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Breast and Ovarian Cancer Risk Assessment and Prevention

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Breast cancer occurs in one in eight women in the United States, which equals a 12% lifetime risk in the general population. In the absence of any clear hereditary syndrome, having one first-degree relative affected by breast cancer confers an approximately twofold elevation in risk, and having two first-degree relatives affected by breast cancer confers an approximately fourfold elevation in risk. Ovarian cancer, in contrast, is a relatively rare cancer in the United States, with an approximate 1.5% lifetime risk. Having one first-degree relative with ovarian cancer roughly doubles that risk to about 3–5%.

For most women, there are multiple factors that lead to the development of their breast or ovarian cancer, including, but not limited to, genetics, breast tissue composition, lifetime estrogen exposure, lifestyle, and abnormal biopsy findings. A small percentage of women affected by breast and ovarian cancer have clearly identifiable, hereditary causes of their cancer, such as BRCA gene mutations. These hereditary mutations actually are quite rare. For instance, approximately only 5% of patients with breast cancer have a BRCA gene mutation. Clear guidelines, based on family history, exist to determine whether patients are eligible for genetic testing for hereditary mutations. A combination of breast and ovarian cancer in the same family or a pattern of breast cancer affecting younger (< 50) women in a family are examples of factors that can increase candidacy for testing. It is always the most helpful to begin testing in individuals in the family who have a cancer diagnosis prior to testing those who are unaffected by cancer.

The lifetime risk of breast cancer in the setting of a BRCA1 or a BRCA2 mutation is approximately 40–80%. The risk of ovarian cancer with a BRCA1 mutation is about 40%. With a BRCA2 mutation, ovarian cancer risk is about 20%.

In studies of BRCA mutation carriers, risk-reducing mastectomy decreases breast cancer risk by 85–100% and breast cancer mortality by 81–100%. Bilateral salpingo-oophorectomy (BSO) — removal of the ovaries and fallopian tubes — reduces breast cancer risk by 37–100%, ovarian cancer risk by 69–100%, and all-cause mortality by 55–100%. (Nelson HD. Ann Intern Med 2013). Surgery to remove the tubes and ovaries is recommended after age 35 or once childbearing is complete. This allows a woman time to complete her family and get the benefit of her natural hormones for as long as possible, but still removes the tubes and ovaries before we typically see the earliest onset of ovarian cancer. The risk for ovarian cancer gradually increases over time until the peak period of diagnosis in the 50s and 60s. BSO is strongly recommended in mutation carriers because in women undergoing screening, ovarian cancer is still most commonly found at stage III, when cure rates are only about 20–30%.

Risk-reducing BSO is associated with an approximate 90% reduction in risk for ovarian and fallopian tube cancer. A small residual risk for peritoneal cancer exists because the entire peritoneum cannot be removed. Importantly, BSO can substantially reduce the risk of breast cancer in mutation carriers as well. In women with a BRCA mutation who do not elect risk-reducing mastectomies, surveillance is also a reasonable option. It is recommended that these women get a breast MRI in addition to their mammograms every year.

Most women with a family history of breast and/or ovarian cancer are not BRCA mutation carriers, however. Some lifestyle factors and other interventions can decrease the risk of ovarian cancer, including having children, breastfeeding, having a tubal ligation, and having a BSO. Birth control pill use is associated with an approximate 50% reduction in ovarian cancer risk with five years of use. Healthy lifestyle choices, including frequent exercise, adequate sleep, tobacco avoidance, limited alcohol, avoidance of weight gain, and a diet rich in fruits and vegetables with limited intake of highly processed foods, can be associated with lower cancer risks as well.

Screening methods for ovarian cancer, such as pelvic ultrasound and serum CA-125, have not been shown to improve survival in women found to have cancer during screening, because they do not reliably detect ovarian cancer at an early stage. Both ultrasound and CA-125 have problems with false positive results, where the test is abnormal even though cancer is not present, and false negative results, where the test remains normal even though cancer is developing. These issues improve somewhat after menopause but remain a problem. Therefore, in women with a family history of ovarian cancer who do not have a BRCA mutation, the decision to participate in a screening program for ovarian cancers can be discussed with their treating physician, because guidelines do not formally recommend for or against screening in this setting.

Certain biopsy findings, such as atypical lesions and lobular carcinoma in situ (LCIS), increase a woman's risk of breast cancer. These findings on a breast biopsy are proliferative pathologies, which increase lifetime risk of breast cancer. Proliferative lesions with atypia include atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), and flat epithelial atypia (FEA). These lesions are considered high-risk because they are associated with an increase in the patient's future risk of developing breast cancer. They are generally not considered premalignant lesions, because the cancers that subsequently develop may occur anywhere in the breasts, not necessarily at the site of the atypia. Therefore, when these high-risk lesions are discovered, the focus should be on careful surveillance and consideration of risk-reduction strategies.

Atypical hyperplasias (ADH and ALH), especially multifocal lesions, increase relative risk of breast cancer by four- to fivefold and are associated with a generalized increased risk of both ipsilateral and contralateral breast cancer, although it is higher in the ipsilateral

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breast. The risk of breast cancer with atypical hyperplasia is approximately 19% at 15 years. Less data exists with flat epithelial atypia (FEA) and the relative risk of breast cancer; it may be slightly lower than with ADH/ALH. Surgical consultation is often recommended for these pathologies per the discretion of the radiologist, depending on the adequacy of the core needle biopsy sampling.

LCIS also is a high-risk proliferative pathology with low malignant potential, but it conveys increased risk for ipsilateral and contralateral breast cancer. The absolute risk of breast cancer with LCIS is approximately 1% per year and appears to be lifelong. Estimates of breast cancer risk in comparison to the general population show that women with LCIS have anywhere from a three- to eightfold higher risk of breast cancer. Prior studies have found a 17–20% risk of breast cancer at 15 years with LCIS. Surgical consultation is often recommended for LCIS found on core needle biopsy to exclude the presence of invasive cancer.

In women with elevated risk of breast cancer due to family history or high-risk biopsy findings, enhanced screening can be considered, with modalities such as screening ultrasound and tomosynthesis in conjunction with annual mammography. Moreover, certain medications that target estrogen, which are used to treat breast cancer patients, also have been shown to markedly lower risk of breast cancer in patients with identified increased risk. Such strategies are formally endorsed by the American Society of Clinical Oncology (ASCO).

In the NSABP P1 study, five years of tamoxifen significantly reduced breast cancer risk by 50% in comparison to placebo. However, risk was reduced by 56% among women with a history of LCIS, and by 86% in women with a history of atypical hyperplasias, indicating the effectiveness of medical risk reduction for women with these high-risk proliferative pathologies. The STAR trial established that five years of raloxifene is almost as efficacious as tamoxifen in decreasing breast cancer risk, with about a 38% risk reduction. Raloxifene is indicated for treatment of osteoporosis and therefore is a good choice for breast cancer risk reduction in the patient with low bone density (osteopenia or osteoporosis).

Tamoxifen very slightly increases the risk of uterine cancer in women over the age of 50, but it does not statistically increase the risk of uterine cancer in women under the age of 50. Tamoxifen and raloxifene both slightly increase the risk of a venous thrombotic event, such as a DVT or PE, and thus are contraindicated in women who have previous history of thromboses. Measures must be taken to prevent pregnancy in women using tamoxifen and raloxifene because they are considered teratogenic. The risk of a thrombotic event is even lower with raloxifene than it is with tamoxifen. Common side effects of tamoxifen and raloxifene are hot flashes and occasional vaginal dryness. In breast cancer prevention trials, many more breast cancers were prevented then adverse events were caused. Because of the rare risk of uterine cancer in women over the age of 50 on tamoxifen, raloxifene is preferable unless they have had a hysterectomy.

More recently, the MAP.3 trial revealed that exemestane compared with placebo reduced breast cancer risk by 65% in postmenopausal women with increased risk of breast cancer. Similarly, the IBIS-II trial showed that anastrozole reduced risk of breast cancer by 53% in comparison to placebo. Potential side effects of aromatase inhibitors include decrease in bone density, arthralgias, hot flashes, and vaginal dryness, but not all women experience these side effects.

The goal of the Magee-Womens Hospital of UPMC Breast and Ovarian Cancer Risk Assessment and Prevention programs is to provide individualized risk estimates for patients. A determination is made based on family history whether genetic counseling and/or consideration of genetic testing is needed. Finally, a comprehensive screening and risk-reduction plan is recommended for the patient based on the estimated risk and patient preference.

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Personalized Breast Cancer Screening

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Breast cancer remains the most commonly diagnosed cancer among women in the United States and across the world. Long-term follow-up data from multiple randomized controlled trials and service screening from many countries has shown a mortality reduction of at least 25% and upwards of 35% from screening mammography. Despite this consistent and compelling scientific evidence that screening mammography works, it still is not a perfect examination, and great debate currently exists as to the benefits versus harms of annual screening mammography. Invasive cancers can be missed in dense breasts because they are obscured by overlying normal tissues. In addition, some indolent cancers that would not impact patient life expectancy, such as low nuclear grade DCIS, are over-detected with mammography and then over-treated with surgery and adjuvant treatments.

In the midst of the ongoing debate with respect to the benefits and risks of screening mammography, legislation has been passed in Pennsylvania and many other states mandating that patients be informed of their mammographic breast density and told that additional imaging testing may be helpful. These laws have arisen primarily from a grassroots effort by patients who are rightfully demanding that they have the facts necessary to make informed decisions about their health care.

Alternative and newer imaging technologies have emerged, which offer the potential to mitigate the harms of screening mammography by increasing detection of invasive cancers without increasing DCIS detection and, in some instances, lowering false positive recall rates.

In order to optimize detection of invasive breast cancer as the primary objective and to decrease false positive examinations as the secondary objective, we have developed a personalized screening paradigm at Magee-Womens Hospital of UPMC. This model takes into account each patient's risk of breast cancer, age, and mammographic breast density. The recommendations are based as closely as possible on published literature that demonstrates cancer detection rates and false positive rates for various scenarios, as well as all available guidelines from the NCCN, ACS, and ACR. The paradigm uses the ancillary technologies of ultrasound, tomosynthesis, and MRI. There are no standard guidelines yet to address the entire spectrum of asymptomatic patients across all risks and densities, so our recommendation paradigm may evolve over time.

On average across several trials, screening ultrasound has been shown to increase cancer detection by 3/1000 in women with dense breasts. Much of the work in screening ultrasound has been performed in women who not only have dense breast tissue but who also have elevated risk, so this may be a slight overestimate of benefit in the normal risk population. The majority of these cancers are small stage 1 invasive, and they very possibly pose a clinical danger to the patient if undetected at an early stage. A screening ultrasound takes approximately 30 minutes to perform. It is well-tolerated by patients and uses no ionizing radiation. The largest drawback of screening ultrasound is that it has a relatively high false negative rate; in some studies up to 13%. This can lead to a higher rate of six-month follow up and biopsy of areas that prove not to be cancer. These false positive examinations may increase patient anxiety.

Tomosynthesis is a new technology that is an advanced form of a digital mammogram, during which multiple low-dose projection views are collected and reconstructed into a serial set of 1 mm slices. This technology gives approximately the same radiation dose to the breast as digital mammography and takes about four seconds to perform per view. It is done during the same compression as the mammogram. In multiple trials of screened women from all risk categories, this modality finds an additional two cancers in every 1000 women screened compared to digital mammography alone. Like ultrasound, tomosynthesis finds small invasive cancers that are not seen on traditional mammography. It has not increased detection of DCIS. Tomosynthesis has been found to be useful in fatty and dense breast tissue. This technology lowers screening recall rates by 30–40%, and is therefore more accurate than mammography or ultrasonography. However, because it uses radiation, the dose to the patient when a combination of tomosynthesis and mammography is performed is double that of mammography alone. New software is now FDA-approved whereby the mammogram can be generated from the tomosynthesis data, and the digital mammogram no longer needs to be performed separately. With this synthetically made mammogram, dose to the patient is approximately the same as standard digital mammography, and the advantages of higher accuracy of tomosynthesis over standard mammography are preserved.

The third ancillary exam to consider is MRI. Contrast-enhanced MRI is the most sensitive test available for the detection of breast cancer across all tissue densities. It has been shown to have a cancer detection rate of up to 18/1000 in normal-risk women. However, this examination is expensive, has a relatively high false positive rate, requires intravenous injection of gadolinium, and can take up to 40 minutes to perform. For these reasons, screening MRI is typically reserved for women with a family-based lifetime risk of at least 20–25%. Fast MRI protocols are being developed, which may obviate some of the disadvantages of the current technique and allow for more widespread use, especially in intermediate-risk women. That procedure is not yet ready for clinical implementation at this time.

If a woman wishes to have the additional testing, we have developed the following algorithm:

- **Normal and intermediate-risk women with all mammographic densities except extremely dense are recommended for annual combination mammography and tomosynthesis.**
- **Normal and intermediate-risk women with extremely dense breast tissue by mammography are recommended for annual combination mammography and ultrasound.**
- **Combination annual screening mammography and MRI is recommended for all high-risk women 60 to 70 or younger, regardless of breast density.**
- **After age 60 to 70, MRI may not be beneficial. The patient should revert to mammography and tomosynthesis, or mammography and ultrasound based on the same density stratification that normal and intermediate-risk women follow.**

CASE STUDY:

Breast Cancer-Related Lymphedema Treatment

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B.G. is a 59-year-old woman originally diagnosed with left breast cancer at age 57 after she had self-palpated a left breast mass. Her workup revealed clinical stage II infiltrating ductal carcinoma with left axillary lymph node involvement. She underwent a left modified radical mastectomy and a right prophylactic total mastectomy. Her surgical pathology revealed a 4 cm large left breast tumor and four of 23 axillary lymph nodes positive for metastatic disease and normal right breast tissue. After surgery, she was treated with adjuvant chemotherapy for several months, followed by adjuvant left post-mastectomy radiation therapy and anastrozole (Arimidex®) hormonal therapy.

After her surgery and radiation treatment, she noticed increased swelling in her left arm. She was diagnosed with stage II breast cancer-related lymphedema and began decongestive therapy, including wearing a compression sleeve and doing therapeutic exercises. Her lymphedema stabilized with these measures, and she then focused her attention on breast reconstruction, a process she had originally decided to delay until after completing her breast cancer treatment.

Six months after having finished her radiation treatment, B.G. met with a Magee-Womens Hospital of UPMC plastic surgeon to discuss her reconstructive options. After careful deliberation, she selected autologous, or tissue-based, breast reconstruction. In the spring of 2014, she underwent a delayed bilateral deep inferior epigastric perforators (DIEP) breast reconstruction, a muscle-sparing procedure that uses skin and fat from the lower abdomen to recreate the volume and shape of natural breasts. She had an uneventful procedure and recovery, and completed the process with nipple reconstruction, performed as an outpatient under local anesthesia only, a few months later.

Now, two years after her original diagnosis of breast cancer, B.G. decided it was time to address her left arm lymphedema. She was now using her compression sleeve daily, as well as a lymphedema pump at night. The swelling had not gotten much worse over the two-year period, but she did have a constant sense of heaviness in the limb and occasionally developed mild cellulitis. She made an appointment with the Magee-Womens Hospital of UPMC Lymphedema Education, Screening, Early Detection, and Prevention Program (LESEP). There, she met with specialists who educated her about lymphedema and optimized her treatment.

She also learned about potential surgical options for improving lymphedema, including Lymphatico-Venular Bypass (LVB) and Lymph Node Transfer (LNT) procedures. She learned that modern microsurgical lymphatic surgery has been found to be successful in decreasing symptoms and severity of lymphedema, and in some instances, curative.

At a follow-up visit with her plastic surgeon, B.G. discussed the specifics of lymphedema surgery, as well as expectations from the procedure. She was relieved to learn that recovery was generally much easier, quicker, and less painful than her previous surgeries. She decided to have the surgery performed, and underwent left upper extremity LVB in the fall of 2014. She stayed overnight in the hospital, went home the next day, and went back to work as a financial adviser a week later. She is now almost two months out from her LVB surgery and notices that the feeling of heaviness in her arm has resolved. She still wears her sleeve and knows it is too early to check arm circumference and L-Dex measurements for objective signs of decreased lymphedema, but she's looking forward to continued, gradual improvement.

Lymphedema

The lymphatic system comprises a network of tiny vessels in the skin and subcutaneous tissue that scavenges excess fluid along with proteins, fatty acids, and fats, and transports these bodily substances back into the circulatory system. Lymphedema (LE) is an abnormal state in which the lymphatic system malfunctions, allowing fluid and proteins to accumulate in tissues, causing reversible swelling at first, but ultimately irreversible fibrosis, thickening, recurrent infections, and impaired function and form if it progresses unchecked. In developed countries, the most common cause of LE is cancer and its treatments. LE is a chronic and debilitating condition that results in physical and psychological morbidity.

Breast cancer-related lymphedema (BCRL) results from axillary lymph node metastatic disease, as well as axillary lymph node dissection and radiation therapy for breast cancer. BCRL occurs in up to 40% of women who have undergone axillary node dissection and radiation treatment[1] and may lead to upper limb pain, heaviness, deformity, financial burden, and social stigma. The mainstay of treatment for BCRL has been education and decongestive therapy, consisting of wearing compression garments or sleeves, physical therapy and massage, and lymphedema pump use.[2,3] In addition, specialized skin laser therapy has demonstrated some benefit. Despite these cumbersome and burdensome measures, the best a woman can generally hope for is to prevent BCRL from progressing to a more severe stage.

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Personalized Breast Cancer Diagnosis and Treatment: Clinical Trials

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Clinical trials for the treatment of breast cancer that are currently open include, but are not limited to:

Neoadjuvant Studies

Neoadjuvant therapy for breast cancer is utilized prior to surgery to reduce tumor size, either to allow a nonoperable tumor to become operable, to improve cosmetic outcomes during breast conservation, or to allow a treatment if surgery is contraindicated but would be anticipated at a later date, such as in some pregnant women with breast cancer. Careful patient selection is important to maximize effectiveness of neoadjuvant treatment.

Triple Negative

Patients with ductal cancer with a triple negative phenotype (estrogen receptor (ER), progesterone (PR), and Her2neu negative) are candidates for the Translational Breast Cancer Research Consortium (TBCRC) 030. This randomized *phase II* study compares 12 weeks of preoperative cisplatin versus paclitaxel. The purpose of the study is to evaluate the homologous recombination deficiency (HRD) biomarker score, which is highly associated with defects in homologous recombination pathways, beyond deleterious germline mutations of BRCA1 or 2. The HRD assay will be utilized to predict sensitivity and response to the DNA-damaging agents, cisplatin or paclitaxel. Patients require a mandatory research biopsy and blood draw prior to treatment, and a portion of the surgical specimen will be collected so that exploratory correlative analyses evaluating other novel biomarkers of response to chemotherapy in triple negative breast cancer can be done. After the 12-week dosing period is completed, patients are able to receive additional neoadjuvant or adjuvant chemotherapy, depending on their response to the initial agents.

Her2neu Positive

Two neoadjuvant trials are available at Magee-Womens Hospital of UPMC for women with either ER-positive or ER-negative ductal cancers. The NSABP B52 study, for ER+ patients, is a *phase III* randomized trial that evaluates response rates with neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) with or without estrogen deprivation. Postmenopausal patients will receive aromatase inhibitor (AI), whereas premenopausal patients will receive luteinizing hormone-releasing hormone (LHRH) agonist, as well as AI. For the purposes of the study, postmenopausal is defined as status-post bilateral oophorectomy, age 56 with no menses for at least 12 months prior to study entry, or less than age 56 with no menses for a year and a documented estradiol level in post-menopausal range. In addition to pathologic response rates, the study will evaluate quality of life with the addition of estrogen deprivation, and mechanisms of hormone resistance. Similar to the study above, patients must have blood samples and a tissue biopsy before and after treatment.

In contrast, for patients with Her2neu positive, ER-negative tumors, the TBCRC 026 study is a *phase II* trial assessing early changes on positron emission tomography (PET) scan with response to trastuzumab and pertuzumab (HP). The overarching goal is to identify patients, by utilizing PET scans, who do not require cytotoxic chemotherapy in addition to anti-Her2 therapy. All patients receive HP for 12 weeks. Patients who have a complete clinical response on post-treatment imaging go forward with surgery, whereas those who progress or have biopsy-proven residual disease receive anthracycline- and taxane-based chemotherapy for an additional 12 weeks prior to surgery.

ER-Positive

Postmenopausal patients with ER-positive, Her2 negative ductal cancer who need neoadjuvant treatment are eligible for the ALTERNATE ("**ALT**ernate approaches for clinical stage II or III **ER** positive breast cancer **N**eo**A**djvuant **T**r**E**atment) *phase III* study. This study also requires a pretreatment biopsy. Patients are randomized to receive anastrazole, fulvestrant, or both. If repeat percutaneous biopsy reveals a significant reduction in the proliferation index, Ki67, patients continue on the endocrine therapy; however, if the Ki67 remains high, patients receive chemotherapy. All patients then proceed to surgery. Those who received only endocrine therapy have a modified PEPI (preoperative prognostic index) score measured on their post-treatment tumor tissue. The PEPI score was developed to predict risk of relapse based on post-neoadjuvant endocrine therapy tumor size, lymph node status, Ki67 level, and ER status.[3,4] If the score is zero, which predicted improved disease-free survival in earlier studies, the patients continue on endocrine therapy for a total of five years, and if the score is greater than zero, it is recommended that patients receive chemotherapy followed by five years of endocrine therapy.

Window Trials

Another form of presurgical clinical trial is the so-called "window of opportunity" study. In these *phase 0* trials, patients receive a study drug between the percutaneous core needle biopsy for

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diagnosis and the planned surgical resection. In comparison to neoadjuvant therapy trials for which the end point is usually clinical or pathologic response, the goal of window trials is to evaluate modulation of biological targets after treatment with the anticancer agent. The overarching objective of window trials is to speed drug development by studying an agent's biologic effect and validating molecular targets that might predict benefit in patient subsets.[2,5] This could allow better selection of patients for larger trials that are powered to detect clinical outcomes.[6] Window trials generally have no expected patient benefits beyond identification of relevant biological modulation. They also generally require pre- and post-therapy biopsies. There are three window trials open at Magee-Womens Hospital of UPMC: PINC (Preventing Invasive Neoplasia with Chloroquine), UPCI 13-156, and UPCI 13-164.

PINC (Preventing Invasive Neoplasia with Chloroquine)

This window trial is open to patients with DCIS, a noninvasive form of breast cancer known as stage 0 cancer. Between percutaneous diagnostic core biopsy and surgery, patients receive one chloroquine pill per week for four weeks. Chloroquine is used most widely as an anti-malarial therapy, but in laboratory studies, chloroquine reduces survival of DCIS cell lines compared to vehicle-alone control treatment. Chloroquine inhibits autophagy, a specialized pathway in cells that promotes cell survival during cellular stress such as starvation. It has been found to be effective in DCIS in vitro regardless of estrogen receptor status.

UPCI 13-156

This study evaluates the biologic effects of reparixin, an orally administered agent that, in preclinical studies, modulates cancer stem cells as well as the inflammatory state of the tumor microenvironment. Women scheduled to undergo surgery for breast cancer receive 21 days of treatment prior to the procedure, with a pre- and a post-treatment biopsy.

UPCI 13-164

This novel trial is restricted to patients with ER-positive invasive lobular cancer. Because lobular cancer comprises only about 10% of all invasive breast cancers, historically, it has been treated no differently than the more common ductal cancer. However, at the bench, molecular and biologic diversity is coming to light, so it is quite important to study this disease individually. This study entails randomization to a 21-day treatment with one of three endocrine therapies: anastrazole, fulvestrant, or tamoxifen. In pre- and post-treatment biopsies, changes in the proliferation index, Ki67, will be evaluated in the lobular cancer tissue. Additional correlative studies also are planned.

Adjuvant Clinical Trials

There are several studies in which patients can be enrolled after their surgical management is complete. At Magee-Womens Hospital of UPMC, multiple studies are open for patients with triple negative, Her2neu positive, and endocrine responsive breast cancers.

For example, the RxPonder trial is a *phase III* randomized trial for patients with ER-positive, Her2-negative breast cancer with one to three positive axillary lymph nodes. In these patients, an OcotypeDX score is determined. Patients with a score in the intermediate range are then randomized to standard endocrine therapy alone versus chemotherapy plus standard endocrine therapy. For patients with node-negative ER+ invasive breast cancer, the Oncotype DX test gives prognostic and predictive information. The purpose of the RxPonder trial is to evaluate — in a prospective, randomized study — the utility of OncotypeDX in patients with node positive ER+ cancer.

08-126 is a *phase II* trial evaluating single agent trastuzumab in women over age 60 who are unable, or unwilling, to receive chemotherapy. There also are studies evaluating novel agents like everolimus, an mTOR-kinase in women with resected breast cancer, and several trials developed for women with deleterious BRCA1 or 2 germline mutation.

Metastatic Clinical Trials

Most clinical trials at Magee-Womens Hospital of UPMC are available for patients with metastatic cancer. Some trials are restricted to patients newly diagnosed with stage IV disease, whereas others are for patients who have failed standard conventional therapies. There are clinical trials for patients with metastatic disease that developed at one site, such as the brain, and also for patients who have widespread disease. Many novel agents are being investigated.

Maximizing Clinical Trial Recruitment and Retention With the Use of Research Advocates

The success of clinical trials depends on the recruitment of an adequate number and a diverse representative sample of the target population.[7] Including racial and ethnic minority populations and elderly populations is essential to producing generalizable results and eliminating health care disparities.

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Personalized Breast Cancer Diagnosis and Treatment: Clinical Trials *(Continued from Page 7)*

One-third of publicly funded trials require a time extension in order to meet recruitment goals.[8] Recruitment methods include word of mouth, flyers, newspaper ads, and radio or television spots. Interestingly, in spite of our technology-driven environment, some studies suggest that simple flyers are more time- and cost-effective than radio or TV advertisements.[9] From the patients' perspective, common barriers to clinical trial enrollment include lack of awareness, lack of trust in medical research, unwillingness to be randomized due to preference of treatment, inconveniences with travel, time commitment, and concerns about insurance coverage.[10] Reasons cited by patients for participation in trials include altruism, gaining access to promising new treatments that are not yet FDA-approved, following the recommendation of a trusted physician or friend, having a previous good experience, and viewing clinical trials as important and ethical.[11]

Physicians play a key role in the success of clinical trials because they serve as a gatekeeper, usually helping their patients gain access to a trial, but sometimes discouraging them from participating.[10] The most common barriers to physician participation and cooperation include excessive time commitment leading to reduced clinical efficiency, lack of easy access to clinical trials or information about the eligibility criteria, concerns about intrusion on the doctor-patient relationship, insufficient interest or belief in the relevance of the study question,[12] and uncertainty or feelings of responsibility if study treatments are found inferior.[13]

However, the opportunity to practice "cutting-edge" medicine and to identify new and potentially better ways to help patients are two important reasons that physicians give for enrolling their patients in clinical trials.

To accelerate the progress of our breast cancer clinical and translational research at Magee-Womens Hospital of UPMC, the Breast Cancer Research Advocacy Network (bcRAN) was founded in 2014 to create a partnership between physicians, scientists, and breast cancer survivors. In order to maximize the relevance of research questions to patients with breast cancer, and thereby maximize enrollment, this group connects survivors who can, beyond their personal experiences, speak for the general concerns of breast cancer study populations.[14] In this way, research goals and study feasibility can be developed collaboratively and the quality of the research can be maximized. In addition to working directly with scientists and clinicians to develop study questions, our bcRAN group has been working to increase awareness about participation in research among new patients, and those currently in treatment.

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CASE STUDY: Breast Cancer-Related Lymphedema Treatment *(Continued from Page 5)*

While various surgical techniques have long been offered to try to lessen the severity of LE, evidence of effective improvement has been lacking until more recently.[4] In the last decade, microsurgical techniques, long used by plastic surgeons for breast reconstruction, have been refined and applied to the lymphatic system in the hopes of improving the treatment and in some cases even providing a cure for BCRL.[4] Two procedures have emerged as potentially useful surgical adjuncts to decongestive therapy: lymphaticovenular bypass surgery and lymph node transfer surgery.

Lymphaticovenular Bypass Surgery

Lymphaticovenular Bypass (LVB) surgery involves locating tiny, blocked lymphatic vessels in the arm via several small skin incisions, and connecting them to nearby small veins, which do not have any blockages (Figure 1). It is thought that these connections allow the backed up fluid in the obstructed lymphatic vessels to drain directly into the venous system, bypassing the lymphatic blockages in the axilla.

Several studies have demonstrated improvements in BCRL after LVB.[1,5-7] Retrospective studies have reported up to 83% of patients with objective LE improvement, with durable reduction of excess limb volume by 67%.[6,7] A prospective study from the University of Texas MD Anderson Cancer Center demonstrated subjective improvement in 96% of patients and objective improvement in 74% of patients, with average limb excess volume decrease of about 30% compared to before LVB. It was noted that better results (60% limb volume reduction) were seen in patients with more mild (stage I and II) BCRL than in patients with more severe BCRL (Stage III and IV).[5]

LVB currently is offered for appropriate patients at Magee-Womens Hospital of UPMC, and generally involves staying one night in the hospital with return to work within a few days to a week.

Lymph Node Transfer Surgery

Lymph Node Transfer (LNT) surgery involves removing healthy lymph nodes from an unaffected area of the body, such as the groin or neck, and relocating these lymph nodes to the affected limb. It is thought that this procedure works because the healthy, relocated lymph nodes sprout new lymphatic vessels that grow outward into the tissues and make connections with the blocked lymphatic vessels, allowing the backed up fluid to drain through these new connections (Figure 2).

An early retrospective study showed improvement in BCRL in 83% of patients with return to a normal size limb in 42%.[8] Other retrospective studies also show promise, albeit more modest.[9,10] While research is still at an early stage for LNT, this procedure has the potential to treat lymphedema in scenarios where decongestive therapy and LVB are insufficient.

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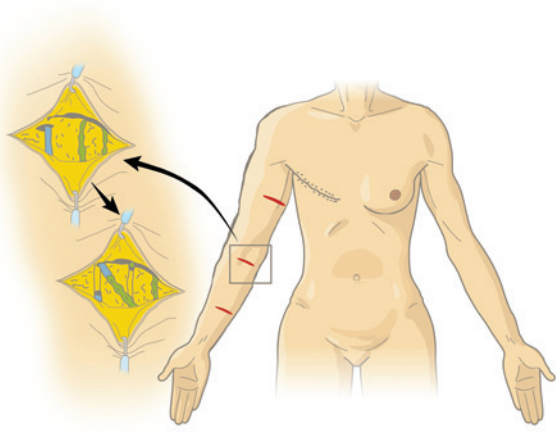

Figure 1. Lymphaticovenular bypass. Through several small skin incisions, obstructed lymphatic vessels (green) are located, divided at one end, and connected to nearby, unobstructed small venules (blue) to allow egress of scavenged fluid from the arm.

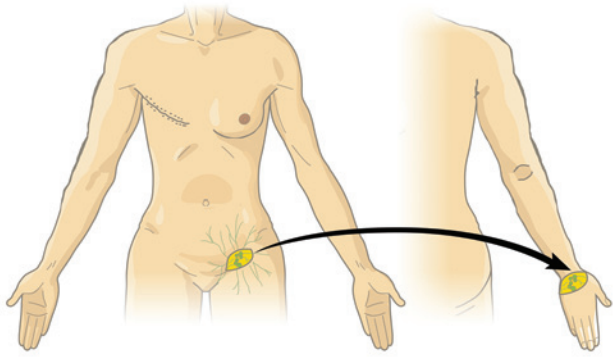

Figure 2. Lymph node transfer. A packet of normal lymph nodes is taken from the groin, along with its small artery and vein, and relocated to the limb affected by BCRL with new artery and vein connections performed. The relocated lymph nodes sprout new lymphatic vessels that communicate with the obstructed lymphatics and allow drainage of the scavenged fluid through the lymph nodes and into their outflow vein.

CASE STUDY: Breast Cancer-Related Lymphedema Treatment (Continued from Page 9)

Summary

Breast cancer related lymphedema is a chronic, burdensome condition that is, at its best, uncomfortable, and at its worst, disfiguring, painful, and potentially limb-threatening. Nonsurgical therapies are crucial to preventing progression of this process to more severe stages. Modern surgical options have opened new frontiers in the treatment of BCRL, have the potential to greatly improve symptoms of lymphedema, and in select cases, may even cure the disease. At the Magee-Womens Hospital of UPMC Lymphedema Education, Screening, Early Detection, and Prevention Program (LESEP), we have BCRL experts that educate patients and help take control of BCRL through comprehensive nonsurgical treatments and new, cutting-edge microsurgical operative techniques before it takes control of peoples' lives. For more information, call 412-661-5380 or 412-648-9680.

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UPMC CancerCenter: MULTIDISCIPLINARY PATIENT-CENTERED CARE (Continued from Page1)

Clinical Pathways Program

Cancer care at every UPMC CancerCenter in your community offers the same high-value standards of care that you would expect at Hillman Cancer Center, thanks to the Clinical Pathways program. Developed by UPMC CancerCenter clinicians, Clinical Pathways provide uniform treatment plans for different types of cancer based on specific patient and disease parameters. Pathways, used throughout UPMC CancerCenter, are constructed and maintained by disease-specific teams of physicians led by experts in academic and clinical medicine.

These physicians review published literature and clinical experience to determine the optimal treatment for a specific disease, stage-by-stage, taking into account common patient characteristics and presentations.

If more than one treatment regimen fits the "best" category, then our experts choose the regimen with the most favorable toxicity profile.

As a top priority for each Pathway, whenever applicable, patients are recommended to participate in relevant clinical trials. Pathways take into account current patient health status when recommending therapy, so that efficacy is maximized while toxicity is minimized. The program recognizes that there will always be circumstances where the recommended treatment is not appropriate for a given patient, and allows for physician discretion in all instances.

We continuously monitor success and make adjustments vital to promoting the very best outcomes for all of our patients.

Access to Clinical Trials

Physicians understand that breakthroughs in research won't make a real impact until they reach the patient. At UPMC CancerCenter and the University of Pittsburgh Cancer Institute (UPCI), our physicians and researchers collaborate to rapidly translate basic science into effective new strategies for the prevention, detection, and treatment of cancer.

Strategies include the development of vaccines to block the progression of many cancers, the incorporation of new technologies that allow physicians to more precisely target treatment, and advances in minimally invasive surgical procedures that are leading to reduced recovery times and better outcomes for patients.

Our research efforts have been recognized continuously by the National Cancer Institute (NCI). The NCI has awarded UPCI the top distinction of Comprehensive Cancer Center since 1990, cementing our commitment to developing a comprehensive research infrastructure that ultimately supports superior cancer care.

Maximizing Clinical Trial Accrual Through Our Community Network

Min Sun, MD, PhD
Oncologist/Hematologist
UPMC CancerCenter at UPMC St. Margaret

UPMC CancerCenter's large community-based network is crucial to clinical trial accrual, while providing patients with convenient access to leading-edge treatments. Currently, there are 16 breast cancer trials open in the UPMC CancerCenter at UPMC St. Margaret, covering all lines of breast cancer treatment. The following case reports a patient who participated in three of these clinical trials.

Case Study: JP

JP is a 58-year-old Caucasian female who presented with a left inflammatory breast cancer, left axillary adenopathy, and at least four hepatic metastases in June 2010. A left breast core biopsy revealed infiltrating ductal carcinoma, grade 2, Nottingham score 6/9, ER weakly positive, PR negative, HER-2/neu amplified by FISH.

She received first-line chemotherapy, Taxotere, Herceptin, and Avastin x 6 cycles under UPCI protocol 08-053 from June 9 to October 26, 2010. Liver lesions completely resolved on PET/CT, but her left breast primary tumor started to progress by the end of the sixth cycle of chemotherapy. She underwent a modified radical mastectomy of the left breast in December 2010. The patient was on maintenance Herceptin and tamoxifen from February through December 2011.

The patient developed enlarged left supraclavicular and left paraaortic lymph nodes in December 2011. She was enrolled in UPCI protocol 09-092 evaluating vinorelbine plus trastuzumab with or without everolimus. The patient had a partial response. Her paraaortic lymph node completely resolved. Her left supraclavicular lymph node decreased in size and remained relatively stable at around 2.5cm in largest dimension for 18 months.

JP's PET/CT on September 10, 2013, revealed FDG avid left supraclavicular and right hilar adenopathy. She received palliative radiation to left supraclavicular and right hilar adenopathy, completed on October 4, 2013. Subsequent PET/CT on Jan. 9, 2014, showed significantly decreased FDG avidity of left supraclavicular lymph node and right hilar lymph node. The patient stayed on maintenance Herceptin every three weeks from October 2013 until the end of June 2014. In June 2014, she developed two new hepatic metastases. She received third-line chemotherapy Kadcyla (Ado-trastuzumab emtansine) 3.6mg/kg Q 21 days from July 11, 2014 to October 2, 2015. She had a near-complete response initially, but developed disease progression again in her liver with similar location of two prior liver metastases. Her left supraclavicular lymph node remains unchanged. After multidisciplinary tumor board discussion, JP decided to pursue surgical resection of resistant clones in her liver. She also participated in *UPCI 14-140, In-Clinic Survey and Chart Review of Women Living U4 Years with Human Epidermal Growth Factor Receptor-2 (HER2) Positive Metastatic Breast Cancer (MBC).*

CONTINUING MEDICAL EDUCATION

Video Rounds is a series of informative and educational short videos, created for physicians and covering a variety of medical and surgical disciplines, including topics such as:

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Part 2: Priscilla McAuliffe, MD and Barry Lembersky, MD discuss high risk lesions and whether surgery is necessary, as well as new systemic therapies for breast cancer.

Part 3: Marsha Haley, MD, Rohit Bhargava, MD, and Rachael Jankowitz, MD, discuss the pathology and radiation oncology considerations for In-Situ Carcinoma.

Concomitant Thyroid and Parathyroid Disease

Sally Carty, MD discusses concomitant thyroid and parathyroid disease and focuses on operative approaches.

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