Inherited Cancers Clinic Seeks to Advance Understanding, Diagnosis and Management of Hereditary Colorectal Cancers

Roughly 5 to 10 percent of all colorectal cancers (CRCs) are considered hereditary and result from mutations and defects in specific genes. Another 25 to 30 percent of patients with CRC may have a family member with a diagnosis of CRC but no known genetic alterations.

A group of inherited syndromes has been associated with a 70 to 100 percent lifetime risk of CRC development, with many of these syndromes also carrying an increased risk of extraintestinal malignancies. These inherited syndromes include Lynch syndrome, familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP) and several hamartomatous polyposis conditions (such as Cowden’s, Peutz-Jeghers and juvenile polyposis).

Using family history and appropriate genetic testing to identify patients with these syndromes can help clinicians estimate a patient’s cancer risk and determine appropriate cancer screening, surveillance or preventive interventions.

Established in August 2017, Mayo Clinic’s multidisciplinary inherited cancers clinic seeks to advance the understanding of hereditary colorectal cancers and their genetic basis to provide comprehensive, effective cancer detection, surveillance and clinical management for these patients.

“Inherited cancers typically present with more than one primary cancer, specific combinations of cancers, such as colon and endometrial cancers, and rare cancers. According to Dr. Samadder, these characteristics and other unique challenges associated with these cancers make consultation at a multi-specialty clinic highly advantageous. At Mayo Clinic, care of individuals with hereditary cancers often involves consultation with specialists from genetics, gastroenterology, oncology, gynecology, colorectal surgery and pathology, and with staff from Mayo Clinic’s tumor board. Specific services provided by the Inherited Cancers Clinic include:

- Personalized risk assessment for any type of cancer or tumor risk
- Coordination of genetic testing
- Tailored cancer screening recommendations
• Communication of information through the family
• High-risk follow-up cancer screening with Mayo physicians
• Discussion at tumor board for complex cases involving medical and surgical decision-making
• Multidisciplinary team approach
• Referral to clinical trials for research as needed

“Using available tools such as simple questionnaires of personal and family history of cancer in outpatient settings helps us improve the identification of high-risk patients and families, detect cancers earlier, and formulate more effective individualized treatment protocols,” says Dr. Samadder (Figure, page 1).

Additional programs
As the Inherited Cancers Clinic continues to evolve, staff members are developing several additional related programs and services:
• A program responsible for coordinating routine immunohistochemistry testing of all surgically removed colorectal and endometrial tumors to aid in the identification of Lynch syndrome, launched in 2017 across Mayo Clinic’s campuses in Arizona, Florida and Minnesota
• A familial cancers tumor board to facilitate discussion of hereditary cancer cases with multispecialty input
• Telegenetics and outreach services to serve patients seen in Mayo Clinic Health System practices and regional hospitals
• A cancer registry and biorepository to support related research
• Educational offerings, including rotations for medical residents, subspecialty fellow and fellowships, and plans for collaboration with Arizona State University College of Health Solutions to initiate a genetic counseling program

In an article published in The American Journal of Gastroenterology, Dr. Samadder and co-authors provide a comprehensive overview of the genetics, surveillance and management of the more common hereditary colorectal polyposis and cancer syndromes. Below is an abridged list of the cancers the authors discussed and an overview of related causes, diagnostic criteria and cancer surveillance recommendations associated with these syndromes.

Lynch syndrome (LS)
Accounting for about 2 to 4 percent of all CRCs, LS is the most common cause of hereditary colon cancer. LS is associated with predominately right-sided colon cancer. Individuals with LS are also at increased risk of extracolonic cancers, including cancers of the endometrium, ovaries, stomach, small intestine, hepatobiliary tract, urinary tract and central nervous system.

Genetic causes:
• An autosomal dominant condition caused by a DNA mismatch repair (MMR) error that leads to mutations in one of five genes — MLH1, MSH2, MSH6, PMS2 and EPCAM

Diagnosis:
• Early identification of patients carrying mutations accomplished using the Amsterdam and revised Bethesda criteria

Cancer surveillance:
• Colonoscopy recommended every one to two years in confirmed mutation carriers, beginning at age 20 to 25
• Currently no universal guidelines to guide screening for extracolonic cancers

Familial adenomatous polyposis (FAP)
The second most common form of hereditary CRC, FAP accounts for about 1 percent of all CRCs. Classic FAP is characterized by the presence of hundreds to thousands of adenomatous polyps throughout the colon and rectum that generally develop during adolescence. If colectomy is not performed, lifetime risk of colon cancer can reach 100 percent.

Individuals with FAP also have a small potential risk of extracolonic cancers, including hepatoblastomas, osteomas and desmoid tumors, as well as cancers of the stomach and pancreas.

Attenuated FAP (AFAP) is a milder form of the disease that typically presents after age 25, with a lower lifetime polyp burden, averaging between 10 and 100 adenomatous polyps.

Genetic causes:
• Autosomal dominant conditions generally caused by germline mutations in the APC gene, a tumor suppressor gene associated with the WNT signaling pathway
• When APC germline mutations not present, polyposis conditions may be associated with other genes, including POLE, POLD1 and GREM1

Diagnosis:
Genetic testing for FAP and AFAP is recommended:
• When single colonoscopy detects more than 10 cumulative adenomatous polyps
• For individuals with 10 or more adenomas and a personal history of CRC
• For individuals found to have more than 20 adenomatous polyps during their lifetime
• For patients diagnosed with FAP and at-risk family members

Cancer surveillance:
• For individuals with an APC mutation or with a family history of clinically diagnosed classic FAP, annual colonoscopy beginning around ages 10 to 12 years, ultimately lead-
ing to colectomy in those with polyposis too great to control via endoscopy
• For individuals with AFAP, colonoscopy every one to two years, beginning during the late teen years to early 20s
• For extracolonic cancers, recommended screenings include upper endoscopy, thyroid ultrasound and consideration for abdominal ultrasound in children

**MUTYH-associated polyposis (MAP)**
Associated with a lifetime CRC risk of 80 percent, MAP sometimes resembles FAP and AFAP, with multiple adenomatous polyps noted on colonoscopy, usually 15 to 100 during a lifetime. Individuals with MAP may also have a higher prevalence of serrated polyps, duodenal polyposis and carcinoma. Reported extracolonic cancers in patients with MAP include ovarian, bladder, skin and breast cancers.

**Causes and genetic diagnosis:**
• An autosomal recessive condition caused by biallelic mutations to the DNA base excision repair gene MUTYH

**Clinical criteria for testing:**
Testing for MUTYH gene mutations is recommended for individuals who clinically present with one or more of these criteria:
• More than 20 colorectal adenomas
• Known family history of MAP
• 10 to 20 adenomas
• Diagnostic criteria for serrated polyposis syndrome (SPS) with some adenomas noted on exam

**Cancer surveillance:**
• For individuals with homozygous MUTYH mutation, colonoscopy starting at age 25 to 30 years and repeated every two to three years if negative, and every one to two years if polyps are found
• For individuals with monoallelic MUTYH mutation, colonoscopy starting at age 40 years and repeated every five years
• For individuals with duodenal polyposis and carcinoma, baseline upper endoscopy beginning at age 30 to 35 years, with future screening dependent upon findings
• Screening timing and frequency influenced by family history and by the number and types of polyps identified on exam

**Hamartomatous polyposis syndrome**
This syndrome has three forms: Peutz-Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS) and Cowden’s syndrome.

**Peutz-Jeghers syndrome (PJS)**
PJS is characterized by the presence of hamartomatous polyps within the gastrointestinal tract and the appearance of mucocutaneous melanin pigmentation. PJS is associated with an increased lifetime risk of both gastrointestinal cancers (colon, pancreas, gastroesophageal, small bowel and stomach) and extraintestinal malignancies (breast, gynecological, lung and testicular).

**Causes and genetic diagnosis:**
• Rare, autosomal dominant conditions found in 50 to 70 percent of individuals with PJS, related to mutations of the SKT11 (previously called LKB1) tumor suppressor gene

**Clinical criteria for diagnosis confirmed by two or more of the following criteria:**
• Two or more PJS-type hamartomatous polyps of the small intestine
• Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia or fingers
• Family history of PJS

**Cancer surveillance:**
• Upper endoscopy and colonoscopy by late teen years, repeating every two to three years for surveillance if normal
• Small bowel assessment via baseline CT or MRI enterography, performed by late teen years and repeated every two to three years thereafter
• Pancreatic cancer screening via MRI and MRCP or endoscopic ultrasonography, every one to two years beginning by age 30 to 35
Established in 2013, Mayo Clinic’s inflammatory bowel disease (IBD) biobank involves researchers and resources at Mayo campuses in Arizona, Florida and Minnesota. The goal of the biobank is to collect biospecimens (serum, tissue, stool and urine) from patients diagnosed with ulcerative colitis (UC) or Crohn’s disease (CD) to advance biomarker research that might one day improve diagnosis, prognosis and treatment of IBD.

Biomarkers have garnered a great deal of attention because of their diagnostic and prognostic potential. Although the field is still young, serologic and genetic markers are expected to help researchers develop therapeutic approaches tailored to an individual’s unique genetic or molecular profiles.

**Process and collaborators**

Biobank participant recruitment and sample collection is underway at Mayo Clinic campuses in Arizona, Florida and Minnesota. Potential patients are identified using a database search by appointment indication, recruited and enrolled after undergoing informed consent process. Once biospecimen samples are obtained and analyzed, relevant data is recorded using a uniform data capture tool across all campuses. To date, the Mayo IBD biobank has collected samples from more than 2,000 Mayo Clinic patients, about 900 of which have been genotyped.

**Current collaborations and biobank-related research projects**

In 2016, Mayo’s IBD investigators joined researchers at seven other IBD centers to form a consortium through the Crohn’s and Colitis Foundation to develop the world’s largest IBD data and biosample exchange. Laura E. Raffals, M.D., a Mayo Clinic gastroenterologist in Rochester, Minnesota, specializing in IBD, serves as the co-principal investigator of this national effort and is leading the team of Mayo researchers to collaboratively conduct research aimed toward discovering new IBD treatment targets and finding a cure for these diseases.

“We are pleased with the number and scope of projects currently underway and by the progress achieved to date by our researchers,” says Dr. Raffals. “We are committed to increasing patient recruitment, pursuing additional collaborations with other organizations and encouraging development of additional translational research projects leading to meaningful advances in the treatment of inflammatory bowel disease.”

Mayo researchers gave presentations highlighting discoveries stemming from work utilizing the Mayo Clinic IBD biobank at the 2017 Digestive Diseases Week (DDW) meeting. Led by Ming-Hsi Wang, M.D., Ph.D., a gastroenterologist and hepatologist at Mayo Clinic’s campus in Florida, IBD researchers from Mayo Clinic’s campuses in Florida, Minnesota and

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**Serrated polyposis syndrome (SPS)**

Previously known as hyperplastic polyposis syndrome, this condition is characterized by multiple serrated colon polyps and an increased lifetime risk of CRC.

**Causes:**

- Genetic makeup is poorly understood; with no single gene identified, clinical criteria are used for the diagnosis.

**Diagnosis confirmed by one or more of these criteria:**

- Five or more serrated polyps proximal to sigmoid colon with two or more larger than 10 mm in size
- Presence of any serrated polyps proximal to sigmoid colon and a first-degree relative (FDR) with SPS
- More than 20 serrated polyps of any size distributed throughout colon

**Cancer surveillance:**

- Colonoscopy at least every one to three years, starting at age 40 and repeated every one to three years if polyps found, or every five years if no polyps found; no special screening guidelines currently for extracolonic cancer surveillance

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**For more information**


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**IBD Biobank Research Focuses on Biomarker Discovery to Improve Diagnosis, Prognosis and Treatment**

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**For more information**

Arizona provided an analysis of the Mayo IBD biobank’s available genotype data, crossing it with phenotype data to identify genetic variants that can predict which patients with inflammatory bowel disease are most likely to respond to TNF-antagonist therapies.

Mayo presenters at DDW also discussed their work describing the genetic risk burden affecting patients with IBD and perianal disease and the response to anti-tumor necrosis factor (TNF) therapy. They examined how a patient’s genetic risk burden or profile affects the disease course and individual responses to biological therapy.

The list of projects that follows demonstrates the wide range of additional questions and hypotheses that Mayo’s IBD biobank investigators are currently addressing.

**Understanding and curing CD requires an epigenetic approach**
Led by William A. Faubion, M.D., a gastroenterologist specializing in IBD at Mayo Clinic’s Minnesota campus, this research team seeks to identify epigenetic DNA methylation patterns associated with recurrent CD. The project aims include building the methylome; conducting multidimensional analyses, including RNA sequencing and deep sequencing for IBD-associated variants; and conducting bioinformatic analyses.

**Rare IBD phenotypes: Analysis of genetic, serologic and clinical factors**
Led by Drs. Faubion and Raffals, this Mayo research team seeks to utilize the large clinical base of the Sinai-Helmsley Alliance for Research Excellence (SHARE) consortium in order to collect the largest cohorts of well-characterized “rare” IBD manifestations. The study’s aims include testing for genetic, serologic and clinical associations in rare subtypes of IBD manifestations and developing models with clinical utility for predicting extraintestinal manifestations.

**Identifying and validating antibody markers of diagnostic and prognostic significance in CD**
This project involves researchers from Mayo Clinic’s campuses in Arizona and Minnesota, working in collaboration with colleagues at Arizona State University. The project’s goal is to use serologic biomarkers to predict disease severity and progression. Specific aims for this project include the identification and validation of antibody markers against human and microbial antigens that can be used for predicting CD severity and risk of disease progression.

**Stool DNA for the surveillance of IBD-associated colonic dysplasia and cancer**
This project, led by John B. Kisiel, M.D., at Mayo’s Minnesota campus, seeks to improve patient outcomes and minimize the burden of invasive and expensive testing. Colonoscopy is currently the primary surveillance tool for colorectal cancer, a major cause of morbidity and mortality in patients with IBD.

With support from Exact Sciences (Madison, Wisconsin) and the Maxine and Jack Zarrow Family Foundation (Tulsa, Oklahoma), Dr. Kisiel and his collaborators have shown that stool DNA testing is sensitive, specific and cost-effective in this application. They hope to bring this technology to patients with IBD in the near future.

**Diagnosis and Management of Small Bowel Bleeding: Update on Diagnostic and Therapeutic Tools**
Diagnosis and management of small bowel (SB) bleeding remains a challenging problem faced by gastroenterologists, both from a clinical and financial standpoint. The increasing age of the patient population, associated comorbidities, and the use of newer anticoagulants and cardiac support devices, including left ventricular assist devices (LVADs), have added further complexity to SB bleeding management.

While advances in endoscopic and radiologic testing have enabled gastroenterologists to successfully navigate difficult SB anatomy, detect mucosal lesions and perform therapy, several important issues require consideration. These include appropriate selection of patients for evaluation, optimal selection and timing of tests, and understanding when a conservative approach might be more cost-effective. In an article published in *Expert Review of Gastroenterology & Hepatology* in 2016, Shabana F. Pasha, M.D., and Jonathan A. Leighton, M.D., gastroenterologists at Mayo Clinic’s campus in Arizona, present an overview of small bowel bleeding to guide decision-making in the management of this disorder.

**What are causes of SB bleeding?**
The majority of patients with SB bleeding have
A variety of endoscopic and radiologic tests are available to evaluate the small bowel for bleeding. “Understanding the advantages and limitations of these tests, as well as their diagnostic yield and therapeutic capabilities, can help clinicians determine the most appropriate choice for a given patient,” says Dr. Pasha.

Diagnostic testing

Capsule endoscopy

Capsule endoscopy (CE) is superior to other diagnostic tests for detection of clinically significant SB findings, making it the first test of choice in the majority of patients with SB bleeding. It provides detailed imaging of the small bowel mucosa, and superior detection of multiple vascular lesions, inflammation and tumors.

However, the test may miss solitary lesions, including SB tumors. Another risk is CE retention, which occurs in up to 1.5 percent of patients with SB bleeding, and may require endoscopic management or surgery for retrieval. Patients with NSAID enteropathy, Crohn’s disease, SB tumors, radiation enteritis and prior SB surgery are at increased risk of retention. “In patients with concern for capsule retention, a patency capsule can be completed prior to the capsule endoscopy to assess for SB patency,” says Stephanie L. Hansel, M.D., M.S., a gastroenterologist at Mayo Clinic’s campus in Minnesota.

The yield of CE is dependent upon timing of the test relative to the bleeding episode. The highest likelihood of detecting treatable SB lesions is when CE is performed within 72 hours of bleeding. The yield significantly declines two weeks after the bleeding episode.

Multiphase CT scan (angiography and enterography)

Multiphase CT enterography (CTE) has a higher sensitivity than capsule endoscopy for the detection of small bowel tumors. The administration of a large volume of neutral or negative oral contrast allows adequate SB distension and evaluation of mucosal details, while IV contrast allows optimal visualization of the mesenteric vasculature.

CT angiography (CTA) without oral contrast is recommended for urgent imaging in patients with active bleeding, especially those with hemodynamic instability. With its rapid imaging capabilities and higher accuracy, CTA has largely replaced the technetium 99m red blood cell scan. Multiphase CT imaging is contraindicated in patients with decreased renal function and IV contrast allergy.

Therapeutic modalities

Deep enteroscopy (DE):

• The primary role of DE is for treatment of SB lesions detected on diagnostic testing. The available DE techniques — balloon-assisted (double-balloon enteroscopy and single-balloon enteroscopy) and spiral enteroscopy — have a comparable diagnostic and therapeutic yield in SB bleeding.

• DE may also be useful for diagnosis of SB bleeding in select patients after negative noninvasive testing, and in patients with postsurgical altered SB anatomy. Similar to CE, the closer that DE is performed to the bleeding episode, the higher the yield of the test.

• DE should be reserved for patients with a high likelihood of SB lesions, as the procedures are relatively invasive, require anesthesia and additional personnel, and are typically longer in duration than standard endoscopy. Adverse events include cardiopulmonary complications, bleeding, ileus, perforation and, rarely, pancreatitis.

Mesenteric angiography:

• Reserved for therapeutic management of patients with severe GI bleeding, mesenteric angiography allows performance of urgent angiographic embolization, especially in...
those with hemodynamic instability. Embolization procedures can have high rates of serious adverse events, including bowel infarction, which may increase with repeat embolizations.

**Intraoperative endoscopy (IOE):**
- IOE is now reserved for management of refractory bleeding, known SB lesions (including tumors and NSAID-related diaphragms), and when endoscopic and radiologic tests are unsuccessful in detecting and treating the underlying source of bleeding.

**Patient outcomes**
Long-term patient outcomes associated with SB bleeding, especially after endoscopic treatment of vascular lesions, are still unknown. Although the recurrence rate of SB bleeding is high, endoscopic treatment typically reduces transfusion requirements. Pharmacological management with octreotide and somatostatin analogues, and thalidomide, has a limited role in SB bleeding.

“At Mayo Clinic, we have experts in capsule endoscopy, multiphase CT imaging, angiography, balloon-assisted enteroscopy and intraoperative enteroscopy. Our expertise and close collaboration of different specialties, including gastroenterology, radiology, cardiology, surgery and others, allows us to offer a multidisciplinary and individualized approach toward management of our patients with small bowel bleeding,” says Dr. Pasha.

**For more information**

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**Role of Novel DNA Methylation Markers in Detection of Advanced Neoplasia in Pancreatic Cysts**

Pancreatic cystic lesions are often detected incidentally on cross-sectional abdominal imaging (such as CT or MRI). A Mayo Clinic study published in *Clinical Gastroenterology and Hepatology* in 2016 reported a prevalence of 41.6 percent for incidental pancreatic cysts in patients undergoing abdominal magnetic resonance imaging (MRI).

The vast majority of these cysts do not harbor advanced neoplasia and are at a low risk of malignant degeneration. Annual incidence of pancreatic cancer (PC) in patients with pancreatic cystic lesions (PCLs) is less than 1 percent. Given that pancreatic resection is associated with a high degree of morbidity and mortality, current guidelines use a combination of clinical and imaging characteristics to identify “high-risk” and “worrisome” cysts that can be selected for surgical resection.

A significant percentage of cysts surgically resected based on these current prediction algorithms are found to be nondysplastic or harbor low-grade dysplasia and would not have justified surgery if detected preoperatively. Experts recommend reserving surgical resection for patients with cysts harboring high-grade dysplasia (HGD) or early invasive cancer. However, none of the currently available cyst fluid biomarkers can accurately detect the presence of HGD or cancer in pancreatic cysts.

“Currently available risk prediction algorithms for detection of advanced neoplasia in pancreatic cysts lack sufficient sensitivity, specificity and diagnostic accuracy,” explains Shounak Majumder, M.D., a Mayo Clinic gastroenterologist in Rochester, Minnesota, whose research focuses on pancreatic diseases. “These issues make assessment of PCLs for malignant potential and surgical case selection extremely challenging.”

To address these issues, Dr. Majumder and gastroenterologist David A. Ahlquist, M.D., also from Mayo Clinic’s campus in Minnesota, led a research team that conducted two sequential case-control studies designed to discover and validate the performance of a panel of novel methylated DNA markers to accurately identify PCLs with HGD or PC. These studies were partly funded by Exact Sciences (Madison, Wisconsin), as part of a larger collaboration between Mayo Clinic and Exact Sciences that focuses on biomarker discovery and cancer diagnostics.

Mayo researchers John B. Kisiel, M.D., Mark D. Topazian, M.D., and Gloria M. Petersen, Ph.D. (from Mayo Clinic’s Minnesota campus); Massimo Raimondo, M.D. (from Mayo Clinic’s Florida campus); and Rahul Pannala, M.D. (from Mayo Clinic’s Arizona campus) were key collaborators for these studies.

**Study goals and design**
The goal of the first study was to discover and validate biomarker candidates present in pancreatic tissue that discriminate HGD and cancer from normal pancreas and low-grade precursor lesions. Discovery tissue samples (fresh frozen and formalin fixed, paraffin embedded) were chosen from Mayo Clinic institutional cancer registries.

After classification was confirmed by pathologists, samples underwent unbiased whole-methylome sequencing. A Mayo Clinic research
team led by Drs. Ahlquist and Majumder then used reduced representation bisulfite sequencing (RRBS) to identify candidate methylated markers capable of distinguishing a case group comprised of high-grade precursor lesions — including intraductal papillary mucinous neoplasms high-grade dysplasia (IPMN-HGD), pancreatic intraepithelial neoplasia-3 (PanIN-3) and invasive pancreatic cancer lesions — from a control group composed of normal pancreas or low-grade precursor lesions including IPMN low-grade dysplasia (IPMN-LGD), PanIN-1, and PanIN-2 lesions.

A panel of top candidate markers from this discovery effort was subsequently validated in an independent tissue set. The top-performing markers were then assayed in pancreatic cyst fluid for a multicenter study. Headquartered at Mayo Clinic’s campus in Minnesota, the multicenter study included cyst fluid contributions from researchers at Baylor College of Medicine, Brigham and Women’s Hospital, Stanford University, University of Michigan, and Yale University.

Results

During the tissue phase of the study, Mayo researchers successfully identified and validated novel methylated DNA markers in pancreatic tissue that accurately discriminate high-grade precursor lesions and cancer from low-grade precursors and normal pancreas tissue. Results presented at Digestive Diseases Week (DDW) and published in abstract form in Gastroenterology in 2016 show that a panel of top tissue markers yielded an area under the receiver operating characteristic (ROC) curve (AUC) of 0.90 (95 percent confidence interval [CI] 84 to 96 percent).

The second phase of the study also yielded promising results, presented at DDW and published in abstract form in Gastroenterology in 2017. In a multicenter study using 134 archival cyst fluid samples, the top-performing methylated DNA marker showed a sensitivity of 81 percent at a specificity of 85 percent for diagnosis of HGD or cancer using the gold standard of surgical histology.

The top four methylation markers individually achieved AUCs of > 0.90.

“This is the first study assessing the performance of methylated DNA biomarkers in pancreatic cyst fluid, identified based on tissue discovery and specifically aimed at detecting advanced neoplasia and discriminating between grades of dysplasia in pancreatic cysts,” explains Dr. Majumder. “Overall, the detection accuracy for these novel methylated markers was significantly better than that provided by the use of currently available cyst fluid markers. These findings demonstrate that cyst fluid-methylated DNA markers can accurately identify cysts with advanced neoplasia that can be targeted for surgical resection.”

Dr. Majumder acknowledges that additional research will need to be conducted to address this study’s potential limitations and to further validate the performance of these novel cyst fluid biomarkers in a prospectively collected sample set. “Studying patients who undergo surgery as well as those followed with surveillance imaging in larger prospective trials will help optimize marker combinations and corroborate these findings,” explains Dr. Majumder.

For more information
