Breast Cancer:
Re-examining current approaches in context of recent data

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December 4, 2016
Breast Cancer

• Most common cancer in women

• Estimated for 2016: 246,660 new cases of invasive breast cancer and 40,450 deaths in women (2600 new cases with 440 deaths in men)

• Estimated for 2016: 61,000 cases of *in situ* breast cancer (83% of which are DCIS) – *in situ* cancers represent >20% of all breast cancers in women

• *Lifetime* risk 1 in 8

*ACS Facts and Figures, Estimates for 2016*
Breast Cancer: an overview of current status*
(*National Cancer Act signed 1971)

SEER9 Incidence 1975-2011 & U.S. Mortality 1975-2010, All Races, Females. Rates are Age-Adjusted
Highlighting 3 topics:

- Screening, chemoprevention, and risk assessment
- Reducing treatment for many patients
- “Personalized medicine” and breast cancer
- Treatment update for *intrinsic subtypes*: recent progress, unmet challenges
Reducing “over-treatment”:

- Ductal carcinoma *in situ* (DCIS)
- (Reducing surgery for invasive breast cancer)
- Eliminating XRT for many women > age 65 (and possibly younger)
- (Hypofractionated XRT to shorten # of daily treatment visits)
- Avoiding adjuvant chemotherapy in more women with estrogen receptor (ER) + early breast cancer
Non-invasive Breast Cancer: Ductal carcinoma in-situ (DCIS)

- Usually presents as microcalcifications on mammogram with no palpable lesion
Non-invasive Breast Cancer: Ductal carcinoma in-situ (DCIS)

• Lesions confined to walls and lumens of ducts and lobules

• 25% of cases and proportion is increasing (30-40% of cancers detected by mammogram are DCIS)

• > 50,000 new U.S. cases of DCIS breast cancer projected for 2016 and increasing
Effect of 3 decades of screening mammography on breast cancer incidence

Figure 1. Use of Screening Mammography and Incidence of Stage-Specific Breast Cancer in the United States, 1976–2008.
Panel A shows the self-reported use of screening mammography and the incidence of stage-specific breast cancer among women 40 years of age or older. Panel B shows the incidence of stage-specific breast cancer among women who generally did not have exposure to screening mammography — those younger than 40 years of age.

Non-invasive Breast Cancer: Ductal carcinoma in-situ (DCIS)

- A pre-invasive malignancy with risk of progression to invasive cancer of at least 30% in that anatomic region of the duct system in earlier studies (* many of those patients had more advanced DCIS, detection by palpation vs. mammography)

- Traditional treatment has been simple mastectomy; excision with free margins + XRT an option; +/- tamoxifen for HR+ cases
Effect of tamoxifen for women with DCIS
Long-term results from the UK/ANZ DCIS trial
in women with locally excised DCIS

Jack Cuzick

I Sestak, SE Pinder, IO Ellis, S Forsyth, N Bundred, J Forbes, H Bishop, IS Fentiman, WD George

32nd San Antonio Breast Cancer Symposium
9 – 13 December 2009
Study design

Randomised 2x2 trial of radiotherapy, tamoxifen or both (elective decision to withhold or provide one treatment)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Tamoxifen</th>
<th>Radiotherapy</th>
<th>Tamoxifen &amp; Radiotherapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised</td>
<td>544</td>
<td>567</td>
<td>267</td>
<td>316</td>
<td>1694</td>
</tr>
<tr>
<td>Breast cancer event</td>
<td>119 (22%)</td>
<td>101 (18%)</td>
<td>22 (8%)</td>
<td>21 (6%)</td>
<td>263 (16%)</td>
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Tamoxifen randomisation – N = 1576
Radiotherapy randomisation - N = 1030

Median follow up – 12.7 years
## Study design

Randomised 2x2 trial of radiotherapy, tamoxifen or both (elective decision to withhold or provide one treatment)

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Tamoxifen randomisation – N = 1576
Radiotherapy randomisation - N = 1030

Median follow up – 12.7 years
The Dilemma

Once we diagnose DCIS, how do we separate “bad” from “good” lesions, i.e. those that will progress to invasive cancer and pose a risk to the patient (and therefore warrant treatment) from those that will not?
A multigene expression assay to predict local recurrence risk for DCIS

A multigene expression assay to predict local recurrence risk for DCIS

<table>
<thead>
<tr>
<th>DCIS Score group</th>
<th>No.</th>
<th>10-Year risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>44</td>
<td>25.9% (14.8% to 43.1%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>53</td>
<td>26.7% (16.2% to 41.9%)</td>
</tr>
<tr>
<td>Low</td>
<td>230</td>
<td>10.6% (6.9% to 16.2%)</td>
</tr>
</tbody>
</table>

Log rank $P = .006$

Rethinking what constitutes adequate margins for invasive breast tumor excision
Optimal Margin Width?

- No definitive data as to what constitutes “adequate” margin and no consensus employed in practice

- 20-30% of patients undergoing lumpectomy for invasive breast cancer undergo reexcision.
  - Half of re-excisions carried out to widen negative but “close” margins
  - Some require oncoplastic procedure

- In meta-analysis of 14,571 patients from 21 prospective trials, RR of local recurrence (LR) is 2.42 (p < .001) if margin is positive but no statistical difference in LR between 1, 2 and 5 mm width when controlled for XRT boost and endocrine therapy

# Trials Comparing Lumpectomy + XRT to Mastectomy:
## Overall Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>#</th>
<th>Stages</th>
<th>Follow Up Yrs</th>
<th>OS: Mastx</th>
<th>OS: Lumpx + XRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-06</td>
<td>1851</td>
<td>1-2</td>
<td>21</td>
<td>47%</td>
<td>46% (NS)</td>
</tr>
<tr>
<td>EORTC</td>
<td>868</td>
<td>1-2</td>
<td>22</td>
<td>45%</td>
<td>39% (NS)</td>
</tr>
<tr>
<td>Danish COOP</td>
<td>731</td>
<td>1-3</td>
<td>20</td>
<td>58%</td>
<td>51% (NS)</td>
</tr>
<tr>
<td>Milan</td>
<td>701</td>
<td>1</td>
<td>20</td>
<td>58%</td>
<td>59% (NS)</td>
</tr>
<tr>
<td>NCI</td>
<td>237</td>
<td>1-2</td>
<td>26</td>
<td>44%</td>
<td>38% (NS)</td>
</tr>
<tr>
<td>Arriagada</td>
<td>179</td>
<td>1</td>
<td>22</td>
<td>52%</td>
<td>60% (NS)</td>
</tr>
<tr>
<td>EBCTCG meta-analysis</td>
<td>4891</td>
<td>1-2</td>
<td>10</td>
<td>71%</td>
<td>71% (NS)</td>
</tr>
</tbody>
</table>
Invasive breast cancer in women ≥ age 70 65
### RT/tamoxifen vs. tamoxifen alone after lumpectomy in women >70 with ER+ breast cancer

<table>
<thead>
<tr>
<th></th>
<th>TamRT (n= 317) (10yr)</th>
<th>Tam (n=319) (10 yr)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast tumor recurrence</td>
<td>6 (2%)</td>
<td>27 (9%)</td>
<td>.0001</td>
</tr>
<tr>
<td>Ultimate mastx</td>
<td>4 (2%)</td>
<td>10 (4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Second primary</td>
<td>36 (12%)</td>
<td>33 (9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Distant mets</td>
<td>21 (5%)</td>
<td>16 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Death</td>
<td>157 (50%)</td>
<td>156 (49%)</td>
<td>NS</td>
</tr>
<tr>
<td>from other causes</td>
<td>145</td>
<td>148</td>
<td>NS</td>
</tr>
<tr>
<td>from breast cancer</td>
<td>12</td>
<td>8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Prime Trial

- Age > 65
- T < 3cm, ER+, - nodes, margins > 1 mm
- Adjuvant endocrine therapy
- Exclusions: Grade 3, + LVI, prior breast cancer

- Median f/u = 5 years
- 658 received WBI, 668 no WBI

- Local recurrence 1.3% with WBI vs. 4.1% without WBI
- Distance recurrence 1% each arm
- OS 94% both arms

Presented SABCS 12/13
Radiation therapy for early breast cancer: faster

- Canadian study, 1224 cases treated with standard XRT (50Gy in 25 sessions over 5 weeks) vs. hypofractionated (42.5Gy in 16 sessions over 22 days)

- 10 year local invasive cancer recurrence rate 6.2% in hypofractionated vs. 6.7% in standard group

- Cosmesis good or excellent in 69.8% hypofractionated group vs. 71.3% in standard group

Reducing use of adjuvant chemotherapy

- Approximately 2/3 of all breast cancers are hormone receptor positive.
- Which patients receiving endocrine therapy also need chemotherapy?
Community-Based Use of Chemotherapy and Hormonal Therapy for Early-Stage Breast Cancer: 1987-2000

<table>
<thead>
<tr>
<th>Age</th>
<th>Chemotherapy Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>~25%</td>
</tr>
<tr>
<td>&lt; 50 years</td>
<td>~75%</td>
</tr>
<tr>
<td>50-69 years</td>
<td>~30%</td>
</tr>
<tr>
<td>70+ years</td>
<td>~5%</td>
</tr>
</tbody>
</table>

Adjuvant chemotherapy use in the year 2000 for women with early-stage ER-positive breast cancer tumors >1 cm and negative nodes (SEER* data)

*Surveillance Epidemiology and End Results Data Base of NCI
J Clin Oncol 2006; 24: 872-877
**Oncotype DX™ 21-Gene RS Assay**

16 Cancer and 5 Reference Genes From 3 Studies

**Proliferation**
- Ki-67
- STK15
- Survivin
- Cyclin B1
- MYBL2

**Estrogen**
- ER
- PR
- Bcl2
- SCUBE2

**Invasion**
- Stromelysin 3
- Cathepsin L2

**HER2**
- GRB7
- HER2

**Reference**
- b-Actin
- GAPDH
- RPLPO
- GUS
- TFRC

RS = + 0.47 x HER2 group score
- 0.34 x estrogen group score
+ 1.04 x proliferation group score
+ 0.10 x invasion group score
+ 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

<table>
<thead>
<tr>
<th>Category</th>
<th>RS (0 - 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>&lt;18</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>18 - 31</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt;31</td>
</tr>
</tbody>
</table>

Oncotype DX® Clinical Validation:
RS as Continuous Predictor

Distant Recurrence at 10 Years

Low-Risk Group  Intermediate-Risk Group  High-Risk Group

Recurrence Score

COPYRIGHT
Standardized Quantitative Oncotype DX Assay

Recurrence Score in N-, ER+ patients

- **Lower RS**
  - Lower likelihood of recurrence
  - Greater magnitude of TAM benefit
  - Minimal, if any, chemotherapy benefit

- **Higher RS**
  - Greater likelihood of recurrence
  - Lower magnitude of TAM benefit
  - Clear chemotherapy benefit

Intergroup - PACCT trial

Node Negative ER+

Oncotype DX Assay

RS < 11
Hormone Therapy

RS 11-25
Randomize
Hormone Rx
vs
Chemotherapy
+ Hormone Rx

RS > 25
Chemotherapy
+ Hormone Rx

TAILORx: Can molecular profiling identify a subgroup of patients for whom chemotherapy can be avoided?
First Result from PACCT (TAILORRx) trial

- For those with recurrence scores (RS) of 0-10 who received only antiestrogen therapy as per protocol design:

  5 year recurrence-free survival just reported as 99%
Molecular Profiling in Breast Cancer

- Human genome project technology now widely applied in oncology
- Allows gene expression profiling of individual tumors
Before 1977

Breast Cancer
1980’s

Breast Cancer

ER+ Breast Cancer

ER- Breast Cancer
1990’s

Breast Cancer

ER+ Breast Cancer

HER2+

ER- Breast Cancer

HER2+

HER2-
2000

Breast Cancer

ER+ Breast Cancer

ER- Breast Cancer

HER2+

HER2-
Distinct subtypes of triple negative breast cancer by gene expression profiling

Triple-negative breast cancer which represents ≈ 20% of total cases is a highly diverse group of cancers, and subtyping is necessary to better identify molecular-based therapies.

Basaloid 1 (BL1)
Basaloid 2 (BL2)
Luminal Androgen Receptor (LAR)
Mesenchymal (M)
Mesenchymal Stem-like (M-SL)
Immunomodulatory (IM)

“3N”

Lehmann BD. J Clin Invest 2011; 121: 2750-2767
Implications of “personalized” care

• Implications on size and difficulty of trials—cost of studying so many subtypes?

• Implications for drug development as specific market gets smaller and smaller—costs, incentives?
Therapy Summary for 2016

ER+ breast cancer

• Longer duration of therapy may be better, but... for all or which patients? (MA.17, ATLAS, aTTom, MA.17R)
Half of Recurrences and 2/3 of Breast Cancer Deaths Occur After Completing 5 Years of Tamoxifen

Risk of late events ≠ need for extended duration of therapy

- Risk of late events *does not necessarily* indicate the need for/ benefit from extended duration of therapy
- Carry over benefit demonstrated for both 5 years of tamoxifen and 5 years of aromatase inhibitor
MA.17: Trial Design

Primary end point: DFS
Secondary end points: OS/safety/QOL

Randomization (All patients disease-free)

Tamoxifen

~5 years adjuvant

Letrozole 2.5 mg qd*

0 – 3 months

Placebo qd†

5 years extended adjuvant

* n=2575 (efficacy); 2154 (safety) in the letrozole arm.
† n=2582 (efficacy); 2145 (safety) in the placebo

### MA.17: DFS

<table>
<thead>
<tr>
<th></th>
<th>Letrozole (n=2582)</th>
<th>Placebo (n=2586)</th>
<th>Abs. Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated 4-y DFS (total population)</td>
<td>94.7</td>
<td>89.8</td>
<td>4.8%</td>
</tr>
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</table>

\( P=0.00004 \)

10 yrs vs 5 yrs breast cancer mortality in ER+ rate ratio* by period in aTTom and ATLAS

<table>
<thead>
<tr>
<th></th>
<th>10 yrs tam. vs 5: aTTom trial (n=6934 ER+/UK)</th>
<th>10 yrs tam. vs 5: ATLAS trial* (n=10,543 ER+/UK)</th>
<th>10 yrs tam. vs 5: aTTom &amp; ATLAS combined (n=17,477 ER+/UK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>years 5-9</td>
<td><strong>1.08</strong> (0.85-1.38)</td>
<td><strong>0.92</strong> (0.77-1.09)</td>
<td><strong>0.97</strong> (0.84-1.15)</td>
</tr>
<tr>
<td>years 10+</td>
<td><strong>0.75†</strong> (0.63-0.90)</td>
<td><strong>0.75 †</strong> (0.63-0.90)</td>
<td><strong>0.75†</strong> (0.65-0.86)</td>
</tr>
<tr>
<td>All years</td>
<td><strong>0.88‡</strong> (0.74-1.03)</td>
<td><strong>0.83‡</strong> (0.73-0.94)</td>
<td><strong>0.85‡</strong> (0.77-0.94)</td>
</tr>
</tbody>
</table>

|                  | †p=0.007                                       | †p=0.1                                          | †p=0.00004                                               |
|                  | §p=0.002                                       | ‡p=0.004                                        | ‡p=0.001                                                |

*Inverse−variance−weighted estimate of the effect in ER+.

### ER+ 10 yrs vs 5 yrs overall survival rate ratio* by period in aTTom and ATLAS

<table>
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<th>10 yrs tam. vs 5: aTTom &amp; ATLAS combined (n=17477 ER+/UK)</th>
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<tr>
<td>years 5-9</td>
<td>0.99 (0.89-1.10)</td>
</tr>
<tr>
<td>years 10+</td>
<td>0.84† (0.77-0.93)</td>
</tr>
<tr>
<td>All years</td>
<td>0.91‡ (0.84-0.97)</td>
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*Inverse–variance–weighted estimate of the effect in ER+

†p=0.0007
‡p=0.008

Duration of AI Therapy
NCIC CTG MA.17R: 10 vs 5 Years of Adjuvant AI

Stratify prior tamoxifen
yes or no

3-5 yr

5 yr

0-2 yr

5 yr

TAM

ANY AI

PLAC

LET

2yTAM

5yTAM

5y Al

5y Al

5y Al

5y Al

COPYRIGHT
Extending Aromatase-Inhibitor adjuvant therapy to 10 years (MA 17R)

• 1918 women enrolled
• Median follow up 6.3 years

• 5 year DFS 95% with letrozole (95% CI 93-96%) vs. 91% with placebo (95% CI 89-93%).
• HR 0.66 (p=0.01) for distant recurrence or contralateral breast cancer
• Approximately half of benefit in DFS was contralateral cancer reduction, half distant recurrence reduction
• No difference OS

• More joint pain and bone loss (including new osteoporosis) in letrozole group
• No overall difference in quality of life subscales

Therapy Summary for 2016

ER+ breast cancer

• Longer duration of therapy may be better, but for *all* or *which patients?* (MA.17, ATLAS, aTTom, MA.17R)

• Value of AI extended to premenopausal (with OFS) *but which patients?* (some, all?)
## 5 year results of SOFT/TEXT

<table>
<thead>
<tr>
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<th>TAM + OFS</th>
<th>EXE + OFS</th>
<th>TAM alone</th>
</tr>
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<tbody>
<tr>
<td>DFS</td>
<td>87.3%</td>
<td>91.1% *</td>
<td>84.7%</td>
</tr>
<tr>
<td>FFBC</td>
<td>88.8</td>
<td>92.8</td>
<td></td>
</tr>
<tr>
<td>FFBC at DS</td>
<td>92.0</td>
<td>93.8</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>96.9</td>
<td>95.9</td>
<td></td>
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* = primary endpoint, HR 0.72, 95% CI 0.60-0.85, p < 0.001) (disease-recurrence, second invasive cancer or death)


Absolute Benefit of Endocrine Therapy for premenopausal women in the TEXT and SOFT trials

- Overall approximate 5% benefit in breast cancer free interval (BCFI) for exemestane + OFS vs. tamoxifen + OFS or tamoxifen alone in these trials (4891 patients)

- A continuous composite measure of recurrence risk including age, nodal status, tumor size and grade, ER, PR and Ki67 expression levels was calculated for each patient.

Absolute Benefit of Endocrine Therapy for premenopausal women in the TEXT and SOFT trials

- In the intermediate to high composite risk patients in SOFT, the absolute benefit in BCFI for exemestane + OFS was up to 10-15%; the benefit of tamoxifen + OFS vs. tamoxifen was seen only in the highest risk group

- For TEXT, the benefits of exemestane + OFS vs. tamoxifen + OFS in BCFI ranged from 5 to 15%

- Patients who did not receive chemotherapy and had the lowest composite risks did well with all endocrine therapies in both trials

Managing Antiestrogen Therapy in 2016

• Both Intensity (for premenopausal women) and Duration of therapy will likely be adjusted based individual risk

• Models for assessing this are being developed.
### MA.17 DFS and Nodal Status

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</tr>
<tr>
<td>(total population)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-y DFS/Node −ve</td>
<td>96.3</td>
<td>93.6</td>
<td>2.7%</td>
<td></td>
</tr>
<tr>
<td>4-y DFS/Node +ve</td>
<td>92.3</td>
<td>84.8</td>
<td>7.5%</td>
<td></td>
</tr>
</tbody>
</table>

NNT = 37 to prevent one recurrence

NNT = 13

Therapy Summary for 2016

ER+ breast cancer

• Longer duration of therapy may be better, but... for all or which patients? (MA.17, ATLAS, aTTom, MA.17R)

• Value of AI extended to premenopausal (with OFS) but which patients? (some, all?)

• Adherence an issue
Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients.

- Prescribed adjuvant tamoxifen or aromatase inhibitor
- 49% took full duration and optimal schedule
- At year 4.5, 32% off therapy; of those still on therapy, 72% were fully adherent
- Highest discontinuation rate in women < age 40 (HR =1.51, 95% CI, 1.23-1.85)

Therapy Summary for 2016

ER+ breast cancer
- Longer duration of therapy may be better, but… for all or which patients? (MA.17, ATLAS, aTTom; MA.17R)
- Value of AI extended to premenopausal (with OFS) but which patients? (some, all?)
- Adherence an issue

HER2+ breast cancer
- 10 year relapse-free survival > 75% for early disease
- BUT major issues remain:
  - What level of amplification is “actionable”?
  - What are the therapeutic implications of HER2+ heterogeneity in bx
  - Many new agents, e.g. pertuzumab, TDM-1 but roles uncertain with conflicting data from small trials
  - CNS recurrence is common, an unsolved problem
Therapy Summary for 2016

3N breast cancer
• The major challenge
• No robust target as yet

• Current interest high in targeting PD-1 and PDL-1 to unleash host immune response
Follow-up After Primary Therapy

- Most recurrences found by patients, not by physicians or tests
- Routine films, scans, tumor markers not indicated in asymptomatic patients
- Annual mammography important
- Suggest interval history and physical exam every 3-6 months initially, extending interval over time

Overall 10-Year Kaplan-Meier Survival Curves for 1243 Breast Cancer Patients Randomized to Intensive Diagnosis or Routine Clinical Follow-up
“Doctor, What can I do?”

Supplements and lifestyle modification: impact on outcome in early breast cancer
Dietary and life style modifications which may decrease recurrence risk in breast cancer survivors

- Weight loss (even small amounts)\(^1,2\)
- Dietary Fat restriction\(^1,2\)
- Limit alcohol consumption (\(?\)\(^4,5\)
- Moderate (or more) exercise vs. sedentary\(^3\)
- Daily aspirin (\(?\)\(^6\)

\(^1\) J Clin Oncol 2005; 23: 3s  
\(^2\) J Clin Oncol 2005: 23: 1370-78  
\(^3\) JAMA 2005; 293: 2479-86  
\(^4\) Kwan ML. J Clin Oncol 2010; 28: 4410-16.  
\(^6\) Holmes MD. J Clin Oncol 2010; 28:1467-1472
Breast Cancer Checklist for the Primary Care Practitioner

For women without breast cancer

• Understand individual risk determinants

• Record and periodically update FH for breast and ovarian cancers (as well as other malignancies), at least two prior generations on maternal and paternal side of pedigree
  – Refer to Genetic Counseling as indicated

• Discuss prevention if risk perceived as high

• Review USPSTF mammography recommendations

• Life style counseling: weight, exercise, alcohol intake
Breast Cancer Checklist for the Primary Care Practitioner

For women with newly diagnosed breast cancer

• No systemic imaging needed for stages 1 or 2

• Record intrinsic subtype (ER+, HER2/neu+, Triple negative)

• Plan for primary treatment (breast conservation vs. mastectomy +/- XRT)

• Plan for adjuvant treatment (endocrine therapy, chemotherapy, both or none, HER2 targeting if indicated, clinical trial participation?)
Breast Cancer Checklist for the Primary Care Practitioner

Follow up for breast cancer survivors

• Hx and PE every 3-6 months initially

• Annual breast imaging

• Gynecology follow up

• Lifestyle counseling