COMET

A Study for Low Risk DCIS
Expanding Knowledge and Options

What is the COMET Study?

COMET stands for Comparing an Operation to Monitoring, with or without Endocrine Therapy for low-risk ductal carcinoma in-situ (DCIS) of the breast. This is the first large randomized clinical trial in the United States (US) to look at different management strategies for low-risk DCIS. The COMET Study will enroll 1200 women with low-risk DCIS at about 100 sites throughout the US. The study is funded by the Patient-Centered Outcomes Research Institute (PCORI).

Why is the COMET Study needed?

You may be surprised to hear that doctors and scientists do not agree with each other about how to describe and treat low-risk DCIS. This is because there has not been enough research about the outcomes of treatment. Because of this, there are differing opinions among doctors. Each year in the United States, more than 50,000 women are diagnosed with DCIS. Guidelines currently recommend that DCIS should be treated in the same way as invasive breast cancer. Almost all patients in the United States (98%) receive surgery to remove the DCIS, and almost half also have radiation therapy following their surgery. Only a small number of patients currently choose not to have surgery or radiation for their DCIS because it is not widely available as an option.

However, studies indicate that many women with low-risk DCIS may not develop invasive cancer in absence of surgery. Many breast cancer doctors and researchers now believe that it might be possible to monitor DCIS rather than operate right away, but they are currently unable to do so without better evidence.

The COMET Study is being conducted across the United States to compare two treatment approaches for low-risk DCIS: Active Monitoring and Surgery. The COMET Study is needed because these treatment approaches have not been compared directly before in patients with low-risk DCIS. We need to understand more about the experiences and outcomes of patients receiving these treatment approaches. The results will enable doctors and patients to better understand the risks and benefits of Active Monitoring and Surgery, and whether both should be recommended for patients with low-risk DCIS in the future.

Ductal Carcinoma in-situ (DCIS) of the breast

What is DCIS?

You are likely to find DCIS described in many different ways. You may see and hear low-risk DCIS being called abnormal cells, precancerous lesion, stage zero, and non-invasive breast cancer. Based on different research studies, some doctors say low-risk DCIS should be called an early-stage cancer, while others believe it does not behave like cancer at all.

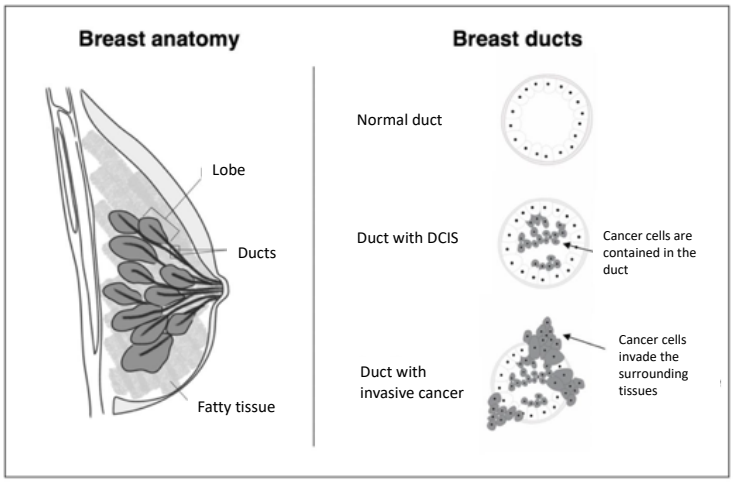
What does 'DCIS' mean?

"DCIS" stands for "ductal carcinoma in situ." "Ductal" means it is contained within the milk ducts of the breast. The word "carcinoma" indicates that under the microscope, the cells look like cancer. The final part of the DCIS acronym, "in situ," signals that these cells are contained (situated) inside the milk ducts in your breast.

Is DCIS cancer, or not?

One of the reasons there is so much debate about what to call DCIS is that the words "cancer" and "carcinoma" provoke such strong emotional reactions. Many people's first response is to want to remove or destroy it as quickly as possible. However, many years of research have shown that cancerous cells are not a single entity or type; some do not grow rapidly, or even at all.

The DCIS cells, when examined under a microscope, can show behaviors in the body that range from rapidly invasive at one end of the spectrum to very slow or even non-growing at the other, staying contained. While doctors agree that cells that show invasion under the microscope need to be removed by surgery or destroyed by radiation or other therapies, there is much more debate and disagreement about what to do with cells that are contained, such as DCIS in the milk ducts of the breast.



What is low risk DCIS?

A level of "risk" is often also added to describe DCIS. DCIS can be categorized as "low" or "high" risk to indicate the probability (likelihood) that it will develop into invasive cancer. Women with low-risk DCIS are less likely to have invasive cancer in the future than women with high-risk DCIS. While low-

risk DCIS has features that indicate the woman has a low probability of developing invasive cancer, this is not the same as no risk. These risk levels are also a source of debate.

Until now, very little research has directly compared the experiences and outcomes of patients receiving different treatments for low-risk DCIS. Research that has been done has involved patients with all types of DCIS, including those with low-risk and high-risk DCIS. Research that combined patients with low- and high-risk DCIS has suggested that fewer women will develop invasive breast cancer or die of breast cancer if they have surgery compared with those who do not have surgery. However, active monitoring was not studied (or was not an option) in this research.

The lack of clarity about the research findings, and particularly how relevant they are to patients with low-risk DCIS, is why more research is needed.

Low- risk DCIS and the COMET Study

The debates about what DCIS should be called and how serious a risk it poses to overall health extend to disagreements between doctors about how it should be treated or managed. Some believe low-risk DCIS should continue to be treated immediately with surgery (and radiation if needed) to reduce the risk of invasive cancer as much as possible. Others believe that many patients with low-risk DCIS do not need surgery or radiation and could avoid or delay having these treatments (and their side-effects) by actively monitoring the DCIS with regular mammograms.

You will find supporters of these two very different approaches. There are also many doctors who would like to be able to offer both treatment options to patients with low-risk DCIS. However, they are currently unable to do so without better evidence. These debates will continue until there is better evidence that directly compares the experiences and outcomes of patients who receive monitoring or surgery. This is the reason we have launched the COMET study.

Treatments in the COMET Study

The COMET Study will look at two different approaches for managing DCIS, described below and shown in Table 1:

Surgery

The aim of Surgery is to remove the DCIS and the tissue around it in an operation. Surgery can remove the milk ducts containing the DCIS (a lumpectomy) or the whole breast containing the DCIS (a mastectomy). Depending on the findings at surgery, this may be followed by radiation therapy. Surgery may be outpatient or require a stay of several days in the hospital. Recovery may take days or weeks. Your time in the hospital and recovering will depend on the type of operation, any side-effects you have, and whether you have a breast reconstruction. You will have checks during recovery, a check-up with a clinician every six months, and annual mammograms.

Active Monitoring

The aim of Active Monitoring is to monitor the DCIS closely. You will have a mammogram and a check-up with a clinician every six months. If no changes in the breast are seen, you will be able to stay on Active Monitoring and avoid surgery and its side-effects. If any changes in the breast are seen on a mammogram, they will be explained to you at your visit. The study doctor may recommend that you continue with Active Monitoring or have more tests, such as a biopsy, to investigate the changes. When you have the test results, you may be able to continue with Active Monitoring, or the results may indicate that you should undergo surgery and radiation therapy, if needed.

Endocrine Therapy

Whether you have Active Monitoring or Surgery, you may be offered endocrine therapy. Taking endocrine therapy is something to consider separately from your main treatment approach and participating in the COMET study. You can discuss it with your doctor.

Advantages and disadvantages of Surgery and Active Monitoring

Surgery and Active Monitoring are different initial approaches to treating low-risk DCIS. Each approach has advantages and disadvantages, and impacts on your life.

With Surgery, the DCIS area and tissue around it are removed. The risk of future invasive cancer is reduced. Depending on the type of operation you have, some or all of your breast will be removed. The tissue that is removed in the operation is carefully examined. At this stage, invasive cancer is found in a small number of patients. More surgery (re-excision) or radiation therapy may be required. You may experience side-effects from the surgery and/or radiation. Some side-effects may affect your daily life and some can be long-term. Surgery (and radiation if given) may cause pain and change the look and feel of your breast. This may affect you physically and emotionally. Some patients choose to have additional surgery to reconstruct the breast; this can have other side-effects. All side-effects are assessed and managed carefully by your clinical team.

With Active Monitoring**,** you have a check-up and mammogram every six months to look for any changes in the breast. Most patients should be able to stay on Active Monitoring for at least 10 years. A small number of patients will have invasive cancer that may worsen. You may experience anxiety from wondering whether your DCIS is growing or changing. If any changes are seen in your breast that concern your doctor, you will be advised to have further tests, such as a biopsy. You might be able to stay on Active Monitoring. However, if the changes are suggestive of invasive cancer, you will be advised to have surgery (and radiation if needed). It is possible that you might need more extensive treatment at this stage than if you had surgery when your DCIS was first diagnosed.

With both Active Monitoring and Surgery, it is important to note that with both Active Monitoring and Surgery there are risks of invasive cancer developing in the breast with DCIS, the other breast, or somewhere else in your body. The advantages and disadvantages of each of the approaches are summarized in Table 2.

Table 1. *Summary of the COMET study treatment approaches*

	Surgery	Active Monitoring
Treatment approach	• An operation to remove the DCIS	• Regular monitoring of the DCIS
Aim of treatment approach	• To remove the DCIS, which may lower the risk of invasive breast cancer.	• To monitor the DCIS with regular mammograms, to avoid surgery unless or until there is evidence of invasive breast cancer
Details of treatment approaches	• Surgery can be a lumpectomy or mastectomy operation, depending on the size of the DCIS, recommendation of the surgeon and patient preference. --**Lumpectomy**: a portion of the breast containing the DCIS is removed. --**Mastectomy**: the whole breast containing the DCIS is removed. • Radiation therapy may also be given, based on a discussion with your doctor that incorporates information such as your medical history, what surgery you had, and the pathology findings.	• A check-up and mammogram six months after you join the study. The mammogram will check for changes in the breast. • If there are no changes, you can stay on Active Monitoring and return in six months for the next mammogram and check-up. • If there are changes seen, they would be discussed with you and you might have a biopsy. • Your options would be to stay on Active Monitoring or change to have surgery.
Hospital stays and visits	• Lumpectomy is generally an outpatient surgery. You go home the same day. • Mastectomy for DCIS may be done as an outpatient, or you may stay overnight. • If the breast is reconstructed, this lengthens the initial hospital stay to 3-5 days and you may require further operations, with recovery each time. • Radiation treatment generally requires daily visits over 3 to 6 weeks. You lie on a table and radiation is targeted to the breast or chest. You will not feel the treatment itself. • You will have check-ups after surgery, a check-up every six months and a mammogram every year.	• You will have a visit for a mammogram six months after joining the study. • You will have an appointment to discuss the findings with the specialist. • If you stay on Active Monitoring, you will need to return every six months for a mammogram and check-up. • If you have changes on a mammogram, you may need further tests such as a biopsy. • If the tests suggest invasive cancer, you will be recommended to have surgery, with or without radiation therapy. • See the left-hand column for details of surgery and radiation.
Time off work or usual activities	• With lumpectomy or mastectomy, most people need 1-3 weeks off work after the surgery. • With breast reconstruction, most people need 3-6 weeks or more off work after each surgery. • With radiation, some people may need 2-4 weeks off work, starting toward the end of treatment	• There is no recovery time. • You will need to take an hour or two out of your work and usual activities for the mammogram and check-ups every six months.
Endocrine therapy	• Can be taken to block hormones that are associated with cancer growth. You can discuss this option with your doctor.	• Can be taken to block hormones that are associated with cancer growth. You can discuss this option with your doctor.

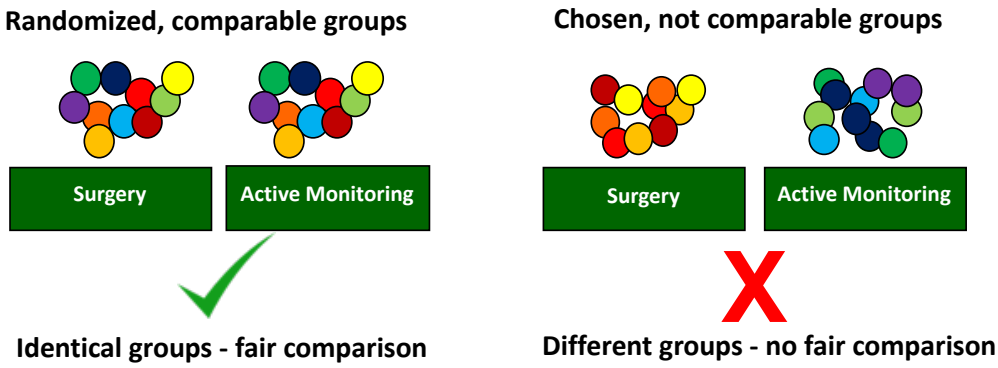
***Table 2**. Side-effects and experiences of the Surgery and Active Monitoring treatment approaches*

	Surgery Approach	Active Monitoring Approach
Common side-effects or experiences	• Scar (small from lumpectomy, larger from mastectomy). • Pain in breast, chest or arm, which may be long lasting. • Loss of skin sensation around scar or across breast. • Blood or clear fluid collections in the wound that slow recovery process. • Concern about the new physical appearance of your breast. • Uneven breasts. • Worry about DCIS recurrence or cancer development or progression despite having had treatment. • Radiation therapy causes fatigue, a sunburn like effect, and changes in the texture of the breast.	• As active monitoring is the first course of treatment, the natural breast remains unchanged. • Missing work and usual activities for each 6-month mammogram and check-up. • Discomfort during mammogram. • Anxiety while waiting for results of mammogram. • Worry that more DCIS could be found, or that the DCIS could grow, or invasive cancer might be found
Less common side-effects and experiences	• Swelling in the breast or arm (lymphedema) if nodal surgery is performed. • Wound infection requiring antibiotics. • Shoulder pain and reduced ability to move arm and shoulder. • Difficulty adjusting to new body image. • Negative impact on sexuality or sexual activity. • Complications from reconstruction (if undertaken) • Rare serious side effects of anesthesia	• If you change to surgery later, you may experience the same risks of side effects as listed to the left.

Participation in the COMET Study

Women who are eligible for the study and choose to join are assigned to receive either active monitoring or surgery through a process called randomization. Randomization is important. It allows a fair comparison of the two approaches. If you are invited to join the study, it is because your doctor believes both approaches are good options for you. We do not know if one is better than the other.

Randomization divides patients into two groups that are as identical as possible except that one group receives Active Monitoring and the other group receives Surgery. The groups need to have identical numbers of younger/older and taller/shorter people, and so on. If the treatment groups are the same as each other, this allows a fair comparison. If you or your doctor choose a treatment, the groups will not end up the same - with the same numbers and colors of spots as shown in the diagram - and then the comparison would not be fair.



If you take part in the COMET study you cannot choose your treatment arm and neither can your doctor. You should only agree to participate in the study if you are prepared to receive either Active Monitoring or Surgery. You will have an equal likelihood of being assigned to Surgery or Active Monitoring. You will be able to ask all the questions you have and discuss randomization in more detail with the COMET study staff.

Follow up in the COMET Study

Most of the exams, tests, and procedures you will have in the COMET study are part of the regular care for your low-risk DCIS using the two approaches.

At the start of the study, six and twelve months after joining, and then annually thereafter, you will be asked to complete surveys. These surveys will ask about your quality of life and feelings you may be experiencing. The surveys will provide important information that will and enable researchers to get a better understanding of the overall experiences for women in both groups.

You will also be asked to donate blood, as well as tissue which has already been removed, as part of the study. No additional tissue will be removed as part of participating in the study. The study will last a minimum of five years. The study team may ask you to remain in the study and follow your progress for up to ten years.

You will have a clinical trial support team. The follow up care in the COMET study for the two approaches is summarized below.

***Table 3**. Details of follow up in the COMET study*

	Surgery	**Active Monitoring**
Frequency of follow-up	• Post-operative checks and post-radiation checks, if given • Check-up every 6 months • Mammogram every 12 months • Blood collection every 12 months • Surveys at baseline, 6 months, 1 year and then annually for five years • After 5 years, mammogram and check-up once a year • Access to your medical record for 10 years to follow your progress	• Check up every 6 months • Mammogram every 6 months • Blood collection every 12 months • Surveys at baseline, 6 months, 1 year and then annually for five years • After 5 years, mammogram and check-up once a year • Access to your medical record for 10 years to follow your progress

For any other information or details about the COMET study, please talk to the study doctor or coordinator in your center.

What it means to take part in the COMET study

If you take part in the COMET study, you will join over 1,000 other women across the US who are helping to compare the options of Surgery and Active Monitoring for low-risk DCIS. The information produced by the study may or may not help you directly. However, you will be contributing extremely valuable data that will provide doctors and patients with clearer information about treatment options and choices for patients with low-risk DCIS in the future.

About the COMET Study Team

The COMET Study is a clinical trial hosted by a national clinical research group - ***Alliance Foundation Trials, LLC*** - and funded by the ***Patient-Centered Outcomes Research Institute*** (PCORI). This study is registered with ***Clinicatrials.gov***.

The Principal Investigator (PI) of COMET is **Dr. Shelley Hwang**, Professor of Surgery and Chief of Breast Surgical Oncology at the Duke University Medical Center and Duke Cancer Institute.

Co-PIs of the study are **Dr. Alastair Thompson**, Professor of Surgery and Chief of Breast Surgical Oncology at Baylor University Medical Center, and **Dr. Ann Partridge**, a breast Medical Oncologist and Professor of Medicine at Harvard Medical School and Dana Farber Cancer Institute.

The members of the **COMET Study Patient Leadership Team** (PLT) are **Liz Frank**; **Deborah Collyar**; **Desiree Basila**; and **Donna Pinto**. Members of the PLT possess vast DCIS experience and expertise including: engagement in breast cancer research for over 20 years; undergoing active monitoring for DCIS; publishing a DCIS e-book; developing a patient advocate research organization; and hosting a DCIS website.

The Project Manager of the COMET study is **Thomas Lynch, PhD,** in the Division of Surgical Oncology at Duke University Medical Center. Study recruitment and implementation is being supported by consultants **Dr. Louise Davies**, of Dartmouth College, and **Jenny Donovan, PhD**, QuinteT research group, University of Bristol, UK.

> *"The COMET Study is long overdue for women like me (diagnosed with low-risk DCIS). This trial will help thousands of women for years to come make difficult treatment decisions based in research rather than uncertainty."*
>
> *Donna Pinto,*
> *COMET Study Patient Leadership Team*