

ADVANCES IN GYNECOLOGY

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Collaborations Across Specialties and Robust Research Heighten Gynecologic Oncology Care

Collaborative care, with support from multiple specialties, together with a determination to improve the quality of life (QoL) experienced by its patients are defining features of the gynecologic oncology care practiced at NewYork-Presbyterian Hospital. The Hospital is comprised of 2 cancer centers—the Herbert Irving Comprehensive Cancer Center, part of NewYork-Presbyterian/Columbia University Medical Center, which is a National Cancer Institute (NCI)-designated comprehensive cancer center, and the Weill Cornell Cancer Center, part of NewYork-Presbyterian/Weill Cornell Medical Center. In addition, a distinctive hallmark of the Hospital is its extensive involvement in clinical drug trials in pursuit of improved care.

“We provide care throughout the entire course of the patient’s disease, from screening and diagnosis to surgical management and adjuvant therapy,” said Jason D. Wright, MD, gynecologic oncologist at the Herbert Irving Comprehensive Cancer Center. “For patients with gynecologic cancer, it is very important that they be seen by a specialist in gynecologic oncology—that has been shown to improve survival.

“A major focus of our group has been to improve the quality of care for women with gynecologic cancers and develop programs to help them through the difficult time of being diagnosed with cancer,” said Dr. Wright, who is also Levine Family Assistant Professor of Women’s Health and Florence Irving Assistant Professor of Obstetrics and Gynecology at Columbia University College of Physicians and Surgeons.

“In the past 2 to 3 years, we have dramatically increased the number of support services that are available for our patients from nutrition services, psychosocial support, and peer-support groups, to access to new drugs through clinical trials and palliative care. For example, my partner, Sharyn N. Lewin, MD, has developed a ‘Woman-to-Woman’ program to pair up patients who have been recently diagnosed with cancer with survivors of gynecologic cancer to help them navigate through the process of diagnosis and treatment, and to help



The gynecologic oncology team at the Herbert Irving Comprehensive Cancer Center.

them deal with the side effects of treatment. Those are resources that patients treated at smaller centers often don’t have access to,” he said.

Evidence-based medical and surgical interventions can provide patients with better outcomes in the short term, reduced recurrences over the long term, and improved QoL. “One of the benefits of a place like the Herbert Irving Comprehensive Cancer Center is that our patients have access to a range of chemotherapeutic drugs and a number of different clinical trial options,” said Dr. Wright.

Access to a network of surgeons and other experts in gynecologic oncology ensures that patients receive superior clinical care as they progress through treatment and management of their conditions. “At the Center, patients have access to many other medical specialists and collaborators, including medical, radiation, and surgical oncologists who can assist with their care,” said Dr. Wright. “For instance, in the OR we sometimes perform collaborative procedures with hepatobiliary and colorectal surgeons and urologists if the cancer is encroaching on another organ. Certainly, the availability of those specialists is important.”

Active Involvement in Clinical Trials

Patients at the Center, as well as those at the Weill Cornell Cancer Center, regularly participate in studies encompassing all areas of cancer

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Genetics Research Across Medical Specialties Now Yielding Secrets and Improving the Practice of Medicine

The decoding of the human genome and subsequent concerted efforts by physician-scientists to decipher the relationships between specific genes and the diseases they influence have already yielded tremendous advancements in medicine. This work is fostering important strides in understanding and caring for people with diseases affecting all health systems, and much of the laboratory and translational studies, as well as clinical research, are being done at Columbia University College of Physicians and Surgeons, Weill Cornell Medical College, and NewYork-Presbyterian Hospital.

Research abounds in every field. Perhaps no area of medicine has been as affected by research into the genetic foundations of disease as much as oncology. Examples of genetic discoveries in oncology are plentiful. An important recent discovery is the revelation that certain cases of glioblastoma are caused by the fusion of 2 genes.¹ Researchers, led by Antonio Iavarone, MD, Professor of Pathology and Neurology at Columbia's Institute for Cancer Genetics at the Herbert Irving Comprehensive Cancer Center, part of NewYork-Presbyterian/Columbia, conducted genetic analyses of patients with glioblastomas, searching for evidence of gene fusions. They found them, with the most common being fusions involving the fibroblast growth factor receptor (*FGFR1* or *FGFR3*) and transforming acidic coiled-coil (*TACC1* or *TACC3*) genes. The protein produced by the fusion of *FGFR-TACC* disrupts the mitotic spindle, causing aneuploidy, and from there tumorigenesis. The finding is important because it provides researchers with a protein target for pharmaceutical research for a cancer that is especially difficult to treat.

Gastroenterologists have been interested in recent work performed by Manish Shah, MD, Director of Gastrointestinal Oncology at Weill Cornell Medical College, who with his colleagues elucidated the heterogeneity of gastric cancer, dividing it into 3 types.² The first type, noncardia gastric cancer, is linked to environmental factors such as high dietary salt, tobacco use, and increasing age; clinical factors such as *Helicobacter pylori* infection and use of nonsteroidal anti-inflammatory drugs; and genetic factors

including immune regulatory single-nucleotide polymorphisms. A second type, diffuse gastric cancer, is associated with *CDH1* mutation and family history and has no known environmental or clinical factors. The third type, proximal gastric cancer, is caused by tobacco and alcohol use; has no known genetic link; and is

Perhaps no area of medicine has been as affected by research into the genetic foundations of disease as much as oncology.

associated with obesity, high body mass index, and gastroesophageal reflux disease. Dr. Shah's work has alerted those performing drug clinical trials that testing should be based on these subtypes and not on gastric cancer as a whole. Because of the genetic differences in subtypes, the effects of drug therapy may vary significantly between groups.

The field of geriatrics was intrigued by a study led by Columbia University researcher Lawrence S. Honig, MD, PhD, Professor of Clinical Neurology in the Taub Institute, an Alzheimer's disease research center funded by the National Institute on Aging.³ Dr. Honig's research found that telomere length relates both to the likelihood of the patient developing dementia and his or her overall remaining life span. This research could lead to the use of telomere length as an accurate biomarker of aging in people, as well as an early warning sign for future dementia.

The researchers examined telomere lengths from DNA samples of white blood cells obtained from 1,983 individuals aged 66 to 101 years. These patients were followed for an average of 8 years. After adjusting for age and education, among other factors, researchers found that those individuals with shorter telomeres had higher rates of both dementia and mortality. The researchers must now examine whether shorter telomeres directly increase the risk for dementia and death, or if the telomeres are being influenced by some other factor that is both shortening telomere length while at the same time increasing dementia and mortality risk.

Within psychiatry, schizophrenia has long been known to be genetic in origin, but the networks of genes involved in this disability have not been well characterized. A recent paper published in *Nature Neuroscience* found a link between schizophrenia and autism.⁴ Columbia researchers examined a collection of mutations associated with schizophrenia and found occult interrelations among genes that had previously been thought to be unrelated. The researchers found that most of the mutated schizophrenia genes were related to 2 main gene networks, which together affect key processes, including axon guidance, synapse function, neuron mobility, and chromosomal modification.

The research, which was led by Dennis Vitkup, PhD, Associate Professor in the Department of Biomedical Informatics at Columbia's Center for Computational Biology and Bioinformatics, also looked at genes mutated in patients with autism and found the similarities were surprisingly robust. Noting that the genetic networks for autism and schizophrenia are closely intertwined, the researchers postulated that many other psychiatric disorders also might share the same genetic networks and interrelated molecular processes.

Significant research on the genetics behind psychological illness is being undertaken at Weill Cornell Medical

College. As just one example, Francis S.Y. Lee, MD, PhD, Professor and Vice Chair for Research in the Department of Psychiatry and Professor in the Department of Pharmacology, who is also an Attending Psychiatrist at the Hospital, directs efforts focused on using genetic models to define the role of growth factors, such as brain-derived neurotrophic factor, and

their affect on the pathophysiology and treatment of affective disorders.⁵

Pulmonology has begun to explore the use of gene-based vaccines targeted against pulmonary infectious organisms. At Weill Cornell Medical College, a team led by Stefan Worgall, MD, PhD, Division Chief of the Pediatrics Pulmonology, Allergy and Immunology Division,

has developed capsid-modified adenovirus vectors^{6,7} to heighten immune responses from genetic vaccines against both *Pseudomonas aeruginosa* and respiratory syncytial virus. In research on the pathogenesis of cystic fibrosis, Dr. Worgall is investigating the interaction of alveolar macrophages with *P. aeruginosa*.

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diagnosis and treatment. A recent study into the novel serum biomarker human epididymis protein 4 (HE4) performed at NewYork-Presbyterian/Weill Cornell demonstrated that it had a superior ability to differentiate between benign and malignant adnexal masses in premenopausal women compared with the commonly used carbohydrate antigen 125 (CA-125) biomarker. Assisted by Robert C. Knapp, MD, Visiting Scholar at Weill Cornell Medical College and developer of CA-125, researchers now are evaluating the utility of HE4 in detection of recurrent ovarian cancer.

Other treatment-related clinical trials have included investigations into the safety and feasibility of surgical debulking with heated intraperitoneal chemotherapy combined with intraperitoneal chemotherapy for ovarian cancer and the use of aurora kinase inhibitors in conjunction with paclitaxel for recurrent ovarian cancer, both of which are ongoing. “We’re members of the NCI’s Gynecologic Oncology Group and participate in open chemotherapy trials and radiation trials, such as examining the effectiveness of positron emission tomography scanning to detect lymph nodes metastasis,” said Kevin Holcomb, MD, Associate Attending in Obstetrics and Gynecology at the Weill Cornell Cancer Center, where he is a member of the Gynecologic Oncology Clinical Program, and Associate Professor of Clinical Obstetrics and Gynecology at Weill Cornell Medical College.

In addition to conducting trials centered on medical treatment options,

researchers at both the Herbert Irving Comprehensive Cancer Center and the Weill Cornell Cancer Center have focused on determining the benefits of minimally invasive, and particularly robotic-assisted laparoscopic surgery for gynecologic cancers. Dr. Holcomb, who also is Director of Minimally Invasive Surgery for the Department of Obstetrics and Gynecology, noted that the benefit of offering advanced robotics technology is to improve patient QoL while providing similar survival outcomes.

“A major focus for us at Weill Cornell Cancer Center is working to improve the quality of our patients’ lives, leaving them with less morbidity from our treatments so they go on to live fruitful lives without any long-standing detriment. I think in that regard, robotics plays a major role,” Dr. Holcomb said. He added that his team is studying robotic-assisted surgery, which involves the use of the da Vinci Surgical System, in gynecologic cancers other than those for which it has already demonstrated benefit, such as in endometrial cancer. “We’ve been performing many robotic surgeries for recurrent ovarian cancer, and really pioneering this,” said Dr. Holcomb, who instructs other surgeons on the technology. “Recently I was able to debulk a patient’s ovarian cancer robotically. She was rendered in complete clinical remission with a surgery that lasted about 2 hours and she didn’t have to stay in the hospital overnight. I think that is a huge benefit and it isn’t being offered in many places.”

Additionally, patients contraindicated for a minimally invasive surgical



Kevin Holcomb, MD, gynecologic oncologist, NewYork-Presbyterian Hospital/Weill Cornell Medical Center.

approach, such as the morbidly obese and patients with severe comorbidities, also have shown positive outcomes when robotics were employed for surgery. “We’re routinely approaching these patients and doing complete staging with robotic assistance,” Dr. Holcomb said. “Obviously, performing primary abdominal surgery in the instance of big, bulky abdominal disease is problematic, but we are finding that there is a role for robotic-assisted surgery. There is the patient who has an isolated recurrence after 3 years of being disease-free, for example, or the patient who has undergone chemotherapy and whose tumor shrank appreciably—very often, I elect to go back and handle these types of cases robotically. They’re not necessarily getting a survival benefit from it, but there is a huge benefit for QoL.”



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Important news from NewYork-Presbyterian Gynecology.

Current research projects, clinical trials, and advances in the diagnosis and treatment of gynecologic diseases

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Nephrologists and psychiatrists, meanwhile, were interested in the results of a large multinational study in which Columbia University played an important role.⁸ The study, led by Ali Gharavi, MD, Associate Director of the Division of Nephrology at NewYork-Presbyterian/Columbia, is the first to link congenital kidney disease, which together with urinary tract defects accounts for about one-fourth of all birth defects in the United States, with neurodevelopmental disorders. The study found that 10% of children born with kidney defects have genomic alterations that have been linked with neurodevelopmental delay and mental illness. The finding is important because it paves the way for identifying subgroups of patients with kidney defects whose treatment will be guided by specific genetic information. The finding also alerts physicians who care for children with congenital kidney disorders that there may be a genetic basis for a neurodevelopmental delay or a mental illness that will occur later in life.

A co-author of this study was Wendy Chung, MD, PhD, Director of Clinical Genetics at NewYork-Presbyterian Morgan Stanley Children's Hospital. Her research interests include the molecular

genetics of obesity and diabetes; congenital heart disease; the genetic foundations of cardiomyopathies, arrhythmias, long QT syndrome, and pulmonary hypertension; congenital diaphragmatic hernias; mental retardation; inherited metabolic conditions; and susceptibility to breast and pancreatic cancers. She is Director of the Pediatric Heart Network Genetic Core, the Pediatric Neuromuscular Network Molecular Core, the New York Obesity Center Molecular Genetics Core, and the Diabetes and Endocrine Research Center Molecular Genetics Core. She also serves as Director of the Clinical Cancer Genetics Program and the Fellowship Program in Cytogenetics and Molecular Genetics.

The field of clinical genetics is rapidly changing and improving the practice of medicine. As the field of genetics continues to grow so too the physician-scientists at Columbia University College of Physicians and Surgeons, Weill Cornell Medical College, and NewYork-Presbyterian Hospital will continue to be at the forefront of integrating genetics into all specialties.

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