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DEPARTMENT OF OBSTETRICS, GYNECOLOGY, AND REPRODUCTIVE SCIENCES

| UPDATES IN |

GYNECOLOGY

Inside This Edition

Message from the Chairman

Dear Colleagues,

I am pleased to share with you again some of the newest clinical work and research from our Department of Obstetrics, Gynecology, and Reproductive Sciences at Magee-Womens Hospital of UPMC.

In this issue of our newsletter, we feature new breast imaging technologies and research led by **Margarita Zuley, MD, FACR**, and we also feature some of our latest findings and grant awards to study vasomotor symptoms and their relationship to overall health by **Rebecca Thurston, PhD**, a behavioral health specialist with our Midlife Health Center.

Emilia Diego, MD, discusses some of the new clinical trials and related research for premenopausal breast cancer she is leading at UPMC, and **Priscilla McAuliffe, MD, PhD**, highlights ongoing work to better understand ductal carcinoma in situ, along with an advocacy program for breast cancer research she was instrumental in helping to co-found with her colleague **Carola Neumann, MD**.

Finally, in this issue, **Harold Wiesenfeld, MD**, the director of our gynecologic infectious diseases program, shares the outcomes of several new research projects and clinical trials related to pelvic inflammatory disease and the routine screening protocols that may better identify individuals with asymptomatic or subclinical sexually transmitted diseases.

As a department, we continue to explore new models of care with quality cost analytics, the regionalization of our specialty services, and by expanding our population genomics initiatives, all of which will be featured in future issues of this newsletter.

Thank you, and best regards.

RP Edwards

Robert P. Edwards, MD
Chairman, Department of Obstetrics, Gynecology, and Reproductive Sciences
Co-Director, Gynecologic Oncology Research, Magee-Womens Hospital of UPMC

Breast Imaging Advances at Magee: Personalized Approaches and New Technologies

Margarita Zuley, MD, FACR, is chief of Breast Imaging at Magee, and professor and vice chair for Quality Assurance and Strategic Development in the Department of Radiology at the University of Pittsburgh. Dr. Zuley heads up one of the oldest and busiest breast imaging divisions and programs in the country, routinely handling more than 100,000 exams every year (nearly 300 a day), and diagnosing in the neighborhood of 1,000 new cases of breast cancer every year. The Division is based out of Magee-Womens Hospital of UPMC, with a current contingent of 19 radiologists on staff. Screening and diagnostic services are performed at 11 facilities across the region, covering everything from ultrasound, MRI, and tomosynthesis, to radioactive seed localization, stereotactic biopsies, and nuclear medicine.

Educational and quality improvement initiatives are numerous in the Division, and include an active peer-to-peer review system that functions in an ad hoc manner whereby radiologists in the Division can read and comment on other prior scans by colleagues and have those notes visible the same day, again for educational and quality improvement purposes.

"We have an extremely busy clinical practice, but I feel it's our research program along with the incredibly collaborative way we interact with our multidisciplinary women's health colleagues at Magee that differentiates us. We routinely discuss cases with our clinical colleagues to ensure that patients receive the highest level of coordinated care. The close relationship we have with the Department of Radiology's Imaging Research Laboratory led by David Gur, ScD, has allowed us to be highly successful in performing research trials that have influenced clinical practice across the world," says Dr. Zuley.

Dr. Zuley also manages an enterprise-wide breast imaging quality committee, formed in 2011, that works to ensure that breast imaging services are standardized across the entire UPMC system and that rigorous quality protocols are in place and followed by all providers and technologists, regardless of where in the system they practice. "The intent of the committee is to ensure the highest level of interpretive skill and patient management is afforded to patients, regardless of the UPMC location they choose for their services," says Dr. Zuley. This includes support for optimized equipment and reporting. UPMC sites participate in the ACR National Mammography Database Registry, which is a quality registry for monitoring of performance. Quarterly meetings of the UPMC breast imaging quality committee occur to discuss issues, new program ideas, and so forth. All UPMC facilities that offer breast imaging participate in the committee and are typically represented by physician, administrative, and quality staff.

New Technologies for Better Imaging: Tomosynthesis and Early Adoption

The Magee Breast Imaging Program has a long history of new technology research and integration. In the 1990s, Magee was home to one of the first MRI units in the country, and in 2006 had one of the very first research tomosynthesis units. Dr. Zuley's group often takes in the very initial prototypes of new pieces of technology if they believe there is some way that it may improve patient care, and over the years they have undertaken many research and clinical trials with manufacturers to help them develop and refine their imaging platforms. "We've been publishing research on tomosynthesis since 2006. One of those publications was instrumental in the FDA granting approval of the technology for widespread adoption and use by providers," says Dr. Zuley. That paper was used as corroborative evidence by the FDA to grant the manufacturer's PMA application for use on clinical patients, showing that tomosynthesis was at least as good as the standard of care 2D mammography of the time.

A 2D mammogram is two flat pictures of a breast taken at different angles. This results in a lot of tissue that is superimposed when a flat picture is taken of a round structure. Standard 2D mammography sometimes suffers in that small cancers can be hidden in the superimpositions, and the superimpositions can also cause false positives. In tomosynthesis, the x-ray is moved through a small arc and takes a series of scans that are then made into a set of 1 mm-thick slices, similar in nature to a CT scan. This results in perhaps 300 views of the breast, depending on its thickness, providing a much higher degree of sensitivity and specificity than a two-image traditional mammogram.

Magee was an early adopter and researcher in the field of tomosynthesis, but its use and implementation system-wide has expanded greatly in recent years. Every Magee Breast Imaging location has tomosynthesis capabilities in place. "We recommend tomosynthesis as our standard of care for all patients except for those few who have extremely dense breast tissue, which is a very small fraction of the total population. We have found that tomosynthesis increases invasive cancer detection while simultaneously decreasing recall rates. It's a more accurate test than 2D mammography alone," says Dr. Zuley.

Next Generation Mammography and Tomosynthesis, and Ultrasound Trials

On the horizon are extensions of mammography and tomosynthesis imaging modalities using contrast enhancement. Two trials are currently in progress at Magee investigating whether the use of contrast could further improve diagnostic specificity. Dr. Zuley is currently running one of these trials, which is evaluating patients who have imaging findings that are of a lower probability of cancer but who still need a biopsy confirmation. "Our trial is investigating the use of contrast to see if we can mitigate the need for a core biopsy in these patients," says Dr. Zuley. The second trial in progress, led by Jules Sumkin, DO, is evaluating the efficacy of contrast-enhanced mammography in women recently diagnosed with breast cancer. The trial is analyzing whether contrast mammography or another novel technology called molecular breast imaging — which uses a very low

dose radioactive agent called sestabmibi — might replace MRI for evaluating the extent of disease in these patients.

Two other trials involving the use of ultrasound in breast imaging are in progress by colleagues of Dr. Zuley in the Breast Imaging Division. The first, led by primary investigator Denise Chough, MD, is currently recruiting patients into a study to assess and compare the use of automated breast ultrasound (ABUS) as either a primary screening approach or supplemental procedure with digital breast tomosynthesis to determine what kind of patient may benefit most from this modality. The second study, also currently recruiting patients, is led by Wendie Berg, MD, PhD, and is evaluating and assessing the potential benefit of technologist-performed whole-breast ultrasound in addition to tomosynthesis in detection of breast cancer in individuals with dense breasts.

A Personalized Approach to Patient Imaging

While tomosynthesis is the recommended standard of care for most patients, that does not mean Magee takes a one-size-fits-all approach to breast imaging for all women. Patients are triaged by the density of their prior mammogram and also by their risk profile. "Women who are of high risk and within a certain age range should actually be undergoing screening MRI in addition to a mammogram. We try to triage these women to our high-risk program for evaluation, and if they qualify, we want them to get an annual MRI," says Dr. Zuley. For women who don't qualify for MRI, tomosynthesis-based screening is recommended unless their breast density is extremely high. For the group with very high densities, our preferred modality is ultrasound screening. "We tailor what we are offering patients to their inherent risk, and the density of their breasts, to give them the best combination possible," says Dr. Zuley.

To facilitate ordering of tests by treating physicians, Dr. Zuley's team recently released a smart set into the electronic health record for physicians that follows the above paradigm, detailing what recommendations a patient has been given for their follow-up imaging tests in the coming year.

The mission of our Division has always been to provide world-class care to our patients. That includes studying and implementing technologies that detect small cancers earlier while at the same time improving our accuracy by lowering the number of false-positive exams, and finding less invasive ways to perform our imaging. We leave no stone unturned in this pursuit," says Dr. Zuley.

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Obstetrical Neurology Parts 1 and 2

Presented by: Robert Kaniecki, MD; Grace Lim, MD, MS; M. Angela O'Neal, MD

Drs. Robert Kaniecki and Grace Lim each present on topics that include headaches in pregnancy and the puerperium, as well as the impact of labor pain on postpartum depression. Dr. O'Neal presents on postpartum neuropathy and reviews the anatomy and clinical findings, and discusses the risk factors.

Infectious Disease Year in Review 2016

Presented by: Neel Shah, MD

Dr. Neel Shah discusses some of the pertinent issues, topics, and guideline changes in infectious disease that have occurred in the last year. He focuses on some of the key concepts related to endocarditis, Zika, HAP/VAP, candida/fungal guideline changes, new antifungals, vaccination, infection control, and stewardship/outbreaks.

Zika: Where Do We Stand?

Presented by: Amesh Adalja, MD

Dr. Adalja provides an update on the recent science breakthroughs and developments with the Zika virus. He reviews some of the clinical basics, microbiology, pathophysiological insights, and the future trajectory of the outbreak.

Fertility Preservation for the Cancer Patient: An Update

Presented by: Stephanie Rothenberg, MD; Erika Friehling, MD; Kyle Orwig, PhD; Hanna Valli, PhD

Drs. Rothenberg, Friehling, Orwig, and Valli discuss various topics on fertility preservation for the cancer patient.

Respiratory Disorders in Pregnancy

Presented by: Francesca Facco, MD

In this three-part presentation, Dr. Facco discusses the physiology and management options for asthma and sleep apnea in pregnancy.

Behavioral Health Research and Care at the Midlife Health Center

The Midlife Health Center (MLHC) at Magee-Womens Hospital of UPMC provides comprehensive care for women in the perimenopause and menopause phases of their lives. **Mary Elizabeth Peterson, MD, NCMP**, is the current director of the center and leads the multidisciplinary clinic in its mission of patient care and research. The clinic is one of very few with all of the treating physicians credentialed as Certified Menopause Practitioners by the North American Menopause Society. Care and consultations are provided at four locations in the greater Pittsburgh area.

Behavioral health services at the MLHC are led by **Rebecca Thurston, PhD**, an internationally recognized expert in menopause research and clinical behavioral care. Dr. Thurston serves in the leadership of the North American Menopause Society as a member of the Board of Trustees and Executive Committee, which is responsible for drafting clinical guidelines for the care of menopausal women. Dr. Thurston joined the clinic several years ago after discussing the needs and challenges of the clinic in meeting the behavioral aspects of care that their patients often exhibit and express.

Having on-site behavioral health care as part of the comprehensive services the clinic offers explicitly acknowledges the close interaction between the physical and behavioral issues at play. Dr. Peterson and the other clinicians in the clinic understand that menopause is truly a biopsychosocial transition where changes in behavioral health, psychological health, mood, sleep, and, of course, all the aspects of physical health are impossible to disentangle if the goal is to provide the most effective treatments and whole-person care possible. "Our clinic is one of very few university-affiliated menopause clinics in the United States that integrates an on-site psychologist into patient care.

Rebecca Thurston, PhD

"I enjoy it, as it keeps me connected to the women I study, and my work at the MLHC gives me the opportunity to translate the research I'm engaged in into clinical care in real-time," says Dr. Thurston.

Dr. Thurston's clinical work typically involves patients who are experiencing mood, anxiety, and sleep disorders, however, these are only a few aspects of behavioral health common during menopause. "We know that issues such as accelerated weight gain are often involved, and we have every effective behavioral intervention for weight loss," says Dr. Thurston, a topic which turns out to be another prominent avenue of clinical research she is pursuing. Obesity, adiposity, and weight during the menopause transition affect vasomotor symptoms and reproductive hormone levels.

The convergence of the biological changes of menopause, coupled with the psychosocial transitions and life stressors, can all lead to significant morbidity and quality of life issues. Researchers are beginning to better understand how such things as cardiovascular and brain health are affected. These associations are part of ongoing and new research by Dr. Thurston and her colleagues.

Vasomotor Symptoms and Their Link to Long-Term Health

Upwards of 70 percent of women have vasomotor symptoms (VMS) during menopause, however, the overall frequency, burden, and severity varies dramatically between women. It was previously thought that VMS lasted for three to five years during the menopause transition, however, this has been proven to be patently wrong. For most women, the duration is closer to a decade. "Some of the newer research has linked VMS to aspects of physiology, biology, and potential health outcomes. They do not just affect quality of life as was previously thought. They can, for some women, signal important changes in vascular health that have real and profound ramifications," says Dr. Thurston.

Dramatic hormonal changes, sleep disturbances, and mood changes are all part of menopause. So, too, are changes in cardiovascular health, with accelerations in cardiovascular disease risk, as well as neurocognitive changes in some individuals. "Many women report problems with memory during the menopause transition. Typically, these have been ascribed exclusively to changes in hormones, but this is turning out to not be correct as well," says Dr. Thurston.

Several past and ongoing studies, including the MS Heart study conducted by Dr. Thurston and colleagues, and the Study of Women's Health Across the Nation (SWAN) study, a longitudinal, multicenter cohort study in progress since 1994, have examined the relationships between vasomotor symptoms and, among other things, a woman's cardiovascular health. "Because of the associations we were seeing in the SWAN study, we embarked upon the MS Heart protocol to measure hot flashes, hormones, and cardiovascular disease risk, and indeed it seems like our hypotheses were supported. Women who have a high frequency of vasomotor symptoms have a clinically worse underlying vascular profile upon imaging tests," says Dr. Thurston.

Members of the MLHC (left to right): Amy Imro, MD, NCMP; Rebecca Thurston, PhD; Mary Elizabeth Peterson, MD, NCMP; Judith Volkar, MD, MBA, NCMP; Katherine Scruggs, MD, NCMP.

Dr. Thurston and colleagues also conducted a small pilot study, within the context of the larger MS Heart study, in which 20 of the 304 study participants were brought back to the lab to undergo brain imaging scans. What the pilot study found was that women with more vasomotor symptoms, specifically those symptoms experienced overnight, seemed to have more white matter hyperintensities in their brains. These white matter hyperintensities are potentially an indicator of small vessel disease in the brain. "What we saw in the peripheral vasculature of these women in other studies, such as SWAN, showed up in this study that looked at the vasculature of the brain," says Dr. Thurston.

New Research — Vasomotor Symptoms, CVD, and Brain Aging

Much of the previous work of Dr. Thurston and her colleagues has laid the foundation for her most recent investigation, a $3.7 million RO1 grant from the National Institute on Aging to study the role of vasomotor symptoms and brain aging in menopausal women. Patient enrollment for the study began in August 2017.

A target of 230 women who do not exhibit cardiovascular disease or dementia will be recruited for the study. These individuals will be assessed and characterized for their vasomotor symptoms in addition to their hormonal, sleep, and risk profile for cardiovascular disease.

The aims of the new study seek to understand what links may exist between vasomotor symptoms during menopause and the development of cognitive decline, which can signal early Alzheimer's disease risk. As VMS are also linked to the development of cardio-vascular diseases, Dr. Thurston's study will assess the role of CVD risk factors, and the presence of subclinical CVD, and their associations to cognitive function and structural or functional changes in the brains of women experiencing VMS.

"Women are disproportionately those who develop Alzheimer's disease and dementias. Women both live longer than men and may be at particular risk for these diseases. Our goal is to understand brain aging in women, find early markers of risk in women, and help guide prevention efforts to preserve women's brain and cognitive health as they age," says Dr. Thurston.

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Infectious Diseases: New Research and New Treatments

Harold Wiesenfeld, MD, CM, is professor of medicine, vice chair for gynecologic services, and director of the Divisions of Gynecologic Specialties and Reproductive Infectious Disease. Dr. Wiesenfeld is active on both the research and clinic fronts with a number of recently completed clinical trials and ongoing research protocols aimed at improving treatments and testing for various conditions that include pelvic inflammatory disease and sexually transmitted diseases.

Finding the Optimum Antibiotic Treatment for Acute Pelvic Inflammatory Disease

Dr. Wiesenfeld recently concluded a randomized clinical trial[1] initiated in 2010 and designed to determine the optimum antibiotic treatment of women diagnosed with acute pelvic inflammatory disease. There has been much uncertainty in the literature and in clinical practice as to whether women with acute pelvic inflammatory disease (PID) should receive additional antibiotics to treat anaerobic organisms that are often responsible for causing the condition. "The current antibiotic recommendations from the Centers for Disease Control and Prevention (CDC) generally do not include much coverage against these organisms that we think play an important role in the development of PID," says Dr. Wiesenfeld.

The study, completed in September 2017, for which Dr. Wiesenfeld is currently in the midst of preparing a manuscript for publication, has been the only clinical trial of PID in the United States for a number of years. The study protocol examined cohorts that received a single intramuscular dose of ceftriaxone 250 mg, doxycycline 100 mg orally twice a day for 14 days, and placebo tablets orally twice a day for 14 days versus those receiving the same doses of ceftriaxone and doxycycline, along with metronidazole 500 mg orally twice a day for 14 days. Dr. Wiesenfeld's primary objective in the study was to compare the eradication of anaerobic organisms from the upper genital tract between women who received the standard outpatient antibiotic treatment to those who received standard outpatient treatment along with the additional course of metronidazole.

The study, which enrolled 200 women, largely demonstrated that the standard course of treatment plus metronidazole eradicated the anaerobic organisms more efficiently versus just the standard treatment alone. "We anticipate that the results of this investigation will be highly influential in the revision of the national and potentially international guidelines for the management of women diagnosed with acute pelvic inflammatory disease," says Dr. Wiesenfeld. Full results of the study are forthcoming.

Mycoplasma Genitalium Research

Since its discovery, the bacterium *Mycoplasma genitalium* has undergone considerable investigation over the past 15 years as a sexually transmitted disease pathogen. "It's an organism that was first described about 30 or 40 years ago, and with the development of polymerase chain reaction techniques we have been able to identify this organism that historically has been very difficult to grow in a lab," says Dr. Wiesenfeld.

There has been a very consistent body of literature associating *Mycoplasma genitalium* with male urethritis, and it is likely a cause of male urethritis in a proportion of men. What is less well understood at present is how much this pathogen affects women, specifically in the development of cervicitis and in pelvic inflammatory disease. "We have completed some important work looking at *Mycoplasma genitalium* and its association with pelvic inflammatory disease, essentially demonstrating that *Mycoplasma genitalium* is identified in women with PID, and it may actually play a role in the pathogenesis of the condition," says Dr. Wiesenfeld.

Additionally, Dr. Wiesenfeld has recently embarked upon a large, NIH-sponsored multisite study that will attempt to determine the prevalence of *Mycoplasma genitalium* in male urethritis among attendees at an STD clinic.

STD Screening — Chlamydia and Gonorrhea — Increasing the Odds

In the STD clinics, patient population rates of infection of chlamydia and gonorrhea among young women (< 25 years of age) is approximately 10 percent. In the family planning clinics, it is perhaps three percent to four percent, while rates for adolescents seen in primary care may be approximately five percent. "We know approximately 10 percent of women who get chlamydia will go on to have PID within the year.. It's a severe complication of a common STD. Despite the availability of very good diagnostic tests for these two bacterial infections, less than 50 percent of young, sexually active women are being screened for the diseases, which if left untreated can lead to PID and infertility," says Dr. Wiesenfeld.

A new study, sponsored by the CDC Foundation and led by Dr. Wiesenfeld, seeks to significantly change the screening rate. The study — STD Testing in Outpatient Practices (STOP)[4] — is a study meant to increase the proportion of young women who are screened for chlamydia and gonorrhea.

There are likely a number of missed opportunities and barriers to getting more young women screened. These include the historical requirement to undergo a pelvic examination, the requirement for a physician or other health care provider to recognize that an individual is in need of STD screening, and other factors. This study will try to

determine whether routinely offering STD screening by medical assistants during the initial patient intake process, treating it as if it were another vital sign, will enhance screening rates in a variety of primary care offices.

"We are collaborating with OB/GYN offices, primary care physicians, internal medicine physicians, and pediatricians to determine whether this kind of routine approach will overcome some of the barriers to STD testing. Our hope is that we will see a tremendous increase in the proportion of young women being screened, and thereby increase the likelihood of identifying asymptomatic or subclinical infections that can go on to develop serious health consequences for these women," says Dr. Wiesenfeld.

Clinical Program Advances

Since 1996, Dr. Wiesenfeld has operated the Vaginitis and Vulvar Disorders Clinic at Magee-Womens Hospital, one of only a few centers in the country to offer a multidisciplinary referral clinic for women with reproductive infectious diseases and vulvar disorders. Dr. Wiesenfeld and his colleagues see patients throughout the week in the clinic — on average 15 to 20 referrals a week — and provide treatment and counseling for complicated, complex, or recurrent vaginal infections, as well as other STDs. "We provide highly specialized care for these patients, as well as the opportunity to participate in cutting-edge clinical trial research."

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Department News Briefs

Developing a Comprehensive Center for Ovarian Biology Research

The Magee-Womens Research Institute received a $3 million grant from the Eden Hall Foundation to develop and launch a new Comprehensive Ovarian Biology Research Center. With a matching $3 million award from UPMC, the new center will focus its work on advancing the understanding of ovarian cancer and its molecular and physiological traits that lead to its development and recurrence.

Immunotherapy Clinical Trials for Ovarian and Cervical Cancer

Oncology researchers at Magee-Womens Hospital of UPMC and the UPMC Hillman Cancer Center are involved in numerous clinical trials for the treatment of ovarian cancer.

One new phase II trial in development is for recurrent ovarian cancer, which is sensitive to standard platinum-based therapy. Patients enrolled in this study will receive a six-week course of chemotherapy delivered intraperitoneally, along with pembrolizumab and the immunotherapy agent Ampligen.

A second immunotherapy trial in development, a phase II study, will use an Adoptive Cell Transfer Therapy for patients with metastatic or recurrent cervical cancer. Patients enrolled in this trial will have a biopsy of the tumor and surrounding environment collected in the operating room, preserved, and then sent to Lion Pharmaceuticals, which will analyze and harvest the patient's tumor-infiltrating lymphocytes (TILs) present within the biopsy that have recognized the tumor as foreign. These TILs are the effector cells that are responsible for the majority of all immunotherapies, including the checkpoint inhibitor such as nivolumab, pembrolizumab, and the PD1/PDL1 inhibitors.

The patient's harvested TILs will be expanded in quantity using a cellular proliferation technique, with the goal of reintroducing them into the patient in much higher quantities than exist natively in the hope that they cause a much greater immunologic response and attack or suppress the patient's tumors. Patients in this trial will undergo a lymphodepletion regimen to suppress their immune system prior to reintroducing their harvested, expanded TILs.

Ovarian Cancer Cells Manipulate Surrounding Normal Cells to Aid Tumor Growth

Tumors do not grow in isolation but are surrounded by a rich microenvironment that contains blood vessels, fibroblasts, immune cells, and a multitude of other components. Cancer cells can influence their microenvironment through extracellular signaling mechanisms to enable and/or enhance their ability to grow and metastasize, such as through the promotion of angiogenesis and immune tolerance.

Lan Coffman, MD, PhD, assistant professor of medicine, is a medical oncologist and researcher who specializes in ovarian cancer. She is particularly interested in understanding how carcinoma-associated mesenchymal stem cells (CA-MSCs) develop within the tumor microenvironment, and how they act to promote ovarian cancer growth. Recent findings in her laboratory demonstrated that cancer cells are able to transform normal mesenchymal stem cells into CA-MSCs through epigenetic alterations.

Premenopausal Breast Cancer: Specialty Care for Younger Women

In the United States, the incidence of premenopausal breast cancer, or cases seen in individuals under the age of 45, is approximately 13.8 percent.[1] With the American Cancer Society[2] estimating for 2017 approximately 255,180 newly diagnosed cases of breast cancer, this translates to approximately 35,214 new cases of breast cancer diagnosed at a young age. Although the types of breast cancer diagnosed in young women tend to be similar to that in older age groups, there is a slightly higher proportion of HER2 positive and triple-negative breast cancer types in the younger age group. "In a younger patient population, women tend to present with a higher-stage disease simply because women under the age of 40 are not invited to participate in a regular breast screening program with annual mammograms, unlike women over the age of 40 or 50. We do not screen this population with routine surveillance as we do with older individuals, says **Emilia Diego, MD**, surgical oncologist and program director of the Magee-Womens Hospital of UPMC Young Women's Breast Cancer program.

Stage-for-stage comparisons between older and younger cases, in terms of prognosis, are typically similar, with perhaps slightly worse outcomes with the younger populations.[3] In younger patients, most cases tend to be estrogen-receptor positive varieties, which may portend a better prognosis, but in the younger patient population there also is proportionally a larger fraction of more aggressive tumors. "With respect to recurrence after successful treatment of the primary lesion, rates tend to be slightly higher than in older patients, but it is also a function of the biology of the tumor in question," says Dr. Diego. Regardless, treatment remains multimodal and multidisciplinary precisely to prevent recurrence in the future.

Since 2015, this care for young women with breast cancer has been provided at the Breast Cancer Specialty Care Clinic at Magee-Womens Hospital of UPMC.

The Breast Cancer Specialty Care Clinic at Magee

Dr. Diego and her colleagues typically treat about 300 new cases of breast cancer each year in women under the age of 45. Since 2015, Dr. Diego and her colleagues have operated what they call a virtual, multidisciplinary clinic for their younger patients, seeing on average 60-70 new cases each year in the clinic. Patient visits and consultations for the entire spectrum of care they will require are all done in a single day, covering everything from imaging tests, fertility preservation, and genetic counseling, to surgical and medical oncology, reconstructive surgery, and any other discipline needed for a particular patient's needs. "The approach can be exhausting and sometimes overwhelming, but our patients in the end are universally grateful for the approach. We are saving the patients time by avoiding appointments on multiple days; it allows for better participation by family members who accompany patients, and it actually allows us to somewhat shorten the time interval between the first diagnosis and their first treatment by at least a week or two, depending on the case," says Dr. Diego.

When the clinic first began, patients would essentially be in the same place, and all the treating clinicians would come to the clinic and see the patient at the designated time throughout the day. Clinics occurred once every two weeks. Through this approach, Dr. Diego and colleagues had the ability to see three patients during the day. In 2016, Dr. Diego made changes to the operational function of the clinic to allow for greater patient access and volume.

"Now, appointments are part of the respective clinician's regular schedule, and we move the patient around within Magee for each of her consultations. This has allowed us, using the same model of care, to see four patients every week. Functionally everything is the same, but we've increased our ability to handle more patients in the clinic," says Dr. Diego.

Clinical Trials for Reducing the Extent of Surgery

Dr. Diego and colleagues at Magee are set to begin participation in two new clinical trials[4,5] in the next several months exploring if surgery can be eliminated in a subset of patients who are extremely responsive to chemotherapy approaches. "It may sound a bit heretical, but there appears to be a patient population that is so responsive to chemotherapy that if we actually administer it to them before any surgical intervention, and then perform the surgery to remove the area where we believe the cancer used to be after chemotherapy, some of the postsurgical reporting shows no evidence of tumor in the collected tissues. This begs the question: If there is nothing in the breast to remove from a tumor perspective, why do the surgery?" says Dr. Diego.

The current standards of care obviously still include surgical intervention, but if some patients can be spared surgery, having equal or better outcomes, it's incumbent upon science to explore a less invasive pathway for those who might benefit the most. This type of research being explored at Magee and elsewhere is at the forefront of breast cancer treatment and is really a continuation of the trend that has been in existence since the 1950s, where surgical interventions for breast cancer have steadily become less invasive and more focused. Historically, breast surgery used to remove the breast, muscles, even shoulders and arms in some cases until as late as the 1950s. The paradigms of treatment and their effectiveness have continued to evolve since.

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About the Department

The Department of Obstetrics, Gynecology, and Reproductive Sciences encompasses a full range of specialties and clinical services for patients, as well as a broad research portfolio and accredited subspecialty training programs for physicians.

Patient care is centered at Magee-Womens Hospital of UPMC, home to one of the largest and most respected clinical care programs in the country. Magee-Womens Hospital of UPMC is recognized as a National Center of Excellence in Women's Health by the U.S. Department of Health and Human Services. At Magee, more than 10,000 babies are delivered each year, and the hospital currently operates the largest neonatal intensive care unit in Pennsylvania, treating more than 1,500 patients annually.

Divisions and Specialty Women's Health Services

Magee-Womens Hospital of UPMC offers a full spectrum of obstetric, gynecologic, and reproductive health services and specialty programs for patients. These include:

General Obstetrics and Gynecology — Featuring specialty programs and treatments for endometriosis, uterine fibroids, and other common conditions.

Gynecologic Oncology — In collaboration with the UPMC Hillman Cancer Center, the gynecologic oncology program provides a comprehensive, multidisciplinary approach to the treatment of gynecologic cancers.

Breast Cancer and Breast Surgery — Magee-Womens Hospital is a national leader in breast cancer research, clinical trials, and patient care for patients with breast cancers and other disorders.

Maternal Fetal Medicine — For complicated pregnancies, the maternal fetal medicine program offers consultation, diagnostic testing, and care management for high-risk pregnancies before, during, and after pregnancy.

Midlife Health Services — Physicians in the Midlife Health Services program specialize in the treatment of the symptoms of menopause, and on those women experiencing premature or perimenopause with accompanying symptoms.

Midwifery — Midwifery services at Magee are comprehensive, from prenatal care through labor and delivery, and are provided by a team of board-certified midwives licensed in both nursing and midwifery.

Minimally Invasive Gynecologic Surgery — With one of the largest contingents of fellowship-trained surgeons on staff, the minimally invasive gynecologic surgery program offers state-of-the-art treatments and procedures for a range of issues that include hysterectomy, ovarian cysts, endometriosis, pelvic pain, and others.

Obstetrical and Gynecological Ultrasound — Women's imaging services at Magee are provided by specially trained, board-certified physicians and staff skilled at various breast imaging and ultrasound-guided biopsies, OB ultrasound, bone density scans, and other diagnostic imaging tests.

Reproductive Endocrinology and Fertility — The Center for Fertility Preservation and Reproductive Endocrinology provides patients with on-site access to a full range of diagnostic and treatment programs for infertility issues for both women and men, including in vitro fertilization, fertility preservation, preimplantation genetics, and preconception counseling, among other services and support.

Reproductive Genetics — The Division of Reproductive Genetics and Genomics provides clinical evaluation and genetic counseling to men and women with genetic/genomic disorders, including preconceptional, prenatal, adult, and cancer cases.

Urogynecology and Pelvic Reconstructive Surgery — The Division of Urogynecology specializes in the diagnosis and treatment of a range of conditions that include chronic urinary tract infections, pelvic organ prolapse, urinary incontinence, and pelvic pain.

Fellowship Training Programs

The Department of Obstetrics, Gynecology, and Reproductive Sciences currently offers a number of accredited fellowship-training programs for prospective physicians:

- Maternal Fetal Medicine
- Medical Genetics Residency
- Reproductive Endocrinology and Fertility
- Female Pelvic Medicine and Reconstructive Surgery
- Gynecologic Oncology
- Reproductive Infectious Diseases and Immunology
- Minimally Invasive Gynecologic Surgery
- Family Planning

Areas of Research

As the top recipient of NIH-funded research grants for obstetrics and gynecology in the country, researchers at Magee-Womens Hospital and collaborative partners at the Magee-Womens Research Institute are deeply involved in many novel basic, translational, and clinical studies. Primary research areas include:

- Reproductive development
- Pregnancy and newborn medicine
- Infectious diseases
- Gynecology
- Reproductive endocrinology and fertility
- Women's cancer
- Women's health and wellness
- Genetics

Breast Cancer Research and Advocacy

Priscilla McAuliffe, MD, PhD, is a breast cancer surgeon and researcher, and director of the Breast Disease Research Repository. Dr. McAuliffe has specific interests in the pre-malignant neoplasms, ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS), and the mechanisms by which these malignancies occur. Dr. McAuliffe's overarching research goal is to halt the development of invasive ductal or lobular breast cancer. Dr. McAuliffe's group studies two related themes. The first examines the interplay between the body's immune system and the growth of breast ductal or lobular cells. The second involves the role of cellular survival mechanisms, such as autophagy, in the progression from in situ to invasive breast cancer. Building on her training in molecular genetics, Dr. McAuliffe's translational studies utilize tissue culture, murine models, and clinical specimens acquired directly from the operating room, as well as from retrospective evaluations and clinical trials.

Some of Dr. McAuliffe's recent research involves characterizing xenografts derived from patients with neoadjuvant chemotherapy-resistant tumors, and the development of new in vitro models of DCIS also derived directly from patient specimens. As director of the Breast Disease Research Repository, Dr. McAuliffe revitalized the patient consenting and tissue collection approach, and this has resulted in a much larger volume and selection of tissue samples becoming available to other researchers both within and outside of the University of Pittsburgh.

Developing New Models for DCIS Research

"DCIS has an outstanding survival rate, but we know that within the group of patients who carry this diagnosis, there is a big range in how the disease will act. Historical studies suggest that a significant number of patients who have very low-grade DCIS are probably being overtreated, but there is a small proportion of patients whose disease will progress to invasive disease. The issue is that currently, we are unable to accurately identify which patients will ultimately end up with invasive disease, and which one's disease will remain indolent," says Dr. McAuliffe.

Furthermore, treatment for DCIS depends on the size of the lesion and/or if there are multiple foci of disease present and can range from lumpectomy followed by radiation therapy to mastectomy, and in most cases endocrine therapy such as tamoxifen or aromatase inhibitor. "Given that most cases of DCIS neither progress nor reoccur in the future, these are significant interventions. There is a critical need to better identify those patients who could simply be placed on surveillance, and those whose DCIS should be more aggressively handled," says Dr. McAuliffe. Developing better modeling techniques for DCIS holds the promise of answering this set of questions.

As Dr. McAuliffe explains, historically, researchers studied breast cancer using commercially available cell lines. These cell lines were discovered and derived decades ago from patients who had advanced breast cancer. "As we have learned over the years, and as we continue to discover the unique aspects of breast cancer, the field has realized that these commercially available cell lines are not the ideal source for experimentation because they do not recapitulate the DCIS cases being seen in the clinic."

To begin to resolve this issue, Dr. McAuliffe and colleagues, working within the University of Pittsburgh's long-standing tissue procurement program, recently expanded the program to begin to include a more diverse collection of breast diseases. The current tissue procurement and handling protocols ensure that all relevant pathological and diagnostic information is available, and that the biopsied tissue is processed in a relatively short amount of time to maintain their properties for the tissue culturing process. Their process is outlined in detail in their paper in the journal *Breast Cancer Research and Treatment* published in 2015. Her team is currently analyzing these initial cultured DCIS cell lines to understand how close they are to the native biopsies and how they compare to the existing commercial cell lines. "Our initial paper characterizes our methodology and processes for harvest and culture, and now we are working to understand just how accurately these samples replicating the behavior of DCIS as it develops and grows in patients."

The Breast Cancer Research Advocacy Network

Co-founded in 2014 by Dr. McAuliffe and **Carola Neumann, MD**, associate professor of pharmacology and chemical biology, the Breast Cancer Research Advocacy Network (BCRAN) is designed to foster partnerships between breast cancer survivors and

Breast Cancer Research Advocacy Network (BCRAN) Mission

- Enhance the relevance of research questions to breast cancer patients, survivors, and co-survivors.
- Connect scientists to survivors and co-survivors who can speak for the concerns of the breast cancer population, beyond their personal experiences, so that research goals and study feasibility can be developed cooperatively.
- Increase the awareness about participation in research among new patients and those currently in treatment to improve clinical trial recruitment and enrollment.
- Include patients and survivors in developing critical science questions to increase funding for high-quality research.

researchers to advance and accelerate the progress being made in cancer research to ultimately devise new therapies and diagnostic paths for breast cancer.

Dr. Neumann currently leads the efforts of BCRAN along with Karen DiVito, a breast cancer survivor. Dr. McAuliffe acts as the program's clinical advisor, helping to steer aspects of the program from a clinical perspective, and assisting patients and physicians with clinical trials. The BCRAN group is composed of more than 20 patient survivors who are advocate for and educate other patients in the research and clinical trials realm.

"Dr. Neumann, Karen, and all the other volunteers and contributors have done a tremendous job in education and advocacy for research. Research is critically important to advancing our understanding of breast cancer in the hopes of better treatments and lasting cures, but it is not possible without the support and dedication of patients in the midst of their disease course. It can be daunting for patients to understand how they can participate, if they are willing, in clinical trials and other research, and everything that goes with that. The work of BCRAN is making this easier and friendlier because our advocates have themselves been through and/or are still part of that world. This peer-to-peer interaction is key to the program's success," says Dr. McAuliffe.

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[3] BCRAN program details can be found at: http://upci.upmc.edu/wcrc/patientAdvocacy.cfm.

Premenopausal Breast Cancer

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"We don't see many institutions exploring this avenue of investigation right now, but as a group we felt that in order to be at the forefront of care in terms of exploring cutting-edge treatment for breast cancer, it would be a mistake not to involve ourselves in this question and research because it holds the potential for a radical change in practice. I don't think it's that large of a stretch to say that in some cases, in the future, we won't be doing surgery at all. In fact, I hope that's the case for this group of women," says Dr. Diego.

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Recent Publications

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