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### DIGESTIVE HEALTH QUARTERLY

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Our mission is to improve the health and well-being of each person we serve. This newsletter is brought to you by the Swedish Digestive Health Institute with the aim of increasing knowledge and understanding of digestive health, innovations, and treatments, to ensure health for a better world.

## The epigenetics of obesity



Fran Broyles, M.D.

Obesity and diabetes may yet be the greatest chronic disease epidemic in the history of human existence. Since 1975, the global obesity rate has almost tripled according to the World Health Organization. By 2030, nearly 50% of adults in the U.S. will have obesity.<sup>1</sup>

Modern life has changed the way we eat, sleep, work and move. But the rise of high-calorie diets and sedentary lifestyles doesn't fully explain why so many more patients are facing increased risks of metabolic diseases and other comorbidities of obesity.

A genetic component to obesity offers a partial explanation, but it typically takes more than a generation for such a dramatic change to occur. Another culprit has emerged in the epigenome, the structure which controls how our DNA is expressed.

### Directions for the directions

Once you receive your genetic code from your parents, you're pretty much stuck with it. Mutations accumulate over time—sometimes with dire consequences like cancer—but generally you keep the genes you've been given.

But on top of our genome is another structure called the epigenome made up of molecules and proteins that stick to DNA structures or modify the histone proteins that keep them

*(continued on page 2)*

## NEWS AND EVENTS

### Save the date for the 10th Annual Swedish & Providence Nurses Endoscopy conference — Saturday, January 29th, 2022.

- Registration is coming soon!
- Current plans for a hybrid conference both in-person and virtual options.

### Observances

- **Celiac Awareness - September 13th** - A day that is dedicated to creating awareness about Celiac disease, an autoimmune disorder that impacts approximately 3 million Americans.
- **Childhood obesity month - September, 2021** - Currently 1 in 5 children has obesity and are at risk for other chronic health conditions.

September is dedicated to creating awareness and promoting healthy growth to prevent obesity.

- **GERD Awareness - November 21-27** - Gastroesophageal disease, or GERD is a fairly common condition affecting 18-28% of Americans. This week is dedicated educating individuals and providers about GERD and treatment options.
- **Diabetes Awareness Month - November, 2021** - Every November is a time to educate and to provide resources for individuals with diabetes. Millions of people are living with diabetes, and this is a chance to generate awareness for the growing epidemic.

## The epigenetics of obesity (continued)

organized. From the Greek *epi* for over or upon, the epigenome controls how genetic information is expressed in each person's body. At any given time, only a part of your genes are turned on and are actively providing the instructions to make proteins. That's because the epigenome blocks expression of some genes, and boosts others.

The way that your genetic code is expressed can change over time due to your environment, your lifestyle, and even your parents' lifestyle. This flexibility allows organisms to change within one generation and take on new traits that are presumed to be advantageous in future environments.

But when environment changes again those epigenetic alterations may become maladaptive. For example, studies of historical records during famines have shown a link between malnourished pregnant mothers and the next generation's adult body size and risk of diabetes.

### What parents might not realize they pass on

Along with a set of genes, parents also pass on epigenetic information to their children. For fathers, dietary choices can cause epigenetic changes in sperm that predisposes their children to obesity<sup>2</sup>. And while women produce a lifetime's worth of eggs in utero, their lifestyle and environment during pregnancy—particularly the first trimester—can also lead to an increased risk of obesity for their developing baby.

A mother who has obesity, excessive gestational weight gain, or disrupted sleep is more likely to give birth to a baby who will become overweight or obese and develop diabetes.<sup>34</sup> Smoking during pregnancy by either parent can also put children at risk for childhood obesity.<sup>5</sup>

### The changeable epigenome

Changes to the epigenome don't have to be permanent. New research suggests that treatments for obesity like nutrition changes, physical exercise, pharmacological treatment and bariatric surgery are enough to reverse epigenetic changes that promote obesity.<sup>6</sup> Not only can this type of intervention help patients, but it may improve the health of future generations.<sup>7</sup>

More research is needed to fully understand just how obesity treatments influence the epigenome to better treat patients, but the topic is rapidly gaining interest as a tool to curb the rise in obesity. And with next generation sequencing, the epigenome is more accessible to researchers than ever.

### The physician's perspective

At SDHI, endocrinologist Fran Broyles, M.D., and obesity medicine physician Enrica Basilico, M.D., want to spread the message about the link between epigenetic changes and obesity. In a field where obesity is often seen solely as a lifestyle choice, they want to encourage providers to consider that there are other factors out of the patient's control that contribute to obesity.

"Obesity is not a character flaw or a choice, it is a disease state," says Dr. Basilico. "This idea is a grave disservice to our patients and prevents us from treating obesity appropriately, aggressively and without judgement." "The more we understand about epigenetic change the more effective we will be in treating this disease."

Dr. Broyles adds "If you don't understand that there are other pieces of the picture, then you're not going to be able to have the compassion and the expertise to help people navigate out of it. We do not judge people with hypertension despite the fact that nutrition choices and activity impact it."

The prevalence of obesity makes this a critical issue for all providers, not just bariatric and endocrine specialists. All physicians play a vital role in treating and referring patients for obesity care. This will not just help them, but also future generations. ■

(continued on next page)

## PROFILE: Dr. Enrica Basilico

Dr. Enrica Basilico is board certified in both obesity medicine and internal medicine. She completed her undergraduate studies at the University of California Berkeley before going to medical school at New York University. She completed an internship in Obstetrics and Gynecology at New York Hospital Cornell Medical Center before returning to NYU for a residency in primary care where she was chosen to serve as the program's chief resident.

During her residency at NYU, she first developed her skills and interest in doctor-patient communication—which she believes is the cornerstone of any effective therapeutic relationship. After completing her chief residency, Dr. Basilico took her extensive training and skills to build her own practice in Manhattan.

Over the course of 20 years of internal medicine practice, she became increasingly drawn to the treatment of obesity which she saw affecting so many aspects of her patients' health and well-being. This strong commitment and interest led her to become a diplomate of the American Board of Obesity Medicine in 2018. Later, in 2020 she dedicated her focus to obesity medicine and was selected to become the Medical Director of Medical Weight Loss at the Swedish Bariatric Metabolic and Endocrine Center.

Since her time at Swedish, she has built a strong network of like-minded providers who are also committed to treating metabolic disorders. She feels fortunate to be part of a growing community of providers who are dedicated to treating patients with compassion. Dr. Basilico is passionate about working with people to help them reach their wellness goals. She works with her patients to effectively address the strong forces that promote weight gain. Her evidence-based approach focuses on addressing the biological factors affecting a person's metabolism, developing new sustainable habits, using anti-obesity medication when appropriate and creating plans that are tailored specifically to the individual. She works to help her patients find value-based motivation to improve their quality of life.

She feels privileged to live in Seattle and in her spare time she enjoys, cooking, spending time with her family and their pandemic puppy, and looks forward to traveling again. ■



### SWEDISH WEIGHT LOSS SERVICES

Our specialists evaluate patients for both surgical and non-surgical interventions depending on their unique needs. Patients will find compassionate care teams who provide expert care and support to help them live their healthiest lives. To learn more about the services of Swedish Weight Loss, please go to [swedish.org/wls](https://swedish.org/wls).

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## Beyond the scope: alternatives for colon cancer screening

Colonoscopy has long been considered the gold standard in screening for colon cancer. It's sensitive and specific, catching well over 90 percent of precancerous lesions and cancer. And because colonoscopy removes precancerous polyps, it can prevent cancer, not just diagnose it. But for those few people who can't—or won't—have a colonoscopy, there are options.

Screening matters because colon cancer is preventable and treatable with early detection. According to the *American Cancer Society*, the five-year survival rate for patients with localized colon cancer is 91 percent. With distant spread, only 14 percent survive. Colon cancer claims about 52,000 lives each year and is the third most common cause of cancer death in the U.S. Yet only 68.8 percent of adults were up to date with recommended screenings—and that was before the COVID pandemic. That means **nearly a third** aren't getting screened.

Dr. Nicholas Procaccini has been a gastroenterologist at Swedish for the past ten years. He screens between 600 and 700 patients for colon cancer in a typical year. "The vast majority of people can safely have a colonoscopy," he says.

Relatively rare contraindications include the inability to discontinue blood thinners, recent cardiac events, or other major medical issues. Patients with severe disabilities might find bowel prep especially burdensome. Patients with serious heart issues, and patients who do not have the support network to get a ride home, may not be good candidates because of sedation.

Admittedly, colonoscopies have drawbacks even for those who qualify: the inconvenience of the colon prep, the cost to insurance or the patient if self-paying (about \$2,200), and the (small) risk of perforation and other complications. And some patients just don't want a colonoscopy, says Procaccini. They may experience anxiety, embarrassment, or general hesitancy. In these cases, it helps to meet patients where they are. "While I prefer colonoscopy, and it's the form of screening I choose personally, it is important for reluctant patients to know there are other options," says Procaccini.

Since some screening is better than no screening, it's helpful to understand alternatives to colonoscopy. These include stool tests, a blood test, and a somewhat less-invasive imaging procedure. The tests vary widely in sensitivity, specificity, and cost. These options may allow

patients to avoid colonoscopy if they're healthy, but not if they have positive results. And there's always the risk of missing something.

### Cologuard

The colon regularly sheds its lining, including any precancerous or cancerous cells. Cologuard uses gene sequencing to detect the DNA of these altered cells (polyps or tumors). It's a stool test, with collection possible in the patient's home.

The test isn't appropriate for high-risk patients. Guidelines state that patients *should not use the test if* they have: a history of colorectal cancer, adenomas, or other related cancers; a positive result from another colorectal cancer screening test within the past six months; a condition that places them at high risk for colorectal cancer, including Inflammatory Bowel Disease (IBD), specific hereditary syndromes, or a family history of colorectal cancer. Those patients should go directly to colonoscopy.

The FDA approved Cologuard in 2014 based on a clinical trial (about 10,000 patients) called DeeP-C, published in the *NEJM*. The test's ability to detect cancer was comparable to colonoscopy, especially for early-stage disease.

Screening Method	Overall Cancer Detection	Early-Stage Cancer	Polyps w/ High-Grade Dysplasia
Cologuard	92.3%	94%	69.2%
FIT	73.8%	73.3%	46.2%
Screening Method	Serrated Sessile Polyps	False Positives	Cost
Cologuard	42.4%	13%	\$649
FIT	5.1%	5%	\$60

Table 1. Comparison of Cologuard to FIT in the DeeP-C Study

Cologuard didn't do as well at detecting precancers, however. That included polyps with high-grade dysplasia and serrated sessile polyps, sometimes known as the "*evil twin*" of cancer precursors for their tendency to become malignant. Procaccini notes that it's essential, when counseling patients, to distinguish between Cologuard's ability to detect cancer and its lesser ability to detect precancerous polyps.

## Beyond the scope: alternatives for colon cancer screening (continued)

Cologuard yields false positive and false negative results: 13 percent of people in the DeeP-C study without cancer or a precancerous polyp received a positive test result, and eight percent of people with cancer received a negative result.

If a patient has a positive Cologuard result, their physician should refer them for a colonoscopy. However, if the test is negative, the patient does not need a colonoscopy and can go another three years before repeating the test.

### FIT (Fecal Immunochemical Test)

FIT is the most commonly used fecal occult test and was the most accurate non-invasive option before Cologuard hit the market. FIT uses an *antibody* to human globin that does not cross-react with dietary meats, so patients don't have to change their diets before the test. While FIT has greater specificity than Cologuard and a lower rate of false positives, FIT is also significantly less sensitive than Cologuard for both cancer and precancerous cells. Providence and some other insurance plans recommend FIT (which is about a tenth the cost of Cologuard) because of its cost-effectiveness, and Swedish recommends use of FIT.

The FIT is commonly ordered by primary care physicians or gastroenterologists. If a patient has a positive FIT result, their physician should refer them for a colonoscopy. However, if the test is negative, no colonoscopy is indicated, and the test should be repeated in a year.



Nicholas Procaccini, M.D.

### Epigenetic Blood Test

The Methylated SEPT9 test has been available since 2016. It utilizes a blood draw, which some patients prefer to a stool sample. It uses PCR to seek epigenetic changes to a gene that codes for scaffolding proteins in cells. Colon cancer adds excess methyl groups to the Septin9 gene during cell division. However, SEPT9 testing only detects between 48 and 70 percent of colon cancers, with wide variance in clinical trials. It does not appear to be as sensitive as FIT for cancer detection. And it does not reliably detect precancerous lesions.

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## Focus on DHI Research

Caliberte AS, Brandabur JJ, Chang S-C, et al. Changes in Hemoglobin Levels in Patients with Hiatal Hernia and Anemia Demonstrates A Durable Resolution When Surgery Utilized. *Foregut*. 2021. DOI: 10.1177/26345161211025277

In this issue of the DHI newsletter, we highlighted the less common symptoms related to a hiatal hernia. Of these uncommon symptoms, anemia is one that requires some thought and attention. When anemia is identified at the primary care level, referral to GI medicine is frequently the next step in care to assess for the source of bleeding from the GI tract. An obvious source such as a cancer is often not found, and the only significant finding may be a hiatal hernia.

The purpose of this study was to describe the patterns of care in patients presenting with anemia and a hiatal

hernia with no other source of blood loss. Care and treatment across our institute and in the Swedish/ Providence system is widely varied. Medical therapy in the form of transfusion, iron and/or PPIs lead to resolution of the anemia in only 1/3 of patients. Although it is widely known that hiatal hernia repair will cure the anemia, many patients endured multiple other studies and medicines before referral to surgery which took a median of 454 days with an interquartile range of 129-1332 days.

Surgery led to improved quality of life but also cure of the anemia in almost 75% of patients. The presence of Cameron's ulcers which is frequently a reason for referral lead to resolution in 85% but even when these ulcers were not found, the anemia resolved in over 62%. We encourage our readers to consider this as a possible mechanism for anemia with prompt referral to resolve the anemia. ■

## Atypical symptoms of hiatal hernias

Most physicians know that acid reflux is the most frequent symptom associated with a hiatal hernia. Sometimes, however, hiatal hernias can present with atypical symptoms—and without the classic symptoms of GERD. Patients can experience these symptoms for years, confusing physicians and patients alike. Some patients assume they will always feel like this.

**Table 1: Some Non-GERD Symptoms of Hiatal Hernias**

Anemia	Early satiety	Postprandial nausea
Bloating	Exaggerated digestive sounds	Shortness of breath
Chest or back pain	Excessive belching	Upper abdominal pain
Cough	Hoarseness	Vocal fatigue
Difficulty swallowing	Lowered vocal range	

Non-GERD or atypical symptoms of hiatal hernias can include early satiety, shortness of breath, anemia, difficulty swallowing, and chest or back pain after eating. Positional changes (such as bending over) may worsen the pain and shortness of breath.

Patients with large hiatal hernias may experience exaggerated digestive sounds and excessive belching. Food and liquid getting caught while moving through the herniated portion of the stomach, forming a bolus. The resulting backup can produce chest pressure, discomfort, and pain as the bolus slows through the hernia. Belching happens when ingested air is trapped within the hernia and may provide temporary relief from symptoms.

Some symptoms are less obviously related to hernias. “We see a lot of patients with a cough. Also throat symptoms, voice fatigue,” says Dr. Alex Farivar, a thoracic surgeon at Swedish since 2009 and a leader in the Foregut surgery program. About 15 percent of the patients Farivar treats for hiatal hernias present without classic reflux symptoms. Farivar likes a challenge and went into thoracic surgery in part because he enjoys the complexity of the work.

Diagnosing hernias presenting with non-GERD symptoms is a challenge that involves tests to rule in or rule out competing diagnoses and often requires collaboration across multiple specialties, including gastroenterology, thoracic surgery, ENT, and pulmonary.

When a patient has a large hiatal hernia, a substantial portion of the stomach moves into the chest cavity. As the stomach rubs against the crura of the diaphragm, it can irritate the wall of the stomach, leading to Cameron’s ulcers. Bleeding from Cameron’s ulcers leads to the *anemia* mentioned above when chronic and slow, or upper GI bleeding when brisker. “Even if Cameron’s ulcers are not visible on endoscopy, large hernias can still cause and be associated with chronic anemia,” says Farivar. Unexplained, difficult-to-treat anemia should trigger endoscopy and possible referral to a thoracic surgeon, Farivar says.

To make things more complicated, shortness of breath, another non-GERD hernia symptom, is sometimes *caused by chronic anemia*. Shortness of breath is one of the most challenging symptoms to attribute directly to a hernia, says Farivar. A workup for shortness of breath may include pulmonary function tests and CT scans to understand lung abnormalities.

### Testing, Testing

If a patient presents with throat problems but no known reflux, physicians may test their esophageal function. This is especially true if treatment of other diagnoses has not led to improvement, says Farivar. One of his most utilized tests is esophageal manometry. In this procedure, the physician passes a flexible tube containing pressure sensors through the patient’s nose into the esophagus. The sensors evaluate the pressure used by the esophagus in coordinating the passage of food down the throat.

Sometimes patients have **laryngopharyngeal** reflux, a silent form that affects the throat, including the part that contains the pharynx or “voice box.” Symptoms in those cases could include fatigue, hoarseness, or other changes to the voice. For example, Farivar says he sees several cases a year in which a patient’s vocal range has dropped lower. Farivar may order a 24-hour pH

## Atypical symptoms of hiatal hernias (continued)

impedance test to help detect laryngopharyngeal reflux. A pH impedance test can document both weakly- and non-acidic events and connect symptoms to these events.

A similar 24-hour test for the **hypopharynx** (excluding the esophagus) uses a device called *ResTech*. This test evaluates noncardiac chest pain and throat and lung symptoms. ResTech is minimally invasive and quite sensitive. A narrow catheter in the posterior oropharynx, above the upper esophageal sphincter, records pH values twice every second.

Suppose the results of these tests are abnormal. In that case, Farivar will often consult with colleagues in other specialties to assess the role of sinus problems and pulmonary disease in contributing to esophageal symptoms. "Often, a coordinated multi-specialty approach is needed," says Farivar.

Even if a patient does not present with classic GERD, reflux of acid and non-acid materials lower in the throat can cause chest pain, cough, hoarseness, pneumonitis, voice fatigue, and Barrett's esophagus. Barrett's esophagus is a known risk factor for esophageal cancer; about 10 to 15 percent of patients with Barrett's will develop esophageal cancer.

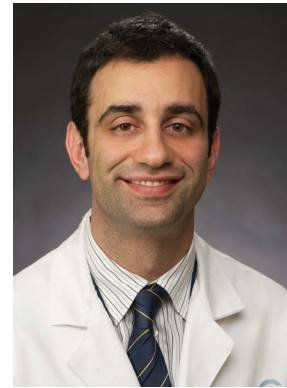
Some patients present with postprandial nausea, upper abdominal pain, and bloating. In those cases, says Farivar, "we'll do a more detailed evaluation for

gastroparesis," a condition in which the stomach muscles are less motile than usual. A gastric emptying study aids in this assessment.

All patients suspected of having a hiatal hernia receive an upper GI series, says Farivar, whether they complain of GERD or non-GERD symptoms. For those who have significant dysphagia, he generally adds a timed barium swallow study.

Even in expert hands, a detailed history may not provide all the reassuring data physicians seek to disclose a link between a patient's symptoms and a hiatal hernia. In these cases, various tests can help understand changes in function that may point to a hernia.

When patients have been appropriately assessed but fail to respond to conservative lifestyle changes and medications, minimally invasive surgery could fix the hernia and improve the patient's quality of life. "It is not uncommon to hear patients who ultimately decide on surgery say that they wish they had done something more for the past ten years," Farivar says. ■



Alex Farivar, M.D.

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## Beyond the scope: alternatives for colon cancer screening (continued)

### Virtual Colonoscopy

Virtual colonoscopy, or colonography, is *less invasive* than colonoscopy but more invasive than a stool or blood test. It uses a CT scan to show cross-sections of the colon. The images are digitally combined and manipulated. The result is a 3-D view of the inside of the colon, similar to a topographic map.

Virtual colonoscopy is good at catching large polyps but less effective at detecting small ones. Virtual colonoscopy also has a 14 percent false-positive rate. Procaccini adds that virtual colonoscopy has particular trouble finding flat polyps. In the topography of the colon, slight rises are more challenging to spot than steep hills.

The procedure requires bowel prep similar to that for colonoscopy, plus patients must ingest a small amount of barium. A tube is inserted into the rectum to inflate the bowel with air or carbon dioxide during the procedure.

It can be uncomfortable since patients are not sedated. Procaccini says this is a “rarely used” procedure.

### Changing Landscape

While new technologies have emerged in colon cancer screening, guidelines have changed regarding age at first colonoscopy. According to the American Cancer Society, adults at average risk for colon cancer should begin screenings at age 45 rather than 50. One reason for the change is that the incidence of colon cancer in people ages 20 to 49 has increased 55 percent in the past twenty years.

Procaccini notes that if everyone age 45 and above received a colonoscopy at recommended intervals, there wouldn't be enough endoscopists to meet the demand. “There just aren't enough people,” he says. But with supplementation by non-invasive tests such as Cologuard and FIT, the overall screening rate could increase, saving patients' lives. ■