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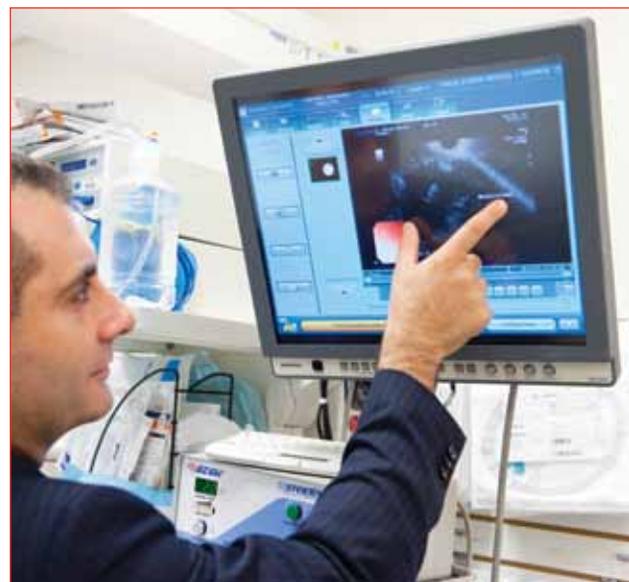
Advancements in Cancer Surveillance Provide Earlier Diagnoses of GI Malignancies

Early detection and diagnosis of cancer can be critical as it drives treatment decisions and affects survival rates. Advancements in cancer surveillance and treatment—such as probe-based confocal laser endomicroscopy (pCLE) and the use of molecular markers—are helping NewYork-Presbyterian Hospital physicians and surgeons to provide early and accurate diagnoses, comprehensive therapeutic interventions, and robust patient care.

The use of pCLE in advanced endoscopy is changing the way Michel Kahaleh, MD, Chief of Endoscopy, NewYork-Presbyterian/Weill Cornell Medical Center, diagnoses and treats malignancies of the digestive tract, specifically those located within the pancreatic and bile ducts. pCLE is an innovative tool for in vivo imaging of the gastrointestinal tract. pCLE uses light that is funneled through a confocal opening, which reduces scattered outside light. Because only one spot (ie, the confocal) can be imaged at a time, all other light spots located on either vertical or horizontal planes must be scanned in order to produce dynamic images. A contrast agent (eg, fluorescein) can be injected to create high-contrast images.

pCLE allows real-time evaluations of tissue at the cellular level, so cancerous or precancerous tissue can be quickly identified. After an injection of fluorescein, the area without adequate uptake will appear darker while the normal area will appear lighter, permitting mapping of the duct that is being investigated. Physicians are then able to remove or treat the diseased tissue. “Confocal imaging is basically a live biopsy—you look at the cell itself,” said Dr. Kahaleh. The identification of diseased tissue provides the map required for the clinician to offer the appropriate intervention.

Currently, the Center for Advanced Digestive Care at NewYork-Presbyterian/Weill Cornell is one of only a handful of US hospitals that actively uses pCLE technology. In fact, Dr. Kahaleh was one of the first physicians to use this technology and had a primary role in developing the inflammatory criteria by which pCLE images are interpreted. To



Michel Kahaleh, MD

address the limitations of the Miami classification, Dr. Kahaleh and colleagues developed descriptive criteria for benign inflammatory strictures: vascular congestion, dark granular patterns with scales, thickened reticular structures, and increased space between scales. The new criteria, called the Paris classification, improved the accuracy of pCLE for determining malignant versus benign strictures.

Dr. Kahaleh recently contributed to a key study that compared the feasibility and benefits of real-time pCLE of the pancreatic duct with cytologic and histologic results. In this study, 5 patients with pancreatic ductal disease who underwent endoscopic retrograde cholangiopancreatography and pCLE were analyzed. Real-time confocal images were analyzed based on the Miami classification criteria. The criteria included thick white or dark bands, presence of epithelium or dark clumps, interstitial fluorescein leakage, and vascular congestion.¹

The investigators found that in 3 of the cases, thick dark bands or epithelium were present, indicating malignancy, whereas the other 2 cases

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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.

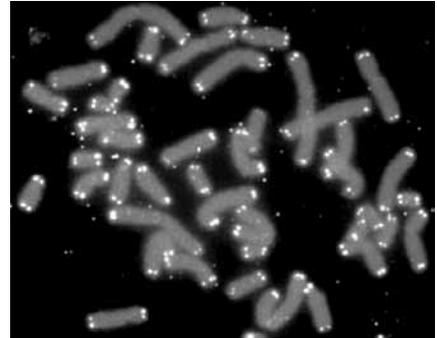
Research abounds in every field. Perhaps no area of medicine has been as affected by research into the genetic foundations of disease as much as oncology. Examples of genetic discoveries in oncology are plentiful. An important recent discovery is the revelation that certain cases of glioblastoma are 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 at 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 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



Telomere length relates to likelihood of developing dementia and overall life span.

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.

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.⁴

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^{5,6} 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*.

Nephrologists and psychiatrists, meanwhile, were interested in the results of a large multinational study in which Columbia University played an important role.⁷ 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.

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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indicated benign strictures. One patient with thick dark bands subsequently underwent a Whipple procedure, which revealed a main duct intraductal papillary mucinous neoplasm with severe dysplasia. The other 2 patients with thick dark bands were started on a chemotherapy regimen for pancreatic adenocarcinoma.

Overall, the study results showed that pCLE might be an effective tool for diagnosing indeterminate pancreatic duct

strictures and for surveying abnormal pancreatic ducts while planning surgical interventions.

This technology expedites the patient's entire experience, combining the initial diagnostic visit with the possibility for immediate treatment or removal of the diseased tissue. pCLE can be used in the pancreatic duct as well as the bile duct, esophagus, rectum, colon, and stomach. It also can provide more incentives to the surgeon to resect a suspicious lesion and

provides the oncologist with more data to start chemotherapy.

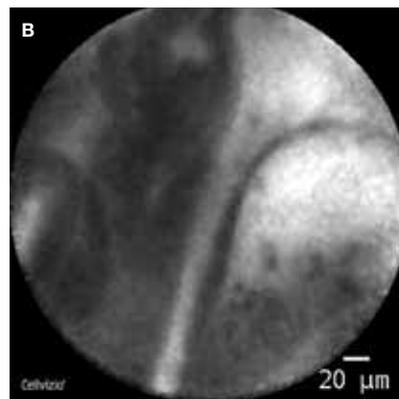
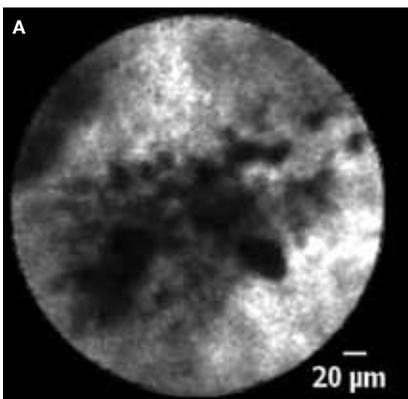
pCLE provides real-time histology and may be effective for detecting and classifying biliary and pancreatic strictures. The pCLE device is small enough to access the small biliary tree and durable enough to withstand precise placement or adjustments to the probe tip. In terms of biliary imaging, the probe is maneuvered through a side-viewing endoscope and into the biliary tree using a rotatable catheter or cholangioscope.

At the Center for Advanced Digestive Care, cutting-edge technology like the pCLE is combined with patient-centric care. The use of innovative tools and collaborations between the medical and surgical teams enables the Center to offer comprehensive, effective patient care.

Molecular Markers and Endoscopic Techniques

Tamas A. Gonda, MD, Assistant Attending Physician, NewYork-Presbyterian/Columbia University Medical

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A) Confocal imaging of a patient with sclerosing cholangitis; and B) confocal imaging of an abnormal pancreatic duct lesion.



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Center, also emphasizes the importance of early detection and treatment of gastrointestinal malignancies. He uses endoscopic techniques along with molecular markers to detect these abnormalities.

Within the scope of early detection and early diagnosis, Dr. Gonda's research focuses on cancers of the pancreas and esophagus, Barrett's esophagus, and pancreatic cyst surveillance. In several of these conditions, molecular markers may provide the opportunity to identify cancerous transformation before it is detectable by either imaging or histology.

"In the biliary tract, there are some diseases—notably, primary sclerosing cholangitis—which are high-risk conditions for progression to biliary malignancies. Molecular markers, especially fluorescent in situ hybridization or FISH, already play a significant role in identifying those patients who have developed cancer or precancerous lesions," Dr. Gonda explained.

Recently, Dr. Gonda investigated the additional benefit of detecting mutations in the cell-free component of bile duct biopsies and the potential advantage of adding this modality to FISH and brush cytology. The mutational analysis used 17 markers, including *KRAS* point mutation

and loss of heterozygosity at multiple loci.

The results showed that residual supernatant fluid from cytology brushes can be used to secure adequate amounts of DNA for mutational analysis. The study also demonstrated that mutational analyses on cell-free DNA specimens might contribute to the diagnostic yield, especially in cases where brush specimens have low cellularity, which is a common problem encountered in biliary diagnostics.²

Pancreatic cystic neoplasms are another area where a combination of molecular markers and endoscopic imaging may play a significant role in identifying patients at the highest risk. At the Pancreas Center of NewYork-Presbyterian/Columbia the goal of several screening programs and protocols is to detect patients who have not yet developed pancreatic cancer but who carry a high risk for developing it. This early detection may offer an opportunity for prevention of pancreatic cancer in this population of patients.

Endoscopic biopsies may also increasingly influence treatment decisions in pancreatic cancer. Dr. Gonda noted that research is moving toward targeted therapies and the use of molecular markers to identify the best possible treatment options. "One of our goals is to try to

provide targeted or tailored therapy based on molecular profiles of the tumors. Identifying certain mutations, such as *KRAS* or *BRCA-1* or *-2*, and others, will hopefully drive treatment decisions once the diagnosis of cancer has been established," Dr. Gonda said.

"NewYork-Presbyterian/Columbia is unique in our very comprehensive approach, from expert diagnostic modalities—such as endoscopy, therapeutic endoscopy, and molecular diagnosis—to therapeutic expertise in both oncology and surgery. This approach can bring significant improvement in the diagnosis and treatment of esophageal, gastric, and biliary diseases," said Dr. Gonda.

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