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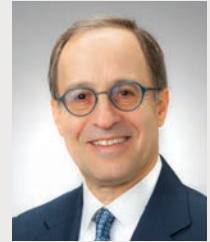
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Message from the Chief



Have you followed the controversy on ivermectin? It's an extraordinary story still in evolution. Laboratory data in vitro demonstrated that ivermectin in high doses could kill COVID-19. Whether that translates to humans is another matter. A study from Egypt suggested that ivermectin was effective against COVID-19. However, the data in that study was suspect, and in fact, the publication was subsequently withdrawn. Some misinformed commentators seized upon ivermectin and touted it as a potentially effective therapy for COVID-19. The basis for this is not in science but rather in the belief that there is a conspiracy to deny effective medication to people, such as a plot by vaccine manufacturers to encourage vaccine use instead of other alternatives. The battle is extending further as lawsuits are being launched throughout the country by patients and families demanding that ivermectin be used in their care, often in severely ill COVID-19 cases on a ventilator. Some judges have ordered hospitals to administer the drug. Other judges have said they would not order a hospital to administer an unproven, unapproved treatment that could potentially have detrimental effects on health.

The rush and frenzy to obtain ivermectin is not without consequence. The national poison data system recorded that from July to August 2021 cases of ivermectin toxicity exposure tripled to 459. Pharmacists are reporting difficulty in stocking the drug, with prescriptions increased to 88,000 from 3,600 prior to the pandemic. Instances of individuals using the veterinary preparation of ivermectin, prescribed for horses, has resulted in significant toxicity. Dr. Arthur Caplan, a bioethicist at NYU, has commented that going to a hospital is not like going to a restaurant. You don't order your own treatment. Medicine can't be subjected to having to practice according to patient demand backed by court orders. Yet, because of the emergence of significant distrust in authorities and in institutions, this sort of controversy is not going away. How to resolve it will challenge hospitals, physicians, and patients for the seeable future.

At the University of Pittsburgh's Division of Gastroenterology, Hepatology and Nutrition, we can only strive to pursue truth by applying the scientific method in a diligent, scrupulous, and objective manner. In this issue of Digest, we focus on keeping people healthier by looking beyond what's obvious and treating the entire person. We cover how dietary changes can help prevent colon cancer and other diseases, and we'll explore how to approach often difficult-to-diagnose conditions like cyclic vomiting syndrome and Wilson's disease. This issue also takes a closer look at how we treat patients with liver disease and pancreatic cancer, including criteria for noninvasive assessment and early detection.

In this spirit, we've established UPMC Total Care-IBD, the nation's first patient-centered, multidisciplinary program for people with IBD. Our comprehensive approach to IBD enables us to offer individualized strategies to ease symptoms and help improve lives. We value the opportunity to partner with you and share more about this approach.

Through innovation coupled with rigorous scientific method, we make advances that matter to our patients, their loved ones, and the medical community. It is my pleasure to share our progress in this edition of Digest.

Thanks for joining us.

To good health,

Robert E. Schoen, MD, MPH

Professor of Medicine and Epidemiology
UPMC Endowed Chair of Gastroenterology, Hepatology and Nutrition
Chief, Division of Gastroenterology, Hepatology and Nutrition



Affiliated with the University of Pittsburgh School of Medicine, UPMC Presbyterian Shadyside is ranked among America's Best Hospitals by *U.S. News & World Report*.

UPMC LIFE CHANGING MEDICINE

Dietary Prevention of Colon Cancer and Other Noncommunicable Westernized Diseases

Westernized diseases, including colorectal cancer, diabetes, and cardiovascular disease, are a major threat to health care in the United States. The diet consumed by people living in high-income countries is a common underlying factor of these vastly different pathologies. The Westernized diet is low in fiber and high in meats, polyunsaturated fats, and simple carbohydrates. We have made key strides in understanding why the lack of fiber in the Westernized diet is deleterious and why consuming at least 50 grams of fiber daily is beneficial.



Stephen J.D. O'Keefe, MBBS, MSc, MD

Professor of Medicine, Division of Gastroenterology, Hepatology and Nutrition

Director, African Microbiome Institute, Stellenbosch University - South Africa

A healthy diet has long been lauded as an essential part of a healthy lifestyle conducive to disease prevention. While the nutrients and healthy fats digested in the stomach and small intestine are essential, the nondigestible fiber from plant foods that passes through the colon is crucial for good health as well.

Colon cancer is the second leading cause of cancer-related deaths worldwide. The American Cancer Society predicted that in 2020, approximately 148,000 individuals would be diagnosed with colorectal cancer and approximately 53,000 would die from the disease¹. Environmental pressures in genetically susceptible individuals promote colon cancer. A low-fiber diet places environmental pressure on the colonic epithelium, as well as on the stomach, esophagus, breast, prostate, pancreas, and liver. Moreover, the obesity that can result from a Westernized diet is associated with 17 different types of cancer. A high-fiber diet is associated with a lower risk of all cancers, a lower risk of cardiovascular and respiratory diseases, and a reduction in all-cause mortality².

A major way that diet is either protective against colon cancer or promotes malignancy is through the bacteria in the colon, the microbiota. Dietary fiber feeds the colonic microbiota, which are highly active metabolically. When presented with sufficient fiber, the microbiota catalyze saccharolytic fermentation and produce biotin, polyphenols, and short-chain fatty acids, including acetate, propionate, and butyrate. These metabolites promote mucosal health and reduce inflammation. When the diet is high in meat and fat and low in fiber, the microbiota produce a different set of metabolites that include

hydrogen sulfide, ammonium products, and bile acid. This promotes mucosal inflammation and increases cancer risk. A minimum of 50 grams of fiber a day is needed to promote good health and minimize colon cancer risk.

The production of butyrate by the gut microbiota through the fermentation of dietary fiber is particularly important. Butyrate is the primary energy source of the colonocytes, the epithelial cells of the colon³. Butyrate is also immunomodulatory and anti-inflammatory. It stimulates Treg activation and exerts epigenetic regulation of the inflammatory response through its metabolism into a histone deacetylase inhibitor. Additionally, butyrate plays important roles in mucosal defense by stimulating the production of mucus and the formation of tight junctions. Taken together, these actions stimulated by the production of butyrate are anticarcinogenic. Dietary studies support that a high-fiber diet allows an individual to eat increased quantities of meat, which promotes carcinogenesis, without increasing the risk of colon cancer.

Dietary Switch Studies

In 1970, Denis Burkitt, MD, a British surgeon working in Uganda, proposed that individuals should ingest at least 50 grams of fiber daily to reduce the incidence of Westernized diseases. Substantial evidence gathered over the last 50 years supports this recommendation⁴.

To better understand the effects of dietary fiber on the colonic microbiota and colon cancer risk, Dr. O'Keefe started with the observation that colon cancer is not common in rural Africa, where its incidence is less than five per 100,000 people. In contrast, it is prevalent in

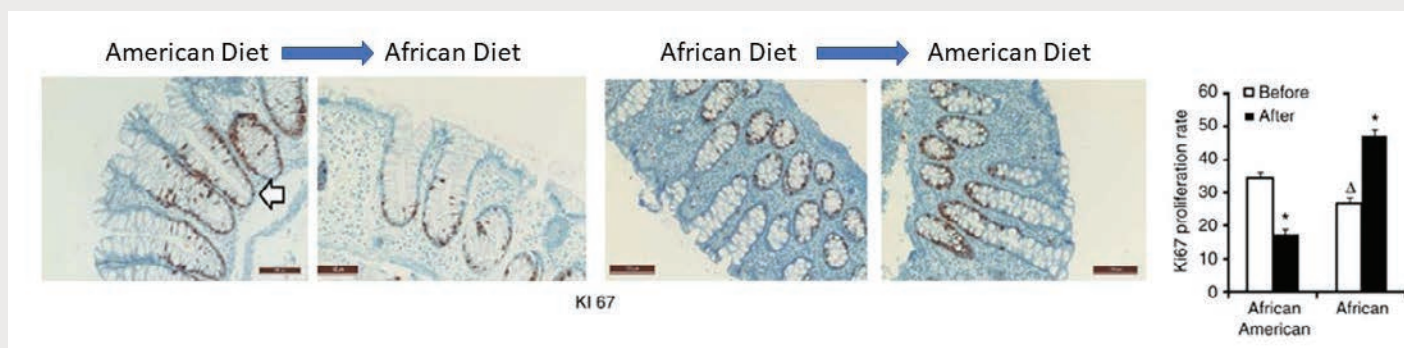


Figure 1. Proliferation in epithelial crypt cells, as indicated by Ki67 staining, in colonic mucosal biopsies from dietary-switch-study participants.⁵

African Americans, with an incidence from 2012 to 2016 of 45.7 per 100,000 people, despite similar genetics between these populations. Additionally, studies have shown that within one generation of immigrating to a Westernized country, colon cancer risk mirrors that of the new country, indicating that this increased risk of colon cancer comes from the environment rather than from genetic factors. The diet of rural Africans differs markedly from that of Americans. Most notably, the American diet is high in

meat, fats, and simple carbohydrates, and the African diet is very high in fiber. The average American eats approximately 15 grams of fiber a day; the average rural African eats 50 to 120 grams.

Dr. O'Keefe and his colleagues at UPMC, in South Africa, and elsewhere conducted a dietary switch study during which a group of 20 African Americans increased fiber consumption to 55 grams per day and decreased fat intake, and a group of 20 rural Africans decreased fiber consumption to 12 grams per day and

tripled their fat intake for two weeks⁵. Participants were between the ages of 50 and 65 years and were age-matched and sex-matched between the groups of healthy volunteers. Meals for all participants were provided and served in-house at a nutrition coordinating center to promote adherence to the study diet and accurate records of ingestion. A colonoscopy was performed before and after the dietary switch to look for markers of colorectal cancer risk.

After only two weeks of the dietary switch, there was decreased proliferation in the colonic epithelium of Americans given an Africanized, high-fiber diet and increased proliferation in the colonic epithelium of rural Africans fed a Westernized diet. (Figure 1) Additionally, markers of inflammation increased in Africans and decreased in Americans after the dietary switch. Dr. O'Keefe and his colleagues performed extensive profiling of the microbial metabolites present before and after the dietary switch in each group. The high-fiber dietary switch resulted in increased saccharolytic fermentation and increased production of butyrate and other short-chain fatty acids and suppressed synthesis of secondary bile acids, which are inflammatory, in the colon of African American participants. The inverse was observed in rural African participants. The study strongly suggested that the level of dietary fiber consumed can convert the colon from a cancer-promoting environment to a cancer-preventing environment in as little as two weeks⁵.

Dr. O'Keefe is now expanding his dietary studies to Alaskan Natives, a population

Figure 2. High-fiber foods readily available in the United States

Food	Serving Size	Fiber (grams)
Fruits		
Raspberries	1 cup	8
Apple	1 medium	4.5
Strawberries	1 cup	3
Vegetables		
Artichoke	1 medium	10
Green peas	1 cup	9
Edamame	1 cup	10
Grains		
Whole wheat spaghetti	1 cup	6
Bran flakes	¾ cup	5.5
Oatmeal	1 cup	5
Legumes		
Lentils	1 cup	15.5
Black beans	1 cup	15
Kidney beans	1 cup	16
Nuts and Seeds		
Chia seeds	1 oz	10
Almonds	1 oz, about 23 nuts	3.5
Pistachios	1 oz, about 49 nuts	3

with the highest incidence of colorectal cancer (89 per 100,000 population) and mortality from colorectal cancer (40 per 100,000 population) worldwide. The Alaskan Native diet consists almost exclusively of meat and fat. When the colonic microbiota and microbial metabolites in Alaskan Native individuals vs. rural African individuals were compared, the profiles were completely different.⁶ In Dr. O'Keefe's NIH-funded study (NCT03028831), Alaskan Native participants are supplementing their traditional diet with 50 grams of resistant starch fiber per day, which is soluble and easy to drink, as one arm of a four-week randomized controlled trial.

Fiber Consumption to Combat Obesity and Type 2 Diabetes

With African urbanization, there has been an increase in obesity, colon cancer, and other Westernized, noncommunicable diseases. Not surprisingly, the gut microbiota is different between individuals living in urban Africa and in rural Africa⁷. The best solution to this problem is to restore traditional foods, education, and exercise. Enhanced understanding of why this is happening and how to counteract it will have implications for managing similar, long-standing problems in developed countries.

These studies in rural and urban Africans and Alaskan Natives have important implications for all Americans and others living in Westernized societies. High-fiber diets can be used to treat obesity and may provide a novel way to manage type 2 diabetes by promoting intestinal microbiota that produce short-chain fatty acids. Dr. O'Keefe is exploring this at UPMC in an NIH-funded clinical study in

collaboration with Terry Hartman, MD, at Emory University. The Pitt-Emory Legume Study will test the ability of high-fiber diets to reduce obesity, diabetes, and colon cancer (NCT04780477). Participants in this randomized controlled trial will consume either a high-fiber diet with 25-30 grams of dietary fiber per day from legumes or a healthy American control diet. The participants will be between 40 and 75 years of age and at high risk for colon cancer due to being overweight or obese and having a history of a colon polyp in the past three years. The primary endpoints of the study are body weight and proliferation of the colonic epithelium as a biomarker of colon cancer risk. Insulin resistance, biomarkers of systemic inflammation, the microbiome, and gut transit time will also be assessed. Moreover, this important study will assess the long-term effects of the dietary intervention, with a follow-up in approximately three years, when participants undergo their next scheduled surveillance colonoscopy. Dr. O'Keefe is hopeful that the study will provide a scientific framework for a dietary modification program to promote weight control and reduce mortality from colorectal cancer and other Westernized diseases.

Colon cancer and other Westernized diseases can be attributed to microbiota-diet interactions, and there is increasing evidence that consuming at least 50 grams of fiber per day may prevent these diseases. High-fiber diets have the potential to resolve major public health concerns and allow Americans to live longer and have a better quality of life as they age.

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Awards and Recognition

Patients rated **Jaideep Behari, MD, PhD**, as a top UPMC physician in gastroenterology, earning him a 2020 UPMC Excellence in Patient Experience Award. Of the more than 7,600 UPMC physicians and advanced practice providers, Dr. Behari is among only 48 award recipients. Dr. Behari is an associate professor of medicine with the UPMC Center for Liver Diseases and the Division of Gastroenterology, Hepatology and Nutrition. He also directs the UPMC FLOW (Fatty Liver, Obesity, and Wellness) Clinic.

Eva M. Szigethy, MD, PhD, was celebrated as the 2021 Excellence in Health Care Honoree at the Western PA/WV Chapter of the Crohn's & Colitis Foundation's "Night of Steel" event. Dr. Szigethy is a professor of psychiatry, medicine, and pediatrics, and director of Behavioral Health with the Chief Medical and Scientific Office at the University of Pittsburgh School of Medicine. She also serves as co-director of UPMC Total Care-IBD.

UPMC Total Care-IBD: Accepting Referrals

As the nation's first patient-centered, multidisciplinary program for people with IBD, UPMC Total Care-IBD provides UPMC Health Plan members with enhanced access to an IBD gastroenterologist, specialized health care professionals (including a dietician, behavioral health expert, etc.), and a full spectrum of support services to develop personalized treatment plans. Patients who prefer to remain with their existing gastroenterologist can still enroll and take advantage of the program's offerings.

- To enroll a patient or ask medical questions, call **412-647-2183**
- To request an in-person or virtual educational Grand Rounds or a discussion with our team, email **joj2@pitt.edu**

New Grants

Jaideep Behari, MD, PhD: NIH R01 – "Novel Determinants for Progression of Non-Alcoholic Fatty Liver Disease to Hepatocellular Carcinoma and Other Health Outcomes"

David Levinthal, MD, PhD (in collaboration with Carnegie Mellon University PI, David Creswell, PhD): NIH R01 – "Mindfulness Meditation Training for Irritable Bowel Syndrome"

Anna Evans Phillips, MD, MS: NIH R01 – "Pancreatic Quantitative Sensory Testing (P-QST) to Predict Treatment Response for Pain in Chronic Pancreatitis (P-QST)"

Robert Schoen, MD, MPH: NCI Community Oncology Research Program and NRG Oncology – "FORTE [Five- or Ten-Year Colonoscopy for 1 to 2 Non-Advanced Adenomatous Polyps]"

UPCOMING EVENT

IBD U.N.I.T.E. 2022: The IBD Over the Lifespan

Free virtual event

Saturday, March 5, 2022
9 a.m.

Contact: joj2@pitt.edu

Registration opens January 2022.

This event is open to patients, family members, and loved ones, and it is an accredited symposium for nurses and dietitians.

Topics will include:

- The history of IBD and the impact of medical advancements on treatment strategies
- Case studies
- Education for new patients
- Fertility, nutrition, and behavioral health concerns
- Caregiver support
- Ostomy decisions
- Long-term patient care

Cyclic Vomiting Syndrome: Recognition and Guidelines for Treatment

Nausea and vomiting have many etiologies, and cyclic vomiting syndrome (CVS) is not the first diagnosis that comes to mind for an adult presenting to the emergency department. Even when physicians recognize the episodic nature of the patient's distress, CVS has historically been considered a pediatric disease, when, in fact, it occurs in 1%-2% of adults. Adults with CVS almost always receive fragmented care, and a diagnostic delay of five to six years from the onset of symptoms is typical. David Levinthal, MD, PhD, co-director of the UPMC Program for Gut-Brain Health, is one of only a handful of international CVS experts. Dr. Levinthal stresses that recognition of CVS is key to treatment. Moreover, effective treatments exist for most patients.



David Levinthal, MD, PhD

Assistant Professor, Department of Medicine

Director, the UPMC Neurogastroenterology and Motility Center

CVS is characterized by four phases.

(Figure 1) Each attack begins with a prodromic phase, followed by an emetic phase, and then a recovery phase. Between episodes, there is a “well” phase, during which the patient is typically, but not always, asymptomatic. Sweating and nausea are common during the prodrome phase, which is similar to the prodrome experienced by migraine sufferers. Episodes often begin suddenly in the early morning. Patients describe this sudden onset as “feeling like a switch flipped,” which suggests a nervous system state change. Sympathetic nervous system activation likely contributes to CVS pathogenesis, and CVS episodes are typically accompanied by tachycardia, dizziness, salivation, and paleness of the skin. During the emetic phase, the patient experiences severe nausea and vomits or retches repeatedly. Stomach pain may accompany vomiting. The emetic phase can last for hours or days. The recovery phase begins when vomiting and retching stop and lasts until normal energy and appetite return. Intravenous fluids may be required to rehydrate the patient and allow recovery.

Patients with CVS experience multiple episodes of vomiting each year. The diagnostic criteria known as the Rome IV criteria define the cyclic nature of CVS as two acute-onset episodes within six months that are at least a week apart and each lasts for less than seven days with an absence of vomiting between episodes¹. Laboratory tests, upper GI endoscopy, and imaging tests are used to rule out other causes of nausea and vomiting.

CVS has many features in common with migraine, epilepsy, and panic disorder. All four disorders are triggered by similar internal and external conditions. Patients suffering from each disorder experience some form of prodrome and symptom onset with a circadian pattern, notably an early morning onset in many. Prior adverse or traumatic life events are linked with an increased likelihood of each condition. These similarities suggest a common neurogenic etiology and, moreover, suggest that patients with CVS could benefit from trials of therapies that are currently available for the treatment of migraines, seizures, or panic disorder².

In 2019, the American Neurogastroenterology and Motility Society (ANMS) and the Cyclic Vomiting Syndrome Association (CVSA) published guidelines for the management of CVS in adults.³ Dr. Levinthal developed these guidelines with his colleagues, fellow experts in neurogastroenterology. The guidelines are a fundamentally important tool for the recognition of CVS by primary care and emergency medicine physicians and for getting patients the diagnosis and treatment required to mitigate CVS.

Similar to migraines, CVS is treated with prophylactic therapies, such as preventive medication and identifying and avoiding triggers, and abortive therapies for relief when an attack occurs. Most patients respond to readily available medications.

For prophylaxis, tricyclic antidepressants, such as amitriptyline, are strongly recommended as a first-line medication in patients with moderate-to-severe CVS.

Topiramate or Aprepitant are recommended as alternative prophylactic medications³. Prophylactic lifestyle changes include identifying and avoiding triggers, regular exercise, good sleep hygiene, stress management, avoiding fasting and dehydration, and avoiding cannabis and opiates. Additionally, evidence-based psychotherapy may be indicated to address psychiatric comorbidities that can contribute to CVS.

When patients present to the emergency department during a CVS episode, a combination of anti-emetics, analgesics, and sedation is likely to yield relief. Serotonin antagonists and triptans are conditionally recommended by the ANMS and the CVSA to abort acute attacks after symptoms develop. At UPMC, we are participating in the CVS Hope trial (NCT04645953), a clinical trial of a serotonin type III receptor inhibitor that is administered with a novel delivery system. The delivery system works like a vaping device and has kinetics similar to IV administration. This may provide patients with an easy-to-administer and effective abortive medication for rapid relief at home when an episode of CVS begins.

Due to the rarity of the disorder, clinical studies of CVS could be substantially accelerated by the development of a nationwide CVS disease registry with recruitment of CVS patients from multiple tertiary-care centers. At UPMC, Dr. Levinthal is developing a registry of patients with gut-brain disease and has

accrued approximately 50 CVS patients from the UPMC GI registry. Additionally, Dr. Levinthal actively collaborates with Thangam Venkatesan, MBBS, at the Medical College of Wisconsin, who maintains a registry with approximately 1,000 patients with CVS. Analyses using this large registry or a nationwide disease registry hold great promise to reduce the incidence of CVS and improve the quality of life of adults with CVS.

In one such study, Drs. Levinthal and Venkatesan examined intolerance to uncertainty in adults with CVS by recruiting patients from Dr. Venkatesan's database to complete validated questionnaires measuring their intolerance to uncertainty, their anxiety, and their quality of life.⁴ CVS patients with a higher intolerance to uncertainty had a poorer quality of life, quantitated using both physical-health and mental-health scales, and higher rates of anxiety disorders. The patient's intolerance to uncertainty did not affect the frequency of their CVS episodes or their utilization of health care for CVS episodes. Intolerance of uncertainty is a modifiable cognitive trait, and cognitive behavior therapy can be considered as a targeted therapy to improve the quality of life of patients with CVS based on their disease etiology. Identification of similar modifiable cognitive traits that contribute to the morbidity of CVS will likely improve the quality of life of CVS sufferers.

When caring for patients with gut-brain disorders at the UPMC

Neurogastroenterology and Motility Center, Dr. Levinthal is frequently the first health care provider to diagnose CVS and set a patient who has been suffering for years on a path toward management of their disease. He stresses that this does not need to be the case, however. Primary care physicians, emergency department providers, and gastroenterologists can be on the lookout for patients with symptoms indicative of CVS and expand their examination to include a patient's history of vomiting, family history of migraine, and whether a prodrome phase occurs during each episode. Recognition of CVS is key to improving the lives of these patients. CVS is treatable in most patients with drugs that are widely available and known to be well-tolerated. Guidelines are available to help non-specialists catch and care for patients with CVS who respond readily to standard treatments. The UPMC Neurogastroenterology and Motility Center is a resource for both patients and physicians seeking expertise in CVS, as well as other GI conditions that require holistic, cross-disciplinary treatment approaches due to their complexity.

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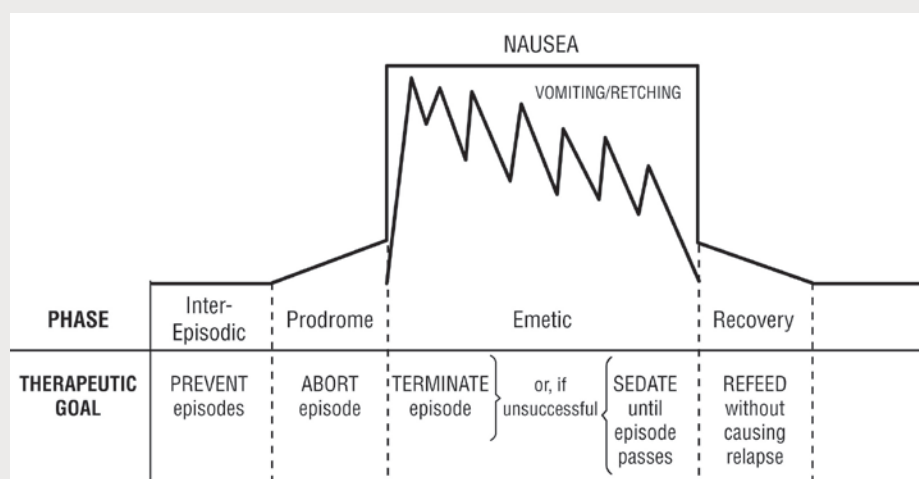


Figure 1. The four phases of CVS. Originally published by Fleisher et al.⁵ Reused under the terms of the Creative Commons Attribution License.

Clinical Utility of Non-invasive Liver Disease Assessment

Clinicians must routinely assess liver fibrosis to diagnose and monitor the progression of a variety of liver diseases, including hepatitis, chronic alcohol abuse, and nonalcoholic fatty liver disease. Traditionally, fibrosis has been assessed by liver biopsy, which is invasive and carries risks. Blood tests and imaging tests are minimally invasive and provide an alternative assessment of liver fibrosis. At the UPMC Center for Liver Diseases, Andres Duarte-Rojo, MD, and his colleagues leverage non-invasive liver disease assessment daily to improve patient care.



Andres Duarte-Rojo, MD, PhD
 Division of Gastroenterology, Hepatology and Nutrition
 Medical Director, Liver Transplantation
 Medical Director, UPMC Center for Liver Diseases

Figure 1. Proposed algorithm for fibrosis stratification, screening, and management of patients with liver diseases. NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; HCC, hepatocellular carcinoma. F0-F4, Fibrosis staging (F0 indicates no fibrosis, F4 is severe, irreversible fibrosis or cirrhosis). From Altamirino et al.² Used with permission.

Liver biopsy has traditionally been indicated to assess fibrosis caused by liver disease but causes pain in 84% of patients, as well as bleeding and other complications. Additionally, liver biopsy is inconvenient to both the patient and the health care system due to the cost, time, and resources necessary to perform a biopsy. When successfully performed, liver biopsy specimens are small, representing only 1/50,000 of the liver with considerable sampling variability, and a single sample does not capture the dynamic process of fibrosis. Fortunately, non-invasive methods for liver disease assessment have been developed and are increasingly being validated for a variety of indications. Moreover, in some patients these tests can be ordered and interpreted by physicians who are not liver disease specialists to better determine who would benefit from referral to a specialty center.

There are two types of tests for non-invasive liver disease assessment (NILDA) — blood-based tests and imaging-based tests. Blood-based tests are widely available but not widely used by non-specialists. Imaging tests are more accurate than blood-based methods but require specialized equipment. Nonetheless, most tertiary care centers

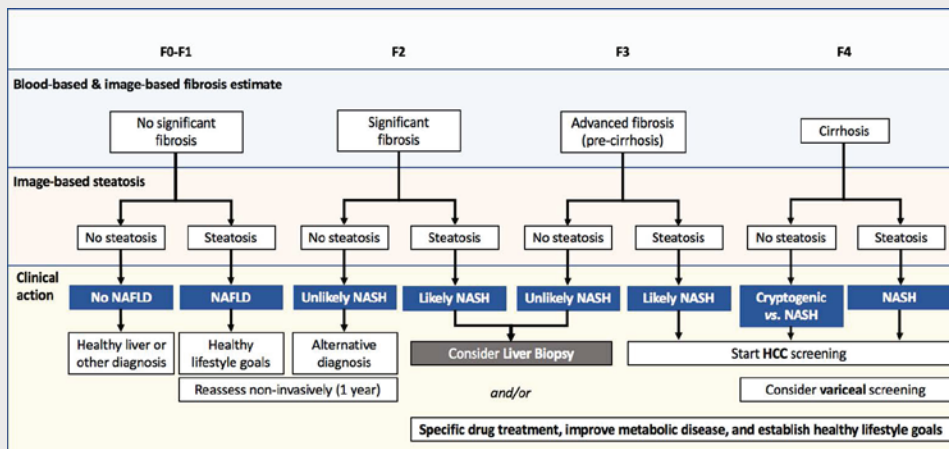
in North America have the necessary hardware and software for NILDA using imaging.

Blood-Based Non-Invasive Liver Disease Assessment

Blood-based tests for liver disease assessment leverage markers of liver function and other physiologic processes as surrogates of the degree of liver fibrosis. The information needed for the blood-based assessments can be obtained from tests routinely processed by clinical laboratories. These include the prothrombin index, platelet count, and alanine transaminase (ALT) and aspartate transaminase (AST) levels. Extracellular matrix components such as hyaluronate may also be evaluated. The values obtained from the routine laboratory tests are then plugged into formulas proven to reflect the degree of fibrosis present. More than a half dozen blood-based tests have been established, some available commercially and some from academic sources. These include the FibroTest, APRI, FIB-4, NAFLD Fibrosis Score, Hepascore, FIBROSpect II, ELF score, and FibroMeter. I recommend the Fibrosis-4 (FIB-4) test, especially to nonspecialists. It has excellent diagnostic power and is widely available, free to use, easy to understand, and well validated¹. The FIB-4 test combines standard biochemical assessments—platelet count, ALT, and AST—with patient age in its calculation of liver fibrosis.

Imaging-Based Non-Invasive Liver Disease Assessment

Imaging tools for NILDA measure the liver stiffness through elastography, a medical imaging modality that maps the elastic properties and stiffness of soft tissue. As fibrosis progresses, the liver tissue becomes stiffer. There are three major imaging tests based on elastography:



transient elastography (TE), magnetic resonance elastography (MRE), and shear-wave elastography (SWE). These three techniques are equally good at diagnosing advanced fibrosis. MRE is superior to TE and SWE in detecting less advanced fibrosis. Additionally, standard ultrasonography can be used to diagnose steatosis -- fatty deposits in the liver -- and grade steatosis as mild, moderate, or severe. The magnetic resonance imaging technique of quantitating the proton density fat fraction (MRI-PDFF) is also useful in determining the degree of steatosis, as it accurately measures liver fat².

In our clinic, the UPMC Center for Liver Diseases, TE is often the first assessment performed in patients with chronic liver disease who need to be staged for fibrosis. TE captures 100X the area sampled in a biopsy and yields immediate results. When we use TE to rule out cirrhosis prior to a treatment or procedure, further tests, such as a biopsy, are typically not necessary. In patients with chronic liver disease, TE is done every six to 12 months to see if the patient's disease is progressing or regressing.

NILDA is particularly useful to ensure that liver biopsies are being performed on the correct patients in accordance with evidence-based recommendations. **(Figure 1)** If the only indication for doing a liver biopsy is to stage liver fibrosis, the physician should not do the biopsy. If the NILDA tells you what you need to know, a biopsy is typically unnecessary. Depending on the modality, NILDA has an accuracy of 70%-90%. The more fibrosis present, the more reliable the result. Non-invasive imaging assessments are most accurate when detecting cirrhosis. There will always be some patients who require biopsy after non-invasive assessment, and biopsy may be indicated to assess liver disease etiology, inflammation, or graft rejection.

Applications of Non-Invasive Liver Disease Assessment

Portal hypertension

Portal hypertension is a complication of cirrhosis that negatively impacts prognosis. NILDA can be used to determine if portal hypertension is clinically significant and guide hepatologists after cirrhosis is

diagnosed. The non-invasive assessments may allow the hepatologist to determine who will need an endoscopy and who will have a higher risk of liver complications, particularly after surgery. We can also use NILDA to determine which patients should be surveilled for liver cancer.

Liver Transplantation

We recently started performing TE during our yearly clinical follow-up visits with all liver transplant recipients. Doing TE annually promotes early detection of liver disease, whether it is new disease or a recurrence of the liver disease that necessitated the transplant. Non-invasive assessment should have the same utility in liver transplant recipients as has been proven for nontransplanted patients with liver disease. This approach promises to improve patient care and long-term outcomes after liver transplantation.

Noninvasive methods of assessing liver disease may also have utility in assessing livers from extended-criteria donors during organ procurement. In a proof-of-concept study, we found that TE measurements, namely the controlled attenuation parameter and liver stiffness measurement, may be useful surrogates in assessing liver steatosis and fibrosis prior to organ procurement³. Using MRI-PDFF, we can assess steatosis without obtaining a liver biopsy from a potential donor.⁴ In a study of 143 living-liver donors, we found that donors who met other criteria for donation with no or mild steatosis (less than 20%) detected by MRI-PDFF experienced favorable postsurgical outcomes, including liver regeneration. Thanks to this technology, very few living donors undergo biopsy prior to liver donation at UPMC.

Non-Invasive Liver Disease Assessment in the Primary Care Setting

Widespread adoption of blood-based liver disease assessments has the potential to improve health care utilization. Blood-based tests, such as the FIB-4, are widely available, and the studies supporting their use are more than sufficient. The American Academy for the Study of Liver Diseases is currently writing guidelines that should encourage the use of non-invasive methods for liver

disease assessment, and I am proud to be part of this worthwhile effort. It is our hope that the publication of guidelines by our professional society will promote non-invasive liver disease assessment by both specialists and nonspecialists.

Expanded application of NILDA, particularly of blood-based assessments of liver fibrosis, would help us triage our patients. Many patients seen at the UPMC Center for Liver Diseases are found to have steatosis, so the only recommendations after seeing the specialist are lifestyle changes, such as lowering alcohol consumption, losing weight, and eating a healthier diet. Primary care physicians comfortable with ordering and interpreting the blood tests could spare some patients a trip to the liver specialty center. When a blood-based, non-invasive assessment suggests the presence of fibrosis, a referral to a specialty center, such as UPMC Center for Liver Diseases, should be actively pursued. Our world-renowned hepatologists provide expert care for a full range of liver conditions, with access to cutting-edge treatments for all disorders of the liver and considerable expertise in liver transplant for end-stage disease.

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Pancreatic Cancer Surveillance: Who Should Be Screened and How Should Screening Be Conducted?

Pancreatic adenocarcinoma is notoriously difficult to detect and is often diagnosed at a late stage. As a result, the five-year survival from pancreatic adenocarcinoma is only 10.8%. Population screening for pancreatic cancer is not feasible. Therefore, the first step in identifying pancreatic cancer at an early and potentially resectable stage is narrowing the population to be tested so that surveillance is possible. Randall E. Brand, MD, Beth Dudley Yurkovich, MS, MPH, CGC, and Eve Karloski, MS, CGC, of the UPMC Hereditary GI Tumor Program, are experts at assessing pancreatic cancer risk based on known risk factors, and are exploring how to improve risk assessment, surveillance protocols, and outcomes in patients with pancreatic adenocarcinoma.



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Pancreatic cancer is rare, accounting for only 3.2% of new cancer diagnoses but for 7.9% of cancer deaths in the United States.¹ Finding pancreatic adenocarcinoma when it is potentially resectable and aggressively treating systemic disease is currently the best approach to reduce mortality from pancreatic adenocarcinoma, but this is a formidable challenge. One approach used by the UPMC Hereditary GI Tumor Program is offering pancreatic cancer surveillance to patients who have an increased risk for pancreatic cancer based on family history or hereditary syndromes.

Risk Assessment

There are several situations when a physician might want to refer a patient to the UPMC Hereditary GI Tumor Program based on a family history of pancreatic cancer. Some patients may benefit from risk assessment because they have a first-degree relative (parent, sibling, or child) with pancreatic adenocarcinoma, because there are several family members with pancreatic cancer, or because there is a mix of pancreatic adenocarcinoma and related cancers, including breast, colorectal, and ovarian cancers. Others may be referred to discuss surveillance because they are already known to have an increased risk for pancreatic cancer due to a hereditary syndrome or pathogenic gene variant.

To begin the process of assessing the pancreatic cancer risk in an individual with a genetic syndrome or a family history of pancreatic adenocarcinoma and related cancers, the patient should be referred to the UPMC Hereditary GI Tumor Program,

located at UPMC Shadyside. They will meet with a genetic counselor who will compile a detailed personal history and family history to formally assess risk. The genetic counselors can then determine whether genetic testing, if not already performed, is likely to give actionable information that may help the patient. This is a highly individualized process, and genetic testing is not always part of the risk assessment. The patient will also meet with Dr. Brand to discuss a management plan. (**Figure 1**)

The Role of Genetic Testing

All patients with pancreatic adenocarcinoma are offered genetic testing in accordance with current clinical guidelines, which allows for the possibility of targeted therapeutics. Additionally, genetic testing helps identify at-risk family members. Pancreatic cancer risk is associated with pathogenic germline variants in at least 13 genes: APC, ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, and TP53.² When an actionable pathogenic gene variant is found in an affected individual, this information can be used to test their family members. First-degree relatives are eligible for testing if their affected family member is not available for testing.

Who Should Be Offered Surveillance?

For many individuals, the risk assessment leads to counseling on preventive strategies, such as healthy eating, not smoking, and exercise. For some, however, we also offer pancreatic cancer surveillance. When considering

surveillance, it is crucial that we first evaluate whether the patient could benefit from surveillance. If the individual is not a candidate for surgery, then they are not a candidate for surveillance, because the care team would not be able to act on any findings. The genetic profile and family history then further define candidacy.³ (Figure 2)

All surveillance should be based on expert opinion at a specialty center and should be conducted in the setting of research. We never perform surveillance without first counseling the individual who is concerned about developing pancreatic cancer. Each person needs to understand the risks, benefits, and limitations of surveillance for pancreatic adenocarcinoma. Most proceed with surveillance, but some decline. We are mindful of the emotional stress caused by each round of surveillance and the fact that we cannot guarantee that surveillance will detect pancreatic adenocarcinoma at a potentially resectable, early stage.

Surveillance Protocols

We generally begin surveillance when the high-risk individual is 45-55 years of age or 10 years younger than the youngest age of pancreatic cancer diagnosis in the family, depending on the criteria met. We initiate surveillance at younger ages in individuals with Peutz-Jeghers syndrome or familial atypical multiple mole melanoma (FAMMM) syndrome. Additionally, if an individual determined to be at high risk for pancreatic adenocarcinoma develops new-onset diabetes, surveillance should be initiated.

People who meet pancreatic cancer surveillance criteria are advised to undergo annual imaging of their pancreas by endoscopic ultrasound (EUS) or magnetic resonance imaging (MRI). While a blood test for CA 19-9 is a good marker for pancreatic cancer progression and response to treatment, it is not useful and should not be used in pancreatic cancer screening or surveillance.

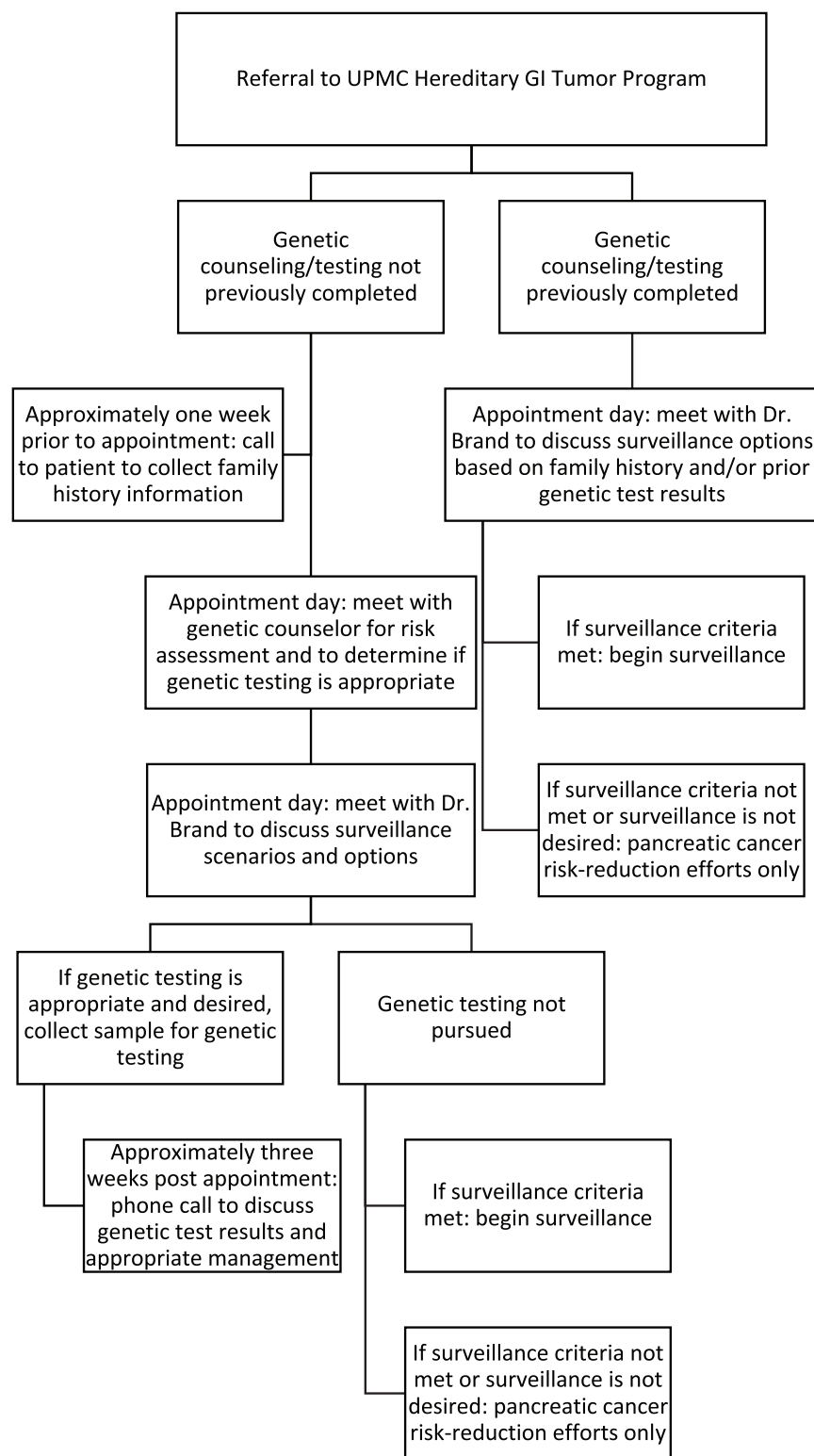
Care at UPMC's Specialty Center

When a pancreatic abnormality is found during imaging, the care team develops a management plan for the patient. At UPMC, we employ a multidisciplinary

team approach to pancreatic cancer surveillance and treatment that integrates the expertise of surgeons, gastroenterologists, radiologists, pathologists, certified genetic counselors, and other specialists.

Reaching a consensus on treatment as a multidisciplinary team ensures all aspects of patient care are considered for patients. This multidisciplinary approach may also mitigate socioeconomic disparities in care that can affect survival.

Figure 1. Care Pathway for Evaluation of Pancreatic Cancer Risk



The team approach at UPMC is helpful when pancreatic cysts are detected during pancreatic cancer surveillance. The expertise accessed through the multidisciplinary clinic is a better resource than any single physician or surgeon in determining how cysts should be managed.

Additionally, when patients come in to see us at UPMC, they are offered the ability to participate in research studies, clinical trials, and research consortiums. We participate in two major pancreatic cancer consortiums—the Cancer of the Pancreas Screening (CAPS)⁵ consortium, led by Michael Goggins, MD, at Johns Hopkins University School of Medicine, and the Pancreatic Cancer Early Detection (PRECEDE) consortium. We also participate in the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC). Within the CPDPC, led by our colleague Dhiraj Yadav, MD, MPH, in the Division of Gastroenterology, Hepatology and Nutrition, the new-onset diabetes (NOD) cohort is particularly relevant when considering surveillance in patients at risk for pancreatic adenocarcinoma.

Outcomes of Surveillance

Surveillance with imaging promotes detection of pancreatic adenocarcinoma at an earlier stage in a subset of high-risk individuals. Of 354 high-risk individuals who underwent pancreatic cancer surveillance from 1998 to 2014 as part of the CAPS 1-CAPS 4 consortiums, 24 developed pancreatic adenocarcinoma or high-grade dysplasia. Most (10 adenocarcinoma and 10 high-grade dysplasia) were detected during routine surveillance, but four adenocarcinomas were detected due to symptoms in patients who were either late for annual surveillance or who had discontinued surveillance. Of 10 adenocarcinomas detected during surveillance, nine were resectable. Only one of the tumors detected outside of surveillance was resectable. Additionally, three-year survival for all the patients in this cohort who developed pancreatic adenocarcinoma was 57%, an improvement over three-year survival of approximately 9% for patients with pancreatic adenocarcinoma in the United States during the same timeframe.

Whether surveillance will improve survival in larger populations of at-risk individuals is not yet clear, but this data is promising.

Improving Surveillance and Outcomes in the Years Ahead

The success of current surveillance protocols in detecting pancreatic adenocarcinoma at an earlier stage in highly selected patients is encouraging, but the protocols only capture a fraction of pancreatic cancer cases each year. Additional biomarkers for early diagnosis and risk prediction are needed, and their identification, funded through the National Cancer Institute’s Early Detection Research Network, is one of our current research focuses at UPMC. Our Pancreatic Adenocarcinoma Gene Environment Risk (PAGER) study will reveal biomarkers to determine who is at risk for pancreatic adenocarcinoma and who is a good candidate for more invasive tests. Through our research studies and consortium participation, we are striving to develop ways to detect pancreatic cancer earlier, when it may be easier to treat. This is an essential step

to improve outcomes for patients with pancreatic cancer and individuals at risk for this deadly disease.

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Figure 2. Genetic and family history criteria that define an individual as high-risk for pancreatic adenocarcinoma and a candidate for surveillance.

Surveillance candidate regardless of family history	Surveillance candidate if first- or second-degree relative with pancreatic adenocarcinoma	Surveillance candidate if first-degree relative with pancreatic adenocarcinoma
Pathogenic gene variant present	Pathogenic gene variant present	Familial Pancreatic Cancer
STK11 (Peutz-Jeghers Syndrome)	ATM	A family in which at least two individuals who are first-degree relatives to each other have been diagnosed with pancreatic adenocarcinoma and for whom no genetic cause has been identified
CDKN2A (FAMMM)	BRCA1	
	BRCA2	
	EPCAM/MLH1/ MSH2/ MSH6/PMS2 (Lynch Syndrome)	
	PALB2	
	TP53	
Regardless of pathogenic variant status		
Hereditary pancreatitis		

News and Updates

Andres Duarte-Rojo, MD, PhD, has been named medical director at the UPMC Center for Liver Diseases.

His predecessor, **Naudia Jonassaint, MD, MHS**, has been named vice chair for diversity and inclusion, Department of Medicine. Dr. Jonassaint also was recently named a 2021 Best and Brightest Executive MBA by *Poets & Quants for Executives*.

Randall Brand, MD, was elected national president for The Collaborative Group of the Americas on Inherited Gastrointestinal Cancer. The organization works to improve understanding of the basic science of inherited colorectal cancer and inherited gastrointestinal cancers, and the clinical management of affected families.

ACG Magazine highlighted the life's work and purpose of **David Whitcomb, MD, PhD**, in his article, "Perspectives and Advice to Trainees and the Next Generation of Physicians and Scientists."

Jacob Lipkin, MD, was named chief gastroenterology fellow at UPMC on July 1, 2021.

UPMC hospital staff gathered for "White Coats Against Racism" on the one-year anniversary of George Floyd's murder. Participants knelt silently outside UPMC Presbyterian in Oakland in remembrance of Floyd's life and to protest racism and police brutality.

New Faculty

The Division of Gastroenterology, Hepatology and Nutrition welcomes:

- Fadi Francis, MD, clinical associate professor of medicine
- Dempsey L. Hughes, MD, clinical assistant professor of medicine
- Kunut Kijisrichareanchai, MD, clinical assistant professor of medicine
- Janet Kwok, MD, clinical assistant professor of medicine
- Ravy Vajravelu, MD, MSCE, assistant professor of medicine
- Charles Gabbert, MD, Medical Director; Advanced Endoscopist, UPMC St. Margaret Gastrointestinal Lab & Procedure Unit

Case Presentation: When the Liver Fails

An 18-year-old female with no significant past medical history presented with one week of general malaise, nausea, vomiting, and jaundice. Aside from intermittent migraines, for which she takes sumatriptan as needed, she was in her usual state of health up until presentation. She took no other medications regularly. She endorsed occasional alcohol use but denied tobacco use or illicit drugs. She had recently self-quarantined for possible COVID-19 exposure but never developed symptoms.



Nelson Valentin, MD, MSc
UPMC Gastroenterology Fellow, Year II

At her initial presentation, her blood work and liver function tests were notable for a total bilirubin of 15.7 mg/dL and direct bilirubin of 8.9 mg/dL, ALT 9 IU/L, AST 115 IU/L, ALP 18 IU/L. Within 48 hours of presentation, her blood work worsened with a total bilirubin of 44.4 mg/dL, ALT <5 IU/L, AST 95 IU/L, ALP 10 IU/L. In addition, her evaluation was notable for Coombs-negative hemolytic anemia, low ceruloplasmin, and coagulopathy with an INR of 2.5. Her mental status remained intact, but she exhibited asterixis. A comprehensive viral serology workup was negative. She underwent a right upper quadrant ultrasound, with Dopplers showing a normal liver with patent hepatic vessels. A contrasted CT abdomen and pelvis showed a normal liver with mild splenomegaly. Given concerns for acute liver failure, she was transferred to a tertiary center for an expedited liver transplant evaluation.

What are the next steps?

This patient was diagnosed with Wilson's disease (WD), a rare, genetic disorder that causes excessive copper accumulation in the liver, brain, and other organs. Normal copper intake is 2-5 mg/day, of which 40%-60% is absorbed by the stomach and duodenum via portal circulation. The copper is mainly bound to ceruloplasmin in the liver. Ceruloplasmin-bound copper is secreted into the plasma where it plays a major role in Fe²⁺ oxidation in plasma. After the ceruloplasmin is broken down, unbound copper binds to bile proteins and is excreted in bile.

In Wilson's disease, there is a mutation in the ATP7B gene that encodes a copper transport ATPase. This leads to issues with incorporating the copper in ceruloplasmin, as well as the liver's ability to excrete copper in bile. Clinical features can be highly variable and can range from

asymptomatic to acute liver failure. There is a wide age spectrum of involvement between five and 55 years of age, with neurologic manifestations more common in later disease. Kayser-Fleischer (KF) eye rings are present in only 40%-60% of patients and usually present with concomitant liver disease. See **Figure 1** for a diagnostic template to support Wilson's disease treatment paradigms.

Patients will typically require chelator treatments for one to five years before going on maintenance therapy. Pharmacological therapy may include chelating therapies, such as D-penicillamine or trientine, or zinc. Neurological deterioration can occur with side effects such as fever, rash, aplastic anemia and other blood disorders, retinitis, gastritis, and possible changes in immune function. Switching to zinc monotherapy for maintenance can be beneficial, since zinc may be more specific to binding copper than chelators. Patients should avoid copper-enriched foods, such as shellfish, chocolate, mushrooms, etc. Patients typically require lifelong maintenance therapy, and treatment monitoring should be performed at least twice per year.

In patients with Wilson's disease, progression to acute liver failure (ALF) is rare and accounts for only 2%-3% of all U.S. ALF cases. However, ALF can be the first presentation of the disease, especially in young patients. Early identification is critical, since fulminant Wilson's disease is considered fatal without liver transplantation. As such, patients with fulminant Wilson's disease qualify as status 1A for liver transplantation as per UNOS criteria. Please see **Figure 2** for a diagnostic approach to fulminant Wilson's disease.

Conclusions

Our patient met criteria for fulminant Wilson’s disease given her presentation and laboratory findings highly suggestive of WD. She was listed as a status 1A for liver transplantation within 24 hours of presentation to UPMC. The patient received an offer within 24 hours and was transplanted four days after initial presentation. The liver explant had copper deposition consistent with WD. The patient was treated with five doses of penicillamine after transplantation, and her postoperative course was without complications. Following basiliximab induction and a routine steroid taper, the patient was started on tacrolimus and mycophenolate mofetil. The patient was discharged home on postoperative day nine.

Wilson’s disease is a rare cause of ALF in the United States, but a high clinical suspicion is warranted. Fulminant Wilson’s disease is fatal without liver transplantation. In many cases, serum copper and 24-hour urinary excretion of copper may not be readily available, so practitioners need to rely on other clinical features. Medical professionals should consider Wilson’s disease if a young patient presents with very high

bilirubin and low ALP (typically <40 IU/L) in the absence of other indicators. Fulminant Wilson’s disease qualifies as a status 1A priority listing for UNOS, and liver transplantation is curative for Wilson’s disease.

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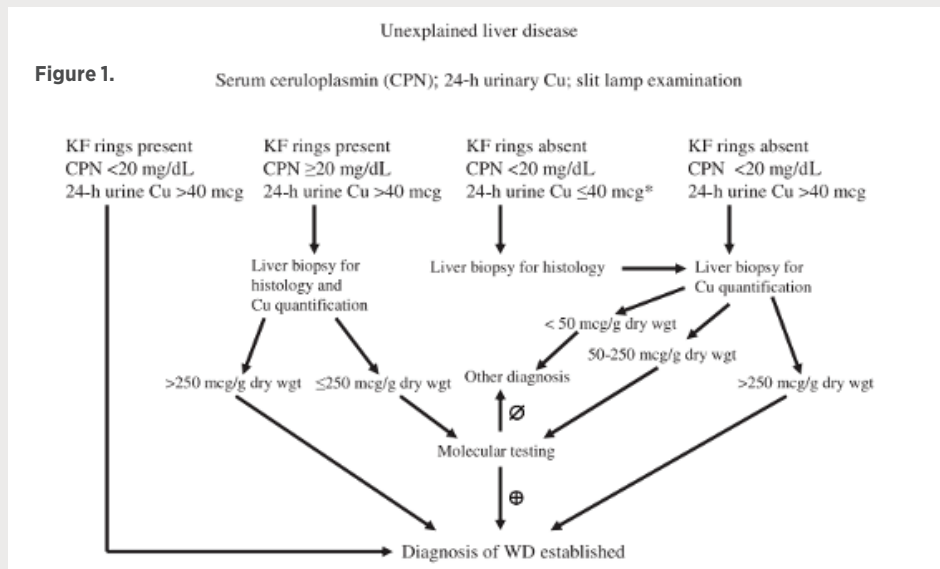
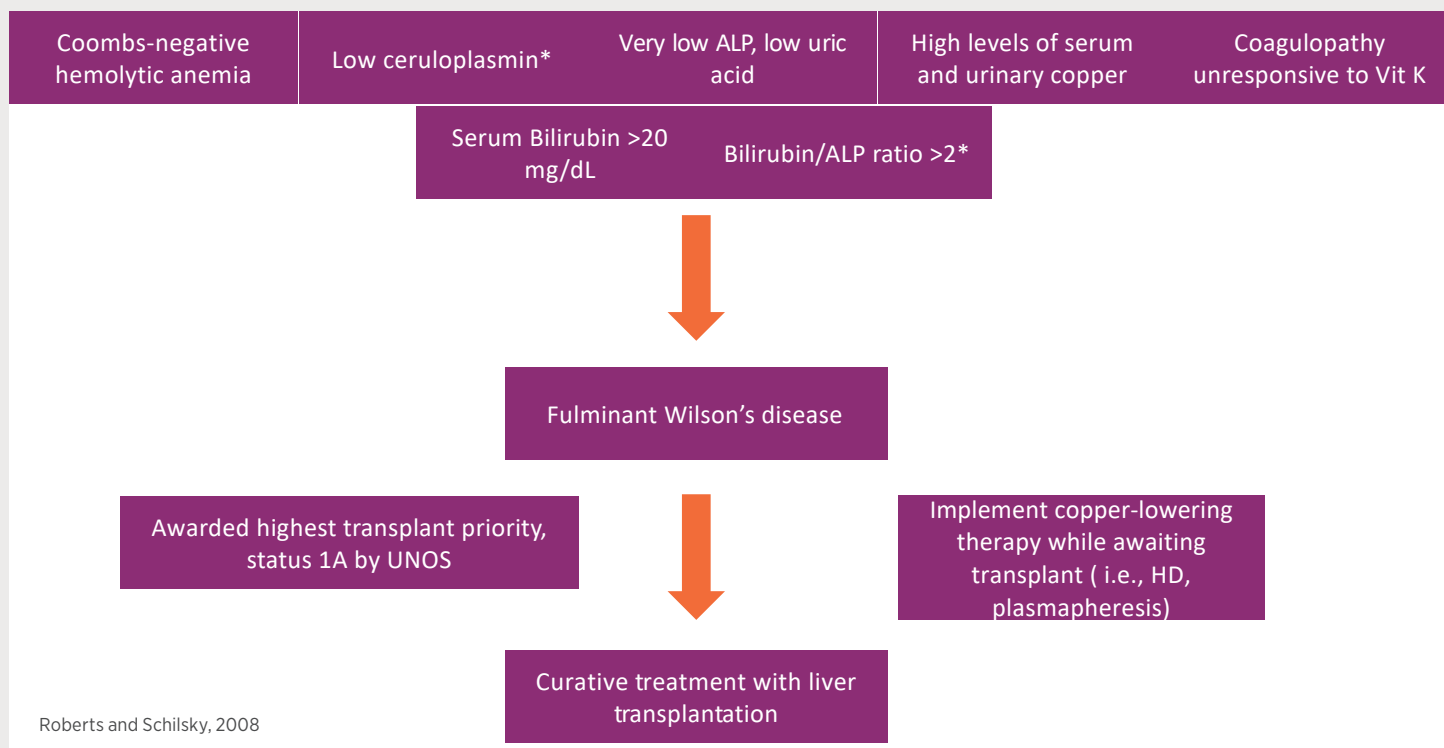


Figure 2.



ABOUT THE UPMC DIVISION OF GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

The Division of Gastroenterology, Hepatology and Nutrition is one of the leading centers for gastrointestinal clinical care and research in the country.

The UPMC Digestive Disorders Center is a comprehensive care program for patients that covers the full range of digestive health conditions, including:

- Inflammatory Bowel Diseases
- Cancer Prevention and Treatment
- Functional Bowel Disorders
- Hepatic Disorders and Diseases
- Pancreatic and Biliary Diseases
- Nutrition Support

The Division also includes seven Centers of Excellence that provide specialized care for complex cases and conduct research on numerous fronts to better understand, and develop treatments for, disorders and diseases of the gastrointestinal and related systems.

Centers of Excellence

- Pancreas and Biliary Center
- Center for Liver Diseases
- Center for Intestinal Health and Nutrition Support
- Center for Women's Digestive Health
- IBD Center and UPMC Total Care-IBD
- GI Cancer Prevention and Treatment Center
- Neurogastroenterology and Motility Center

To learn more about the UPMC Division of Gastroenterology, Hepatology and Nutrition, please visit UPMCPhysicianResources.com/GI.

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About UPMC

A \$23 billion health care provider and insurer, Pittsburgh-based UPMC is inventing new models of patient-centered, cost-effective, accountable care. The largest nongovernmental employer in Pennsylvania, UPMC integrates 92,000 employees, 40 hospitals, 800 doctors' offices and outpatient sites, and a more than 4 million-member Insurance Services Division, the largest medical insurer in western Pennsylvania. In the most recent fiscal year, UPMC contributed \$1.7 billion in benefits to its communities, including more care to the region's most vulnerable citizens than any other health care institution, and paid more than \$900 million in federal, state, and local taxes. Working in close collaboration with the University of Pittsburgh Schools of the Health Sciences, UPMC shares its clinical, managerial, and technological skills worldwide through its innovation and commercialization arm, UPMC Enterprises, and through UPMC International. *U.S. News* consistently ranks UPMC Presbyterian Shadyside among the nation's best hospitals in many specialties and ranks UPMC Children's Hospital of Pittsburgh on its Honor Roll of America's Best Children's Hospitals. For more information, go to UPMC.com.