



- In This Issue**
- 2 At the Forefront of Minimally Invasive Gynecologic Surgery
 - 4 Cancer Genetics Program: Screening and Counseling for High-Risk Patients
 - 6 A Hub of Innovation: The Gynecologic Cancer Program at Magee
 - 8 A Full Spectrum of Care: The Center for Fertility and Reproductive Endocrinology
 - 10 Endometriosis and Minimally Invasive Surgery
 - 12 On the Leading Edge of Breast Cancer Treatment and Research
 - 14 Uterine Fibroids — Evolving Treatments and New Research

UPDATES IN GYNECOLOGY

Message from the Chairman



Dear Colleagues,

I am pleased to share with you recent updates and accomplishments from our gynecologic specialties and gynecologic oncology divisions. The research and clinical programs of our department and Magee-Womens Hospital of UPMC continue to lead the field with new and novel research, and ever-evolving clinical care aimed at improving outcomes and providing the best possible patient care across our many areas of expertise.

As the number one NIH-funded research program in the country for obstetrics and gynecology, we continually strive to keep the pursuit of rigorous basic, translational, and clinical research as a foundational element of our mission to improve patient care. We also place a heavy emphasis on training and education with our seven clinical fellowship programs, and a multitude of annual physician and researcher-led conferences and symposia.

In the pages that follow, we provide updates and new learnings from our outstanding minimally invasive gynecologic surgery program led by Ted Lee and Suketu Mansuria, and new developments in our treatment approaches to endometriosis and uterine fibroids from colleague Richard Guido.

The work of our Center for Fertility and Reproductive Endocrinology, led by Joseph Sanfilippo, continues to expand its clinical services for patients both in terms of capabilities and geographic reach, as well as related research initiatives to devise improvements in fertility treatment options.

With our Cancer Genetics Program, screening, counseling, and research efforts are now being led by Phuong Mai, who joined our program in May, 2016 after having served at the National Cancer Institute.

Finally, our breast and gynecologic cancer programs continue to break new ground with research, treatments, and screening techniques for metastatic disease. These programs, and our collaborations with colleagues from the UPMC CancerCenter and University of Pittsburgh Cancer Institute, are driving our delivery of patient care toward new frontiers.

It is a great privilege to lead such a varied department and dedicated staff. It also is a great honor to share with you our work on some of the biggest challenges facing gynecologic medicine today.

With kind regards,

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

At the Forefront of Minimally Invasive Gynecologic Surgery

The Center for Minimally Invasive Gynecologic Surgery (MIGS), led by director Ted Lee, MD, and assistant director Suketu Mansuria, MD, is at the forefront of minimally invasive surgical techniques and is conducting innovative research to advance the discipline — breaking new ground for the treatment of many common gynecologic conditions.

With colleagues Richard Guido, MD, Nicole Donellan, MD, and Noah Rindos, MD, the fellowship-trained surgeons of the MIGS center constitute one of the largest and busiest minimally invasive surgical programs in the United States, performing more than 1,000 surgical cases each year. “Over the last couple of years, we’ve really focused our attention on quality improvement initiatives, not only in terms of the quality of care that we are providing but also the patient experience,” says Dr. Mansuria.

Implementing ERAS Protocols

Enhanced Recovery After Surgery (ERAS) protocols are becoming more prevalent across the range of surgical disciplines and practices.

Dr. Mansuria and colleagues took on an implementation protocol, borrowing some of the principles and practices of ERAS and applying them to their minimally invasive cases. “We felt that a lot of what ERAS was built upon for large, open surgeries, things like better pain control and decreased nausea and vomiting after surgery were applicable to our minimally invasive cases,” says Dr. Mansuria. Working with colleagues in anesthesia, nursing, and other areas, the center developed its own version of ERAS for minimally invasive cases and launched the protocols in August 2016. Dr. Mansuria and colleagues are collecting and analyzing data for research protocols at present, but preliminary findings are



Suketu Mansuria, MD

pointing to patients doing better in the recovery room with reduced pain, and less nausea and vomiting.

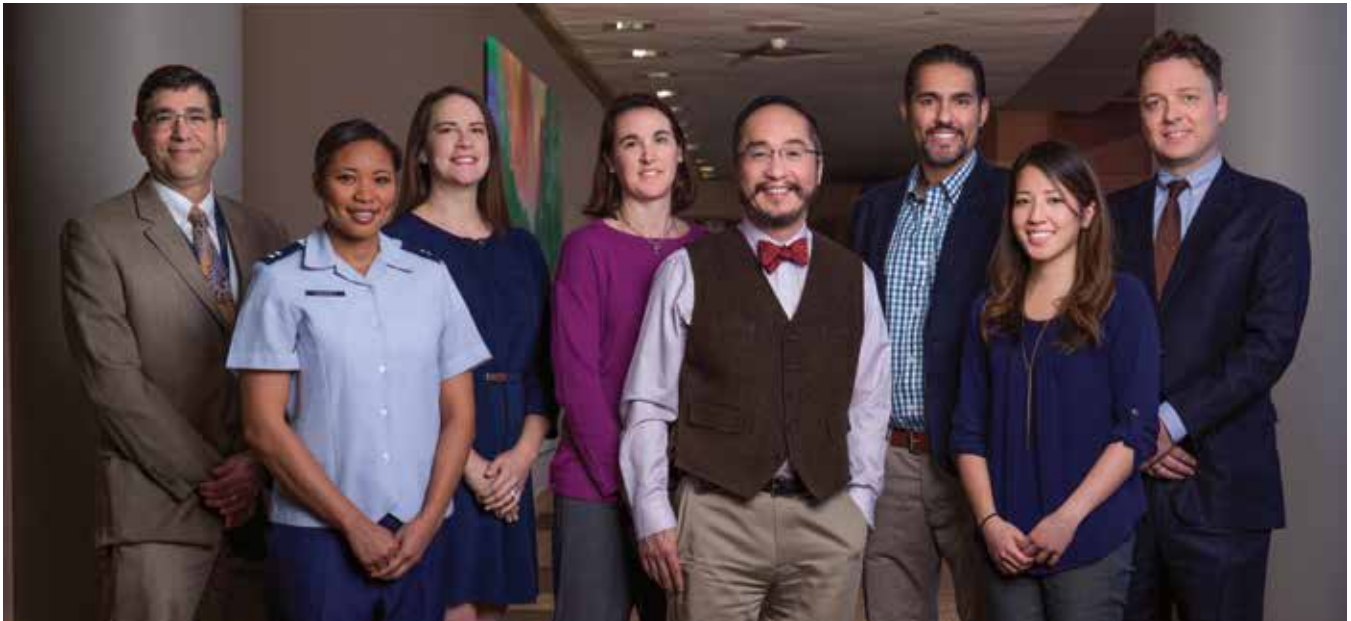
Changes in Hysterectomy Trends and Patient Outcomes Following Implementation of a Clinical Pathway

Minimally invasive hysterectomy typically affords less post-surgical pain, a faster recovery, and fewer complications than open procedures. A goal of the MIGS group in recent years has been to increase the percentage of laparoscopic, robotic, or vaginal procedures. “Our desire was to reduce the number of abdominal hysterectomies and do it across the entire UPMC system, not just in our practice at Magee,” says Dr. Mansuria. To effect change on a system-wide level, physicians had to be engaged, and become partners in care. “We wanted physicians to be involved in the decision-making process to truly see that this approach is better for all of our patients.”

Dr. Mansuria and colleagues put together a team to analyze UPMC patient data, comparing outcomes from minimally invasive hysterectomies to open procedures. Using evidence-based recommendations from the American College of Obstetrics and Gynecology (ACOG) and internal UPMC data, a pathway was developed that would offer guidance and recommendations to the surgeon as to the best route for performing the hysterectomy. Questions about the size of the uterus, comorbidities, and other factors are used to develop the recommendation. “At this point, it’s still up to the physician to decide whether they want to follow those recommendations, but the pathway helps identify good candidates for a minimally invasive hysterectomy,” says Dr. Mansuria. For those clinicians who do not feel comfortable doing surgery minimally invasively, the pathway assists with referral of the patient to a specialist.

The pathway was implemented in 2012 across the then 14 hospitals within the UPMC system. Data from the implementation was compared from 2012 to 2014. “In a caseload of well over 6,000 hysterectomies system-wide, we saw a 39 percent reduction in abdominal hysterectomies with an equivalent increase in minimally invasive hysterectomies,” indicates Dr. Mansuria.

Beyond just a reduction in open surgical cases, the data was collected and followed for post-surgical complications. “We are not only doing more minimally invasive hysterectomies, but we are also improving patient care,” says Dr. Mansuria. Length of stay has significantly decreased, and there have also been significant reductions in surgical site infections, readmissions, and blood transfusions. Metrics for the pathway implementation are still being collected and further research is ongoing.



The Minimally Invasive Gynecologic Surgery team.

L to R: Richard Guido, Christina Ramirez (fellow), Mallory Stuparich (fellow), Nicole Donnellan, Ted Lee, Suketu Mansuria, Lisa Chao (fellow), Noah Rindos

New Research

Research by the MIGS group is continually developing as the discipline evolves. Recent research efforts have included a number of studies. One investigation looked at the use of IV Tylenol® to see if it could reduce the amount of narcotics patients needed for pain control after surgery. Narcotics can cause nausea and vomiting, leading to a vicious cycle of more pain. Dr. Mansuria's team wanted to see if they could control pain with non-narcotic methods, specifically with IV Tylenol. This randomized controlled trial was recently completed and they are currently analyzing the data with results to follow in the future. Additional trials are in development to test ways to reduce recovery room time and speed up the time to discharge. Dr. Mansuria also is conducting several studies aimed at identifying ways to reduce the costs of minimally invasive hysterectomies.

Leading the Way in Fellowship Training

Minimally invasive gynecologic surgery fellowships are now considered the most competitive fellowship within the obstetrics and gynecology field and the third most competitive fellowship within all of medicine. "We think we have one of the most competitive fellowships in the country. With five fellowship-trained surgeons in the group, we have the patient volume to sustain a large program. The beauty of our fellowships is not only do they receive outstanding

training from our surgeons, they are learning how to be future leaders within the field of minimally invasive surgery. The vast majority of our fellows go into academic positions once they leave. They are very active in the research world, leaving our program with a certificate in clinical research," says Dr. Mansuria.



Cancer Genetics Program: Screening and Counseling for High-Risk Patients

The Cancer Genetics Program at Magee-Womens Hospital of UPMC provides services to help patients assess whether they are at significantly increased risk of developing certain cancers due to a predisposition to a hereditary cancer syndrome based on their personal or familial history. Beyond providing genetic counseling and testing, the program provides recommendations to patients and families with a cancer predisposition about appropriate risk management options. In the absence of a hereditary cancer predisposition, the program offers a comprehensive cancer risk assessment that takes into account family history along with other personal or environmental risk factors.

A joint program between Magee-Womens Hospital and the UPMC CancerCenter, the Cancer Genetics Program sits within the Department of Reproductive Genetics and is led by Phuong Mai, MD, MS, medical director of the program. Dr. Mai joined the center in May 2016, after having served at the National Cancer Institute in the Clinical Genetics Branch of the Division of Cancer Epidemiology and Genetics. A board-certified medical oncologist with additional training in cancer genetics, Dr. Mai specializes in the research of hereditary cancer predisposition syndromes, cancer risk assessment, and risk management.

"The goals of our program are to obtain a better understanding of the various hereditary cancer syndromes, to better predict individual cancer risks associated with these syndromes, to provide risk-appropriate management recommendations that will lead to cancer risk reduction and detection of cancers at their earliest stages, and to provide support to individuals and families with a hereditary cancer syndrome," says Dr. Mai.

Dr. Mai works along with other program physicians Devereux Saller, MD, and Aleksandar Rajkovic, MD, PhD, and the program currently has four board-certified genetic counselors — Darcy Thull, MS, CGC, Rachelle Huziak, MS, CGC, Christa Goyda, MS, CGC, and Christina Bittner, MS, CGC. Together, the program's physicians and counselors are referred and see close to 1,000 new patients per year from across the greater western Pennsylvania region.

The Cancer Genetics Program also works closely with the UPMC Hereditary GI Tumor Program, which is located at the Hillman Cancer Center. The UPMC Hereditary GI Tumor Program provides a multidisciplinary approach to the identification and management of families with hereditary predispositions to gastrointestinal cancers, and is led by Randall Brand, MD, and has two board-certified genetic counselors, Beth Dudley, MS, CGC, and Eve Karloski, MS, CGC.

Support for Patients and Expanding Services

The Cancer Genetics Program offers a full complement of cancer genetic counseling and testing, and cancer risk assessment services for patients with a personal or family history suggestive of a genetic predisposition to cancer. Testing for such syndromes



Phuong Mai, MD, MS

as Hereditary Breast and Ovarian Cancer, Li-Fraumeni Syndrome, Multiple Endocrine Neoplasia, and other hereditary cancer syndromes are routinely conducted. "There is still a lot that we don't know in terms of the cancer spectrum and level of risk associated with certain cancer syndromes. To be able to further refine cancer risk for the individual so that we can make appropriate and individualized recommendations on how to manage their risk is one of the areas we concentrate on with our program," says Dr. Mai.

Much transpires in the counseling sessions with patients. Detailed family histories are taken, tests and findings are explained in detail, and basic information about inheritance is discussed along with some basic biology. If a particular syndrome is suspected or identified, the syndrome-related cancers, level of risk, and available risk management options are discussed in detail. "We also touch upon some of the psychological and social functioning issues that could impact the well-being of the patient or their family members; if there is a need for ongoing psychosocial support, we try to recognize this and make the appropriate referrals to our behavioral health colleagues," says Dr. Mai.

For patients at too far of a distance to travel, telemedicine services are available. "Because we serve such a large geographical area, we conduct and are looking to expand our telemedicine capabilities and infrastructure for those individuals who simply cannot travel to our main facilities in Pittsburgh for counseling sessions," says Dr. Mai.

Research and Training

Research and training are critical aspects of the Cancer Genetics Program. For Dr. Mai specifically, she has an ongoing interest in the management of Hereditary Breast and Ovarian Cancer syndrome as well as Li-Fraumeni Syndrome. Understanding the psychological and social impact on individuals and families with hereditary

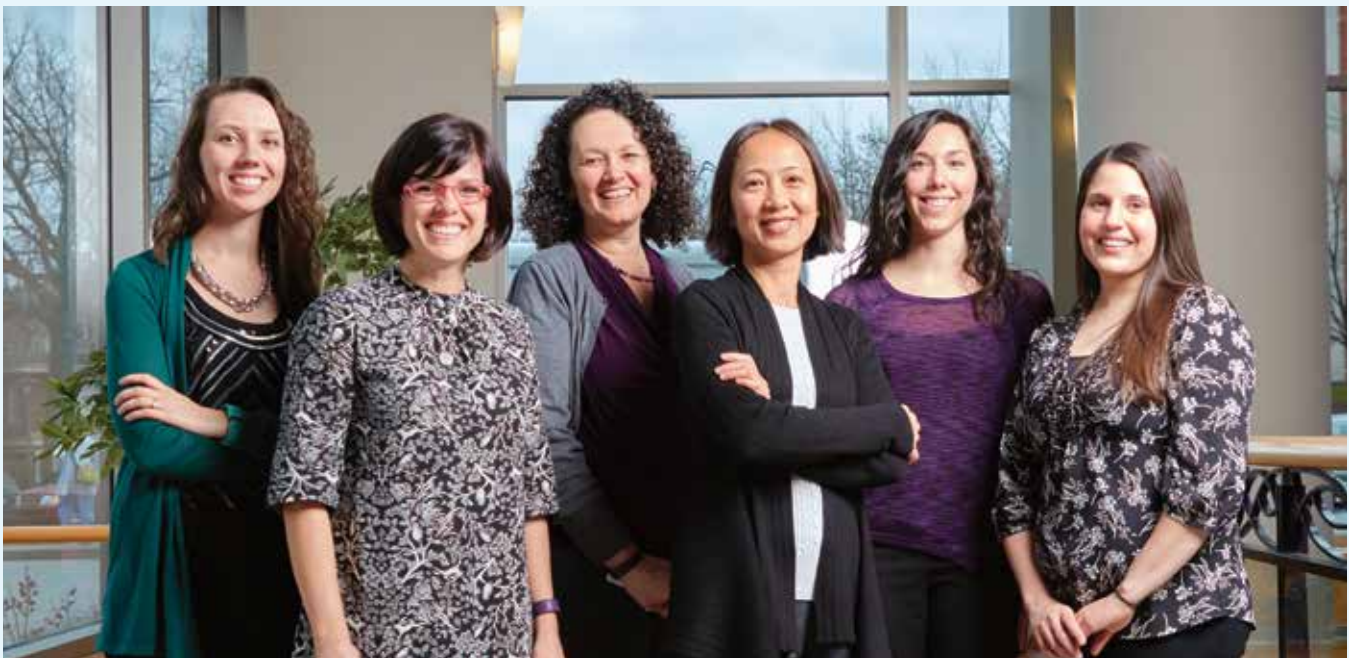
cancer syndromes and how to provide appropriate support is of great importance to Dr. Mai and her colleagues.

The program is a member of an international consortia studying specific cancer syndromes. Some of these syndromes are quite rare, and the most effective way to collect a critical mass of evidence is to collaborate with other institutions.

On the training front, the Cancer Genetics Program works closely with the Genetic Counseling Master's Program at the University of Pittsburgh School of Public Health. Genetic counseling students rotate through the program in their second year as part of their clinical training. The program also offers continuing medical education and training for professionals looking to expand their knowledge base and become more familiar with hereditary cancer risk and hereditary cancer syndromes.

Referrals and Additional Program Information

For more information about the program, or to refer a patient for counseling, please call 1-800-454-8156 or visit UPMCCancerCenter.com/GeneticCounselingServices.



Cancer Genetics Team. Left to Right: Eve Karloski, Christina Bittner, Darcy Thull, Phuong Mai, Christa Goyda, Beth Dudley

A Hub of Innovation: The Gynecologic Cancer Program at Magee

The Magee-Womens Gynecologic Cancer Program has been a leading voice in gynecologic oncology and research for more than two decades, growing in that time to become the third largest program of its kind in the United States. The program is jointly led by Robert P. Edwards, MD, chair of the Department of Obstetrics, Gynecology, and Reproductive Sciences, and Director of Research and Outreach for the program, and Joseph L. Kelley, MD, director of the Division of Gynecologic Oncology and the Magee-Womens Gynecologic Cancer Program.

One of the first specialties within UPMC to establish outreach centers throughout western Pennsylvania, the program currently consists of hubs at Magee-Womens Hospital and the Hillman Cancer Center, with 16 strategically placed locations in the region, and two secondary hubs located at UPMC Passavant and UPMC Hamot. This approach, and similar outreach efforts pioneered by the gynecologic oncology program, is being replicated for other service lines at Magee including maternal-fetal medicine and urogynecology.

With nine gynecologic oncologists on staff, along with a host of other caregivers and disciplines, the program typically sees approximately 150 new ovarian cancer cases every year, and treats close to 400 patients either in consultation, active treatment, or surveillance. Dr. Edwards and his colleagues also treat between 400 and 600 new uterine cancer cases every year with surgery or other therapies. “Our number of new cervical cancer cases has



Robert P. Edwards, MD

actually decreased in recent years. This is attributable to the advent of human papilloma virus (HPV) prevention strategies and a number of outreach and interventional programs we are a part of with state and local governmental agencies across western Pennsylvania,” says Dr. Edwards.

Growth and Innovation Go Hand in Hand

The continual growth and expansion of the program over years has led not only to an increased capacity to see and treat more women in need, but also to the program’s ability to carry on new and novel research for better and more effective treatments. The robust philanthropy program that is part of the Magee-Womens Research Institute has enabled Dr. Edwards and program leaders to seek out and recruit new faculty. “Our newest hire, Lan Coffman, will be joining our program in the near future. She brings with her a research interest in cancer stem cells, and we’re very excited to have her and her expertise join our mission here at Magee,” says Dr. Edwards.

In May 2016, Phuong Mai, MD, MS, was brought to the program to lead the cancer genetics screening and counseling programs. Previously with the National Cancer Institute, Dr. Mai is one of only a few specially trained cancer geneticists in the country. At Magee, she is focusing on prevention and the use of telemedicine to expand these important services to a larger geographic region.

“Our long-term goals are to improve the translational component of our program by bringing on board additional, innovative clinical and translational scientists to work with our existing cohort of physicians and researchers. We’ve built a world-class program at Magee over several decades that has changed patient care for the better, but the work is not nearly done. We can and will continue to grow and improve at every level,” says Dr. Edwards.

Clinical Research Is at the Heart of Innovation

Clinical research is at the heart of the gynecologic oncology program at Magee. The program is one of only four centers in the country holding a SPORE grant from the National Cancer Institute (NCI). Awarded to programs for their ability to promote innovative clinical research, the Magee program is a shared effort with Roswell Park in Buffalo, New York. In conjunction with other NCI-funded protocols, the Magee program has a number of unique clinical trials to offer patients

Dr. Edwards indicates that other new projects are set to kick off in the near future. One of these study protocols will be investigating immunotherapy with patient-derived T cells, in conjunction with Lion Biotechnologies, Inc.

Another current trial in progress is investigating endometriosis as one of the causative agents for the development of ovarian cancer and how to prevent it. “We have a biomarker that we are testing that appears to be able to attack ovarian cancer before it develops from endometriosis. This research is showing promise and we hope to publish more on our research in the near future,” says Dr. Edwards.

Banking on It

The Gynecologic Cancer Program also maintains a very large tissue and serum bank from its patients dating back to 1994. “We have more than 20,000 gynecologic cancer specimens from past patients that we can use in a number of ways to evaluate patient outcomes, look for new and innovative approaches to ovarian cancer, and other studies,” says Dr. Edwards. Again, the scale of the program and its history allow researchers from various disciplines to conduct research that otherwise would be difficult or impossible to do without the on-site resources and history contained within the tissue bank.

The Battle Against HPV and Associated Cancers

Efforts to stem the tide of HPV-associated cancers and risk are ongoing dating back to the mid-1990s with the Magee program taking part as one of the premier centers in early HPV prophylactic studies. Currently, a number of trials are in progress where, beside T cell therapies for the treatment of active cancer, researchers are also looking at trials to prevent the development of cancer in patients who have already contracted HPV but don't have cancer yet. “One of these trials in development will attempt to develop gene therapy technologies to immunize patients after they've been infected with HPV, but before they actually develop the cancerous condition to clear the human papilloma virus after it becomes established,” says Dr. Edwards.

In terms of prevention of HPV, Dr. Edwards has been a part of the Cancer Prevention and Control Committee for the Commonwealth of Pennsylvania. This group has been actively engaged in strategies and outreach efforts statewide to improve the participation in the HPV prophylactic vaccine program. “At present, the participation rate in target populations is approximately 38 percent. Our goal is to increase that to 50 percent of the adolescents and young women and men,” says Dr. Edwards.

Intraperitoneal Therapy for Ovarian Cancer

Dr. Edwards has for many years collaborated extensively with surgical oncologist David L. Bartlett, MD, vice chairman for surgical oncology and gastrointestinal services at the UPMC CancerCenter and University of Pittsburgh Cancer Institute. Dr. Bartlett has been a pioneer in the development and use of hyperthermic intraperitoneal chemoperfusion (HIPEC) to treat a number of cancers. Dr. Edwards' work with Dr. Bartlett has brought this technique to bear on ovarian cancer, and the two have collaborated to create and implement a number of new, innovative programs around HIPEC and advanced surgery.



Dr. Edwards and Dr. Bartlett prepping for surgery.

“Our center is very committed to the use of peritoneal therapy for ovarian cancer. We've been performing trials using peritoneal therapy since 1995. With more than 22 years of experience with this approach, we have some of the best outcomes in the country with the use of HIPEC to treat ovarian cancer,” says Dr. Edwards.

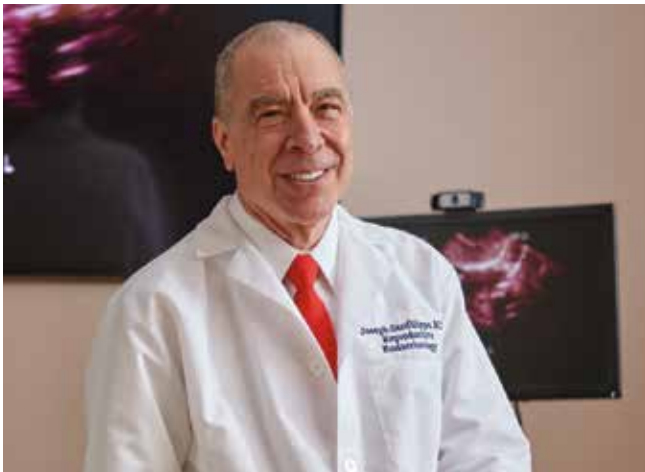
A current phase I trial is looking at new immunotherapy approaches, combining chemotherapy with immunotherapy administered in the peritoneal cavity for ovarian cancer. Magee is the only place in the country right now with such a trial and focus of research.

Beyond clinical practice and research, Dr. Edwards and Dr. Bartlett conduct an international conference on HIPEC therapy. The Twelfth International Symposium on Regional Cancer Therapies was held from February 18-20 in Snowbird, Utah. Sponsored by the University of Pittsburgh and UPMC CancerCenter, the symposium attracts hundreds of physicians and researchers from around the world, and has become one of the premier conferences in the country for the advancement of peritoneal therapies and their application.

A Full Spectrum of Care: The Center for Fertility and Reproductive Endocrinology

The Center for Fertility and Reproductive Endocrinology at Magee-Womens Hospital is the largest center of its kind serving the greater western Pennsylvania region. Under the direction of Joseph Sanfilippo, MD, MBA, the center offers treatments, services, and consultations for the entire spectrum of fertility and reproductive endocrinology conditions.

Currently, the center has five physician specialists who see patients at Magee-Womens Hospital where the full capabilities of the center reside, and nine additional clinic locations strategically placed across the region to provide convenient access to the full range of services Dr. Sanfilippo and his colleagues are able to provide. Additionally, telemedicine services and consultations are currently available at three locations.



Joseph Sanfilippo, MD, MBA

Because this is a teaching and training center, Dr. Sanfilippo and his colleagues have the ability to provide treatments and services for virtually any patient, regardless of the relative rarity or overall complexity of their case. Difficult cases, or patients who have been poor responders to treatments in the past are not shielded away from. From cases of didelphic uterus or other müllerian anomalies to polycystic ovaries, the overall case load is diverse. "Our program is designed to cover the entire gamut of reproductive endocrinology and infertility. It's designed that way because we have an obligation as a training center for subspecialists to provide an education that's all encompassing. Therefore, we literally see patients across the entire life span from newborn through midlife to menopause," says Dr. Sanfilippo.

The fellowship training program at the center attracts some of the very finest clinicians from around the world who desire subspecialty training in fertility and reproductive endocrinology. "Our program covers surgical training, IVF, and the medical aspects of reproductive endocrinology and infertility," says Dr. Sanfilippo.

A Busy, Diverse, Multidisciplinary Practice

Clinicians at the center treat on average 1,500 new patients every year and attend to well over 4,000 return visits, making for an impressive case load. Patients seek out treatment from the center not only from the region but from across the country and internationally. Patients also seek out the center for consultation and treatment for a range of conditions that include endometriosis, uterine fibroids, genetic conditions, reproductive tract anomalies, and other fertility-compromising issues.

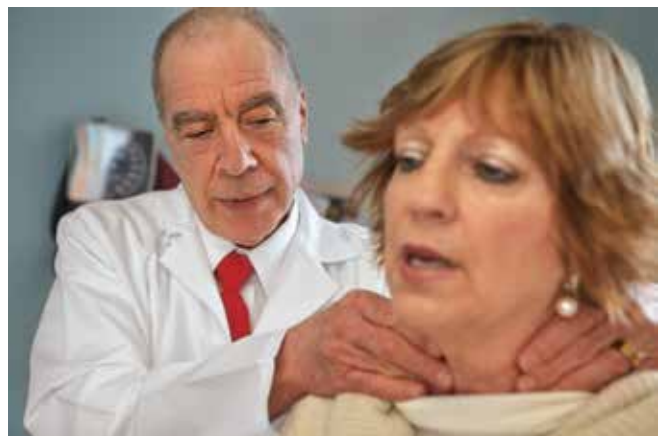
Specialized, On-site Capabilities and Services

Within the center sits a complete armamentarium of services and specialized areas that are brought to bear on patient care and the research efforts of clinicians. Procedures, testing, counseling, and laboratory work are conducted in house. "All of our aspects are housed at Magee, including patient care and consultation, the IVF lab, and our andrology laboratory," says Dr. Sanfilippo.

The IVF Lab at the center is directed by Sharon Anderson, PhD, HCLD. The IVF lab offers a full complement of services for women. Women with decreased ovarian reserve, individuals identified as poor responders who have failed treatments at other centers, and unexplained reasons for infertility are routinely seen by the specialists at Magee who bring to bear specialized protocols for the treatment of these complex and complicated cases.

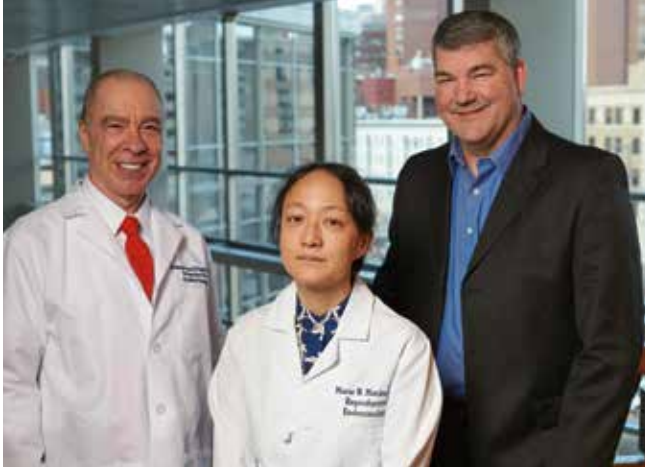
For assisted hatching procedures, the in-house laser system is employed. Assisted hatching entails making a small incision with the laser in the zona of the embryo prior to implantation. "This technique can be employed with women of advanced maternal age or who have failed previous IVF cycles to increase their chances for a successful pregnancy," says Dr. Sanfilippo.

Another aspect of the center is the in-house andrology laboratory dedicated to male fertility testing and analysis. The lab is able to analyze semen and sperm samples for motility, density, morphology, and other characteristics critical to determining possible causes of male infertility.



Fertility Preservation Options for Special Cases

Fertility preservation services within the center are far reaching for women and men, but also for younger boys and girls facing difficult medical conditions, the treatments for which could compromise their long-term fertility. Cryopreservation techniques and services for collecting and preserving sperm, testicular tissue, ovarian tissue, eggs, oocytes, and embryos are available on site for patients.



Dr. Sanfilippo along with Marie N. Menke, MD, and Kyle Orwig, PhD

“For cancer patients, we offer a 24/7 service, working closely with referring oncologists so that we can quickly consult with and treat a patient in need of immediate chemotherapy, radiation, or surgery to preserve their fertility options for the future should the cancer treatments compromise their natural ability to conceive,” says Dr. Sanfilippo. This close collaboration with oncology specialists also minimizes the patient’s time lost prior to starting their cancer therapies. For younger, prepubescent patients, Dr. Sanfilippo’s center has the abilities for in vitro maturation and cryopreservation of gonadal tissues.

Dr. Sanfilippo and his colleagues at the center, including program director Kyle Orwig, PhD, also operate The Fertility Preservation in Pittsburgh program, a joint initiative of Magee-Womens Hospital, Children’s Hospital of Pittsburgh of UPMC, and the Orwig Lab, and is affiliated with the Oncofertility Consortium. The program offers services and conducts research into patient fertility for those individuals who are in need of chemotherapy, or have already had one dose of chemotherapy and, for whatever the reasons, did not act in advance to preserve their gamete tissues, be it female or male. “Our program reaches out to these patients through our center and several partner institutions, and that really translates into our seeing individuals from all over the world,” says Dr. Sanfilippo.

Ongoing Research

The Center for Fertility and Reproductive Endocrinology is actively engaged in numerous research efforts with specialists working in stem cell research related to fertility preservation, ovarian physiology, menopause, preimplantation genetic screening, and other areas. Kyle Orwig, PhD, professor of medicine in the Department of Obstetrics, Gynecology, and Reproductive Sciences at the University of Pittsburgh, directs the Orwig Laboratory and is focused on research into stem cells, germ lineage development, fertility, and infertility. “One active study Dr. Orwig is conducting as principal investigator is the potential for reoccurrence of malignancy with oocytes or sperm that have been subjected to chemotherapy,” says Dr. Sanfilippo. On other research fronts, the pioneering work of Aleksandar Rajkovic, MD, PhD, professor of obstetrics, gynecology, and reproductive sciences, and director of Reproductive Genetics, has led to advances in research and clinical applications of preimplantation genetic screening, alongside his other research interests in the developmental control of the reproductive tract and relationships to infertility, aging, menopause, and tumorigenesis. “We work very closely with Dr. Rajkovic and the Division of Medical Genetics and Genomics. This has allowed us to bring services in-house that most other centers have to contract to third parties,” says Dr. Sanfilippo.



Inside the cryopreservation lab.

For Further Reading

For more information about current programs, research, and active clinical trials at the Center for Fertility and Reproductive Endocrinology, please see the following resources:

- UPMC.com/MageeInfertility
- Mageewomens.org
- FertilityPreservationPittsburgh.org

Endometriosis and Minimally Invasive Surgery

Minimally Invasive Surgery and Endometriosis

Leading the efforts in minimally invasive surgery for patients at Magee-Womens Hospital of UPMC is Ted Teh Min Lee, MD, director of minimally invasive gynecologic surgery (MIGS) and the director of the MIGS fellowship program. Dr. Lee is a skilled surgeon and passionate educator to colleagues in the field and young surgeons in training. Dr. Lee's practice is entirely dedicated to minimally invasive surgical options for women, believing that most benign gynecologic surgical conditions should be treated in a minimally invasive fashion. Dr. Lee's clinical practice currently includes minimally invasive surgery for the treatments of endometriosis, including cases of severe endometriosis involving the bowel, bladder, and ureter, uterine fibroids, abnormal uterine bleeding, urinary incontinence, and pelvic organ prolapse. The benefits of laparoscopic procedures for patients are what drive Dr. Lee to pursue excellence in his surgical practice, and to pass along that knowledge to fellows in training.

A Dedication to Education

Dr. Lee spends a significant part of his time as an educator, researcher, and is active in numerous peer organizations. He has received the Golden Laparoscope Award for best surgical video from the American Association of Gynecologic Laparoscopists (AAGL) four times in the recent past, and he frequently lectures on the subject and performs live surgical procedures around the world to demonstrate current techniques and pass along his accumulated knowledge to colleagues.

Since assuming the directorship of the MIGS fellowship program in 2001, Dr. Lee has trained and mentored numerous surgeons in minimally invasive surgical procedures, and he continues to provide leadership and guidance of the program. "Education is at the heart of my practice. It's a way to give back and expand the use of minimally invasive surgical techniques to offer patients the best possible outcomes for their condition," says Dr. Lee.

Approaches to Diagnosing Endometriosis

Endometriosis typically presents in two different ways. Most patients seek care for endometriosis either because of pain (the majority of cases) or infertility issues. But frequently they do overlap. From onset of symptoms to diagnosis, the average length of time is about nine years. Dr. Lee indicates that there are a number of factors that can contribute to this delay, things such as the patient's just trying to live with the pain, family dynamics, and at times a heavy reliance on imaging and blood tests which frequently can be misleading.



Ted Teh Min Lee, MD

For Dr. Lee, the first part of the process when seeing a new patient is a rigorous approach to collecting a detailed history, coupled with a targeted exam that includes a rectovaginal examination, which is neglected at times by gynecologists. If warranted, diagnostic tests such as MRI and endorectal ultrasound are ordered to aid in the surgical planning process. While fundamental and low-tech in nature, the patient's history and physical examination are still the most useful tools to aid in diagnosing cases of endometriosis.

The presence of endometriosis can only be confirmed through surgery. "However, with a detailed patient history and a targeted physical examination prior to surgery, we are able to predict pathology in about 90 percent of our cases. The use of purely exploratory laparoscopy is the exception and not the rule for our endometriosis cases," says Dr. Lee.

A Multidisciplinary Approach to Surgery

Complexity of endometriosis surgery varies depending on the extent of the condition and if neighboring structures are involved. If the endometriosis has indeed invaded other structures, it may require various levels of bowel surgery, from discoid resection with primary repair or segmental resection with anastomosis to a ureteral anastomosis or re-implantations. "These are complex surgeries, and there's a lot at stake for the patient," says Dr. Lee.

For these and other reasons, Dr. Lee and his MIGS group have invested an innumerable amount of time over many years developing a collaborative, multidisciplinary surgical process, partnering with their colleagues in general surgery and urology at Magee. Dr. Lee's surgical teams have a high degree of familiarity with one another which has been developed through close collaboration and years of working side by side in the operating suite. This familiarity, built on trust, mutual respect, and a collaborative surgical approach is responsible for and enhances the team's ability to achieve the best outcomes possible for their patients. "We work as a team, but the gynecologic surgeon is the leader in these cases because of our intimate knowledge of the patient's history and what may be most important to them in terms of fertility preservation and other quality of life aspects, the extent of their pathology, and our experience and training with minimally invasive surgical techniques," says Dr. Lee.

Dr. Lee and his colleagues spend considerable time with patients during a meticulous informed consent process prior to surgery. This process empowers the surgeon to use their full surgical armamentarium as they understand thoroughly the patient's goals for care, while the patient knows in detail the potential risks, complications, and outcomes scenarios. The patients become more invested in their own care through this detailed, informed consent process by having a better understanding of their condition and the procedure required to correct it.

Abdominal Wall Endometriosis and C-Sections

Dr. Lee and his colleagues are actively engaged in a number of research areas. One recent study¹, published in latter part of 2014 reviewed 12 years of cases to determine whether there was a correlation between abdominal wall endometriosis and patients who had a prior Cesarean section birth. This study is the largest currently in the literature investigating the pathophysiology and natural history of this unique correlation between C-sections and abdominal wall endometriosis.

Abdominal wall endometriosis is a sub-type of endometriosis frequently associated with C-sections. It also is a condition that can be overlooked, particularly in women who have had a hysterectomy and are still experiencing pain. "Abdominal endometriosis occurs predominantly in patients with C-sections when the uterus is opened during the procedure and some of the tissues within the uterus become implanted in the abdominal wall," says Dr. Lee.

Some cases of abdominal wall endometriosis can be obvious and relatively easy to confirm because they are located directly underneath the skin with a visible mass that becomes larger with the patient's menstrual cycle. Other cases, such as those that are deeper or growing in the fascia of the rectus muscle,

can go undiagnosed during a physical exam. For Dr. Lee, "It is a condition that should be suspected in any patient who has had a C-section and is experiencing unilateral pain that gets worse with menstruation or if the patient has pain when they cough. The diagnosis is fairly easy with an MRI. However, if you don't look for it you won't find it and that's probably true for a lot of patients with endometriosis who have had a hysterectomy."

A Potential New Diagnostic Tool

A promising, noninvasive tool for the diagnosis of endometriosis and endometriosis-associated ovarian cancer (EAOC) using plasma microRNA profiling and biomarkers has been under investigation, and the research team, including Dr. Lee, published their findings of the study² in the journal *Clinical Cancer Research* in 2013. Three different microRNA signatures were identified that were "reflective of disease-specific pathogenic mechanisms." The authors concluded that for the first time they found, "distinct plasma microRNA expression patterns that may serve as highly specific and sensitive diagnostic biomarkers to discriminate between healthy, endometriosis, and EAOC cases." Studies of the technique are ongoing. For Dr. Lee, "It would be interesting to see how this tool can be applied. The presence of endometriosis does not always mean that it is the reason behind a patient's symptoms. Surgery provides definitive diagnosis, but this testing may one day prove to be a very effective clinical tool in conjunction with our current diagnostic armamentarium."

References

1. Ecker AM, Donnellan NM, Shepherd JP, Lee TT. Abdominal Wall Endometriosis: 12 Years of Experience at a Large Academic Institution. *Am J Obstet Gynecol.* 2014; 21(4): 363.e1-5.
2. Suryawanshi S, et al. Plasma MicroRNAs as Novel Biomarkers for Endometriosis and Endometriosis-Associated Ovarian Cancer. *Clin Cancer Res.* 2013; 19(5): 1213-1224.



On the Leading Edge of Breast Cancer Treatment and Research

The Magee-Womens Breast Cancer Program is one of the largest and busiest treatment and research centers in the United States. The program typically sees 1,600 new breast cancer cases each year, and on average 11,000 to 12,000 patients for various types of treatments and participation in numerous ongoing clinical trials.

The program has, over the last several decades, contributed innumerable to the evolving understanding of the various types of breast cancer, how to best treat them with the current clinical tools at hand, and pioneering new treatment modalities and avenues of research to advance patient care and improve outcomes. Working as a part of the Cancer Genome Atlas Project created by the National Cancer Institute (NCI) in 1997, researchers at Magee-Womens Hospital of UPMC have been responsible for providing the tumors for sequencing for nearly a quarter of the approximately 750 breast cancer types in the current database.

Clinicians from the program, along with members of the Department of Pathology, are responsible for the development of the Magee Equations^{1,2} used to calculate the risk of recurrence with ER positive, lymph node negative breast cancers. Coupled with ongoing research and clinical trials, new findings in metastatic disease, immunotherapy, and new testing procedures, the Magee-Womens Breast Cancer Program is truly at the center of the search for better, more effective treatments for the many types of breast cancer.

Toward a Better Understanding of Metastatic Disease and Its Treatment

Most individuals with metastatic breast cancer are able to survive for significant periods of time. Recent years have seen an explosion in clinical trials and new pursuits involving various immunotherapies, PARP inhibitors, targeted treatments for HER2 negative and positive cancer, and other avenues of research and treatment to better characterize and combat metastatic disease. "We have a database of almost 1,800 patients that we've collected over nearly 20 years, coupled with outcomes. We use this database in conjunction with clinical specimens that we've taken from these individuals to try to develop a comprehensive molecular and genomic portrait, as well as a clinical portrait of what metastatic breast cancer is like," says Adam Brufsky, MD, PhD, professor of medicine, associate chief, Division of Hematology/Oncology, and co-leader of the Magee-Womens Breast Cancer Program.

An important part of the ongoing research for advanced-stage cases is the screening of individuals for clinical trials at all times. "We try very hard to get more patients involved in clinical trials. Our multidisciplinary group dedicated to patients who have stage IV disease is always looking at what is available and how certain patients may benefit," says Shannon Puhalla, MD, assistant professor of medicine, director of breast cancer clinical research,

and the leader in the program for patient enrollment in clinical trials and tissue donations.

Another aspect of metastatic disease research ongoing in the program is the collection of tissue from patients with metastatic disease. "This effort is led by my colleague Adrian Lee, PhD. Dr. Lee and the group's efforts are part of an international effort to specifically develop a similar type of data repository as the Cancer Genome Atlas but for metastatic disease," says Dr. Puhalla. Since metastatic disease is very difficult to cure at present, this research to categorize types of metastatic disease, why they spread in the first place, and how metastatic breast cancer should be treated in a manner different to primary breast malignancies is of utmost importance given overall mortality rates for metastatic breast cancer.



Adam Brufsky, MD, PhD

Dr. Brufsky points out that a number of research projects are currently ongoing investigating brain metastases, estrogen receptor mutations, and their role in metastatic breast cancer. "Steffi Oesterreich and Adrian Lee, two of our basic translational researchers, are pushing into new areas and changing to a great degree how we think about some of the problems posed by metastatic disease," says Dr. Brufsky.

Metastatic Patient Navigator

For individuals with stage IV metastatic breast cancer, the Breast Cancer Program at Magee has a special Metastatic Patient Navigator Program in place to better understand and care for the unique needs of this patient subset. With recently acquired

funding from the Susan G. Komen® organization, the program consists of a medical oncologist, research nurse and nurse practitioner, a patient navigator, social work services, and research staff. Program members meet weekly to discuss every patient and coordinate care, discuss possible clinical trial enrollment options, and refer patients and families in need to social and psychosocial support services. “This program has just started, but with the funding we have acquired, we’ll be able to make additional inroads in better managing our patients with metastatic disease,” says Dr. Puhalla.

Immunotherapy and Targeted Treatment Approaches

Historically, very difficult to treat cancers such as lung cancer and melanoma have been revolutionized in recent years by the advent and progression of immunotherapies. “Breast cancer has been a little bit slower on the uptake, but right now there is much that is being looked at in terms of immunotherapy studies,” says Dr. Puhalla. At present, the Breast Cancer Program at Magee has immunotherapy studies in progress for patients with triple-negative and HER2 positive breast cancer, in both early- and late-stage settings.

Recent research has led to published findings on the HER2 protein³. HER2 positive cancers that tend to be resistant to chemotherapy have been shown to be modifiable, or sensitized by introducing the Herceptin antibody which binds to the HER2 protein. “What we found is that in women who had HER2 negative breast cancer when we examined the brain metastasis, they actually had HER2 positive breast cancer. Anti-HER2 agents become possible therapeutic approaches. This research will continue, but the preliminary studies point to possible significant clinical relevance,” says Dr. Brufsky.

Circulating Tumor DNA — AKA Liquid Biopsy

A recent investigator-initiated study by members of the program and related research colleagues has been working with circulating tumor DNA, also known as a liquid biopsy. This noninvasive blood test is capable of identifying tumor DNA in a patient’s blood stream. A clinical trial is currently in progress looking at different types of hormonal treatments and correlating those with findings in the circulating tumor DNA. “What’s exciting about this trial is the potential to do tumor biopsies where it would otherwise be very difficult or impractical to do one, for example, to serially biopsy a metastatic site or readily biopsy brain lesions. With these blood tests, we can monitor changes in the tumor DNA in a noninvasive manner. This approach has the potential to really change the field and make it much easier to follow these tumors over time,” says Dr. Puhalla.

Other Clinical Trials and Research Prospects

Sentinel lymph node mapping has been around for a long time, using wire localization for breast surgery. At Magee, clinicians and researchers have pioneered seed localization as an alternative, and research and clinical use continue to expand with this methodology.



Shannon Puhalla, MD

On a completely different front, Dr. Brufsky has been extensively involved in research and clinical trials for the use of intravenous bisphosphonates, specifically zoledronic acid, for individuals needing aromatase inhibitors as part of their breast cancer therapy. Dr. Brufsky and his research colleagues were primarily interested in two outcomes. The first was preventing bone loss in breast cancer patients. The second, Dr. Brufsky explains, was that “we knew from some of the preclinical data and one clinical trial completed in 1996 that women receiving bisphosphonates for early-stage breast cancer had a lower incidence of metastatic disease, in particular of the bone.”

A multicenter international study, in which Dr. Brufsky and Magee were a crucial part of, designed large clinical trials of the bisphosphonate regimen that showed some preventative benefits of recurrence at one and two years. Follow-up studies and a meta-analysis published two years ago, for which Dr. Brufsky penned the editorial in the journal *Lancet*, further showed a three percent reduction in the risk of death in postmenopausal women who have breast cancer and who have received bisphosphonates for at least two years. “More needs to be done on this front, but we have shown clinically relevant usage of bisphosphonates in postmenopausal women with metastatic breast cancer, and right now it appears that we may be able to modestly impact the natural history of the disease,” says Dr. Brufsky.

References and Additional Reading

1. Path.UPMC.edu/onlineTools/ptvr.html
2. Path.UPMC.edu/onlineTools/MageeEquations.html
3. Lee, et al. Intrinsic Subtype Switching and Acquired ERBB2/HER2 Amplifications and Mutations in Breast Cancer Brain Metastases. *JAMA Oncol.* 2016; Dec 7. Epub ahead of print.

Uterine Fibroids — Evolving Treatments and New Research

The Fibroid Treatment Center at Magee-Womens Hospital of UPMC was established in 2008 by Richard Guido, MD, who currently serves as co-director of the center with Philip Orons, DO. Drs. Guido and Orons, along with their colleagues and staff at the center provide comprehensive, collaborative care for the diagnosis and treatment of various types of uterine fibroids and their associated symptoms and complications.

Collaborative, Patient-Centric Care

To provide patients with the highest quality, efficient care, the Fibroid Treatment Center combines the expertise of both board-certified gynecologists and interventional radiologists trained in minimally invasive treatment procedures. Dr. Guido explains that the partnership and collaboration between the gynecologists and interventional radiologists is the foundation of how the center treats patients. “The design of our center allows the patient to be seen and consult with both disciplines during the same visit. We conduct exams and testing, obtain imaging if necessary, discuss the patient’s specific situation, and then collaboratively consult with her about the various treatment options available and which may be most effective,” says Dr. Guido.

The Fibroid Treatment Center sees approximately 300 to 400 new patients each year, and the approaches to treating these patients cover the spectrum of current, evidence-based surgical procedures and nonsurgical interventions to fibroid management. On the surgical front, clinicians in the Fibroid Treatment Center are able to provide a range of approaches to fibroid management. This includes a specialty in minimally invasive surgical procedures, and the utilization of a recently FDA-approved radiofrequency volumetric thermal ablation technique Dr. Guido has been performing and conducting research on in several past and ongoing clinical trials. “There is a tendency for patients who go to surgeons to always get surgery. Our goal is to focus on the patient’s symptoms and educate them about what their options are. We work with them to decide what’s the best course of treatment,” says Dr. Guido.

New Research for Promising Treatment Options

Staying ahead of the curve in terms of available treatment options, new techniques, and a better understanding of the pathophysiology of uterine fibroids is of primary concern to the clinicians in the center. The way forward is in research and clinical trials, and Dr. Guido and colleagues are and have been involved in several new studies in recent years.

The Halt trial^{1,2} of radiofrequency volumetric thermal ablation for uterine fibroids, in which Dr. Guido and the Fibroid Treatment

Center were a part, showed significant reductions in the severity of participant’s symptoms, improved quality of life scores, and reduced repeat surgical interventions through 24 and 36-month follow-ups.

Another current, multicenter trial in progress at Magee-Womens Hospital (patient recruitment was recently completed) is the SONATA study³ of a sonography-guided transcervical ablation technique for the treatment of uterine fibroids. This study is testing the efficacy and safety of the Sonata™ system to perform incisionless, uterus-preserving radiofrequency ablation with ultrasound guidance for several types of myomas. This minimally invasive procedure totally avoids the need to enter the peritoneal cavity. If successful, this trial will open up a new, minimally invasive system for gynecologists to use as they assess and counsel patients on which treatment options may be most appropriate and successful for their specific condition.

References

1. Guido RS, Macer JA, Abbott K, Falls JL, Tilley IB, Chudnoff SG. Radiofrequency Volumetric Thermal Ablation of Fibroids: A Prospective, Clinical Analysis of Two Years’ Outcome From the Halt Trial. *Health Qual Life Outcomes*. 2013; 11:139.
2. Berman JM, Guido RS, Garza Leal JG, Pemueler RR, Whaley FS, Chudnoff SG, Halt Study Group. Three-Year Outcome of the Halt Trial: A Prospective Analysis of Radiofrequency Volumetric Thermal Ablation of Myomas. *J Minim Invasive Gynecol*. 2014; 21(5): 767-774.
3. ClinicalTrials.gov Identifier: NCT02228174



Richard Guido, MD

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 ranked in the top 12 hospitals for gynecologic care by *U.S. News and World Report*, and 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 CancerCenter, 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 for 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 such as hysterectomy, ovarian cysts, endometriosis, pelvic pain, and others.

Obstetrical & 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 Infertility

The Center for Infertility and Reproductive Endocrinology provides patients with onsite 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 including 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



200 Lothrop St.
Pittsburgh, PA 15213-2582

Department of Obstetrics, Gynecology, and Reproductive Sciences

Magee-Womens Hospital of UPMC

300 Halket Street
Pittsburgh, PA 15213
412-641-4220

Robert P. Edwards, MD
Chairman

For consults and referrals, please call UPMC's 24-hour physician OnDemand service at **1-866-884-8579**.

A \$14 billion world-renowned health care provider and insurer, Pittsburgh-based UPMC is inventing new models of patient-centered, cost-effective, accountable care. UPMC provides nearly \$900 million a year in benefits to its communities, including more care to the region's most vulnerable citizens than any other health care institution. The largest nongovernmental employer in Pennsylvania, UPMC integrates 65,000 employees, more than 25 hospitals, more than 600 doctors' offices and outpatient sites, and a more than 3 million-member Insurance Services Division, the largest medical and behavioral health services insurer in western Pennsylvania. Affiliated with the University of Pittsburgh Schools of the Health Sciences, UPMC ranks No. 12 in the prestigious *U.S. News & World Report* annual Honor Roll of America's Best Hospitals. UPMC Enterprises functions as the innovation and commercialization arm of UPMC, while UPMC International provides hands-on health care and management services with partners in 12 countries on four continents. For more information, go to UPMC.com.