Audio Companion for SESAP® 16
BREAST — Category 2

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Benign Breast Diseases

Diagnosing Fibroadenomas: If the core biopsy results confirm that the mass is a fibroadenoma, no further treatment is needed. A core biopsy indicating this diagnosis will correlate with other clinical findings. If the mass is excised, the surgeon is looking for those same clinical findings and negative margins that would confirm diagnosis. Once the biopsy or excision is complete, the patient is counseled on her risk of developing future fibroadenomas. A diagnosis of fibroadenomas does not increase the patient’s risk of developing breast cancer in the future.

Triple Test Diagnostic Criteria for Fibroadenomas: When determining likelihood of performing a biopsy for suspicion of a fibroadenoma, the best practice for the breast surgeon would be to perform what is referred to as a “triple test.” First, the mass has to appear to be a fibroadenoma upon clinical examination (eg, slow-growing or not growing at all). Second, the mass must have a history of remaining stable on imaging. The mass must feel smooth, mobile, and not irregular upon physical examination. Finally, imaging is performed to collect histologic or cytologic findings. The imaging study and the biopsy must be consistent with fibroadenoma characteristics. If the biopsy does not demonstrate existence of a fibroadenoma, the findings are not adequate to confirm diagnosis. When considered together, the triple test is 98% accurate in diagnosis of a fibroadenoma. This test can be considered for patients who are aged ≤40 years. In the radiology literature, 2 of those 3 criteria are enough in order to confirm diagnosis; in other words, the imaging study is consistent with a fibroadenoma, and the patient has a clinically benign history of breast masses. The imager will assign the mass as a Breast Imaging Reporting and Data System (BIRADS) 3 lesion. The patient should come back in 6 months for an imaging study to show stability of the mass, then once again for a 1-year follow-up. If the mass remains stable, the image will be downgraded to a BIRADS 2.

Fat Necrosis: Fat necrosis is fat that has been devitalized, usually because of trauma. Upon physical exam, fat necrosis can be alarming, as it feels and looks similar to that of a malignant mass. However, ultrasound is now able to determine pathognomonic findings that usually indicate fat necrosis. With routine breast imaging, a lucent lesion is usually adequate to make a diagnosis of fat necrosis. However, due to the physical nature of the fat necrosis, a core biopsy can be done to rule out a malignant mass. Fat necrosis would be easily interpreted with a core biopsy. In terms of risk, fat necrosis does not turn into cancer. If the core biopsy shows fat necrosis, we are very comfortable with this diagnosis as long as there is some clinical history of trauma in the area that can explain the mass.

Sclerosis Adenosis: Sclerosis adenosis on a core biopsy can explain a mammographic finding and is generally accepted to be concordant with increased density, or a mass, or architectural distortion in the breast, as long as it is of an appropriately low BIRAD score. Sclerosis adenosis is not generally associated with an increased risk of developing breast cancer, in contrast to other histologic diagnoses, such as lobular carcinoma in situ.

Concordance of Information

Case Study: Lobular Carcinoma In Situ: Lobular carcinoma in situ usually does not appear on imaging findings. If a core biopsy was ordered, there was an imaging finding that required investigation. For example, if a surgeon needs to identify a mass and the findings came back concluding that the masses are calcifications in the benign ductal profile, but incidentally, lobular carcinoma in situ is identified, the question you set out to investigate has been answered: What caused these calcifications? The calcifications are benign, however lobular carcinoma in situ has also been identified. In many settings, a surgeon will proceed with excisional biopsy; however, in this scenario, to assure that there is not an adjacent malignancy, the surgeon will collaborate with the radiologist and the pathologist to confirm that the question that was being addressed by the biopsy has been answered: a benign finding with no calcifications in the lobular carcinoma in situ. For this patient, it would be reasonable to observe
her and not subject her to an excisional biopsy. However, if a center or program pursues this policy, the pathologist, radiologist, and the surgeon must be in agreement that there is concordance with the pathology findings, the imaging findings, and the physical findings.

**Importance of Creating Concordance of Information:** As a breast surgeon, it is important to have an agreed-upon lexicon of terms. When referencing “concordance”, we are referring to the agreement of imaging findings with the findings on histology. In other words, if the histology finding is benign, but the imaging finding raises suspicion, the report would read that the mass is benign, with discordant findings. In this scenario, the surgeon would proceed with excisional biopsy due to the risk of sampling error. When a core biopsy is performed, the entire lesion is not removed; rather, a sample of the lesion is extracted and tested, therefore there is the risk that the sampled portion is benign, but immediately adjacent to that, there is a malignancy. When the mammographer performs a biopsy, it is standard that once the pathology report comes back, the mammographer reviews the images and looks at the pathology report to be sure that there is concordance between what is seen histologically and what is seen on the mammogram. In the case of sclerosing adenosis, if the biopsy shows sclerosing adenosis, which is a benign finding, the mammographer will then determine if it will explain what is being seen on the mammogram. If it does answer that question, the finding is benign and concordant. However, if the biopsy report shows a fibroadenoma, for example, and the imaging finding shows a stellate mass in the breast, the finding is benign and discordant because the imaging findings are very suggestive of a malignancy. The mammographer and the breast surgeon must collaborate to review the pathology, imaging, and physical findings in order to make sure that what is being seen on the mammogram and what is being felt on physical exam are concordant with each other.

### Lobular Carcinoma In Situ

**Management of Pleomorphic vs Routine Lobular Carcinoma In Situ:** Pleomorphic lobular carcinoma in situ is inadequately characterized. Many people would indicate that part of the problem is misdiagnosis, an effect of difference of opinion on the part of the pathology reports whereas the pathology report identifies the lesion as lobular carcinoma in situ when, in fact, the lesion is actually a malignancy. However, routine lobular carcinoma in situ is considered a non-malignant lesion and should be treated as such. The risk of metastasis approaches zero. Instead, it should be treated as an increased risk factor for developing breast cancer at some point. Pleomorphic lobular carcinoma in situ, on the other hand, would be treated by most surgeons with excision of the lesion to negative margins. However, we should move away from mastectomy, as this would be disfiguring for the patient. However, because there is some uncertainty as to the best management of pleomorphic findings, we should be more aggressive than we would for routine lobular carcinoma in situ.

**Risk Factors:** The risk of a patient developing an invasive breast cancer after receiving diagnosis of lobular carcinoma in situ increases 1% to 2% per year. The invasive cancer could be ductal or lobular, but more frequently, it is ductal and the risk is bilateral. Patients with this diagnosis are true high-risk patients. Fortunately, pleomorphic lobular carcinoma in situ is rare enough that there is not enough data to determine if the pleomorphic variant poses a higher risk for developing a breast cancer, as the condition is often misdiagnosed and the patient does not have pleomorphic lobular carcinoma in situ. However, one would assume that the risk factors would remain in the same percentage rates of 1% to 2% per year.

### Atypical Breast Lesions

**Treatment of Atypical Ductal or Atypical Lobular Hyperplasia:** Treatment of an atypical ductal hyperplasia would include core biopsy, and, if there are enough data to support a non-insignificant risk of an adjacent malignancy, an excisional biopsy would then be performed. For atypical lobular
hyperplasia, typically, surgeons would use the same criteria as they would for lobular carcinoma in situ. In terms of the risk for developing a malignancy, atypical lobular hyperplasia and routine lobular carcinoma in situ are both non-malignant lesions. However, excisional biopsy is recommended to be sure there is not an adjacent malignant lesion.

**Risk Factors:** Both lobular carcinoma in situ and atypical lobular hyperplasia are considered high-risk lesions for developing atypical ductal hyperplasia. There is debate among breast doctors as to the level of risk of developing atypical ductal hyperplasia; however, we can assume that the risk is between 2.0% and 2.5% increase per year. In summary, lobular carcinoma in situ, atypical ductal hyperplasia and atypical lobular hyperplasia are true high-risk lesions. Women who have biopsies demonstrating these lesions are considered high-risk and should be considered high-risk in terms of screening for breast cancer in the future or perhaps actively intervening in some way to reduce their risk.

**BIRADS Scoring in Mammography**

**Origin of BIRADS:** The Breast Imaging Reporting and Data System (BIRADS) is a universal lexicon of scores used to clarify findings in mammography reports between mammographers, surgeons, and patients. It began in the late 1990’s after a mandate by the federal government was issued in order to standardize breast imaging. The American College of Radiology helped to construct the BIRADS system, which is a scoring system for mammograms.

**Scoring System:** The BIRADS is separated into 6 scores. A BIRADS score of 0 indicates that the mammographer needs additional imaging. This score does not necessarily mean that a malignancy has been found; it is only suggesting that clearer images are needed in order to properly assess the mass to make an informed decision. Several factors call for a score of 0 (eg, the patient moved, the image was blurry, etc). A BIRADS score of 1 indicates a normal mammogram with normal breast parenchyma and no suspicious breast tissue. A score of 2 is an indication of a normal mammogram that has a benign finding. The finding could indicate anything from calcifications to various benign tumors or necroses. A 1-year follow-up is recommended for BIRADS 2. A score of 3 indicates that there is a finding on the mammogram and that the finding cannot be classified as being perfectly benign. This score carries a ≤2% risk of being a malignant mass. A follow-up is recommended after 6 months. If, at the 6-month follow-up, the mass is stable, the BIRADS score of 3 will remain in effect. An additional 6-month follow-up is recommended if the mass appears to be stable. If the patient maintains a stable mass at the second follow-up, the BIRADS score is downgraded to a 2. A BIRADS score of 4 is an indeterminate mammogram score. It indicates that the likelihood that the finding is malignant is between 3% and 94%. A biopsy is very strongly recommended, preferably a minimally invasive biopsy such as stereotactic core biopsy, an ultrasound-guided core biopsy, or an MRI or contrast-enhanced mammogram. The mammographer is communicating that there was an indeterminate finding that is concerning. Once the mass has been removed and biopsied, the pathology reports are assessed to be sure the mass matches the clinical findings. If the mass can be identified as a benign finding, the BIRADS score is downgraded to a 2. A BIRADS score of 5 indicates that there is >95% chance that the mass is malignant. Finally, a BIRADS score of 6 indicates a patient who has already had a biopsy that has been proven to show malignancy but additional imaging is needed to further characterize the lesion.

**Discordant Findings Associated With BIRADS 4**

**Further Classification:** When classifying a BIRADS score of 4, some mammographers are content with identifying the mass as a single score. However, there is another school of thought such that mammographers will further segregate the scores into A, B, or C, due to the expansive gap of risk percentage (3% to 94% chance of malignancy). A BIRADS score of 4C is the most suspicious,
whereas a score of BIRADS 4A is the least suspicious. While it is mandatory by federal law to assign a BIRADS score to mammograms, it is not mandatory to sub-classify a score of 4. Mammography, as a whole, is the most subjective of all the various types of radiology. One needs to make sure that their breast imager is an experienced breast imager; if there is any question about the imager’s confidence in scoring, it can be difficult to get an accurate picture or classification of the mass.

**Benefit of Core Biopsy:** A BIRADS 4 lesion is not unusual and the call back rate for mammography is typically in the 12% to 15% range. This indicates that many biopsies are recommended based on routine screening. Those biopsies are best performed in a minimally invasive fashion (eg, core biopsy or fine needle aspiration biopsy), not just any excisional biopsy. This raises an important issue in the field of breast surgery, as there have been data that indicates a high percentage of surgeons who are doing excisional biopsies on women that will yield very low results. The typical yield for a BIRADS 4 lesion is in the 20% to 30% malignancy range. For the majority of patients, excisional biopsy is showing no pathology and the patient is left with a scar. If a core biopsy is performed, there is less repercussion for the patient.

**Risk-Based Screening**

**Over-Treatment of Breast Cancers:** Risks associated with frequent and early screening have changed over time. Due to a lack of clarity among the lay public and physicians, there is no consensus of what constitutes a harm of screening. In general, breast physicians could agree breast cancers are over-treated, however, it is difficult to determine which types of breast cancers are being over-treated and which ones will remain clinically unimportant to a patient. Until we can figure out which ones are most important, it will be difficult to know how to best manage screenings.

**University of Virginia Screening Guidelines:** At the University of Virginia, we believe that screening, and health care in general, should be personalized. This is the trend we are beginning to see in the future of health care. We have several ways in which we can determine a patient’s risk factor for developing breast cancer. The patients who have been identified as high risk would need to be screened early, frequently, and with more sensitive tests. The future of breast care is moving in such a way that more personalized tests will be developed with more accurate risk calculators for women in order to determine at which age screening should begin. However, our current guidelines are that screening start at age 40 for intermediate or high-risk women with an annual mammography. For women who have >20% risk, we will add on an MRI screening as well. For average risk women, we have moved screening to age 45 years and have recently considered screening every other year for those women. There will be controversy amongst professionals regarding screening at a later age biannually, however, risk-based screening is certainly the direction in which we are moving.

**Contralateral Prophylactic Mastectomy: Misguided, Misunderstood Treatment**

**Anxiety-Based Drivers:** The most difficult scenario that we at the University of Virginia face frequently is the concept of contralateral prophylactic mastectomy. While we agree that mastectomy is an appropriate method of treatment for the breast affected by cancer, we cannot agree that we are substantially reducing the risk of developing additional breast cancers by removing the other breast. The risk of developing a breast cancer in the other breast is 4% to 6% over 10 years. Even if the patient were to develop a breast cancer in the opposite breast, we would be very likely to catch it early and cure it. The decision to remove the unaffected breast is solely emotional. The patient does not wish to endure this scenario again, so the decision is made to remove the healthy breast along with the diseased one. While the initial diagnosis and subsequent treatment of breast cancer is not the best time to make a decision of this caliber, it is quickly becoming a trend in the United States, especially over the past 15 years.
This is quite concerning to breast surgeons, as the National Institutes of Health released a position paper years ago that stated women could be treated with breast preservation. At that point, women began treatment with lumpectomies. However, recently there has been a resurgence in bilateral mastectomy. It is a very difficult conversation to have with a patient, as it is not data-driven.

**Counseling Patients Toward Best Practices:** When counseling a patient who has just been diagnosed with breast cancer, we must determine what her definition of “best practice” is. Is her best choice data-driven medical advice, or is it her own peace of mind? If a high-risk patient is treated for breast cancer, perhaps a BRCA 1 or 2 mutation or a woman who had radiation therapy in the past for a separate cancer, a contralateral prophylactic mastectomy is reasonable, as her risk of developing breast cancer over a 10 year period could be as high as 20% to 25%. However, for the average risk patient, the risk is only 4% to 5% over a 10-year period. For these average risk patients, counseling would involve asking her what she thinks her risk is of developing breast cancer again. The typical patient response to this question is 50% to 60%. At that time, medically driven data are presented which show that her real risk is substantially smaller than what she has determined. Once data are presented to her, it is then up to her to decide if she would like to rely on the medical data, or continue with her wishes to remove the healthy breast. This brings to the surface another difficult conversation; one in which the patient’s peace of mind is at stake. For some patients, the peace of mind is worth the risk of undergoing another major surgery.

**Risks Associated With Contralateral Prophylactic Mastectomy:** Data from the National Surgical Quality Improvement Program (NSQIP) suggest that contralateral prophylactic mastectomy appears to increase the risk of postoperative complications in the first 30 days by 50%. For some patients, this can pose a real threat as any type of delay due to complications can cause a delay in receiving any adjuvant treatment for the cancer. Ideally, we would like our breast cancer patients to wait to make a decision on contralateral mastectomy a year out from surgery and treatment. This gives her time to have lived with the healthy breast for a year to see how she feels about it. If, at that point, she were still concerned with her risks of developing another breast cancer, then it would be reasonable to proceed with additional surgery.

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**Sentinel Lymph Node Biopsy**

**Best Practice for Sentinel Lymph Node Biopsy:** Sentinel lymph node biopsy became a prominent means of treatment of breast cancer in the late 1990s. Most trainees are facile to a sentinel lymph node biopsy because this is the method used in order to stage the axilla. When sentinel lymph node biopsy was first introduced, the recommendation was to perform the biopsy then proceed with a complete axillary dissection for at least 20 cases. Most hospitals required some degree of training in order to prove that their false-negative rate was <5% and that their ability to identify the sentinel lymph node was at least 90% accurate. In most modern series, the likelihood of identifying the sentinel lymph node approaches 100% accuracy; in cases where a sentinel lymph node biopsy was done followed by a complete axillary dissection, the risk of a false negative is <5%. In regard to multi-center national trials, the incidences of false-negative sentinel lymph nodes were in the 10% range, which is a generally accepted range today.

**Using Tracers to Detect Sentinel Lymph Nodes:** Other data show that the learning curve for sentinel lymph node biopsy is less steep if 2 tracers are used. When a sentinel lymph node biopsy is performed, a substance is injected into the breast that is then taken up by the lymphatic system and brought into the sentinel lymph nodes. The 2 most common tracers that are used are technetium-labeled sulfur colloid and lymphazurin. However, it is not uncommon for surgeons to use methylene blue as well. All 3 of these tracers achieve similar results, but the learning curve in attaining the ability to identify those lymph nodes is less steep if 2 of them are used. At University of Virginia, we use lymphazurin and technetium labeled sulfur colloid.

**Injection Sites for Sentinel Lymph Node Tracers:** In the earlier years of its introduction, it was believe that it made a big difference in accuracy when injected next to the tumor. However, over time,
studies were conducted where 1 tracer was injected next to the tumor and the other tracer was injected next to the areola. The concordance rate of the mapping was very high using this method. In general, it is not vital to inject the tracer next to the tumor. At UVA, we inject in the quadrant where the tumor is located, closer to the areola and more superficial, being careful to stay in the breast tissue and not mark the skin to risk tattooing the patient.

**Reoperative Sentinel Lymph Node Biopsy:** Previous breast surgery of any kind can interfere with mapping. If a patient presents with a local recurrence in the breast or chest wall after a mastectomy, the accuracy in the ability to map a sentinel lymph node is 40%. The mapping rates were based on how extensive the previous axillary surgery was. If the patient had a previous axillary dissection, the likelihood of mapping is lower, whereas the patient who had a previous sentinel lymph node biopsy is able to see an 80% mapping accuracy. Furthermore, the patient who has had previous axillary surgery will experience the likelihood of mapping to a non-common site (eg, contralateral axilla, or the mammary nodes, or Rotter’s nodes) was a little bit higher and does sometimes cause interesting lymphoscintigraphy and surgery. Patients who have not had previous axillary surgery but who have a large lumpectomy scar can also pose an issue. This brings back the idea of doing core biopsies to diagnose breast cancer rather than excisional biopsies because that can decrease mapping rates to the sentinel node requiring an axillary dissection for that patient. Therefore, you have done this patient a disservice by performing an excisional biopsy if it was not absolutely necessary in order to diagnose her with breast cancer.

**Axillary Dissection**

**When to Perform Axillary Dissection:** Axillary staging should not be performed on patients who are having a lumpectomy for ductal carcinoma in situ on core biopsy. Ductal carcinoma in situ should not metastasize to lymph nodes in any clinically meaningful way, so there is no reason to assess the axilla in this setting. However, the 1 caveat to this is if the patient has ductal carcinoma in situ and is going to undergo a mastectomy due to the risk of upstaging with mastectomy. In this case, the mapping rates for sentinel lymph node after mastectomy are going to be substantially lower than they would have been if the breast were left intact. The key difference is that the breast is being removed rather than being preserved. If you have upstaging when performing a lumpectomy for ductal carcinoma in situ, one could always go back and perform the sentinel lymph node biopsy because there will be an intact breast. If a mastectomy is performed and there is no intact breast, the majority of breast surgeons today, will do a sentinel lymph node biopsy.

**Managing the Axilla in Neoadjuvant Chemotherapy:** If the patient has a clinically negative axilla prior to neoadjuvant chemotherapy, most surgeons would proceed with a sentinel lymph node biopsy and accept those results as accurate in order to stage the axilla for further treatment. One of the major topics of debate in this area currently is the treatment of a patient who has neoadjuvant chemotherapy who, prior to having chemotherapy, had a biopsy that was proven to be positive for disease in the axilla. Another area of debate amongst breast surgeons is how to proceed for a patient who has had an excellent clinical response to neoadjuvant chemotherapy; should we perform a sentinel lymph node biopsy, or should we immediately perform the axillary dissection? There are numerous studies being conducted at this time that will address these issues.

**Upstaging Pathologic Specimen:** It is not unsurprising to hinge on the size of the core biopsy when diagnosing ductal carcinoma in situ. The higher the volume of the biopsy, the less sampling error there will be; however, today there is approximately 12% risk of finding a small invasive cancer in a patient who is being operated on for ductal carcinoma in situ.
Triple Negative Breast Cancer

Management Approaches: One of the most important things to remember is that histologies, such as triple negative breast cancer or HER2 positive breast cancer, are very important for the adjuvant treatment of that disease. In terms of surgical management however, there is little difference. Triple negative breast cancer is a very aggressive disease so it is vitally important that these patients receive chemotherapy because endocrine therapy will not work. While we are very aggressive in adjuvant treatment, this does not mean the patient is not a good candidate for breast conservation. The risk of local recurrence for these patients is very similar to those patients who have a routine ER positive breast cancer. If the tumor is >1 cm in size, medical oncologists are likely to recommend cytotoxic chemotherapy because there are no other systemic treatment options for such a patient. However, the mistake that surgeons make sometimes is suggesting a mastectomy when this is simply not always the case.

Gynecomastia

Treatment of Gynecomastia: For males, gynecomastia is a very common cause for referral to a breast clinic. Typically, these patients are looking for reassurance that they do not have a breast cancer and that they are not at an increased risk for developing a breast cancer in the future. We do not prescribe any specific treatments for this issue, as the majority of gynecomastia is idiopathic. However, a few instances in which to explore would be a pituitary tumor, increased usage of marijuana, and the usage of certain medications that could lead to gynecomastia as a side effect. There is a percentage of men who are concerned with the physical traits of gynecomastia to the point that they seek reconstructive surgery, which is an appropriate and reasonable method of treatment. This treatment would involve a combination of liposuction and subcutaneous mastectomy.

Breast Cancer in the Male Patient

Occurrence of Breast Cancer: The incidence of male breast cancer in the United States is just more than 2000 cases per year. Approximately 1% of the breast cancers we see in the United States are in male patients. These patients come to us after a newly identified breast mass that cannot be classified as gynecomastia. For the adult male, a bilateral, 1-view mammogram is ordered because gynecomastia is very clear on a mammogram. As we age, it is not uncommon to develop some degree of gynecomastia. Screening is not required in these patients unless he comes from a very high-risk family or is a BRCA mutation carrier.

Disease Outcomes and Progression: Stage per stage, men and women fair exactly the same in regard to breast cancer outcome and progression. In fact, men may fair slightly better than women. The key thing to remember with staging breast cancer in men is that when staging the breast we talk about the T-stage and direct skin involvement. A high T-stage is equivalent to a stage 3 breast cancer. When men develop breast cancer, the breast is very small and there is not much room. The patient could have a 1 cm cancer with skin involvement, whereas it is unusual for a woman to have a 1 cm breast cancer with skin involvement. Even comparing men and women stage per stage is not fair because men are going to fair better because the tumor volume at risk to metastasize is much smaller than it is for a woman.
**Common Benign Breast Conditions: Mastalgia**

**Diagnosis and Treatment:** For women, the main concern with coming into a breast clinic is the possibility of her having a breast cancer. The patient who is presenting with breast pain should have adequate breast imaging. If the breast imaging is completely normal and her physical exam is normal, then reassurance is typically all that is needed. Breast pain is very common and it is usually cyclical. Breast pain is not an indication that the patient has breast cancer or is at an increased risk to develop it later on. However, one should always consider breast cancer in a patient with unilateral focal breast pain. While it is generally true that breast cancers are not painful, sometimes a rapidly growing breast cancer can cause pain. For the majority of the time, mastalgia is not a sign of malignancy. For the small sub-population of women whose day-to-day activities are limited by breast pain, the first line of treatment would be a non-steroidal anti-inflammatory medication. If the pain is still persistent and prohibits her from carrying out normal duties and responsibilities, she could be referred to an endocrinologist for management with tamoxifen or another agent that acts on the pituitary.

**Tamoxifen as Treatment:** While tamoxifen is effective at controlling breast pain, the side effects of using the medication mimic symptoms of menopause; as if you are trading off 1 set of symptoms for another. For most women, the menopausal symptoms are worse than the breast pain so discontinuation is advised.

**Common Benign Breast Conditions: Nipple Discharge**

**Normal Nipple Discharge:** Nipple discharge is normal in most women. Usually, one would notice nipple discharge if the breast is squeezed, or in the shower, or after sex. When the nipple discharge becomes spontaneous, that is when we would become inquisitive. The patient notices it on her bra or night clothes and it doesn’t go away. Another thing we would find concerning is the presence of blood in the discharge. Normally, nipple discharge comes in a variety of colors. When the discharge is bloody and if it is copious and spontaneous. In summary, if the nipple discharge is not spontaneous and is not bloody, and only occurs when the nipple is squeezed or when wearing tight clothing, etc., that is normal and no cause for concern. Nipple discharge that is clear and blood-tinged, copious, and spontaneous is typically the symptoms of a papilloma or a sign of malignancy.

**Diagnosis and Treatment:** Ductal carcinoma in situ and invasive breast cancer can sometimes present in a similar way. The usual recommended workup is routine breast imaging. If you have breast imagers who are facile at performing galactography or a ductogram, those tests may be ordered as well. If the ductogram is abnormal and the filling defect is close to the nipple, typically closer than 1 cm – 2 cm, one would note it. If the defect is further from the nipple, a clip would be placed in the area and the patient would be taken to the operating room for a central duct excision. The clip would be localized with a wire or radioactive seed and the central duct excision would be performed. It is not unusual that the filling defect will be > 2 cm from the nipple. In those cases, we like to localize it. If the filling defect is close enough to the nipple that we know it will come out with a routine central duct excision, we will not bother localizing it. If the galactography or ductogram is completely normal, the standard thing to do is to proceed with a central duct excision with the idea that if there is a malignancy there it will likely be very close to the nipple and will come out with a central duct excision. When performing the central duct excision, we typically use a probe in order to keep the excision in the correct placement. Using the probe can be cumbersome, but with persistence, the probe can be placed in the fluid-producing duct. One of the positive outcomes of a central duct excision is that the symptoms are eradicated.
Evaluating the Importance of Scoring Systems in Breast Cancer Diagnoses

Various scoring systems are used to describe the histologic grade of a breast cancer on a pathology report. Once a woman has been diagnosed with breast cancer, scoring systems are not particularly important in the immediate period while determining treatment options. She has a breast cancer so we are talking to her about local treatment options and her potential for systemic therapy. We frequently counsel women regarding their risk of contralateral breast cancer; however, once a woman has a breast cancer we have very nice longitudinal data demonstrating what the risk of contralateral breast cancer is based on her age at diagnosis, the molecular features of her index cancer, and the treatment that she is going to receive for her index cancer. These systems are not a large part of how we counsel women regarding their contralateral breast cancer risk when women are already diagnosed.

Scoring Systems in Benign Breast Disease: Scoring systems can be used when counseling women who have not received a diagnosis of breast cancer – women who are coming in with abnormal mammograms proven to be benign, or women coming in because they want to talk about their risk and family history. In these situations, scoring systems can be helpful to inform the discussion. However, it is important to remember that the systems are all quite different. They have different input variables, and there is not one that is necessarily better than the others. On a broad level, 1 system may be best for an individual but not for another.

Determining MRI Screening Threshold

Breast MRI is only recommended for breast cancer screening in women with a high lifetime risk for breast cancer. The widely accepted threshold at which women become eligible for screening via breast MRI is when they have a >20% lifetime risk of breast cancer.

Candidates for MRI Breast Screening: There has been a lot of publicity and discussion around who should have MRI screening. The cutpoint of lifetime risk of 20% comes from previous studies demonstrating that women at that level of risk could benefit from the addition of MRI screening as far as increased detection of malignancy. However, that numerical value was generated from populations of women who were at that level of risk based on their family histories of breast cancer.

The Role of Family History in Determining Models: When determining eligibility for MRI screening, it is important to use a model that accounts for family history. The lifetime breast cancer risk of >20% is supposed to be generated by models that largely rely on family history. There are certainly other women who are at increased risk of breast cancer that may be generated by other factors, not necessarily their family histories, such as a previous history of benign breast disease; we do not have clear guidelines for when MRI should be used in those women. The guidelines regarding MRI screening should be used in women whose risk is driven by family history.

Contralateral Breast Cancer: Risk Factors & Effect of Antiestrogen Therapy

Many women with a diagnosis of breast cancer overestimate their risk of developing a contralateral breast cancer. Important risk factors for contralateral breast cancer include age of their first breast cancer diagnosis, the molecular features of their first breast cancer diagnosis (such as the tumor’s estrogen receptor [ER]), and the treatment they will receive for their index breast cancer.

Contralateral Risk vs Antiestrogen Therapy: Treatment for women with ER+ index breast cancers will include antiestrogen therapy (“hormonal therapy”). The risk of contralateral breast cancer while using this type of therapy is actually quite low. Data from the SEER registry support that the annual hazard for contralateral breast cancer is 0.3% - 0.5% per year, which is much lower than what most women expect. All factors regarding a woman’s current cancer and her current treatment must be
incorporated into the risk assessments for contralateral breast cancer. The older data, before we incorporated effects of treatment, would counsel women that the risk of contralateral breast cancer was about 0.7% per year over 10 years. We now understand that the molecular biology of the tumor and the treatments that we use for the index cancer have a substantial risk reduction. The same impact is seen with women who have HER2+ breast cancers who receive anti-HER2 therapy. Those therapies are also very effective at reducing the risk in breast cancer recurrence and reducing the risk of contralateral breast cancer over time.

**Associated Risks and Benefits of Hormonal Therapy**

Antiestrogen therapy is often administered to women with ER+ breast cancer. For most women, hormonal therapy is very safe. However, we must distinguish between a premenopausal woman and a postmenopausal woman taking hormonal therapy when we discuss the downsides of antiestrogen therapy. **Treatment in Premenopausal Women:** For premenopausal women, tamoxifen is administered, which is a very safe medication. The most commonly cited risks of tamoxifen, or most commonly cited serious risks of tamoxifen, include an increased risk of Deep Vein Thrombosis (DVT) and pulmonary embolism and an increased risk of uterine cancer. However, those risks are quite minimal in premenopausal women. **Treatment in Postmenopausal Women:** In postmenopausal women, depending on other comorbidities, the risk of DVT, pulmonary embolism, and an increased risk of uterine cancer can be higher and, therefore, preferentially we try not to use tamoxifen in postmenopausal women; instead, we prefer to use the class of medications called aromatase inhibitors, which do not carry the same effect of increasing DVT or increasing risk of uterine cancer. Nonetheless, those risks are still very small compared to the benefits obtained by using hormonal therapy in a woman who has an ER+ breast cancer. **Risk of Contraindications in Administering Hormonal Therapy:** Type of tumor, nodal involvement, risk of relapse, and history of contraindications must be taken into consideration when prescribing the use of hormonal therapy. If previous history of an associated side effect exists, we try to understand if there is an explainable cause for her previous history. For example, if the patient presents with a history of DVT, we must determine if she actually has a hypercoagulation disorder. Was this following an injury and immobility? Is there reason to think that she was at transient risk, or is this a real risk of venous thromboembolism (VTE) for this patient? Once all of those risks and benefits are taken into account, an informed decision can be made whether tamoxifen is appropriate for that patient or not. Unfortunately, in the premenopausal women, there is not another alternative that does not require ovarian suppression. If a premenopausal woman with a high-risk cancer presents, and you feel it is very important to provide some type of antiestrogen and you cannot give tamoxifen, then the alternative is ovarian suppression, which also comes with its own set of side effects.

**Determining Onset of Mammography Screening**

Determining a woman’s likelihood of developing a breast cancer is imperative when deciding on the onset of mammography screening. If a woman is at a low or normal risk of developing breast cancer, then the process becomes one of shared decision-making between patient and physician. There is the possibility of false positives for some women. The new guidelines for women with a lower risk of breast cancer suggest starting screening later on or doing biannual screening. However, women with an elevated risk, women who have a family history of breast cancer, or women who have had a previous biopsy showing proliferative changes, should adhere to the traditional guidelines of starting mammographic screening either at the age of 40, or 10 years younger than the youngest affected family member.
**False Positive Results in MRI Screening:** The likelihood of receiving a false positive result increases when the frequency of breast examinations, mammograms, ultrasounds, and MRI screenings increases. For the woman who has an average risk for breast cancer, we discuss the likelihood of a false positive and possible downstream consequences. Breast density is also a factor to consider when increasing the amount of screenings. Most women are not worried about their false positive possibilities. Instead, they are more worried about the possibility of a false negative or a missed diagnosis of breast cancer.

**Using MRI to Diagnose Adenocarcinomas when Mammogram is Negative:** Further investigation is needed if a biopsy confirms a diagnosis of adenocarcinoma, but the mammogram is negative. In this setting, a breast MRI is clearly indicated and will identify the underlying lesion in about two-thirds of cases. This affords women the opportunity to have the same discussion regarding their local therapy treatment options. The MRI shows a lesion, a biopsy is performed, the diagnosis is established, and then we decide whether a woman is a candidate for breast conservation or requires mastectomy in the setting of the known lesion. If the MRI is negative, any significant disease burden within the breast has been ruled out. There is the possibility of a microscopic lesion that is not showing, but the MRI has ruled out any significant disease burden that we no longer consider mastectomy the only option. There are many women who are treated with axillary node dissection because of the adenopathy and whole breast radiation therapy for local control of the breast. The outcomes have been very good with this approach.

**Determining the Source of Adenocarcinoma:** If the MRI is negative, steps need to be taken to examine the patient’s other risk factors and appropriately exclude other primary lesions. In most cases it is going to be occult breast carcinoma unless there is a red flag in her history to suggest otherwise.

**Diagnosis and Treatment of Paget’s Disease**

**Diagnosing Paget’s Disease:** Paget’s disease is a clinical diagnosis. Making a clinical diagnosis requires an awareness of physical changes that occur to the nipple or the nipple-areola complex, and possessing a high level of suspicion when you see these physical changes. A biopsy must be performed to either confirm or rule out presence of Paget’s disease. Clinicians are advised to avoid assuming that an erosion or ulceration of the nipple is from trauma, and to have a low threshold for performing a biopsy to establish the diagnosis.

**Confirming Diagnosis with Breast Imaging:** Breast imaging is an important part of making a diagnosis when a woman presents with classic changes in the nipple-areola complex. A diagnosis of Paget’s disease is established when mammography or ultrasound imaging in the retroareolar position shows an abnormality, and a biopsy of the breast demonstrates a pathologic carcinoma. However, if breast imaging is normal, a biopsy must still be performed to be sure the changes you are seeing are not the result of another disease.

**Treatment Options for Paget’s Disease:** Similar to the situation with occult breast cancers, many women with Paget’s disease will present with normal mammograms. Historically, we thought that meant they required mastectomy because we were not sure where the underlying disease was or the extent of it. Now that we utilize breast MRI, if a woman with Paget’s disease is interested in considering preserving the breast, the MRI may show the extent of the underlying lesion. If the lesion is confined to the central area of the breast or directly posterior to the nipple-areola complex, she may be a candidate for a central lumpectomy, in which we would remove the nipple-areola complex, obtain a negative margin on the breast parenchyma, preserve the breast mound, and continue on with whole breast radiation therapy. However, if the MRI does not show a lesion, the physician and the patient will make the decision either to attempt a central lumpectomy and hope that they get a clear margin on the breast parenchyma, or to proceed with mastectomy. In recent years, the trend has moved from automatically doing mastectomy for all Paget’s disease patients, to considering the viability of breast conservation. The imaging modalities we now have help determine if a patient is an appropriate candidate. However,
we must understand that the final determination of whether a woman can save her breast comes from the pathologic evaluation of the tissue and being able to obtain a clear margin.

**Lymph Node Biopsy:** Paget’s disease may be the external manifestation of an invasive breast cancer in the breast, or it may be the external manifestation of intraductal (“in situ”) breast cancer. If a woman presents with a preoperative diagnosis of invasive breast cancer, a sentinel node biopsy would be performed. If the patient presents with a diagnosis of Ductal Carcinoma In Situ (DCIS), surgeons must factor in different clinical variables to help them decide if node biopsy is appropriate. If a central lumpectomy has been performed, going back and performing the sentinel node biopsy is still viable. The ability to take a “one-step-at-a-time” approach has not been lost if you choose to perform the central lumpectomy and see if there is invasive disease or not. There are other factors that can suggest a higher likelihood of finding invasive disease (e.g., the presence of a mass lesion on imaging, high-grade DCIS, or calcifications that extend over several centimeters). Surgeons may often use those criteria to weigh the risks and benefits of performing the sentinel node biopsy at the first procedure and discussing the advantages and disadvantages of that approach with the patient.

**Need for Further Therapy:** If all the disease is in situ, further therapy would include whole breast radiation (assuming you have achieved negative margins), and a discussion of whether or not the patient is a candidate for hormonal therapy, given that her DCIS was ER+ and if she is interested in pursuing hormonal therapy. If the patient is found to have invasive breast cancer on final pathology, the subsequent treatment decisions would be made based on the molecular features of that cancer and an appropriate nodal evaluation.

**Outcome of Breast Conservation:** There is no difference in the outcome of breast conservation between a woman with Paget’s disease and a woman with early stage breast cancer without Paget’s disease. There are no increased rates of local failure and no differences in overall survival by treating Paget’s disease with conservative therapy.

### Inflammatory Breast Cancer

**Diagnosing Inflammatory Breast Cancer:** A diagnosis of inflammatory breast cancer can be difficult to make, depending on how well the patient is able to relay the history to the physician. The classic diagnostic criteria for inflammatory breast cancer are the sudden onset and progression of breast swelling, and erythema. In inflammatory breast cancer, erythema is supposed to encompass greater than one-third of the area of the breast and is frequently associated with edema of the skin, or the so-called peau d’orange (“orange peel”) look of the skin. There may or may not be an underlying mass lesion present on the mammographic findings. The role of the skin biopsy to show dermal lymphatic invasion is complementary. A positive skin biopsy is not needed to make a diagnosis of inflammatory breast cancer if all the other clinical signs and symptoms are present. The rapid and diffuse nature of skin involvement is key in distinguishing these changes from a woman who presents with a neglected breast cancer. In that case, the patient has had a mass in the breast for several months and over the last few months she has noted some development of erythema or skin edema at the site of the mass. Those changes would not be consistent with inflammatory disease. Those changes would be consistent with a local advanced breast cancer that has now resulted in erythema from the local changes in the tumor. Time, course, and extensive involvement are imperative in making that differentiation. It comes down to how well we are able to elucidate those findings and facts from the patient.

**Treatment:** Inflammatory breast cancer falls into the category of what we typically term “inoperable cancer.” These patients should be treated with upfront systemic therapy. It is critical that they first have appropriate staging workups prior to starting treatment due to their higher incidence of presenting with metastatic disease than patients with non-inflammatory breast cancer. Surgery is an important part of the treatment plan but should only be undertaken once the systemic therapy has been delivered and the response has been evaluated. If the patient still has significant skin changes and does not have a good
response to systemic therapy, surgery may be delayed in favor of additional systemic therapy and/or radiation therapy to the breast. Response is very important in determining when someone is an appropriate candidate for surgery.

**Outcomes of Systemic Therapy:** Postmastectomy radiotherapy outcomes are significantly better than they were 10 or 15 years ago when the trimodal approach (chemotherapy, radiation therapy, and surgery) is used. However, they are still far inferior to women presenting with non-inflammatory breast cancer. This remains an important area of research for us in trying to elucidate the differences between inflammatory disease versus non-inflammatory disease and the potential drivers used to develop new targeted therapies. Breast cancer cannot be considered as 1 disease; rather, it encompasses several different subtypes (eg, triple negative disease, HER2 positive disease, and ER+ disease).

Even with our best available therapies within those subtypes, patients with inflammatory disease fare a bit worse than patients with non-inflammatory disease. Patients need intensive trimodality therapy and we still need more research to try to identify novel agents to target this disease. When you look at them in totality, inflammatory breast cancers are more likely than non-inflammatory breast cancers to be ER negative. The differences between the 2 are still being researched. They certainly have upregulation of genes and angiogenesis, but there has not been a lot of preclinical work supporting the use of angiogenesis inhibitors. We are researching the drivers that distinguish this disease from non-inflammatory breast cancer.

**The Role of Genetics in Breast Cancer**

**When to Utilize Genetic Testing:** The National Comprehensive Cancer Network (NCCN) have put forth very straightforward indications for genetic testing. However, criteria are constantly being added to the list. Dana-Farber/Brigham and Women’s Cancer Center use the following criteria to refer a patient for genetic testing: a patient that has more than 1 first-degree relative with a history of breast cancer, a family history of both breast and ovarian cancer on the same side of the family, a history of early onset breast cancer (meaning age <45 years), or a triple negative breast cancer at age <60 years. There are also scenarios in which patients do not have any first degree relatives but they have an extended number of second degree relatives with breast or breast and ovarian cancer. Oftentimes, family history of breast cancer is only reported on the maternal side of the family. However it is also important to ask about family history on the paternal side. Ancestry is also critical in determining risk of breast cancer. Patients who are of Ashkenazi Jewish descent have a much higher likelihood of carrying an inherited predisposition to breast cancer. Those patients will frequently be referred for testing regardless of any other tumor characteristics or family history.

**Choosing the Appropriate Genetic Test:** The testing used today is quite simple. In the past, we only tested for BRCA1 and BRCA2 in the majority of our patients. Today, that routine has been replaced by the use of so-called “panel testing.” These panels may have up to 30 genes on them. Several different companies are developing their own panel tests. Controversy surrounds discussions as to which panel test should be used and which ones insurance companies will pay for. Genetics counselors are encouraged to move into the forefront in order to help us to understand who should have testing, what kind of testing is available, and how to advise patients. Genetic counselors typically advise that there are no specific panel tests that are better than others. A patient’s family history, risk profile, suspicions about a disease that occurs less commonly (eg, Lynch syndrome, Cowden syndrome), or finding the most common breast cancer associated genes, are reasons to use genetic panel testing. Differing clinical scenarios may cause you to prefer one panel test to another, depending on what you are looking to explore. There are some genes that we understand the risks that they impart and there are other genes we are just beginning to accumulate information on. It is not uncommon for a patient who has just had genetic panel testing to come in having had a mutation in a gene that we know very little about; this makes counseling her on her risk of contralateral breast cancer challenging. For example,
say she already has 1 breast cancer that led her to have the genetic test performed. Let’s say the panel test turns up that she has a Checkpoint Kinase 2 (CHEK2) mutation and she wants to know how that impacts her risk of developing a contralateral breast cancer over time. We have no information to help us give her an accurate risk assessment. As a result, we extrapolate from what we know about breast cancer gene 1 (BRCA1) and breast cancer gene 2 (BRCA2). However, for many of these genes, we know that the risk is not nearly that high so we are asking patients to make decisions regarding their contralateral breast cancer risk when we have very little information to help them make that decision.

**Genetics Counselors:** Advising should begin with genetics counselors and all genetic testing should be done in the context of appropriate counseling. In some areas of the United States, hospitals are experiencing a shortage of genetics counselors. As genetic testing becomes more and more complex, it is important to have counselors in place who understand the limitations of the available data and that not all positive tests carry the same weight. These conversations carry over into the surgical clinic as we are making our surgical treatment decisions. It is very important to keep geneticists and neurogenetics counselors in these conversations as a resource when a panel comes back with a mutation or a finding that you are not familiar with.

**Online Genetics Testing:** Online genetic testing panels are marketed directly to patients. Results are available for downloading on a patient’s phone via an app. If those tests come back with something that we know a lot about (e.g., BRCA1, BRCA2, Cadherin 1 [CDH1], or phosphatase and tensin homolog [PTEN] mutation), we are able to counsel women and there is potentially no harm done. However, when those tests come back with genes that we know very little about, women are left trying to make decisions on their own. I had a patient who did genealogy as a hobby, so her children bought her a test kit online as a gift. She took the test and found out she is a mutation carrier. These types of stories are going to be more and more common to hear.

**Contralateral Prophylactic Mastectomy**

We have witnessed what many in our field refer to as an epidemic of contralateral prophylactic mastectomy (CPM) in women who are diagnosed with unilateral breast cancer. More recent data suggests that up to 40% of women who have had a mastectomy after being diagnosed with unilateral breast cancer will choose to remove the contralateral breast as well. A patient who has a significantly higher risk of contralateral breast cancer, such as mutation carriers and women who have a previous history of mantle radiation in adolescence, warrants a full discussion of the benefits of contralateral prophylactic mastectomy. However, the majority of women who chose this approach are not at an increased risk for contralateral breast cancer. Women who are being treated for an index ER+ breast cancer have only have a 3% to 5% risk of contralateral breast cancer over the next 10 years after diagnosis. Performing a contralateral prophylactic mastectomy in that scenario is not impacting her risk of contralateral breast cancer because the risk is so low to begin with.

**Helping Patients Understand the Value of Breast Conservation:** A great deal of time has been spent trying to understand patients’ motivations behind electing this aggressive surgical option. It is important to counsel them that CPM is not going to prevent the cancer that they have from coming back. It is not going to improve their survival. It is not going to decrease the likelihood that they will experience a recurrence of their breast cancer. However, for many women, removing the breasts gives them a greater peace of mind and relieves anxiety. Many physicians are working to untangle the level of anxiety that comes with a breast cancer diagnosis and the level of fear and worry about a second breast cancer diagnosis. Patients need to know what their real risks are. For the majority of women, the risk of contralateral breast cancer over a 10-year period is very low. Great strides have been taken recently to try to understand how these decisions are made and to develop decision aids or shared decision-making models to help physicians help patients walk through this choice and to understand the benefits and risks from taking this approach.
Contraindications: A breast cancer diagnosis carries with it anxiety and fear of recurrence. Because we live in such a connected society, women are able to get information from any source. People are talking about how mastectomy was the right choice for them and how good they feel about their choice. It then becomes hard for another woman to opt for breast conservation after seeing a successful story from another woman. Many celebrities in the media discuss the choices they made and how successful they were but we do not hear people speaking out about saving their breasts. It is quite challenging to teach women to think about the choices they are making. She needs to be informed not only about the good results, but that there is a significant minority of women, 25% to 30%, of women who are not happy with the decision to have contralateral mastectomy. They experience more pain than anticipated, required more surgeries, and experienced a decrease in sexual desire and self-confidence. The only women discussing contralateral mastectomy positively are the women who are very satisfied with the results. More counseling is needed in regard to both the positive and negative side effects of the treatment, but this will take some time. Even with all our approaches to reeducate women on the importance of breast conservation, there are still going to be some women who are determined that mastectomy is the right approach for them. In those situations, we cannot tell them that they are wrong. However, we spend a considerable amount of time listening to the patient and figuring out her driving factor so that we can present information to the patients to help them in making these decisions.

Breast Reconstruction

Skin- and Nipple-Sparing Mastectomy: Although we refrain from saying that there is a “usual” case, skin-sparing mastectomy is the most common approach for women who desire immediate breast reconstruction. This procedure involves preserving the skin envelope within the breast. Today, we are seeing more women opting to preserve the nipple, or the nipple-areola complex. When preserving the nipple, special precaution should be taken so there is no involvement of the retroareolar ducts. Skin sparing and nipple sparing afford women very desirable cosmetic outcomes. The oncologic safety of the 2 procedures is fairly well established - the skin sparing more so than the nipple sparing. We are seeing more data emerging that show the rates of local recurrence are not significantly higher, assuming that there is not a significant amount of breast tissue or breast ductal tissue left behind the nipple. However, not everybody is a good candidate for this approach so it requires a multidisciplinary discussion between the breast surgeon and the plastic, or reconstructive, surgeon in selecting patients who are appropriate to keep the nipple-areola complex. The nipple-areola complex needs to be in the appropriate position on the reconstructed breast. For women who have a significant amount of ptosis, this may not be the case after reconstruction has been completed.

Patient Safety and Overall Satisfaction: Each patient presents us with a different scenario and oncologic safety of offering these approaches is very important but we must also take into consideration what the reconstructive outcome will be. Each woman will have to make her own decision regarding what her expectation is regarding breast reconstruction. It is very rare that these procedures require a 1-time surgery so women considering these procedures need to understand all the risks and benefits. This approach frequently requires multiple procedures and a process to go through before you achieve the final result. One of the most important things to be remembered is that these women are making an immediate reaction by removing both breasts even though it seems like the most appropriate thing to do. They want to be rid of the breast, be rid of breast cancer, and to sleep peacefully at night. A balance must be maintained of being sensitive to her wishes but also equipping her with the most accurate information regarding her risks.
Pregnancy and Breast Cancer

Many physical breast changes occur naturally with pregnancy. However, it is important not to dismiss a breast lump or a breast finding as mastitis, or another pregnancy-associated change. If a woman is of an age that she could be at risk for breast cancer, imaging studies and ultrasounds need to be performed to look at any breast abnormality. There is no harm or exposure from ultrasound in the pregnant patient. Pregnant patients can also undergo mammography with appropriate shielding in place if it is essential in making the diagnosis. Depending on the stage of the pregnancy or the gestational age of the baby, breast conservation may be an option. If a diagnosis is made in the first trimester, mastectomy will be the preferred approach, however we are now seeing an increasing use of preoperative therapy in pregnancy-associated breast cancer. We now have safety data that states chemotherapy may be administered during pregnancy without any negative side effects to the baby. This affords the woman an opportunity to start her treatment and receive breast conservation, if interested, either toward the end of the pregnancy or after the delivery. These are complicated scenarios that depend a lot on the stage of diagnosis. Determining the stages of the lesion and the pregnancy and maintaining viability of the pregnancy are factors to be taken into consideration when determining best practices.

Pregnancy After Breast Cancer: Historically, encouraging women to become pregnant after a cancer diagnosis was considered a bad idea. We would counsel women that they needed to wait at least 2 to 5 years before even considering a pregnancy. We were concerned that a subsequent pregnancy would increase the risk of relapse. All of our data is still retrospective with respect to this question. There has yet to be any true signal that pregnancy after breast cancer portends a worse outcome for the mother. We still encourage women to complete all of their therapy; sometimes in the setting of HER2 positive disease, that is a whole year of therapy. In the setting of ER+ disease, that may be 5 years of therapy. We encourage women to complete the anticipated treatment, but there is a prospective trial going on now, internationally, that monitors the outcome of women who opted to stop their tamoxifen therapy before the 5 years are completed in order to get pregnant. While we still have a lot of research ahead of us, we have gotten away from the 1-size-fits-all approach of discouraging pregnancy after breast cancer.

Chemotherapy Regimen: For the pregnant patient there are certain agents that should not be used. The standard chemotherapy that we give today for preoperative therapy is anthracycline (AC) and Cytoxan. Depending on the initial stage of the disease and where patients are in their treatment course, additional therapy may be deferred, or you can go ahead with taxane. Anti-HER2 therapy is not administered during pregnancy but traditional chemotherapy is fine.

Screening Guidelines

Screening guidelines for breast cancer change frequently. It is important for the general surgeon to stay abreast of all new guidelines and to work with the patient in terms of her safety and need for screening. In the past, there were 2 schools of screening guidelines; today, we have 3 schools of screening guidelines. Guidelines: Traditional guidelines are liberal and suggest starting screening at age 40 years, with no specified age limit, and include clinical breast exams. These guidelines are still endorsed by the American College of Radiology and by the American Society of Breast Surgeons. The second set of guidelines, which are set by the U.S. Preventive Services Task Force, are very conservative and rely heavily on data. These guidelines do not show evidence for screening women aged 40 to 49 years, or after age 75 years. The only women they suggest screening are those aged 50 to 74 years, and it is further suggested that the screenings are scheduled biennially, occurring every other year. The final set of guidelines is the new American Cancer Society (ACS) guidelines, which were introduced in 2015. These guidelines suggest annual screening starting at age 45 and ending with age 54. At age 55, biennial screening is recommended with no prescribed age cut off. One of the major differences in the
new ACS guidelines is that they no longer suggest clinical breast exams, however, they state that women should have the option to adhere to the traditional guidelines. 

**Need for New Data Sets:** Most of the data being used to drive these current guidelines are outdated. The best example of this is the Canadian National Breast Cancer Screening Study, which was published in 2014 in the *British Medical Journal*. The study was used to justify screening for women aged 40 to 49 years; however, the study was conducted between 1980 and 1985 using inferior mammography equipment that did not meet the quality standards of the United States. The detection rate for breast cancer in young women was really low for survival rates. Because our tests are ever evolving, new data are needed in order to mold the new guidelines for screening so that we are better serving our patients.

**Digital Mammography in the United States**

**Tomography to Replace Traditional Mammography:** In the United States, screening is increasingly moving towards the use of tomography. At Oregon Health and Science University (OHSU), the traditional mammogram has been replaced with 3D mammography, or tomography. These tomograms are not to be confused with those of the 1970s and 1980s. Today, tomography is composed of 3D computerized images. Tomography is beneficial for women with dense breasts and it boasts the least risk, as opposed to the MRI. As tomograms become more popular across the United States, the need for MRI breast screening will decrease.

**Decreased Rate of False Positives:** The use of tomography will decrease the rate of false positives in patients. We are now able to get a clearer picture of breast tissue using 3D tomography than we could with traditional mammograms. Another benefit of using the new tomography technology is that we will begin to see a lower rate of BIRADS 0 scores, thus decreasing the need for re-screening.

**Rate of Interval Cancer:** The rate of cancers that are identified between screenings is likely to decrease, however they will probably never reach zero. Eighty percent of patients with complaints of breast issues will have benign diagnoses. Twenty percent of those patients will have a BIRADS 5 score, which means it is suspected that they have breast cancer until biopsy proves otherwise. We could try to draw that number out even more, but there is the possibility that we could be missing some cancers. Because of updated biopsy procedures and techniques, we are decreasing the need for open surgical biopsies. The only time we would move forward with a biopsy is to follow up with a needle core biopsy. With biopsies becoming safer and more accurate with immunostaining and other improved techniques, we are able to follow more lesions. However, with all these new advances, we must still be cautious and diligent in detecting cancers, which is of the negative effects of the more conservative screening guidelines.

**Overtreatment of Early Breast Cancer**

**Overtreatment of Lobular Carcinoma In Situ:** Lobular carcinoma in situ (LCIS) is, perhaps, being over treated if we look at it in terms of risk. LCIS is a non-obligate precursor risk lesion, which means that it does not become a site-specific cancer. It is usually found incidentally while the patient is undergoing treatment for other medical issues. LCIS increases risk of breast cancer bilaterally, and that risk increase is 1% - 2% per year. It is these patients who are currently considered for chemotherapy prevention or are considered for some of the more liberal screening guidelines. The lesson for the general surgeon is if the lesion is LCIS, these are the patients that should be increasingly screened and considered for chemotherapy prevention, however, it is not a surgical target.

**Overtreatment of Ductal Carcinoma In Situ:** There has been controversy in the past year regarding the overtreatment of ductal carcinoma in situ (DCIS). This was spawned by a paper published by Steven Narod, in the *Journal of the American Medical Association* (JAMA) in 2015 where Narod stated that, after researching the SEER database, he found that the death rate for DCIS was 3.5%, which was not an
expected rate for this disease. After being interviewed about his findings by the New York Times, it was suggested that he meant DCIS did not need to be treated aggressively. It is believed that he was misquoted and the controversy was born. Perhaps what he meant was that DCIS did not need to be treated as aggressively after successful surgery. Later on, Kevin Hughes, Director of The Breast Center at Massachusetts General Hospital, published a paper in Breast Cancer Research and Treatment highlighting 3 important points regarding a diagnosis of DCIS: first, DCIS must be surgically removed; second, mortality is not the only end point for this disease, many other outcomes exist (ie, development of invasive cancer, loss of breasts, recurrence, nodal involvement); and finally, DCIS is not a single disease; each patient should be treated on a case-by-case basis. For example, darker ethnicities yield a worse prognosis in DCIS. The more carefully we look at the factors of DCIS (grade, size, necrosis, receptor status), we are able to customize a treatment plan for each patient that is best suited.

Personal Experience: A young, African American premenopausal woman presented with concerning symptoms. Her mammogram showed extensive calcifications. We performed a few core biopsies that confirmed high-grade DCIS. She had previously been placed on tamoxifen, which proved to be ineffective because the calcifications were not disappearing. The calcification was surgically excised and it was found that she had a microinvasion and a positive sentinel node. These cases are important to note, as it confirms that DCIS cannot be treated in generalities. Treatment of this disease needs to be customized for each patient based on her factors.

Oregon Health and Science University Treatment Guidelines for DCIS

Lumpectomy: For the patient who exhibits little or no risk factors for surgery, and she presents with worrisome features, we would excise the tumor and perform a biopsy. DCIS requires surgery and is still considered the standard of care for this diagnosis. There is some controversy regarding margins, but at Oregon Health and Science University, we excise to no ink on margins, which are the new guidelines for invasive cancer. Unfortunately, some patients may require mastectomy if the disease is extensive, but most of our patients can be treated with only a lumpectomy.

Determining Need for Radiation Therapy: If DCIS is low grade, we do not offer radiation therapy; if it is high grade, we will offer radiation therapy. If DCIS is intermediate grade, we perform an Oncotype DCIS, which is a test that radiation therapists are using increasingly to help them determine if a patient would benefit from radiation therapy. Patients with ER-positive cancer will also be treated with tamoxifen, as well as those who do not want to proceed with surgery, or who have already had surgery. However, it is important to note that operating on DCIS is the standard of care. DCIS is a very serious diagnosis that can progress quickly to an invasive cancer. Invasive cancer cannot be ruled out with adequately treating DCIS.

Gene Expression Testing

Oncotype Testing Options: Oncotype DX is a 21-gene assay test that helps radiation therapists determine the need for adding chemotherapy to surgery and hormone therapy for the patient with node-negative invasive DCIS. Oncotype DCIS differs slightly from Oncotype DX in that the Oncotype DCIS is generally classified as a Genetic Expression Profile (GEP). We are seeing increasing numbers of radiation therapists using Oncotype DCIS to determine which patients do not need radiation. These data correlate with the Van Nuys scores, which were conducted by Melvin Silverstein with the Van Nuys Clinic in California. Oncotype DCIS culls out those patients with DCIS who have higher risk for recurrence so that we are reducing the death rate from this disease.

GEP Used for Tumor Genetics: While GEP is not useful in genetic counseling, it is beneficial for profiling tumor genetics. Genetic counselors look to the patient’s genome to discover any risks of
developing breast cancer, while the GEP tests are used in order to assess characteristics of tumors such as growth history, demographics, and histologic and immunochemical features. Performing genetic profiling on tumors brings us closer to providing personalized medical treatment.

**The Future of GEP:** In the future, we will begin seeing increasing use of big data; for example, the early breast trial data that is conducted by Dr Pio and published in the *New England Journal of Medicine* every year. Large amounts of information are now more easily accessible with the technological advancements we have seen over the years. Doctors will be able to pull up charts and graphs to show patients these data and where they stand in terms of prognosis, survival rates, and treatment. Having information presented in this way will make counseling patients easier and more efficient. We will also begin to see more GEP tests coming out for various cancers. The challenge therein lies in determining which GEP tests will be the most useful. Oncotype DX and Oncotype DCIS are very good tests that are well established. Another challenge we face is that the FDA will approve tests before we know what the clinical use is.

**Triple-Negative Breast Cancer Treatment**

**Terminology:** Luminal A cancers, which are most cancers, will produce an ER expression. These are the cancers that look most like normal breast cells and have the best prognosis. Luminal B cancers are similar to luminal A cancers in that they are ER positive. They may be PR positive, but they have amplified oncogene HER2; the prognosis for this type of cancer is slightly worse than luminal A. Finally, HER2 cancers produce the largest amount of gene expression. These cancers have a better outcome than the luminal cancers.

**Treatment:** The challenge with triple-negative cancers is that there is no current target for treatment. The only option available for these patients is cytotoxic chemotherapy; they are not eligible for hormone therapy, as they cannot obtain growth factors.

**Prognosis in Minorities:** Fortunately, triple-negative cancers make up the smallest percent of cancers, accounting for 12% of all breast cancers. Patients are frequently young African-American or non-white women. Socioeconomic status and lack of available medical care may factor into the survivability of minorities with triple-negative cancer; however, there is some degree of biologic factors that contribute to survivability.

**Prognosis in Genetic Carriers:** Patients who are *BRCA1* positive usually have worse biology cancers than the general population, as we see more triple-negative cancers in these populations. *BRCA2* have risk factors that are similar to that of the general population. Most of these cancers are invasive ductal cancers and are mostly high-grade and should be considered for cytotoxic chemotherapy. Patients with these genes also need to be considered for genetic counseling, as part of the new guidelines for genetic counseling is to include triple-negative breast cancers, particularly if the patient is young, because there is a link between these types of cancers and BRCA-1.

**Breast Preservation:** Triple-negative cancers are more locally aggressive. They are nodal, have distant metastatic potential, and produce more cases of local recurrence. However, they can recur after both breast preservation and mastectomy, therefore breast preservation is not contraindicated. These patients are the ones who receive chemotherapy upfront. Half of those patients will have a pathologic clinical response (CR); however, we do not have sufficient data to show that it will actually improve survival. This is not true in high-risk triple negatives. When you look at triple negatives, especially young non-white patients who achieve a path CR with neoadjuvant chemotherapy, there is mounting evidence that those patients are the group that actually have a survival benefit from a neoadjuvant approach.
Cytotoxic Chemotherapy

**Standard of Care:** The standard of care for triple-negative breast cancer is the use of Adriamycin, Cytoxan, and a taxane (ACT). Adriamycin is an anthracycline; these are dangerous drugs and they are the ones associated with classic alopecia and cardiotoxicity. These drugs are the reasons we order baseline multigated acquisition scans (MUGA) and cardiac function scans. They are also vesicants that cause sclerosis, which is the reason ports are placed in patients. Cytoxan is a somewhat safer drug although it can cause hemorrhagic cystitis. The taxanes that are commonly used are paclitaxel or docetaxel. We now have biologics such as Herceptin® (trastuzumab and pertuzumab) for HER2-positive patients that act on slightly different parts of the HER receptor.

**Controversy in Neoadjuvant Therapy:** There is some controversy regarding the use of Adriamycin in the standard of care. Because of its toxicity and contraindications, doctors are beginning use a combination of Cytoxan and other taxanes instead of Adriamycin. Leaving Adriamycin out of the standard of care reduces risks of cardiotoxicity and alopecia. Current trends show that the use of ACT is more prominent on the east coast of the United States than that of the west coast. There are studies being conducted at the University of California Los Angeles that suggest we can leave Adriamycin out of the treatment plan. However, for neoadjuvant therapy, we are still seeing ACT used frequently.

Lumpectomy

The “Achilles heel” of lumpectomy is the need to re-excise the margins. Research has been conducted over the last decade to determine how we can minimize the need for secondary procedures. Not only does the patient have to go back in for surgery, which causes anxiety, she may decide that she wants a mastectomy so that she may avoid further re-excisions.

**Quality Measurements:** The rate of re-excision is as high as 70%; the average need for re-excision is about 20% to 40%, nationwide. The first step in lowering the rate is to track the rates. In the last decade, frozen sections and imprint cytology have been used to reduce the amount of secondary surgeries. Imprint cytology is a process in which the excised mass is rolled onto a slide, allowing the surgeon to look for additional tumor cells. This process has been proven in multiple trials to decrease the rates of a second lumpectomy. Another process we are using now is intraoperative radiography. In this process, x-ray machines are placed in the operating room. Once the excised portion has been retrieved, it is placed inside the machine and a specimen radiograph is produced. The surgeon is able to closely view the area to determine if additional tissue must be excised.

**New Guidelines:** New guidelines were introduced last year and were endorsed by the Society Surgical Oncology (SSO) and the American Society for Therapeutic Radiation Oncology (ASTRO). They are also supported by the American Society of Breast Surgeons (ASBS) and the American Society of Clinical Oncology (ASCO). The guidelines state that in order to procure adequate lumpectomy margins, you must show that the tumor is off of the ink. In the past, 5 to 10 mm was an acceptable margin; however, new guidelines state that as long as there is no sign of the tumor in the ink, you have reached a negative margin. We are optimistic that these new guidelines, along with frozen sections and imprint cytology, will reduce the rate of re-excision well below the average of 20% to 40%, and in return, lumpectomy will become more attractive to women. Regardless of the pathology, no tumor on ink is the standard we are looking for. Receptor status and histology are determinants of nodal spread and distance spread, not for local recurrence.

**MRI Unsuccessful for Decreasing Re-Excision Rates:** The use of MRI is not an effective way to check margins. The machine may pick up several things that may or may not be concerning to surgeons. It is possible that MRI would show masses that would otherwise be eradicated by radiation therapy, because MRI does not produce the best picture, surgeons would be forced to reoperate. In fact, the use of MRI increases mastectomy rates, thus increasing medical harm to the patient.
Lymphedema: Diagnosis and Risk Factors

Clinical Diagnosis: Lymphedema is frequently over-diagnosed in some cases. If we are only listening to the patient’s complaints, it is easy to diagnose their issue as lymphedema. However, in many cases, it may be that the patient is suffering from intercostal brachial numbness, which is numbness in the anterior-posterior part of the upper arm caused by loss of intercostal nerves. This numbness can sometimes feel to the patient as if the arm is swelling. However, if a volumetric test is performed, we find that lymphedema is present in up to only 7% of patients who have just had sentinel node biopsy. If radiation was needed, the rate is at least 20%. To reduce the risk of lymphedema, we will either dissect the axilla or radiate the axilla; performing both procedures increases the risk of lymphedema.

Weight Gain Yields High Rate of Diagnoses: In the past, patients who had axilla node dissection were told certain activities to avoid: needle sticks, having blood pressure taken, getting burned, and exercising. The Cochrane Analysis has dismissed all of these claims. The only thing that can be proven as a cause of lymphedema, besides surgery and radiation, is weight gain. Therefore, it is important to discuss with patients that they need to have a careful watch on their weight. It is necessary to have this discussion, as the outcome is in the patient’s hands.

Lymphedema: Node Dissection

Axillary Lymph Node Anatomy: There are 3 levels of lymph nodes in the axilla and they are all named for their position to the pectoralis minor. Nodes lateral are level 1 and drain mostly the breast. Nodes behind the pectoralis minor are level 2 and drain both breast and arm. It is in level 2 that we start to risk lymphedema; dissecting too high into level 2, which are above the vein and against the chest wall and drains into the arm.

Node Dissection Techniques: In past literature, it was best practice to take out the level 3 nodes. The National Cancer Institute performed studies that looked at those packages separately and labeled them for the pathologist. In those days, level 3 nodes were almost never involved in node positivity. Unless there is evidence of nodal disease in the armpit, it is inadvisable to remove level 3 nodes. In my practice, we do what we call a 1.5 level in which we leave the top of level 2 nodes. We identify the long thoracic and the thoracodorsal which sit on top of the subscapularis muscle, and we leave the upper nodes that are on the confluence of the vein to the chest wall that goes into the thoracic outlet and comes out to where the level 3 nodes are located. In some Japanese studies, literature states that best practice is to stay below the highest intercostal nerve. In other studies, in particular by Kleinburg, a technique called reverse sentinel mapping is performed. This technique involves injecting isosulfan blue into the medial upper arm and the place where the axilla is exposed. This leaves behind blue-stained nodes and it allows you to see where the nodes drain. The use of these techniques could decrease the rate of lymphedema to ≤7%.

Node Dissection in Mastectomy Patients: The Z11 data does not yet pertain to mastectomy patients. When we are presented with a patient who is having a mastectomy and her sentinel node is positive, the current standard of care at OHSU is to limit the dissection to level 1 and the bottom-most part of level 2. We do this because we have randomized control trials that have just opened to look at the possibility of performing or not performing an axillary dissection and a mastectomy. If the sentinel node is positive, the odds of finding more disease in the axilla are 20%.

Lymphedema: Surgical Treatment

Microsurgery: There are 2 major categories of surgery for lymphedema: is elephantiasis, or massive localized lymphedema, and the other is reconstructing myelolymphatics. For elephantiasis,
we are removing all the engorged tissue and engrafting slaps. Reconstructing myelolymphatics is a procedure that has been around for a long time but comes and goes in popularity. In this procedure, the plastic surgeon takes lymph tissue from nondependent areas, finds lymphatics vessels, and then anastomosis them to several lymphatics in the axilla or in the groin. They will then look for clips or markings made by the general surgeon at the time of surgery to figure out where they are and then perform microsurgical anastomosis using bridging tissue.

**Institutional Bias:** Patients should be referred to special microsurgical centers to have this procedure, and there also needs to be more data on the subject. However, the best option for these patients is prevention and minimizing the risk of the condition in the first place. Lymphedema depends on the rates and the impact, depending on how you define it. If sophisticated volumetric analysis is used, you will be able to find asymptomatic lymphedema on patients.

**Chronic Lymphedema**

**Risk for Cancer:** Longstanding chronic lymphedema has a permissive effect on tumor growth due to the fact that lymphedema is a permissive environment, Th2 cytokines. These cytokines permit various types of cancers: melanomas, non-melanomas, Kaposi sarcomas, lymphomas, and most commonly, cancers of the lymphatics. These are locally aggressive cancers that will spread to remaining nodes and metastasize and cause polyps; the eponym of which is the classic lymphedema-induced cancer, Stewart-Treves Syndrome, which was identified by Fred Stewart and Norman Treves at Sloan-Kettering in the 1950s and 1960s.

**Cancer in the Morbidly Obese Patient:** As we are beginning to see less massive edema, we will start to see less of the Stewart-Treves syndrome. Massive localized lymphedema will begin to replace the disease in patients who are classified as morbidly obese. Morbid obesity is carcinogenic and is not a problem that will be easily or quickly eradicated.

**Preventative Drugs for Breast Cancer Patients**

**P01 and P02 Drug Trials:** Two major trials were conducted in the 1990s that finished in early 2000. Both trials, named P01 and P02, were conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP). P01 compared tamoxifen versus placebo for prevention of breast cancer in patients who are at higher risk; these patients had a Gail model risk, which is based on age, parity, breast biopsies, and gross demographic factors. If the Gail model risk score is 1.6-fold or higher than the population risk, the patient is a high-risk patient. These patients were entered into the trial and randomized, some receiving tamoxifen and others receiving a placebo. Patients who were given tamoxifen experienced a 50% decrease in the incidence of developing ER/PR breast cancer. There was no impact on receptor negative breast cancer. Chemoprevention only impacts hormone receptor positive tumors. The P02 trial, also known as the STAR (Study of Tamoxifen and Raloxifene) trial resulted in the FDA approval for use of the drugs in osteoporosis. These are antiestrogen drugs that do not have most of the side effects. Both drugs were shown to be effective in the STAR trial to lower the risk of ER/PR positive breast cancers in high-risk patients. As a result, the FDA approved both drugs for chemoprevention in high-risk patients.

**Outcomes of the STAR Trial:** When the study was first received, it was thought that tamoxifen and raloxifene would be the drugs of choice; however, 2 things occurred which have diminished the enthusiasm for their use. First, the drugs have unwanted side effects, ie, endometrial cancer, and increased risk of venous thromboembolism (VTE), especially in postmenopausal women. Second, with the introduction of gene testing, we begin to question if the risk of developing breast cancer is the patient’s family’s risk, or the patient’s actual risk. These are autosomal dominant genes, and half of
patients in those families do not have that gene. If the patient has a family history, she will be gene
tested. If her gene test shows negative risk, her risk goes back into the population risk and she does not
need to be on chemotherapy prevention.

**Prevention in the DCIS Patient:** Patients who have DCIS with excision are not candidates for
chemotherapy prevention. We are treating the patient to lower the risk of recurrence. The goal of DCIS
treatment is to minimize local recurrence. If the patient is high-risk, radiation can be added; if the risk is
low and the tumor is small, we would not prescribe radiation. Tamoxifen is an adjuvant therapy for
patients with noninvasive breast cancer.

**Venous Thromboembolism and Deep Vein Thrombosis:** In the case of a patient who develops VTE,
it is essential to review the data collected in the P01 and P02 trials. The data showed that you could
decrease the risk of the incidence of breast cancer, but the data did not show an overall survival benefit
because they were not meant to do so. We are faced with treatment that lowers risk of breast cancer, but
has not been shown to improve survival. If there were no benefit to staying on tamoxifen, we would no
longer prescribe it for patients if there were contraindications present. For the patient who develops deep
vein thrombosis (DVT), particularly in the calf, we would not treat them with the traditional 6 months of
Coumadin; we would treat them with a shorter course of a new antithrombin agent or a short course of
Lovenox®. This is a patient who does not have genetic or other indicators and is not protein S or protein
C deficient. Because a drug provoked the condition, the patient can be placed on a short course of an
anticoagulant. The question therein lies in determining at which point we are still committed to
chemotherapy prevention. You could consider, if they are postmenopausal, to put them on the aromatase
inhibitor (AI). However, if the patient is premenopausal, it may become necessary to stop chemotherapy
prevention altogether.

**Tamoxifen as Hormonal Adjuvant Therapy**

Because the aromatase inhibitor (AI) does not block ovarian estrogen progression, it is not an effective
treatment. If the patient is on AI, and she is premenopausal, she would require an added ovarian suppression.
Tamoxifen is usually prescribed for premenopausal women because it is designed to block ovarian
estrogen production. If the patient has already received chemotherapy, she has been forced into a
postmenopausal state. At that point, she can be switched to an AI and, by doing so, she is less symptomatic.
The challenge is being sure that she is receiving adequate calcium, vitamin D, and bisphosphonates.
Patients will be switched to an AI typically sometime between 3 and 5 years. They will be on 10 years
of hormone therapy, but it is typically not tamoxifen. Patients who are postmenopausal are at higher risk
for osteoporosis, and must receive DEXA scans and take supplements, if necessary.