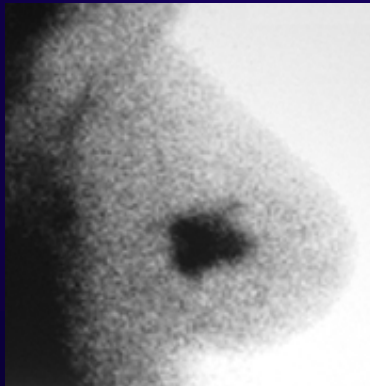
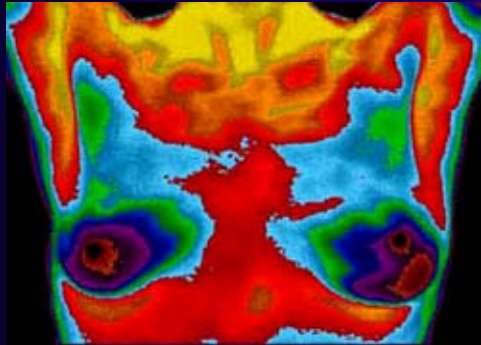
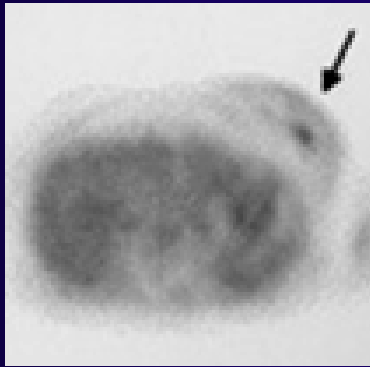
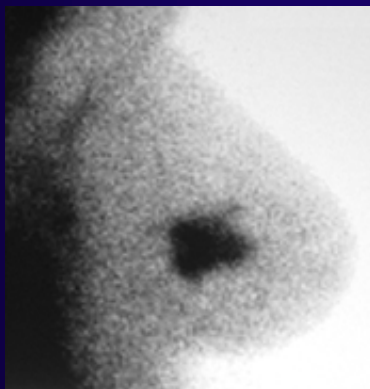
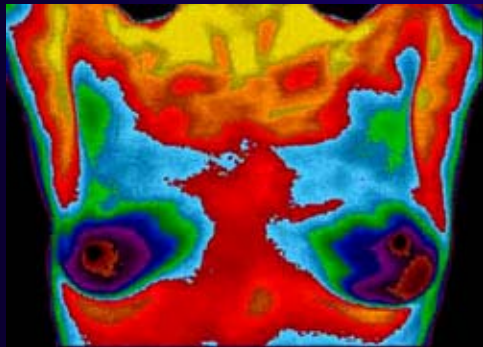
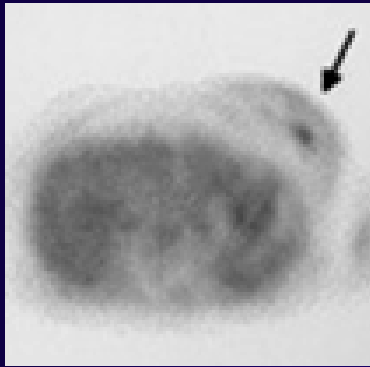


# Alternative Breast Imaging Techniques

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Edward A. Sickles, M.D.



This lecture was initially created by Dr. Lori Strachowski and has been updated, with her permission

# Breast Cancer

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- 192,000 new cases / year  
of invasive carcinoma
- 40,600 deaths / year
- Highly publicized and  
politicized disease

# “Conventional” Breast Imaging Modalities

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- Mammography
- Ultrasound
- MRI

# Anatomy vs. Physiology

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- Anatomy-based imaging depicts morphologic abnormalities
  - Cellular events → physical alterations → morphologic manifestations
- Contrast-enhanced imaging depicts perfusion abnormalities
  - Indirectly related to tumor neovascularity
- Physiology-based imaging depicts cellular abnormalities
  - Cellular events precede morphologic / vascular changes
  - Potentially provides earlier lesion detection
  - May more accurately characterize detected lesions
    - Benign vs. malignant
    - Viable tumor vs. fibrosis / necrosis

# Alternative Imaging Techniques

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- Scintimammography (sestamibi)
- Positron Emission Tomography / Mammography
- CT Scanning
- Thermography
- Electromagnetic Imaging Techniques
  - Electrical Impedance (EI) Scanning
  - Microwave Imaging (MI) Spectroscopy
  - Near Infrared (NIR) Spectroscopy

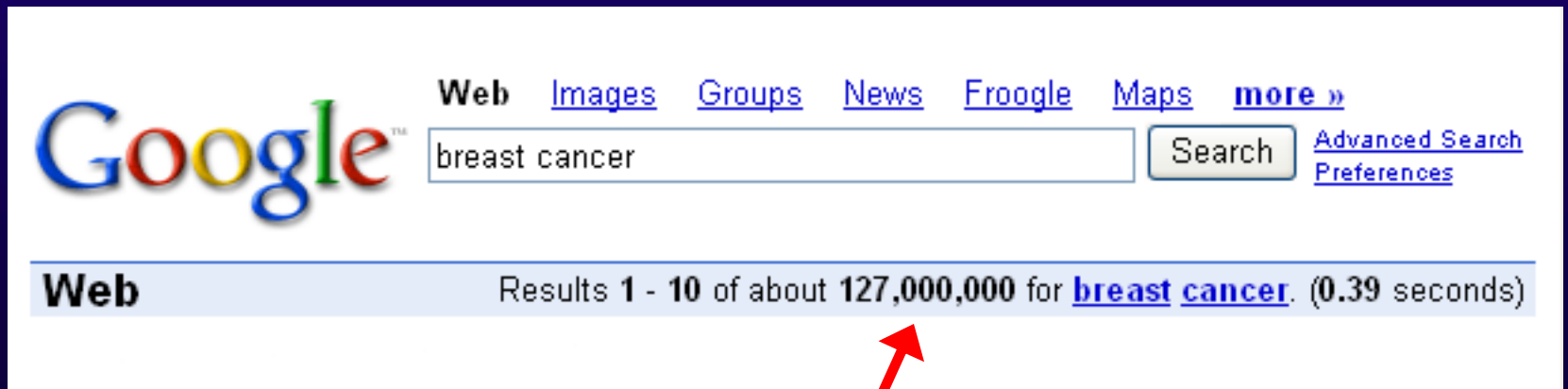
# Why Be Informed on Alternative Breast Imaging Techniques ?

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- Misinformation concerning breast cancer is widespread (e.g., lifetime breast cancer risk has been publicized as 1 in 8)
- Internet content is not “peer-reviewed”

# Why Be Informed on Alternative Breast Imaging Techniques ?

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The image shows a screenshot of a Google search interface. At the top left is the Google logo. To its right are navigation links: [Web](#), [Images](#), [Groups](#), [News](#), [Froogle](#), [Maps](#), and [more »](#). Below these is a search input field containing the text "breast cancer". To the right of the input field is a "Search" button. Further right are links for [Advanced Search](#) and [Preferences](#). Below the search bar, a blue horizontal bar displays the search results: "Web Results 1 - 10 of about 127,000,000 for [breast cancer](#). (0.39 seconds)". A red arrow points from the bottom center of the image towards the number "127,000,000" in the results bar.

# Scintimammography

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- Breast cancer uptake incidentally noted during Thallium-201 cardiac imaging
- Tc-99m sestamibi better for breast imaging; uptake in mitochondria of metabolically active cells
- Approved by FDA in 1997 as an adjunctive test for breast cancer diagnosis

# Scintimammography

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- Review of initial studies late 1990's, over 2000 patients
  - Average size: 2.5 cm
  - Two-thirds palpable
  - Only 40% to 60% accuracy for lesions  $< 1$  cm
  - Limiting factors
    - Spatial resolution
    - Tumor volume

# Scintimammography

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- Multicenter study, published 2000, 673 patients, 42 institutions
- All patients had tissue diagnosis (mammo / US / palpation), of which 40% were malignant

	Palpable	Nonpalpable
Sensitivity	87%	61%
Specificity	76%	87%
PPV	77%	70%
NPV	86%	82%

- Suggested possible use: mammographically indeterminate lesions that are > 1 cm, palpable, or in dense breasts

J Nucl Med 2000;41:1973-1979

# Scintimammography

---

- Multicenter study, published 2002, 558 patients, 42 institutions
- All patients had tissue diagnosis (mammo / US / palpation), of which 39% were malignant

	Fatty	Dense
Sensitivity	72%	70%
Specificity	80%	78%
PPV	72%	67%
NPV	81%	81%

- Diagnostic accuracy of scintimammographically is not affected by breast density

# Scintimammography: Recent Development

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- High-resolution breast-specific gamma camera
  - Improved spatial resolution
  - Images closer to the chest wall
  - Mimics standard mammographic views

# Scintimammography

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- High-resolution breast-specific gamma camera
- 40 patients: BI-RADS “5” at mammography
- No work-up with US or MRI for extent of breast disease
- Scintimammo interpretation not blinded to mammo findings
- 26 patients malignant (26 / 40 = 65%; 29 breasts, 35 lesions)
  - Overall scintimammo sensitivity: 91% (32 / 35 lesions)
  - Scintimammo sensitivity for lesions < 1 cm: 77% (7 / 9 lesions)
  - Scintimammo: 3 false negs (2 smallest cancers, 1 deep cancer)
- 14 benign (9 scintimam neg, 5 scintimam pos; specificity = 64%)

# Scintimammography

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- High-resolution breast-specific gamma camera (BSGI)
- 146 patients, 167 biopsied lesions (BSGI for various indications)
- 83 lesions malignant (67 invasive carcinoma, 16 DCIS)
- Median cancer size (if known): invasive 15 mm, DCIS 7 mm )
  - Sensitivity: 96% (80 / 83 cancers)
  - Specificity: 60% (50 / 84 benign lesions)
  - PPV: 70% (80 / 114 positive lesions)
  - NPV: 94% (50 / 53 negative lesions)
- 6 lesions positive at BSGI were occult at mammography / US

# Scintimammography Screening

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- 94 high-risk (Gail model) women with normal screening mammography and clinical breast examination
- High-resolution breast-specific gamma camera (BSGI)
- If positive: targeted US (diagnostic mammo not performed)
- If visible at US: US-guided biopsy
- Screening: 78 negative, 16 positive (17% recall rate)
  - 9 biopsies were benign (10% false-positive biopsy rate)
  - 2 biopsies were invasive ductal carcinoma (9 mm each)
  - 5 positives not visible at US had negative BSGI 6 mos later

# Scintimammography

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- Limitations
  - Still somewhat limited spatial resolution
  - Still insufficiently high negative predictive value to avert biopsy
  - Relatively high radiation dose
- Future
  - Larger, multicenter studies
  - Breast-specific tracers
  - Equipment to biopsy lesions positive only at scintimammography

# Positron Emission Tomography

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- Developed in 1970's;  
accepted for breast  
imaging in past 10 years
- Tracer: FDG (2-deoxy-2-  
[F18] fluoro-D-glucose), a  
glucose analogue that gets  
“trapped” in cells with  
glycolytic activity
- “Hot spots” indicate high  
metabolic activity

# PET: Technique

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- Preparation:
  - Low sugar diet 24 hrs
  - No food or drink for 4 hrs (except water)
- 10 mCi of FDG injected IV 45-60 min prior
- Patient supine
- Image acquisition: 30-75 min
- Radiation dose: 6 mSv (average dose equivalent)
- FDG half-life: 109 min

# Breast PET: Indications

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Center for Medicare & Medicaid Services (HCFA)

investigated breast PET for:

- Initial diagnosis as an adjunct to mammography
- Initial staging of axillary lymph nodes
- Whole-body staging and re-staging
- Evaluation of treatment response

# Breast PET: Indications

---

Effective 10/02, approved by CMS\* as an ADJUNCT imaging tool for:

- Staging and re-staging
  - Locoregional recurrence
  - Distant metastasis / recurrence
- Evaluation of treatment response
  - Local: neoadjuvant chemotherapy
  - Distant metastasis

\* Center for Medicare & Medicaid Services  
Published May 2002

# PET: Staging and Re-staging

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## Locoregional recurrence

- Local
  - Breast S/P lumpectomy
  - Chest wall S/P MRM
  - Differentiate scar vs. cancer recurrence

# PET: Locoregional Recurrence

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- Regional lymph nodes
  - Identify tumor in normal size nodes
  - Differentiate reactive from metastatic enlarged nodes
  - Better at mediastinal and internal mammary nodes than CT
    - 10/33 pts suspected of only local recurrence had unsuspected mediastinal or internal mammary disease

# PET: Staging and Re-staging

---

- Distant metastatic disease
  - Advantages over conventional imaging
    - Large FOV
    - Half-life: 2 hrs
    - Overall less radiation
  - Sensitivity: 85% - 93%
  - Specificity: 73% - 79%

# PET: Metastatic Disease

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- Whole-body PET vs. Conventional Imaging (defined as mammography, US, CT, MRI and bone scintigraphy - based on routine clinical management parameters)

Modality	CI	PET
Sensitivity	79%	93%
Specificity	68%	84%
NPV	59%	80%

# PET: Metastatic Disease

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- Caveat: PET has two low-sensitivity areas
  - Brain
    - High background FDG in cerebral gray matter
  - Bone
    - Bone scintigraphy more sensitive for osteoblastic lesions

# PET: Treatment Response

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- Locally advanced disease (neoadjuvant chemotherapy)
- Distant metastases (chemotherapy)
- Advantages of PET
  - If response, rapid decrease in glucose metabolism
  - Anatomic changes often lag
  - Earlier recognition of ineffective therapy allows more prompt change in treatment
- Limited supporting data
  - Lack of a better alternative

# Other Indications for Breast PET

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*Not* approved by CMS:

- Initial diagnosis as an adjunct to mammography
- Initial staging of axillary lymph nodes

# PET: Adjunct for Initial Dx

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- Meta-analysis of 13 studies: 606 pts with positive mammograms (BI-RADS 4 or 5)
- Sensitivity: 89%
- Specificity: 80%
- Major limitations of this evidence:
  - Small study sizes (mean, < 50 pts per study)
  - Large mean tumor sizes (2-4 cm)
  - High pre-test probability of malignancy

# PET: Adjunct for Initial Dx

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- Conclusion: insufficient literature on detecting lesions:
  - < 1.5 cm
  - with a lower probability of malignancy

c/o Jacqueline Brunetti, MD  
Columbia University

# PET: Initial Staging of Axilla

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5-year breast cancer survival rates

Stage 0	100%
Stage I	100%
Stage II a	92%
Stage II b	81%
Stage III a	61%
Stage III b	54%
Stage IV	20%

American College of Surgeons National Cancer Data Base

# Breast Cancer Staging: TNM

Stage 0	Non-invasive; DCIS	
Stage I	< 2 cm, N0, M0	
Stage II a	2 – 5 cm, N0, M0	
Stage II b	2 – 5 cm and/or ipsilateral axillary LN's OR > 5 cm, N0	M0
Stage III a	Any size + matted ipsilateral LN's OR > 5 cm + ipsilateral axillary LN's	M0
Stage III b	Any size with skin, chest wall +/- ipsilateral internal mammary nodes OR inflammatory carcinoma	M0
Stage IV	Metastasis	

# PET: Initial Staging of Axilla

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- Accurate LN staging has important prognostic implications
- Options:
  - Standard axillary lymph node dissection (ALND)
    - High associated morbidity
  - Limited ALND: “sentinel node” approach
  - PET: the most accurate *noninvasive* method

*Is PET good enough?*

# PET: Initial Staging of Axilla

---

- Meta-analysis: 4 studies, 203 pts
  - Sensitivity: 81% (40 – 93%)
  - Specificity: 95%
  - False-negative rate: 19%
- Conclusion: Surgical options remain the standard of care

# PET: Initial Staging of Axilla

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- Prospective multicenter study of axillary nodal staging (Johns Hopkins, U of Michigan, Duke): 360 pts
  - Sensitivity: 61%
  - Specificity: 80%
  - Positive Predictive Value: 62%
  - Negative Predictive Value: 79%
- Poor sensitivity for smaller and fewer nodal metastases
- Sensitivity for Invasive Lobular Ca: 25% (less FDG avid)

# PET Limitations: Cost

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- Scanner: \$1.9 million
- FDG: \$250 - \$800 (no difference with or without on-site cyclotron)
- Medicare reimburses \$2200 (average)
- Break-even volume
  - 700 scans per year
  - 2-3 scans per day

# PET Limitations: Other

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## Tumor size

- May miss 1/3 of invasive cancers < 1 cm

## Tumor type

- More likely to identify invasive ductal cancer and miss invasive lobular cancer and non-invasive cancer (DCIS)

# Breast PET: Indications

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CMS issued a final PET National Coverage Decision (NCD) on April 3, 2009, expanding coverage for diagnosis and initial staging to nearly all cancer types

- However, because no new evidence was submitted with respect to breast cancer, CMS did not include breast cancer among the expanded - coverage tumors

# Breast PET: Indications

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“CMS is not making any change to the current coverage policy for FDG PET in breast cancer. We continue to cover FDG PET imaging for the initial treatment strategy for male and female breast cancer only when used in staging distant metastasis. FDG PET imaging for diagnosis and initial staging of axillary nodes will remain noncovered.”

# PET Future: Dynamic imaging

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Univ. of Pennsylvania study, 54 patients, dual-time-point imaging with FDG suggests:

- Uptake in malignancies increases on second scan
- Decreasing or no change in uptake in normal breast tissue and benign lesions
- Threshold for malignancy based on SUV ( $\text{time}_1$ ,  $\text{time}_2$ )
- Sensitivity: 85%
- Specificity: 83%

# PET Future: ↑ Tracer Specificity

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New tumor-specific tracers are being investigated

- 16-[F-18]fluoro-17-estradiol (FES)
  - Estrogen receptor positive breast cancer
  - 75% of breast cancers are ER +
  - Promise in tailored therapy
- 3'-deoxy-3' [F-18]fluorothymidine (FLT)
  - Cancer with high proliferative activity
  - Dynamic acquisition analysis with FLT more predictive than FDG in evaluating tumor response to chemotherapy

# PET Future: ↑ Spatial Resolution

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- Positron Emission Mammography (PEM)
- 2 compression paddles each with detectors containing 1000 photodetecting crystals
- MLO and CC projections
- 10-minute acquisition
- Dynamic and 3D reconstructive technology

# Positron Emission Mammography

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- Suggests a promising role in assessment of multifocal and multicentric disease, and surgical margins
- Multicenter study, 44 patients
- 39/44 index lesions identified (sensitivity: 89%)
- 4 of 5 incidental cancers found (3 of which were not seen on any other imaging modality)
- 19 patients undergoing breast conservation, PEM predicted
  - Positive margins: 6 of 8 (75%)
  - Negative margins: 11 of 11 (100%)

# Positron Emission Mammography

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- Multicenter study, 77 patients, multiple readers
- Sensitivity: 90%
- Specificity: 86%
- Positive Predictive Value: 88%
- Negative Predictive Value: 88%
- 3 mammo-occult cancers (intermediate-grade DCIS)
- PEM more accurately assessed extent of tumor than either mammography or ultrasound

# PET/CT Imaging of Breast Cancer

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- Co-registration on PET and CT images allows combined functional and anatomic imaging using a single scanner.
- Combined PET/CT provides information that cannot be obtained with either PET or CT alone.

# PET/CT Imaging of Breast Cancer

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- PET scanning adds functional information that may be helpful in elucidating equivocal findings at CT.
- Additional anatomic information from CT may be helpful in elucidating subtle metabolic findings at PET
- PET/CT most helpful in detection of unsuspected distant metastases during a whole-body exam

# Breast PET/CT: Potential Clinical Uses

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- Assessment of distant metastatic disease
- Staging of local / regional disease to plan treatment
- Monitoring early response to neoadjuvant chemoRx
- Molecular probes for breast cancer

# Breast CT Scanning

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- Two prototype dedicated breast CT units were produced in the late 1970's and > 3000 patients were studied
- Coronal-plane scanning before and after IV injection of iodine
- Results showed contrast enhancement for most breast cancers, but image quality was limited and overall clinical results were mixed
- The prototype dedicated breast CT units were never commercially marketed nor sold
- More recently, experience with multi-detector whole-body CT (MDCT) has shown promising preliminary results in cancer detection and diagnosis (AJR 2003; 181:679-686. AJR 2008; 190:1644-1651.)

# Breast CT Scanning

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- Using a prototype unit, CT slices are obtained in the coronal plane, and re-formatted for display in other planes
- CT depicts (in cross-section) all types of mammographically visible lesions, including microcalcifications
- No breast compression; 17-second breath hold
- Same radiation dose as MLO/CC screening mammography
- May decrease screening recalls for summation artifact
- May increase cancers detected, if used with contrast enhancement
- May facilitate image-guided biopsy

# Breast CT: Pilot Clinical Studies

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- 69 women, abnormal mammography, pre-biopsy
- CT with no breast compression
- 17-second breath holding to reduce motion blur
- No contrast-enhancement imaging

# Breast CT: Pilot Clinical Studies

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- 4 of 69 exams excluded, poor CT image quality
  - 2 exams: motion blur
  - 2 exams: lesion not included in image field
- 58 of 65 (89%) mammography lesions visible at CT
  - 4 benign lesions not visible
  - 3 cancers not visible

# Breast CT: Pilot Clinical Studies

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- Subjective review of lesion visibility, comparing CT versus standard MLO / CC view mammograms
  - Overall, no difference in lesion visibility
  - Masses seen better at CT
  - Microcalcifications seen better at mammo
  - CT examination more comfortable

# Breast CT: Pilot Clinical Studies

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- Contrast-enhanced CT done after scout CT, using 100 ml Visipaque, 4 ml/sec, 45-140 sec delay
  - 24 cancers studied (all visible at CT)
  - All malignant calcification lesions enhanced
  - 11 benign lesions studied (no-to-minimal enhancement)

Lindfors K. Presented at SBI, April 2009.

# Breast CT: Potential Clinical Uses

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- Screening (high-risk, ?? average risk)
- Adjunct to (?? replacement for) diagnostic mammo
- Extent-of-disease assessment
- Imaging-guided biopsy / ablative procedures

# Breast CT: Current Limitations

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- Visualization of microcalcifications
- Visualization of the axillary tail
- Long interpretation time
- Bilateral contrast-enhanced scans

# Thermography

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- Introduced late 1950's
- Theory: tumor vascularity generates heat, detected at the skin surface via infrared imaging
- Popular in 1970's
- BCDDP involved 3 exams:
  - Clinical breast exam
  - Mammography
  - Thermography
- Results showed no additional efficacy for thermography

# Thermography: Technique

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No breast contact or compression,  
no radiation, no injection

## Preparation:

- 5 days prior: no sun exposure
- 24 hrs: no physical contact
- 4 hrs: no exercise
- 15 min: nude acclimation in cool room (64°F – 72°F)

## Examination:

- Digital acquisition: 15-20 min
- Cost: \$150-200

# Thermography

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- FDA approved in January 1982 as an adjunct to mammo
- Credentialing
  - International Academy of Clinical Thermologists
  - International Thermographic Society
  - American Academy of Thermography
  - American Association of Medical Infrared Imaging
- Recommended guidelines
  - Age 20: baseline (2 exams, 3 months apart)
  - Age 20 – 30: every 3 years
  - Age > 30: annually

# Thermography: Claims

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- BCDDP's negative results are "seriously flawed"
- Over 800 peer reviewed studies; over 300,000 women; follow-up for up to 12 years
- Sensitivity and specificity: 90%
- Increases mammographic sensitivity by 10% to 95%
- Detects cancer up to 10 years before any other procedure
- Adjunct to mammography: ↑ long term survival by up to 61%
- Highest known risk factor for future development of breast cancer (10 times greater than 1<sup>st</sup> degree relative)
- Persistent abnormal thermography exam: 22 times higher risk for future breast cancer

# Thermography

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- USC/Norris Cancer Center, multicenter trial, 4 years, 5 institutions, 875 BI-RADS 4 or 5 biopsied lesions, readers were given mammo images and findings

Sensitivity	97%
Specificity	14%
PPV	24%
NPV	95%

- Poorest results with lesions characterized as microcalcifications (NPV 99% if these 45% excluded)

# Thermography

---

- USC/Norris Cancer Center, multicenter trial, 4 years, 5 institutions, 875 BI-RADS 4 or 5 biopsied lesions, readers were given mammo images and findings

However, only 12% of all lesions were read as negative, and only 6.5% of all lesions were noncalcified and read as negative

- Poorest results with lesions characterized as microcalcifications (NPV 99% if these 45% excluded)

# Thermography: Future

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- Enjoys some popularity among advocacy groups
- Limitations:
  - Only a risk marker
  - FP-induced anxiety
  - Cannot precisely localize a malignancy
  - Not a substitute for mammography
- Large-scale studies underway ( 2 DOD grants)

# Thermography: Future

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- 22 “Qualified Centers” in 14 states
  - Arizona
  - California
  - Colorado
  - Illinois
  - Indiana
  - Kentucky
  - Louisiana
  - Michigan
  - Nebraska
  - Ohio
  - Pennsylvania
  - Texas
  - Virginia
  - Wisconsin

# Thermography: Future

---

- 22 “Qualified Centers” in 14 states

- Arizona
- California
- Colorado
- Illinois
- Indiana
- Kentucky
- Louisiana
- Michigan
- Nebraska
- Ohio
- Pennsylvania
- Texas
- Virginia
- Wisconsin

Only 3 of  
these Centers  
have an  
M.D. on staff

# Summary

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- Conventional breast imaging techniques remain the “gold standard”
- Alternative techniques are being developed and will continue to be developed; some may succeed but most will remain investigational
- The future likely will involve more and more of a multi-modality approach to breast imaging