Fall 2016

Cleveland Clinic

Ob/Gyn & Women's Health Perspectives

An Update for Physicians from Cleveland Clinic's Ob/Gyn & Women's Health Institute

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Genetic Risk Assessment for Breast and Gynecologic Cancers Using Multi-gene Panel Testing

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Dear Colleagues and Friends:

This issue of *Ob/Gyn & Women's Health Perspectives* highlights developments in breast cancer diagnosis, the treatment of chronic pelvic pain and a new and improved way that residents are being taught gynecologic surgery skills.

- In our cover story, Mariam AlHilli, MD, discusses which patients might benefit from **multigene panel testing for breast cancer**—an approach that is both cost-effective and time-effective, but has limitations. Therefore, it is helpful to know when the potential benefits are likely strong enough to consider recommending this approach.

Also in this issue, you will read about:

- **A nonpharmacologic treatment for chronic pelvic pain.** M. Jean Uy-Kroh, MD, and Elim Shih, MD, are recruiting subjects for a clinical trial of a nonimplanted intravaginal electrical stimulation device with exciting potential for the elimination of chronic pelvic pain.
- **How Cleveland Clinic has changed the way gynecologic surgery is taught.** We have completely rethought the way we train residents. Rosanne Kho, MD, spells out the elements of our new program designed to ensure a future generation of highly skilled gynecologic surgeons.
- **Why yearly mammograms may not be necessary.** While the controversy continues, Holly Thacker, MD, and Dr. Shih make a strong case against the need for yearly mammograms in a thoughtfully crafted opinion piece.

We hope you find the information in this issue of *Ob/Gyn & Women's Health Perspectives* useful in your practice. As always, we welcome your comments, feedback and suggestions. Please do not hesitate to contact me, or anyone else on our staff, if we can answer your questions or partner with you in the care of your patients.

Sincerely,

Tommaso Falcone

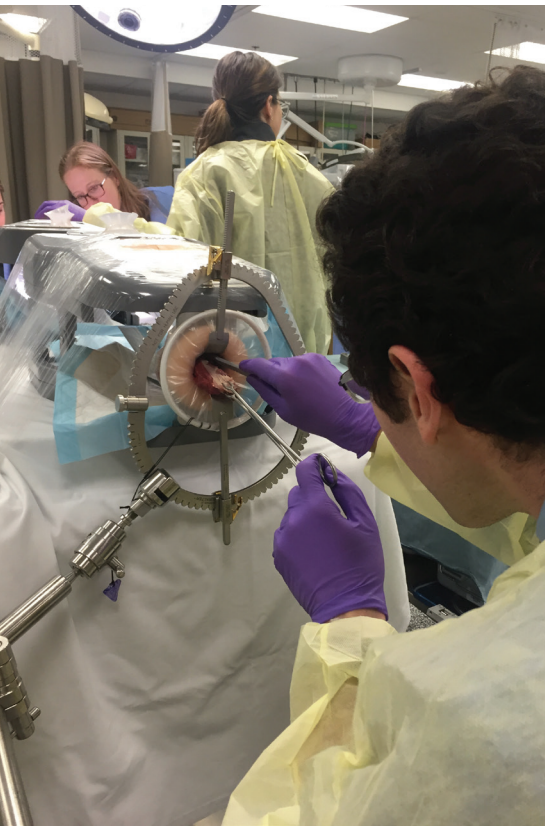
Tommaso Falcone, MD, FRCSC, FACOG
Professor & Chairman, Department of Obstetrics and Gynecology
Chairman, Ob/Gyn & Women's Health Institute

Breaking Tradition in Teaching Gynecologic Surgical Skills to Residents

By Rosanne M. Kho, MD

Maria has had large fibroids for many years and now has secondary anemia from menorrhagia. After failing multiple medical therapies, she has decided to pursue hysterectomy. She requests her surgery be done before July, when new medical students and residents will be starting. Clearly concerned, she emphasizes, "I don't want them practicing on me."

Medical students and residents are traditionally expected to perform procedures after having observed only a few. The adage coined by William Halstead, MD, close to 100 years ago, "See one, do one, teach one," described the medical and surgical training of the time that continues in many academic institutions today. The expectation that young trainees be able to perform and teach after very little exposure (only one) has, not surprisingly, created a fearful learning environment and distrustful patient-doctor relationship.



It's not so acceptable anymore

In the field of gynecology, a large number of surgical procedures has been introduced in the past three decades as our focus has shifted from open to endoscopic (including robot-assisted) and minimally invasive surgeries (MIS). The introduction of high-tech procedures mandated more effective teaching methods. In the current climate, "learning by doing" (on the patient) has become less acceptable. As surgical educators, we need to seek alternative methods of teaching surgical principles and provide procedural experience outside the clinical setting.

Here at Cleveland Clinic, we are extremely fortunate to have a multitude of teaching resources and a bright, talented group of ob/gyn residents. For MIS training, we developed a comprehensive series of teaching modules that cover hysteroscopic, vaginal, laparoscopic and robotic approaches. The modules focus not just on the flow and technique of specific procedures (such as vaginal hysterectomy and laparoscopic suturing), but also on mastery of female pelvic anatomy, understanding of surgical principles to avoid complications (such as the use of energy in MIS and achieving hemostasis) and setup of equipment (such as varied endoscopic systems, including robotic). We utilize specific teaching tools that include web-based curricula and hands-on workshops held in our spacious and well-equipped simulation center. With educational support from various vendors, we provide access to high-fidelity pelvic and uterine models, equipment and devices that are brought into the dry and wet labs to teach fundamental surgical knowledge and provide procedural experience. We intend to conduct the modules on a bi-yearly rotation to ensure that all residents are exposed to all topics.

Nurturing confidence and competence

When invasive and high-risk surgical procedures are involved, we move away from "see one, do one, teach one." Breaking the tradition is facilitated in a setting like ours in which all necessary ingredients are available: a dedicated and responsive educational staff, eager and receptive trainees, and leading-edge physical and technological resources. Our trainees no longer need to "practice" on our patients. By providing our residents with ample and effective introductory exposure and teaching outside the operating room and clinical setting, we hope to nurture their confidence and competence in performing gynecologic surgery.

Dr. Kho is Director of Benign Gynecologic Surgery in the Women's Health Institute. She can be contacted at 216.444.6337 or khor@ccf.org.

Genetic Risk Assessment for Breast and Gynecologic Cancers Using Multi-gene Panel Testing: A New Paradigm

By Mariam AlHilli, MD

On June 13, 2013, the U.S. Supreme Court made a landmark decision that broke the monopoly on *BRCA1* and *BRCA2* gene testing held by Myriad Genetics. Testing for *BRCA1* and *BRCA2* alone and in combination with other genes is now available through several companies.

Traditionally, individuals susceptible to hereditary cancers were screened based on history and offered testing for mutations in a single gene or a set of genes associated with a particular syndrome (e.g., *BRCA1* and *BRCA2* for hereditary breast and ovarian cancer or mismatch repair genes for Lynch syndrome). Today, advances in next-generation sequencing allow simultaneous testing for multiple genes that are associated with hereditary cancers.

Multigene panel testing

Multigene panel testing encompasses tests for a wide range of mutations, including:

- Mutations in homologous recombination (HR) *(BRCA1/2, ATM, BARD1, BRIP1, CHEK2, MRE11A, NBN, PALB2, RAD50, RAD51C, RAD51D)*
- Mismatch repair genes *(MLH1, MSH2, MSH6, PMS2, EPCAM)*
- Breast cancer susceptibility genes *(CDH1, PTEN, STK11, TP53)*
- Other cancer susceptibility genes

This is a highly cost-effective and time-effective method for the simultaneous evaluation of multiple genes. It has allowed for the identification of 40 to 50 percent more individuals with hereditary cancer gene mutations than is possible testing for *BRCA1* and *BRCA2* alone. However, these tests have some noteworthy limitations.

- Multigene panel testing is more likely to detect rare variants of unknown significance or novel variants with unknown pathological or clinical significance.
- There are limited data on the degree of cancer risk associated with each gene identified or the age-adjusted risks attributable to the genes.
- There are no guidelines on the management of many deleterious mutations identified.
- It is unclear if these individuals would benefit from risk-reduction strategies.

Multigene panel testing for gynecologic cancers

Women with *BRCA1* mutations have a 65 to 85 percent risk for breast cancer and a 39 to 46 percent risk for ovarian, fallopian tube and primary peritoneal cancers by age 70.

Similarly, women with *BRCA2* mutations have a 45 to 85 percent risk of breast cancer and a 10 to 27 percent risk of ovarian cancer by age 70.

Mutations in other genes, including *BRIP1, RAD51D* and *RAD51C*, have been associated with a 10 to 15 percent lifetime risk of ovarian cancer.

Approximately 20 to 25 percent of ovarian carcinomas are thought to result from a hereditary predisposition.

While the *BRCA1* and *BRCA2* genes are responsible for the vast majority of hereditary ovarian cancers, several other genes within the HR pathway have been shown to contribute to a similar phenotype. Patients with these phenotypes have a better prognosis and clinical response to platinum therapies. In addition, they are likely to benefit from targeted therapies (PARP inhibitors) that exploit defects in the HR pathway.

Current guidelines issued by the National Comprehensive Cancer Network and the Society of Gynecologic Oncologists recommend genetic counseling and testing for all women with ovarian cancer, regardless of age or family history.

In addition, patients with a history consistent with hereditary breast and ovarian cancer should be given the option of pursuing panel testing when other cancer types are present in the family, rare syndromes are being considered or the results would influence medical management.

Dr. AlHilli is a staff physician in the Departments of Obstetrics and Gynecology and Women's Health. She specializes in the management of women with gynecologic cancers. Dr. AlHilli can be reached at 216.445.0747 or alhillm@ccf.org.

Are Annual Mammograms Necessary?

By Holly L. Thacker, MD, and Elim Shih, MD

The number of women who must be screened to save one life is high. So are the risks of harm from overdiagnosis and false-positive results. Screening mammography has come under increased scrutiny as evidence of potential harm grows.

To add to the confusion, the American Cancer Society recommends an annual screening mammogram from ages 45 to 54, followed by biennial screening from age 55 onward. The U.S. Preventive Services Task Force (USPSTF) recommends biennial screenings starting at age 50, with an individualized protocol from ages 40 to 49 based on risk assessment and shared decision-making.

Screening mammography has been shown to reduce breast cancer mortality by 15 to 25 percent. These data are based on eight major randomized controlled trials that began enrollment more than 30 years ago. These figures may not be relevant today, given advanced mammographic techniques and more effective therapies. Moreover, the number of women who must be screened to save one life is 1,904 for women in their 40s, 1,339 in their 50s and 377 in their 60s.

As physicians, our challenge is to provide individualized, cost-effective recommendations that take into account the potential harms.

How the controversy began

The controversy began with a *Lancet* article by Peter Gotzsche, MD, and Ole Olsen, MD. These researchers looked at published studies on breast cancer screening and concluded that all but two were too flawed to have reliable results. The flawed trials demonstrated benefit for mammography; the acceptable studies showed little to no benefit.

Screening risks

The major harms associated with screening mammography are overdiagnosis and false-positive results. Psychological harm and radiation exposure are also real risks.

Overdiagnosis occurs when a condition is diagnosed that would otherwise not proceed to cause symptoms or death. The strongest evidence for overdiagnosis is found in long-term follow-up of a randomized, controlled trial in which a screening group is compared with a control group. If all screening-detected disease represents cancers that are destined to progress to clinical disease, the excess should disappear during long-term follow-up. The persistence of cases that never develop is the best evidence that overdiagnosis has occurred.

The rate of breast cancer overdiagnosis in several studies as noted by the USPSTF varies from 1 percent to 54 percent. If we accept a 22 percent overdiagnosis rate (a commonly quoted and average accepted rate), the annual cost of this error is estimated at $1.2 billion. At this time, we do not have markers that determine whether screening-detected cancers will progress, so all women are treated.

A false-positive mammogram is one that prompts automatic recommendation for additional imaging or tissue biopsy in a woman without breast cancer. False positives are more common in younger women and those with dense breasts. The likelihood of a false positive is 61 percent for women starting annual screenings at age 40 and 42 percent for women starting biennial screenings at age 40. If we accept a conservative 11 percent false-positive rate based on several published studies, these patients cost the healthcare system a minimum of $2.8 billion per year.

The bottom line

The bottom line is that screening mammography is not a yearly, one-size-fits-all requirement for women over age 40. Those at high risk for breast cancer should be offered yearly mammograms with tomosynthesis (3-D imaging) or even breast MRI, as appropriate. However, the decision for average-risk women should be individualized based on risk.

Dr. Thacker, Director of Cleveland Clinic's Center for Specialized Women's Health, can be reached at 216.444.9240 or by email at thackeh@ccf.org.

Dr. Shih is a former fellow in the Women's Health Institute.

Chronic Pelvic Pain: Trial Examines Novel Intravaginal Electrical Stimulation Therapy

By M. Jean Uy-Kroh, MD, and Elim Shih, MD

Chronic pelvic pain is a complex diagnosis that encompasses multiple conditions and organ systems. Its treatment is also challenging due to an incomplete understanding of pain processing.

Evidence confirms opioids worsen chronic pelvic pain by lowering pain thresholds and increasing pain sensitivity. Nonpharmacologic therapies are the treatment of choice. Physicians should counsel patients on the therapeutic benefit of restorative sleep and exercise.

One novel therapy using intravaginal electrical stimulation is currently under investigation at the Women's Health Institute.

We are actively enrolling subjects in the INSPIRE (INtravaginal Stimulation for Pelvic Pain Improvement and Relief) trial, which is a randomized, controlled trial utilizing a nonimplanted, intravaginal electrical stimulation device within the comfort and privacy of the patient's home.

Study design

The INSPIRE trial is a 12-week research study. We seek women diagnosed with chronic pelvic pain lasting longer than six months. Subjects are randomized into one of two study groups. One study group will use an active device, and the other will use a sham device.

The trial requires four visits to Cleveland Clinic's main campus. After enrollment, subjects must commit to perform home sessions using the device six times per week, 12 minutes per session, for a total of 12 weeks.

If the trial proves the active device significantly reduces pain, then the active device will be provided to all women in the study at no cost.

Being proactive matters

At Cleveland Clinic, we encourage women to take a more active role in the treatment of their chronic pelvic pain. If proven effective through ongoing research, a novel domiciliary device may be an alternative or adjunct therapy for chronic pelvic pain.

Dr. Uy-Kroh, Director of the Chronic Pelvic Pain Program, can be reached at 216.444.0551 or uykrohm@ccf.org.

Dr. Shih is a former fellow in the Women's Health Institute.

Ob/Gyn & Women's Health Institute: A Sampling of Open Trials

GYNECOLOGIC CANCERS

A Phase 3 Placebo-Controlled Study of Carboplatin/Paclitaxel with or without Concurrent and Continuation Maintenance Veliparib (PARP inhibitor) in Subjects with Previously Untreated Stage III or IV High-Grade Serous Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

Principal Investigator: Peter Rose, MD

Research Line: 216.445.8090

A Phase I/II Study of Ruxolitinib with Front-Line Neoadjuvant and Post-Surgical Therapy in Patients with Advanced Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

Principal Investigator: Peter Rose, MD

Research Line: 216.445.8090

A Randomized Phase II/III Study of the Combination of Cediranib and Olaparib Compared to Cediranib or Olaparib Alone, or Standard of Care Chemotherapy in Women with Recurrent Platinum-Resistant or Refractory Ovarian, Fallopian Tube or Primary Peritoneal Cancer (COCOS)

Principal Investigator: Peter Rose, MD

Research Line: 216.445.8090

INCONTINENCE

Altis 522: A Post-Market Evaluation of the Altis® Single Incision Sling System versus Transobturator or Retropubic Mesh Sling in the Treatment of Female Stress Urinary Incontinence

Principal Investigator: Marie Paraiso, MD

Research Line: 216.445.8090

MENOPAUSE

VeLVET: A Randomized Clinical Trial Comparing Vaginal Laser Therapy to Vaginal Estrogen Therapy in Women with Genitourinary Syndrome of Menopause (GSM)

Principal Investigator: Marie Paraiso, MD

Research Line: 216.445.8090

PELVIC PAIN

INSPIRE: Treatment of Pain Using a Nonimplanted Intra-Vaginal Electrical Stimulation Device Compared to a Vaginal Dilator in Chronic Pelvic Pain Patients

Principal Investigator:
M. Jean Uy-Kroh, MD

Research Line: 216.445.8090

For a complete list of Ob/Gyn & Women's Health Institute clinical trials, please visit **my.clevelandclinic.org/services/ob-gyn-womens-health/research-innovations.**

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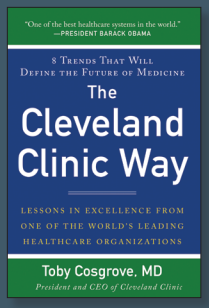

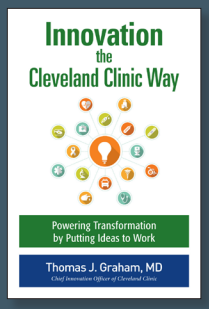

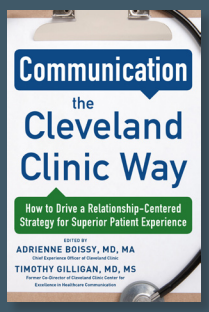

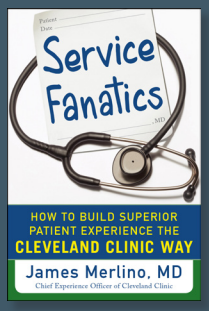

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About Cleveland Clinic

Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,400 physicians and researchers represent 120 medical specialties and subspecialties. We are a main campus, more than 150 northern Ohio outpatient locations (including 18 full-service family health centers and three health and wellness centers), Cleveland Clinic Florida, Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland Clinic Canada, Sheikh Khalifa Medical City and Cleveland Clinic Abu Dhabi.

In 2016, Cleveland Clinic ranked No. 2 in *U.S. News & World Report*'s "Best Hospitals" survey. The survey ranks Cleveland Clinic among the nation's top 10 hospitals in 13 specialty areas, and the top hospital in heart care (for the 22nd consecutive year).

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