

ILC Symposium 2026

Background to Session Presentations for Advocate Attendees

International Invasive Lobular Carcinoma (ILC) Symposium
San Francisco, California, September 23–25, 2026

Important Note About These Materials

These background sheets were developed as informational resources to help advocate attendees prepare for the ILC Symposium. They are not summaries of the presentations, and were developed without the input of the speakers. Advocate authors used their own methodology and available information through the internet using the presentation title as a starting point. The sheets include a section named “What this talk is likely to cover and why,” which reflects advocate interpretations or speculations about topics that may be discussed. These are not statements or conclusions from the presenters.

These materials are for information background purposes only and are not intended as medical advice. This document has not been reviewed by scientists, researchers, or clinicians. If you have a question or concern about any of the contents of this booklet, please reach out to LBCA staff member Gitte Joergensen gitte@lbca.org. We hope that you find them useful!

How This Guide Is Organized

The background sheets follow the order of the Symposium scientific program. Each section begins with the Scientific Session title, followed by the presentations in agenda order.

Acknowledgements

LBCA is enormously grateful to the advocates who developed these background sheets and to the mentors who provided guidance and assisted with finalizing them.

Background Sheet Writers: S Abdul Qadir, A Ashida, J Bentham, A Dev, M Dominiecki, C Gustafson, G H Joergensen, J Hogan, L Hutcheson, J Kirkham, M Mitchell-Daniels, J Nielsen, A Russell-Parliman, J Spence, K Spencer.

Write-up Mentors: G H Joergensen, L Hutcheson, J Moran, B Neilsen, L Petitti, D Romer, B Sulick.

SCIENTIFIC SESSION 1: Genetics, Risk, and Exposures

Wednesday, September 23, 2026 | 1:30–2:45 pm

Moderators: Fresia Pareja, MD, PhD and Nicole Dearing

Presentations:

1. Pathogenic germline variants in invasive lobular breast cancer

Giovanni Corso, MD, PhD — European Institute of Oncology (IEO), Milan, Italy

2. Hormonal exposures in ILC development

Cathrin Brisken, MD, PhD — Institute of Cancer Research (ICR), London, UK

3. Latest data in hormone replacement therapy

Mindy Goldman, — MD University of California, San Francisco (UCSF)

4. Lobular carcinoma in situ: management strategies

Tari King, MD — Winship Cancer Institute of Emory University / Emory University

Scientific Session 1: Genetics, Risk, and Exposures
Pathogenic Germline Variants in Invasive Lobular Breast Cancer
Presenter 1: Giovanni Corso, MD, PhD

Background: Dr. Giovanni Corso is a breast surgeon and cancer genetics researcher at the European Institute of Oncology (IEO) in Milan, Italy. His work focuses on hereditary breast cancer, particularly the role of CDH1 and other inherited genetic variants in invasive lobular breast cancer (ILC). He is internationally recognized for his research on hereditary lobular breast cancer and hereditary diffuse gastric cancer syndrome.

Most cases of invasive lobular carcinoma (ILC) occur sporadically, meaning they are not caused by an inherited genetic change. However, a small proportion of breast cancers are associated with pathogenic germline variants, in other words, genetic changes that are present from birth, can be passed from parent to child, and increase the risk of developing certain cancers.

The genes BRCA1 and BRCA2 are the best-known inherited breast cancer susceptibility genes, but ILC has a particularly important association with CDH1, the gene that encodes the cell adhesion protein E-cadherin. Loss of E-cadherin is a defining feature of ILC biology, and inherited CDH1 pathogenic variants are associated with Hereditary Diffuse Gastric Cancer (HDGC) syndrome, which also increases the lifetime risk of developing lobular breast cancer.

Today, genetic testing often uses multigene panel testing, allowing healthcare providers to evaluate several cancer susceptibility genes at the same time. Current guidelines recommend referral for genetic counseling and consideration of germline testing for individuals who meet specific personal or family history criteria. Identifying a pathogenic variant can influence screening recommendations, treatment decisions, options to reduce future cancer risk, and recommendations for at-risk relatives through cascade testing.

Although our understanding of hereditary breast cancer has grown considerably, important questions remain. Researchers continue to investigate which inherited genetic variants contribute specifically to ILC risk, whether current testing criteria identify everyone who could benefit from genetic testing, and how genetic findings can be used to provide more personalized care for people living with ILC.

What the Talk Is Likely to Cover, and Why: Dr. Giovanni Corso has spent much of his career studying the inherited genetic changes that can increase the risk of developing invasive lobular breast cancer (ILC). Based on his research, this presentation will likely focus on which inherited gene changes are most important in ILC, especially CDH1, and how genetic testing is helping doctors identify individuals and families who may have an inherited cancer risk.

You may also hear about multigene panel testing, which looks at several cancer-related genes at the same time, and how this has changed what we know about hereditary breast cancer. While BRCA1 and BRCA2 are the most familiar breast cancer genes, researchers now know that other genes, including CDH1, can be particularly important for some people with ILC. Another topic may be how genetic test results can affect medical care. For example, finding an inherited pathogenic variant may influence cancer screening, decisions about risk-reducing surgery, treatment planning, and whether other family members should consider genetic counseling or testing.

Although we have learned a great deal about hereditary breast cancer over the past decade, there is still much to discover about inherited risk specifically in ILC. Dr. Corso's work has helped move this field forward, and this presentation is likely to highlight both what we know today and the important questions researchers are still working to answer.

Why This Matters to People with ILC: If you've ever wondered whether your breast cancer might be hereditary or whether your children, siblings, or other relatives could also be at increased risk, this session is especially relevant. Genetic testing can do more than identify an inherited mutation. It can help guide screening, treatment decisions, and recommendations for family members. As researchers learn more about the genes linked to ILC, they hope to make genetic testing more precise and care more personalized for people living with lobular breast cancer.

Key Terms and Definitions:

E-cadherin: A protein that helps keep cells connected. Loss of E-cadherin is a defining feature of invasive lobular carcinoma (ILC).

Germline Pathogenic Variant: An inherited change in a gene that is present from birth and increases the risk of developing certain cancers.

HDGC (Hereditary Diffuse Gastric Cancer) Syndrome: An inherited cancer syndrome, usually caused by CDH1 pathogenic variants, that increases the risk of diffuse gastric cancer and lobular breast cancer.

Multigene Panel Testing: A genetic test that evaluates several cancer susceptibility genes at the same time, rather than testing one gene individually.

Resources and Key references:

Lobular Breast Cancer Alliance (LBCA); National Cancer Institute (NCI); National Library of Medicine / PubMed; ClinicalTrials.gov; National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology

Corso G, Intra M, Trentin C, Veronesi P, Galimberti V. *CDH1 germline mutations and hereditary lobular breast cancer*. *Familial Cancer*. 2016;15(2):215–219.

Corso G, Figueiredo J, De Angelis SP, et al. *E-cadherin deregulation in breast cancer*. *Journal of Cellular and Molecular Medicine*. 2020;24(11):5930–5936.

Scientific Session 1: Genetics, Risk, and Exposures

Hormonal exposures in ILC development

Presenter 2: Cathrin Brisken, MD, PhD

Background: Professor Cathrin Brisken is a physician-scientist and internationally recognized expert in breast biology and endocrine signaling. Based at the Institute of Cancer Research (ICR), London, her research focuses on how estrogen, progesterone, and other hormones influence normal breast development and the earliest stages of breast cancer. Her laboratory has made major contributions to understanding how hormone signaling influences the development of invasive lobular carcinoma (ILC) and other hormone receptor-positive breast cancers.

Most invasive lobular carcinomas (ILC) are estrogen receptor (ER)-positive, meaning their growth is influenced by hormones such as estrogen. However, hormones do much more than fuel established cancers; they play an essential role in normal breast development throughout life, from puberty and pregnancy to menopause.

Researchers use the term hormonal exposures to describe all the hormones the breast is exposed to over a lifetime. These include naturally occurring hormones as well as external hormones, such as those used in hormone replacement therapy (HRT) and some forms of hormonal contraception. Scientists are studying how these exposures may influence the risk of developing breast cancer, including ILC.

While many risk factors for breast cancer are shared across different subtypes, growing evidence suggests that ILC may have unique hormonal biology. Compared with invasive ductal carcinoma (IDC), ILC is more likely to be strongly hormone receptor-positive and may be influenced differently by hormonal risk factors. However, researchers are still working to understand exactly how hormones contribute to the development of ILC and why this subtype behaves differently. Understanding how hormones influence the earliest stages of ILC could help identify new approaches to prevention, improve risk prediction, and uncover new treatment strategies in the future.

What the Talk Is Likely to Cover, and Why: Professor Cathrin Brisken has spent much of her career studying how hormones influence normal breast development and how changes in these biological processes can contribute to breast cancer. Based on her research, this presentation will likely explore how lifetime exposure to hormones, including estrogen and progesterone, may influence the development of ILC. You may hear about how hormones regulate normal breast tissue, why ILC is overwhelmingly hormone receptor-positive, and how hormone signaling in ILC may differ from other breast cancer subtypes. Professor Brisken's laboratory has also developed innovative models that allow researchers to study ILC more accurately, providing new insights into how these cancers develop and spread.

Another topic may be how understanding hormone biology could eventually improve how we prevent, detect, and treat ILC. While hormone therapy (i.e., endocrine therapy) is already a cornerstone of treatment for most people with ILC, researchers are continuing to investigate why some tumors respond well to hormone therapy while others eventually become resistant. Professor Brisken's recent research has also examined how the environment surrounding an ILC tumor can influence cancer growth and treatment response, helping researchers identify potential new targets for future therapies. This presentation is likely to connect decades of fundamental laboratory research with emerging opportunities to improve care for people living with lobular breast cancer.

Why This Matters to People with ILC: Many people diagnosed with ILC wonder whether hormones played a role in their cancer or what hormonal exposures may have influenced their risk. While this session is unlikely to provide simple answers for individuals, it will explain what researchers know and are still learning about how hormones influence ILC development.

Key Terms and Definitions:

Estrogen Receptor (ER): A protein found on many breast cancer cells that allows them to respond to estrogen.

Most ILCs are ER-positive.

Hormonal Exposures: A person's lifetime exposure to hormones, including naturally occurring hormones and those from medications such as hormone replacement therapy (HRT) or hormonal contraception.

Hormone Receptor-Positive (HR+): Breast cancers that grow in response to estrogen and/or progesterone. Most ILCs are hormone receptor-positive.

Progesterone: A naturally occurring hormone that works alongside estrogen to regulate normal breast development. Researchers are studying its role in the development of ILC.

Resources and Key references:

Lobular Breast Cancer Alliance (LBCA); National Cancer Institute (NCI); National Library of Medicine / PubMed; ClinicalTrials.gov; National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology

Briskin C. Progesterone signalling in breast cancer: a neglected hormone coming into the limelight. *Nature Reviews Cancer*. 2013;13(6):385–396.

Flaherty RL, Sflomos G, Briskin C. Is There a Special Role for Ovarian Hormones in the Pathogenesis of Lobular Carcinoma? *Endocrinology*. 2024;165(5):bqae031.

Scientific Session 1: Genetics, Risk, and Exposures

Latest Data in Hormone Replacement Therapy

Presenter 3: Mindy Goldman, MD

Background: Professor Mindy Goldman is a gynecologist and internationally recognized expert in menopause, hormone therapy, and the care of women after cancer. She is Professor Emeritus of Obstetrics, Gynecology and Reproductive Sciences at the University of California, San Francisco (UCSF), where she directed the Gynecology Center for Cancer Survivors and At-Risk Women. Her work focuses on helping women manage menopausal symptoms after cancer while balancing quality of life with long-term health and safety.

Many people diagnosed with ILC experience menopause naturally or as a result of cancer treatment. Symptoms such as hot flashes, sleep disturbance, vaginal dryness, sexual dysfunction, and bone loss can have a major impact on quality of life.

Hormone replacement therapy (HRT), also called menopausal hormone therapy (MHT), is the most effective treatment for many menopausal symptoms. However, because most ILCs are strongly estrogen receptor-positive (ER+), the use of systemic hormone therapy after an ILC diagnosis is complex and often controversial.

Large studies suggest that combined estrogen-progestogen therapy can increase breast cancer risk in some women, while the effects of estrogen-only therapy are more nuanced. However, much of the available evidence comes from studies of breast cancer overall, rather than ILC specifically. Researchers continue to study when hormone therapy may be appropriate, which patients may benefit, and how different hormone formulations and non-hormonal alternatives compare.

What the Talk Is Likely to Cover, and Why: Based on Professor Goldman's clinical and research interests, this presentation will likely review the latest evidence on hormone replacement therapy and how it applies to women with a history of breast cancer or those at increased risk.

You may hear about the different types of hormone therapy, including systemic and local (vaginal) estrogen, current recommendations from professional societies, and how healthcare providers balance symptom relief with potential risks.

The presentation may also discuss newer non-hormonal treatment options for menopausal symptoms, areas where evidence is evolving, and the importance of individualized decision-making based on a person's symptoms, medical history, and personal preferences. You may also hear why decisions about hormone therapy are increasingly individualized, balancing symptom relief, quality of life, and breast cancer risk.

Why This Matters to People with ILC: Questions about menopause and hormone therapy are among the most common concerns for people living with ILC. Many people experience significant menopausal symptoms but are uncertain about which treatments are safe after an ER-positive breast cancer diagnosis. This session will help explain the latest evidence, current recommendations, and why conversations about hormone therapy should always be individualized and made together with your healthcare team.

Key Terms and Definitions:

Hormone Replacement Therapy (HRT)/Menopausal Hormone Therapy (MHT): Medications containing estrogen, with or without progesterone, used to treat menopausal symptoms.

Systemic Hormone Therapy: Hormones taken as pills, patches, gels, or sprays that circulate throughout the body.

Local (Vaginal) Estrogen: Low-dose estrogen used to treat vaginal symptoms with minimal absorption into the bloodstream.

Resources and Key references:

Lobular Breast Cancer Alliance (LBCA); National Cancer Institute (NCI); National Library of Medicine / PubMed; ClinicalTrials.gov; National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology

Goldman M. *Menopausal hormone therapy for breast cancer survivors*. Maturitas. 2025.

The NCCN Clinical Practice Guidelines in Oncology: Survivorship. Menopause and sexual health sections.

Scientific Session 1: Genetics, Risk, and Exposures
Lobular carcinoma in situ: management strategies
Presenter 4: Tari A. King, MD, FACS, FSSO, FASCO

Background: Professor Tari King is a breast surgeon and internationally recognized expert in breast cancer risk assessment, prevention, and the management of high-risk breast lesions, including lobular carcinoma in situ (LCIS). She is Chief of the Division of Breast Surgery and Chief Surgical Officer at the Winship Cancer Institute of Emory University. Her research spans the continuum from breast cancer prevention and risk assessment to surgical management and personalized treatment. Through her leadership in national clinical trials and guideline development, she has helped shape current approaches to managing LCIS and reducing breast cancer risk.

Despite its name, lobular carcinoma in situ (LCIS) is not considered breast cancer. Instead, it is a marker that indicates an increased risk of developing breast cancer in the future, in either breast. Many people diagnosed with LCIS will never develop invasive breast cancer, but they may benefit from increased surveillance and strategies to reduce their future risk.

There are different types of LCIS. Classic LCIS is usually managed with careful monitoring and consideration of risk-reducing medications. In contrast, pleomorphic and florid LCIS are less common, behave differently, and may require more aggressive treatment, including surgery.

Management decisions are individualized and take into account factors such as age, family history, genetic testing results, imaging findings, and personal preferences. Researchers continue to refine the best strategies for surveillance, risk reduction, and treatment to help patients avoid both under-treatment and unnecessary procedures.

What the Talk Is Likely to Cover, and Why: Professor Tari King has spent much of her career helping patients understand their breast cancer risk and make informed decisions about managing high-risk breast conditions, including lobular carcinoma in situ (LCIS). Based on her research and clinical leadership, this presentation will likely review how our understanding of LCIS has evolved and what current evidence tells us about the best management strategies.

You may hear about the differences between classic LCIS and the less common pleomorphic and florid variants, as these can influence treatment recommendations. The presentation may also discuss when surveillance is appropriate, when surgery or risk-reducing medications should be considered, and how factors such as family history, genetic testing, imaging findings, and patient preferences help guide individualized care.

Another topic may be how recommendations for LCIS continue to evolve as researchers gain a better understanding of which individuals are most likely to benefit from different management strategies. Professor King's work has helped move the field toward more personalized, evidence-based care that aims to reduce breast cancer risk while avoiding unnecessary treatment whenever possible.

Why This Matters to People with ILC: An LCIS diagnosis can be confusing and sometimes frightening, especially because the word "carcinoma" suggests cancer. This session will help explain what LCIS is, how it differs from invasive breast cancer, and why management varies from person to person. Understanding today's approach to LCIS can help patients make informed decisions and feel more confident discussing their options with their healthcare team.

Key Terms and Definitions:

Classic LCIS (Lobular Carcinoma In Situ): A non-invasive breast lesion that increases the risk of developing breast cancer in either breast. It is generally considered a marker of increased risk rather than breast cancer itself.

Pleomorphic LCIS: A less common and more aggressive variant of LCIS with abnormal-looking cells. It is often

managed differently from classic LCIS and may require surgery.

Surveillance: Ongoing monitoring using regular clinical breast exams and breast imaging (such as mammography and, for some people, MRI) to watch for the development of breast cancer.

Risk-Reducing Endocrine Therapy: Medications such as tamoxifen, raloxifene, or aromatase inhibitors that can lower the risk of developing hormone receptor-positive breast cancer in selected individuals.

Resources and Key references:

Lobular Breast Cancer Alliance (LBCA); National Cancer Institute (NCI); National Library of Medicine / PubMed; ClinicalTrials.gov; National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology

King, T. A., Pilewskie, M., Muhsen, S., Patil, S., Mautner, S. K., Park, A., Eaton, A., Stempel, M., and Morrow, M. (2015). *Lobular carcinoma in situ: A 29-year longitudinal experience evaluating clinicopathologic features and breast cancer risk*. *Journal of Clinical Oncology*, 33(33), 3945–3952. <https://doi.org/10.1200/JCO.2015.61.4742>

Oppong, B. A., and King, T. A. (2011). *Recommendations for women with lobular carcinoma in situ (LCIS)*. *Oncology (Williston Park)*, 25(11), 1051–1058.

SCIENTIFIC SESSION 2: The ILC Cell and Microenvironment

Wednesday, September 23, 2026 | 4:00–5:15 pm

Moderators: Rachel Natrajan, PhD and Carolyn Reuss

Presentations:

1. **Unique proteomic features of ILC**
Chip Petricoin, PhD — George Mason University
2. **Tumor microenvironment in ILC**
Fatima Mechta-Grigoriou, PhD — Institut Curie, Paris, France
3. **Metabolism in ILC**
Rebecca Riggins, PhD — Georgetown University / Georgetown Lombardi Comprehensive Cancer Center
4. **New methods to study cell cycle in ILC**
Wayne Stallaert, PhD — University of Pittsburgh

Scientific Session 2: The ILC Cell and Microenvironment

Unique Proteomic Features of ILC

Presenter 1: Emmanuel (Chip) Petricoin, PhD

Background: The proteome is the entire set of proteins expressed by a cell, genome, tissue or organization at a specific time and under specific conditions. Proteomes are constantly transforming in response to external and internal factors. Proteomics is the study of the proteome. It involves understanding protein expression, structure, function, and interaction. While genomics reflects the potential activity in a cell based on the genetic code, proteomics captures the actual activity in the cell.

A proteomic signature is a unique, measurable pattern of multiple specific proteins found in blood, tissues, or body fluids that acts as a biological fingerprint for a disease. Invasive lobular carcinoma (ILC) exhibits a distinct proteomic signature compared to the more common invasive ductal carcinoma (IDC). The most defining and unique feature of ILC's proteomic signature is the complete loss of the E-cadherin protein.

Dr. Petricoin has recently studied proteomics of ILC. His findings have shed light on the distinct biological vulnerabilities of ILC and explain why it can behave so differently from the more common IDC. He also co-invented the Reverse Phase Protein Array (RPPA) technology, which measures functional, "activated" (phosphorylated) protein signaling rather than static DNA mutations. In essence, RPPA acts as a live traffic map. It measures the physical abundance of the final proteins themselves in the cell, proving whether a genetic instruction was successfully carried out by the cell. He demonstrated that this is critical in accurately analyzing ILC tumors. He has also developed another method for analyzing the uniquely formed ILC tumors that is different from that usually used to analyze tumors that form in lumps. Because ILC grows in diffuse, single-file lines blended seamlessly with surrounding tissue (rather than forming a solid lump), the typical method of analyzing bulk tumor chunks frequently yields incorrect protein signatures due to healthy tissue contamination. To solve this, Dr. Petricoin developed a method to overcome the issue of "bulk tissue inaccuracies" in ILC detection. It is called Laser Capture Microdissection (LCM). It manually extracts pure ILC tumor threads away from contaminating stromal tissue and has demonstrated that it enables getting a clinically accurate proteomic portrait of ILC's active drug-resistance mechanisms.

What the Talk is Likely to Cover and Why: Dr. Petricoin's profiling studies of ILC have mapped highly active, targetable pathways in treatment-resistant metastatic lobular breast cancers. Most recently he was a co-author of a multi-institutional phase II breast cancer study that revealed that patients with ILC achieved a 4.6-fold higher odds of response to a combination neoadjuvant therapy (enzalutamide (AR inhibitor) and fulvestrant (a SERD)) compared to those with IDC. The research also demonstrated the importance of utilization of the RPPA he co-invented to identify key molecular distinctions between the two breast cancer subtypes.

The findings from this phase II clinical trial included:

1. The androgen receptor (AR) dropped more significantly during treatment in ILC cases
2. In addition to the standard of care treatment of targeting estrogen, co-targeting AR may be key for killing lobular tumors - ILC tumors showed lower baseline levels of critical cell cycle and survival proteins
3. Other essential tumor drivers were "starved" with the therapy

I suspect he will discuss the findings from this study, explain the importance of RPPA in studying ILC and discuss what further study might be necessary to determine how best to test the efficacy of this targeted therapies further using the findings from this recent study.

Key Terms and Definitions:

Androgen Receptor (AR): In breast cancer AR is a protein inside or on cancer cells that binds to androgens (a group of sex hormones that include testosterone, which also referred to as “male hormones”). Unlike the standard estrogen or progesterone receptors usually tied to breast cancer, the AR can act differently depending on the cancer type, sometimes slowing tumor growth or serving as an alternative treatment target.

E-cadherin protein function: The “E” stands for “epithelial”—the cells lining body cavities and surfaces, including breast milk ducts and lobules. Crucial for cell adhesion, E-cadherin proteins sit on the cell surface and attach to internal anchoring proteins. E-cadherin functions much like Velcro, binding epithelial cells together to form organized, stable tissues. When E-cadherin is lost, inactivated, or not functioning properly, epithelial cells become separated and loose, causing them to slip by other cells and infiltrate surrounding tissue in single file, linear strands. This growth pattern makes ILC especially hard to detect. E-cadherin loss also affects other proteins that influence ILC.

Laser Capture Microdissection (LCM). A lab method used to look through a microscope and cut out or pull out specific, individual cells from a mixed tissue sample using a tiny laser

Protein: A protein is a complex, 3-dimensional molecule. It is made up of a chain of smaller molecules called amino acids. The number and type of amino acids in a chain determine a protein’s configuration and its function. In a sense, genes contain the instructions for biological processes, and proteins carry out the work. There are two general types of proteins. Structural proteins provide structure and support tissues. For instance, collagen proteins form tough fibers that anchor the breast and help maintain its shape. Functional proteins include enzymes (which regulate activities within cells), hormones (which regulate activities between cells), and antibodies (which fight infection).

Selective Estrogen Receptor Degradar (SERD): A type of medicine that binds to estrogen receptors inside cells and destroys them. By wiping out these receptors, the drug stops the hormone estrogen from attaching and telling cancer cells to grow.

Stromal tissue: The structural, supporting part of an organ or gland. It acts like the scaffolding or framework that holds the functional cells together

Targetable pathways: Targeted pathways in cancer are specific chains of cell signals that tell cancer cells to grow, divide, and survive. Think of them as a line of dominoes inside a cell; when the first piece falls, it triggers continuous, uncontrolled tumor growth. Specialized drugs block these specific paths to stop the cancer without harming normal cells

Resources and Key references:

<https://doi.org/10.1158/1557-3265.SABCS24-PS18-07> Richer J et al., Abstract PS18-07:

Differential odds of response in ILC versus IDC correlate with changes in the TIME in a phase II trial of pre-operative fulvestrant with or without enzalutamide. *Clin Cancer Res* (2025) 31 (12_Supplement): PS18-07

<https://www.the-scientist.com/what-is-proteomics-70892>

<https://medlineplus.gov/genetics/understanding/howgeneswork/protein/>

Scientific Session 2: The ILC Cell and Microenvironment

Tumor Microenvironment in ILC

Presenter 2: Fatima Mechta-Grigoriou, PhD

Background: The tumor microenvironment (TME) plays an important role in determining how cancers respond to treatment. In a study published in *cancers* in 2022 investigators carried out an in-depth analysis of the TME in ILC following laser-capture microdissection of the tumor stroma, specifically focusing on cancer-associated fibroblasts (CAFs) within the tumor stroma.¹ The relationship between inflammatory cancer-associated fibroblasts (iCAFs), which are a specific type of CAF, and tissue-resident memory T (T_{RM}) cells is one of the most critical structural and chemical "conversations" happening within the tumor microenvironment. While iCAFs belong to the tumor's support structure (stroma) and T_{RM} cells are local immune system soldiers, recent oncology research shows they directly interact to control whether an immune system can successfully fight off a tumor.

Dr. Fatima Mechta-Grigoriou and her team at the Institut Curie in Paris has been studying the microenvironment of ILC and this past May published a landmark study in *Nature Communications*, which has reportedly solved a major biological puzzle regarding how the hallmark loss of E-cadherin (CDH1) directly reshapes the stroma and drives the immune dynamics specific to ILC.² (Per AI translation simplified summary of the cited study): Dr. Mechta-Grigoriou and her team discovered a "chain reaction" in invasive lobular breast cancer (ILC) where a single genetic flaw completely rewrites the surrounding tissue to help the tumor hide from the immune system.

The breakthrough findings can be broken down into three simple steps:

1. The Missing Glue Causes Cellular Traffic The study found that the missing molecular "glue" (missing E-cadherin) sends a bad signal to nearby healthy structural cells called fibroblasts. Instead of transforming into helpful healing cells, they get trapped as inflammatory cancer associated fibroblasts (iCAFs) and pile up inside the tumor stroma.

2. A Trap for Immune Cells These trapped inflammatory fibroblasts act like a magnet, releasing signals that lure immune fighter cells (TILs) right into the center of the tumor. Usually, having immune cells inside a tumor is a good thing, but here it becomes a trap.

3. The Immune Disarming (Immune Escape) Once the immune cells arrive at the center, the E-cadherin-deficient cancer cells disarm them. The cancer cells prevent these immune fighters (T_{RM} cells) from latching on or turning "on" to fight. Because the immune cells are lured in but completely neutralized, the tumor achieves immune escape. This explains a long-standing medical mystery of why ILC patients with high immune cell levels often have a poorer prognosis.

Based on the breakthroughs from Dr. Mechta-Grigoriou's study, doctors and researchers can target specific "weak links" in this multi-step cellular chain reaction to dismantle the immune trap and make immunotherapies work effectively.

1. Stripping Away the Fibroblast "Magnet" (Targeting FAP⁺ iCAFs)

¹ Gómez-Cuadrado L, Bullock E, Mabruk Z, Zhao H, Souleimanova M, Noer PR, Turnbull AK, Oxvig C, Bertos N, Byron A, Dixon JM, Park M, Haider S, Natrajan R, Sims AH, Brunton VG. Characterisation of the Stromal Microenvironment in Lobular Breast Cancer. *Cancers* (Basel). 2022 Feb 11;14(4):904. doi: 10.3390/cancers14040904. PMID: 35205651; PMCID: PMC8870100.

² Djerroudi L, Mhaidly R, Kieffer Y, Damei I, Croizer H, Selvarasa V, Gentric G, Fuhrmann L, Goncalves A, Caly M, Richardot C, Leclerc R, Laas E, Malhaire C, Cao K, Houthuijzen JM, Kloosterman P, Jonkers J, Benoist C, Renault V, Bidard FC, Vincent-Salomon A, Mechta-Grigoriou F. E-cadherin inactivation shapes tumor microenvironment specificities in invasive lobular breast cancer. *Nat Commun*. 2026 May 12. doi: 10.1038/s41467-026-72844-4. Epub ahead of print. PMID: 42120423

Because FAP⁺ inflammatory fibroblasts (iCAFs) act as the structural anchors luring immune cells into a trap, neutralizing them is a top priority.

- **FAP-Targeted Therapeutics:** Doctors can utilize antibodies or antibody-drug conjugates (ADCs) directed against Fibroblast Activation Protein (FAP) to selectively eliminate or deactivate these iCAFs, removing the inflammatory signals that attract T cells.
- **FAP-CAR-T Therapy:** Emerging cellular therapies involve engineering CAR-T cells to seek out and destroy FAP-expressing stroma cells rather than the tumor itself, clearing the way for regular immune cells to function.

2. Disabling Fibroblast Signaling Pathways (Targeting mTORC)

As supported by complementary microenvironment studies, ILC fibroblasts rely heavily on the mTORC signaling pathway to secrete pro-inflammatory cytokines and maintain their trapped state. By turning off the mTORC "switch," using mTORC inhibitors, doctors can stop the fibroblasts from creating the local immune-suppressive environment.

3. Re-activating the Trapped Immune Cells (i.e., Enabling T_{RM} Cells)

The final step of the trap involves keeping resident memory T cells (T_{RM}) unattached and inactive.

- **Enhancing Retention Integrins:** Because the immune escape relies on a failure to retain and activate ITGAE-expressing T_{RM} cells, combination therapies could seek to artificially boost or bypass these specific cell adhesion/activation pathways.
- **Strategic Immunotherapy Combinations:** Since traditional checkpoint inhibitors (like anti-PD-1/PD-L1) often fail in ILC due to this local disarming, pairing them with the stromal-disrupting therapies mentioned above (like FAP-inhibitors) ensures that when T cells arrive at the tumor center, they remain active, armed, and ready to destroy the cancer.

What the Talk is Likely to Cover and Why: I expect that Dr. Mechta-Grigoriou will talk about all of these potential targets for therapies identified now that her research has found the reason explaining why despite the fact that ILC have a lot of CAFs, they have not been able to suppress the ILC tumors. She will likely discuss what studies are underway to reverse the trap and may describe what she and colleagues perceive are the best targets. She might also discuss what may already be in clinical trials or under study. She might also talk about what specifically is next for this team.

Key Terms and Definitions:

Enabling T_{RM} Cells: refers to the scientific methods and therapeutic strategies used to unlock, activate, or generate Tissue-Resident Memory T (T_{RM}) cells so they can effectively destroy cancer tumors or infections.

Laser-capture microdissection is a precise laboratory technique used to isolate specific, individual cells or small clusters of cells from a mixed (heterogeneous) tissue section under a microscope.

The mTORC signaling pathway is the central "master switch" that controls cell growth, proliferation, and metabolism in the human body

TILs = for Tumor-Infiltrating Lymphocytes, which are naturally occurring white blood cells that have successfully left the bloodstream to migrate directly into a tumor to recognize and destroy cancer cells.

Tumour microenvironment (TME), i.e., the surrounding cells, blood vessels, immune cells and supportive tissue that interact with the cancer cells.

Resources and Key references: See the two studies cited in the footnotes above that include the May 2026 study.

Scientific Session 2: The ILC Cell and Microenvironment

Metabolism in ILC

Presenter 3: Rebecca Riggins, PhD

Background: Dr Riggins' laboratory has been at the forefront of understanding the unique biology and metabolism of invasive lobular carcinoma (ILC), particularly how metabolic changes contribute to endocrine resistance. Dr Riggins' work is helping to demonstrate that the ILC hallmark - loss of **E-cadherin**, not only alters how ILC tumour cells communicate, move and interact with their surroundings but can also affect how they obtain and use energy. The research suggests ILC fuels itself differently from most other breast cancers. Rather than relying mainly on glucose (sugar), ILC may increasingly use fats, cholesterol and certain amino acids as alternative fuel sources. It may also depend more heavily on its mitochondria - the tiny "power stations" inside cells that generate energy.

What the Talk is Likely to Cover and Why: Unlike the more common invasive ductal carcinoma (IDC), ILC appears to undergo significant metabolic rewiring as it develops resistance to endocrine therapy. Rather than relying primarily on estrogen signalling, resistant ILC cells may increasingly start to exploit alternative metabolic pathways i.e., change how they handle fats and cholesterol in a way that enables them to survive without estrogen and continue growing. Understanding these metabolic changes and what they enable the ILC cell to do could result in identification of new vulnerabilities that may be the target of new lobular-specific metabolic treatments.

Points Dr. Riggins may make regarding the significance for ILC patients:

- Can biomarkers identify patients likely to benefit from future targeted metabolic treatments?
- Could metabolic biomarkers help guide more personalised treatment decisions?
- Could a better understanding of ILC metabolism lead to new treatment approaches and improved outcomes?

Key Terms and Definitions:

- **E-cadherin** - a calcium-dependent protein that helps epithelial cells stick together, maintain tissue structure, and act as a tumor suppressor. The "E" stands for epithelial, meaning it is found on cells that line the surfaces of your skin, organs, and glands. It is a tumor suppressor gene that has been lost in invasive lobular cancer
- **Metabolism** - The chemical processes cells use to produce energy and make the building blocks needed for growth.
 - **Cholesterol metabolism:** Resistant ILC activates cholesterol synthesis pathways, which may contribute to endocrine resistance; this raises the question of whether cholesterol-lowering approaches could complement treatment for ILC.
 - **Glutamine and glutamate metabolism** Amino acids that cancer cells can use as fuel and as raw materials for growth. Emerging evidence suggests ILC may rely more heavily on specific amino acids. Laboratory studies suggest blocking glutamate transport reduces tumour growth and mitochondrial activity.
 - **Lipid Metabolism** – This is the means by which ILC cells increase production and use fats. They may provide energy and building blocks for tumour growth; They may be a potential therapeutic target in treating ILC.
- **Metabolic rewiring** - The ability of cancer cells to change how they obtain energy and nutrients in order to survive treatment. Altering how they obtain energy can create endocrine resistance.
- **Oxidative phosphorylation (OXPHOS)** - A highly efficient process inside mitochondria that produces energy (ATP). Some endocrine-resistant ILC cells appear to depend more heavily on this pathway for producing energy than glycolysis. This dependence in ILC suggests mitochondrial metabolism could represent a therapeutic vulnerability

Advocate take-home message: ILC is not simply ductal breast cancer without E-cadherin. It has its own distinctive metabolic biology that may change further as endocrine resistance develops. Understanding how ILC uses fats, cholesterol, amino acids and mitochondrial energy and how this relates to increasing resistance to endocrine therapies could provide a road map in the future for doctors treating ILC and patients with this disease to have a more personalised treatment strategy, that uses therapeutic tools beyond endocrine or chemo therapy targeting the biology driving their specific ILC.

Resources and Key references:

Du., T., Sikora, M.J., Levine, K.M., Tasdemir, N., Riggins, R.B., Wendell, S.G., Van Houten, B. and Oesterreich, S. (2018) Key regulators of lipid metabolism drive endocrine resistance in invasive lobular breast cancer. Breast Cancer Research, 20(1), 106. Or click here: <https://doi.org/10.1186/s13058-018-1041-8>

Mobin, D., Olukoya, A.O., Bahnassy, S., Ranjit, S., Young, T. and Riggins, R.B. (2025) OR30-08 Pharmacological inhibitors of glutamate transport and metabolism suppress oxidative phosphorylation in invasive lobular carcinoma. Journal of the Endocrine Society, 9(Suppl. 1), bvaf149.2430. Or click here: <https://doi.org/10.1210/jendso/bvaf149.2430>

Riggins, R.B. (2021) LBCA Scientific Blog: Rebecca Riggins, PhD – Discussing the Challenges of ILC-Specific Research and Potential Solutions. Lobular Breast Cancer Alliance. Or click here: <https://lobularbreastcancer.org/lbca-scientific-blog-rebecca-riggins-phd/>

Scientific Session 2: The ILC Cell and Microenvironment

New methods to study the cell cycle in ILC

Presenter 4: Wayne Stallaert, PhD

Background: The cell cycle is the process by which cells grow, copy their DNA and divide into two new identical cells. Until recently, researchers could only study the average behaviour of thousands of tumour cells at once, making it difficult to understand how individual cells behaved. Dr Wayne Stallaert and colleagues have developed cell-cycle mapping, a new approach that allows researchers to track and study individual tumour cells as they divide, pause or move between different cell-cycle states within intact tissue. This provides a much more detailed picture of tumour behaviour than was previously possible with single measurements and is now being applied to cancers such as invasive lobular carcinoma (ILC).

What the Talk is Likely to Cover and Why: Rather than following a single route through the cell cycle, tumour cells can take different pathways. Some continue dividing, while others pause, enter a resting state, or restart growth. Dr Stallaert's team is using cell cycle mapping to investigate how which pathway a cell takes is influenced by its tumour microenvironment (TME), i.e., the surrounding cells, blood vessels, immune cells and supportive tissue that interact with the cancer cells. Understanding these interactions with the ILC cell's microenvironment will likely provide new insights into how ILC tumours grow, change/adapt over time and respond to treatment.

Significance for ILC patients:

Could cell-cycle mapping reveal how individual ILC tumour cells behave differently, even within the same tumour?

Could understanding cell-cycle plasticity help explain why some tumour cells survive, adapt or become resistant to treatment?

Could these new approaches provide researchers with a better understanding of ILC biology, helping to inform future research into overcoming treatment resistance?

Key Terms and Definitions:

- **Ki-67** – A protein marker that measures the percentage of actively dividing cells in a tumor sample. It gives a snapshot of how quickly a tumour appears to be growing but cannot show how individual cells change their behaviour over time.
- **High cell-cycle plasticity** – a specific subset of cells which are significantly more capable of adapting their cell cycle than other cells to enable them to bypass cell stressors such as the toxic affects of therapies that target rapidly dividing cells, helping some adapt and survive treatment and/or switch into a state of quiescence.
- **Quiescence** – A resting state also referred to as dormancy in which cells temporarily stop dividing (but they keep the ability to restart and may later begin growing again).
- **Spatial profiling or biology** is a molecular technique that maps the transcriptome, genome, or proteome within a tumor. Helps researchers understand how the tumour microenvironment influences cancer cell behaviour and may identify areas where tumour cells behave differently.

Advocate take-home message: ILC tumour cells do not all behave in the same way. Some may stop dividing, while others pause, adapt or resume dividing, allowing them to survive despite treatment. Cell-cycle mapping provides a much more detailed picture of how individual ILC tumour cells behave than traditional measures of tumour

growth, such as Ki-67, which provides only a measurement of how many cells are actively dividing at one point in time and not the causes. A better understanding of these differences could help researchers learn how treatment resistance develops in ILC and inform future research into more personalised treatment approaches.

Resources and Key references:

Kedziora, K.M. and Stallaert, W. (2024) 'Cell cycle mapping using multiplexed immunofluorescence', in Castro, A. and Lacroix, B. (eds.) *Cell Cycle Control. Methods in Molecular Biology*, vol. 2740. New York, NY: Humana. Or click here: https://doi.org/10.1007/978-1-0716-3557-5_15

Shenoy, Santosh (2020) Cell plasticity in cancer: A complex interplay of genetic, epigenetic mechanisms and tumor micro-environment, *Surgical Oncology*, vol. 34, 154-162 ISSN 0960-7404, <https://doi.org/10.1016/j.suronc.2020.04.017>

Shah, O.S., Nasrazadani, A., Foldi, J., Atkinson, J.M., Kleer, C.G., McAuliffe, P.F., Johnston, T.J., Stallaert, W., da Silva, E.M., Selenica, P., *et al.* (2024) 'Spatial molecular profiling of mixed invasive ductal and lobular breast cancers reveals heterogeneity in intrinsic molecular subtypes, oncogenic signatures, and mutations', *Proceedings of the National Academy of Sciences of the United States of America (PNAS)*, 121(31), e2322068121. Or click here: <https://doi.org/10.1073/pnas.2322068121>

Stallaert Lab. (n.d.) *Research*. University of Pittsburgh. Or click here: <https://www.stallaertlab.com>

SCIENTIFIC SESSION 3: Mechanisms of Metastasis

Thursday, September 24, 2026 | 8:00–9:15 am

Moderators: Julia Houthuijzen, PhD and Andrea Lener

Presentations:

1. **Metastatic interactome: collective cell migration in breast cancer**
Kevin Cheung, MD — Fred Hutch Cancer Center / University of Washington
2. **Autophagy in breast cancer**
Jay Debnath, MD — University of California, San Francisco (UCSF)
3. **Novel treatment targets in metastatic ILC**
Chris Lord, PhD — Institute of Cancer Research (ICR), London, UK
4. **Tissue mechanics in ER positive breast cancer**
Valerie Weaver, PhD — University of California, San Francisco (UCSF)

Scientific Session 3: Mechanisms of Metastasis

Metastatic interactome: collective cell migration in breast cancer

Presenter 1: Kevin Cheung, MD

Background: Metastasis is the spread of a primary tumor to other locations in the body. It is a key concern in cancer treatment as it is responsible for the majority of cancer morbidity and mortality. Metastasis patterns differ for lobular (ILC) vs ductal (IDC) breast cancer. First, metastasis tends to occur over a longer time period for ILC compared to IDC. Second, although both ILC and IDC metastasize to the bones, liver, and lungs, ILC metastasis can occur in different areas. For example, ILC may spread to the gastrointestinal tract, the peritoneum, the reproductive tract, skin, or the lining of the brain or orbital sockets. These differences in metastasis patterns point to fundamental differences in the way ILC tumors metastasize compared to IDC.

Understanding how tumors metastasize can help researchers find ways to treat or prevent metastasis. Until recently, it was thought that metastasis was driven by the movement of single cancer cells that break away from the primary tumor and circulate in blood or lymph (circulating tumor cells, or CTCs). However, the journey from a primary tumor site to a new location such as the lungs or bones is complicated and perilous for single CTCs. The journey for a single CTC involves transitioning to a different cell type (epithelial-mesenchymal transition, EMT) so that it can leave the extracellular matrix and move into the blood vessel as a single cell without self-destructing (anoikis). Once in the blood vessel, it has to survive the rough ride in the bloodstream while avoiding immune cells. Given these challenges, among others, it is very difficult for a single cell to survive and multiply in a distant location in the body.

However, recent research demonstrates that clusters of tumor cells can avoid many of the challenges faced by single cells and thus are far more likely to result in successful metastasis. Tumor cell clusters are comprised of different tumor cell types (leaders and followers) as well as non-cancerous cells such as fibroblasts and immune cells. Traveling as a cohesive group means that cells don't have to transition to other cell types to enter the blood stream, and as a group there is more protection from immune cells. Although single CTCs greatly outnumber tumor cell clusters in the bloodstream, multiple studies have found that most metastases result from collective migration of tumor cell clusters. Yamamoto et al. (2023A) provide an overview of the challenges for single cells and "benefits" of clusters for avoiding these challenges. Cheung and Horne-Badovinac (2025) review what is known about the migration of tumor clusters (collective migration), including composition of clusters, mechanisms for cluster movement, and external cues that influence speed and direction of travel.

Knowledge of the ways in which collective migration of tumor cells relate to metastasis can lead to potential treatments. For example, one approach is to find medications that can break up tumor cell clusters before they can metastasize. This involves identifying proteins and tumor cell components that are important for tumor cell adhesion and finding drugs that target those components. Another option is to try to prevent formation of clusters in the first place. For example, research conducted by Yamamoto et al. (2023) found that necrosis of primary tumors leads to increased formation and presence of tumor cell clusters in the blood; therefore, finding drugs that can disable primary tumor necrosis may help prevent metastasis.

Given that tumor clusters maintain tight connections between tumor cells that are often mediated by E-cadherin, several questions about the mechanisms and role of collective migration in metastasis for ILC compared to IDC arise. Since the loss of E-cadherin is a defining feature of ILC, how do ILC tumor cell clusters form and maintain connections with other cells during collective migration? Are differences in composition or behavior of tumor cell clusters for ILC compared to IDC related to the difference in metastasis patterns observed for ILC compared to IDC? Research conducted by Kahlil et al (2017) suggests that clusters of CTCs drive metastasis for both IDC and ILC despite the loss of E-cadherin in ILC. They found that ILC cell clusters maintain connections using a different cellular protein, CD44, and that ILC tumor clusters were smaller and thinner than the IDC clusters. Therefore,

targeted therapeutic approaches based on knowledge of collective migration could be tailored for ILC and continued research on the subject of collective migration for ILC should be a priority.

What the Talk is Likely to Cover and Why: The Cheung lab (kevincheunglab.org) is on the forefront of research on collective migration of tumor cells and how this process relates to metastasis of breast cancer. By understanding how tumor clusters move and what factors influence their behavior, therapeutic methods may be developed to “eradicate breast cancer cells, prevent their metastatic dissemination, and overcome their therapy resistance.” The talk may be expected to describe the results of recent research conducted by the lab on several possible topics relevant to understanding metastasis in ILC. One recent research focus is on the role of necrosis in the formation and behavior of tumor clusters. The development of therapeutic methods that target necrosis in the primary tumor may reduce the potential for metastatic spread and drug resistance. Cheung’s lab is currently attempting to find an antibody to block the production of the protein angiopoietin-like 7 (A7) that could prevent necrosis and dramatically reduce the number of tumor clusters in the bloodstream. Another research focus is on factors that affect the growth and progression of triple negative breast cancer, such as identifying factors associated with focal adhesions (Rosenthal et al., 2026) and production of proteins such as the growth factor epigen by tumor clusters (Wrenn et al., 2020).

Key Terms and Definitions:

Anoikis: programmed cell death that occurs when a cell that requires external attachment, e.g. epithelial cells, is detached from an extracellular matrix

CD44: a cell surface glycoprotein expressed by ILC cells

CTC: circulating tumor cell

E-cadherin: a protein present on the external surface of the cell that aids connection to neighboring cells; absent in ILC cells

EMT: epithelial-to-mesenchymal transition. An epithelial tumor cell loses (or reduces) the ability to attach to other cells through the loss of external proteins such as E-cadherin and develops an increased ability to move on its own.

Metastasis: Spread of a tumor from the primary location (e.g., in the breast) to other parts of the body such as lungs, liver, or bones.

Necrosis: Death of cells and body tissue due to injury, disease, lack of blood flow, or adverse environmental conditions. Necrotic tissue cannot be revived.

Resources and Key references:

<https://lobularbreastcancer.org/metastatic-ilc-information/>

<https://www.mbcalliance.org/projects/here-all-year/metastatic-lobular-breast-cancer/>

K.J. Cheung et al. 2016. Polyclonal breast cancer metastases arise from collective dissemination of keratin 14-expressing tumor cell clusters, *Proc. Natl. Acad. Sci. U.S.A.* 113 (7) E854-E863, <https://doi.org/10.1073/pnas.1508541113> (2016).

Cheung KJ and Horne-Badovinac S. 2025. Collective migration modes in development, tissue repair and cancer. *Nat Rev Mol Cell Biol.* 2025 Oct;26(10):741-758. doi: 10.1038/s41580-025-00858-9. Epub 2025 Jun 5. Erratum in: *Nat Rev Mol Cell Biol.* 26(11):902. doi: 10.1038/s41580-025-00911-7. PMID: 40473829; PMCID: PMC12456157.

Khalil AA et al. 2017. Collective invasion in ductal and lobular breast cancer associates with distant metastasis. *Clin Exp Metastasis.* 34(6-7):421-429. doi: 10.1007/s10585-017-9858-6. Epub 2017 Sep 11. PMID: 28894989; PMCID: PMC5711975.

Leslie, M. 2026. A bad crowd: Tumor cells often metastasize in clusters with other cells, offering novel targets for treatments. *Science Magazine*, April 9, 2026. <https://www.science.org/content/article/roaming-gangs-tumor-cells-help-spread-cancer-can->

drugs-break-them

- Yamamoto et al. 2023. Metastasis from the tumor interior and necrotic core formation are regulated by breast cancer-derived angiopoietin-like 7, *Proc. Natl. Acad. Sci. U.S.A.* 120 (10) e2214888120, <https://doi.org/10.1073/pnas.2214888120>.
- Yamamoto, A., Doak, A.E., and Cheung, K.J. 2023. Orchestration of Collective Migration and Metastasis by Tumor Cell Clusters. *Annual Review Pathology: Mechanisms Disease*. 18:231-256. <https://doi.org/10.1146/annurev-pathmechdis-031521-023557>
- Rosenthal KJ et al. 2026. AKAP2 is required for assembly of cytoskeletal signaling complexes that promote growth and metastasis of triple-negative breast cancer. *J Biol Chem*. 2026 Apr;302(4):111329. doi: 10.1016/j.jbc.2026.111329. Epub PMID: 41763306; PMCID: PMC13022629.
- Wrenn E et al. 2020. Regulation of Collective Metastasis by Nanolumenal Signaling. *Cell*, 2020; 183, 395-410.e1

Scientific Session 3: Mechanisms of Metastasis

Autophagy in breast cancer

Presenter 2: Jay Debnath, MD

Background: Autophagy, the process of recycling damaged components within a cell, has been found to play a role in both tumor growth and metastatic spread. In autophagy, a cell encompasses damaged components into compartments that are then dissolved into basic elements to be used again for various purposes. By disposing of damaged components and recycling the materials, autophagy protects the integrity of cellular structures and prevents survival and reproduction of cells that are damaged. Therefore, it is an important process for preventing cancer formation and growth; this is supported by numerous studies that link genetic mutations that inhibit autophagy to higher rates of certain cancers.

However, the role that autophagy plays in cancer is complex and varies by cancer stage (Yu et al., 2024). In early stages it suppresses tumor growth by reducing genetic mutations and the production of inflammatory oxidative molecules within cells. However, in mid- to late-stages it encourages tumor growth and metastatic spread. As the tumor grows, cancer cells start to hijack the process of autophagy and use it to enable survival in conditions that would normally result in cell death. Normal cells are programmed to die (a process known as apoptosis) if they are damaged or experience hypoxia or nutrient limitation. Cancer cells can use autophagy to avoid cell death and gain necessary energy sources to survive in these adverse environments. Survival in adverse environments, including those caused by chemotherapy, means that autophagy is also associated with resistance to cancer treatment.

In addition to increasing survival in adverse environmental conditions, autophagy is associated with changes to the cell that allow migration. For example, normal epithelial cells undergo planned cell death when they detach from other cells and float freely (a process known as anoikis). Autophagy helps cells survive detachment from other cells or the extra-cellular matrix so that they can freely move in the bloodstream to colonize new locations.

Research on the importance of autophagy in lobular cancer could be important for the development of new therapies for ILC. Loss of E-cadherin, which is the protein that attaches cells to each other, is a defining feature of ILC. The loss of E-cadherin is a stressful event for a cell, so it is possible that autophagy is a key process in the development and progression of ILC. Research has shown a difference in autophagy proteins between IDC and ILC (Cha et al., 2014), so it is possible that treatments that target autophagy in lobular cancer could be developed – and also that treatments for IDC that target autophagy may not be suitable for ILC.

What the Talk is Likely to Cover and Why: The talk could include a general discussion on the nuanced and dual role of autophagy in breast cancer at different stages and how that might relate to the treatment of ILC. The Debnath lab at the University of California San Francisco has been investigating several aspects of autophagy and breast cancer. For example, recent research has identified a mechanism for cancer progression resulting from inhibition of autophagy. Cells that are autophagy deficient sequester specific proteins, NBR1 and SQSTM1, that ultimately activate a process to transform the cell into an aggressive form (Mondal et al, 2025). Because most therapeutic approaches involving autophagy are focused on inhibition of autophagy, targeting NBR1 and SQSTM1 protein production or sequestering may be an important complement to treatments that inhibit autophagy. In general, other research by the lab focuses on understanding autophagy in epithelial cells and its role in cancer formation and understanding the relationship between autophagy and metastasis. Autophagy is a complicated process and a field of active research for cancer and other diseases. Although there is a demonstrated link between it and cancer formation and progression, additional information on mechanisms and effects of its promotion or inhibition is needed to understand how it can be targeted for cancer therapy.

Key Terms and Definitions:

Anoikis: a type of programmed cell death that occurs when a cell that requires external attachment, e.g., epithelial cells, is detached from an extracellular matrix.

Apoptosis: Programmed cell death when a cell is damaged or encounters adverse environmental conditions.

Autophagy: A process important for maintaining cell integrity; a cell surrounds damaged components (such as DNA or proteins) in a compartment that allows the contents to be broken down into basic building.

Resources and Key references:

<https://debnathlab.ucsf.edu/research>

Cha YJ, Kim YH, Cho NH, Koo JS. Expression of autophagy related proteins in invasive lobular carcinoma: comparison to invasive ductal carcinoma. *Int J Clin Exp Pathol*. 2014 May 15;7(6):3389-98. PMID: 25031766; PMCID: PMC4097258.

Kenific CM, Thorburn A, Debnath J. Autophagy and metastasis: another double-edged sword. *Curr Opin Cell Biol*. 2010 Apr;22(2):241-5. doi: 10.1016/j.ceb.2009.10.008. Epub 2009 Nov 27. PMID: 19945838; PMCID: PMC2854304.

Mondal G, Gonzalez H, Marsh T, Leidal AM, Vlahakis A, Phadatare PR, Bustamante Eguiguren S, Bruck M, Naik A, Magbanua MJM, Huppert LA, Wiita AP, Roose JP, Rosenbluth JM, Debnath J. Autophagy-targeted NBR1-p62/SQSTM1 complexes promote breast cancer metastasis by sequestering ITCH. *Nat Cell Biol*. 2025 Jul;27(7):1098-1113. doi: 10.1038/s41556-025-01689-8. Epub 2025 Jun 27. PMID: 40579454; PMCID: PMC12740005.

Yang ZJ, Chee CE, Huang S, Sinicrope FA. The role of autophagy in cancer: therapeutic implications. *Mol Cancer Ther*. 2011 Sep;10(9):1533-41. doi: 10.1158/1535-7163.MCT-11-0047. Epub 2011 Aug 30. PMID: 21878654; PMCID: PMC3170456.

Yu T, Rui L, Jiumei Z, Ziwei L, Ying H. Advances in the study of autophagy in breast cancer. *Breast Cancer*. 2024 Mar;31(2):195-204. Doi: 10.1007/s12282-023-01541-7. Epub 2024 Feb 5. PMID: 38315272; PMCID: PMC10901946.

Scientific Session 3: Mechanisms of Metastasis

Novel treatment targets in metastatic ILC

Presenter 3: Chris Lord, PhD

Background: Invasive lobular carcinoma (ILC) is the second most common type of breast cancer, making up roughly 10 to 15 percent of cases, and it behaves differently from the more common ductal type. The defining feature of almost all ILC is the loss of a protein called E-cadherin, which normally acts like molecular Velcro that holds breast cells together. When the gene that makes E-cadherin, called CDH1, is switched off, cancer cells grow in single-file lines, spread in unusual patterns, and become hard to see on standard imaging. Loss of E-cadherin is found in up to 90 percent of lobular cancers.

Most ILC is estrogen receptor positive (ER positive), which means the cancer is fueled by the hormone estrogen. Since there have been very few studies to determine the best therapy for ILC in both the early stage and once it is metastatic, the standard backbone of treatment is that for ER positive ductal carcinoma, which is hormone i.e., endocrine therapy, drugs that block or lower estrogen, often combined with other targeted drugs such as CDK4/6 inhibitors. Studies have also shown that it is often the case that ILC responds less well to chemotherapy than ductal cancer.

The big idea behind novel targets here is synthetic lethality. This is the strategy that produced a class of drugs called PARP inhibitors for cancers with faults in the well-known BRCA genes, a discovery Professor Lord helped make in 2005. The concept is to find a second weakness that becomes deadly only when a specific gene is already broken in the tumor. The hope is to exploit the E-cadherin defect that defines ILC and attack the cancer cells while sparing healthy ones.

Current Status and the Key Controversy: There is no targeted therapy approved specifically because a tumor has lost E-cadherin. The most prominent attempt to change that came from Professor Lord's own laboratory. Using gene-editing screens, his team found that ILC cells lacking E-cadherin were unusually sensitive to blocking a protein called ROS1, and that an existing lung cancer drug, crizotinib, could exploit this. That led directly to the ROLO trial, one of very few trials in the world designed specifically for advanced lobular breast cancer.

The central, and humbling, controversy this talk must address is that ROLO did not work as hoped. Results reported at the San Antonio Breast Cancer Symposium in December 2024 showed that crizotinib was **not** effective, either combined with the hormone drug fulvestrant in ER positive lobular disease or on its own in other CDH1-altered cancers. This is a striking example of a promising laboratory finding that did not help patients in the end, and it raises the field's hardest question: why do strong laboratory results so often fail once they reach patients, and how do we find targets that hold up against the real complexity of human tumors.

What the Talk is Likely to Cover and Why: Expect Professor Lord to use synthetic lethality as the main thread, walking the audience from the PARP inhibitor success story through the E-cadherin and ROS1 hypothesis to the disappointing ROLO result. Rather than treating ROLO as a dead end, he is likely to frame it as a lesson that is reshaping how the field hunts for ILC targets. This expectation is grounded in his recent work and public statements.

First, he has emphasized a concept his group calls synthetic lethal penetrance, or robustness: the idea that a target is only worth pursuing if its killing effect holds up across the huge genetic variety found in real patients' tumors. He argues the field must prioritize targets likely to work broadly, not just in a single tidy laboratory sample. Second, his 2024 work with colleagues analyzed biological patterns across nearly a thousand ILC tumors to predict patient

outcomes, identify who benefits from chemotherapy, and find new weaknesses unique to lobular cancer that could be targeted. This signals a shift from a single-drug bet toward a systematic search for the next generation of ILC targets. Expect him to argue that metastatic ILC deserves its own dedicated trials rather than being folded into general ER positive studies, and to point to large-scale gene screening as the way to find what comes after ROS1.

Key Terms and Definitions:

Invasive lobular carcinoma (ILC): The second most common type of breast cancer. Cells grow in single-file lines because they have lost the ability to stick together, which makes the disease hard to detect on imaging and to remove cleanly with surgery

E-cadherin: A surface protein that acts like glue, binding healthy breast cells together. Its loss is the hallmark of lobular breast cancer and causes the single-file growth pattern.

CDH1: The gene that carries the instructions for making E-cadherin. When CDH1 is mutated, deleted, or chemically silenced, the cell stops producing working E-cadherin. CDH1 changes are found in most lobular cancers.

Estrogen receptor positive (ER positive): Cancer that grows in response to the hormone estrogen. Most lobular cancers are ER positive and are treated with drugs that block or lower estrogen (hormone therapy).

Synthetic lethality: A strategy that targets a second vulnerability which only becomes deadly when a specific gene is already broken in the cancer. Healthy cells keep the first gene intact and survive, so the approach can spare normal tissue. PARP inhibitors for BRCA-mutated cancer are the classic example.

PARP inhibitors: A class of drugs (such as olaparib) that kill cancer cells which already carry a broken DNA-repair gene, especially BRCA. They were the first big success of the synthetic lethality strategy.

Synthetic lethal penetrance (robustness): Professor Lord's term for how reliably this killing effect holds up across many different tumors. A target with high penetrance keeps working despite the genetic differences between patients, which is essential for success in real patient trials.

ROS1: A type of signaling protein (a tyrosine kinase). Laboratory work suggested ILC cells lacking E-cadherin leaned on ROS1 to survive, making it a candidate target.

Crizotinib: An existing drug that blocks ROS1 (and related proteins), already approved for certain lung cancers. It was repurposed and tested against lobular breast cancer in the ROLo trial.

CDK4/6 inhibitors: A class of targeted pills (such as palbociclib) given with hormone therapy for ER positive breast cancer. They block proteins that cancer cells use to divide.

ROLo trial: A phase 2 trial that tested crizotinib in advanced, E-cadherin negative lobular breast cancer and other CDH1-altered cancers. Results reported in 2024 to 2025 were negative, meaning the drug did not provide the hoped-for benefit.

Metastatic (advanced) breast cancer: Cancer that has spread beyond the breast and nearby lymph nodes to distant sites. In ILC this often includes the abdominal lining, digestive tract, and ovaries. It is treatable but not currently curable.

Functional genomics screen: A laboratory technique, often using CRISPR gene editing, that systematically switches genes on or off across thousands of conditions to find which genes a cancer cell cannot survive without. It is the main tool Professor Lord uses to find new targets.

Resources and Key references:

icr.ac.uk, breastcancernow.org, pubmed.ncbi.nlm.nih.gov, aacrjournals.org, clinicaltrials.gov, cell.com

Bajrami I, Lord CJ, et al. E-Cadherin/ROS1 Inhibitor Synthetic Lethality in Breast Cancer. *Cancer Discovery*. 2018;8(4):498-515. <https://pubmed.ncbi.nlm.nih.gov/29610289/>

Okines A, Turner NC, Lord CJ, et al. Phase II Study of ROS1 Targeting with Crizotinib in Advanced E-cadherin Negative Lobular Breast Cancer (ROLo). *Clin Cancer Res*. 2025;31(12 Suppl): Abstract P2-07-24 (SABCS 2024). <https://doi.org/10.1158/1557-3265.SABCS24-P2-07-24>

Alexander J, Lord CJ, Haider S, et al. Pathway-based signatures predict patient outcome, chemotherapy benefit and synthetic lethal dependencies in invasive lobular breast cancer. *Br J Cancer*. 2024;130(11):1828-1840. <https://www.icr.ac.uk/research-and-discoveries/find-a-researcher/detail/dr-chris-lord>

Breast Cancer Now. A new lethal weapon against lobular breast cancer (web article on Professor Lord's ROS1 and crizotinib research). <https://breastcancernow.org/about-us/research-news/new-lethal-weapon-against-lobular-breast-cancer>

Front Line Genomics. A Conversation with Chris Lord. 2025 (interview describing synthetic lethal penetrance and precision medicine strategy). <https://frontlinegenomics.com/the-process-of-translating-always-starts-with-understanding-someone-elses-language-a-conversation-with-chris-lord/>

Scientific Session 3: Mechanisms of Metastasis
Tissue Mechanics in ER Positive Breast Cancer
Presenter 4: Valerie M. Weaver, PhD

Background: Most breast cancer research focuses on the genes and molecules inside cancer cells. Dr. Weaver studies a different angle: the physical environment around the cells. Her field, mechanobiology, asks how the stiffness, tension, and structure of breast tissue influence whether cancer forms, grows, and spreads. The starting observation is familiar to every patient. Tumors feel like a firm lump because they are physically stiffer than normal breast tissue. Dr. Weaver's central insight is that this stiffness is not just a result of cancer. It is also a driver of it.

The tissue around cells is the extracellular matrix, or ECM, built largely from collagen. In breast cancer, an enzyme called LOX (lysyl oxidase) cross-links collagen fibers, making the tissue progressively stiffer, much like adding rebar to concrete. Cells sense this stiffness through surface anchors called integrins. When the matrix stiffens, integrins cluster and switch on internal signals, working through focal adhesions and growth pathways such as ERK, that push the cell toward growth, survival, and invasion. This conversion of a physical force into a biological signal is mechanotransduction.

This matters intensely for ER positive disease. About 80 percent of breast cancers are estrogen receptor positive, meaning they are fueled by estrogen, and lobular cancer in particular is over 90 percent ER positive. So the question of how mechanics interacts with hormone signaling is, in effect, a question about the most common form of the disease.

Current Understanding and Why It Is Important: Two facts are well established from Dr. Weaver's foundational work. First, breast tumors stiffen as they progress, and LOX-driven collagen cross-linking is a key cause, not merely a side effect. Second, forcing the matrix to stiffen in laboratory models is enough to push pre-cancerous cells to become invasive, which shows that mechanics can actively drive the disease forward.

The important and still-developing area is the link to hormones and risk. Women with high mammographic density, meaning more dense, fibrous tissue on a mammogram, have a higher lifetime risk of breast cancer, and dense tissue is stiffer tissue. The open questions Dr. Weaver's work addresses are how to measure tissue stiffness reliably across a whole tumor, which varies region to region, and whether targeting the physical environment with drugs that reduce fibrosis or soften the tissue could complement standard hormone therapy. The practical promise is a second category of treatment and prevention targets that sit outside the cancer cell itself.

What the Talk is Likely to Cover and Why: Expect Dr. Weaver to connect the physics of breast tissue directly to estrogen and progesterone biology, because that is the focus of her most recent and most relevant research. In a 2024 study, her team showed that a stiff matrix and high integrin mechanosignaling activate ERK, which boosts progesterone receptor signaling and a pathway called RANKL. This expands the pool of stem and progenitor cells in the breast, which raises cancer risk. Crucially, they found the same pattern, elevated RANKL and more progenitor cells, in the stiff, dense breast tissue of women with high mammographic density.

Based on this, the talk is likely to argue three things. First, that tissue stiffness and hormone signaling are not separate stories but one connected loop, which is especially relevant to ER positive disease. Second, that mammographic density should be understood mechanically, as stiffness that actively raises risk, not just as a screening nuisance that hides tumors. Third, that this opens real opportunities to step in: blocking the RANKL pathway, which is already targeted by existing bone-health drugs, to potentially lower risk in women with high density, and targeting collagen cross-linking and fibrosis to slow the disease. Expect her also to highlight newer tools from her group, such as AI-based mapping of stromal stiffness across tumors (STIFMap), reflecting her view that a tumor's physical variation must be measured to be treated.

Key Terms and Definitions:

Mechanobiology, mechanotransduction, and mechanosignaling: Mechanobiology is the study of how physical forces such as stiffness and tension affect cells. Mechanotransduction is the process by which a cell converts a physical force into a chemical or genetic signal. Mechanosignaling is the internal signaling that results. When integrins sense a stiff matrix, the mechanosignaling they set off pushes cells toward growth and invasion. This is the core of Dr. Weaver's field.

Extracellular matrix (ECM): The scaffold of proteins, mainly collagen, that surrounds cells and gives tissue its structure and stiffness. Cancer remodels and stiffens the ECM.

Collagen cross-linking: The chemical bonding of collagen fibers to one another, which makes tissue stiffer and more rigid, similar to reinforcing concrete. In tumors this stiffening helps drive invasion.

LOX (lysyl oxidase): An enzyme that cross-links collagen and is a major cause of tissue stiffening in breast tumors. It is often elevated in cancer and tied to poorer outcomes, which makes it a potential drug target.

Integrins: Anchor proteins on the cell surface that connect a cell to the matrix around it and let it sense how stiff its environment is. When the matrix stiffens, integrins cluster and switch on growth and invasion signals.

Focal adhesions: The points where integrins cluster and attach the cell to the matrix. They act as hubs that turn mechanical signals into internal chemical signals.

ERK (and related pathways such as PI3K and AKT): Internal signaling proteins that relay messages inside the cell. In Dr. Weaver's mechanism, a stiff matrix switches on ERK, which then boosts progesterone receptor and RANKL activity. PI3K and AKT are related pathways that carry growth and survival signals.

Estrogen receptor positive (ER positive): Cancer that grows in response to the hormone estrogen. About 80 percent of breast cancers, and over 90 percent of lobular cancers, are ER positive and are treated with hormone-blocking therapy.

Progesterone receptor (PR) and RANKL: PR responds to progesterone; RANKL is a signaling molecule downstream of it. Dr. Weaver's work links tissue stiffness to PR and RANKL activity, which expands breast stem-progenitor cells and raises risk. RANKL can be blocked by existing drugs such as denosumab, making this pathway a promising target.

Mammographic density: How much dense, fibrous tissue shows up on a mammogram. High density both hides tumors and, per Dr. Weaver's research, reflects stiffer tissue that independently increases breast cancer risk.

Fibrosis: Excess buildup of stiff, fibrous connective tissue. In the breast it adds to stiffness and, per this research, to cancer risk and progression. Antifibrotic drugs aim to reduce it.

Stem-progenitor cells: Early, flexible cells that renew tissue. A larger pool of them in the breast is associated with higher cancer risk, and stiff tissue appears to expand that pool.

STIFMap: An artificial intelligence tool from Dr. Weaver's group that maps how stiff the supporting tissue (stroma) is across different regions of a tumor, capturing physical variation a single measurement would miss.

Resources and Key references:

weaverlabsurgery.ucsf.edu, surgicaloncology.ucsf.edu, cell.com, nature.com, pubmed.ncbi.nlm.nih.gov, aacr.org, rupress.org

Levental KR, Weaver VM, et al. Matrix Crosslinking Forces Tumor Progression by Enhancing Integrin Signaling. *Cell*. 2009;139(5):891-906. <https://pubmed.ncbi.nlm.nih.gov/19931152/>

Northey JJ, Weaver VM, et al. Mechanosensitive hormone signaling promotes mammary progenitor expansion and breast cancer risk. *Cell Stem Cell*. 2024;31(1):106-126.e13. [https://www.cell.com/cell-stem-cell/fulltext/S1934-5909\(23\)00432-0](https://www.cell.com/cell-stem-cell/fulltext/S1934-5909(23)00432-0)

American Association for Cancer Research. A Mechanosensitive Hormone Signaling Pathway Increases Breast Cancer Risk. 2024 (plain-language summary of the Northey and Weaver

study). <https://www.aacr.org/professionals/research-funding/grantees/aacr-grantee-uncovers-a-mechanosensitive-hormone-signaling-pathway-promoting-breast-cancer-risk/>

Stashko C, Weaver VM, et al. A convolutional neural network STIFMap reveals associations between stromal stiffness and EMT in breast cancer. *Nat Commun*. 2023;14(1):3561. <https://www.nature.com/articles/s41467-023-39085-1>

Sedwick C. Valerie Weaver: Overcoming cancer's stiff resistance. *J Cell Biol*. 2011;193(5):802-803 (profile explaining stiffness, integrins, and mechanotransduction). <https://pmc.ncbi.nlm.nih.gov/articles/PMC3105548/>

SCIENTIFIC SESSION 4: Model Systems and Pathology

Thursday, September 24, 2026 | 10:15–11:30 am

Moderators: Anne Vincent-Salomon, MD, PhD and Ciara Gustafson

Presentations:

1. **The expanding repertoire of preclinical models of ILC**
Adrian Lee, PhD — University of Pittsburgh / UPMC Hillman Cancer Center
2. **Somatic genome editing in rats enables ILC modeling**
Yi Li, PhD — Baylor College of Medicine
3. **A New Era for ILC Histologic Variants: From Improved Morphological Criteria to AI-Based Prediction**
Lounes Djerroudi, MD, PhD — Institut Curie, Paris, France
4. **Mitotic vulnerabilities of ILC**
Ruth Keri, PhD — Case Western Reserve University

Scientific Session 4: Model Systems and Pathology
The expanding repertoire of preclinical models of ILC
Presenter 1: Adrian Lee, PhD

Background: While invasive lobular breast cancer (ILC) has long been recognized as different from invasive ductal cancer, there has been increasing interest in studying and understanding ILC in the past 10 years. There are several types of preclinical models, i.e., models that do not involve testing in humans, that have been used to study all breast cancer types. They include specialized cell lines, mouse models, and patient-derived organoids.

Cell lines are in vitro tumor models that are widely used in cancer research because they show numerous intrinsic features of cancer and exhibit gene expression patterns similar to primary human tumors. Cancer cell lines are established by isolating cancer cells from patient-specific organs and then growing them in a sterile, temperature-controlled environment within plastic laboratory vessels (such as flasks, dishes, or multi-well plates). The cells are submerged in a nutrient-rich liquid that provides the essential nutrients they need to survive and are maintained in an incubator at 37°C with 5% carbon dioxide to mimic conditions inside the human body. They are the foremost preclinical cancer model due to management ease, inexpensiveness, immortality, limited cellular heterogeneity, and high proliferation rates.³

Laboratory mouse models are also commonly used to study how human breast cancer develops, spreads, and responds to treatments. Mouse models are developed through three primary techniques: xenografts (implanting human tumor cells into mice), genetically engineered mouse models (GEMMs) (altering the mouse's own DNA), and chemically induced models. The type of mouse model developed and used in a study will be specific to the type of research being conducted.

Patient-Derived Xenografts (PDX) and Cell Line Xenografts (CDX): Researchers implant human tumor cells or tissues directly into immunocompromised mice (so the mouse's body doesn't reject the human tissue), typically into the mammary fat pad.

Syngeneic Models: Mouse cancer cells are injected into immunocompetent (normal immune system) mice. This allows scientists to study the tumor's interaction with the immune system and test immunotherapies.

Genetically Engineered Mouse Models (GEMMs): Researchers use gene-editing technologies (like the Cre-Lox system) to alter specific genes in the mouse's mammary tissue. This allows them to simulate spontaneous tumor growth driven by human mutations, such as knocking out the *BRCA1* gene or expressing the *HER2* oncogene.⁴

Both specialized cell lines and mouse models pose challenges because they are hard to maintain and do not necessarily behave as tumors do in humans. Patient-derived organoids (PDO) represent a relatively new model for ILC. They are derived from real patients' tumors and therefore have the potential to better represent what happens in humans.

Unlike traditional cancer cells that are grown in a flat layer in a laboratory dish, patient-derived organoids (often called PDOs) are tiny, three-dimensional clusters of living cells grown in a laboratory from a patient's own tumor. They are sometimes referred to as "mini tumors" because they retain many of the characteristics of the original cancer, including its genetic makeup and behavior and more closely resemble how tumors exist inside the body. They also have the capacity for self-renewal and proliferation while maintaining the physiological structure and

³ Cancer models in preclinical research: A chronicle review of advancement in effective cancer research
<https://pmc.ncbi.nlm.nih.gov/articles/PMC8212826/>

⁴ Mouse models of Breast Cancer. <https://pmc.ncbi.nlm.nih.gov/articles/PMC6492279/>

function of the tissue from which they are derived.⁵

What the Talk is Likely to Cover and Why: This talk is likely to cover the benefits of studies that use PDOs as compared to other pre-clinical models, the progress that has been made in creating them, and ongoing challenges in their development and use. Topics that are likely to be covered in this talk:

- The benefits of studies that use patient-derived organoids over other pre-clinical models
- Obtaining the tissue if you want to develop your own organoids – the starting material is patient tissue. So, there will likely be a discussion of how to get the tissue and the appropriate patient and organizational consents
- Available biobanks of patient-derived organoids for researchers who do not want to create their own – the benefit of using organoids from these biobanks is that the researchers have already determined the growth conditions that work to keep these organoids going, eliminating some of the guesswork of creating them on your own
- Growth conditions for patient-derived organoids
- How PDOs are being used in research

Key Terms and Definitions:

Biomarker: A measurable characteristic, such as a gene, protein, or other molecule, that provides information about a person's disease or how they may respond to treatment.

Cell Culture: The process of growing living cells in a laboratory under carefully controlled conditions.

Drug Resistance: When cancer cells stop responding to a treatment that was previously working, allowing the cancer to continue growing.

Drug Screening: Testing many different drugs or drug combinations in the laboratory to determine which ones work best against cancer cells.

Extracellular Matrix (ECM): A gel-like material that surrounds cells and provides support. In organoid research, scientists use specialized gels that mimic this environment so cells can grow naturally.

Microenvironment (Tumor Microenvironment): The surrounding environment where a tumor grows, including blood vessels, immune cells, connective tissue, and other nearby cells that influence how the cancer behaves.

Molecular Profiling: Analyzing a tumor's genes, proteins, and other molecules to better understand its characteristics and identify potential treatment options.

Passage Number: Passage number refers to the number of times a cell line or organoid has been subcultured (harvested and transferred to a new vessel) since it was first isolated or thawed. It is a vital metric that researchers use for tracking a culture's age, as cells can undergo genetic drift and phenotypic changes over time. Researchers keep track of how many passages a cell line or organoid has undergone as this will be factored in to understanding the impact of a study on a patient's tumor. It is usually recommended to retire cell lines after a specific number of passages to ensure consistent results.

Tumor Heterogeneity: The fact that cancer cells within the same tumor—or between different patients—can vary in their genetic makeup and behavior. This is one reason why the same treatment may work well for one patient but not another.

Whole Genome Sequencing: A laboratory technique that determines the complete DNA sequence of a person's or tumor's genetic material, helping researchers identify mutations that may influence treatment.

⁵ **Cancer organoids: A platform in basic and translational research. 2023**
<https://pmc.ncbi.nlm.nih.gov/articles/PMC10491878/>

Scientific Session 4: Model Systems and Pathology
Somatic genome editing in rats enables ILC modeling
Presenter 2: Yi Li, PhD

Background: It is always a challenge to develop models that can be used to study cancer outside of humans. With increasing interest in studying invasive lobular breast cancer (ILC), researchers are trying to find the best model systems to study ILC. These model systems include: cell lines, xenografts, mouse models, and patient-derived organoids.

Cell lines are an in vitro tumor model that is widely used in cancer research because they show numerous intrinsic features of cancer and exhibit gene expression patterns similar to primary human tumors.⁶

Patient-Derived Xenografts (PDX) and Cell Line Xenografts (CDX) are made by implanting human tumor cells or tissues directly into immunocompromised mice (so the mouse's body doesn't reject the human tissue), typically into the mammary fat pad.

Laboratory mouse models are also commonly used to study how human breast cancer develops, spreads, and responds to treatments.

All pre-clinical models pose challenges because they can be hard to maintain and do not always behave as tumors do in humans.

Developing a model of ILC in rats can provide benefits over some of the other models, in particular mouse models:

- Rat models better mimic human breast cancer biology in terms of:
 - Hormone responsiveness (they have estrogen and progesterone receptors unlike mice)
 - Tumor progression
 - Histology (what it looks like under the microscope)
 - Molecular characteristics
- Better for studying early breast cancer development
- Because they are larger than mice, they can be easier to study (blood samples, tissue biopsies, imaging can all be easier)
- Easier to study drug delivery
- Better modeling of metastasis – follows the same pattern as humans

What the Talk is Likely to Cover and Why: This talk is likely to cover the benefits of using rat models of ILC as compared to other pre-clinical models and how particular issues have been overcome to make it possible. Topics that are likely to be covered in this talk:

- The limitations of mouse models of ILC
- The aspects of rat anatomy and biology that make them ideal for studying ILC
- How issues with somatic genome editing have been overcome to make rat models possible⁷
- How rat models can be used to study ILC
- Work in progress coming from this new rat model of ILC

⁶ Cancer models in preclinical research: A chronicle review of advancement in effective cancer research
<https://pmc.ncbi.nlm.nih.gov/articles/PMC8212826/>

⁷ Bu W, Lee TD, Anurag M, et al. Rat somatic genome editing enables ER+ breast cancer modeling. *Proc Natl Acad Sci U S A*. 2026;123(26):e2529653123. doi:10.1073/pnas.2529653123

Key Terms and Definitions:

Biomarker: A measurable characteristic, such as a gene, protein, or other molecule, that provides information about a person's disease or how they may respond to treatment.

Cell Culture: The process of growing living cells in a laboratory under carefully controlled conditions.

Estrogen Receptor (ER): A protein found on some breast cancer cells that allows them to respond to the hormone estrogen. Many invasive lobular cancers are estrogen receptor-positive, meaning they grow in response to estrogen.

Mammary Gland: The scientific name for breast tissue in humans and the equivalent tissue in animals such as rats.

Microenvironment (Tumor Microenvironment): The surrounding environment where a tumor grows, including blood vessels, immune cells, connective tissue, and other nearby cells that influence how the cancer behaves.

Molecular Profiling: Analyzing a tumor's genes, proteins, and other molecules to better understand its characteristics and identify potential treatment options.

Progesterone Receptor (PR): A protein found on some breast cancer cells that responds to the hormone progesterone. It is often measured along with the estrogen receptor because it helps guide treatment decisions.

Tumor Heterogeneity: The fact that cancer cells within the same tumor—or between different patients—can vary in their genetic makeup and behavior. This is one reason why the same treatment may work well for one patient but not another.

Whole Genome Sequencing: A laboratory technique that determines the complete DNA sequence of a person's or tumor's genetic material, helping researchers identify mutations that may influence treatment.

Scientific Session 4: Model Systems and Pathology

A New Era for ILC Histologic Variants: From Improved Morphological Criteria to AI-Based Prediction

Presenter 3: Lounes Djerroudi, MD, PhD

Background: Invasive lobular carcinoma is not one single uniform disease. Pathologists recognize classic ILC and several non-classic variants. These variants may differ in appearance, biology, prognosis, imaging behavior, and possibly treatment response. Djerroudi's work shows that knowing the ILC variant (subtype) could be essential for understanding individual prognosis and guiding important treatment decisions between patients.

What the Talk is Likely to Cover and Why: Some ILC variants, especially pleomorphic and solid ILC, may behave more aggressively and have different molecular features from others. A lobular tumour may be labelled differently depending on how it is reviewed, which makes research harder and can dilute important findings. Research, trials and treatment decisions should ideally factor in the real biological differences among the variants.

Main ILC variants (subtypes):

Variant	Description	Why it matters
Classic ILC	The “typical” lobular pattern: small cells, often growing in single files, usually ER-positive	Often considered the reference group; may behave differently from non-classic variants
Pleomorphic ILC	Lobular cancer cells look more abnormal/aggressive under the microscope	Often higher grade; associated with worse outcomes in some studies and may have more HER2-related changes
Solid ILC	Tumour grows in sheets rather than classic single-file strands	Can be harder to distinguish from ductal cancer; may be biologically more aggressive
Alveolar ILC	Tumour cells grow in small clusters	Recognised variant; clinical significance still being clarified
Tubulolobular / tubular elements	Looks partly tubular and partly lobular	Can cause diagnostic confusion; may be misclassified without careful pathology
Signet-ring / histiocytoid variants	Rare forms with unusual cell appearance	Important because they can be difficult to diagnose correctly

Significance for ILC patients:

- Do some ILC variants relapse earlier or behave more aggressively?
- Do some variants respond differently to endocrine therapy, chemotherapy or targeted drugs?
- Should trials stratify ILC patients by variant rather than grouping all ILC together?
- Are imaging failures worse in some variants or metastatic patterns?
- Should pathology reports routinely state the ILC variant?

Advocate take-home message: A “Lobular” diagnosis may not tell us enough. We need pathology reports, datasets and clinical trials to record ILC variant type, because different variants may have different risks and treatment needs.

BONUS - Be your own advocate – take-home questions to think about and some further reading on lobular breast cancer:

- Was my ILC classified as classic or non-classic?
- Were pleomorphic, solid, alveolar, tubulolobular or other variants considered?
- Was E-cadherin/p120 staining used to support my diagnosis?
- Is variant type captured in this trial dataset?
- Are outcomes being analysed separately for classic versus non-classic ILC?
- Should/Could/How is.... my variant classification influence imaging, prognosis or treatment strategy?

Resources and Key references:

Djerroudi L, El Sabeh-Ayoun A, Benoist C, Pierron G, Masliah-Planchon J, Fuhrmann L, Kieffer Y, Carton M, Ramtohul T, Callens C, Renault V, Bidard FC, Mechta-Grigoriou F, Vincent-Salomon A. Molecular and Clinical Portrait of HER2-low Invasive Lobular Carcinomas. *Mod Pathol*. 2024 May;37(5):100463. doi: 10.1016/j.modpat.2024.100463. Epub 2024 Feb 28. PMID: 38428737. <https://pubmed.ncbi.nlm.nih.gov/38428737/>

Zhang H, Peng Y. Unique Molecular Alteration of Lobular Breast Cancer: Association with Pathological Classification, Tumor Biology and Behavior, and Clinical Management. *Cancers (Basel)*. 2025 Jan 27;17(3):417. doi: 10.3390/cancers17030417. PMID: 39941785; PMCID: PMC11816017. <https://pmc.ncbi.nlm.nih.gov/articles/PMC11816017/>

Scientific Session 4: Model Systems and Pathology

Mitotic vulnerabilities of ILC

Presenter 4: Ruth Keri, PhD

Background: Professor Keri's laboratory focuses on breast cancer biology, endocrine resistance, cell-cycle regulation and therapeutic vulnerabilities arising from abnormal cell division (mitosis). While her laboratory is not exclusively dedicated to invasive lobular carcinoma (ILC), its work has identified important mitotic regulators that may represent future therapeutic targets in lobular breast cancer.

What Are Mitotic Vulnerabilities? Mitosis is the normal process by which one cell divides to produce two identical daughter cells. During this process, each new cell must receive an exact copy of the chromosomes that contain the cell's genetic information. Healthy cells have systems in place to ensure this happens accurately.

Cancer cells, however, often accumulate genetic abnormalities that make cell division more difficult and less reliable. To survive, they become increasingly dependent on specific proteins that help organise and complete mitosis correctly. This dependence is known as a mitotic vulnerability. If these proteins are blocked, cancer cells may be unable to divide successfully and eventually die, while normal cells are less affected because they are not as dependent on these pathways.

The defining feature of most invasive lobular carcinoma (ILC) is the loss of E-cadherin, usually caused by alterations in the CDH1 gene. E-cadherin is a protein that helps cells stick together and maintain the normal structure of breast tissue. When it is lost, it affects:

- **Cell adhesion** – how cells stick together.
- **Cell polarity** – how a cell is organised so that different parts can carry out specific functions.
- **Tissue architecture** – the way cells are arranged within tissues.
- **Cytoskeletal organisation** – the cell's internal framework that gives it shape and helps it move.
- **Cellular signalling** – how cells communicate with one another.

Researchers increasingly believe that these changes do more than alter the appearance and behaviour of ILC cells. They may also place extra stress on the process of cell division, forcing lobular cancer cells to rely more heavily on specific mitotic proteins for survival. If this proves to be true, these proteins could become valuable new targets for future treatments.

What the Talk is Likely to Cover and Why: Researchers increasingly believe that the changes caused by CDH1 loss place additional stress on cell division, forcing ILC cells to rely more heavily on specific mitotic pathways for survival. This creates the possibility that ILC has unique mitotic vulnerabilities that could be exploited therapeutically.

Professor Keri's laboratory identified LIN9 as a critical regulator of genes involved in mitosis. Research has shown that reducing LIN9:

- Causes major defects in cell division.
- Prevents cancer cells from completing mitosis successfully.
- Increases sensitivity to anti-cancer treatments.

The laboratory has also identified NEK2, a protein involved in:

- **Centrosome separation** – two centrosomes (structures that organise tiny protein fibres) move to opposite sides of the cell, preparing it for division.
- **Spindle formation** – the cell builds a spindle made of protein fibres that attach to chromosomes and pull them apart.
- **Chromosome segregation** – the spindle fibres separate the duplicated chromosomes so each new daughter cell receives one complete set.

Experimental studies suggest that inhibiting NEK2 can:

- Disrupt mitosis.
- Increase chromosomal instability.
- Promote cancer-cell death.
- Enhance responses to taxane chemotherapy.

Resources and Key references:

This landmark study from 2020 identifies the LIN9/NEK2 pathway as a key driver of taxane resistance in triple-negative breast cancer (TNBC). Researchers found that suppressing NEK2 restores tumor sensitivity to taxanes by increasing mitotic abnormalities, providing a novel strategy to overcome chemotherapy resistance.

Sahni JM, Summers MJ, Itani DM et al. *LIN9 and NEK2 Are Core Regulators of Mitotic Fidelity That Can Be Targeted to Overcome Taxane Resistance in Breast Cancer*. Cancer Research. 2020;80(8):1693–1708. Or click here to read...
<https://pmc.ncbi.nlm.nih.gov/articles/PMC7165041/>

SCIENTIFIC SESSION 5: Diagnostics and Clinical Management

Thursday, September 24, 2026 | 1:15–2:30 pm

Moderators: Suzanne Conzen, MD and Jade Moran

Presentations:

1. Unique aspects of ILC in pre-menopausal patients

Rachel Jankowitz, MD — Penn Medicine / Abramson Cancer Center, University of Pennsylvania

2. Modifiable risk factors impacting ILC outcomes

Karen van Baelen, MD, PhD — KU Leuven / University Hospitals Leuven, Belgium

3. Management of the axilla in ILC

Priscilla McAuliffe, MD, PhD — UPMC Hillman Cancer Center / University of Pittsburgh School of Medicine

4. Immunotherapy in ILC: tumor microenvironment for treatment selection

Jason Mouabbi, MD — The University of Texas MD Anderson Cancer Center

Scientific Session 5: Diagnostics and Clinical Management

Unique aspects of ILC in premenopausal patients

Presenter 1: Rachel Jankowitz, MD

Background: ILC is diagnosed most often in post-menopausal patients, meaning that comparatively little research has focused specifically on pre-menopausal ILC. However, emerging evidence suggests that age and menopausal status may be important when considering the biology and treatment of ILC. In a study of pre-menopausal patients, ILC initially appeared to have more favorable outcomes than IDC, but this advantage diminished over time because ILC was associated with a greater risk of events occurring later after diagnosis. This is consistent with the well-recognized tendency of ILC to recur many years after the original diagnosis. (Yoon et al., 2023)

The majority of ILC is hormone-receptor positive, making endocrine therapy a central component of treatment. However, endocrine therapy works differently depending on whether a patient is pre- or post-menopausal. In pre-menopausal patients, the ovaries remain the major source of estrogen. Tamoxifen blocks estrogen signaling at the estrogen receptor, whereas aromatase inhibitors (AIs) reduce estrogen production in tissues outside the ovaries. Therefore, an AI generally needs to be combined with ovarian function suppression (OFS) in a pre-menopausal patient. OFS can be achieved medically or surgically. For hormone-receptor-positive breast cancer overall, randomized trials have demonstrated that adding OFS to endocrine therapy can reduce recurrence in selected pre-menopausal patients, particularly those with higher-risk disease. However, these studies were conducted primarily in breast cancer populations that included relatively few patients with ILC. Consequently, it is not clear whether the same treatment strategies are equally effective for ILC.

Another important consideration for pre-menopausal patients is the impact of treatment beyond cancer control. OFS and endocrine therapy can cause symptoms associated with loss of ovarian function and can affect fertility, sexual health, bone health, and quality of life. For a younger patient, these considerations may influence treatment decisions over many years.

What the Talk is Likely to Cover and Why: In a review of systemic treatment for pre-menopausal HR+ breast cancer, Dr. Jankowitz highlighted unanswered questions surrounding the optimal type and duration of endocrine therapy and the need for biomarkers to identify which patients require additional treatment. (Jankowitz et al., 2013). Her subsequent work has focused specifically on whether ILC should be treated as simply another form of ER+ breast cancer. In a clinical trial she led, endocrine response in ILC was investigated directly rather than assuming that treatment responses observed in other breast cancers would automatically apply to ILC. The rationale was that ILC may have distinct biological mechanisms underlying endocrine response and resistance. (ClinicalTrials.gov NCT02206984)

This makes endocrine therapy in pre-menopausal ILC one of the likely themes of the presentation. A key question is whether tamoxifen, AI + OFS, or other endocrine approaches provide the greatest benefit for these patients. A recent ILC-specific study found that tamoxifen remains commonly used in pre-menopausal ILC, while the use of OFS and AI therapy has increased, particularly among patients with stage II–III disease. However, the study also emphasized that there is insufficient evidence to determine the optimal endocrine treatment specifically for pre-menopausal ILC. (Record et al., 2023)

Dr. Jankowitz has also been involved in research examining how ILC is represented in clinical trials. A 2024 international systematic review found that ILC is frequently not reported separately from other breast cancer subtypes in clinical trials. This makes it difficult to determine whether treatments work differently in ILC and limits the evidence available for ILC-specific treatment decisions. (Jankowitz et al., 2024)

Overall, the important message to listen for is whether the presenter believes that menopausal status changes the way ILC should be treated, or whether the current approach of applying general HR+ breast cancer treatment guidelines to ILC remains appropriate. The major challenge is that the evidence base for pre-menopausal ILC is relatively small, while ILC's distinctive biology—including its dependence on estrogen signaling, endocrine resistance, and propensity for late recurrence—suggests that a one-size-fits-all approach may not be sufficient.

Key Terms and Definitions:

ILC – Invasive Lobular Carcinoma: A breast cancer characterized by a distinctive growth pattern and usually loss of E-cadherin. Most ILC is ER+ and HER2-negative.

IDC – Invasive Ductal Carcinoma: The most common form of invasive breast cancer and the comparison group used in many ILC studies.

ER+ – Estrogen Receptor Positive: Cancer cells contain estrogen receptors and can use estrogen signaling to promote their growth. Most ILC is ER+.

HR+ – Hormone Receptor Positive: Cancer cells express estrogen and/or progesterone receptors and may respond to endocrine therapy.

HER2-negative: Tumor does not have abnormally high levels of the HER2 protein or HER2 gene amplification.

Endocrine therapy: Treatment that blocks estrogen signaling or reduces the amount of estrogen available to hormone-receptor-positive cancer cells.

Tamoxifen: Endocrine therapy that blocks estrogen receptors in breast tissue commonly used in pre-menopausal patients.

AI – Aromatase Inhibitor: A drug that decreases estrogen production in tissues outside the ovaries. In a pre-menopausal patient, an AI is generally combined with ovarian function suppression.

OFS – Ovarian Function Suppression: Treatment that stops or substantially reduces ovarian estrogen production. It can be achieved with medication or surgery.

Endocrine resistance: When a hormone-receptor-positive cancer stops responding adequately to endocrine therapy and continues to grow or eventually recurs.

Late recurrence: Recurrence occurring many years after the original breast cancer diagnosis. ILC has a particularly persistent risk of recurrence over time.

E-cadherin (CDH1): A protein that helps neighboring cells stick together. Loss of E-cadherin is a defining feature of classic ILC and contributes to its characteristic dispersed growth pattern.

ESR1: The gene that encodes estrogen receptor alpha (ER α). Changes in ESR1 can contribute to resistance to endocrine therapy, particularly in advanced hormone-receptor-positive breast cancer.

Resources and Key references:

Yoon TI, Jeong J, Lee S, et al. Survival Outcomes in Premenopausal Patients With Invasive Lobular Carcinoma. *JAMA Network Open*. 2023;6(11):e2342270. doi:10.1001/jamanetworkopen.2023.42270.

Jankowitz RC, McGuire KP, Davidson NE. Optimal systemic therapy for premenopausal women with hormone receptor-positive breast cancer. *Breast*. 2013;22 Suppl 2:S165–S170. doi:10.1016/j.breast.2013.07.032.

Sreekumar S, Levine KM, Sikora MJ, et al. ER Regulation in Invasive Lobular Breast Carcinoma. *Endocrinology*. 2020;161(9):bqaa109. doi:10.1210/endo/bqaa109.

Record H, Clelland E, Rothschild HT, et al. Tamoxifen or aromatase inhibitors with ovarian function suppression in pre-menopausal stage I-III lobular breast cancer. *NPJ Breast Cancer*. 2023;9:88. doi:10.1038/s41523-023-00594-3.

Reporting on invasive lobular breast cancer in clinical trials: a systematic review. *NPJ Breast Cancer*. 2024.

Scientific Session 5: Diagnostics and Clinical Management

Modifiable risk factors impacting ILC outcomes

Presenter 2: Karen van Baelen, MD, PhD

Background: Some breast cancer risk factors are modifiable, meaning they can potentially be changed, while others—such as age, genetics, and reproductive history—cannot be changed. Established breast cancer risk factors include alcohol consumption, physical inactivity, excess body weight, and certain reproductive and hormonal exposures. However, an important distinction is that evidence that a factor is related to an increased risk of developing breast cancer does not necessarily mean that changing that factor after diagnosis will affect survival.

This distinction is particularly important for ILC. Because ILC is strongly hormone receptor-positive and appears to have biological relationships with estrogen signaling, reproductive and hormonal factors may have particular relevance to this subtype. However, much of the evidence about lifestyle and breast cancer outcomes comes from studies of breast cancer as a whole rather than ILC specifically.

Body weight and BMI: Body mass index (BMI) is one of the most studied potentially modifiable risk factors associated with breast cancer. Higher BMI is associated with worse outcomes in several breast cancer populations, although the relationship is complicated by menopausal status, tumor subtype and treatment. Importantly, Karen Van Baelen and colleagues have specifically investigated this question in ILC. In their 2023 study of patients with primary ILC, BMI was associated with several clinicopathological features and survival outcomes. The study provides ILC-specific evidence that body weight may be relevant to the biology and prognosis of this disease rather than simply extrapolating from studies of breast cancer overall. (Van Baelen et al., 2023) The mechanisms are biologically plausible. Adipose tissue can influence estrogen levels, insulin signaling, inflammation and other metabolic pathways. These mechanisms may be particularly relevant in ER+ cancers such as ILC. However, an association between BMI and outcome does **not** prove that intentionally losing weight after an ILC diagnosis will improve survival. Clinical trials are needed to establish whether changing body weight changes cancer outcomes.

Physical activity: Physical activity is another potentially modifiable factor associated with breast cancer outcomes. In breast cancer populations overall, regular physical activity is associated with lower risks of recurrence and breast cancer death. Exercise may influence insulin sensitivity, inflammation, body composition and hormone metabolism. However, there is much less ILC-specific evidence. Therefore, a likely point of discussion is whether the benefits observed across breast cancer populations apply equally to ILC, and whether lifestyle interventions should be studied specifically in people with ILC.

Alcohol: Alcohol consumption is an established risk factor for developing breast cancer, and risk generally increases with increasing alcohol intake. Alcohol may influence estrogen levels and other biological pathways involved in breast cancer development.

Reproductive and hormonal factors: Reproductive factors, including age at first full-term pregnancy and number of pregnancies, are associated with breast cancer risk. Their relationship with ILC may be particularly interesting because ILC is strongly hormone receptor-positive. Van Baelen and colleagues recently examined parity and age at first full-term pregnancy specifically in relation to ILC. Their 2026 case-only analysis investigated whether these reproductive factors were associated with ILC characteristics. Because these factors generally cannot be changed after diagnosis, they are better considered risk or disease-characterization factors than lifestyle interventions. Nevertheless, they may help researchers understand ILC biology and whether reproductive history is associated with particular ILC phenotypes. (Van Baelen et al., 2026)

What the Talk is Likely to Cover and Why: Dr. Van Baelen's 2023 study, *Association of body mass index with clinicopathological features and survival in patients with primary invasive lobular breast cancer*, directly examined BMI in ILC. This suggests that body weight and metabolic factors will be an important component of the presentation. The study is particularly relevant because it asks whether a factor that is already known to influence breast cancer risk and outcomes also has a measurable relationship specifically within ILC. (Van Baelen et al., 2023). Her more recent research broadens the concept of "modifiable risk factors" to include factors occurring across a person's life course. In her 2026 study examining parity and age at first full-term pregnancy, Van Baelen and colleagues investigated reproductive factors specifically in relation to ILC. This suggests that the presentation may discuss how hormonal and reproductive exposures shape ILC risk and biology, while distinguishing these from factors that can actually be changed after diagnosis. (Van Baelen et al., 2026)

A key point to listen for is therefore the difference between association and causation. Observational studies can identify relationships between BMI, reproductive history, lifestyle or other characteristics and ILC outcomes, but they cannot necessarily establish that changing the factor will change survival. This distinction is especially important when discussing weight, diet or exercise with patients, because cancer outcomes are influenced by tumor biology, stage, treatment and many other factors.

Finally, the presentation is likely to highlight a major gap in the field: we have much stronger evidence about modifiable factors and breast cancer overall than we do specifically for ILC. Van Baelen's systematic review of ILC clinical trials found that ILC is frequently not reported separately, making it difficult to determine whether results from broader breast cancer trials apply equally to patients with ILC. (Van Baelen et al., 2024)

The most important takeaway may therefore be that improving ILC outcomes is not simply a matter of telling patients to "live healthier." Instead, the field needs better ILC-specific evidence to determine which patient-level factors truly influence prognosis, which can be changed, and which interventions actually improve outcomes.

Key Terms and Definitions:

BMI – Body Mass Index: A measure calculated from weight and height that is commonly used to categorize body weight in population studies. BMI is a population-level measure and does not directly measure body fat.

Metabolic factors: Biological characteristics related to processes such as body weight, insulin signaling, glucose metabolism and inflammation.

Parity: The number of pregnancies resulting in a birth. Parity is generally considered a reproductive/life-course factor rather than a modifiable factor after diagnosis.

Resources and Key references:

Van Baelen K, Nguyen H-L, Hamy-Petit A-S, et al. Association of body mass index with clinicopathological features and survival in patients with primary invasive lobular breast cancer. *Eur J Cancer*. 2023;191:112988. doi:10.1016/j.ejca.2023.112988.

Van Baelen K, Nguyen H-L, Vangoitsenhoven M, et al. The association between parity, age of first full term pregnancy and invasive lobular breast cancer: a case-only analysis. *Cancer Treat Res Commun*. 2026;47:101186. doi:10.1016/j.ctarc.2026.101186.

Van Baelen K, Van Cauwenberge J, Maetens M, et al. Reporting on invasive lobular breast cancer in clinical trials: a systematic review. *npj Breast Cancer*. 2024;10:23. doi:10.1038/s41523-024-00627-5.

Zels G, Van Baelen K, Chang ACC, et al. Clinical and histopathological characterization of metastatic lobular breast cancer: lessons learned from post-mortem tissue donation programs. *npj Breast Cancer*. 2026;12:48. doi:10.1038/s41523-026-00912-5.

World Cancer Research Fund/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Breast Cancer*. (Source: WCRF/AICR Breast Cancer Continuous Update Project.)

World Health Organization. *Breast cancer: risk factors and prevention*. (Source: World Health Organization.)

American Cancer Society. *Breast Cancer Risk Factors*. (Source: American Cancer Society.)

Scientific Session 5: Diagnostics and Clinical Management

Management of the axilla in ILC

Presenter 3: Priscilla McAuliffe, MD, PhD

Background: Professor Priscilla McAuliffe is a breast surgical oncologist at the UPMC Hillman Cancer Center and Assistant Professor of Surgery at the University of Pittsburgh School of Medicine. Her clinical and research interests include invasive lobular carcinoma (ILC), lobular carcinoma in situ (LCIS), breast-conserving surgery, and axillary management. She leads breast surgery clinical trials and is particularly interested in improving surgical care by reducing unnecessary procedures while maintaining excellent cancer outcomes.

The axilla is the area under the arm where lymph nodes are located. These lymph nodes are one of the first places breast cancer cells may spread, so evaluating them is an important part of breast cancer staging and treatment planning. Historically, many people with breast cancer underwent axillary lymph node dissection (ALND), in which many lymph nodes were removed. While effective, this surgery can increase the risk of complications such as lymphedema, shoulder stiffness, numbness, and reduced arm mobility.

Today, many patients can safely undergo a much smaller operation called a sentinel lymph node biopsy (SLNB), where only the first few lymph nodes most likely to contain cancer cells are removed. Large clinical trials have shown that many patients do not benefit from removing additional lymph nodes, allowing surgeons to reduce the extent of surgery while maintaining excellent cancer outcomes.

For people with invasive lobular carcinoma (ILC), however, the picture is less straightforward. ILC can sometimes be more difficult to detect on imaging and, in some cases, may involve more lymph nodes than expected. Researchers continue to study whether treatment recommendations developed largely from studies of invasive ductal carcinoma (IDC) apply equally well to people with ILC.

What the Talk Is Likely to Cover, and Why: Professor McAuliffe has focused much of her research on improving breast surgery while avoiding unnecessary procedures whenever it is safe to do so. Based on her clinical and research interests, this presentation will likely review current approaches to managing the lymph nodes in people with ILC and how these strategies are evolving.

You may hear about when a sentinel lymph node biopsy is sufficient, when a more extensive axillary lymph node dissection may still be recommended, and how decisions are influenced by tumor size, imaging findings, pathology results, and planned treatments such as chemotherapy or radiation. Because invasive lobular carcinoma can sometimes spread differently from other breast cancers, the presentation may also discuss whether current surgical guidelines fully address the unique characteristics of ILC. Researchers are continuing to study how to reduce surgical side effects without compromising accurate staging or long-term cancer outcomes.

Why This Matters to People with ILC: This session will discuss how doctors decide when it is recommended to remove only a few lymph nodes vs. when more extensive surgical excision of lymph nodes is recommended and why such recommendations continue to evolve. Understanding modern axillary management can help you have more informed conversations with your healthcare team about surgery, possible side effects such as lymphedema, and the latest evidence guiding treatment for ILC.

Key Terms and Definitions:

Axilla: The underarm area that contains lymph nodes involved in breast cancer staging.

Sentinel Lymph Node Biopsy (SLNB): Removal of the first one or a few lymph nodes that drain the breast to check whether cancer has spread.

Axillary Lymph Node Dissection (ALND): Surgery to remove many lymph nodes from the axilla, usually when cancer involvement is more extensive.

Lymphedema: Swelling of the arm or chest caused by disruption of normal lymphatic drainage after lymph node surgery or radiation.

Resources and Key references:

Lobular Breast Cancer Alliance (LBCA); National Cancer Institute (NCI); National Library of Medicine / PubMed; ClinicalTrials.gov; National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology

Carleton, N., Zou, J., Fang, Y., et al., and McAuliffe, P. F. (2022). *Is the Choosing Wisely Recommendation for Omission of Sentinel Lymph Node Biopsy Applicable for Invasive Lobular Carcinoma?* Annals of Surgical Oncology, 29, 633–641. <https://doi.org/10.1245/S10434-022-12003-3>.

Carleton, N., Zou, J., Fang, Y., et al., and McAuliffe, P. F. (2021). *Outcomes After Sentinel Lymph Node Biopsy and Radiotherapy in Older Women With Early-Stage, Estrogen Receptor–Positive Breast Cancer.* JAMA Surgery, 156(10), 944–951.

Scientific Session 5: Diagnostics and Clinical Management
Immunotherapy in ILC: tumor microenvironment for treatment selection
Presenter 4: Jason A. Mouabbi, MD

Background: Dr. Jason Mouabbi is a medical oncologist at The University of Texas MD Anderson Cancer Center specializing in hormone receptor-positive metastatic breast cancer and invasive lobular carcinoma (ILC). He serves as Chair of the Scientific Advisory Board of the Lobular Breast Cancer Alliance (LBCA) and is internationally recognized for his work advancing clinical care and research in ILC. His research focuses on the unique biology of lobular breast cancer, including the tumor microenvironment, endocrine resistance, precision medicine, and clinical trials designed to develop more personalized treatments for people living with ILC.

Most breast cancers are considered “immunologically cold,” meaning they contain relatively few immune cells that recognize and attack cancer. This is especially true for invasive lobular carcinoma (ILC), which is usually hormone receptor-positive (HR+) and generally responds less well to immunotherapy than cancers such as melanoma or triple-negative breast cancer.

Immunotherapy is a type of cancer treatment that helps the body’s immune system recognize and destroy cancer cells. While it has transformed treatment for several cancers, it is not currently a standard treatment for most people with ILC. Researchers are working to understand why this is the case and whether some people with ILC may still benefit.

One area of growing interest is the tumor microenvironment—the network of immune cells, blood vessels, connective tissue, and other normal cells that surround a tumor. This environment can either help the immune system attack cancer or protect the cancer from immune cells. Scientists are discovering that not all ILC tumors have the same microenvironment, and these differences may influence how cancers grow, spread, and respond to treatment. Understanding these differences could help identify which patients are most likely to benefit from immunotherapy or other targeted treatments in the future.

What the Talk Is Likely to Cover, and Why: Professor Jason Mouabbi has helped lead research into the unique biology of invasive lobular carcinoma (ILC), including how the tumor microenvironment influences cancer behavior and treatment response. Based on his research, this presentation will likely explore why most ILCs have relatively low immune activity and what that means for the use of immunotherapy.

You may hear about the different types of immune cells found within and around ILC tumors, how these cells interact with cancer cells, and why some tumors may be better able to evade the immune system than others. The presentation may also discuss biomarkers that could help identify which patients are most likely to benefit from immunotherapy or future combination treatments.

Another topic may be how researchers are combining immunotherapy with other treatments, such as endocrine therapy, targeted therapies, or antibody-drug conjugates, to make immunotherapy more effective in ILC. As our understanding of the tumor microenvironment grows, these discoveries may help guide more personalized treatment strategies and improve outcomes for people living with lobular breast cancer.

Why This Matters to People with ILC: Although immunotherapy is not currently a standard treatment for most people with ILC, researchers are making important progress in understanding why. This session will explain how the immune system and the tumor microenvironment influence ILC and why these factors may help predict which treatments are most effective. As scientists learn more about the biology of ILC, these discoveries could lead to new treatment options, more personalized care, and future clinical trials designed specifically for people living with lobular breast cancer.

Key Terms and Definitions:

Immunotherapy: A type of cancer treatment that helps the body's immune system recognize and attack cancer cells.

Tumor Microenvironment (TME): The network of immune cells, blood vessels, connective tissue, and other normal cells surrounding a tumor that can influence how cancer grows and responds to treatment.

Biomarker: A measurable feature, such as a protein or genetic change, that may help predict how a cancer will behave or whether it is likely to respond to a particular treatment.

Immune Checkpoint Inhibitor: A type of immunotherapy drug that removes “brakes” on immune cells, allowing them to better recognize and attack cancer cells.

Resources and Key references: Lobular Breast Cancer Alliance (LBCA); National Cancer Institute (NCI); National Library of Medicine / PubMed; ClinicalTrials.gov; National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology

Mouabbi, J. A., Meric-Bernstam, F., Nasrazadani, A., Nelson, B. E., Salem, B., Kushnarev, V., et al. (2024). *The multiomic tumor microenvironment landscape of invasive lobular carcinoma / of the breast. Journal of Clinical Oncology*, 42(16).

Mouabbi, J. A., Hassan, A., Lim, B., Hortobagyi, G. N., Tripathy, D., and Layman, R. M. (2022). *Invasive lobular carcinoma: An understudied emergent subtype of breast cancer. Breast Cancer Research and Treatment*, 193(2), 253–264. <https://doi.org/10.1007/s10549-022-06527-5>

SCIENTIFIC SESSION 6: Clinical Trial Results and Advocacy

Thursday, September 24, 2026 | 3:45–5:00 pm

Moderators: Megan Kruse, MD and Deborah Romer

Presentations:

1. **PELOPS**

Rinath Jeselsohn, MD, PhD — Dana-Farber Cancer Institute

2. **Neoadjuvant neratinib**

Laura Kennedy, MD — Vanderbilt University Medical Center

3. **LOBSTER**

Maria Karsten, MD Charité – Universitätsmedizin Berlin, Germany

4. **Integrating patient advocates in ILC research (N/A)**

Mo Rimawi, MD — Baylor College of Medicine

Scientific Session 6: Clinical Trial Results and Advocacy

PELOPS (Palbociclib and Endocrine Therapy for Lobular Breast Cancer Preoperative Study)

Presenter 1: Rinath Jeselsohn, MD, PhD

Background: PELOPS is a research study led by the Dana-Farber Cancer Institute that is evaluating whether adding a drug called palbociclib to endocrine therapy before surgery can improve outcomes in early-stage, hormone receptor-positive breast cancer. This study included lobular breast cancer patients to promote a better understanding of how Invasive Lobular Carcinoma (ILC) might respond differently to these therapies.

The study had a window treatment phase followed by a treatment phase. In the window treatment phase, participants were treated with a two-week course of tamoxifen or letrozole. In the treatment phase, participants were randomized to receive endocrine therapy in combination with palbociclib or endocrine therapy alone for a total duration of 24 weeks.

The clinical trial associated with this study started in 2016 and has 195 individuals enrolled in it. The study is now in phase 2. The estimated study completion date is 2031. The key investigators in this study are: Otto Metzger (Principal Investigator), Rinath Jeselsohn (Lead Translational and Correlative Science Investigator), and Agostina Nardone (Translational Research Collaborator).

One of the most important findings coming out of PELOPS is that tamoxifen suppressed cell-cycle pathways in ductal cancers, but not in lobular cancers, while letrozole suppressed these pathways in both. These translational findings are increasingly viewed as the most influential outcome of PELOPS for the lobular breast cancer field. PELOPS is frequently cited as one of the better examples of a trial that specifically generated lobular-focused data and tissue samples for future research.

What the Talk is Likely to Cover and Why: One of Dr. Rinath Jeselsohn's research hypotheses is that lobular breast cancer has a different estrogen receptor biology than ductal breast cancer and may respond differently to endocrine therapies. In terms of the PELOPS research study, she is helping analyze biologic factors and how they relate to treatment response in lobular breast cancer.

Based on this, her talk may focus on what PELOPS has taught researchers about:

- Tamoxifen resistance in lobular breast cancer
- Why aromatase inhibitors may be more effective in some ILC patients
- The unique estrogen receptor biology of lobular breast cancer
- How these findings are shaping the next generation of lobular-specific clinical trials

She may also talk about the importance of PELOPS for ILC, as ILC has historically been underrepresented in clinical trials. PELOPS intentionally included and analyzed patients with ILC, researchers collected tumor samples before and after treatment, creating a valuable resource for understanding how lobular cancers respond to endocrine therapies, and the trial has generated ongoing research examining why lobular cancers may respond differently to hormone therapies than ductal cancers. This type of work is helping researchers move toward lobular-specific treatment strategies rather than treating all ER-positive breast cancers as biologically identical.

Key Terms and Definitions:

Cell Cycle Pathway: The series of molecular signals that control how and when a cell grows, copies its DNA, and divides into two new cells.

Endocrine Therapy (hormone therapy): A treatment that slows or stops the growth of cancers that use hormones (primarily estrogen and/or progesterone) to grow.

Palbociclib: A CDK4/6 inhibitor that blocks proteins involved in cancer cell growth and division

PELOPS: Palbociclib and Endocrine Therapy for Lobular Breast Cancer Preoperative Study

Resources and Key references:

dana-farber.org, clinicaltrials.gov, lobularbreastcancer.org

European Society for Medical Oncology (ESMO). *The Management of Invasive Lobular Breast Cancer is Evolving*. Summary of PELOPS findings demonstrating differential response of ILC versus IDC to tamoxifen and letrozole.

Weiss AC, et al. *Axillary Management and Outcomes After Neoadjuvant Endocrine Therapy in the PELOPS Trial*.

Jeselson R., Russo D., Jin Q., Kurnia P., Gomez Tejeda J., Prasad K., Sherman S., Demeo M. K., Huang Y., Brock J., Dillon D. A., King T. A., Yardley D., Mayer I. A., Symmans W. F., Stewart C., Winer E., Tayob N., Getz G., . . . Metzger O. (2025). Primary results and the transcriptomic analysis of PELOPS, a randomized phase II study of neoadjuvant palbociclib with or without endocrine therapy for breast cancer patients with invasive lobular carcinoma or invasive ductal carcinoma [Abstract]. *Clinical Cancer Research*, 31(12 Suppl), Abstract PS18-06.

Grinshpun A, Dustin D, Cai M, Hughes M, DiLullo M, Moore M, Yardley D, Mayer IA, Symmans WF, Mayer EL, Winer EP, Lin NU, Tolaney SM, Metzger O, Jeselson R. Circulating tumor DNA in neoadjuvant endocrine therapy for early breast cancer. *ESMO Open*. 2026 Mar;11(3):106067. doi: 10.1016/j.esmoop.2026.106067. Epub 2026 Feb 10.

Weiss A, Jin Q, Tayob N, Wrabel E, DeMeo M, Carter J, Constantine M, Faggen M, Block C, Fenton MA, Lo KMS, Openshaw T, Yardley D, Kennedy L, Bedrosian I, Mittendorf EA, Jeselson R, Metzger Filho O, King TA. Axillary Management and Outcomes After Neoadjuvant Endocrine Therapy in the Randomized PELOPS Trial. *Ann Surg Oncol*. 2026 Mar;33(3):2275-2283. doi: 10.1245/s10434-025-18697-5. Epub 2025 Nov 23.

Scientific Session 6: Clinical Trial Results and Advocacy

Neoadjuvant neratinib

Presenter 2: Laura Kennedy, MD

Background: This Phase II clinical trial is evaluating whether adding the targeted therapy neratinib to standard endocrine therapy before surgery can improve treatment outcomes for patients with stage I–III, hormone receptor-positive, HER2-mutated invasive lobular carcinoma (ILC). Unlike HER2-positive breast cancers that overexpress the HER2 protein, this study focuses on patients whose tumors are HER2-negative by routine testing but contain an activating HER2 (ERBB2) gene mutation, a genetic alteration that may drive cancer growth and resistance to standard endocrine therapy.

Participants receive neoadjuvant (preoperative) endocrine therapy together with neratinib before surgery. During treatment, researchers collect tumor biopsies, blood samples, and imaging studies to better understand how HER2-mutated lobular breast cancers respond biologically. These samples will allow investigators to study biomarkers of treatment response, circulating tumor DNA (ctDNA), and patient-derived organoids that may help guide future treatment strategies.

The clinical trial opened in 2024 and is currently recruiting approximately 30 participants across multiple cancer centers in the United States. It is a Phase II study sponsored by Vanderbilt Ingram Cancer Center with support from the National Cancer Institute and Puma Biotechnology. Because HER2 mutations occur in only a small percentage of invasive lobular carcinomas, this represents one of the first prospective clinical trials designed specifically for this molecular subtype of ILC.

One of the most important aspects of this study is its precision medicine approach. Rather than treating all estrogen receptor-positive lobular breast cancers the same way, researchers are testing whether identifying HER2 mutations can help match patients to a targeted therapy that blocks the abnormal HER2 signaling driving tumor growth. The tissue and blood samples collected throughout the study are also expected to become an important resource for future research focused on HER2-mutated invasive lobular carcinoma.

What the Talk is Likely to Cover and Why: Dr. Laura Kennedy's research focuses on improving treatment options for patients with invasive lobular carcinoma by identifying molecular features that may predict response to targeted therapies. Based on the goals of this study, her presentation may focus on:

- Why HER2 mutations represent an important therapeutic target in a subset of invasive lobular breast cancers.
- How neratinib works and why combining it with endocrine therapy before surgery may improve treatment response.
- The value of neoadjuvant therapy for studying tumor biology and measuring how cancers respond before surgery.
- How tumor tissue, circulating tumor DNA, and laboratory-grown organoids may help researchers develop more personalized treatment strategies for patients with ILC.

She may also discuss the importance of designing clinical trials specifically for lobular breast cancer. Historically, patients with invasive lobular carcinoma have often been grouped together with invasive ductal carcinoma despite important biological differences. By focusing exclusively on HER2-mutated ILC, this study has the potential to improve understanding of this rare subtype and help move the field toward more individualized treatment strategies based on tumor biology rather than treating all hormone receptor-positive breast cancers as biologically identical.

Key terms and Definitions:

Circulating Tumor DNA (ctDNA): Small fragments of DNA released by cancer cells into the bloodstream that may help researchers monitor how a tumor is responding to treatment.

Endocrine Therapy (Hormone Therapy): Treatment that slows or stops the growth of hormone receptor-positive breast cancers by lowering estrogen levels or blocking estrogen's effects.

HER2 (ERBB2) Mutation: A change in the HER2 gene that can activate cancer growth, even when the tumor is considered HER2-negative by standard pathology testing.

Neoadjuvant Therapy: Treatment given before surgery to shrink a tumor and allow researchers to study how well a therapy works.

Neratinib: An oral tyrosine kinase inhibitor that blocks HER2 signaling pathways and is being studied as a targeted therapy for HER2-mutated invasive lobular breast cancer.

Organoids: Miniature three-dimensional tumor models grown from a patient's own cancer cells that allow researchers to study treatment response in the laboratory.

Precision Medicine: An approach to treatment that uses the genetic and molecular characteristics of a patient's tumor to help select the most appropriate therapy.

Resources and Key references:

National Cancer Institute (NCI), ClinicalTrials.gov, Lobular Breast Cancer Alliance

National Cancer Institute. Neoadjuvant Neratinib for the Treatment of Stage I–III HER2-Mutated Lobular Breast Cancers. NCI-2023-04468.

ClinicalTrials.gov. Neoadjuvant Neratinib in Stage I–III HER2-Mutated Lobular Breast Cancers. ClinicalTrials.gov Identifier: NCT05919108.

Lobular Breast Cancer Alliance. Neoadjuvant Neratinib in Stage I–III HER2-Mutated Lobular Breast Cancers.

National Cancer Institute Trial Summary: <https://www.cancer.gov/clinicaltrials/NCI-2023-04468>

ClinicalTrials.gov Trial Record (NCT05919108): <https://clinicaltrials.gov/study/NCT05919108>

Lobular Breast Cancer Alliance Clinical Trial

Listing: <https://lobularbreastcancer.org/neoadjuvant-neratinib-in-stage-i-iii-her2-mutated-lobularbreast-cancers/>

Scientific Session 6: Clinical Trial Results and Advocacy

LOBSTER

Presenter 3: Maria Karsten, MD

Background: LOBSTER (GBG 118) is a randomized Phase II clinical trial designed specifically for patients with invasive lobular carcinoma (ILC), making it one of the few breast cancer studies focused exclusively on lobular disease rather than combining lobular and ductal breast cancers into a single study population.

Although invasive lobular carcinoma is the second most common subtype of breast cancer, it remains underrepresented in clinical research. Increasing evidence suggests that ILC possesses unique biologic characteristics and may respond differently to treatment than invasive ductal carcinoma (IDC). As a result, researchers are increasingly developing studies designed specifically for lobular breast cancer.

LOBSTER is evaluating whether adding capivasertib, an AKT inhibitor, to fulvestrant, an estrogen receptor degrader (SERD), can improve treatment response before surgery in patients with high-risk, hormone receptor-positive (HR+), HER2-negative invasive lobular breast cancer.

Approximately 120 postmenopausal women with newly diagnosed high-risk ILC are expected to enroll. Participants are randomized to receive either fulvestrant alone or fulvestrant combined with capivasertib for approximately 10 weeks before surgery.

The primary goal of the study is to determine whether the addition of capivasertib increases Complete Cell Cycle Arrest (CCCA), measured by a significant reduction in the Ki-67 proliferation marker. Researchers hope these findings will help identify more effective, biology-driven treatment approaches for patients with lobular breast cancer.

What the Talk is Likely to Cover and Why: Based on the trial design and current understanding of lobular breast cancer biology, Dr. Karsten's presentation may discuss:

- Why invasive lobular carcinoma requires dedicated clinical research
- The role of the PI3K/AKT signaling pathway in lobular breast cancer
- How capivasertib works as a targeted therapy
- The rationale for combining capivasertib with fulvestrant
- Early biologic findings and treatment response measures, including Ki-67 reduction
- How LOBSTER may help identify patients most likely to benefit from targeted therapies

The future of personalized treatment strategies for invasive lobular carcinoma

Why this matters for patients: Historically, treatment recommendations for invasive lobular carcinoma have largely been based on studies dominated by patients with ductal breast cancer. LOBSTER is notable because it was designed specifically for patients with ILC and focuses on the unique biology of lobular disease.

Many lobular tumors harbor alterations in the PI3K/AKT pathway, making this an important target for investigation. By studying targeted therapy in the neoadjuvant setting, researchers hope to better understand which patients may benefit from precision treatment approaches earlier in their care.

LOBSTER joins a growing group of lobular-focused studies, including PELOPS and NERINA, that are helping move the field toward treatment strategies developed specifically for patients with invasive lobular breast cancer.

Key Terms and Definitions:

AKT Pathway: A signaling pathway involved in cell growth, survival, and metabolism. Abnormal activation may contribute to cancer development and treatment resistance.

Capivasertib: A targeted therapy that blocks AKT proteins and may slow cancer cell growth. **CCCA (Complete Cell Cycle Arrest):** A measure of how effectively treatment stops cancer cell proliferation.

Fulvestrant: A selective estrogen receptor degrader (SERD) that blocks and destroys estrogen receptors on cancer cells.

HER2-Negative: Breast cancer that does not overexpress the HER2 protein.

HR-Positive (Hormone Receptor-Positive): Breast cancer that uses hormones such as estrogen and/or progesterone to grow.

ILC (Invasive Lobular Carcinoma): The second most common type of breast cancer, originating in the milk-producing lobules.

Ki-67: A marker used to measure how rapidly cancer cells are dividing.

LOBSTER (GBG 118): A Phase II neoadjuvant clinical trial evaluating capivasertib plus fulvestrant versus fulvestrant alone in patients with high-risk invasive lobular breast cancer.

PI3K/AKT Pathway: A cellular signaling network frequently altered in breast cancer that helps regulate cell growth and survival.

Resources and Key references:

ClinicalTrials.gov Trial Record <https://clinicaltrials.gov/study/NCT06607757>

German Breast Group (GBG) <https://www.gbg.de>

European Union Clinical Trials Register <https://euclinicaltrials.eu>

Karsten MM et al. Phase II Neoadjuvant Study Evaluating Capivasertib Plus Fulvestrant Versus Fulvestrant in Patients With Primary High-Risk Lobular Breast Cancer (LOBSTER).

PELOPS Trial (NCT02764541) <https://clinicaltrials.gov/study/NCT02764541>

Dana-Farber Lobular Breast Cancer Research Program <https://www.dana-farber.org>

SCIENTIFIC SESSION 7: Endocrine Resistance and Novel Targets

Friday, September 25, 2026 | 8:00–9:00 am

Moderators: Pete Simpson, PhD and Megan-Claire Chase

Presentations:

1. Endocrine therapy resistance in ILC

Ariella Hanker, PhD — UT Southwestern Medical Center

2. Liquid biopsy other than blood

François Richard, PhD Institut Jules Bordet / Université libre de Bruxelles, Belgium

3. Combined vulnerabilities and potential interventions

Patrick Derksen, PhD — University Medical Center Utrecht, Netherlands

Scientific Session 7: Endocrine Resistance and Novel Targets

Endocrine therapy resistance in ILC

Presenter 1: Ariella Hanker, PhD

Background: Hormone therapy, also called endocrine therapy, is a primary treatment used to slow down or stop the growth of breast cancers that rely on hormones like estrogen to grow/survive. Estrogen can latch on to the hormone receptors on a cancer cell, causing the cell to further multiply. Endocrine therapy blocks this process by either lowering the body's overall estrogen levels or by directly competing with estrogen to latch onto these receptors.

Medications like selective estrogen receptor modulators (SERMs) compete with estrogen by binding to these receptors and locking themselves in place, preventing the cancer cells from turning on any cancer-growth genes. Other drugs, known as selective estrogen receptor degraders (SERDs), go a step further by binding to these receptors and destroying them entirely, leaving estrogen with nothing left to attach to. While hormone therapy has proven to be beneficial for many cases of breast cancer, a major hurdle in cancer care is treatment resistance. Treatment resistance happens when cancer cells figure out how to bypass these drugs and keep growing anyway. This can happen either immediately or after hormone therapy has been working successfully for a while. Invasive lobular carcinoma (ILC) behaves differently compared to other types of breast cancer, largely due to the loss of E-cadherin protein. The loss of this protein caused ILC cells to grow in loose, singular threads rather than solid lumps. Because of its unique genetic and structural features, ILC often responds less predictably to these standard therapies and shows differing patterns of spread.

Dr. Hanker's research focuses on uncovering these pathways that cancer cells use to survive hormone therapy treatments in lobular breast cancers. To study these patterns and drug resistance mechanisms, she uses specific methods such as single-cell genomic analyses, next-generation sequencing, and patient-derived organoids, to track how tumor cells evolve and adapt. Tumor cells are rarely uniform; they contain a mix of different cell types and mutations (tumor heterogeneity). Because of this, some cells naturally survive drug exposure and act as survivors, continuing to multiply. By using these advanced testing models, Dr. Hanker studies how these cells adapt and interact with their surrounding environment, helping researchers find new ways to understand these survival pathways and stop advanced breast cancer from progressing.

What the Talk is Likely to Cover and Why: Dr. Hanker's profiling studies of hormone receptor-positive breast cancers have mapped critical immune pathways and microenvironment interactions in treatment-resistant disease. Most recently, she led a multi-institutional study analyzing tumor samples from patients treated with hormone therapy. Her research compared samples that responded positively to treatment against those that developed resistance, indicating that the immune microenvironment actively drives treatment failure.

The findings from the study included:

1. Resistant tumors showed a higher presence of activated immune cells, specifically CD8+ T cells, alongside heightened inflammatory chemical signals.
2. Hormone therapy triggered specific chemical messenger genes, like CXCL11, which allowed breast cancer cells to grow and survive even when hormone-blocking drugs are present.

I suspect she will discuss the findings from this study and explain the importance of looking at immune cell interactions in the environment surrounding cancer cells. She could introduce the possibility of expansion of hormone therapy as a combined treatment for ILC, targeting both the cancer cell receptors and the immune cells around it.

Key Terms and Definitions:

E-cadherin: A “glue” protein that normally helps cells stick together to form neat, organized “lumps” of tissue. In certain cancers like invasive lobular carcinoma, this protein is missing, allowing cancer cells to break apart, move more freely, and become harder to detect.

Single-Cell Genomic Analysis: A laboratory method used to read the genetic material of individual cells one by one. This makes it possible to see the unique differences and mutations hidden inside a mixed population of tumor cells.

Next-Generation Sequencing: An advanced DNA-sequencing technique that allows researchers to scan vast amounts of the genetic code at once to spot mutations or large patterns across the entirety of the DNA genome that drive disease.

Patient-Derived Organoids: Three-dimensional “mini tumors” grown in a laboratory. The samples are taken from the actual biopsy tissue of a patient, which mimics how a real tumor behaves so researchers can test which drugs will work best.

CD8+ T Cells: A type of white blood cell in the immune system (often called a killer T cell). Their normal job is to tag and destroy infected or cancerous cells in the body. However in Dr. Hanker’s study found that rather than attacking the tumor, the “tricked” immune cells end up releasing signals (like growth chemicals) that the cancer cells can use to feed, survive, and keep growing.

CXCL11: A chemical messenger protein (also known as a chemokine) released by immune cells in the body to attract more immune cells to areas of infection. Research shows that sometimes they can be “tricked” by cancer cells to help them survive and grow. In the study, this is exactly what happened. Because the CD8+ T cells were transformed into messengers rather than attackers of the cancer cells, when CXCL11 was released from these “tricked” immune cells, it further helped the growth of the cancer as opposed to destroying it.

Resources and Key references:

Cleveland Clinic. (2023). T Cells: What They Are, Function and Types.

<https://my.clevelandclinic.org/health/body/24630-t-cells>

Kong, T., and Ma, C. X. (2026). Unraveling TIME: CD8+ T cell– and CXCL11-driven endocrine resistance in breast cancer. *The Journal of Clinical Investigation*, 136(3), e200923.

<https://doi.org/10.1172/JCI200923>

Mendonsa, A. M., Na, T. Y ., and Gumbiner, B. M. (2018). E-cadherin in contact inhibition and cancer. *Oncogene* , 37 (35), 4769–4780. <https://doi.org/10.1038/s41388-018-0304-2>

Napolitano, F., Hanker, A. B., et al. (2025). CD8+ T cells in the tumor microenvironment modulate the response to endocrine therapy in breast cancer. *The Journal of Clinical Investigation* , 136(3), e188458. <https://doi.org/10.1172/JCI188458>

Weiswald, L.-B., Poulain, L., et al. (2024). Patient-derived tumor organoids: a new avenue for preclinical research and precision medicine in oncology. *Experimental and Molecular Medicine*, 56 (7), 1545–1558. <https://doi.org/10.1038/s12276-024-01272-52>.

Scientific Session 7: Endocrine Resistance and Novel Targets

Liquid biopsy other than blood

Presenter 2: François Richard, PhD

Background: Liquid biopsies have become an incredibly useful tool in modern medicine, allowing doctors to detect, track, and understand cancer. Liquid biopsies primarily rely on analyzing tiny fragments of a tumor's genetic material that floats around in the body, known as circulating tumor DNA (ctDNA). Traditionally, medical professionals have focused almost entirely on using blood plasma samples (taken from a standard blood draw) to analyze this ctDNA. While using blood plasma has provided a general idea into how a disease like breast cancer is behaving in the body, it does not always capture a complete picture of what is happening under the surface—especially in complex breast cancers like invasive lobular carcinoma (ILC).

Advanced and metastatic breast cancers, especially ILC, are famously complicated because of their ability to shift and adapt as they travel to different regions within the body. Because of ILC's adaptation, each body region that it travels to varies from the next. Unlike more common breast cancers that form solid masses, ILC completely lacks the E-cadherin protein, which allows cancer cells to form "lumps". A lack of this protein causes ILC tumors to grow in loose, singular threads that can seamlessly integrate into surrounding tissues. When an ILC tumor multiplies and spreads additional cells across various tissues, relying solely on blood samples can create blind spots for doctors trying to measure the extent of metastatic spread. For example, if a tumor is small and is not shedding a lot of its fragmented ctDNA into the bloodstream, the "signal" from a standard blood draw can read "normal", as the ctDNA is overshadowed by the healthy DNA circulating from other tissues.

To solve this problem, Dr. Richard's research explores expanding liquid biopsies beyond standard blood samples. He aims to investigate if other alternative, localized bodily fluids can successfully bridge the gap for tracking complex cancers like ILC. In individuals whose breast cancer has spread, tumor cell fragments can accumulate in cavities and fluid pockets within the body. These areas "trap" the ctDNA, allowing it to be present in larger, highly detectable quantities in comparison to regularly circulating blood. Some examples of these spaces are the peritoneal cavity (area inside the abdomen), pericardial sac (surrounds the heart), pleural cavity (between the lungs and chest wall), and the surfaces that surround the brain and spinal cord. By testing these alternative biofluids, researchers can create a more accurate, multi-site picture of how an ILC tumor is growing and where it is spreading.

What the Talk is Likely to Cover and Why: In Dr. Richard's recent multi-institutional and post-mortem research, he evaluates how effectively these non-blood fluids measure metastatic breast cancer profiles. He compared cohort samples across multiple different biofluids to map tumor detectability.

The findings from his studies include:

1. CtDNA can be detected across a wide range of biofluids, but frequency and amount vary significantly. CtDNA was most frequently recovered in blood, followed by ascites, pleural fluid, and finally cerebrospinal fluid.
2. Alternative biofluids capture compartment-specific data that standard blood samples missed. CtDNA could not be detected in the blood plasma of 4 patients in a subset cohort of 12 patients. However, alternative biofluids successfully identified ctDNA in 3 of those 4 cases.
3. Phylogenetic reconstruction (like a family tree) reveals that sites of metastasis are not equally represented across all biofluids. For example, metastasis in the brain is measured significantly better in cerebrospinal fluid than blood plasma.

I suspect Dr. Richard will discuss the advantages of using different biofluids for tumor profiling and metastasis patterns. He will likely highlight how biofluids around the site of metastasis impact the sensitivity of a liquid biopsy,

and what further clinical validation is needed to integrate non-blood liquid biopsies into standard workups for metastatic disease.

Key Terms and Definitions:

Ascites (ASC): An abnormal accumulation of protein- and cell-rich fluid within the peritoneal cavity (the fluid-filled space in the abdomen). This fluid can be evaluated for abdominal metastatic involvement.

Cerebrospinal Fluid (CSF): A clear fluid that surrounds the brain and spinal cord. This can provide detection of central nervous system (includes the brain and spinal cord) metastases.

Circulating Tumor DNA (ctDNA): Small fragments of tumor DNA released into bodily fluids by cell death mechanisms. These mechanisms leave non-invasive remnants of the tumor circulating in the body, which serve as a biomarker for tracking tumor burden (an approximation of the total amount of cancer present in the body).

Liquid Biopsy (LB): A minimally invasive test that analyzes materials derived from a tumor found in blood or other bodily fluids to monitor and characterize cancer.

Phylogenetic Reconstruction: A computerized method used like a family tree to compare genetic information to determine how different tumor cell samples relate to one another. Every cancer begins with one abnormal cell in one specific area. As cancer grows and cells move and interact with different areas in the body, they will “pick up” variations that affect their genetic makeup. Cells in the original site of the tumor will develop one set of changes; cells that travel to other parts of the body will exhibit a different set of genetic changes. By comparing the similarities and differences between these cells, researchers can determine the timeline of a cancer’s spread. For example, if a breast origin cancer cell exhibits more similarities to a liver cancer cell than a lung cancer cell, that person’s breast cancer probably spread to the liver first, followed by the lung.

Pleural Fluid (PF): Fluid accumulating in the pleural cavity between the lungs and the chest wall.

Resources and Key references:

Cleveland Clinic. Ascites [Internet]. Cleveland (OH): Cleveland Clinic; 2026 [updated 2024 Oct 16; cited 2026 Aug 13]. <https://my.clevelandclinic.org/health/diseases/14792-ascites>

Richard F. A New Horizon in Cancer Care: The Promise of Multi-Source Liquid Biopsies [Online commentary/article]. BioVox. Published November 26, 2025.

<https://biovox.eu/a-new-horizon-in-cancer-care-the-promise-of-multi-source-liquid-biopsies/>

Richard F, Maetens M, Van Baelen K, Desmedt C, et al. ctDNA detectability and representativeness in seven body liquids from patients with metastatic breast cancer. *Nat Commun.* 2025;16(1):65838. doi:10.1038/s41467-025-65838-1.

Scientific Session 7: Endocrine Resistance and Novel Targets

Combined vulnerabilities and potential interventions

Presenter 3: Patrick Derksen, PhD

Background: E-cadherin is the main driver of cell adhesion in ILC. E-Cadherin (Cadherin 1) is a protein that is encoded by the CDH1 gene. The loss of E-cadherin, a key cell-to-cell adhesion protein encoded by the CDH1 gene, is the defining molecular hallmark of ILC. Normal epithelial cells stick together via the E-cadherin molecules. In ILC, genetic alterations or mutations in CDH1 disrupt this system. Without adhesion, cancer cells separate and infiltrate surrounding tissue individually or in narrow, single-file strands, making tumors harder to detect via standard physical exams or mammograms.

Dr. Derksen has researched how E-cadherin loss leads to metastatic ILC in the mammary gland. He has studied specifically how, when cells lose a protein called alpha-catenin or a-catenin, they cannot connect E-cadherin (the glue holding cells together) to F-actin (the internal skeleton of the cell). This breaks the “cellular anchor.” As a result, the cells separate and take on the shape and behavior of ILC. In his most recent studies, he has been focused on identifying mechanisms behind why ILC cells remain dormant and what triggers them to cause late-stage metastatic recurrences.

What the Talk is Likely to Cover and Why: Dr. Derksen’s studies have covered E-Cadherin loss and the development of ILC and why ILC is different from the more common hormone receptor positive breast cancer of no special type (NST – previously called ductal carcinoma). He has also studied how ILC’s distinct molecular landscape includes high rates of “overactive” PI3K-AKT pathways, which tell cells to grow and survive, and how this, along with the ER receptor, which is often in ILC “feeding” the cancer, together changes how the receptor changes and does or does not respond to endocrine therapy. He will likely discuss his findings and different implications for resistance to different endocrine therapies, including aromatase inhibitors and tamoxifen, SERDs and CDK4-6 inhibitors, and PARP inhibitors, and the circumstances under which recurrence or metastasis is more likely to occur. He will likely also discuss his findings regarding what approaches and combinations of therapies may help keep ILC cells dormant, in particular, the effects of introducing afadin into ILC cells.

Key Terms and Definitions:

E-cadherin protein function: The “E” stands for “epithelial” the cells lining body cavities and surfaces, including breast milk ducts and lobules. Crucial for cell adhesion, E-Cadherin proteins sit on the cell surface and attach to internal anchoring proteins E-Cadherin functions much like Velcro, binding epithelial cells together to form organized stable tissue. When E-cadherin is lost, inactivated, or not functioning properly, epithelial cells become separated and loose, causing them to slip by other cells and infiltrate surrounding tissue in single file, linear strands. The growth pattern makes ILC especially hard to detect.

A-catenin: is a cell adhesion protein that normally links the E-cadherin/catenin complex to the actin cytoskeleton.

Afadin: Afadin is a multimodal scaffolding protein with essential functions in cell–cell adhesion. It has been found to stop breast cancer from spreading. It does this by building a strong physical bridge between the cell wall and the inner skeleton of the cell. This strong link helps cells stick together and stay in place. Mouse xenograft experiments based on cell lines and primary patient-derived breast cancer organoids demonstrate that Afadin loss induces single-cell lobular-type invasion phenotypes and overt dissemination to the lungs and the peritoneum. “Reintroducing wild-type Afadin or specific functional domains (such as the coiled-coil region critical for F-actin and α -catenin binding) helps restore proper cell-cell adherens junctions and reverses single-file invasive phenotypes,” i.e., adding afadin back to an ILC cell can stop metastasis. Rather than inducing direct cytotoxicity or cell death (apoptosis) to eradicate established tumors, restoring Afadin functions as a tumor suppressor

mechanism that reinforces cell adhesion and restrains the physical dissemination and metastatic spread characteristic of invasive lobular carcinoma (ILC).

CDH1 gene: is a tumor suppressor gene that makes E-cadherin.

PI3K/AK/mTOR: is a pathway that helps cells survive, grow, and proliferate. In breast cancer, this pathway is frequently overactive (commonly due to mutations or activation of upstream signals), which can contribute to tumor growth, resistance to therapy, and more aggressive disease.

ROS1: It is a gene that controls normal cell growth and survival.

PARP Inhibitor: Is a targeted oral medication that blocks the PARP protein, preventing cells with BRAC1 or BRAC2 mutations from repairing their damaged DNA.

SERD = Selective Estrogen Receptor Degradar: A type of medicine that binds to estrogen receptors inside cells and destroys them. By wiping out these receptors, the drug stops the hormone estrogen from attaching and telling cancer cells to grow.

Ki-67: is a protein marker measured in pathology reports to see how fast cancer cells are dividing.

Resources and Key references:

Rätze MA, Enserink LN, Ishiyama N, van Kempen S, Veltman CH, Nijman IJ, Haakma WE, Caldas C, Bernards R, van Diest PJ, Christgen M, Koorman T, Derksen PW. Afadin loss induces breast cancer metastasis through destabilisation of E-cadherin to F-actin linkage. *J Pathol.* 2025 May;266(1):26-39. doi: 10.1002/path.6394. Epub 2025 Mar 3. PMID: 40026293; PMCID: PMC11985701.

<http://Pubmed.ncbi.nlm.nih.gov/25757734> Lobular breast cancer:molecular basis, Patrick W B Derksen

<https://derksenlab.org/project/ILC> Project Invasive Lobular Breast Cancer ILC Journal of Pathology dot.org/10.1002/path6205 Patrick W B Derksen

SCIENTIFIC SESSION 8: Advanced Imaging and Artificial Intelligence

Friday, September 25, 2026 | 10:00–11:00 am

Moderators: David Lim, MD, PhD and Nikoo McGoldrick

Presentations:

1. **Clinical trial on AI detection of ILC on mammography**
Manisha Bahl, MD — Mass General Brigham / Harvard Medical School
2. **Contrast enhanced mammography in ILC**
Molly Hogan, MD — University of California, San Francisco (UCSF)
3. **Whole body MRI for metastatic ILC**
Elleke Dresen, MD, PhD — KU Leuven / University Hospitals Leuven, Belgium

Scientific Session 8: Advanced Imaging and Artificial Intelligence

Clinical trial on AI detection of ILC on mammography

Presenter 1: Manisha Bahl, MD

Background: Dr. Manisha Bahl is a breast imaging expert and Associate Medical Director at Massachusetts General Brigham, an associate professor of radiology at Harvard Medical School, and a Fellow of the Society of Breast Imaging. She is leading crucial research on using artificial intelligence (AI) to improve the detection of invasive lobular carcinoma (ILC) on mammograms.

AI-STREAM trial (Artificial Intelligence for Breast Cancer Screening in Mammography) is a clinical trial to see how AI as “second reader” compares alongside human radiologists checking mammography images. AI is not a replacement for radiologists, but should be a powerful tool used to aid in diagnosing and more efficient workflows for radiologists. The thought is AI will catch cancer at early stages and cancers that the human eye missed. There are also results that doctors caught that AI missed. The AI software is only as good as the team training the software.

AI is a clinical reality in medical imaging today. The conversation has shifted from how it can be used to safely and effectively detect abnormalities in human tissue. AI for breast imaging helps general radiologists; it can support as an equivalent to a breast-trained radiologist.

What the Talk is Likely to Cover, and Why: Dr. Bahl has spent the majority of her career making advances in breast imaging and detection of cancers. The AI-STREAM trial showed that the overall accuracy performed at a high-level. The sensitivity to identify cancers was nearly 90%. The cohort for the trial had 24,253 women from six hospitals, this provided a largely diverse population.

AI reduces the need for callback imaging. It reduces the time from screening to a diagnostic mammogram. AI can save about 4 to 6 weeks of time waiting for additional imaging.

The idea is using AI to detect subtle differences in tissues along with health data of patients, can help determine potential biomarkers for lobular breast cancer and will allow for earlier detection for better outcomes for patients.

Dr. Bahl is training the AI to detect subtle patterns of lobular breast cancer. She wants patients to be aware that it is a useful tool when it identifies subtle changes in the breast tissue seen on mammography.

Why This Matters to People with ILC: The Mammography Screening with Artificial Intelligence (MASAI) trial in Sweden has confirmed AI can significantly reduce the workload and improve workflow for radiologists. This gives way for earlier diagnosis, earlier staging, and potentially less toxic treatment options. Survival rates increase with earlier diagnosis.

“Lobular cancer has a puzzling pattern: Some patients look high-risk based on their clinical features but low-risk based on their genomics stemming from tissue-testing result,” Dr. Arya Roy, MD Ohio State University Comprehensive Cancer Center

Key Terms and Definitions:

Artificial Intelligence (AI): is a branch of computer science that builds machines to do tasks that usually need human intelligence. A database is used to learn, solve problems, and make decisions.

Breast Imaging-Reporting and Data System (BI-RADS): is a standardized risk assessment tool and lexicon developed by the American College of Radiology for breast imaging (Mammograms, ultrasounds, and MRIs). Radiologists use it to categorize test results and recommend follow-up actions.

Breast Density: The ratio of fibrous and glandular tissue to fat. Dense breast tissue can make it hard to visualize abnormalities on mammograms.

Computer-Aided Design (CAD): It is the use of computer software to create, modify, analyze, or optimize digital 2D and 3D models.

Early Detection of Breast Cancer: ~~The theory that finding breast cancer early finds cancer before symptoms appear drastically~~ improves survival rates and often allows for less aggressive treatment.

Lunit INSIGHT MMG: is an AI software that helps doctors find breast cancer on Mammograms. Uses color maps, abnormality scores. The Radiologist still reviews images. This AI just assists what the human eye may miss.

Resources and Key references:

Lobular Breast Cancer Alliance (LBCA); National Cancer Institute (NCI); National Library of Medicine/PubMed, Clinical Trials.gov, Food and Drug Administration FDA, Radiology Society of America (RSNA)

Do, S., Bahl, M. *Mapping the AI “Mind”: What the AI-STREAM Trial Reveals About Cancer Detected and Missed. RSNA Radiology: Artificial Intelligence, Volume 8, Number 1,* <https://doi.org/10.1148/ryai.251002>.

Chang, Y et.al, *Artificial Intelligence for Breast Cancer Screening in Mammography (AI-STREAM: A Prospective Multicenter Study Design in Korea Using Ai-Based CADe/x*, Journal of Breast Cancer, 2022 Jan6;25(1):57-68.

<https://pmc.ncbi.nlm.nih.gov/articles/PMC8876543/>.
https://www.lunit.io/wpcontent/uploads/resources/Lunit_Global%20Breast%20onepager.pdf

Harper, A, and Kistler, S, *How AI is helping us find lobular breast cancer earlier, giving better treatment options*, Ohio State Health and Discover, October 2, 2025, <https://health.osu.edu/discovery-and-innovation/research-advances/ai-detects-lobular-breast-cancer>.

Scientific Session 8: Advanced Imaging and Artificial Intelligence

Contrast-enhanced mammography in ILC

Presenter 2: Molly Hogan, MD

Background: Dr. Molly Hogan is a Board-Certified Radiologist with a specialty in breast imaging at Memorial Sloan Kettering Hospital, primarily located at MSK Monmouth, New Jersey. Her research includes improving the detection of invasive lobular carcinoma (ILC) on diagnostic imaging exams.

Contrast-enhanced mammography (CEM) combines a standard mammogram with an iodine-based contrast dye injected into a vein. The contrast highlights areas of increased blood flow, which can make some breast cancers easier to see. CEM is used in both screening and diagnostic settings and has higher sensitivity for breast cancer detection than standard mammography or ultrasound, with studies reporting sensitivity approaching that of breast MRI. CEM may also have specialized uses, such as imaging selected patients after breast cancer cryoablation (Corines et al., 2023).

Because CEM uses an iodine-based contrast agent, it may not be appropriate for people with certain prior reactions to iodinated contrast or some kidney conditions. Availability may also depend on the equipment and radiologist expertise at your imaging center.

The Contrast-Enhanced Mammography Imaging Screening Trial (CMIST), supported by GE HealthCare, the American College of Radiology, and the Breast Cancer Research Foundation, is studying the use of CEM for breast cancer screening. The trial is registered on [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT05625659) (NCT05625659).

CEM is also being studied as an alternative to breast MRI for assessing residual disease after neoadjuvant treatment. Because contrast can highlight blood flow associated with tumors, CEM may provide additional information beyond standard mammography and may be less costly and faster to perform than breast MRI in some settings.

What the Talk is Likely to Cover, and Why: Dr. Hogan will most likely discuss the potential advantages of using CEM in patients with ILC. CEM is more sensitive for detecting ILC than conventional mammography, and research suggests that its diagnostic accuracy and ability to assess tumor size may be comparable to breast MRI in some settings. CEM is also generally faster to perform and may be less costly than MRI.

Because CEM includes standard mammographic images, it can show microcalcifications, which may not be visible on MRI. CEM may also provide an alternative for some patients who are unable to undergo breast MRI.

Recent research comparing CEM with MRI for preoperative staging of ILC has shown promising results, including fewer false-positive findings with CEM in some studies. Studies have reported sensitivity as high as 98% for detecting ILC, although results vary depending on the study and patient population.

Why This Matters to People with ILC: ILC can be difficult to see on standard mammography because of its distinctive growth pattern. CEM may improve detection by using contrast to highlight areas of increased blood flow and can help identify the extent of disease, including multifocal or multicentric tumors. It is also generally faster and may be less costly than breast MRI, although availability varies by imaging center. CEM provides another potentially valuable imaging option for people with ILC, but no imaging test is perfect. Because of the diffuse growth pattern of ILC, the extent of disease can be underestimated with any imaging method.

Key Terms and Definitions:

Breast Imaging-Reporting and Data System (BI-RADS): is a standardized risk assessment tool and lexicon developed by the American College of Radiology for breast imaging (Mammograms, ultrasounds, and MRIs).

Radiologists use it to categorize test results and recommend follow-up actions.

Contrast Enhanced Mammography (CEM): is an advanced breast imaging test that combines a standard X-ray mammogram with an intravenous iodine-based dye. The dye highlights new blood vessels that grow around tumors, making cancer easier to spot in dense breast tissue.

Breast Density: The ratio of fibrous and glandular tissue to fat. Dense breast tissue can make it hard to visualize abnormalities on mammograms.

Computer-Aided Design (CAD): It is the use of computer software to create, modify, analyze, or optimize digital 2D and 3D models.

Early Detection of Breast Cancer: Finding breast cancer early before symptoms appear and tumors are large. It is important as it is thought to improve survival rates and often allows for less aggressive treatment.

Multifocal Breast Cancer: there are two or more cancer tumors in the same section (quadrant) of one breast.

Multicentric Breast Cancer: two or more separate cancer tumors develop in different quadrants (sections) or separate areas of the same breast. It differs from multifocal cancer, where tumors are clustered in the same section

Resources and Key references:

Lobular Breast Cancer Alliance (LBCA); National Cancer Institute (NCI); National Library of Medicine/PubMed, Clinical Trials.gov, Food and Drug Administration FDA, Radiology Society of America (RSNA) <https://www.acr.org/News-and-Publications/Media-Center/2023/First-Patients-Enrolled-in-Contrast-Enhanced-Mammography-Imaging-Screening-Trial>

Corines, M., Sogani, J., Hogan, M., Mango, V., The Role of Contrast-Enhanced Mammography After Cryoablation of Breast Cancer, *American Journal of Roentgenology*, Vol 222, Issue 2, November 29, 2023, <https://doi.org/10.2214/AJR.23.30250>.

Jochelson MS, Lobbes MBI. *Contrast-enhanced Mammography: State of the Art. Radiology*. 2021. <https://pubmed.ncbi.nlm.nih.gov/33650905/>

Jochelson MS, Mukhtar RA. *Contrast mammography—a promising tool for the pre-operative evaluation of lobular breast cancer. European Journal of Radiology*. 2023. <https://pubmed.ncbi.nlm.nih.gov/37523873/>

Hogan, M., et al., Contrast-Enhanced Digital Mammography Screening for Intermediate-Risk Women With a History of Lobular Neoplasia, *American Journal of Roentgenology*, Vol 216, Issue 6, March 31, 2021, <https://doi.org/10.2214/AJR.20.23480>.

Hogan, M., et al., Contrast-enhanced mammography in the assessment of residual disease after neoadjuvant treatment, PubMed, April 2023, <https://pubmed.ncbi.nlm.nih.gov/36754936/>

Lobbes, M. et al., The performance of contrast-enhanced mammography and breast MRI in local preoperative staging of invasive lobular breast cancer, PubMed, 2023 Jul: 164: 110881, <https://pubmed.ncbi.nlm.nih.gov/37201248/>.

Sven, J. E. et. Al., Comparison of contrast-enhanced mammography and breast MRI in tumour extent assessment: A systematic review and meta-analysis, *European Journal of Surgical Oncology*, Vol 52, Issue 3, March 2026, 111410, <https://www.sciencedirect.com/science/article/pii/S0748798326000296>

Scientific Session 8: Advanced Imaging and Artificial Intelligence

Whole-body MRI for metastatic ILC

Presenter 3: Elleke Dresen, MD, PhD

Background: Invasive lobular carcinoma (ILC) is the second most common histologic subtype of breast cancer, distinguished by loss of E-cadherin and a discohesive, single-file growth pattern. That growth pattern has direct imaging consequences: ILC tends to spread diffusely into the peritoneum, retroperitoneum, GI tract, and bone marrow rather than forming discrete masses, and it is often low-grade and low-metabolism — meaning the imaging tools built around ductal breast cancer (mammography, standard CT, FDG-PET, and RECIST-based measurement) can understage or under-monitor metastatic ILC. MRI-based approaches, particularly whole-body diffusion-weighted MRI (WB-DWI/MRI) and estrogen-receptor-targeted PET, are the leading proposed solutions and are the subject of active, ILC-specific research.

What the Talk is Likely to Cover and Why: There are three critical imaging issues in metastatic ILC, and key researchers addressing them:

Standard-of-care imaging misses metastatic disease in ILC more often than it does in ductal cancer, because CT and bone scans struggle with diffuse, infiltrative lesions. Whole-body diffusion-weighted MRI is emerging as a systemic staging alternative that doesn't rely on forming a discrete mass to be detected. Kosmin and colleagues found whole-body MRI identified progressive bone-metastatic disease earlier than whole-body CT or bone scintigraphy, and a related study found that adding whole-body MRI to routine imaging changed real-world treatment decisions and turned up discordant findings in roughly a fifth of patients assessed for response. Dr. Raphaëla ("Elleke") Dresen, an abdominal/oncological radiologist at KU Leuven and University Hospitals Leuven, has spent over a decade building this evidence base for whole-body diffusion MRI across ovarian cancer, GI tumors, and neuroendocrine tumors, and is now Principal Investigator on a KU Leuven-funded project (2024–2028) developing an AI-driven quantitative WB-DWI-MRI algorithm specifically to improve staging and prognostication in ILC — directly targeting this detection gap.

The tumor-measurement standard used in nearly all clinical trials — RECIST v1.1 — requires discrete, measurable lesions, which ILC's infiltrative growth pattern often doesn't provide. This has a documented downstream effect: Van Baelen and colleagues' 2024 systematic review of 93 phase III/IV breast cancer trials found ILC inclusion rates were even reported in only 13 of them, and just 3 performed an ILC-specific subgroup analysis. A 2025 consensus paper from the European Lobular Breast Cancer Consortium network explicitly proposes functional, quantitative MRI biomarkers — such as change in apparent diffusion coefficient (ADC) — as an alternative to RECIST for tracking ILC response over time, building on ADC-based response monitoring already validated in bone-metastatic breast cancer more broadly.

ILC tumors often metabolize sugars slower than other cancer tumors, and therefore the standard 18F-FDG PET/CT scan can under-detect lesions that are otherwise clinically significant. Dr. Gary Ulaner (Hoag Family Cancer Institute; formerly Memorial Sloan Kettering) led a head-to-head trial showing that estrogen-receptor-targeted 18F-FES PET/CT — now FDA-approved — detected more metastatic ILC lesions than FDG PET/CT in the majority of patients studied, since ILC is nearly always ER-positive. This raises an open, unresolved question of how whole-body MRI, FES-PET, and FDG-PET should be sequenced or combined for metastatic ILC, since no consensus imaging protocol yet exists.

Taken together, the researchers working on this problem frame it less as of a shortage of imaging tools, and more as a shortage of ILC-specific validation, reporting, and response-assessment standards for the tools that already exist and are proven in other settings.

Key Terms and Definitions:

MRI (Magnetic Resonance Imaging): An imaging technique using a strong magnetic field and radio waves, without ionizing radiation, to produce detailed images of soft tissue.

Whole-Body MRI (WB-MRI): An MRI protocol imaging most or all of the body in one session, used for systemic cancer staging without radiation exposure.

Diffusion-Weighted MRI (DWI / WB-DWI): A functional MRI sequence measuring the restricted movement of water in densely packed tumor tissue; often combined with whole-body MRI for staging and treatment-response monitoring, without requiring contrast injection.

ADC (Apparent Diffusion Coefficient): A quantitative value derived from diffusion-weighted MRI reflecting how freely water moves in tissue; a rising ADC during treatment suggests a tumor is responding.

PET/CT (Positron Emission Tomography/Computed Tomography): A combined scan overlaying a radioactive-tracer-based functional image (PET) onto an anatomical CT image.

FDG-PET/CT: PET/CT using a radioactive glucose analog tracer; standard for many cancers but less reliable in low-metabolism tumors like ILC.

FES-PET/CT (16 α -18F-Fluoro-17 β -Fluoroestradiol PET/CT): An FDA-approved, estrogen-receptor-targeted PET tracer used to detect ER-positive lesions, including in recurrent or metastatic breast cancer, independent of tumor metabolic rate.

RECIST (Response Evaluation Criteria in Solid Tumors): The standardized rule-set used in trials and practice to measure tumor size on imaging and classify response to treatment; requires discrete, measurable disease, which is a documented limitation for ILC.

Central pathology review: Independent confirmation of a diagnosis (such as ILC) by a panel or reference pathologist, separate from the original local diagnosis; frequently absent in the trials that currently define ILC's standard of care.

Resources and Key references:

pubmed.gov, clinicaltrials.gov, research.kuleuven.be, nature.com, annalsofoncology.org, jnm.snmjournals.org, pubs.rsna.org, lobularbreastcancer.org

Ciriello G, Gatza ML, Beck AH, et al. Comprehensive Molecular Portraits of Invasive Lobular Breast Cancer. **Cell**. 2015;163(2):506-519. doi:10.1016/j.cell.2015.09.033

Van Baelen K, Van Cauwenberge J, Maetens M, et al. Reporting on invasive lobular breast cancer in clinical trials: a systematic review. **npj Breast Cancer**. 2024;10:23. doi:10.1038/s41523-024-00627-5
Clinical challenges and proposed solutions for patients with invasive lobular breast cancer. **Annals of Oncology**. 2025. [https://www.annalsofoncology.org/article/S0923-7534\(25\)00857-9/fulltext](https://www.annalsofoncology.org/article/S0923-7534(25)00857-9/fulltext)

Kosmin M, Padhani AR, Gogbashian A, et al. Comparison of Whole-Body MRI, CT, and Bone Scintigraphy for Response Evaluation of Cancer Therapeutics in Metastatic Breast Cancer to Bone. **Radiology**. 2020;297(3):622-629. doi:10.1148/radiol.2020192683

Bhaludin BN, Tunariu N, Senthivel N, et al. Does the addition of whole-body MRI to routine imaging influence real-world treatment decisions in metastatic breast cancer? **Cancer Imaging**. 2022;22(1):1-14. doi:10.1186/s40644-022-00464-4

Tran E, Joe BN. Use of Whole-Body MRI in Metastatic Breast Cancer. *Radiology: Imaging Cancer*. 2022;4(6):e229023. doi:10.1148/rycan.229023

Ulaner GA, Jhaveri K, Chandarlapaty S, et al. Head-to-Head Evaluation of 18F-FES and 18F-FDG PET/CT in Metastatic Invasive Lobular Breast Cancer. *Journal of Nuclear Medicine*. 2021;62(3):326-331. doi:10.2967/jnumed.120.247882

Zels G, Van Baelen K, De Schepper M, et al. Clinical and histopathological characterization of metastatic lobular breast cancer: lessons learned from post-mortem tissue donation programs. *npj Breast Cancer*. 2026. <https://www.nature.com/articles/s41523-026-00912-5>

KU Leuven Research Portal. Development of an AI-driven quantitative algorithm for whole-body diffusion-weighted MRI to improve staging and prognostication of invasive lobular breast cancer (Project 3M250483; Promotor: R.C. Dresen). 2024–2028. <https://research.kuleuven.be/portal/en/project/3M250483>

SCIENTIFIC SESSION 9: SNMMI Special Session — Imaging in ILC

Friday, September 25, 2026 | 1:00–2:15 pm

Moderators: Pooja Advani, MBBS, MD and Amy Russell-Parliman

Presentations:

1. **ILC: Review of initial staging modalities, CT, and bone scan**
Gary Ulaner, MD, PhD — Hoag Family Cancer Institute
2. **Staging solutions for metastatic disease: FDG and FES PET**
Hannah Linden, MD — Fred Hutch Cancer Center / University of Washington
3. **Emerging PET imaging modalities: FAPI and PSMA**
Wenhui Zhou, MD, PhD — Fred Hutch Cancer Center / University of Washington
4. **Research and trials regarding theranostics for breast cancer**
David Mankoff, MD, PhD — University of Pennsylvania / Penn Medicine

Scientific Session 9: SNMMI Special Session — Imaging in ILC

ILC: Review of initial staging modalities, CT, and bone scan

Presenter 1: Gary Ulaner, MD, PhD

Background: Imaging for Invasive Lobular Carcinoma (ILC) can be challenging due to the unique way that ILC tumors grow and the way it spreads in the case of distant metastases. Imaging plays an important role at initial diagnosis of distant metastases (when ILC has spread to parts of the body beyond the breast and local lymph nodes) because it provides valuable information for staging and can inform the choice of therapies and prognosis. Imaging is also important for patients with already known metastases because it can inform the patient and team if the current therapy is working, and can inform which therapies may be chosen next. While there are no stand-alone ILC-specific staging guidelines, there are several that point to additional considerations in the case of ILC. For example, the NCCN guidelines suggest several modalities that may be useful in the clinical workup of metastatic breast cancer. There are several governing bodies that establish these clinical guidelines, which include NCCN and ESMO.

Controversy or inconsistencies remain in patient access to certain imaging modalities, and there is a lack of definitive research that indicates which modality is the best for ILC patients in all scenarios. CT scans can be useful in detecting disease in many sites, including nodes, lung, and liver; however, they can be less sensitive for detecting disease in the bone. However, identifying what the “best” or ideal imaging modality for ILC patients has yet to be established since research is ongoing. This can cause confusion and increased anxiety among patients when it comes to the staging and surveillance of metastatic disease.

What the Talk is Likely to Cover and Why: Dr. Gary Ulaner is a diagnostic radiologist and nuclear medicine physician with a research focus on novel Positron Emission Tomography (PET) agents used in cancer care, specifically breast cancer. Given the panel and focus of topics to be covered by other presenters, it is likely that Dr. Ulaner will set the stage on the current standard-of-care imaging modalities, particularly CT and bone scan, and identify what the ILC-specific challenges are with these modalities. He will likely discuss how ongoing research is working to identify improved mechanisms for staging and metastatic disease monitoring in ILC. Dr. Ulaner has worked to identify and publish Appropriate Use Criteria for FES-PET and continues to focus on alternative imaging modalities to support improved imaging for ILC.

Key Terms and Definitions:

Staging: Cancer staging is the process that describes the extent of cancer in the body and whether the cancer has spread from where it first formed to other sites in the body. There are two forms of staging: clinical prognostic stage (which is done before surgery and is based on exam, history, imaging, and biopsy findings) and pathological prognostic stage (which is done when surgery is the first treatment and is based on clinical information identified from the tissue and lymph nodes removed during surgery).

NCCN: National Comprehensive Cancer Network is a nonprofit alliance of 34 leading cancer centers.

(www.nccn.org)

ESMO: European Society of Medical Oncology represents over 50,000 members globally and serves as a reference for oncology education and information. www.esmo.org

Sensitive: sensitivity in the context of this document pertains to the ability of an imaging modality to identify lesions that exist. In other words, how well the test identifies true positive findings.

FDG avid: This describes whether the PET scan shows the glucose metabolic activity occurring in the cancer cells. When something is less FDG (fluorodeoxyglucose) avid, it means that the cells do not exhibit this particular metabolic activity as strongly (i.e., cancer cells are not ‘eating’ up the sugar (FDG) as fast as other cancer cells might), and therefore may not show up on the image the PET scan produces that is ‘looking’ for it.

Novel Positron Emission Tomography (PET) agents: These are new radiopharmaceuticals used to enhance what can be seen on a PET scan

PET: Positron emission tomography (PET) scanning is one of the most frequently used molecular imaging procedures.

(<https://snmmi.org/common/Uploaded%20files/Web/Patient%20Center/Fact%20Sheet/What%20is%20PET%202026.pdf>)

FES-PET: FES-PET is a diagnostic procedure used to detect estrogen receptor-positive (ER+) breast cancer metastases. It uses a PET scanner and a radiotracer called FES (18F-Fluoroestradiol) to find the estrogen receptor in cancer cells. (<https://snmmi.org/Patients/Patients/Procedures/FES-PET-for-Breast-Cancer.aspx>)

Resources and Key references:

Dr. Gary Ulaner 'blog' from LBCA: LBCA Scientific Advisor Dr. Gary Ulaner Describes Promising Methods in Clinical Trials for Better ILC Detection, November 19, 2020.

<https://lobularbreastcancer.org/lbca-scientific-blog/>

NCCN Clinical Practice Guidelines in Oncology, Breast Cancer, v.6.2026, July 29, 2026.

https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Summary: Appropriate Use Criteria for Estrogen Receptor-Targeted PET Imaging with 16 α -¹⁸F-Fluoro-17 β -Fluoroestradiol, Gary A. Ulaner, David A. Mankoff, Amy S. Clark, Amy M. Fowler, Hannah M. Linden, Lanell M. Peterson, Farrokh Dehdashti, Brenda F. Kurland, Joanne Mortimer, Jason Mouabbi, Dae Hyuk Moon, Elisabeth G.E., de Vries, Journal of Nuclear Medicine, Mar 2023, 64 (3) 351-354: DOI: 10.2967/jnumed.123.265420

Stages of Breast Cancer, National Cancer Institute website.

<https://www.cancer.gov/types/breast/stages>

TNM Staging for Breast Cancer, National Cancer Institute website.

<https://www.cancer.gov/types/breast/stages/tnm-staging-system>

Scientific Session 9: SNMMI Special Session — Imaging in ILC

Staging solutions for metastatic disease: FDG and FES PET

Presenter 2: Hannah Linden, MD

Background: Staging metastatic breast cancer is an important step in the treatment planning process. While CT and bone scans are familiar imaging tools used in practice, increasingly, PET (positron emission tomography) imaging with a radioactive tracer has been used in breast cancer staging. The most common and frequently used PET tracer used has been FDG PET (Fluorodeoxyglucose PET) scanning for systemic staging. A PET scan with FDG measures the metabolic activity in cancer cells. This can have limitations in imaging some ILC tumors because of the diffuse growth pattern and the fact that ILC tends to (but does not always) have lower (or slower) metabolic activity of glucose. More recently, FES PET (fluorestradiol PET) was approved for use in metastatic ER-positive breast cancer. FES PET uses a radiotracer to specifically “map” estrogen receptor status of cancerous lesions throughout the body.

What the Talk is Likely to Cover and Why: While FDG PET and FES PET are complementary imaging modalities, they are not interchangeable—largely because of what the imaging is measuring in the body. FDG PET generally is used for initial staging and for tracking active disease progression or treatment response over time. And FES PET can identify whether metastatic lesions across the body are ER-positive—which can help guide treatment decisions around endocrine therapy use. ER-positive lesions that show up on an FES PET are more likely to be responsive to endocrine treatments, while if known metastases do not show up on an FES PET, this is a strong indicator that the tumor would not be responsive to endocrine therapies, and thus, an alternative therapy choice could be considered. FES PET has also been shown to be beneficial in identifying bone metastases in patients with metastatic ILC, where they may not have been visible on an FDG PET scan.

In 2025, Dr. Linden published an article about the complementary roles and dual use of FDG and FES PET in the staging and management of ILC. We can expect that this talk will address the various aspects of each modality and how each can paint a fuller picture of metastatic disease spread, heterogeneity, and response to treatment in the body. Dr. Linden is also likely to discuss the distinct limitations of use for both FES and FDG PET scans, including timing and washout periods and background uptake in certain body parts.

Key Terms and Definitions:

Staging (the process of determining the stage of cancer): cancer stage describes the extent of cancer in the body and whether the cancer has spread from where it first formed to other parts of the body. Cancer stage is based on the size and location of the primary tumor, the spread of cancer to nearby lymph nodes or other parts of the body, the grade of the tumor, and whether certain biomarkers are present.

PET (positron emission tomography) imaging: Positron emission tomography (PET) scanning is one of the most frequently used molecular imaging procedures. Molecular imaging is a type of medical imaging that provides detailed pictures of what is happening inside the body at the molecular and cellular level. Most molecular imaging procedures involve an imaging device and an imaging agent, which are used to visualize cellular activity, such as the chemical processes involved in metabolism, oxygen use, or blood flow. (SNMMI, What is PET 2026?, <https://snmmi.org/common/Uploaded%20files/Web/Patient%20Center/Fact%20Sheet/What%20is%20PET%2026.pdf>)

FDG PET (Fluorodeoxyglucose): In nuclear medicine, which is a branch of molecular imaging, the imaging agent is a radiotracer, a compound that includes a radioactive atom, or isotope. In the case of an FDG PET scan, the PET radiotracer is known as FDG (18F-fluorodeoxyglucose), a compound derived from a simple sugar and a small amount of radioactive fluorine. Once the FDG radiotracer is injected and accumulates in the body’s tissues and organs, its natural decay includes emission of tiny particles called positrons that react with electrons in the body. This reaction produces energy in the form of a pair of photons. The PET scanner, which is able to detect these photons, creates three-dimensional images that show how the FDG is distributed in the area of the body being

studied. (SNMMI, What is PET 2026?,

<https://snmmi.org/common/Uploaded%20files/Web/Patient%20Center/Fact%20Sheet/What%20is%20PET%2026.pdf>)

FES PET (fluoroestradiol): The description of the PET scan and the FDG PET scan above provides the basic description of the imaging modality, but in this case, a different radiotracer is used called “fluoroestradiol F-18” which allows PET imaging to identify estrogen receptor-positive lesions throughout the body where the tracer has ‘bound’ to the estrogen receptor on the cancerous cells.

Heterogeneity: Tumor heterogeneity means that not all cancer cells are the same. Cells can be different in their shapes, behaviors, or mutations within the same tumor and/or between the same types (i.e., breast cancer) of tumors in different parts of the body. This can make treatment complex because some medicines might kill some cancer cells while leaving other cells intact.

Washout period: a washout period is a required time frame where a patient must stop taking specific medications before an imaging test. Some medications bind to the same cell sites (like estrogen receptors) that a specialized PET tracer needs to target and bind to. Stopping the drug lets the tracer bind properly to ensure the scan can be interpreted properly.

Background uptake: this refers to the normal, baseline level of radioactive tracer absorbed by healthy tissues and organs throughout the body

Resources and Key references:

Manohar, P., Peterson, L.M., Jenkins, I.C. *et al.* [18 F]-Fluoroestradiol PET (FES-PET) and [18 F] Fluorodeoxyglucose PET (FDG-PET) Imaging May Aid in Managing Therapy in Patients with Metastatic Lobular Breast Cancer. *Mol Imaging Biol* **27**, 410–420 (2025).

<https://doi.org/10.1007/s11307-025-02015-2>

<https://link.springer.com/article/10.1007/s11307-025-02015-2>

FES/FDG Imaging Augments the Metastatic Breast Cancer Diagnostic and Treatment Landscape (Commentary Article, September 13, 2023) <https://www.onclive.com/view/fes-fdg-imaging-augments-the-metastatic-breast-cancer-diagnostic-and-treatment-landscape>

Invasive Lobular Breast Cancer Training Series LBCA: Training on Invasive Lobular Carcinoma for General Radiologists On Demand, Free online training on systemic staging presented by Dr. Gary Ulaner, <https://mskcc.cloud-cme.com/course/courseoverview?P=0andEID=56679>

Chen AW, Zeballos Torrez CR, Peterson LM, Muzi M, Specht JM, Cohen EA, Linden HM, Kontos D, Mankoff DA. Novel 4D radiomics applied to dynamic FES PET images to improve prediction of breast cancer response to ER-targeted therapy. *Eur J Nucl Med Mol Imaging*. 2026 Apr;53(5):3128-3139. doi: 10.1007/s00259-025-07570-y. Epub 2025 Nov 23. PMID: 41275453; PMCID: PMC13013131.

Stages of Breast Cancer, National Cancer Institute <https://www.cancer.gov/types/breast/stages>

Scientific Session 9: SNMMI Special Session — Imaging in ILC

Emerging PET imaging modalities: FAPI and PSMA

Presenter 3: Wenhui Zhou, MD, PhD

Background: PET (positron emission tomography) imaging is a rapidly evolving field of molecular imaging. Molecular imaging provides detailed pictures of what is happening inside the body at the molecular and cellular level. While other standard imaging (CT, MRI, X-ray) creates anatomical pictures of the inside of the body, molecular imaging allows physicians to evaluate what is happening in the body by measuring chemical and biological processes. A PET scan involves the use of a PET scanner and a radiotracer that is injected into the bloodstream. When the tracer is injected into the body, it begins to accumulate in tissues where it is being 'consumed' or 'bound' to cells of interest—in this case, cancer cells. The agent releases tiny amounts of radiation, which allow the scanner to detect where the agent is in the body. The ability to precisely image the location of cancer tumors and distinguish particular attributes of the cancer are key parts of precision medicine.

What the Talk is Likely to Cover and Why: Wenhui Zhou, MD, PhD, is a radiologist and nuclear medicine physician-scientist who has focused his research on non-FDG targeted radiopharmaceuticals— particularly evaluating targets like PSMA (prostate-specific membrane antigen) and FAPI (fibroblast activation protein inhibitor). FAPI (Fibroblast Activation Protein Inhibitor) is a newer tracer used with PET scans that targets cancer-associated fibroblasts (CAFs), which exist in the tumor microenvironment (TME) rather than on the membrane of the cancer tumor cells themselves. Fibroblast activation protein (FAP) is one type of cancer-associated fibroblasts that exist in the breast cancer tumor microenvironment. FAP presence is high in cancer-associated fibroblasts but low in normal fibroblasts, which means they are not frequently found in normal adult human tissue—therefore making FAPs a good indicator of cancer cells. Early studies show that FAP tracers also show low uptake in normal organs such as the liver, intestine, brain, and spine, which enhances the ability to see true positive results.

Despite its name, PSMA (prostate-specific membrane antigen) is frequently overexpressed in many cancer types and thus presents a targeting opportunity for imaging and treatment. PSMA was initially identified as being overexpressed in prostate cancer. PSMA is the name for the gene FOLH1. Given the presence of PSMA overexpression in a variety of cancer types, Dr. Zhou recently conducted a study using the Cancer Genome Atlas to identify the specific breast cancer subtype(s) that exhibit PSMA overexpression. Dr. Zhou found that FOLH1 was more frequently amplified in basal-like breast cancer (BLBC) as compared to luminal and human epidermal growth factor receptor 2–positive (HER2+) subtypes. FOLH1 expression was higher in BLBC and was negatively correlated with estrogen receptor and progesterone receptor expression.

This research provides a foundation for expanding PSMA-targeted PET imaging and radioligand therapies beyond prostate cancer to specific aggressive breast cancer subtypes, which would likely not be visualized on a scan like an FES PET.

Key Terms and Definitions:

PET scanner: A positron emission tomography (PET) scan is an imaging test that shows how your body's tissues and organs are working (<https://www.mayoclinic.org/tests-procedures/pet-scan/about/pac-20385078>)

Radiotracer: a PET scan uses a small amount of a radioactive substance called a radiotracer to assist in the visualization of a tumor. Depending on the reason for the test, the tracer may show how cells use sugar, how blood flows, or how some proteins or other substances attach to cells (<https://www.mayoclinic.org/tests-procedures/pet-scan/about/pac-20385078>)

Precision medicine: Precision medicine, sometimes known as "personalized medicine" is an innovative approach to tailoring disease prevention and treatment that takes into account differences in people's genes, environments, and lifestyles. The goal of precision medicine is to target the right treatments to the right patients at the right

time. (<https://www.fda.gov/medical-devices/in-vitro-diagnostics/precision-medicine>)

Cancer-associated fibroblasts (CAFs): cancer-associated fibroblasts (CAFs) are cells that enhance the migratory and proliferative properties of cancer cells and play a role in cancer cell invasion, growth, and migration, immunosuppression, metabolic reprogramming, and angiogenesis

Tumor microenvironment (TME): TME is a dynamic system composed of fibroblasts, immune cells, endothelial cells, precursor cells, signaling molecules, and extracellular matrix (ECM) components, which interact closely with tumor cells.

Fibroblast: a fibroblast is a type of cell that contributes to the formation of connective tissue. They also play an important role in healing tissues. (<https://www.genome.gov/genetics-glossary/Fibroblast>)

Radioligand therapy: Radioligand therapy is an emerging strategy in oncology that delivers targeted radiation to cancer cells while sparing surrounding healthy tissues. This is currently being used in prostate and neuroendocrine tumor treatment. (<https://pmc.ncbi.nlm.nih.gov/articles/PMC12607575/>)

Basal-Like Breast Cancer (BLBC): The term “basal-like” comes from studies that examined the patterns of gene activity inside breast tumors. Researchers found that some tumors have gene expression patterns that resemble those exhibited by basal cells, which form the outer layer of the milk ducts. BLBC is one of the less common but more aggressive molecular subtypes of breast cancer. While it shares overlap with triple-negative breast cancer (TNBC), basal-like is defined by its molecular and genetic features rather than by standard clinical tests. (Basal-Like Breast Cancer: <https://www.bcrf.org/blog/basal-like-breast-cancer/>)

Resources and Key references:

Zhou, W., Halder, S., Herwald, S., Ghijsen, M., Shafi, G., Uttarwar, M., Rosen, E., Franc, B., and Kishore, S. (2024). Frequent amplification and overexpression of PSMA in basal-like breast cancer from analysis of The Cancer Genome Atlas. *Journal of Nuclear Medicine*, 65(7). <https://doi.org/10.2967/jnumed.123.266659>

Zhou, W., Franc, B. L., DeMartini, W. B., and Rosen, E. L. (2024). Estrogen receptor–targeted PET imaging for breast cancer. *Radiology*, 312(2), e240315. <https://doi.org/10.1148/radiol.240315>

SNMMI, What Is PET?, 2026.

<https://snmmi.org/common/Uploaded%20files/Web/Patient%20Center/Fact%20Sheet/What%20is%20PET%20026.pdf>

Gilardi L, Airò Farulla LS, Curigliano G, Corso G, Leonardi MC, Ceci F. FDG and Non-FDG Radiopharmaceuticals for PET Imaging in Invasive Lobular Breast Carcinoma. *Biomedicines*. 2023 May 3;11(5):1350. doi: 10.3390/biomedicines11051350. PMID: 37239021; PMCID: PMC10215865.

Scientific Session 9: SNMMI Special Session — Imaging in ILC
Research and trials regarding theranostics for breast cancer
Presenter 4: David Mankoff, MD, PhD

Background: Dr. David Mankoff is the Director of Breast Cancer Molecular Imaging Group at Penn Medicine and a leading researcher in the field of nuclear medicine and molecular imaging. His research focuses on developing, testing, and evaluating PET-based techniques, which are key pillars in precision medicine and theranostics. Clinical trials are an important part of the cancer research process and provide valuable data about new or experimental drugs and/or imaging techniques that aim to improve patient outcomes. Clinical trial data is then used to inform changes in clinical guidelines that guide physician and patient decision-making.

Historically, imaging modalities had been used for the sole purpose of staging and monitoring response to treatment of disease. In other words, patients were imaged to determine the presence of metastatic disease and then to determine whether the metastatic burden had decreased or responded to treatment. Imaging modalities have now advanced to not just indicate the presence of metastatic disease but also to identify whether cells express a specific therapeutic target (as is the case in an FES PET scan). As the field advances with theranostic approaches, these advanced imaging tools can be used to identify therapeutic targets and simultaneously deliver a treatment to the target area. This is the evolving field of theranostics—when imaging and treatment are combined to deliver therapeutic agents directly to cancerous lesions in the body. Theranostic approaches have been successfully implemented with other endocrine-sensitive diseases such as neuroendocrine, thyroid, and most recently prostate cancer.

What the Talk is Likely to Cover and Why: The title of this talk is research and trials regarding theranostics for breast cancer suggests that the focus will be on the emerging field of theranostics specifically for breast cancer. In 2024, in the Journal of Nuclear Medicine, Dr. Mankoff published an interview he had with two leaders in the field, Dr. Gebhart and Dr. Piccart. In this article, the authors posit potential reasons for the relatively slow acceptance of the use of imaging biomarkers in breast cancer and some of the challenges associated with large-scale theranostic clinical trials in breast cancer. We can anticipate that Dr. Mankoff will touch on some of these considerations in his talk, which include the wide range of heterogeneity in target expression among breast cancer subtypes and the critical need for cross-discipline collaboration in the design of these trials.

Key Terms and Definitions:

Precision medicine: Precision medicine, sometimes known as "personalized medicine" is an innovative approach to tailoring disease prevention and treatment that takes into account differences in people's genes, environments, and lifestyles. The goal of precision medicine is to target the right treatments to the right patients at the right time. (<https://www.fda.gov/medical-devices/in-vitro-diagnostics/precision-medicine>)

Theranostics: an advanced medical technology that uses radioactive medicine to combine diagnostic imaging and therapy (<https://www.dana-farber.org/cancer-care/treatment/imaging-services/theranostics>)

Clinical trials: Clinical trials are research studies in which researchers assign participants to get one or more interventions to test what happens in people
(<https://clinicaltrials.gov/study-basics/learn-about-studies#ClinicalTrials>)

Resources and Key references:

Chudgar AV, Mankoff DA. Molecular Imaging and Precision Medicine in Breast Cancer. PET Clin.

2017 Jan;12(1):39-51. doi: 10.1016/j.cpet.2016.08.001. Epub 2016 Oct 4. PMID: 27863565. Young AJ, Pantel AR, Kiani M, Doot RK, Bagheri S, Pryma DA, Farwell MD, Li S, Lee H, Schubert

EK, Secreto A, Zuckerman SP, Nayak A, Choi H, Carlin S, DeMichele A, Mankoff DA, Zhou R, Mach RH, McDonald ES. Kinetic Analysis and Metabolism of Poly(Adenosine Diphosphate-Ribose) Polymerase-1-Targeted ^{18}F -Fluorothanatrane PET in Breast Cancer. *J Nucl Med*. 2024 Dec 3;65(12):1862-1868. doi: 10.2967/jnumed.124.268254. PMID: 39477499; PMCID: PMC11619586.

Molecular Imaging in Breast Cancer. Géraldine Gebhart, Martine Piccart, David Mankoff. *Journal of Nuclear Medicine* Mar 2024, 65 (3) 337-339; DOI: 10.2967/jnumed.124.267461

SNMMI Patient Education Day 2025 General Session Recording. What is Nuclear Medicine and Molecular Imaging? (Dr. Esmá Akin) and How to Understand and Evaluate Clinical Trials (Dr. Gary Ulaner), <https://www.youtube.com/watch?v=BFIWzrACkRQ>

Chen AW, Zeballos Torrez CR, Peterson LM, Muzi M, Specht JM, Cohen EA, Linden HM, Kontos D, Mankoff DA. Novel 4D radiomics applied to dynamic FES PET images to improve prediction of breast cancer response to ER-targeted therapy. *Eur J Nucl Med Mol Imaging*. 2026 Apr;53(5):3128-3139. doi: 10.1007/s00259-025-07570-y. Epub 2025 Nov 23. PMID: 41275453; PMCID: PMC13013131.

The Future of Nuclear Medicine, Molecular Imaging, and Theranostics. Wolfgang A. Weber, Johannes Czernin, Carolyn J. Anderson, Ramsey D. Badawi, Henryk Barthel, Frank Bengel, Lisa Bodei, Irène Buvat, Marcelo DiCarli, Michael M. Graham, Jan Grimm, Ken Herrmann, Lale Kostakoglu, Jason S. Lewis, David A. Mankoff, Todd E. Peterson, Heinrich Schelbert, Heiko Schöder, Barry A. Siegel, H. William Strauss

Journal of Nuclear Medicine Dec 2020, 61 (Supplement 2) 263S-272S; DOI: 10.2967/jnumed.120.254532

SCIENTIFIC SESSION 10: Radiotherapy, Clinical Trials

Friday, September 25, 2026 | 2:45–3:45 pm

Moderators: Meghan R. Flanagan, MD and Brenda Sulick, PhD

Presentations:

1. Dysfunctional DNA repair: PARPi and radiation sensitivity in ILC

Matt Sikora, PhD — University of Colorado Anschutz Medical Campus / CU Anschutz Cancer Center

2. Tumor heterogeneity from autopsy studies

Christine Desmedt, PhD — KU Leuven, Belgium

3. Radiotherapy in ILC

Elinor Sawyer, MD — King's College London / Guy's and St Thomas' NHS Foundation Trust, UK

Scientific Session 10: Radiotherapy, Clinical Trials

Dysfunctional DNA repair: PARPi and radiation sensitivity in ILC

Presenter 1: Matt Sikora, PhD

Background: Studies have found two different ways in which Invasive lobular carcinoma is vulnerable that Dr. Sikora's presentation will be addressing. In the first case, an area that Dr. Sikora has studied using both in vitro and in vivo in xenografts, the research has focused on a unique DNA repair weakness in ILC and exploiting that weakness with a PARP inhibitor. With respect to radiotherapy, Dr. Sikora has also found that ILCs are particularly susceptible to radiation.

Every cell, whether healthy or cancerous, has DNA and RNA. DNA is sometimes referred to as the instruction manual for your body inside every cell. It tells cells how to grow, work, and survive. In everybody, every day, some DNA gets damaged from normal activities like breathing, digesting food, and sunlight exposure. These activities can cause what can be thought of as "typos" in the recipe book. If the mistakes are left uncorrected, the cells can malfunction, die, or become cancerous and grow, ignoring the normal growth limits. To prevent this, our bodies have a built-in "construction and editing crew," which are proteins with different tasks. Some proteins are constantly checking the DNA strands for issues; some proteins cut out the damaged piece of DNA, leaving a clean gap; others, called polymerase, copy the DNA's matching and undamaged other strand and rewrite it into the gap, and a protein referred to as the "glue" seals the new piece in place. Mutations in genes that create certain DNA repair proteins can significantly increase the risk of cancer. For example, mutations in the BRCA1 gene and its DNA repair proteins can significantly increase the risk of developing breast and ovarian cancer when mutated. It is often the case that drugs found to cause cancer cells to stop growing or die are those that interfere with one of the repair processes of the ILC cell DNA. Studies, including ones done by Dr. Sikora, have demonstrated that, given that ILC is a predominantly estrogen receptor-positive breast cancer subtype and that ILC Cells are potentially reliant on poly (ADP-ribose) polymerase (PARP)-mediated DNA repair mechanisms to sustain tumor growth, certain PARP inhibitors can suppress that ILC tumor growth.

In terms of radiation therapy, it treats breast cancer by creating severe double-strand breaks in cell DNA. Cancer cells are already more vulnerable to DNA breaks and are more lacking in the repair proteins needed to repair the DNA and help the cell survive. Healthy tissue, on the other hand, while impacted by the radiation therapy, tends to recover well from small doses of radiotherapy. Historically, there have been few studies that have analyzed the efficacy of the use of ionizing radiation therapy (XRT) in ILC patients, just as there have been few studies of any type of ILC specifically. Recently, some research has demonstrated that ILC cells may harbor unique defects in DNA damage repair pathways (such as those due to loss of E-cadherin), which could make the ILC cells exceptionally sensitive to radiation-induced damage.

What the Talk is Likely to Cover and Why: It is likely that Dr. Sikora will focus his presentation on his recent research in both how the PARP inhibitor talazoparib in combination with an aromatase inhibitor, suppresses tumor growth and his most recent research on the use of radiotherapy to exploit ILC's particular sensitivity to radiation. In both scenarios, he will talk about how the mechanics related to the estrogen receptor positive status of ILC cells and the proteins that are related to that mechanism particularly, such as MDC1 are factors in the damaged DNA repair mechanics of ILC cells.

In terms of his ILC and PARP inhibitor (PARPi) research, in 2025, Dr. Sikora confirmed that in in vitro studies the PARPi talazoparib was effective in suppressing ILC tumor growth and that effectiveness increased in combination with an aromatase inhibitor. In a published 2026 abstract, he confirmed this again, this time in both in vitro and in

vivo xenograft studies. He will likely report on these results, including what he has learned about why this occurs, and where the research stands in supporting clinical translation.

In terms of ILC and ionizing radiation therapy (XRT), in a 2025 comprehensive review, Dr. Sikora and colleagues explored the challenges and opportunities in treating ILC, focusing on the underexplored, distinct sensitivity of ILC to XRT and attempting to explain it. He found that crucial DNA repair proteins like MDC1 are particularly weak in ILC at repairing DNA when damaged by XRT. He not only calls for more research specifically on XRT and ILC patients, but argues that it cannot be concluded from studies that have focused predominantly on patients with breast cancer NST in determining the safety and adequacy of partial breast radiation, that moving away from whole breast radiation is appropriate for lobular breast cancer patients, and that further study on ILC patients specifically must be conducted. Dr. Sikora will likely talk about the prospective clinical trials with XRT that explicitly factor in ILC histology that he recommends

Key Terms and Definitions:

DNA and RNA: DNA (Deoxyribonucleic Acid) is the genetic material found inside cells responsible for a living organism's development and function. Most of the DNA is found in the nucleus and is organised into structures called chromosomes. RNA (Ribonucleic Acid) is a nucleic acid that is in all living cells that is structurally similar to DNA. RNAs cause biological reactions, control gene expression, and sense and communicate responses to cellular signals. The general rule of molecular biology is that DNA makes RNA makes protein. DNA and RNA, along with proteins, make up the three major macromolecules that are essential for life.

Gene mutations cause cancer by corrupting the specific genes that regulate cell growth, division, and death, causing cells to multiply uncontrollably

Interactome: is a complete map of all the molecular interactions—such as protein-to-protein connections—that happen inside a cell.

Ionizing Radiation Therapy (XRT):

Mediator of DNA damage checkpoint protein 1 (MDC1) and why it matters in ILC in simple terms: MDC1 is normally considered a tumor suppressor because it keeps DNA stable. However, recent research by scientists like Dr. Matt Sikora has revealed that cancer cells can hijack or mistreat MDC1: [1, 2]

- The Estrogen Receptor Distraction: In Invasive Lobular Carcinoma (ILC), MDC1 gets distracted from its day job. The Estrogen Receptor alpha (ER)—which fuels ILC growth—physically binds to MDC1 and drags it away to help regulate gene transcription instead. [1, 2]
- The Vulnerability: Because MDC1 is heavily tied up assisting the Estrogen Receptor, there is not enough free MDC1 to properly organize the DNA repair crew when the cell is hit with radiation or chemotherapy. [1]
- Therapeutic Exploitation: This "distracted MDC1" leaves ILC cells with a hidden, functional defect in repairing DNA. Doctors can exploit this by using PARP inhibitors (PARPi) or radiation, which overload the distracted repair system and force the cancer cells to self-destruct. [1, 2]

PARP Inhibitor (PARPi): is a type of targeted cancer drug that blocks a specific enzyme used by cells to repair damaged DNA. When a PARP inhibitor blocks this enzyme, single-strand breaks in the DNA cannot be repaired. As the cell multiplies, these unhealed tears turn into double-strand breaks (severe damage).

Xenograft in vivo: means a human tumor is transplanted and grown inside a living animal to test how it responds to cancer treatments. The xenograft model techniques allow in vivo tests on human tumors, not on mouse tumors, which do not have the same responses as human tumors.

APBI: Accelerated Partial Breast Irradiation (APBI): a localized, high-dose form of radiation therapy delivered to a specific sub-section of the breast over a significantly shortened timeframe compared to standard radiation

Resources and Key references:

- <https://aacrjournals.org/cancerres/article-abstract/86/7/1605/775636/Altered-MDC1-Interactions-and-Dysfunctional-DNA> Sotnik J, Shackleford M, Nesiba C, Richer A, Fleischmann Z, Swartz J, Rowland C, Musick M, Fu, R Myler L, Opresko P, Mehrotra S, Sokol E, Hesselberth J, Diamond J Skiora M. Altered MDC1 Interactions and Dysfunctional DNA Repair in Lobular Breast Cancer Confers Sensitivity to PARP Inhibition *Cancer Research. April 2026;86(7) :1605-1621*
- <https://doi.org/10.1210/endocr/bqaf043.017> Diamond J, Nesiba C, Rowland C, Shackleford M, Sikora MJ, Sottnik J, Targeting DNA Repair Dysfunction in Lobular Breast Cancer by PARP Inhibition, *Endocrinology. April 2025: 166, Issue Supplement_1 bqaf043.017,*
- <https://pubmed.ncbi.nlm.nih.gov/40640157/> Boysen MR, Speers CW, Sikora MJ. Radiation therapy for lobular breast cancer: opportunities and challenges for leveraging radiosensitivity, *NPJ Breast Cancer. 2025; 11(1):68. doi:10.1038/s41523-025-00788-x*
- <https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2021.617439/full> Goulding A, Asmar L, Wang Y, Tole S, Barke L, Widner J and Leonard C (2021) Outcomes After Accelerated Partial Breast Irradiation in Women With Triple Negative Subtype and Other “High Risk” Variables Categorized as Cautionary in The ASTRO Guidelines. *Front. Oncol. 11:617439. doi: 10.3389/fonc.2021.617439*

Scientific Session 10: Radiotherapy, Clinical Trials

Tumor heterogeneity from autopsy studies

Presenter 2: Christine Desmedt, PhD

Background: Research in the field of metastatic disease is importantly hampered by limited tissue availability. Metastatic lesions are often difficult to reach for sampling, and even if one small biopsy can be obtained, it might not reflect the profile of other lesions in this heterogeneous disease state. Furthermore, taking multiple samples from a living patient from many organs is painful and dangerous. In answer to this, research tissue donation programs called rapid autopsy programs have been set up, where samples are taken from different metastatic lesions in the short time frame after death. These programs have the potential to become a cornerstone for the further development of personalized medicine by enhancing our knowledge in the fields of cancer development, progression, dormancy, treatment resistance, and surrogate profiling in liquid biopsies. Such programs can be instrumental in guiding clinical trial design and generating innovative patient-derived models that can be used for validating scientific hypotheses and testing novel therapeutic approaches. Dr. Desmedt oversees the rapid autopsy program in Leuven called UPTIDER (Uz/ku Program for **P**ost-mortem **T**issue **D**onation to **E**nhance **R**esearch).

Women and men with metastatic breast cancer followed in UZ Leuven, or referred to the centre specifically for UPTIDER, can decide to participate in the project after consultation with their family and their treating physician. At time of death, our 24h/7d on-call team is notified, and the patient is transported to the hospital for a carefully performed tissue donation. Unlike in the case of body donation to science, in UPTIDER the body is returned to the family within 24 hours, to minimize the impact on grieving. In addition to the samples donated through this program, the project relies on the extensive repository of the biobank of UZ Leuven where blood liquid biopsies, surgical specimens, and tissue biopsies are stored and available for research.

This program allows collection of multiple metastatic lesions at the same time from every single site of cancer in the patient's body, which allows for analysis of how the lesions have evolved in relation to one another through a method called phylogenetic reconstruction. The samples can be frozen within hours of a patient's death, ensuring that the cancer cells are still fresh enough to be studied accurately in a lab. Evaluating lesions that have responded differently to a certain treatment makes it possible to look for reasons why one lesion escaped that treatment while another one was still sensitive, giving unique insights into mechanisms of therapy resistance. Also, larger samples can be retrieved through tissue donation than would be possible through a biopsy. This is necessary when there is a desire to do multiple examinations on one lesion, and when larger samples are needed as is the case for the development of experimental models. Also, importantly, tissue donation in UPTIDER is combined with the investigation of liquid biopsies as well (e.g., blood, urine, ascites) from the same patient. Because both liquid and tissue samples can be analysed at the same time, we can get important insights into how well the characteristics of a certain lesion are represented in a liquid. This knowledge is important in determining how to learn about a patient's tumor profile through the sampling of blood or other liquids, ultimately eliminating the need for a tissue biopsy. Last, scientists can use the samples gathered in this way to grow "living" tumor models (organoids) that can be used to test new drugs.

Ultimately, this will enable gaining critical knowledge that can then be used to guide treatment decisions and make choices of therapies that are better tailored to the individual patient and her cancer characteristics. By studying mILC in all of these ways, it is expected that new targets will be identified for future drug development for breast cancer patients.⁸

⁸ https://gbiomed.kuleuven.be/english/research/50488876/54887282/ltbcr_uptiderproject

What the Talk is Likely to Cover and Why: Dr. Desmedt has been working on a study of metastatic invasive lobular carcinoma (mILC) using the UPTIDER mILC samples and mILC samples from a similar program called Hope for OTHERS established by Dr. Steffi Oessterich at UPMC and Magee-Womens Hospital in Pittsburgh, PA. She is likely to present and elaborate on findings that were shared in her study published in February 2026. Clinical and histopathological characterization of metastatic lobular breast cancer: lessons learned from post-mortem tissue donation programs. In that study, samples were studied of 12 patients who passed away from mILC. The study looked at cell parts such as the hormone receptors and signaling pathways in the original cancer site and the spread sites, and also reviewed the medical scans done on the patient before death to see how closely they matched what was found in the autopsy. They reported that the mILC lesions had different characteristics in different spots. In general, they had lower levels of female hormones ER and PR and higher growth rates than the original breast tumor. They also found that in part because the tumors in different parts of the body change over time, the scans done missed a lot of the mILC lesions, matching only between 70-78% of the time. Their findings confirm that testing just one mILC lesion does not give the full picture of a patient's mILC and that because the mILC cells are varied, treating a patient based on the traits of just one tumor spot could mean the treatment might completely miss or fail to affect other mILC spots in the body.

Dr. Desmedt will likely explain in some more detail what studies they conducted on the mILC samples and their methods. She will also likely elaborate on the findings and possibly identify potential targets for therapies. She may discuss what her research means for current or new combination drug therapies that can when administered together to a patient target the different metastatic lesions. She may also talk about what she has learned about the dramatic difference between what the scans picked up in the patient before she passed away and what the autopsy found in terms of which sites had the greatest discrepancy and what if anything can be done about this.

Key Terms and Definitions:

Ascites: is the abnormal buildup of excess fluid inside the abdominal cavity (belly). It is not a disease itself, but rather a prominent sign of an underlying medical condition. The accumulation occurs in the narrow peritoneal space between the two layers of tissue that line the abdomen and wrap around the internal organs.

Female hormones ER and PR: ER is estrogen, and PR is progesterone

How combination therapies target varied lesions: Chemotherapy kills rapidly dividing cells everywhere, while targeted therapy attacks a specific genetic mutation. When immunotherapy drugs are added, these train a patient's immune system to recognize and attack cancer cells throughout the body regardless of small differences between them.

Organoid: A tiny 3D, lab-grown copy of a tumor created by placing the tumor cells in a special gel so that they grow into a small 3D ball instead of a flat layer. This mini organ mimics how the cancer acted and grew inside the body. To test a drug on an organoid, it is put into a plastic plate, and the drug is added to it, and the organoid can be studied to see how many of the cancer cells then die.

Phylogenetic Reconstruction: This is a scientific process of inferring the evolutionary history and ancestral relationships among a group of organisms, genes, or species, which are typically displayed in a branching diagram that looks like a family tree. In the context of studying mILC lesions, it means creating a sort of family tree to depict the relationships between the cancer's traits and genetic makeup, including how they connect and descend from the original tumor.

Resources and Key references:

<https://pmc.ncbi.nlm.nih.gov/articles/PMC13036049/> Zels G, et al, Clinical and histopathological characterization of metastatic lobular breast cancer: lessons learned from post-mortem tissue donation programs. NPJ Breast Cancer. 2026 Feb 20;12(1):48. doi: 10.1038/s41523-026-00912-5.

Scientific Session 10: Radiotherapy, Clinical Trials

Radiotherapy in ILC

Presenter 3: Elinor Sawyer, MD

Background: Invasive lobular carcinoma (ILC) shows unique clinical vulnerability to ionizing radiation therapy despite showing resistance to chemotherapy, with evidence indicating that radiation effectively reduces local recurrence and improves overall survival. Translational research indicates that ILC cells may harbor unique defects or deficiencies in DNA damage repair pathways (such as specific anomalies in γ H2AX foci formation and E-cadherin), which could explain why the cancer cells are exceptionally sensitive to radiation-induced damage. The fact that ILC grows diffusely suggests that whole breast radiation is better than abbreviated partial breast radiation. Accelerated Partial Breast Irradiation or APBI focuses a high dose of radiation strictly on the empty tumor bed and a tiny 1-to-2-centimeter margin around it. Because microscopic ILC cells routinely drift further into other quadrants of the breast undetected, an abbreviated or partial field can easily miss these cells entirely. Major oncological consensus bodies such as the National Comprehensive Cancer Network (NCCN) have historically integrated this reasoning into their guidelines. While WBI remains the gold standard for most ILC cases, recent data from *The International Journal of Radiation Oncology* suggests that highly selected, early-stage ILC patients (e.g., small tumors, completely clear surgical margins, and no lymph node involvement) may achieve acceptable local control with modern external-beam APBI.

Dr. Sawyer was a co-author on a study on partial-breast radiotherapy after breast-conserving surgery for patients with early-stage breast cancer that supported their hypothesis that partial-breast radiotherapy using a standard radiation technique can reduce late toxicity without jeopardising local tumour control. The study excluded ILC patients.

Dr. Sawyer is currently investigating the genetics of ILC and how the environment in the breast contribute to ILC development. She wants to understand why some patients with ILC have a recurrence. Her study hopes to develop better ways to detect and prevent ILC relapses. It will look at the differences between tumors that relapsed within 5 years or after more than five years since diagnosis. They will look at the gene activity in patient ILC samples and at the healthy cells around the ILC cells and the patients' immune system. The study is intended to identify ways to predict which ILC patients should receive more intense treatment at diagnosis.

Dr. Sawyer is part of the LBCUK's Scientific and Medical Advisory group. In a spring of 2025 videotaped interview by Jane Hill of Lobular breast Cancer UK, Dr. Sawyer indicated that she notes that mammograms do such a poor job at detecting ILC, women with ILC should have access to the modalities that find ILC better like MRI and Contrast Enhanced Mammograms (CEM). In her studies of women with ILC and relapse, she will also be evaluating the modalities they have had access to and will likely have more data to make the case. In the immediate term, she is joining with LBCUK and others in promoting a change in the NHS Screening Programme that will allow women with high breast density to be routinely offered access for their breast cancer screening to MRI and/or CEM. She also described how she hopes that soon other PET scans that have dyes that work better with ILC, such as FAPI/PET, will be available more widely and not only for monitoring metastatic ILC lesions but also for sizing the ILC tumor in early-stage breast cancer and to prevent what so often happens, that the post-surgical pathology shows that the tumor was larger than initially thought.

Dr. Sawyer also went on in the interview to promote the use of liquid biopsy tests to enable earlier detection of an ILC in the blood long before it is detected with imaging. In her study of genetic scores and relapse in breast cancer (313-SNP breast cancer polygenic risk score – PRS313) she has been studying tests that will predict relapse and will be pushing for changes in screening for women with scores that suggest high risk for breast cancer recurrence and/or for women in whom ILC has been found in the blood stream – these women should have access to the

better imaging modalities and potentially to drugs to treat certain genetic mutations found. She mentioned the promising ctDNA study going on now TRAK-ER trial, being conducted by Royal Marsden Hospital.

What the Talk is Likely to Cover and Why: It is hard to predict what she will talk about specifically, but it may focus on testing the safety and efficacy of using APBI with patients with ILC after breast-conserving surgery. She may also discuss the promise of FAPI/PET and where things stand in the UK on providing access to it and other imaging modalities more useful than mammograms for patients with ILC. She may also provide an update on her research on where and whether the use of the polygenic risk score she helped develop will be used to determine which women should have access to better screening modalities and specific drugs.

Key Terms and Definitions:

Anomalies in γ H2AX foci formation: This refers to abnormal patterns, counts, or persistence of H2AX spots in the cell nucleus.

Breast cancer polygenic risk score: This is a number calculated by adding up tiny changes in thousands of places in the DNA that is an estimate of your total genetic risk of getting breast cancer.

Contrast-Enhanced Mammograms (CEM): an advanced breast imaging test that combines a standard digital mammogram with an intravenous iodine-based contrast dye to highlight abnormal blood vessels and detect hidden tumors. It provides a faster, lower-cost alternative to a breast MRI and improves detection of ILC.

E-cadherin: (epithelial cadherin) is a calcium-dependent protein that helps epithelial cells stick together, maintain tissue structure, and act as a tumor suppressor. The "E" stands for epithelial, meaning it is found on cells that line the surfaces of your skin, organs, and glands

PET and FAPI/PET Scans: A PET scan (positron emission tomography) is an imaging test that shows how your organs and tissues are working at a cellular level. It uses a safe, injected radioactive tracer—often a form of radioactive sugar—to measure blood flow, oxygen use, and metabolism. A FAPI/PET (Fibroblast Activation Protein Inhibitor) is an advanced molecular imaging test that targets the structural microenvironment surrounding a tumor rather than the tumor cells themselves. It is combined with radioactive elements like **Gallium-68 or Fluorine-18** to visually "light up" active areas of tissue remodeling

Resources and Key references:

<https://doi.org/10.1038/s41523-025-00788-x> Boysen, M.R., Speers, C.W. and Sikora, M.J.

Radiation therapy for lobular breast cancer: opportunities and challenges for leveraging radiosensitivity. *npj Breast Cancer* 11, 68 (2025).

<https://www.youtube.com/watch?v=H6D6pjeJovM>. Jane Hill with Oncologist Elinor Sawyer on YouTube. April 2025

<https://pmc.ncbi.nlm.nih.gov/articles/PMC12580823/> Timbres J, Kohut K, Mavaddat N, Easton DF, Petridis C, Roylance R, Schmidt MK, Sawyer EJ. Breast Cancer Polygenic Risk Score Associated with Outcomes after In Situ Breast Disease. *Cancer Epidemiol Biomarkers Prev.* 2025 Nov 3;34(11):1936-1945.

<https://clinicaltrials.gov/study/NCT04985266> The TRAK-ER trial is a multi-centre, randomised, open-label trial in patients with early stage oestrogen receptor positive (ER+) human epidermal growth receptor-2 negative (HER2-) breast cancer, who have detectable circulating DNA (ctDNA) but no overt macroscopic disease on imaging. TRAK-ER aims to demonstrate that fulvestrant plus palbociclib improves relapse-free survival compared to standard endocrine therapy in this patient group.