pathway. Current NZ advanced breast cancer guidance describes first-line treatment as chemotherapy plus dual HER2 blockade with trastuzumab and pertuzumab. For early HER2-positive disease, treatment remains stage-based and typically involves surgery, chemotherapy and HER2-directed therapy in the neoadjuvant and/or adjuvant setting, depending on tumour size, nodal involvement and response. Although lobular histology may influence imaging interpretation and expectations around treatment response, HER2-positive ILC is still generally managed according to broader HER2-positive breast-cancer standards rather than a distinct lobular-specific algorithm.

For triple-negative advanced disease, NZ guidance supports pembrolizumab plus chemotherapy in PD-L1-positive first-line disease, with platinum regimens and later-line chemotherapy or antibody-drug conjugate options depending on context. For germline BRCA1/2-mutated HER2-negative advanced disease, PARP inhibitors such as olaparib, registered but not funded in NZ, are accepted options.

In summary, there is still no routine standard therapy given solely because a cancer is lobular. What exists instead is an accumulating set of clues that lobular disease often needs different imaging, different expectations around chemotherapy, and probably different resistance-focused drug development.

3. New Zealand research on lobular breast-cancer

The clearest NZ lobular breast cancer research strength is the CDH1/E-cadherin axis, where Professor Parry Guilford and the University of Otago (UO) have had a longstanding role. Hereditary diffuse gastric cancer (HDGC), caused by mutations of the inherited E-cadherin gene CDH1, was first identified in NZ through a partnership between UO researchers and an affected Bay of Plenty whānau (family group). Female CDH1 mutation carriers have a 39%–55% lifetime risk of lobular breast cancer, with annual breast MRI recommended from age 30. UO notes there are about 25 known families with HDGC in NZ. As CDH1 loss is a defining feature of

ILC biology, Guilford's work is relevant for those with lobular breast cancer, i.e. for a broader group than those with hereditary HDGC.

Prof. Guilford's lobular breast cancer work sits mainly at the mechanistic and translational end of the research pipeline. Breast Cancer Foundation NZ (BCF) and Breast Cancer Cure describe the programme as "synthetic lethal targeting of lobular breast cancer", focused on exploiting vulnerabilities created by loss of CDH1/E-cadherin to develop new treatments. NZ therefore already has a significant foothold in one of the most biologically central questions in ILC: what therapeutic vulnerabilities arise when E-cadherin is lost.

The second area of NZ strength is imaging research. The LUMINA FAPI PET-CT* trial, recruiting across Auckland, Waikato, Bay of Plenty, and Palmerston North, aims to stage lobular cancers more accurately, and plans to recruit 50 patients from around the country. BCF reports that about 450 women are diagnosed with lobular breast cancer each year in NZ, noting that its single-layer growth pattern can make it harder to detect on mammography. BCF has reported to BCAC that as of May 2026 45 patients have already been recruited to the trial and scanned, that extra follow-up scans have been added through a sub-study, and that travel support is being provided to widen participation.

The third NZ strength is data infrastructure. The BCF Breast Cancer Register, Te Rēhita Mate Ūtaetae (the Register), provides an important national breast-cancer data source. The Register includes multiple fields, including histology, therapies, follow-up, loco-regional recurrence, and advanced breast cancer. Researchers can request de-identified data, allowing them to understand treatment and outcomes for different breast cancer stages and subtypes. This data gives NZ the ingredients for subtype-specific lobular analyses, even if those analyses are not yet highly visible in public reporting.

A further emerging strength is local population-level ILC research. Yuting Yang, a PhD candidate at the University of Auckland supervised by Dr Annette Lasham, is undertaking research on ILC in NZ using Register data and related datasets. This work is important because it can help clarify whether ILC behaves differently from invasive ductal carcinoma / invasive breast carcinoma of no special type (IDC/NST) in the NZ population, including in relation to stage at diagnosis, tumour characteristics, receptor profile, treatment patterns, recurrence, metastatic disease, survival, and equity of outcomes. Dr Lasham and colleagues are developing and expanding a "Not a One-Size-Fits-All" Breast Cancer Screening Model for NZ. Medical oncologist Abbey Wrigley seeks to collaborate in developing a better understanding of ILC and its implications for NZ patients and services. This adds further local clinical and research involvement and may help connect registry-based findings with practical questions about patient pathways, treatment decision-making, and service planning.

A current grant application seeks to examine whether ILC needs to be treated differently from IDC/NST in NZ. If funded, this would be a significant step toward answering one of the central practical questions in lobular breast cancer, i.e. whether the biology and clinical behaviour of ILC should translate into different approaches to imaging, systemic therapy, follow-up, metastatic assessment, trial design, and/or patient support.

In summary, NZ is strongest in hereditary biology, CDH1/E-cadherin science, lobular imaging, and breast-cancer data infrastructure. It also now has emerging registry-based ILC research through the University of Auckland and a current grant application focused on whether ILC should be treated differently from IDC in NZ. What is still missing is a clearly coordinated national ILC programme that links biology, imaging, registry analytics, patient experience, treatment outcomes, and clinical trials. In other words, NZ has important pieces of the puzzle, but does not yet have the full puzzle assembled.

4. What the next research and clinical steps might be

First, better imaging and staging are a priority. The international ILC survey put imaging and early detection at the top for patients, and both FES-PET* and FAPI*-based approaches are showing promise. A prospective study found FES-PET/CT changed stage in 3 of 17 patients with ER-positive ILC, and head-to-head data suggest FES can compare favourably with FDG* in metastatic lobular disease. NZ's LUMINA study fits squarely into this need.

Second, histology-specific trial design needs to improve to provide accurate measures of treatment response in ILC. Response Evaluation Criteria in Solid Tumours (RECIST) is the gold standard for measuring response in oncology. RECIST defines treatment success by the measurable shrinkage of distinct solid tumours. This measure is clearly problematic for diffuse, non-measurable metastatic lobular disease, and trial reporting by histology remains weak. Lobular disease needs prospective trials that either stratify or enrich for ILC, use

endpoints that make sense for diffuse disease, and report outcomes separately rather than burying data from lobular patients inside that from larger breast cancer cohorts.

Third, the biggest biological target area is probably endocrine resistance. The international ILC survey ranked this as top ILC priority for clinicians and researchers, and several new mechanistic studies have begun. A paper published in *Cell Death and Disease* (2025) identified the downregulation ASS1 (arginosuccinate synthase) as a mechanism of acquired tamoxifen resistance in ILC and showed that restoring ASS1 expression or inhibiting pyrimidine biosynthesis could re-sensitise lobular cancer models to tamoxifen. That is exactly the kind of illumination of lobular-specific resistance biology that could eventually change treatment.

Fourth, the field needs more work on targetable lobular vulnerabilities. The molecular portrait work implicates PTEN/AKT, FOXA1, and TBX3-related biology, while NZ's Guilford programme is explicitly pursuing synthetic lethality downstream of CDH1 loss. This is promising, but this research is currently largely translational rather than influencing standard-of-care. Potentially, the next step will require taking these mechanisms into well-designed clinical studies with biomarkers built into trial design.

The ESMO commentary explains why this needs to be done carefully. ROS1 inhibition was a biologically attractive research target because it appeared synthetically lethal with E-cadherin loss, but early clinical trials combining endocrine therapy with ROS1 inhibitors have been negative. That does not undermine the synthetic-lethality concept; rather, it shows that lobular-specific hypotheses need prospective trials that incorporate correlative biology. Other ILC-relevant approaches, including AKT inhibition and HER2-targeted therapy for HER2-mutated ILC, are now being explored internationally.

Fifth, NZ-specific next steps are now becoming clearer. Data from the Register could be used to produce routine ILC-specific national reports on stage at diagnosis, tumour biology, treatment patterns, recurrence, metastatic sites, survival, and equity of outcomes. Yuting Yang's University of Auckland (UoA) PhD work using registry data is an important step in this direction and should be viewed as part of the emerging national evidence base. If her current grant application is successful, her research could help answer the highly practical question of whether ILC needs to be treated differently from IDC/NST in NZ. New Zealand could also support multicentre tissue and blood collection linked to imaging, registry data, treatment response, and outcomes.

The bottom line: lobular breast cancer is now clearly understood as biologically and clinically distinct, but therapy remains only partly adapted to that fact. NZ already has credible building blocks for a coordinated research programme that could include OU and Guilford's/CDH1 science, synthetic-lethality research, a strong breast-cancer data platform in the Register, lobular-specific imaging research through LUMINA, emerging UoA registry-based ILC research, and a grant proposal seeking to determine whether ILC needs to be treated differently from IDC/NST in NZ. The real opportunity now is to connect these pieces into a coordinated national research strategy that moves us from awareness of biological differences to subtype-specific evidence and ultimately to ILC subtype-specific care.

Key to scanning methodology acronyms

PET: A Positron Emission Tomography (PET) scan is an advanced imaging test that tracks metabolic activity in your cells using a safe radioactive tracer and is used to diagnose and evaluate conditions including cancer. It is usually combined with a CT scan for maximum accuracy.

CT: A Computed Tomography (CT) scan uses X-rays and computer software to create detailed, cross-sectional 3D images of your body, used to stage cancer and determine whether or where it has spread beyond the breast.

FES-PET: an advanced, non-invasive imaging procedure that uses a radioactive tracer called Fluoroestradiol (FES) to detect oestrogen receptor-positive (ER+) breast cancer. It can help locate metastases, assess ER expression across disease sites, and support endocrine-therapy decision-making where available. In ILC, it is promising because many tumours are strongly ER-positive and can be difficult to measure or biopsy, but it should still be described as an evolving tool rather than a routine standard in NZ.

FAPI-PET/CT: Fibroblast Activation Protein Inhibitor-PET is an emerging pan-cancer imaging technique that targets fibroblast activation protein (FAP), which can be highly expressed in cancer-associated stromal tissue. Early studies suggest it may improve lesion contrast and detection in some cancers compared with FDG-PET, but its role in ILC remains investigational. NZ's LUMINA study is therefore important because it is testing whether FAPI-PET/CT can improve staging and assessment specifically for lobular breast cancer.

FDG-PET: A fluorodeoxyglucose-PET (FDG-PET) scan is a nuclear imaging test that uses a mildly radioactive sugar tracer to map how cells use energy. Because highly active cells, including many cancers, consume more sugar, FDG-PET is widely used for cancer staging and response assessment. Some ILC lesions can be less FDG-avid or harder to measure than other breast cancers, which is one reason FES-PET and FAPI-PET/CT are being explored.

References and source notes

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