In today’s breast cancer treatment paradigm, most systemic therapy is prescribed and delivered by medical oncologists with surgeons taking the forefront in operative interventions and minimally invasive approaches to biopsy or extirpation of tumors. Very early in the treatment of breast cancer, surgeons were instrumental in the development of endocrine therapy. Oophorectomy for the treatment of premenopausal patients with advanced breast cancer was first reported in 1896. In the 1950s and 60s, surgeons also performed adrenalectomies to assist with the management of metastatic breast cancer. Today, the science of endocrine therapy has evolved, and oral targeted therapies have been developed. As surgeons are integral in the management of breast cancer and are often the first to evaluate and educate patients on their disease, a broad knowledge of current endocrine therapy approaches is necessary. Understanding indications for endocrine therapy and being comfortable with prescribing and managing adverse events of endocrine therapy allows many more patients to be offered neoadjuvant endocrine approaches and/or to be managed in their community if medical oncology is not readily available locally. This resource guide reviews the salient points of indications for chemotherapy and endocrine therapy, as well as prescribing and managing side effects of endocrine therapy.
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Treatment of hormone receptor-positive (HR+) breast cancer with endocrine therapy is the current standard of care. Most patients with HR+ breast cancer will receive a course of endocrine therapy, usually for 5 years and in some cases for as long as 10 years. Some of these patients will also be treated with chemotherapy. With the inception of adjuvant systemic therapy for breast cancer, the decision for administration of chemotherapy was based predominantly on tumor size and lymph node involvement, and risk estimation often using Adjuvant! Online®. More recently, management of systemic therapy has evolved, and tumor biology is a key determinant in this decision making. Approximated tumor biology is derived from the estrogen receptor, progesterone receptor status and HER2 status of the tumor. Additionally, many institutions also report on Ki-67, which is a proliferation index measure with high proliferation rates (Ki-67 >15-20%) typically being associated with more aggressive behavior. This information gives us some hint as to the biology and possible behavior of the tumor. Understanding molecular breast cancer subtypes is foundational for accurately assessing clinical risk.

- Luminal A – ER strongly positive, PR strongly positive, HER2 negative, Ki-67 low to intermediate
- Luminal B – ER positive, PR negative or positive, HER2 negative, Ki-67 intermediate to high
- HER2 enriched – Either ER+ or ER- and HER2 amplified
- Basal type – Triple negative (ER negative, PR negative, HER2 negative)

Currently, in managing hormone receptor-positive (HR+) invasive breast cancer, genomic tumor assays are often employed to assist in decision making regarding the benefit of systemic chemotherapy being added to endocrine therapy. National Comprehensive Cancer Network (NCCN) guidelines recommend consideration of genomic testing in patients with HR+ tumors 1 cm or larger who are healthy enough to undergo chemotherapy, if indicated. Patients with T1b lesions (5-9mm) should have genomic assay considered if there are associated unfavorable features such a poor histologic grade or lymphovascular invasion. Patients with low-risk tumor signatures can be spared the exposure to cytotoxic chemotherapy and its long-term consequences. This section will review the most commonly used genomic tests for HR+ breast cancer, indications for testing, and interpretation of test results.

Appropriate use of genomic testing by the breast surgeon can reduce unnecessary treatment delays, help individualize patient treatment, and reduce unnecessary morbidity (by avoiding chemotherapy use in low-risk patients). Genomic studies can be ordered on the core biopsy or the surgical specimen. Although there were concerns for concordance between core biopsy and surgical specimen in the past, more recent studies have shown excellent alignment, with greater than 94% correlation of the core biopsy with the surgical specimen testing on prognostic studies. The core biopsy specimen is accurate and necessary for neoadjuvant approaches to therapy. However, test submissions using the surgical specimen
instead of the core biopsy in patients not being considered for neoadjuvant therapy is currently the most common practice standard.

We will review the following genomic tests in this resource guide (there are additional genomic panels available so this list is by no means exhaustive): Oncotype DX, MammaPrint, EndoPredict, as well as Breast Cancer Index (BCI).

**Oncotype DX**

Oncotype DX is a 21-gene assay developed by Genomic Health to determine the potential benefit of chemotherapy added to endocrine therapy in patients with HR+ HER2- breast cancer. It is both predictive and prognostic. It has been validated and can be applied in node negative or in patients with involved nodes. The Oncotype DX recurrence score (RS) generated ranges from 0–100, and risk categories initially established were low risk (<18), intermediate risk (18-35), and high risk (>35). The TAILORx trial provided Level 1 evidence that validates Oncotype DX in node negative patients. The cutoff points for low risk, intermediate risk, and high risk were different in the TAILORx [Trial Assigning Individualized Options for Treatment (Rx)] and were Low (0–10), Intermediate (11–25), and High (>25).

The results of TAILORx showed that the majority of patients with HR+, HER2-, node-negative breast cancer do not have inferior outcomes when they receive endocrine therapy, and do not receive chemotherapy. Specifically, this study showed that:

1. Women age >50 with a recurrence score of 0-25 had no benefit from chemotherapy
2. Women age >50 with a recurrence score of 26-100 did benefit from chemotherapy
3. Women aged <50 with a recurrence score of 0-16 had no benefit from chemotherapy
4. Women aged <50 with a recurrence score of 16-25 had some benefit from chemotherapy (approx. 1.6% for RS 16-20 and 6.5% for RS 21-25)
5. Women aged <50 with a recurrence score of 26-100 did benefit from chemotherapy

Review of node-positive patients in the SEER database as well as SWOG 8814 showed that the RS was predictive of distant recurrence in patients treated with endocrine therapy alone. Those with a score of <18 had an excellent outcome.

Currently, based on available data, the majority of women younger than age 50 years, with positive nodes and a RS over 18 should be recommended for systemic chemotherapy.

**MammaPrint**

MammaPrint® was first described in 2006. It is a 70-gene DNA assay developed by Agendia (Irvine, CA). MammaPrint is a binary assay, with tumors assigned as low or high risk. MammaPrint has been validated as a prognostic assay in the adjuvant setting for breast cancer therapy, with low-risk tumors having a better prognosis and survival compared to high-risk tumors and it is also as a predictive biomarker. The MINDACT (Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy) trial
showed that patients with HR+, HER2- breast cancer who were deemed high risk for recurrence according to traditional clinicopathologic characteristics (as determined through use of Adjuvant! Online®) but had a low MammaPrint score could safely be spared chemotherapy. This data is valid in patients with node-negative disease and also in node-positive disease (with 1-3 positive lymph nodes) and is assigned as Level one evidence. In patients with HR+, HER2-, node-negative breast cancer, the MammaPrint assay may be used in those with high clinical risk to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit. Women in the low clinical risk category did not benefit from chemotherapy regardless of genomic MammaPrint risk group; therefore, the MammaPrint assay is not recommended for these patients. Patients with high-risk clinical picture but low-risk MammaPrint only have a 1-2% benefit from the addition of chemotherapy and can be managed with endocrine therapy alone. MammaPrint low risk does not vary by age. Women younger than age 50 years including those with 1-3 positive nodes with low risk MammaPrint did not derive benefit from chemotherapy.4

EndoPredict

The EndoPredict Test® (Myriad Genetics, Salt Lake City, Utah) combines EndoPredict – an mRNA-based assay that uses RT-PCR and the patient’s tumor size and nodal status to assign patients with early-stage HR+, HER2- breast cancer a score that reflects likelihood of distant recurrence within 10-15 years of diagnosis, benefit from chemotherapy and risk of late recurrence. Understanding the risk of a late recurrence can inform decisions for prolonged endocrine therapy. This particular assay is interesting because it combines genomic evaluation with clinical information of the patient to assign risk. Patients with a score of <3.3 are at low risk for recurrence, and those with a score of ≥3.3 are at high risk for recurrence.5 This genomic test would be preferably used in the adjuvant setting as it is impacted by knowing the nodal status. NCCN supports EndoPredict as Level 2a evidence for patients with both node negative and 1 to 3 positive nodes.

Breast Cancer Index

The Breast Cancer Index (BCI) as developed by Biotheranostics Inc., San Diego, CA. The BCI is a combination of two diagnostic tests – the 2-gene, HoxB13/IL17BR ratio index (HI), as well as the Molecular Grade Index, a real-time RT-PCR, 5-gene microarray assay. The BCI has been retrospectively validated to predict the likelihood of late (5-10 years after treatment) recurrence, as well as the likelihood of benefit from a 10-year course of adjuvant endocrine therapy in women with early-stage, lymph node-negative, estrogen receptor-positive (ER+) breast cancer.6

BCI may be useful to determine the risk of late relapse (proven prognostic value), as well as the possible predicted benefit of endocrine therapy and the category of evidence is noted as 2A.
Surgeons and Genomic Testing

Breast surgeons should be familiar with and comfortable interpreting these assays.

There are inherent advantages to having the surgeon identify the appropriate patient for genomic testing. For example, the time to reach a decision about the administration of systemic chemotherapy can be much shorter when the surgeon orders the test than when it is ordered by the medical oncologist at the patient’s first postoperative visit.

Gene expression profiling in ER+/HER2- Invasive Breast Cancer:

- OncotypeDx 21 genes CLIA Prognostic Node neg, PredictiveChemotherapy benefit, Level 1 evidence, For node + prognostic Level 2A evidence.
- MammaPrint 70 genes FDA Prognostic for node neg and 1-3 node + Level 1 evidence.
- EndoPredict 12 genes CLIA Prognostic Node neg and 1-3 node + Level 2A evidence.
- Breast Cancer Index 7 genes Prognostic node neg Level 2A evidence.
Section 2 – Endocrine Therapy for the Treatment of Hormone Receptor-Positive Breast Cancer

Section 2A – Classes of Drugs Oncotype DX

Selective Estrogen Receptor Modulators (SERMS)

This class of drugs act as an estrogen agonist or antagonist depending on the target tissue. These drugs vary in their agonist versus antagonist properties on the breast, uterus, bone, liver, and cardiovascular system. Many of these drugs were actually developed for the management of osteoporosis. Although there are numerous drugs in this category, the drug most commonly used for the treatment of breast cancer is tamoxifen. Tamoxifen is effective in both pre- and postmenopausal women for HR+ breast cancer and is also effective in the management of HR+ breast cancer in men. For breast cancer chemoprevention, both tamoxifen and raloxifene are used.

- Tamoxifen – 20 mg/day (breast cancer treatment and also prevention, side effects include uterine cancer and thromboembolic events)
- Raloxifene – 60 mg/day (breast cancer prevention, uterine events less common than with tamoxifen)

Aromatase Inhibitors (AIs)

In postmenopausal women, the majority of estrogen production comes from adipose tissue, muscle and breast tissue, as well as the adrenal glands. Aromatase is the enzyme that participates in the last step in conversion of androgens into estrogen. Blockage of this step results in lowering estrogen levels, and has been shown to be beneficial in the treatment of breast cancer. These drugs are approved in the treatment of postmenopausal women only. If they are used in premenopausal women there must be concomitant ovarian suppression given. There are two categories of aromatase inhibitors (AIs): 1) non-steroidal AIs (anastrozole and letrozole), which bind reversibly to the aromatase enzyme, and 2) steroidal AIs (exemestane) which are androgen substrate analogues and bind irreversibly to the aromatase enzyme.

- Anastrozole (Arimidex) – 1 mg/daily
- Letrozole (Femara) – 2.5 mg/daily
- Exemestane (Aromasin) – 25 mg daily

Selective Estrogen Down Regulators (SERDS)

Currently, the only SERD available for clinical use is fulvestrant, which is an antiestrogen. It binds to the estrogen receptor and degrades it. The action is dose dependent. It was initially used in metastatic HR+ breast cancer for patients who developed resistance to tamoxifen or to AI therapy. It has very low oral availability so is administered as a monthly injection. Studies have shown effectiveness at 250 mg dose, but the best results were associated with higher dosing. The current recommended dose is 500 mg given monthly. This is given as a
divided dose - 250 mg (5 ml) in each buttock, which is a significant volume as intramuscular injection. Use of fulvestrant is recommended for patients with metastatic breast cancer who progress on aromatase inhibitors or who have compliance issues with daily oral medication. Some early studies do suggest that fulvestrant may have better long-term disease control over anastrozole.8,9

Fulvestrant is currently being evaluated as neoadjuvant endocrine therapy in operable breast cancer in the Alternate clinical trial.

**Section 2B – Neoadjuvant Endocrine Therapy**

Adoption of neoadjuvant endocrine therapy (NET) in the United States has been slow, but its use is slowly increasing. Numerous studies have shown an excellent response rate in postmenopausal women with large strongly HR+ breast cancer, with downstaging from mastectomy to lumpectomy in more than 50% in some series. Indications for NET include postmenopausal patients with large strongly HR+ tumors to allow downstaging in hopes of breast conservation and patients for whom in vivo observation of tumor response will inform decision for chemotherapy. In this patient subset, response to NET and measurement of preoperative endocrine prognostic index (PEPI) score can guide decision making regarding need for adjuvant chemotherapy. NET is an emerging practice in HR+ breast cancer. Note that there is limited data on the use of NET in premenopausal women, and it should only be done in the setting of a clinical study or under extenuating circumstances where access to standard of care may be delayed.

**Clinical Management of Patients Treated with Neoadjuvant Endocrine Therapy**

Once therapy is started, the patient should be monitored for response. Ideally, the shortest treatment course should be 3 months and treatment with neoadjuvant endocrine therapy is usually for 3-6 months. The tumor’s response should be assessed by clinical examination, and ultrasound evaluation of tumor size (or other imaging) can be performed periodically and at any time when there is clinical concern for tumor growth.

When using NET to assess tumor endocrine responsiveness and guide decision making regarding use of chemotherapy, repeat assessment with core biopsy and measurement of Ki-67 should be performed after 1 month on therapy. Ideally, for confirmation of adequate response to NET the Ki-67 should fall to 10% or less.10 If there is not a fall in Ki-67 noted in the core biopsy, then treatment should be adjusted to either conversion to neoadjuvant chemotherapy or proceeding with surgical intervention. If there is clearly response to NET documented by Ki-67, the therapy is continued for 3-6 months, and occasionally up to 1 year if patients are showing continued response. If the goal is downstaging for breast conservation, then 6 months or more of treatment may be preferable.

NET achieves high response rates (20-76% across all studies). Aromatase inhibitors achieve higher rates of breast-conserving surgery compared to tamoxifen11, 12 (Table 1).
Table 1. Randomized clinical trials evaluation of endocrine agents in the neoadjuvant setting

<table>
<thead>
<tr>
<th>Trials profile</th>
<th>Study population</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td><strong>Trial</strong></td>
<td><strong>Treatment arm (n)</strong></td>
<td><strong>Phase</strong></td>
</tr>
<tr>
<td>P024(1)</td>
<td>A: Letrozole (162) B: Tamoxifen (175)</td>
<td>IIb–III</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMPACT(2)</td>
<td>A: Anastrozole (113) B: Tamoxifen (108) C: Tamoxifen + anastrozole (109)</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROACT(3)</td>
<td>A: Anastrozole (228) B: Tamoxifen (223)</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Russian trial(4)</td>
<td>A: Exemestane (76) B: Tamoxifen (75)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAGE(5)</td>
<td>A: Anastrozole + goserelin (98) B: Tamoxifen + goserelin (98)</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACOSOG Z1031(6)</td>
<td>A: Exemestane (124) B: Letrozole (128) C: Anastrozole (125)</td>
<td>II</td>
</tr>
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BC – breast cancer; BCS – breast conservative surgery downstaging; ER – estrogen receptor; HR – hormonal receptor; OR – objective response rate; PgR – progesterone receptor; NA – not available.

* In improved feasible surgery in hormone therapy only group (n = 314).
*α None were BCS candidates at baseline; 14% deemed inoperable.
*β Pretreatment surgical assessment available for 220 patients–96 eligible for BCS.
*γ 386 of the patients either required a mastectomy or were deemed inoperable at baseline.
*∞ Among candidates for mastectomy only at presentation.

Adapted from Barroso-Sousa et al(13)
Pathological response: NET is unlikely to result in pCR; however, the goal is to achieve a PEPI score of 0, which is prognostic for excellent outcomes following NET. PEPI Score is measured after 3 months of neoadjuvant endocrine therapy. Patients who downstage to a T1/2 tumor with negative nodes and a Ki-67 of less than 10% obtain a PEPI score of 0-1, which is associated with excellent outcomes with endocrine therapy alone.


Although there is inconsistency between institutions in the measurement of Ki-67, repeat measurement within a single institution should yield accurate comparison for assessing response to therapy.

- Achieving Ki-67 <10% at 2-4 weeks of therapy is predictive of achieving PEPI score of 0
- Achieving Ki-67 <10% at 2-4 weeks of therapy with preoperative aromatase inhibitor therapy is prognostic of good outcomes
- Patients with Ki-67 <10% at diagnosis are extremely unlikely to increase their Ki-67 while on NET

Optimal duration of NET not clearly defined, but responses may take longer than chemotherapy. Most studies have evaluated 3-6 months of treatment. Maximal responses may take up to 1 year. Of note, downstaging occurred more often at 6 months over 3 months duration of treatment. Note that there is limited data on the use of NET in premenopausal women.14

Section 2C – Adjuvant Therapy for the Management of Hormone Receptor-Positive Invasive Breast Cancer

Endocrine therapy is the most commonly used treatment for breast cancer. It is an effective adjuvant and neoadjuvant therapy for patients with estrogen- and/or progesterone-positive invasive breast cancer, although use in the neoadjuvant therapy setting remains uncommon and only investigational for patients with ductal carcinoma in situ (DCIS). There are several choices of drugs that may be used and the selection for an individual patient may be influenced by comorbid conditions such as history of thromboembolism or osteoporosis. It may also be directed by concerns for side effect profile.

Selective Estrogen Receptor Modulators (SERMS) may be considered in any patient with estrogen and/or progesterone positive invasive or noninvasive breast cancer. In contrast, aromatase inhibitors are prescribed primarily for postmenopausal patients. Aromatase inhibitors may be considered for premenopausal patients only if ovarian suppression is delivered concurrently. Multiple clinical trials have confirmed improved outcomes with aromatase inhibitors as compared to SERMS. Both categories of endocrine therapy improve local, regional, and distant disease-free survival. Neither are considered the primary treatment of local or regional disease. The decision tree for the selection of endocrine therapy is well defined and predicated on extensive clinical trial data.
Prior to starting adjuvant endocrine therapy for HR+ breast cancer, appropriate tumor evaluation should be performed to ensure that the patient will not benefit from systemic chemotherapy. If systemic chemotherapy is needed, then endocrine therapy should start after completion of chemotherapy. Endocrine therapy may be started after radiation, or during radiation therapy for patients with higher risk disease after multidisciplinary discussion. In making a decision on the type and length of endocrine therapy, we consider patients in four groups as listed below.

**Premenopausal – Low Risk**

This group is best treated with tamoxifen. The recommend length of therapy is 5 years.

- **Dose:** 20 mg PO once daily
- **Most common adverse events:** Hot flashes, joint pain, mood and sleep disruption.
- **Precautions:** history of clotting disorder

**Premenopausal – High Risk**

This group of patients should receive adjuvant tamoxifen therapy with a planned course of 5 years. In high-risk patients, consideration for continuing therapy to 10 years may be appropriate with a switch to an aromatase inhibitor over the course of therapy. A word of caution on managing women who were premenopausal prior to the start of chemotherapy and stop menstruating post-chemotherapy. These patients should be treated with tamoxifen until it is clear that they will not resume ovarian function. Aromatase inhibitors are not effective if ovarian function resumes. It may take up to 2 years to be certain that a patient is truly menopausal. This may be ascertained with laboratory studies (luteinizing hormone, follicle-stimulating hormone, and estradiol).

This group of patients may also benefit from ovarian suppression in addition to tamoxifen. Two trials, SOFT (Suppression of Ovarian Function Trial) and TEXT (Tamoxifen and Exemestane Trial), showed a benefit in disease-free survival in high-risk, HR+ patients with ovarian suppression over tamoxifen alone. At 8 years, disease-free survival was 79% with tamoxifen alone, 83% with tamoxifen plus ovarian suppression, and 85% with exemestane plus ovarian suppression. The overall survival at 8 years was similar at 91% (tamoxifen), 93% (tamoxifen plus ovarian suppression), and 92% (exemestane plus ovarian suppression). Side effects were more frequent with the use of ovarian suppression. These side effects were mainly musculoskeletal, osteoporosis, and vaginal dryness/dyspareunia. The incidence of grade 3 side effects was 25% with tamoxifen alone, 31% tamoxifen plus ovarian suppression, and 32% exemestane plus ovarian suppression.

**Postmenopausal – Low Risk**

Patients with low-risk, HR+ breast cancer who are postmenopausal are usually managed with an aromatase inhibitor. In patients with significant osteoporosis, there may be consideration of tamoxifen to help maintain bone health. The sequential use of tamoxifen (for 2 years) followed by an aromatase inhibitor (for 3 years) is also an option.
• Drugs: Anastrozole, Letrozole, Exemestane or Tamoxifen
• Indication: postmenopausal women only
• Dosing: Anastrozole (1 mg PO daily), Letrozole (2.5 mg PO daily), Exemestane (25 mg PO daily), tamoxifen (20 mg PO daily)
• Most common adverse events: Joint pain, osteopenia/osteoporosis, mood and sleep disruptions
• Check bone density (DEXA) before starting

Postmenopausal – High Risk

This group of patients should be treated with aromatase inhibitor therapy with a planned course of 5 to 10 years. For those experiencing side effects, switching to another aromatase inhibitor may improve side effects. This group of patients should also be offered bone directed therapy with bisphosphonates. The length of bone directed therapy is predicated on following their DEXA scan (T score) and may continue after aromatase inhibitor therapy is stopped if they have significant osteopenia.

Bone Directed Therapy - Studies have shown that patients who entered natural menopause, those on ovarian suppression or chemotherapy induced menopause benefited from therapy with zoledronic acid or clodronate. These benefits were reduced bone recurrence and improved overall survival. Per American Society of Clinical Oncology (ASCO), these patients should be offered zoledronic acid 4 gm IV every 6 months for 3-5 years or clodronate 1600 mg daily for 2-3 years.

Length of Adjuvant Therapy

The standard recommendation for adjuvant endocrine therapy is for 5 years. There are indications for shorter as well as longer duration of therapy. The landmark study looking at the length of tamoxifen therapy was done by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) and is a meta-analysis of 55 trials encompassing 30,000 patients. The findings were 1 year of tamoxifen reduced recurrence by 21%, 2 years by 29%, and 5 years by 47%. There was a reduction in mortality by 12%, 17%, and 26%, respectively. This is where the initial recommendation for 5 years of tamoxifen came from.16

Over time, the question of extending therapy beyond 5 years was raised. NSABP B-14 looked at this question and found that adding an additional 5 years of tamoxifen to complete 10 years improved disease-free survival from 86% to 92%. However, overall survival for longer tamoxifen therapy was only 96% compared to 94% for 5 years (p=0.08) so 5 years was felt to be adequate. This is true for many patients although it became clear that there are some patients who do benefit from longer duration therapy. Several studies looking at the use of aromatase inhibitors beyond 5 years of initial endocrine therapy have been performed. Some include starting with tamoxifen with conversion after 2 or 3 years over to an aromatase inhibitor. There is an advantage to receiving an aromatase inhibitor in postmenopausal patients. A meta-analysis was performed of many of the aromatase inhibitors beyond 5 years studies. It showed that there is benefit for subgroups that would fall into high risk with positive nodes, larger tumor size, receipt of chemotherapy and both ER+ and PR+ showing
an improvement in outcome.\textsuperscript{12} There is also a trade off in increasing toxicity from longer duration therapy. This can be seen in higher cardiovascular risk. For higher risk patients with osteopenia, using the BCI or EndoPredict to ascertain benefit of aromatase inhibitor therapy beyond 5 years could be beneficial. If they are low risk for late recurrence, then stopping after 5 years could improve their long-term bone health and reduce other aromatase inhibitor associated side effects.

\textit{Indications for Shorter Duration Therapy – Desire for Pregnancy}

As mentioned earlier, shorter durations of tamoxifen do still offer significant reductions in recurrence. For many women with breast cancer in their childbearing years, a 5-year course of tamoxifen would impact their ability to conceive and carry a pregnancy to term. In these situations, a shorter course of tamoxifen can be entertained. Of course, this is most appropriate for low-risk patients. The recommendation is for 18 months to be the shortest course given with a preference for 2 years. Tamoxifen should be stopped 2-3 months prior to conception/or attempts as it is associated with congenital abnormalities.\textsuperscript{18} This will allow it to wash out of the system. There is an ongoing trial, POSITIVE (Pregnancy Outcome and Safety of Interrupting Therapy for Women With Endocrine Responsive Breast Cancer), looking to better delineate the nuances of managing endocrine therapy around pregnancy.

\textbf{Section 2D – Adjuvant Bisphosphonate Therapy}

Decreased bone density leading to osteopenia, osteoporosis, and increased risk of fractures is one of the most common side effects of adjuvant aromatase inhibitor therapy. Bisphosphonate therapy has been shown to mitigate this risk and delay the development of osteopenia/osteoporosis associated with aromatase inhibitor therapy.

Interestingly, a recent meta-analysis revealed that the use of adjuvant bisphosphonate therapy for early-stage HR+ breast cancer led to a decrease in bone metastases, and improved breast cancer survival. This was noted only in postmenopausal women, and regardless of bone density results at the start of therapy.

These findings justify the use of adjuvant bisphosphonate therapy concurrently with adjuvant endocrine therapy in postmenopausal women with HR+ breast cancer.

\textbf{Section 2E – Adjuvant Therapy for Ductal Carcinoma in Situ}

Ductal carcinoma in-situ management may include surgical resection, radiation therapy, and endocrine therapy. Following surgery and/or radiation therapy, endocrine therapy for the treatment of hormone receptor-positive DCIS treatment aims to prevent recurrence of further in-situ or invasive carcinoma. It is important to note that adjuvant endocrine therapy for DCIS has not led to improved overall survival.

- In the NSABP-24 trial, tamoxifen 20 mg daily for 5 years compared to placebo following lumpectomy and radiation therapy for DCIS led to a significant reduction in breast cancer recurrence (in-situ and invasive).
• In the NSABP-35 trial, tamoxifen 20 mg daily was compared to anastrozole 1 mg daily in postmenopausal women with DCIS treated with lumpectomy and radiation therapy. In this study, the overall event rate was low with most patients having excellent outcomes. Importantly,
  o Anastrozole achieved a better breast cancer free interval and disease-free survival compared to tamoxifen in women younger than age 60 years. There was no difference between the two drugs in women older than age 60 years
  o Anastrozole achieved a significant reduction in contralateral invasive breast cancer compared to tamoxifen
  o There was no difference in overall survival between the two arms
  o Anastrozole was associated with a higher rate of osteoporotic fractures; while tamoxifen was associated with a higher risk of thromboembolic events

In women who undergo bilateral mastectomies for DCIS, adjuvant endocrine therapy is not usually recommended.

**Section 2F – Endocrine Therapy Alone in the Elderly**

The geriatric patient population needs special consideration when selecting treatment. Multiple comorbidities and functional issues may be present and can impact treatment tolerance and outcomes. Evaluation of functional status and ability to tolerate treatment should be taken into consideration when formulating treatment plans. After the age of 70 years, the percent of breast cancers that are estrogen positive and will respond to endocrine therapy rises. One study showed that after age 85 years over 90% of breast cancers will be estrogen positive and less the 9% will be HER2+. In patients older than 75 years with comorbid conditions and poor functional status, it may be best to treat with endocrine therapy as the primary therapy with surgical intervention only for clinical progression of disease. Several studies have shown that at least 50% of patients will eventually progress (these studies were performed with tamoxifen), but there was no difference in breast cancer specific death between those who had primary endocrine therapy with surgery for progression versus those who had surgery up front. In fact, more than 60% of patients in one study died of other causes with cardiac disease being most common. There is a higher percentage of patients older than 80 years present with locally advanced breast cancer as they have stopped screening and having routine breast exams. Primary endocrine therapy for many would be preferable to downstage disease.19,20

An excellent and easy to use tool for geriatric evaluation is available online from the Cancer and Aging Research Group (the CARG tool). This will calculate the ability or lack thereof to undergo significant treatment. There are other geriatric performance tools that can be used to help predict longevity and give input on treatment plan and life expectancy. ePrognosis is another available online tool for predicting life expectancy. These tools can be helpful in evaluating patients older than 75 years when making decisions for primary endocrine therapy versus surgical intervention up front.

Although most of the studies in this group were performed with tamoxifen as the endocrine therapy, we recommend aromatase inhibitor therapy as this is associated with higher
response rates. In some patients with less responsive disease, the addition of an oral CD4/6 inhibitor may afford longer response duration obviating the need for surgical intervention.

Monitoring to assure local control and continued response is key in managing this patient population. Surgical intervention should be performed if disease progression is noted.
Section 3 – Chemoprevention of Breast Cancer

General Considerations of Chemoprevention

Identifying high-risk patients is the first, and most straightforward, step in chemoprevention. Discussing the benefits and risks of chemoprevention with an individual patient is more challenging. The National Cancer Institute (NCI) noted that while roughly 15% of U.S. women between the ages of 35-79 years have over a 1.67% 5-year risk of developing breast cancer, only 5% would have overall benefit from taking chemopreventive medication. The NCI published Benefit/ Risk Index charts to help clinicians and their patients make informed decisions on medication use.21-22,23,24

Currently, 3 medications are available for use in chemoprevention of breast cancer—tamoxifen, raloxifene, and exemestane. The American Society of Clinical Oncology (ASCO) 2013 practice guidelines recommend that exemestane’s use as a chemopreventive agent is through a clinical trial.

Tamoxifen

Pharmacology:

Tamoxifen is a triphenylethyline compound, which is chemically similar to estradiol. It is a SERM. A competitive inhibitor of estradiol, it binds with the estrogen-receptor protein. Tamoxifen exerts an antiestrogenic effect on breast tissue and an estrogenic effect on the skeletal system. It has been associated with lower cholesterol levels.

Dosing:

For chemoprevention of ER+ breast cancer, the recommended dose of tamoxifen is 20 mg PO daily for 5 years. A recent randomized trial comparing daily tamoxifen 5 mg or placebo for 3 years following surgery for atypical ductal hyperplasia, lobular carcinoma in situ, or ER+ DCIS in 500 patients with a mean follow-up time of 5.1 years showed a 50% reduction in development of invasive breast cancer or DCIS. This achievement in breast cancer risk reduction on the lower dose was achieved without an increase in venous thromboembolism (VTE) or endometrial cancer associated with a 20 mg dose of tamoxifen. There were also fewer reports of vasomotor symptoms with the 5 mg dose of tamoxifen. While currently not standard of care, lower dose tamoxifen may be an option for individual patients.

Indications:

Tamoxifen is potentially indicated for women 35 years and older who have a >1.66% 5-year risk of developing breast cancer, based on a validated risk model, or who have a personal history of LCIS. Tamoxifen may be used in premenopausal and postmenopausal patients.
**Benefits:**

Data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT; P-1) revealed that high-risk patients taking tamoxifen 20 mg daily for 5 years had a 49% decreased risk of developing invasive breast cancer and a 50% decreased risk of developing noninvasive breast cancer as compared to women taking a placebo for 5 years.

**Contraindications:**

Tamoxifen is not indicated in patients who have a personal history of thrombotic events, such as deep vein thrombosis, pulmonary embolism, stroke, or transient ischemic attack. Tamoxifen should not be given to patients who will be immobilized for long periods or who are at high risk for thromboembolic events.

Tamoxifen use is contraindicated in patients who are or who may become pregnant and in patients who are breastfeeding. Following tamoxifen ingestion, it takes 2 months to clear the body.

**Warnings/Considerations:**

Tamoxifen use increases the risk of endometrial cancer, especially in women 50 years and older, from 1:1000 to approximately 2:1000. Fortunately, most of the endometrial cancers associated with tamoxifen use are stage I at diagnosis. Tamoxifen is also associated with an increased risk of vaginal discharge. In all patients, but especially in patients older than 50 years, tamoxifen use increases the risk of ischemic stroke. Tamoxifen use is associated with a slightly increased incidence of cataracts (RR 1.14). In postmenopausal women, patients taking tamoxifen have higher rates of requiring cataract surgery (RR 1.57).

Patients on tamoxifen report more hot flashes. Results of the 1998 NSABP BCPT study showed that 45.7% of the tamoxifen group compared to 28.7% of the placebo group noted hot flashes as being bothersome.

NSABP BCPT did not show an increased incidence of ischemic heart disease with tamoxifen use. Patients may experience improved lipid profiles and cholesterol levels while on tamoxifen.

**Raloxifene**

**Pharmacology:**

Raloxifene, a non-steroidal benzo thiophene derivative, is also a SERM. It has an estrogen-agonistic effect on the skeletal system. In 1997, raloxifene was the first SERM to be approved for the treatment of postmenopausal osteoporosis. Raloxifene acts as an estrogen antagonist on breast tissue and may be considered for use in breast cancer chemoprevention. Raloxifene also has been shown to reduce serum cholesterol.
**Dosing:**

For chemoprevention of ER+ breast cancer, the recommended dose of raloxifene is 60 mg PO daily for 5 years.

**Indications:**

Raloxifene is potentially indicated for postmenopausal women 35 years and older who have a > 1.66% 5-year risk of developing breast cancer based on a validated risk model, or who have a personal history of LCIS.

**Benefits:**

The Multiple Outcomes of Raloxifene Evaluation (MORE) study, a randomized double-blind trial involving 7705 postmenopausal women documented improvement in bone mineral density as well as a 65% reduction in breast cancer risk following 3 years of treatment with raloxifene and calcium.\(^2\) The Continuing Outcomes Relevant to Evista (CORE) trial, in which more than 65% of the MORE trial participants (n=5213) extended raloxifene or placebo use by 4 years, showed a 50% reduction in breast cancers among the raloxifene group. The NSABP Study of Tamoxifen and Raloxifene (STAR) trial (n=19,747), comparing postmenopausal patients receiving 5 years of tamoxifen 20 mg/day and raloxifene 60 mg/day, showed an advantage in reduction of invasive breast cancers for tamoxifen with similar incidence of noninvasive breast cancer between the two drugs.\(^2\) Women taking tamoxifen had a lower incidence of invasive breast cancer but an increased incidence of endometrial cancer and VTE events. The STAR trial update, with a median follow-up period of 81 months, revealed tamoxifen to be superior to raloxifene in reducing the longer-term risk of invasive breast cancer (50% vs. 38% reduction). Both were equally effective in reducing the longer-term risk of developing noninvasive breast cancer.

**Contraindications:**

Raloxifene is contraindicated in premenopausal patients, including patients who are or who may become pregnant. It is also contraindicated in patients who are breastfeeding.

Raloxifene is contraindicated in patients who have a personal history of thrombotic events, such as deep vein thrombosis, pulmonary embolism, stroke, or transient ischemic attack. Raloxifene should not be given to patients who will be immobilized for long periods and are at high risk for thromboembolic events.

Raloxifene should not be given to patients on cholestyramine or estrogen.

**Warnings/Considerations:**

Raloxifene is associated with an increased risk of VTE. The MORE study participants receiving raloxifene experienced a 3-fold increased risk of VTE when compared to the patients on placebo. This VTE risk is highest during the initial months of therapy. However, when compared with tamoxifen use in the STAR trial, the tamoxifen group had a higher
incidence of VTE events than the raloxifene group. Patients report leg cramps and hot flashes while on raloxifene. About 1 in 14 patients report leg cramps and 1 in 10 patients report hot flashes while on raloxifene.

Raloxifene is not associated with an increased risk of endometrial cancer or sarcoma.

**Exemestane**

*Pharmacology:*

Exemestane is a steroidal aromatase inhibitor. By irreversibly blocking the enzyme aromatase, which is critical in estrogen synthesis, exemestane decreases circulating estrogens. This in turn affects estrogen dependent target organs, like breast and bone.

*Dosing:*

For chemoprevention of breast cancer, the recommended dose of exemestane is 25 mg PO daily for 5 years.

*Indications:*

Exemestane is potentially indicated for postmenopausal women 35 years and older who have a >1.66% 5-year risk of developing breast cancer based on a validated risk model, or who have a personal history of LCIS. The FDA has approved the use of exemestane for the treatment of breast cancer but not in the reduction of breast cancer risk.

*Benefits:*

The NCIC Clinical Trials Group Mammary Prevention 3 trial (NCIC CTG MAP.3) randomized 4560 postmenopausal high-risk patients to receiving exemestane 25 mg, exemestane 25 mg plus celecoxib or placebo. With a median follow-up of 3 years, a 65% relative reduction in breast cancer was seen.29

*Contraindications:*

Exemestane is contraindicated in premenopausal patients, including patients who are or who may become pregnant. It is also contraindicated in patients who are breastfeeding.

*Warnings/Considerations:*

Hot flashes may occur in more than 30% of patients taking exemestane. Arthralgias are a common side effect of exemestane. Exemestane can cause a decrease in bone mineral density.
Chemoprevention Summary

Younger patients have the greatest benefit for chemoprevention, with current follow-up showing a sustained benefit of breast cancer risk reduction at 10 years for those who completed 5 years of tamoxifen therapy.

The two SERMs and one aromatase inhibitor used as chemopreventive agents each have unique features that allow individual choice based on a patient’s risk, medical history, age, and stage of life. Premenopausal patients are limited to tamoxifen, where as a postmenopausal patient may choose between the agents based on her bone health and whether she still has her uterus.

Specific follow-up recommendations for patients on tamoxifen who still have their uterus, include a baseline pelvic exam followed by a yearly pelvic exam, with immediate work-up of abnormal vaginal discharge or bleeding to rule out endometrial cancer.

Postmenopausal patients on exemestane need assessment and follow-up exams for their bone density, since the antiestrogenic effect of exemestane may cause or exacerbate osteoporosis. Postmenopausal patients with osteoporosis and elevated breast cancer risk are excellent candidates for raloxifene, which targets both issues.

Use of Pharmacologic Interventions for Breast Cancer Risk Reduction: American Society of Clinical Oncology Clinical Practice Guideline
Section 4 – Side Effect Management of Endocrine Therapies

Many of the endocrine therapies have overlapping side effects such as hot flashes, vaginal atrophy, and hair thinning. The management of these symptoms will be the same regardless of which drug is responsible for the side effect.

Hot Flashes or Vasomotor Symptoms

Management Options

In counseling patients, there are several triggers of vasomotor symptoms that can be avoided. Alcohol, caffeine, spicy foods, hot showers or rooms, and smoking are all associated with increasing or inciting vasomotor symptoms.

Traditional Treatment

There are several drug options that can be enlisted to help manage vasomotor symptoms. Options include use of:

- Gabapentin (start low dose 300 mg daily, and titrate up to 300 mg TID)
- Clonidine 0.5 mg twice a day (may be associated with hypotension)
- Venlafaxine (Effexor) dosed at 37.5 gm to 75 mg bid (dry mouth)
- Oxybutanin (Ditropan) 2.5 gm bid or 2.5 mg for 1 week increased to 5 mg bid (diarrhea, dry eye, and difficult urination)

Complimentary Options

- Acupuncture- Studies show lifestyle modification and 30-minute session per week was more effective than gabapentin or venlafaxine.
- Black cohosh- A key component of many natural remedies. It is no longer considered a “phytoestrogen.” It does not interact with the estrogen receptor but with the opioid receptor in the brain hence its ability to treat vasomotor symptoms. Recent studies suggest no increase in risk of recurrence in HR+ breast cancer. In fact, there is the suggestion that it may act as a mild aromatase inhibitor.
- Acteane/Estroven- menopausal remedies containing black cohosh and arnica- These are also to use in ER+ breast cancer. This is in line with many of the supplements thought to be “phytoestrogen” having no interaction with the estrogen receptor.
- Relizen- Swedish pollen- This is not a phytoestrogen and some preliminary studies show a decrease in the number of hot flashes.

Thromboembolic Events

Avoid use of tamoxifen in patients with a history of coagulopathy such as Protein C and S or factor V Leiden. In premenopausal women with this history, ovarian suppression with GnRH analog and aromatase inhibitor would be a better option.
Management

Treat as per clinical standard.

Uterine Cancer

Management

Investigate postmenopausal vaginal bleeding with uterine ultrasound and possible endometrial biopsy. In premenopausal women, obtain an ultrasound.

Vaginal Atrophy/Dyspareunia

This symptom can be safely managed in several ways. The simplest is to recommend lubrication. There are several over the counter options that are oil or water based. For many women, this is helpful, but they still have discomfort and itching in addition to painful sex. Non-hormonal options are preferred; however, if these fail, then low dose vaginal hormonal therapies can be considered. Estradiol cream or tablets, usually 10 micrograms to be used daily for 2 weeks and then inserted two to three times per week thereafter. Finally, there are some vaginal rejuvenation techniques that are being explored that show future promise.32

Cardiac Events

Tamoxifen and raloxifene are associated with a lower incidence of cardiac events. The aromatase inhibitors may also be associated with an increase in cholesterol. This may be monitored with routine annual cholesterol and triglyceride panel.33

Osteopenia/Osteoporosis

This is most associated with aromatase inhibitor therapy. A baseline bone density is important. Based on consensus statement, all patients placed on aromatase inhibitor therapy should receive instruction on the role of exercise, calcium, and Vitamin D supplementation in maintaining bone health.

Bone directed therapy should be given for osteopenia for all patients with:

1. T score < -2.0
2. T score < -1.5 with one additional risk factor
3. Two risk factors even with a normal bone mineral density (BMD)

Patients with normal BMD and no risk factors should be managed on the basis of BMD loss during the first year. That is, DEXA scan should be repeated after 1 year of therapy.

Risk factors for osteopenia/osteoarthritis include: T- score of -1.5, age > 65 years, low BMI (<20 kg/m2), family history of hip fractures, personal history of fragility fracture, oral corticosteroid use for greater than 6 months, rheumatoid arthritis, and smoking.
NOTE: Bone directed therapy is offered to all postmenopausal women with HR+ breast cancer, independent of bone density, based on improved survival.34

Musculoskeletal Complaints/Joint Aches

This is associated with AI therapy. The etiology is unclear. Data suggest that women with good Vitamin D levels have less incidence of joint and musculoskeletal symptoms. Women who are Vitamin D deficient experience more achiness. Vitamin D repletion is therefore one way to improve these symptoms. Changing aromatase inhibitors is also often helpful, in many patients these symptoms improve over time.35

Cognitive Function

There is some suggestion that patients on AI over time may experience diminishment in cognitive function. Inquire about memory loss or depression so that appropriate intervention can be made. In this situation, a switch to tamoxifen may be appropriate.
This statement was developed by the Society’s Endocrine Therapy working group and on August 6, 2019, was approved by the Board of Directors.

**Endocrine Therapy Working Group Members & Financial Disclosures**

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