# Updates in Breast Cancer Screening AND Management of Ductal Cancer In Situ-A Precancerous Lesion: Observation vs Surgery – COMET Trial

Sandhya Pruthi, MD
Professor of Medicine, Mayo Clinic
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# Disclosure

## Relevant Financial Relationships

None

## Off-Label/Investigational Uses

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# Learning Objectives

- Review screening mammogram risks, benefits and limitations
- Shared decision making approach in counseling about the pros and cons of screening mammography
- Understand how DCIS is a precancerous /non-invasive lesion
- Discuss new options for the management of ductal cancer in-situ

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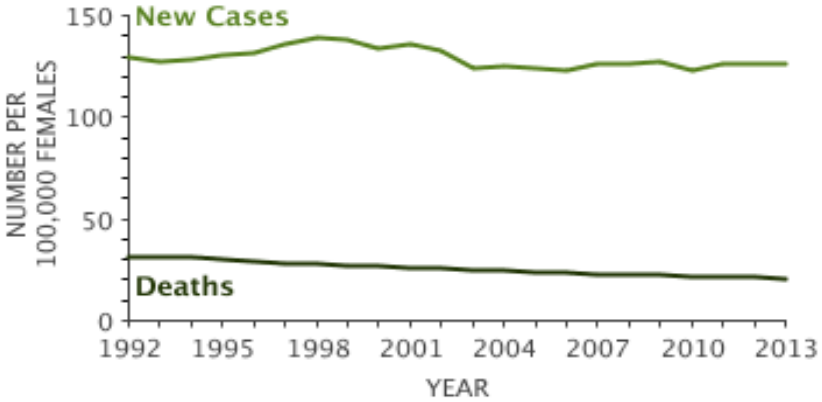
## At a Glance

| | |
|---|---|
| Estimated New Cases in 2016 | 246,660 |
| % of All New Cancer Cases | 14.6% |
| Estimated Deaths in 2016 | 40,450 |
| % of All Cancer Deaths | 6.8% |




**Percent Surviving 5 Years**

**89.7%**

2006–2012

**Number of New Cases and Deaths per 100,000**: The number of new cases of female breast cancer was 125.0 per 100,000 women per year. The number of deaths was 21.5 per 100,000 women per year. These rates are age-adjusted and based on 2009–2013 cases and deaths.

**Lifetime Risk of Developing Cancer**: Approximately 12.4 percent of women will be diagnosed with female breast cancer at some point during their lifetime, based on 2011–2013 data.

**Prevalence of This Cancer**: In 2013, there were an estimated 3,053,450 women living with female breast cancer in the United States.

https://seer.cancer.gov/statistics/types/incidence.html

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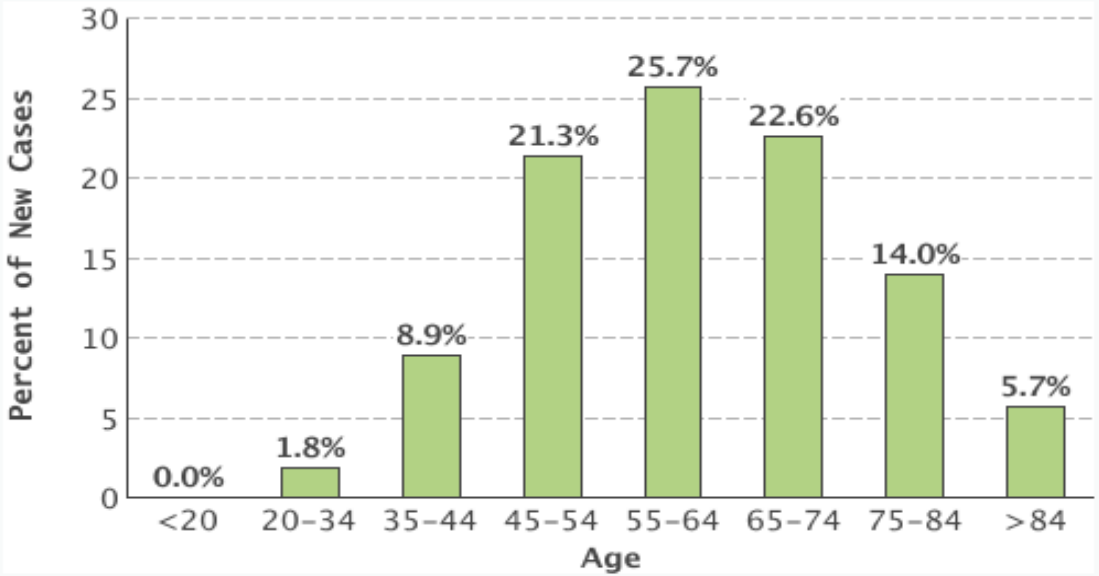
## Who Gets This Cancer?

Female breast cancer is most common in middle-aged and older women. Although rare, men can develop breast cancer as well. The number of new cases of female breast cancer was 125.0 per 100,000 women per year based on 2009-2013 cases.

### Percent of New Cases by Age Group: Female Breast Cancer




Female breast cancer is most frequently diagnosed among women aged 55-64.

**Median Age At Diagnosis**

62

SEER 18 2009-2013, All Races, Females

https://seer.cancer.gov/statistics/types.html

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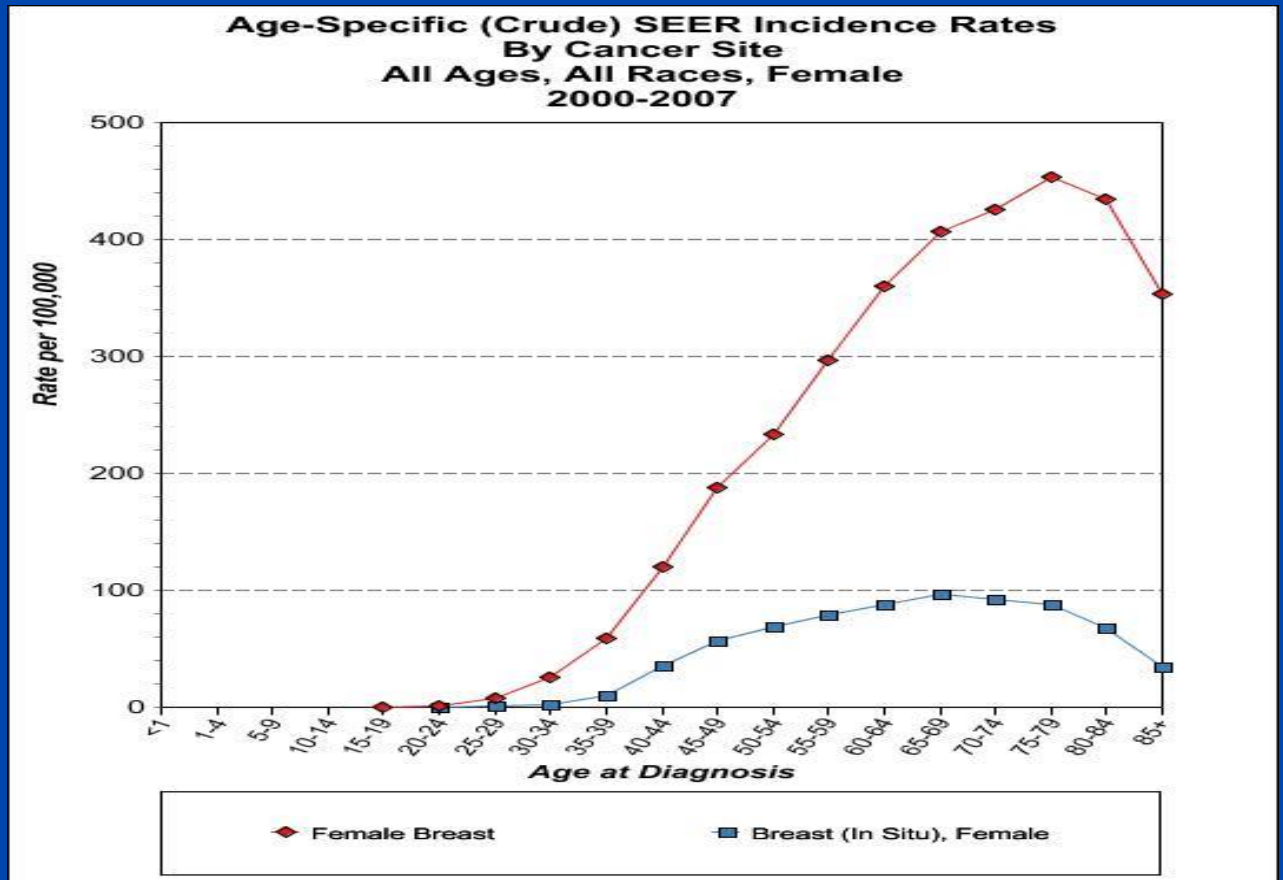


Cancer sites include invasive cases only unless otherwise noted.
Incidence source: SEER 17 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana and New Jersey).
Rates are per 100,000.
Datapoints were not shown for rates that were based on less than 16 cases.

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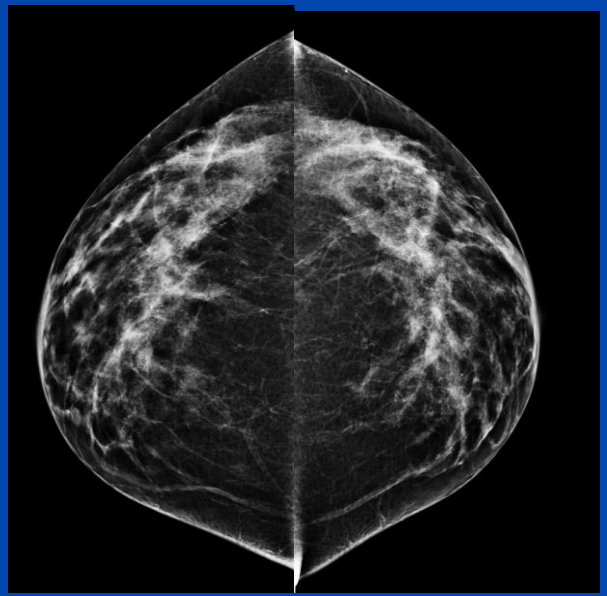
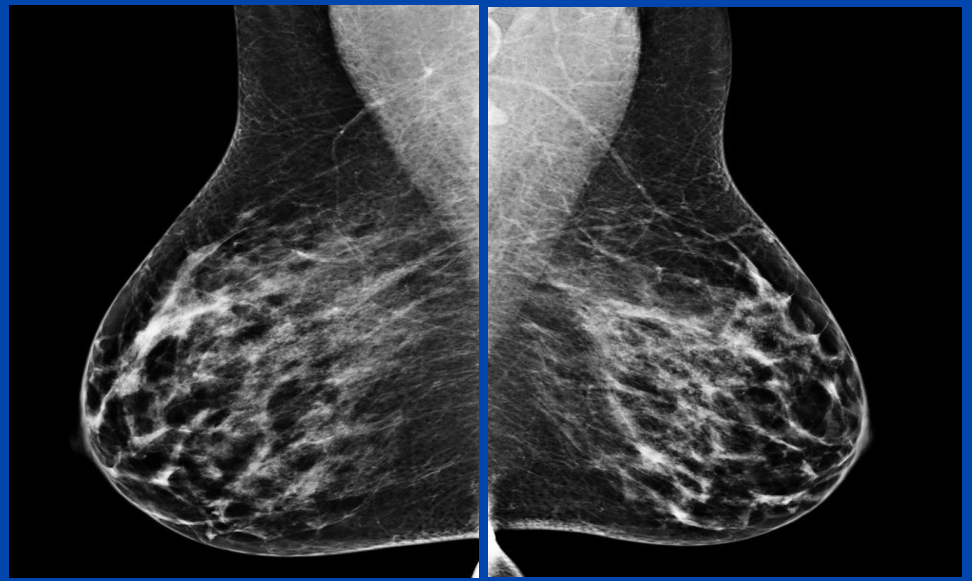
# Screening Mammogram

- Best available screening tool for breast cancer
- Detect breast cancer at earlier and more curable stages of disease





Cancer Facts and Figures 2018- ACS

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# Intent of Screening Mammogram

- For women 50-74 years
  - 26% (20-35%) reduction in mortality from breast cancer
  - Benefits vs limitations
- For women 40-49 years
  - 15-25% decrease in mortality
  - Controversy with age at which to initiate and frequency of screening mammogram
  - Benefits vs limitations
- Since 1989- decline in breast cancer deaths- due to early detection by screening mammography and treatment

**Siegel RL et al, CA Cancer J Clin, 2017**
**Fletcher SW et al: NEJM 348(17):1672, 2003**

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# Screening Mammography: Benefits, Risks, and Limitations

## Risks

- **Radiation exposure**
- Minimal risk and less than background radiation in the environment

- **Overdiagnosis**

Some cancers, about 1 out of 5 grow slowly and may never have caused symptoms or problems

## Benefits

**Decrease the chance of death from breast cancer**

**Improved treatment options:**

Breast cancers in women who undergo screening mammography are smaller and less advanced in stage.

Early detection offer women the option of breast conserving therapy

## Limitations

**Call back(false positive):**

- additional imaging- ultrasound or mammogram

**Breast Biopsy**

1 out 10 times a biopsy is needed to confirm if a patient has cancer

- lead to anxiety and distress while waiting for results

**Dense breasts**

Small chance that a cancer can be missed

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# Professional Society Guidelines for Breast Cancer Screening in Women with Average Risk

*Table 5.* **Professional Society Recommendations for Breast Cancer Prevention and Screening***

| *Organization, Guideline Date* | *Chemoprevention in Women at Increased Risk, Guideline Date* | *Screening Start Age* | *Mammographic Screening Interval* | *Screening Conclusion Age (Stop Screening at This Age)* |
|---|---|---|---|---|
| U.S. Preventive Services Task Force, 2016 | Discuss tamoxifen or raloxifene, 2013 | 50 y; discuss at 40 y | Biennial | 75 y |
| American College of Obstetrics and Gynecology | No statement | 40 y | Annual | None |
| American College of Radiology | No statement | 40 y | Annual | 5–7 y of remaining life expectancy |
| Canadian Task Force on Preventive Health Care, 2011 | Discuss tamoxifen, 2001 | 50 y | Every 2–3 y | 75 y |
| American Cancer Society, 2015 | Discuss, 2011 | 45 y; discuss 40–44 y | Annual 45–54; Biennial 55–79 | 80 y or 10 y of remaining life expectancy |
| American Society of Clinical Oncology | Discuss: tamoxifen, raloxifene, exemestane, 2013 | No statement | No statement | No statement |
| American Academy of Family Practice, 2010 | Discuss, 2013 | 50 y; discuss at 40 y | Biennial | 75 y |

*"Discuss" indicates that a discussion should take place between the patient and the provider on individual risks and preferences. "Date" refers to date of guideline regarding screening; prevention guidelines generally have a different date.*

Nattinger AB et al, Annals of Internal Medicine, June 2016

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# Mammography Screening:
# What has changed with limitations and benefits?

- Digital conversion- improved quality and decreased radiation dose
- Surgical biopsies have been replaced with percutaneous biopsy
- Decreased mortality was the only benefit
  - Early detection, improved surgical options
  - Atypia now treatable-preventive therapies
  - Supplemental screening options

Pisano ED et al, Radiology 2008

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# Outcomes for screen vs non-screen detected breast cancer

- Breast cancers in women who undergo screening mammography are
  - Smaller and
  - Less advanced stage

than breast cancers in women who do not undergo mammography for screening.

MarmotJNCI 2005;97:1195-1203

Dale et al ASBS 12th Annual meeting (Abstract 1670) April 29, 2011

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## Table 2. Information for Patients Deciding When to Start Getting Mammograms

### Summary

Women in their 40s and their physicians should discuss the pros and cons of starting mammography before 50 years of age. Based on the best scientific evidence, here are the potential benefits and harms for 1,000 women who start mammography at 40 years compared with 50 years:

- One woman diagnosed with breast cancer will not die
- 576 more women will have a false-positive test result
- 67 more women will have breast biopsies with normal results
- Two women will be diagnosed and treated for breast tumors that would never have caused symptoms or problems or needed treatment

Ebell MH et al, American Family Physician, April 2016

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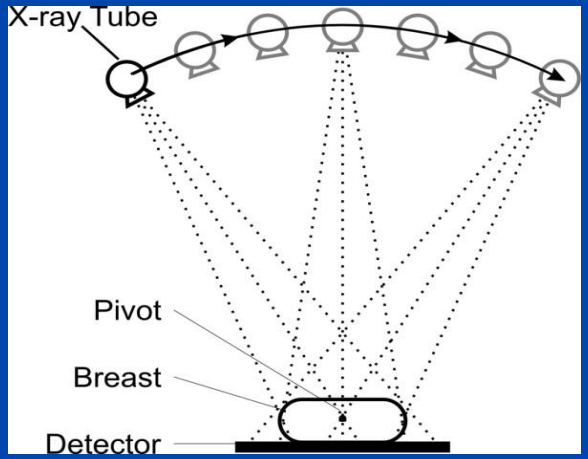
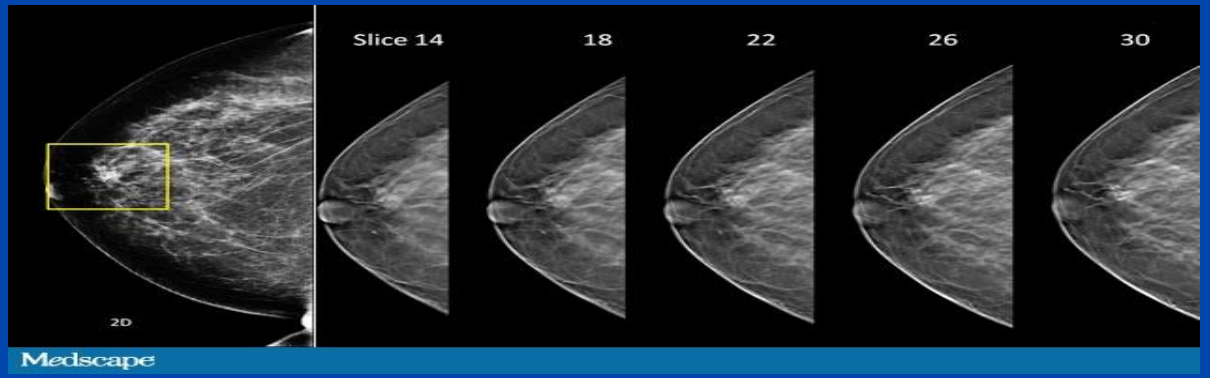
# Breast Tomosynthesis




- Reduce overlapping breast tissue
- Provide 3D technology
  - Improve mass visibility
  - Improve margin visibility
- Low dose
  - 1 to 2x conventional mammography

Friedewald SM et al, JAMA 2014
McDonald E et al, JAMA Oncology 2016

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# 3 D Tomosynthesis

- 7-10% recall rates across US
- New technology- 3 D tomosynthesis
  - 30-40% reduction in recall rates
  - Predominately in dense breast tissue and women younger than 50
  - Significant increase in cancer detection rate
    - Benefits in finding small invasive cancers and lobular cancers
  - Higher rate of cancers in the biopsies
  - Long term follow up is lacking and false negative rate is unknown
- FDA approved - 2011

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Friedewald SM et al, JAMA 2014

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# High risk women and Breast MRI
# American Cancer Society
# Screening Guidelines

Gene mutation
BRCA 1 or 2

First-degree relative with hereditary breast cancer mutation
- if the woman has not yet been tested

History of radiation therapy to the chest between ages 10 and 30

Lifetime risk >20-25% based largely on family history ( IBIS-Tyrer Cuzik risk calculator)

Saslow D, et al. CA Cancer J Clin 2007;57(2):75-89

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# Imaging and Early Detection - High risk

## Breast MRI

- MRI more sensitive than mammography
  - MRI=77-100%
  - Mammography=16-40%

  - MRI in addition to mammography identifies breast cancers not detected with mammography in high risk women

***Warner E. Ann Int Med 148: 671, 2008***

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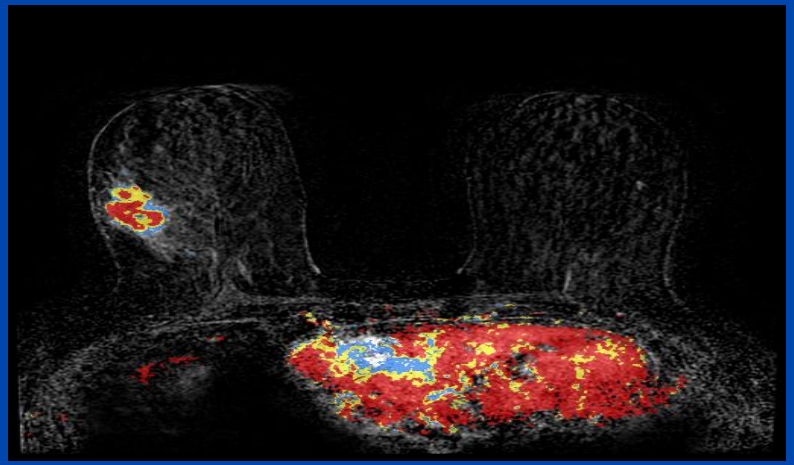
# Breast MRI

- Magnetic energy
- IV dye/contrast agent
- Cancerous tissue has a different blood supply than normal tissue
- False positives 20-30%
- More expensive than mammography



Orel et al: Radiology 205:429, 1997

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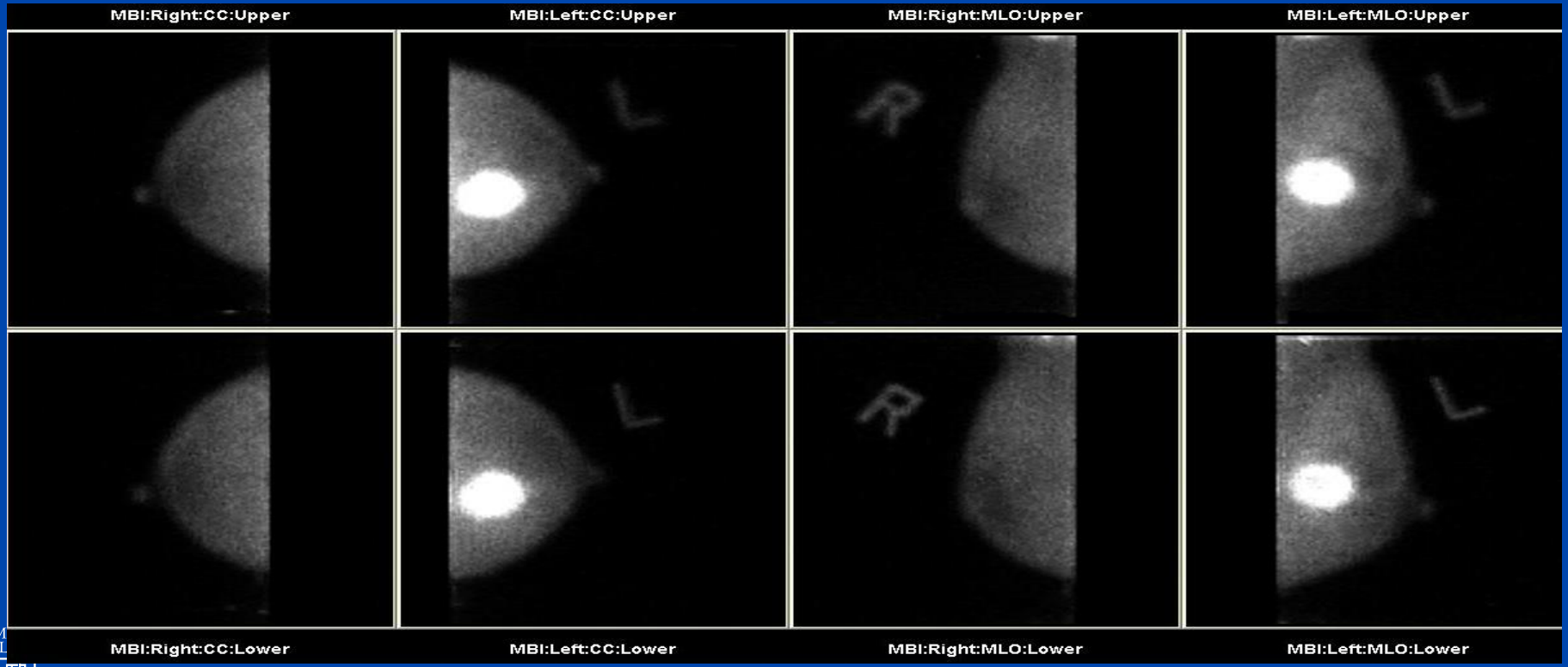
# Molecular Breast Imaging (MBI)

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# MBI

- Pros
  - In a study of 936 patients, 11 cancers detected
    - 1 - mammography only
    - 7 detected by MBI only
    - 2 detected by both
  - Retrospective studies have shown excellent concordance with MRI
  - Lower cost
- Cons
  - MBI does not replace mammography
  - Increased whole body radiation dose (8 mci) only recommended every other year
  - Imaging time is longer than mammography
  - MBI cannot be used for biopsy guidance (in development)

Rhodes DJ et al, Radiology 2011

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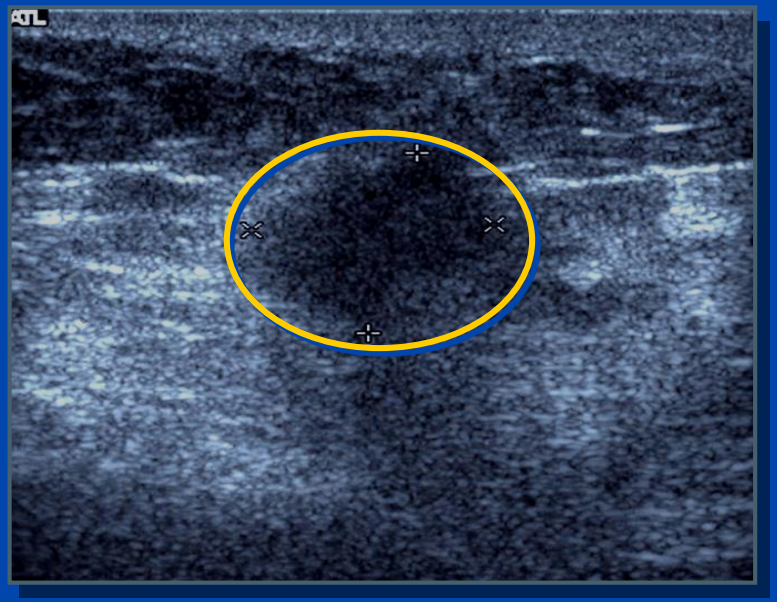
# Breast Ultrasound

- Screening with whole breast ultrasound in conjunction with mammography in high-risk women
- Increase in false positive
- Not able to accurately detect micro-calcifications
- Not shown to decrease breast cancer mortality

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# Breast Ultrasound

Increased detection of breast cancer
(Cancers/1000 women screened)

- MMG only: 7.6
- MMG + U/S: 11.8
- Supplemental yield: 4.2

Increased false positives

- MMG only: 4.4%
- MMG + U/S: 10.4%

Median scan time=19 min (+ 2 min spent with patient)

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Berg W, et al. JAMA 2008;299:2151-63

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# Personal Values- Individualize Discussion

## Breast Cancer Screening Values

- Willingness to undergo interventions to detect breast cancer early
- Perception of mammograms as painful or inconvenient
- Desire for recommendation about mammograms from provider
- Concern about individual breast cancer risk

Nattinger AB et al, Annals of Internal Medicine, June 2016

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# Shared Decision Making

- Step 1:
  - Breast cancer risk
  - Awareness of benefits vs risks and limitations of mammography
  - Personal values

- Most breast cancers occur in average risk women and can affect all women
- Mammogram screening reduces breast cancer mortality for women >40
- limitations: call backs, false positives, potential need for a percutaneous biopsy

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# Shared Decision Making

- Step 2:
  - Decide together

- Review contrasting guidelines among different organizations
- Discuss personal values and individual risks
- Use a shared decision approach to help decide what is right for your patient

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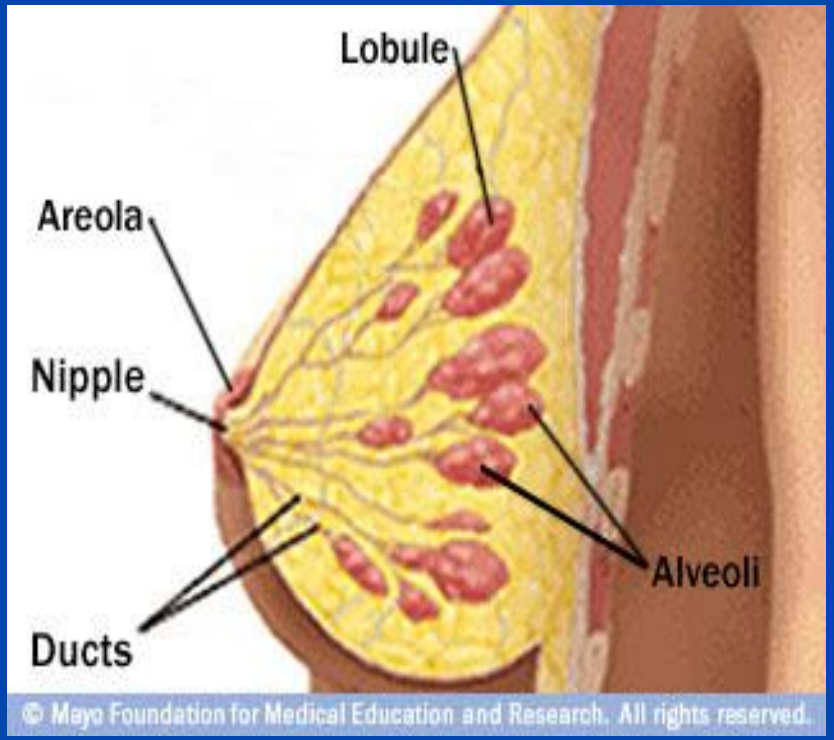
# Breast Anatomy

## Components

- Glandular tissue (lobules), ducts, fibrous tissue, adipose tissue, lymphatic and blood vessels

## Glandular nodularity

- Most pronounced in the upper outer quadrant of the breast
- Varies with menstrual cycle

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# Case #1

A 48 year old woman presents with a new left breast core needle biopsy proven ductal carcinoma in-situ.

The tumor is low grade, estrogen and progesterone receptor positive.

The malignant appearing calcifications on her mammogram involve a 4 cm area.

# Which of the following recommendations are appropriate options at this time?

A. Observation with every 6 month screening mammograms
B. Lumpectomy alone
C. Lumpectomy and breast irradiation
D. Mastectomy with irradiation
E. Tamoxifen for 5 years
F. Clinical trial comparing observation vs surgical treatment

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# Types of Breast Cancer

**Noninvasive or invasive**

**Different cell types (eg, ductal, lobular)**

**Different genomic subtypes**

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# Prognostic Factors

## Primary Prognostic Factors

- Lymph node status
- Tumor Stage
- Hormone receptor
- Tumor Grade

## New Prognostic Factors

- HER2/neu receptor status
- Gene expression profiling

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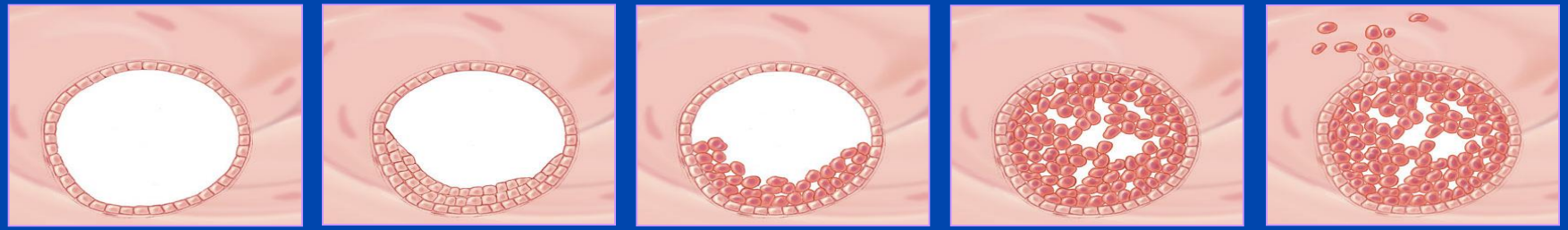
# Intraepithelial Neoplasia



**Normal Duct** | **Intraductal Hyperplasia** | **Atypical Ductal Hyperplasia** | **Ductal Carcinoma *In Situ*** | **Invasive Ductal Carcinoma**

**Normal (noncancerous)--------- Cancer**

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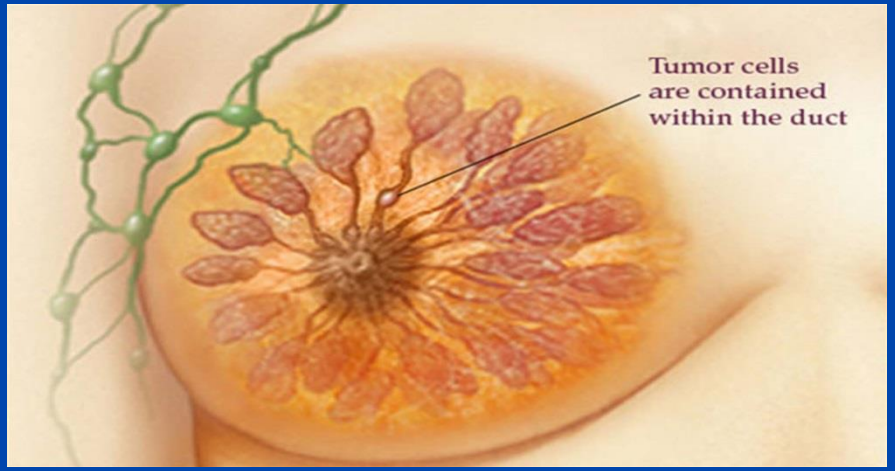
# Non-invasive Breast Cancer

- Neoplastic proliferation of epithelial cells confined to the ductal-lobular system without stromal invasion
- In principle – no metastatic potential
- 1%-2% will eventually develop distant metastasis

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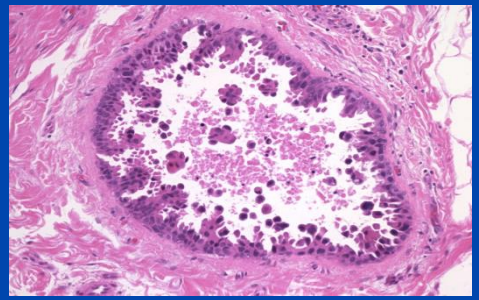
# Epidemiology of DCIS

- Ductal carcinoma ***in situ, precancer, preinvasive cancer***
- Estimated incidence of DCIS:  over 50,000 new cases annually
- Usually diagnosed by calcifications on mammography in asymptomatic patient
- DCIS now comprises over 20% of all mammographically detected breast cancers
- ***Nonobligate precursor of invasive cancer; rate and likelihood of progression are unknown***



American Cancer Society. Cancer Facts and Figures 2015.
Allison K. Cancer 2015.

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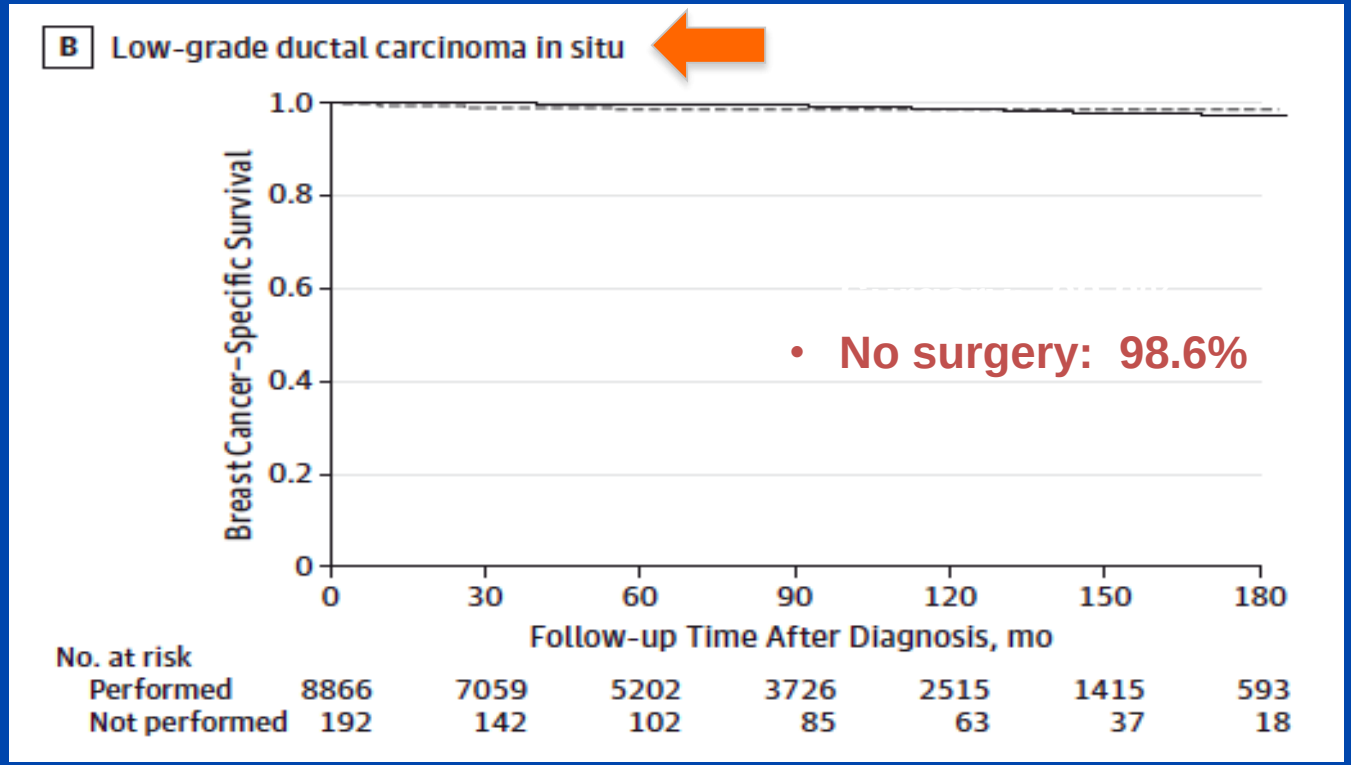
# What happens if you don't "treat" DCIS?
# SEER 1988-2011

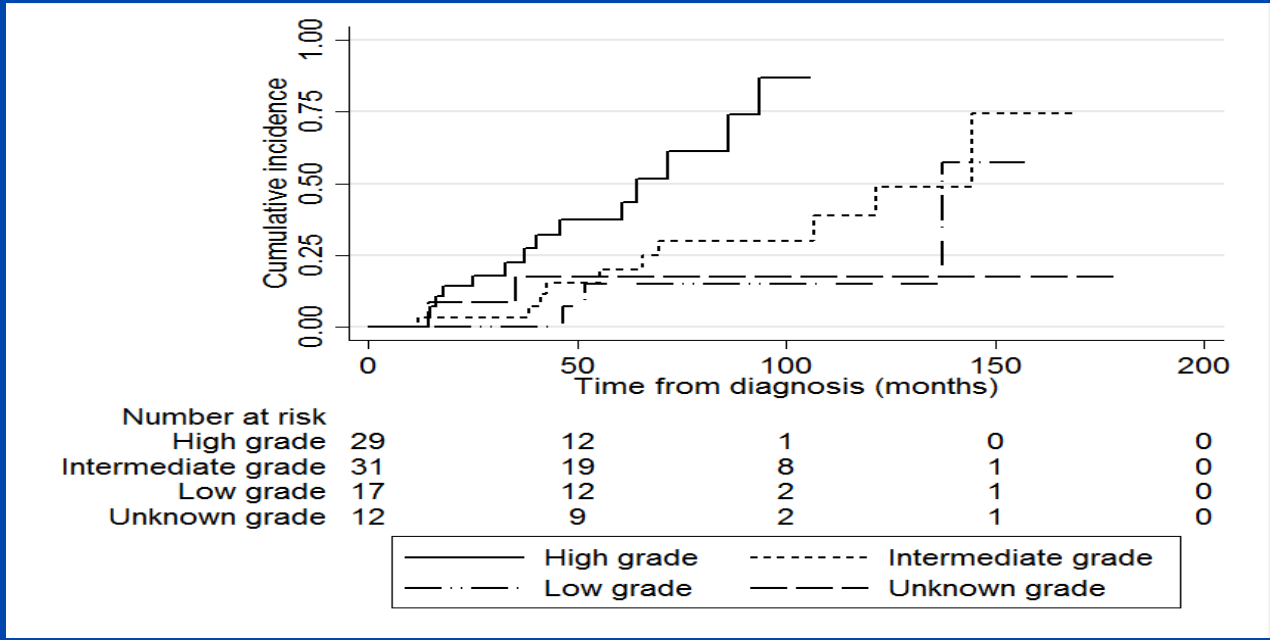



- No surgery: 98.6%

Sagara et al, JAMA Surgery 2015

# Progression of DCIS

- NHSP BSP
- 89 women
- DCIS on core biopsy
- No surgery
- Follow up
- ***Rarely low grade progression***




*Maxwell et al Eur J Surg Oncol 2018

# Active Surveillance Trials for DCIS

- UK (LORIS) and EORTC (LORD) trials have been initiated
- Newly diagnosed clinically “low risk” DCIS
- Primary outcome:  ipsilateral invasive cancer-free survival
- Randomization:  usual care (surgery and/or RT) vs. active surveillance
- Regular surveillance with imaging
- Intervene if evidence of progression to invasive cancer

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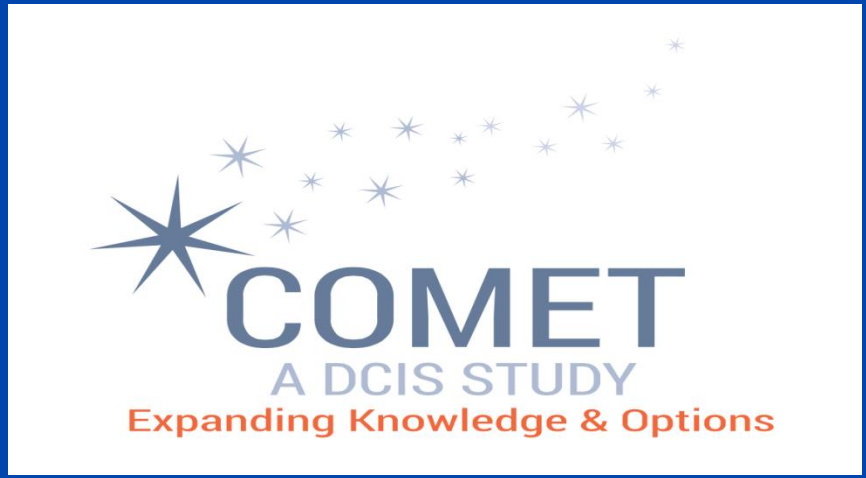
# COMET Trial for low-risk DCIS

## Comparison of Operative to Monitoring and Endocrine Therapy for Low Risk DCIS: COMET

E. Shelley Hwang
Ann Partridge
Alastair Thompson
Advocate Lead: Liz Frank




Sponsors: PCORI and Alliance Foundation Trials (AFT)

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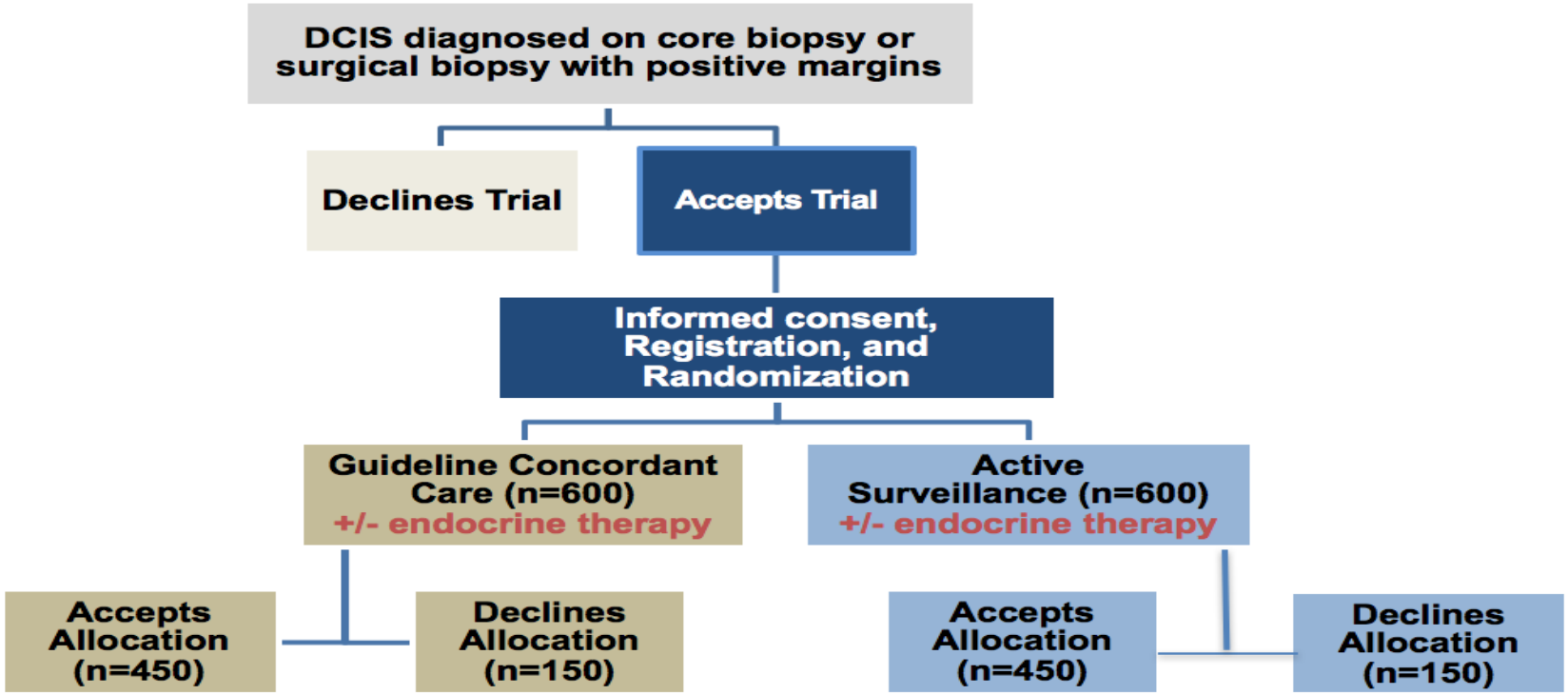
# Study Flow Diagram

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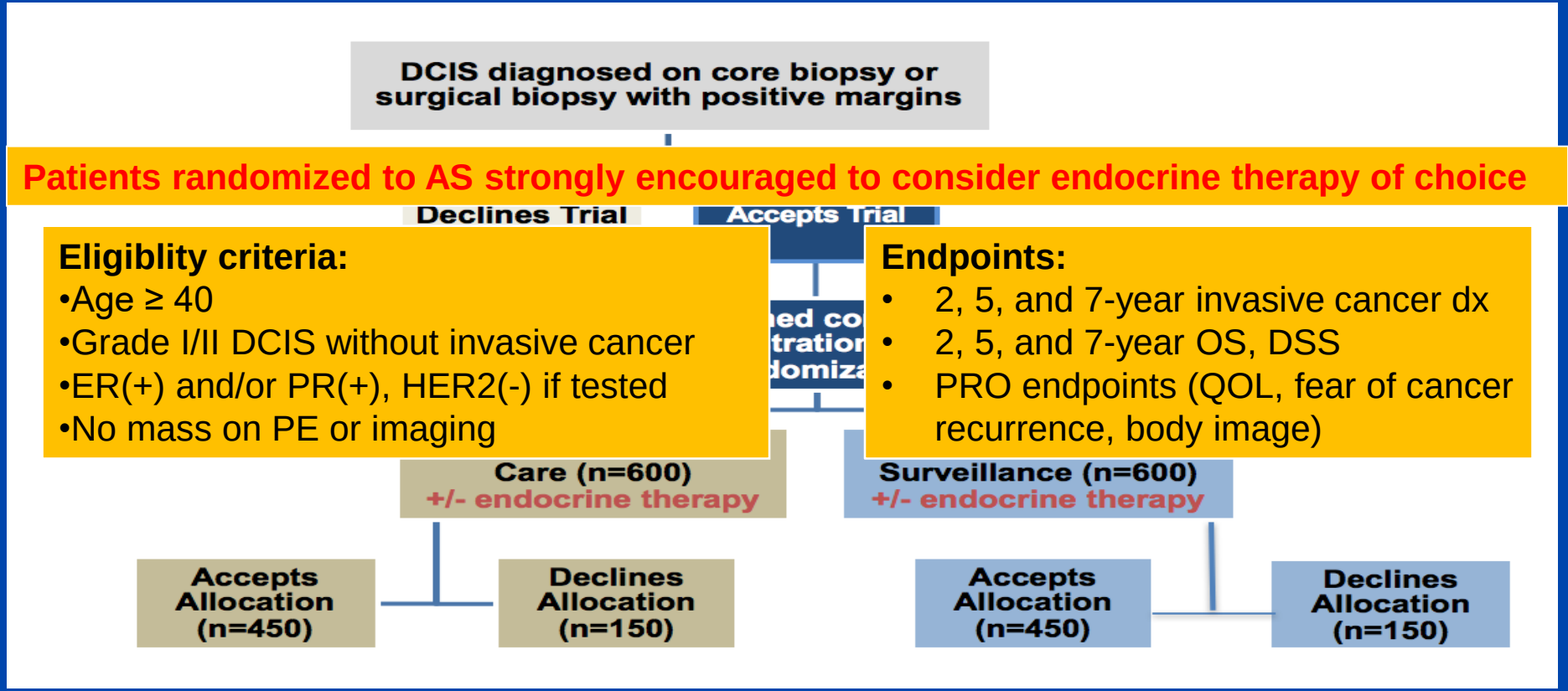
# Study Flow Diagram



# COMET Trial for low-risk DCIS

## *Eligibility Criteria*

- Age >40 at diagnosis; agree to randomization
- Pathologic confirmation of grade I/II DCIS without invasion by 2 local pathologists (microinvasion not allowed)
- ER ≥ 10%; HER2-negative (0, 1+, or 2+ if testing performed)
- No evidence of other breast disease on physical examination and breast imaging within 6 months of registration
- Available for follow up examinations
- Ability to read, understand and evaluate study materials

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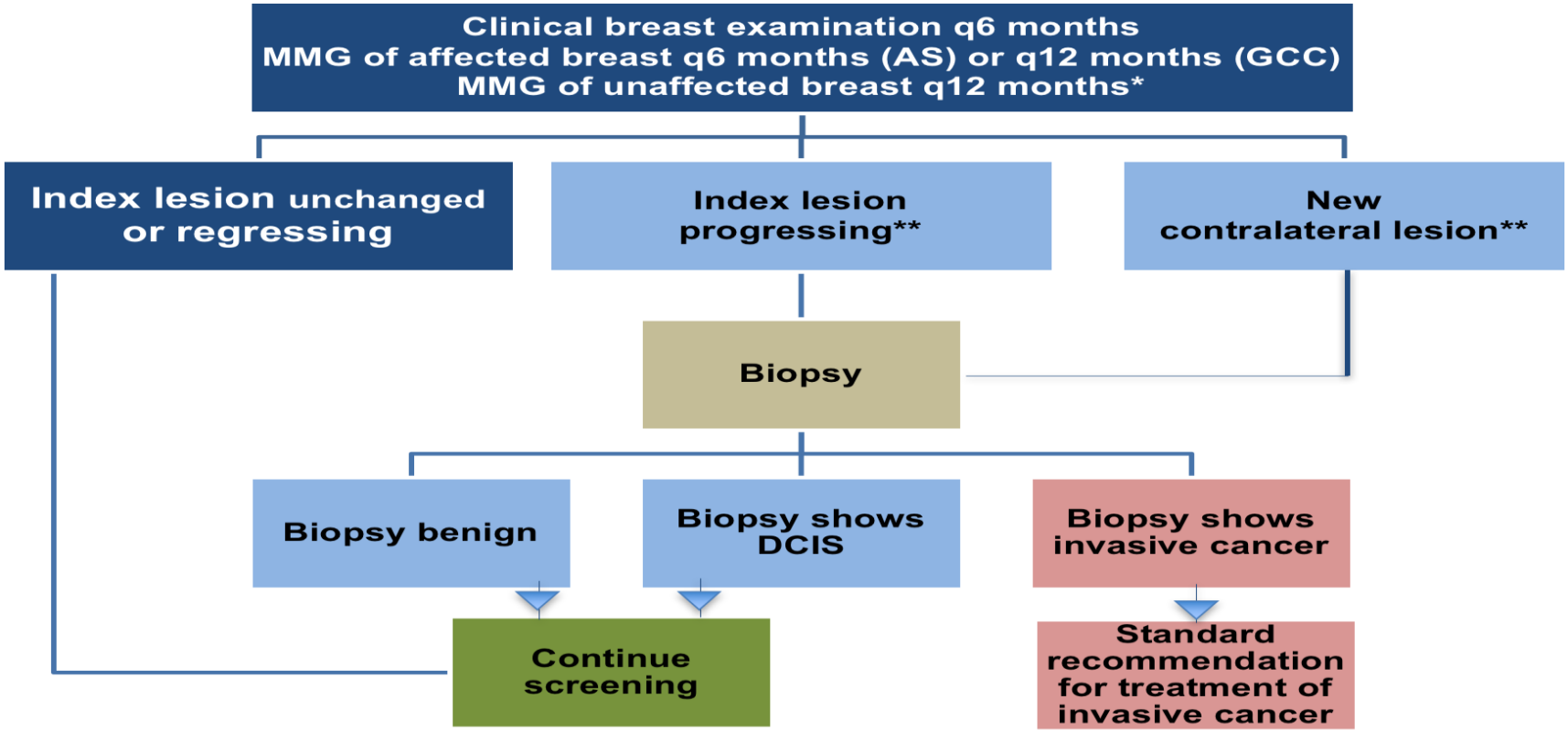
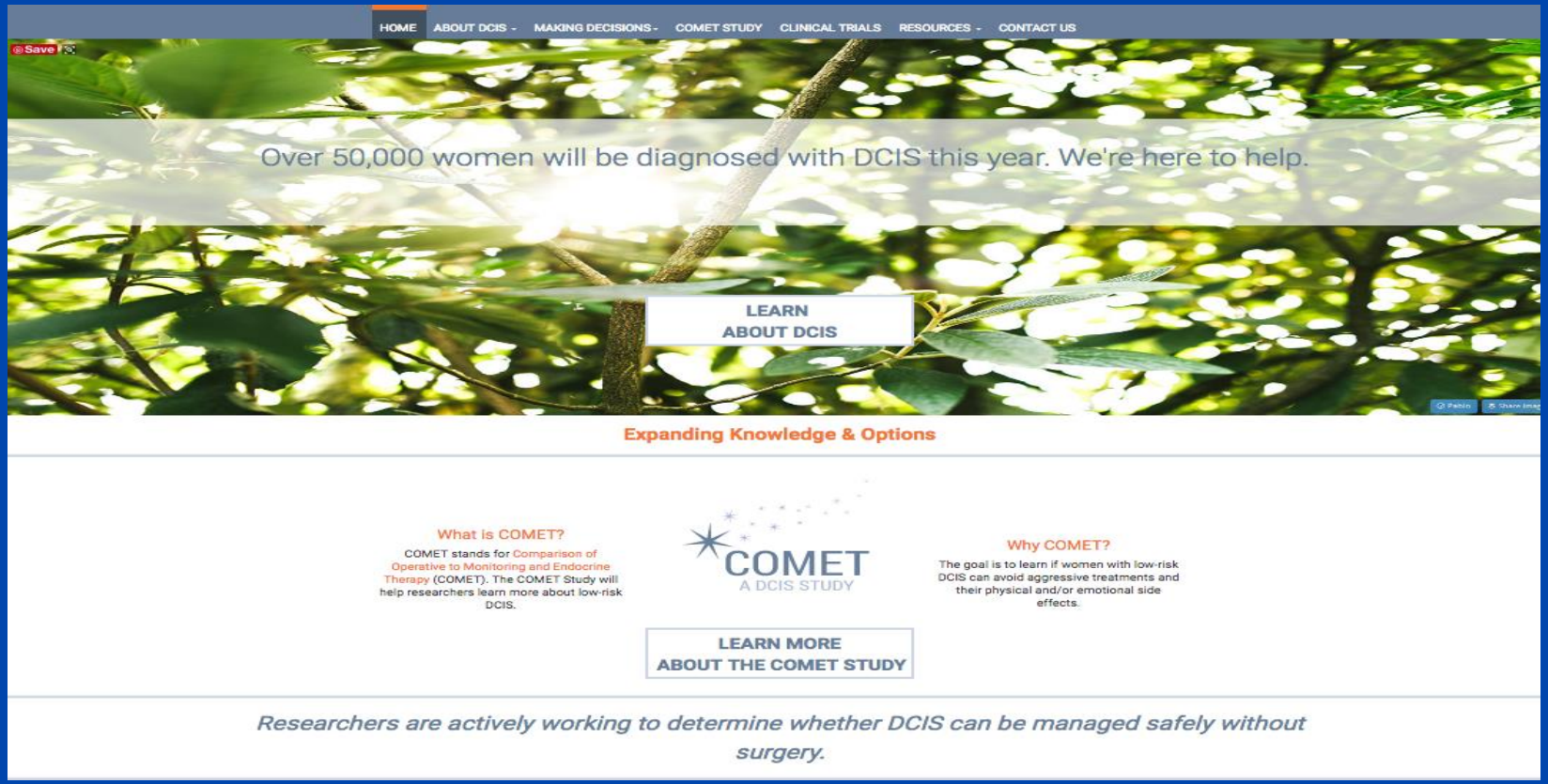
# COMET Trial for low-risk DCIS

## *Active Surveillance Protocol*



# COMET Website – DCISoptions.org



# DCIS language considerations

Using language to promote patient understanding of DCIS and COMET

**Aims:**

- *Reduce fear & confusion*
- *Encourage a sense of calm & agency*
- *Support positive patient experiences*

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# DCIS language: concepts

| Current concept | Suggested concept |
|---|---|
| DCIS as a single condition | Different kinds of DCIS have different levels of risk |
| DCIS as a well understood condition | DCIS is a condition that is not well understood, and many questions remain |
| Relative risk (for populations) | Absolute risk (how risk affects a person over a given period of time) |
| Lack of toxicity associated with standard of care treatment | Standard treatment has risks and complications (surgery, side effects, changes to look and feel of the breast) |
| Standard of care means you must be treated | Active Surveillance may be a choice for some, clinical trials will find out |
| Urgent, emergency, ticking time bomb | Not an emergency, take time to understand and make informed decisions |

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# COMET Trial for low-risk DCIS

**Case 1**

- ✓Ms. B, a 50 yo engineer, has been undergoing mammogram screening for 10 years.
- ✓On routine screening mammography last month, she was noted to have a new cluster of calcifications in the right breast measuring 1.5 cm in extent.
- ✓She undergoes a stereotactic core biopsy that shows G2 DCIS without invasion.
- ✓She is screened and meets eligibility criteria for COMET.

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# COMET Trial for low-risk DCIS

**Case 1**

- ✓DCIS is a noninvasive/preinvasive condition that without treatment, can lead to invasive cancer
- ✓It is unknown what proportion of women will develop cancer if DCIS is untreated
- ✓For women with DCIS that would not have progressed to invasive cancer, treatment carries morbidities without clear benefit
- ✓There is controversy over whether all DCIS should be treated

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# COMET Trial for low-risk DCIS

**Case 1**

- ✓For early stage prostate cancer, men are routinely offered “active surveillance” with treatment only if the prostate cancer progresses
- ✓The COMET study aims to do the same for DCIS and will randomize patients to active surveillance or usual care
- ✓There are 4 international trials including COMET that are trying to answer this question

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# COMET Trial for low-risk DCIS

**Case 1**

✓The patient has considered the data and has a very strong preference for active surveillance. She does not wish to have surgery and is worried about being randomized to the usual care arm



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# COMET Trial for low-risk DCIS

**Case 1**

- ✓The patient has considered the data and has a very strong preference for active surveillance. She does not wish to have surgery and is worried about being randomized to the usual care arm

- ✓***Would you offer her the COMET study?***

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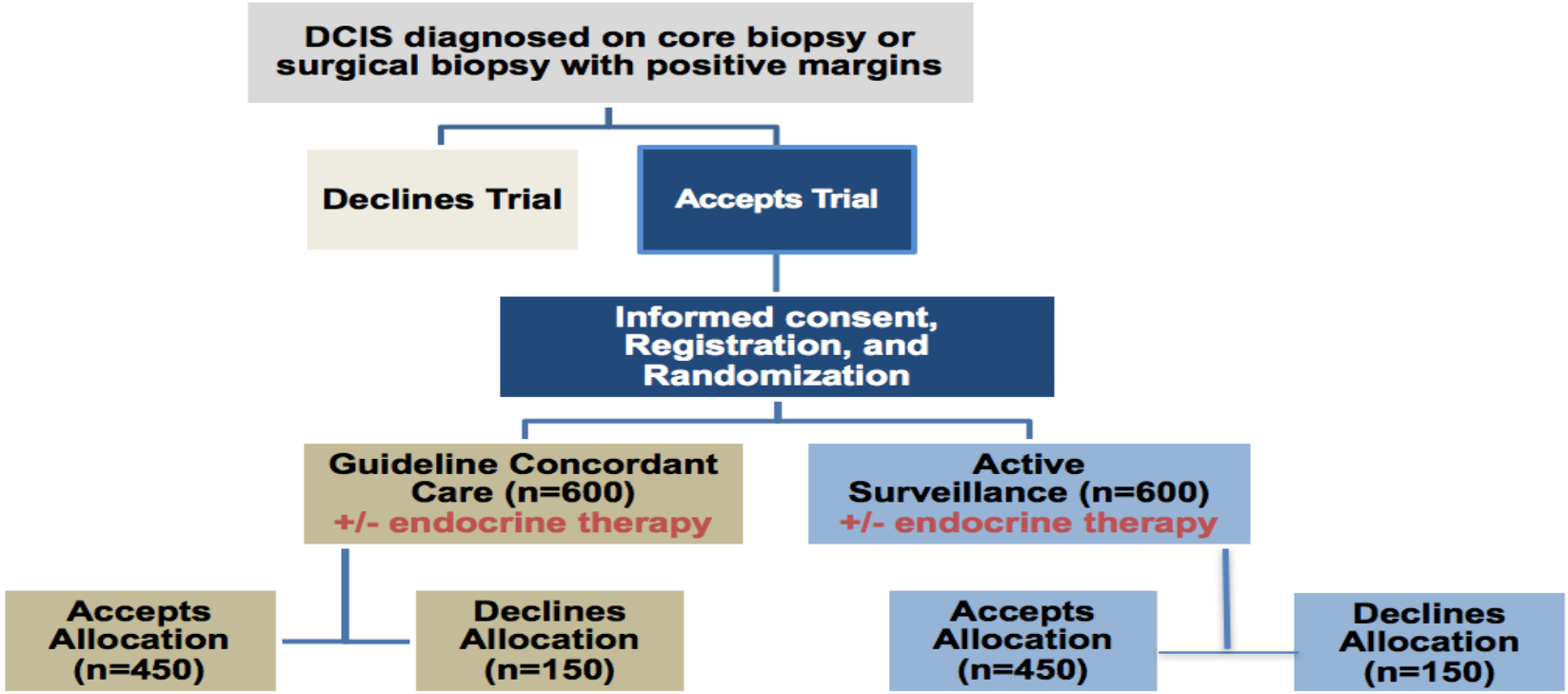
# Study Flow Diagram

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# COMET Trial for low-risk DCIS

**Case 1**

- ✓COMET is a **prospective randomized trial**
- ✓Patients may decline participation or may choose to discontinue the trial at any time
- ✓However, the LORIS study noted that up to one third of patients declined the study due to strong treatment preference
- ✓***ONLY IF the patient wishes to drop out of the study should she be approached to continue to follow for QOL and oncologic endpoints (registry component)***

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# COMET Trial for low-risk DCIS

**Case 2**

- ✓Mrs. E was informed by the radiologist who did her biopsy that she has cancer and needs to have surgery immediately
- ✓She has been screened and found to meet eligibility criteria for COMET with a third pathology review
- ✓You present the study to her; she asks:
- ✓***"Isn't it dangerous to have cancer and not remove it?"***

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# COMET Trial for low-risk DCIS

**Case 2**

- ✓Approximately 10% of women with low risk DCIS may have invasive cancer, even in the biopsy shows only DCIS (Grimm L, ASO 2017)
- ✓COMET will test whether it is necessary to operate on all women with low risk DCIS
- ✓It will also test whether outcomes are better or worse if we adopt a strategy to only operate on women who develop invasive cancer while on surveillance
- ✓***Patients can have surgery now, or may need it later if it develops into invasive cancer***

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# COMET Trial for low-risk DCIS

**Case 3**

- ✓Ms. T is a 67 year old lawyer with a new diagnosis of G1 DCIS
- ✓She has 4.3 cm of microcalcifications.
- ✓She meets all eligibility criteria for COMET

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# COMET Trial for low-risk DCIS

**Case 3**

- ✓Ms. T is a 67 year old lawyer with a new diagnosis of G1 DCIS
- ✓She has 4.3 cm of microcalcifications.
- ✓She meets all eligibility criteria for COMET

- ✓***This seems like a large DCIS; is the patient eligible for COMET?***

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# COMET Trial for low-risk DCIS

**Case 3**

- ✓Extent of calcifications has been associated with higher risk of upstaging to invasive cancer

- ✓***For any DCIS greater than 4 cm in extent, there must be CNB of at least 2 sites in the DCIS that fulfill pathology criteria***

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# COMET Trial for low-risk DCIS

**Case 3**

- ✓You perform a second biopsy which confirms that both sites are low grade DCIS without invasion
- ✓The patient enrolls on the study and is randomized to the active surveillance arm
- ✓You discuss the option of taking tamoxifen for 5 years, but the patient does not wish to take any drugs

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# COMET Trial for low-risk DCIS

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- ✓***Is endocrine therapy required for patients on the active surveillance arm?***

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# Adjuvant Tamoxifen for ER-positive DCIS: NSABP B-24

| | Placebo (n = 368) | | Tamoxifen (n = 364) | | | | |
|---|---|---|---|---|---|---|---|
| Type of BC | No. | % | No. | % | HR* | 95% CI | P† |
| ER positive | | | | | | | |
| Any | | | | | | | |
| BC | 84 | 31 | 58 | 20 | 0.58 | 0.415 to 0.81 | .0015 |
| IBC | 52 | 19 | 33 | 12 | 0.53 | 0.34 to 0.82 | .005 |
| DCIS | 32 | 12 | 25 | 9 | 0.66 | 0.39 to 1.12 | .12 |
| Ipsilateral | | | | | | | |
| BC | 47 | 17 | 39 | 14 | 0.68 | 0.44 to 1.03 | .07 |
| IBC | 26 | 9 | 20 | 7 | 0.61 | 0.34 to 1.09 | .10 |
| DCIS | 21 | 8 | 19 | 7 | 0.76 | 0.41 to 1.42 | .39 |
| Contralateral | | | | | | | |
| BC | 32 | 11 | 18 | 6 | 0.50 | 0.28 to 0.88 | .02 |
| IBC | 21 | 8 | 12 | 4 | 0.51 | 0.25 to 1.03 | .06 |
| DCIS | 11 | 4 | 6 | 2 | 0.47 | 0.17 to 1.27 | .14 |

Allred, DC et al, JCO 2012

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Allred, DC et al, JCO 2012

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# COMET Trial for low-risk DCIS

**Case 3**

- ✓NSABP B24 data indicate a potential benefit for adjuvant tamoxifen for DCIS
- ✓Only in patients with lumpectomy and radiation
- ✓Uncertain whether endocrine therapy will prevent invasive progression
- ✓Clear benefit in contralateral new cancers

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# COMET Trial for low-risk DCIS

**Case 3**

- ✓The patient declines tamoxifen.
- ✓She undergoes follow up mammography every 6 months according to COMET protocol

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# COMET Trial Criteria for Progression

1. New **mass***/architectural **distortion***/ **density*** on surveillance mammogram
2. Extent of suspicious **microcalcifications** - increased by 5mm in at least one dimension from previous mammogram
3. New **palpable** mass on clinical examination
4. New **suspicious** findings on other exams (US, MRI)

.

**ACR Breast Imaging Reporting and Data System (BI-RADS) for mammography in assessment of masses and calcifications. D'Orsi CJ, Sickles EA, Mendelson EB, et al. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology; 2013*

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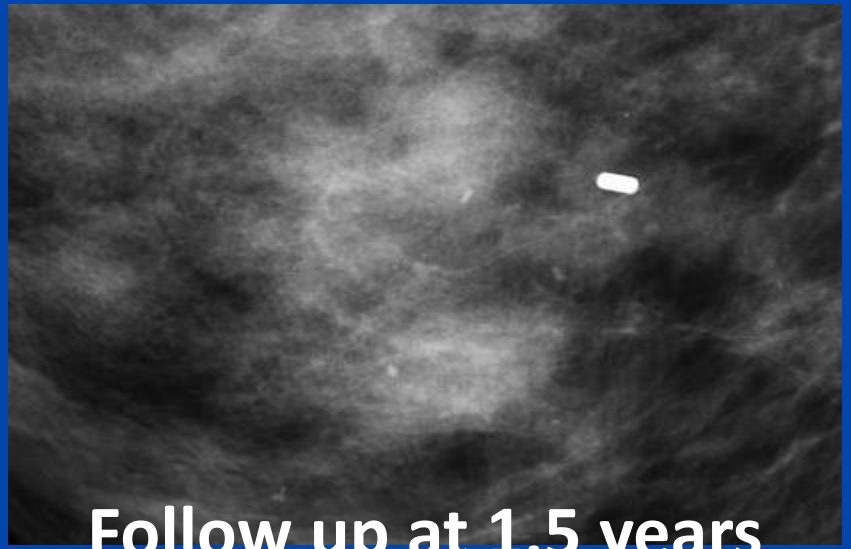
# Imaging Change, Increase in calcifications

**Initial Biopsy**



**Follow up at 1.5 years**

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# COMET Trial for low-risk DCIS

**Case 3**

- ✓A core biopsy is performed that shows a low grade invasive cancer.

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# COMET Trial for low-risk DCIS

**Case 3**

- ✓A core biopsy is performed that shows a low grade invasive cancer.

- ✓***The patient is on the active surveillance arm--is the patient allowed to have surgery?***

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# COMET Trial for low-risk DCIS

**Case 3**

- ✓A core biopsy is performed that shows a low grade invasive cancer.

- ✓***The patient is on the active surveillance arm--is the patient allowed to have surgery?***
- ✓***YES! If invasive cancer is detected during surveillance, it should be treated according to treatment guidelines and practice patterns at your institution***

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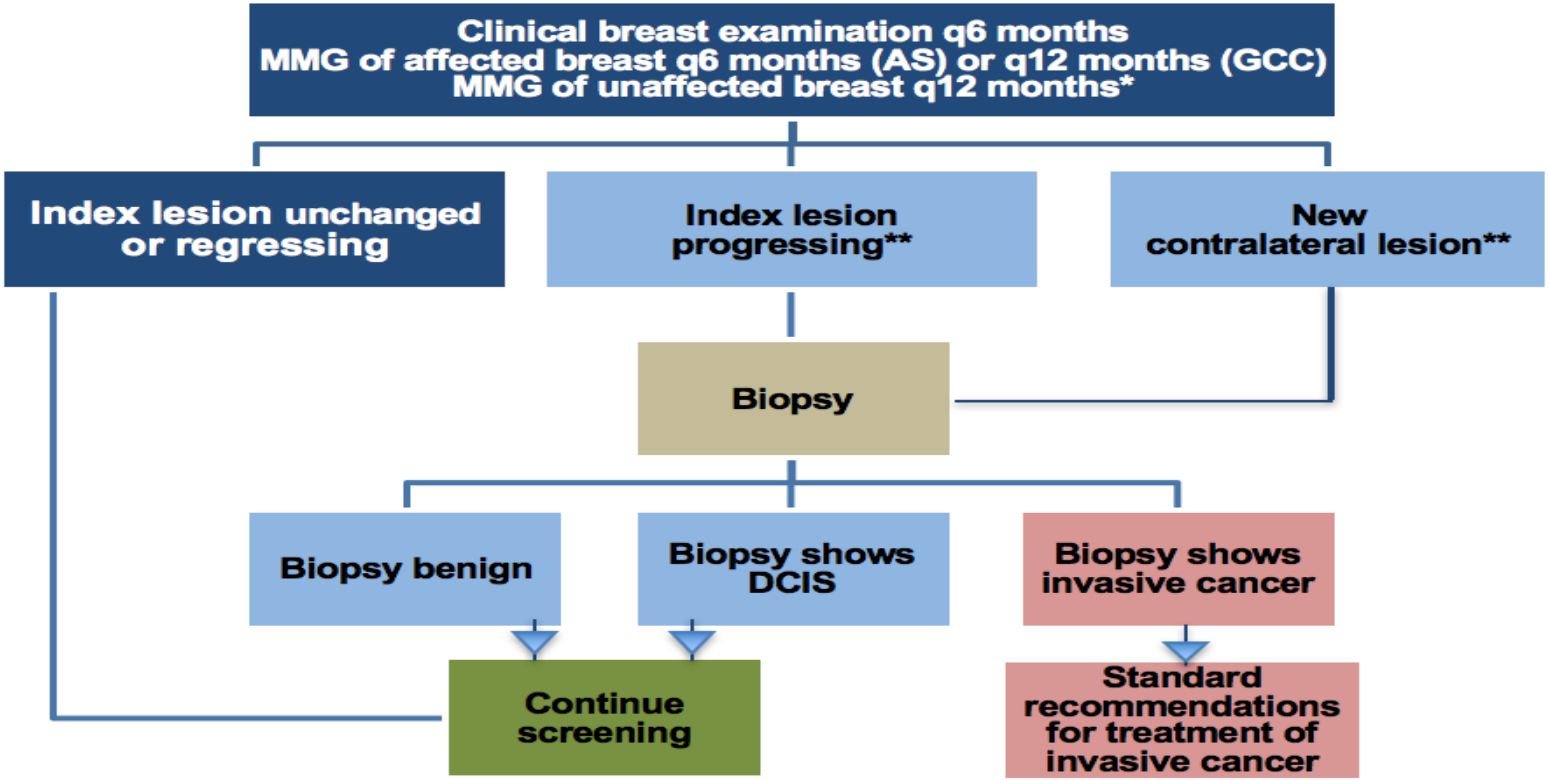
# Study Surveillance Protocol

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# Conclusions

- Most breast cancers occur in average risk women and can affect all women
- Mammogram screening reduces breast cancer mortality for women in their 40's and beyond
- Discuss risks, benefits and limitations
  - These limitations are generally not a barrier to screening
- Discuss treatment options for low and intermediate grade DCIS
  - Lumpectomy alone
  - Lumpectomy and radiation
  - Mastectomy
  - Observation every 6 month diagnostic mammogram
  - Anti-estrogen therapy x 5 years
    - Tamoxifen, raloxifene, aromatase inhibitors
  - Clinical trial- COMET study

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