Digestive Disease Challenges
for the Community Clinician

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Montana Academy of Family Physicians
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The Digestive Health Institute of Montana (DHIM) is the gastroenterology health program of Kalispell Regional Healthcare and its constituent hospitals, Kalispell Regional Medical Center, The HealthCenter and North Valley Hospital. The mission of DHIM is to provide comprehensive, clinically-integrated, state of the art gastrointestinal medical care for the people of Montana and southern Canada. The corollary of this mission is to offer the clinicians regular, local and regional gastroenterology educational opportunities. DHIM consists of twelve talented digestive health specialists: William Cobell MD, Nicholas Costrini MD, PhD, Ramon Generoso MD, Craig Harrison MD, Philip Jaffe MD, Juergen Mueller MD, PhD, Howard Tice MD, Shana Carter ANP, Tessa Skotnicki, PA, Carrie Thompson ANP, Thomas Flass MD (pediatric GI), Daniel Lustig MD (pediatric GI), and Kimberly Longcake ANP (pediatric GI).

The HealthCenter and Kalispell Regional Healthcare have committed substantial and necessary funds for the construction of DHIM’s new principal clinical, endoscopic, and educational workplace. This 27,000 square foot facility will provide local and traveling patients with a quality and comfortable, full service destination for all adult and pediatric digestive health care needs. The DHIM’s gastroenterology clinicians, technical staff, and abundant endoscopic facilities support colonoscopy and EGD procedures, advanced ERCP, endoscopic ultrasound, esophageal disease management (i.e. reflux, Barrett’s metaplasia, endoscopic mucosal resection and motility), small bowel disease management with particular emphasis on inflammatory bowel disease, capsule endoscopy and single balloon panendoscopy. Fecal microbiome transplant care for recurrent C. difficile colitis is available at DHIM.

The new Kalispell main campus Institute building will be completed in early 2018 and will serve as the beacon for clinical and academic services to patients and to Montana and regional clinicians. Beyond the main campus, the Institute supports adult and pediatric clinics in numerous cities in Western and central Montana. In addition, the Institute provides physician education and clinical research programs. The DHIM program entitled Hot Topics in Gastroenterology is the outreach effort designed to support the high quality work of Montana and southern Canadian clinicians. The clinicians and staff of the Digestive Health Institute of Montana look forward to supporting you and your patients. Phone numbers to call to facilitate time-sensitive patient care:

- Digestive Health Institute of Montana .................................................406-752-7441
- Dr. Costrini, Program Director ..........................................................406-300-2524 (cell)
- Dr. Jaffe, Director of Clinical & Endoscopy Services .....................406-309-4237 (cell)
- Pediatric On Call Physician .................................................................406-278-1288

Once you make contact with us, we will work cooperatively with you to provide the cohesive communications you and your patients depend on to achieve the best possible care. Thank you for your support of the Digestive Health Institute of Montana.

Nicholas V. Costrini, MD PhD MBA, Program Director
Colorectal Screening Strategies for 2017

The Two Most Important Developments in Colorectal Cancer Screening:

1. Strategy for Screening
2. Quality Measures and High Risk Lesions of Colonoscopy

One of the greatest responsibilities and privileges of medical care is the prevention of disease rather than management of disease which has already afflicted our patients. Whether from a desire to improve cost efficiency, reduce disease burden, or minimize pain and suffering, it is clear that colorectal cancer (CRC) screening improves statistics for disease prevention and death from CRC. Over the past several years, substantial progress has been made in assessing the merits, risks, and basis for selection of various screening studies. In this unit we will discuss the options available and the advances in our understanding of these options. Additionally, we will discuss the important changes in colonoscopy.

Two substantial changes are taking place regarding the disposition for physicians as they select screening studies and define their value. Over the past decade, the first and most dramatic event has been the shift from discussing the best screening exam to relating that any screening test is better than none. The US Preventative Services Task Force recommendations were released in June 2016 (JAMA 315 (23):2564-2575, 2016.) Compared to their recommendations of 2008, the change in disposition is rather dramatic. The single most important observation is that 30-40% of Americans are not screened and this represents the biggest deficit in this health care matter. The US Preventative Services Task Force (US PSTF) concludes that the single greatest improvement in colon cancer control will be achieved by screening Americans with any test that citizens will accept. In addition, the US PSTF adds that there are no head to head studies demonstrating that any of the screening strategies it considered are dramatically more effective than others although the tests have varying levels of evidence supporting their effectiveness as well as different strengths and limitations. According to the report, the goal of the healthcare community “is to maximize the total number of persons who are screened because that will have the largest effect on reducing colon cancer deaths.”

The second change allows us to ask if colonoscopy is still the “gold standard” for screening. The USPSTF reported a benefit, harms, and burden assessment for the following screening strategies: flexible sigmoidoscopy every five years, FIT–DNA every three years, FIT every year, CT colonography every five years, flexible sigmoidoscopy every decade plus FIT annually, FIT–DNA every year, and colonoscopy every decade. FIT refers to fecal immunologic stool testing for human hemoglobin and DNA refers to stool testing for DNA mutations shed from neoplastic colorectal growth. It is recommended that patients be studied for screening from age 50 through a 75 years of age; a value for screening from 75-85 years is present but diminished; screening is not recommended after age 85. The computer-generated value of these tests was defined in association with data from the Cancer Intervention and Surveillance Modeling Network (CISNET) models. These modeling studies offered the following observations:

1. The life-years gained per 1000 individuals screened were fairly comparable among most strategies. For example, flexible sigmoidoscopy every five years gains 221 life-years versus colonoscopy at 270 life-years gained. Similarly, the colorectal cancer deaths averted per thousand individuals screened varied only slightly. Twenty colorectal deaths are averted per thousand individuals screened by flexible
sigmoidoscopy every five years while colonoscopy every ten years averts twenty-four deaths per thousand individuals screened; these results are different but not dramatically so.

2. The USPSTF did not conclude that all strategies were equal (fida infra.) From computer modeling, all of the strategies, if completed as recommended, will save roughly the same number of lives per thousand people screened. FIT–DNA every year is only somewhat less efficient than colonoscopy every ten years in terms of life years gained or cancer deaths averted.

3. In additional studies, the harms associated with these two strategies are also nearly identical because frequent colonoscopy will be required to manage both true and false positive FIT as well as the true and false positive DNA screening tests. In the modeling studies it is rather dramatic to note that the FIT–DNA strategy will still require nearly 70% of the colonoscopy burden that accrues from the colonoscopy every ten year strategy because of necessary and unnecessary follow-up of results of this non-invasive strategy. The current (Cologuard) stool DNA test includes its own quantitative FIT test.

4. Regarding the strategy of computed tomography colonography (CTC or “virtual” colonoscopy) the task force reported that CTC offered life-years gained per thousand individuals in the range of the other strategies. Similarly, colorectal cancer deaths averted is the same for CTC every five years as with other strategies. When considering the possible harms associated with CTC, the task force noted that because of follow-up colonoscopies needed and because of follow-up for extra colonic findings, the level of harm was significant. CTC sensitivity to detect adenomas measuring 10 mm or larger ranges from 67% to 94%. A bowel prep is required for these levels of sensitivity. Extra colonic findings detected on CTC are common, occurring in 40-70% of screening tests. Five to 30% of these extra colonic findings require diagnostic follow-up. Given the frequency with which incidental findings occurred during CTC, it is difficult to accurately understand the overall balance of benefits and harms from this screening test strategy.

In the computer modeling systems of colon cancer screening strategies, seven are listed but not prioritized. While all are stated as acceptable, they are not equal. There is the concept of “the efficient frontier.” The frontier is a line connecting the strategies with the highest expected gain in life-years per colonoscopy performed. Of the seven strategies, four were efficient (colonoscopy, FIT, CTC, and FIT+FS). One (FIT-DNA) was nearly efficient and two (guaiac testing for occult blood and flexible sigmoidoscopy alone) while included in the strategies list, were concluded to be less effective (i.e. inefficient) when measuring life-years gained.

Screening for colorectal cancer is substantially under used. In addition, there are no empiric data to suggest that any one of the strategies provides a greater net benefit. Accordingly, the best screening test is the one that gets done and the US PSTF concludes that maximizing the total proportion of the eligible population that received screening will result in the greatest reduction in colorectal cancer death. This global recommendation to “get screened by any means possible” differs considerably from recommendations provided by specialty organizations such as the American College of Radiology, the American Cancer Society, the American Gastroenterological Association, and the American College of Gastroenterology. The American College of Gastroenterology recommends a colonoscopy every ten years as a single
preferred screening strategy. If that test is not available or unacceptable, the other strategies can be considered. A similar recommendation was made in 2012 by the National Comprehensive Cancer Network. In 2015 the American College of Physicians recommended that average risk adults ages 50-75 be screened for colorectal cancer by one of four strategies: (1) annual Hemoccult testing or FIT, (2) flexible sigmoidoscopy every five years, (3) high-sensitivity fecal occult blood testing or FIT every three years plus flexible sigmoidoscopy every five years, (4) or colonoscopy every ten years. Finally, in 2016 the Canadian Task Force on Preventative Healthcare recommended that adults age 50-74 be screened for colorectal cancer with fecal occult blood testing (FOBT) every two years or flexible sigmoidoscopy every ten years. It recommended against screening patients over age 75 or using colonoscopy as a primary screening test.

The second topic of this unit is specific to colonoscopy screening and relates to quality measures for colonoscopy and the more important lesions being defined. In broad terms it is the opinion of many experts that colonoscopy is being applied too frequently to those who do not require such surveillance and less frequently to those patients at higher risk. The quality measures and the high risk findings requiring closer follow up are discussed below.

Over the past decade, the process of colonoscopy, whether it is completed for screening or diagnostic purposes, is more likely to achieve the planned objective - preventing cancer or defining the symptomatic pathology if specific quality measures are met:

1. Quality bowel preparation
2. Completion of the exam to the level of the visualized appendiceal orifice
3. Mean withdrawal time of more than six minutes (excluding interventions)
4. Adenoma detection rates exceeding 25%
5. Identification of sessile serrated adenoma and appropriate monitoring
6. Identification of the high-risk (advanced adenoma) colonoscopy findings and appropriate monitoring

THE MOST IMPORTANT COLONOSCOPY IS THE FIRST ONE

1. Quality bowel preparation has come to the forefront as being singularly significant in completing a satisfactory colonoscopy. There are several bowel preparations available and there are several systems for measuring the effectiveness of the bowel prep. A recent study reporting the relationship between the bowel prep and the identification of adenomatous polyps confirms that as the bowel prep becomes less effective the likelihood of missing adenomatous lesions rises. The Boston Bowel Preparation System (BBPS) grades the right, transverse, and left colon with three levels of clarity with a maximum score of nine. As scores fall below six or seven, adenomatous lesions are missed. If the bowel preparation is less than acceptable, BBPS seven or less, it is reasonable and appropriate to accept the endoscopy as less than satisfactory and schedule a repeat colonoscopy in perhaps two to three years. A variety of methods are used to inform the patient of the significance of the bowel preparation including phone calls, presented literature, and now apps for cell phones. The most significant approach to gaining patients’ cooperation and attentiveness to the bowel prep is to inform them that if the bowel prep is less than ideal, an early follow-up exam will be required. Factors which contribute to less than ideal prep include older age group, obesity, alcohol and other drug use,
narcotic use, and multiple comorbidities. Some of these factors may be included in thought processes used to determine if colonoscopy is the correct approach for specific patients.

2. **Completion of the exam.** Colonoscopy to the cecum has always been the objective. However, at the present time the issue has become more concerning and photography of the appendiceal orifice is a quality measure of significance because this is one of the leading zones for missed lesions leading to interval cancer in the proximal cecum perhaps partly hidden by the ileocecal valve. Thus visualizing the ileocecal valve from the junction of the right colon and cecum is no longer satisfactory. Additionally, interval cancers and sessile serrated adenomas are more prominent in the cecum and right colon leading to requirement of greater attentiveness to this area at colonoscopy.

3. **Endoscopic withdrawal time.** The six minute interval refers to the mean time. It also refers to the time of removal of the endoscope with excellent visualization in all four quadrants of a segment of colon independent of intervention time (i.e. biopsies or polyp removal). Multiple studies have confirmed this particular quality measure. Adenoma detection rate falls when withdrawal time falls. Patience is required by all endoscopists.

4. **Adenoma detection rate (ADR)** has come to the forefront of quality endoscopy over the past decade. This particular quality measure is probably one of the most important. Clinical studies have revealed that adenoma detection rates below 15% are associated with a higher incidence of interval malignancy. An interesting point here relates to what is actually the upper limit of the adenoma detection rate. In a very interesting study of patients known to have positive stool DNA screening exams, the follow-up adenoma detection rate approached 50%. In general, diagnostic colonoscopy reveals more pathology than screening colonoscopy. An additional important fact, is that diagnostic colonoscopy is significantly more risky (i.e. associated with more complications) than screening colonoscopy. An ADR of 25% is probably a reasonable but nonetheless probably less than ideal threshold for adequacy of colonoscopy.

5.,6. **Identification of sessile serrated adenoma and high risk adenoma.** While identification of the adenoma and the ADR quality measure are of significance, there is a newer concept which identifies high risk polyps that may require more substantial surveillance. The “high risk adenoma” alternatively known as the “advanced adenoma” has become in some ways the surrogate marker pathology for increased potential for malignancy. This has not been substantiated but is now considered a working hypothesis. The advanced adenoma characteristics include:

- Size greater than 10 mm
- Villous features in more than 25% of the lesion
- High-grade dysplasia
- 3-10 adenomas of any size and a single exam
- Sessile serrated adenoma

If advanced adenomas are lesions of significant interest at colonoscopy rather than the random tubular adenoma, screening for advanced adenoma takes on a new perspective. The ability to define advanced adenoma is three times more effective with colonoscopy than with FIT testing or stool DNA testing. Advanced adenoma findings also have implications for surveillance. The advanced adenoma at index exam means a higher risk for advanced adenoma at later
Unit 1: Colorectal Screening Strategies for 2017

Most significantly, however, cancer at follow-up of advanced adenomas is still in the range of less-interesting screening and surveillance findings. Importantly, after a negative follow-up exam subsequent exams are less likely to reveal advanced adenomatous adenoma; follow-up examination in 3-5 years is recommended.

A few comments about the interval cancer are in order. An interval cancer is one that is detected between scheduled surveillance colonoscopies. It probably occurs in 2-9% of all patients screened. More often these lesions are proximal. If they are found within one year, it is more often related to a missed adenoma or, importantly, partial removal of an adenoma. Approximately 25% of interval cancers are found at the site or in the near vicinity of a partially removed polyp. Because interval cancers tend to occur more commonly in the right colon and cecum, there is some suggestion that because of their different embryologic origins, lesions of the right and left colon may develop via different neoplastic paths. Thus, it is not clear that all interval cancers are secondary to missed lesions. Additionally, interval cancers occur most commonly in the 3-5 year range following colonoscopy for screening or surveillance. Most significant factors in preventing interval cancers are the quality indices in colonoscopy. Colonoscopy must be accepted as an incompletely successful modality for the prevention of colon cancer. Therefore patient who present with gastrointestinal complaints referable to the colon at any time following colonoscopy should be offered diagnostic colonoscopy.

### Incidence of Colorectal Neoplasia In Patients Over 50 Years Old

<table>
<thead>
<tr>
<th>Disease</th>
<th>30-60%</th>
<th>20-53%</th>
<th>3.4-7.6%</th>
<th>0.2-0.6%</th>
<th>5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced Adenoma</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime Risk CRC</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>No Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Test</td>
<td>A</td>
</tr>
<tr>
<td>Negative Test</td>
<td>C</td>
</tr>
</tbody>
</table>

Sensitivity: $A/(A+C)$  probability that test will be positive when disease is present
Specificity: $D/(D+B)$  probability that test will be negative when disease is absent
PPV= $A/(A+B)$  probability that a positive test will predict disease
NPV= $D/(D+C)$  probability that a negative test predicts non-disease
Definition of the Advanced Adenoma

1. Size 10 mm or more
2. Villous features in 25% or more of lesion
3. High Grade Dysplasia
4. 3-10 adenomas of any size

ADVANCES IN COLORECTAL CANCER SCREENING

Risk of AA in 5 year Follow Up Based Upon Number of Polyps

<table>
<thead>
<tr>
<th>NCI</th>
<th>Index Adenomas</th>
<th>% AA at follow up</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td>8.6</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1.7</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>15.3</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>19.6</td>
</tr>
<tr>
<td>+5</td>
<td></td>
<td>24.1</td>
</tr>
<tr>
<td>VA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>2.4</td>
</tr>
<tr>
<td>1-2</td>
<td></td>
<td>4.6</td>
</tr>
<tr>
<td>3-More</td>
<td></td>
<td>11.9**</td>
</tr>
</tbody>
</table>

** Risk equals that of AA at index
ADVANCES IN COLORECTAL CANCER SCREENING

Rates of Detection of Advanced Adenomas and CRC by FIT, Stool DNA and Colonoscopy

Study 1 (Quintero et. al)

<table>
<thead>
<tr>
<th></th>
<th>Participants</th>
<th>AA (%)</th>
<th>Ca (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td>5,059</td>
<td>9.7 *</td>
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</tr>
<tr>
<td>FIT</td>
<td>10,507</td>
<td>2.4</td>
<td>0.3</td>
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</table>

Study 2 (Imperiale et. al)

<table>
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<th></th>
<th>Participants</th>
<th>AA (%)</th>
<th>Ca (%)</th>
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</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td>9,989</td>
<td>7.6</td>
<td>0.7</td>
</tr>
<tr>
<td>FIT</td>
<td>9,989</td>
<td>1.8 *</td>
<td>0.6</td>
</tr>
<tr>
<td>Stool DNA</td>
<td>9,989</td>
<td>3.2 *</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* statistically significant

ADVANCES IN COLORECTAL CANCER SCREENING

Results of Multiple Rounds of Surveillance (3-5 years)

<table>
<thead>
<tr>
<th>Index</th>
<th>1st Follow up</th>
<th>Risk AA 2nd Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRA</td>
<td>HRA</td>
<td>19.3</td>
</tr>
<tr>
<td>LRA</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>NONE</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>LRA</td>
<td>HRA</td>
<td>15.6</td>
</tr>
<tr>
<td>LRA</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>NONE</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>No Adenoma</td>
<td>HRA</td>
<td>11.5</td>
</tr>
<tr>
<td>LRA</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>NONE</td>
<td>3.1</td>
<td></td>
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</tbody>
</table>

HRA predicts HRA
**Surveillance Recommendations**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>1st Follow Up</th>
<th>2nd Follow Up</th>
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</thead>
<tbody>
<tr>
<td>LRA</td>
<td>HRA</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>LRA</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>NONE</td>
<td>10</td>
</tr>
<tr>
<td>HRA</td>
<td>HRA</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>LRA</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>NONE</td>
<td>5</td>
</tr>
</tbody>
</table>

**ADVANCES IN COLORECTAL CANCER SCREENING**

**Summary**

- Screening is proven to save lives
- We are screening some pts too much
- We are screening some pts too little
- Make the first screening the very best
- Pay close attention to prep, time, path
- Reduce the interval cancer rate
- Reduce risk factors
- Increase the availability of screening
Diagnosis and Management of *C. difficile* Infection

For every clinician there are those very “special” clinical events that perhaps lead to a specialty consideration, promote an even more serious awareness of what it means to be a physician, or in some situations remind us of how little we may know about a particular pathologic process and how ill-equipped we are to protect our patients. Commonly, in this last situation, the patient may succumb as we flail and then fail to alter natural history of a lethal disease. Such was my experience when I first evaluated a patient who presented with multiple comorbidities, severe diarrhea, and a flexible sigmoidoscopy revealing classical pseudomembranous colitis. That was in 1974. At that time we knew only that some antibiotics could promote this pathology. We were unaware of the significance of colonic microflora and specifically unaware of the role of *Clostridium difficile* infection and toxin. The patient was a debilitated, chronically ill, 80-year-old dialysis patient, receiving multiple antibiotics in and out of the hospital for decubitus ulcers and bacteremia. She was admitted with severe diarrhea, dehydration, mild abdominal distention, metabolic acidosis, leukocytosis and altered mental status. By today’s standard she would have been admitted to an intensive care unit. When I was in training (Barnes Hospital, Washington University School of Medicine, St. Louis, Missouri) intensive care units were just coming into vogue. House officers managed nearly all seriously ill patients on a medical floor. She had an unrelenting downhill course over the period of several days, developed irreversible septic shock and expired. Forty-three years later, several weeks ago, I saw a similar patient who was diagnosed by stool studies as having *Clostridium difficile* infection with toxin. She was not quite as ill as my patient of memory but had identical, moderately severe, pathognomonic findings at flexible sigmoidoscopy. Stool studies revealed that she had the “epidemic strain” of *C. difficile*, BI/NAP1-027 with tcdC gene mutation. She had had several relapses and I treated her with fecal microbiota transplantation (FMT). She was well in seventy-two hours.

The above patient histories provide much of the historical and current information regarding this most common nosocomial and community-acquired infection. An estimated 500,000 cases of *Clostridium difficile* infection (CDI) occur annually and as many as 30,000 deaths are attributed to CDI. Perhaps one-third of cases are community-acquired. As presented in the cases above, risk factors are: age, antibiotic exposure, co-morbidity, acid suppression, hospitalization or long-term health facility residence, IBD, cancer, and immunosuppression. For cases that are community-acquired, risk factors above are present but less robust. Oftentimes, these patients may have family members with the common risk factors. Regarding age as a risk factor, it is important to be most careful with the oldest patients. Beginning at age fifty and for each decade later, severity of disease and mortality rise incrementally. The pathogenesis of CDI is coming into focus. Four events are required: *acquisition* of *C. difficile* spores in a host with altered colonic bacterial microbiome, *spore germination* into vegetative forms, *production* of virulence factors—toxin A and B, and toxin *endocytosis* into intestinal enterocytes leading to the clinical and endoscopic events reported in the cases above. Over the past decades, CDI frequency and severity have increased. Part of the reason for this is certainly related to prescribing trends for antibiotics but also because of the evolution of more dangerous strains of *C. difficile*.

One strain which has gained notoriety is BI/NAP1/027. This strain produces more toxin A and B, produces an additional toxin (called binary toxin), and is more resistant to fluoroquinolone. We are unsure of the clinical impact of binary toxin. The dysfunctional gene,
tcdC, which normally controls toxin production, fails to do so leading to augmented toxin production. The resistance of BI/NAP1/027 to one of the most frequently prescribed antibiotic classes sets the stage for simultaneous alteration of the intestinal microbiome and unbridled proliferation of CDI. Probably one-third of CDI is now due to this more dangerous strain of *C. difficile*. However, currently management is not strain specific.

In patients who have an appropriate history and present clinically with diarrhea, testing for CDI is appropriate. It is not appropriate to test randomly or to test “for cure” as both toxin and organism may persist for more than a month after treatment and clinical improvement. Toxin AB enzyme immunoassay is available and reasonably sensitive and specific. However, the more sensitive and specific test is polymerase chain reaction (PCR) testing for *Clostridium difficile* toxin gene tcdB. If this test for toxigenic *C. difficile* is positive, no additional testing is needed. In some labs, toxin AB assay is a reflex test. These results promote appropriate clinical action. The PCR test reports the presence of toxigenic *C. difficile* but not the presence of active disease. If the patient is well, the test represents only an epidemiologic definition of the presence of the bacteria in the microbiome. If the patient is ill, it is considered the active pathogen. Clinical data and toxin test provide important corroborative information. For these reasons, bacteriology laboratories are advised to reject testing formed stool as well as to reject testing stool within seven days of a prior negative CDI test or within fourteen days of a prior positive test. (Hence do not submit stool for “confirmation” or for “tests for cure”).

Treatment programs are of both the old and the new variety. Metronidazole (500mg tid for ten to fourteen days) has been used for thirty years and is currently recommended for the very mild cases. Interestingly, there is no FDA approval for the use. If the disease is somewhat more aggressive, vancomycin 125mg qid for ten to fourteen days is recommended. In comparison trials, vancomycin has proven to be therapeutically superior. Solid vancomycin is expensive; the compounded liquid form is much less expensive and equally effective. If the patient has reversible risk factors, address them. Stop antacids, non-essential antibiotics, address home and hospital environment, and carefully monitor status of comorbidities. Another alternative for initial treatment of CDI is fidaxomicin 200mg bid for ten days (Commercial name *Dificid*) which was approved in 2011. It is more expensive but is associated with vancomycin-equivalent cure rates and a lower relapse rate. It is also less likely to promote vanomycin-resistant enterococci or Candida colonization. (L.S. Al-Jashaami, H. L. Dupont. Gastro. And Hep. 12(10):609-616,2016.)

After successful treatment of CDI, the risk of recurrence or re-infection is 25% or higher. Risk factors and symptoms are as in the initial episode in most cases. A second recurrence may occur in half the patients following the first recurrence. As the reason for recurrence is not drug resistance, treat a recurrence as was done for the initial episode. If metronidazole was given, do not repeat this drug due to risk of neuropathy. Vancomycin or fidaxomicin may be repeated. With ever-increasing frequency multiply-recurrent episodes of CDI have required attention. Programs include a long, tapering five-week course of vancomycin, intermittent or pulse doses of vancomycin for three weeks, fidaxomicin or rifaximin for two to three weeks. None of these programs has been uniformly successful. In patients who have had two or more recurrences, restoration of the colonic microbiome has been established as the most effective treatment of CDI. Fecal microbiota transplantation had been used in a few patients in the 1950’s and again in 1970. In the past decade it has become the standard of care for multiply recurrent CDI with a success rate in the 80-90%. It is cost-effective, less expensive than multiple courses of vancomycin, and can be given by nasogastric tube, small bowel infusion, colonoscopy, flexible
sigmoidoscopy, or by enema. Remarkably, the route and depth of application do not dramatically change efficacy. The rectal route is somewhat more effective than other routes. Donor stool must be cleared of pathogens but the physical care of the material seems not to matter. Stool may be fresh, frozen, freeze-dried, thawed for use, prepared in plastic pills, etc. In the past several years, stool banks, such as OpenBiome, have provided safe stool products which are made available to medical centers for treatment of CDI. The Digestive Health Institute and Kalispell Regional Medical Center regularly offer fecal microbiome transplant treatment usually via a flexible sigmoidoscopy or colonoscope with or without sedation. The procedure is safe, easy for patients and medical staff, and most importantly, is extremely effective. Patients are usually well within days. Research regarding immunology-based programs is on-going. The fully human IgG1 monoclonal antibody against toxin B, bezlotoxumab, commercial name Zinplava, has been approved by the FDA as an adjunctive treatment for CDI. When given IV in conjunction with standard of care antibiotics, the recurrence rate is reduced compared to that when treated with antibiotics alone. It is not widely used. There has been some concern regarding congestive heart failure. Active immunization programs are under investigation.
Advances in Acute Diverticulitis

It would seem that nearly every patient presenting to a medical facility with fever, left lower quadrant pain and leukocytosis has acute diverticulitis until proven otherwise. Since our time in medical school, moving the rock of understanding this disorder has not been easy. Advances have been impaired by a lack of new data and some of that general medical practice inertia fostering avoidance of legitimate advances. That notwithstanding, a substantial number of biologic, epidemiologic, and clinical observations have been made in the past five years that require all clinicians to reassess some of the basic questions regarding the diagnosis and management of this most common disorder.

Regarding pathophysiology, the idea that a nut gets caught in a diverticulum leading to inflammation, perforation, and then surgery requires a great deal of reappraisal. While the specific investigations are outside the margins of this presentation, the etiology of the diverticular pockets has genetic predisposition aspects (up to 40%) which have been defined by family studies, probable environmental, diet, and microbiome influences on the gut that occur with aging, and neuro-degenerative and muscular wall changes including a reduction in neurons in myenteric plexus, decreased glial cells promoting denervation hypersensitivity all fostering a high pressure environment in the colon leading to the production of diverticulosis. Some of this is speculative but it must prompt an awareness that the pathophysiology of diverticular disease and diverticulitis is far from the “nuts and bolts” concepts offered in our medical school pathophysiology lectures.

The evolution of thought processes with reference to risk factors, the role of diet in diverticulosis and diverticulitis remain unclear. While it is true that vegetarians have fewer attacks of diverticulitis, this may be because such individuals also have generally healthier lifestyles. In this regard, obesity, smoking and alcohol use are now considered risk factors for diverticulitis. The concept that nuts, popcorn, etc. may play a role in precipitating attacks of diverticulitis could not stand up in the data from the Health Professionals Follow-Up study published in 2008 (JAMA 300: 90 7–14, 2008.) Physical activity may actually reduce the incidence of diverticulitis. Compared to non-users, current users of aspirin and non-steroidal anti-inflammatory drugs have a modest but definable increased risk of developing acute diverticulitis. Smokers are at higher risk for first and subsequent attacks.

In the clinical arena, acute diverticulitis is a great impostor of other disorders. Common misinterpretations of the clinical signs and symptoms lead to misdiagnoses of community-acquired enteritis, IBD, ischemic bowel disease, volvulus, colorectal cancer, appendicitis, nephrolithiasis, ovarian cyst rupture, and pelvic inflammatory disease to name a few. One of the common errors in approaching the patient who may have diverticulitis is in consideration of that common symptom—left lower quadrant pain. While rectal bleeding is also a frequent complication of diverticular disease, it must be remembered that significant pain and concurrent rectal bleeding seldom co-occur in diverticulitis. If they do, acute gastroenteritis, inflammatory bowel disease, or ischemic colitis, or cancer is more likely. The time-honored triad of fever, abdominal pain, and leukocytosis are actually present in less than fifty-percent of patients who are found on CT scanning to have abscess or perforation. In this regard, the CT scan is, however, the principal test in establishing the presence of diverticulitis and its complications.
The management of patients with diverticulitis depends entirely on the severity of illness. Therefore the treatment must be individualized. The management of the most severe disease presenting with gross peritonitis and cardiovascular instability is dictated by the general concepts of operative management in the high risk patient. Surgical intervention in conjunction with cardiovascular stabilization and antibiotics remain generally unchanged. The exact surgical procedure, however, has changed over the past one hundred years. An original three-stage procedure as devised by Mayo Clinic surgeons in the 1920’s was replaced by a much less morbid two-stage procedure, Hartman’s pouch and diverting colostomy only to be replaced by a single stage surgical resection, primary anastomosis with or without diverting ileostomy. All of this may be accomplished with an open, laparoscopic or robotic approach depending on the expertise of the surgeon and the clinical status of the patient. In cases that are not obviously surgical catastrophes the management of diverticulitis has changed substantially. In recent years, an understanding of the role of infection versus inflammation and the awareness of the natural history of diverticulitis has led to considerable change in the disposition regarding antibiotics and elective surgery.

In order to have a useful presentation regarding the changes in suggested management of acute uncomplicated diverticulitis it is worthwhile to recall the general clinical classification of acute diverticulitis which is based on CT findings. (Ambrosetti, et. al. Br J Surg. 84:532-534, 1997.) The “Modified Hinchey” classification is as follows:

0. Mild clinical diverticulitis
   Ia. Colonic wall thickening/confined pericolonic inflammation
   Ib. Confined small (<5cm) pericolonic abscess
II. Pelvic, distant intra-abdominal, retroperitoneal abscess
III. Purulent peritonitis
IV. Fecal peritonitis

Patients who present with mild clinical diverticulitis who have no significant comorbidities can be managed quite conservatively. Patient’s may be started on a clear liquid diet, given mild analgesia, no antibiotics and followed clinically. They may be followed at home or hospitalized for a brief period depending on the overall clinical situation. Regarding antibiotics, studies from the Netherlands and a Cochran review have led the American Gastroenterological Association Institute (AGAI) to recommend that antibiotics in this situation should be used “selectively” rather than routinely. (Gastroenterology 149(7):1950-1976, 2015.) In view of the fact that in stage 0 and 1a antibiotics have not been shown to shorten hospital stay, change recurrence rates, or change risks of complications, and in light of the global plea for better stewardship of antibiotic use, mild diverticulitis may be managed as an inflammatory illness rather than a bacterial disease. Another common consideration in the management of acute diverticulitis is whether or not a colonoscopy is required to rule out other diagnoses and when should it be done. The AGAI recommends that a colonoscopy be done to rule out colon cancer if the patient has not had a recent high quality examination. This recommendation is based upon two considerations. First, the chance of finding cancer is low, perhaps 3-5%, and the risk of iatrogenic perforation seems real. If a colonoscopy is done, delay of 6-10 weeks is in order. Indeed, in that interval the continuation or resolution of symptoms will further qualify the diagnosis.

If patients have an attack of acute diverticulitis, what does the future hold? In contrast to historical perceptions, the reality is quite different. Following an initial episode, the risk of
another attack (20% in five year) and particularly a complicated (stage III-IV) attack (<5%) is quite different than previously thought. In the past, physicians and surgeons would advise patient to have an elective resection of the sigmoid colon in order to “prevent other attacks and particularly attacks that would lead to a colostomy.” Those eventualities are quite uncommon. Hence, it is no longer generally recommended that the patient undergo an elective resection following one or even more uncomplicated attacks of diverticulitis. The long-term adverse effects of sigmoid colon resection, mostly mild, may approach 20%. In addition, there is the issue of “location shift.” In this situation, the surgical resection is followed by another attack of diverticulitis above or below the primary anastomosis location. For all of the above reasons, elective surgical resection of the sigmoid colon no longer has evidence-based support.

In follow-up of an attack, what can be done to prevent future attacks? While we have some clarity regarding risk factors, little research has been done to assess the value of reversing these factors, i.e. weight loss, smoking cessation, etc. There is no evidence that probiotics or mesalamine-based medications help. Fiber may help. Rather, prevention of constipation may help.
One of the most frequent observations regarding the diagnosis of inflammatory bowel disease (IBD) is that it may take three to four months to diagnose ulcerative colitis and up to nine months to diagnose Crohn’s disease. The most common missed diagnosis for IBD is irritable bowel syndrome (IBS). While the disease processes are entirely different, there are some reasonable explanations as to why inflammatory bowel disease and for that matter irritable bowel syndrome are frequently misdiagnosed. Both disorders clearly differ in their pathology but we have learned that there may be indeed significant overlap.

They certainly overlap with regard to potential presentations. Irritable bowel syndrome (IBS) is a multifactorial disorder characterized by a specific set of clinical complaints currently thought to be brought about by the interaction of the central nervous system, the autonomic nervous system, the microflora of the GI tract, and dietary components. It is clearly non-inflammatory “functional pathology.” The term “functional pathology” should imply that the activity of the gut is disrupted and not necessarily the anatomy so as not to be confused with “structural pathology.”

In the case of IBS, patients may be bothered by diarrhea, constipation, abdominal pain, bloating to an extent that the patient’s quality of life is impaired. It is frequently stated that there are no “abnormal laboratory studies in patients with irritable bowel syndrome.” In fact that is not really the case. IBS patients have been demonstrated to have the following abnormalities: They have abnormal microflora compared to the normal population. They also have visceral hypersensitivity characterized by perception of volume distention of the bowel at lower volumes of air or fluid in the lumen of the colon or rectum compared to the normal population. In line with the concept of a functional abnormality of the GI tract, the microflora inside the lumen adversely affects bowel function perhaps via the effect of bacteria breaking down ingested sugars and creating free fatty acids that may stimulate nerve endings. Such a hypothesis is part of the basis for the fodmap diet which has gained prominence in the management of irritable bowel syndrome. The visceral hypersensitivity component suggests indeed that while the mucosa may appear normal the nerve endings may be functioning at a different level promoting increased pressure and pain perception. We currently do not have a routine clinical test to approach the concept of visceral hypersensitivity on a regular basis.

In the management of irritable bowel syndrome (IBS) it’s prudent to take a multifactorial approach to care as it will reflect the multifactorial pathophysiology that we currently consider to be operative in the most common disorder in gastrointestinal medicine. The use of stooling dysfunction medications new to the market over the past several years, fodmap diet, antibiotics to treat bacterial overgrowth syndrome, anti-spasm drugs, antianxiety and anti-depressive medications all can be considered and used successfully in most patients in managing irritable bowel syndrome. From the point of view of the workplace, it is important to point out that irritable bowel syndrome is now considered a chronic disorder for which patient may obtain a degree of workplace support in that this disorder is now covered by the American Disabilities Act.

The most significant advances in the management of inflammatory bowel disease are these:
Unit 4: IBS vs. IBD Challenges in Diagnosis and Management

- Clear definition of remission of disease
- Better understanding of the role and expectations of effectiveness of medications and management
- Increase in the classes of biologics available for management of IBD
- Development of the concept of “personalized IBD care”
- Better understanding of the management principles in pregnancy

The goals of IBD management in 2017 must include: improving quality of life by reducing symptoms; preventing symptomatic relapses which may lead to loss of work and leisure time and perhaps increased hospitalization and surgery; reducing time of steroid exposure; reducing long-term consequences of disease including cancer, fistulae, strictures, malnutrition, and extra-intestinal complications such as osteopenia-related fractures, short-bowel syndrome, disability, and loss of quality of life, and finally IBD-related mortality. In 2017 we have no way to return the immune system’s “tolerance” to the bacterial environment within the GI tract. We use anti-inflammatory drugs (i.e. mesalamine, budesonide corticosteroids); immunomodulators (i.e. azathioprine, 6-MP, methotrexate, cyclosporine, tacrolimus); inhibitors of lymphocyte traffic (i.e. vedolizumab); and pro-inflammatory cytokine inhibitors (i.e. anti-TNF biologics such as infliximab, adalimumab, certolizumab and the anti-IL 12/23 inhibitor ustekinumab.) These thirteen drugs are not all inclusive but make the point that we are not treating the root cause, namely loss of immune tolerance, but rather the inflammatory consequences of the probably genomic-driven disorder of control of the immune system. While patients with IBD have a multitude of gene mutations not found in the general public, we have not defined the single or group of genes responsible for the disruption of the immune system. That is a task for the scientists for the coming decade. For now, we are left to obtain the goals listed above by application of the classes of drugs listed above.

During the past decade, we have attempted to define the best strategies of drug application to obtain at least some of the goals listed above. While short-term goals are those commonly measured, we have no programs that do more than hopefully reach the long-term goals. Specifically, we are not certain that any drug plan alters the natural history of IBD. At best, in 2017 we hope to stretch the natural history to lengthen the time to any disease progression. In the management of “moderate to severe” disease (still defined clinically) either Crohn’s disease or Ulcerative Colitis, we have two decision-trees to consider. We may choose a “bottom up” or “top-down” strategy. The former offers initiation of care with mesalamine, followed by addition of an immunomodulator, then a biologic (anti-lymphocyte traffic agent or anti-procytokine agent). Steroids are used acutely to reduce symptoms until the strategy brings about remission. The “top-down” strategy offers early introduction of the immunomodulator with a biologic to bring about reduction of symptoms, reduce steroid need, and maintain remission. The studies over the past decade to define the best strategy are not definitive but the “top-down” approach is gaining ground as we become more comfortable with the top tier drugs and receive some answers to the obvious questions that practicing clinicians need in order to make informed decisions. In this regard, one of the most respected clinical trials to date regarding the selection of the best strategy for Crohn’s disease is the 2015 REACT (Randomized Evaluation of an Algorithm for Crohn’s Treatment) trial which was designed in a “real world” manner (Lancet, 386: 1825-1830, 2015) Sixty practices in Canada and Belgium with a total of 2000 patients were invited to treat Crohn’s patients with either a “bottom up” or “top down” program. If remission was not achieved in the former group within a few months, they would
switch the patient to a top-down program. At the end of one year, the status of nearly one
thousand patients in each group was assessed. The proportion in remission were the same; the
number of patients with super-infections was less in the top-down group; the number of patients
missing work, entering the ER, being hospitalized or going to surgery was also less in the top-
down group. Thus, while the percentages in remission were equal, the top-down roads to
remission were safer, associated with less “accidents” and side effects. The REACT trial offered to
practicing physicians some answers regarding the safety and outcomes in the community setting
use of immunomodulators and biologics. As discussed above this trial related remission to
symptoms, a follow-up trial is being conducted on a smaller scale to assess the status of the ileal
and colonic inflammation when either strategy is applied. We anticipate the early introduction of
immunomodulators and biologics will be associated with mucosal healing and perhaps bodes well
for at least lengthening the natural history of IBD.

The concept of “personalized IBD care” has not arisen because of our success in IBD
management. To the contrary, it has come about because of our lack of success. Overall, we are
left with the fact that up to 40% of patients treated with immunomodulators fail to respond or
maintain remission. The biologics meet a similar fate. In clinical trials with anti-TNF agents, nearly
half the patients fail to respond and half the responders come out of remission within twenty-four
months. With investigations of these events, there is some evidence supporting the concept that
if serologic drug levels can be maintained in defined ranges, the patients may benefit clinically. To
that end, patients probably benefit from measurements of 6-MP blood levels and from infliximab
and adalimumab blood levels and from measurement of antibody levels to the above listed
biologics. If the immunomodulator levels are satisfactory, remission may be more likely. If the
biologic level is therapeutic and antibodies are absent, patients are more likely to obtain
remission. If remission is not obtained, it may be concluded that the patient will not likely respond
to the anti-TNF class of biologics and a change to another class (anti-lymphocyte traffic or anti-
IL12/23) is a reasonable course. Use of blood levels hopefully will promote a patient-specific
consideration in medication management.

The issue of IBD patient care during pregnancy continues to be of interest. Both Crohn’s
disease and ulcerative colitis are most prevalent during childbearing years. In the main, there is
little evidence to support the commonly held belief that pregnancy itself influences the course of
IBD. However, if the mother is in clinical remission, holding biologics in the last trimester is
acceptable. Relapse may be managed with steroids. On the other hand, the biologic is still likely
very safe during pregnancy for both mother and baby. The safest position for mother and baby is
in IBD remission.

In the setting of family planning, IBD patients should plan pregnancy. In the best case
scenario, mother will be brought into a sustained remission before becoming pregnant. Any form
of contraception is acceptable. Lowest dose estrogen in combined oral agents is preferred. In the
absence of a history of clotting disorders, oral contraception is acceptable in IBD patients. Also
recall that azathioprine/6MP lowers sperm counts. In general, fecundity is normal in IBD patients.
IBD patients may choose to not become pregnant more often than the normal population.
Pregnancy is more difficult in women who have had anal-sparing colectomy compared to post-
ileostomy patients. That notwithstanding the former operation is most often recommended in
ulcerative colitis patients coming to surgery.
Dyspepsia, Reflux, Barrett’s Metaplasia Management

Probably one of the most challenging arenas of digestive healthcare must be that of esophageal disease. On the one hand, patients and physicians are asked to respond to the nearly universal complaint of heartburn which may follow that heavy meal possibly anointed with alcohol and dessert. On the other hand, we are asked to deal with the silently evolving most deadly of cancers, either squamous or adenocarcinoma of the esophagus. Clinicians are continuously worried about this spectrum of esophageal disease principally because they are well aware that in fact, however wide this spectrum, there is a well-defined connection and pathologically evolutionary continuum from esophagitis to esophageal cancer. Physicians are asked to assess, intervene, and protect patients from not only symptoms but also progression of the continuum. In this unit we will discuss some of these important aspects:

- Less dangerous but much more common component of the continuum namely dyspepsia.
- The role of endoscopy in defining esophagitis, stricture, bleeding, evolution and monitoring of Barrett’s metaplasia and diagnosis of cancer.
- The current approach to Barrett’s low-grade and high-grade dysplasia and esophageal adenocarcinoma.
- The time and place for the insertion of surgical intervention either to halt symptoms, perhaps stall the continuum, or cure cancer.

After the common cold, reflux and heartburn are the most common complaints presented to a clinician. While the common cold is typically a community-acquired viral illness with a propensity for seasonal presentation, reflux and heartburn are most often consequences of lifestyle and less often related to anatomy such as hiatal hernia, congenital abnormality, inherited propensity, etc. For this reason, it is more appropriate to provide the sporadically dyspeptic patient with information to seriously address lifestyle issues rather than offering a continuous program of proton pump inhibitors. In this regard, sporadic heartburn can be treated with anti-acids, H2 blockers, or proton pump inhibitors on a when necessary basis. Regarding proton pump inhibitors, the FDA requests that these agents be offered for a period of two weeks several times per year for control of intermittent pyrosis. Simultaneously, lifestyle issues should be investigated. Obesity, smoking, alcohol, stress, excess aspirin non-steroidal anti-inflammatory drugs, night shift work, and obstructive sleep apnea are all reversible risk factors that play a substantial role in the majority of patients with sporadic reflux symptoms (2-3 days per week daytime pyrosis). In the current medical care demand scheme, patients require that physicians provide a medication that works completely and continuously. The concept that the patient is responsible for altering lifestyle issues and that the physician is there to provide a stop-gap amelioration of complaints eludes our society. This shortfall in the approach to managing patient complaints certainly applies to many other areas of healthcare than reflux disease but the implications are rather substantial. It is estimated that approximately 70% of patients taking proton pump inhibitors continuously do not have a specific diagnosis.

As a leading medication prescribed in America (fifty million omeprazole prescriptions annually) with billions of dollars spent on millions of patients, a medication that is statistically very safe may indeed have adverse effects on a large number of patients because the total number exposed to the drugs is exceedingly high. This issue comes up when discussing the
adverse effects of long-term treatment with proton pump inhibitors (PPI). For example when discussing the possible PPI complication of chronic renal disease, the exceedingly low risk is probably 1.5% above that of the general population. These are, of course epidemiologic data, and are subject to all the risks and bias of interpretation. That said, the risk is quite small in terms of percentage. However, in terms of the total number of patients in the United States who could develop chronic renal disease in association with long-term treatment of proton pump inhibitors the number reaches the tens of thousands. If 70% of patients on long-term proton pump inhibitors could be shifted to when necessary, H2 blockers or when necessary PPI, the risks certainly will be resolved. Frequently, when the patient presents with the concurrent need for clopidogrel and PPI, the debate most frequently concerns the biochemical explanation for the interaction between these drugs and how to resolve the matter. The more pertinent question should revolve around the clinical need for each drug on a long-term basis. Very commonly, the proton pump inhibitor may not be needed on a long-term basis. Similarly the long-term merit of clopidogrel is specific cardiac circumstances is also subject to investigation. In summary, sporadic pyrosis should be managed with intense lifestyle modification, when necessary acid suppression with H2 blockers or short-term proton pump inhibitors. Long-term proton pump inhibitors require more than a complaint of dyspepsia. It is essential to establish a specific diagnosis and follow the guidelines for management.

Diagnostic endoscopy should be offered to patients with regular, daily, variably intense pyrosis for more than two months, particularly if there are no parallel, newly acquired risk factors, and if nocturnal symptoms, transient coffee ground emesis, or dysphagia are present. Patients with less intense symptoms who do not respond to a two-week course of acid suppression and life-style modification are also candidates for diagnostic endoscopy. Most commonly, patients in the latter category may have no endoscopic evidence of inflammation either grossly or upon biopsy. This finding is actually a very good outcome for the patient and the endoscopy should be considered exceedingly valuable. In the absence of inflammation, the likelihood of consequences such as bleeding, stricture metaplasia, and cancer are exceedingly rare. Patients can be managed symptomatically with acid suppression and other measures. These patients may have esophageal acid hypersensitivity also known as non-ulcer esophageal reflux disease (NERD). While patients may be symptomatic they can also be strongly reassured that no substantial pathologic consequence is likely to supervene.

Diagnostic endoscopy should be carried out fully understanding that a therapeutic intervention may simultaneously be required. In a patient with recurrent pyrosis who also has new onset dysphagia, the endoscopists should be prepared to obtain multiple biopsies, identify a stricture, offer a likely characterization grossly as benign or malignant and be capable of dilating the stricture at that endoscopy. Most importantly, the endoscopist must be able to identify Barrett’s metaplasia, define its location, its length, any raised lesions, and obtain serial biopsies according to current standards. In addition to potential pathologic developments along the continuum of dyspepsia to cancer, diagnostic endoscopy allows for the diagnosis of common disorders that masquerade as reflux esophagitis. These would include non-steroidal anti-inflammatory drug induced ulcers, para-esophageal hernia associated dysphagia, Candida esophagitis, any H. pylori- mediated pathology gastritis, gastric ulcer disease, pyloric channel narrowing secondary to peptic disease, duodenal ulcer disease, and gastroparesis which could be primary, secondary to comorbidities or medications.

The diagnostic endoscopy with possible concurrent therapeutic intervention is a single most important examination in the physician’s obligation to assess and intervene in the continuum...
of dyspepsia, esophagitis and its complications, Barrett’s metaplasia in all its forms and the continuation to esophageal cancer.

Patients who have developed complications from chronic reflux disease are candidates for long-term proton pump inhibitors. Patients treated short-term for complications typically have a recrudescence of the same pathology. Reflux symptoms recur quickly, strictures recur eventually; Barrett’s may progress over a long period of time. Barrett’s metaplasia must be assessed in the absence of inflammation. If initial biopsies are taken while there is gross obvious inflammatory or microscopic disease, the risk of over-staging the extent of dysplasia is high. Therefore if Barrett’s metaplasia is identified in conjunction with ongoing inflammation, treatment for three to six months with high-dose proton pump inhibitors is in order followed by endoscopic reassessment of the amount of dysplasia. If low-grade dysplasia is found and certainly if high-grade dysplasia is found, the biopsy should be reviewed by an expert pathologist. Multiple studies have shown that patients classified as having low-grade and high-grade dysplasia, upon expert review, more than half the cases have been misclassified. This particular concern has impacted many of the clinical trials attempting to assess the merits of all types of interventions including acid suppression, anti-reflux surgery, radiofrequency ablation of dysplastic Barrett’s and endoscopic mucosal resection of raised lesions in the setting of Barrett’s metaplasia.

The American College of Gastroenterology 2016 guidelines offer a readable system for decision-making when the diagnosis of Barrett’s metaplasia is established. (Shaheen, N. J. et. al. Am. J. Gastro. 111:30-50, 2016.) Patients with Barrett’s metaplasia without dysplasia should continue on a PPI dose as needed to control symptoms. If the patient has no dyspeptic complaints, the PPI standard dose is recommended as it is a reasonable consideration to limit acid exposure to the esophagus and perhaps reduce the risk of progression to dysplasia. Patients with confirmed low-grade dysplasia (LGD) can be followed by surveillance endoscopy at annual intervals in conjunction with PPI coverage. It has more recently become the alternative however to offer endoscopic ablative therapy as LGD may progress to high grade dysplasia (HGD).

Radiofrequency ablation is effective in eliminating both LGD and HGD and is becoming the standard of care. In patients with mucosal abnormalities occurring within a Barrett’s segment (i.e. nodularity, raised lesion, ulceration), endoscopic mucosal resection (EMR) is recommended to define the nature and depth of the lesion. If the lesion is an early cancer and its depth is limited to the lamina propria on EMR or EUS (stage T1a), this can be considered curative and follow-up completion EMR and or RFA for the entire Barrett’s field is recommended.

An alternative to endoscopic ablative treatment for Barrett’s with or without dysplasia is anti-reflux surgery. The capacity of such surgery to prevent esophageal cancer by stalling the continuum of reflux to cancer is controversial. While there is an intellectual rationale to believe that anything that prevents acid from offending the esophagus reduces cancer risk, on the basis of evidence-based information, it is intellectually perilous and contrary to most medical and surgical directives to offer patients anti-reflux surgery as an anti-neoplastic procedure (Spechler, S.J. Dig. Dis. 32:156-163, 2014; Demister, S.R. Ann. Surg.257(4): 583-585, 2013; Shaheen, N.J. ET. Al. Am. J. Gastro.111:30-50, 2016.)

For patients who have Barrett’s HGD in more than one segment of the field and for those...
patients with stages T1b or greater, surgical esophagectomy with or without pre-operative chemotherapy and radiation is recommended.
Fatty Liver and Steatohepatitis Management

The discussion of fatty liver, nonalcoholic steatohepatitis (NASH), and consequent fibrosis and cirrhosis is generally a depressing one. We have difficulty separating these pathologies without biopsy. We have greater difficulty in halting the progression of NASH with fibrosis to cirrhosis. Finally we have the greatest difficulty in developing medications which can significantly alter the natural history of NASH with fibrosis. Currently there is no FDA-recommended treatment for non-alcoholic fatty liver disease. As the leading cause of chronic liver disease we are, however, faced as clinicians with the task of dealing with the information and tools available to us in order to protect our patients from the formidable complications of non-alcoholic fatty liver disease (NAFLD). Non-alcoholic fatty liver disease (NAFLD) is present in perhaps twenty-five percent of the American population and is at least twice as prevalent in the obese population. (Lazo, M., Clark, JM. Semin Liver Dis. 28(4):339-350, 2008). Broadly, seventy-five percent of patients with NAFLD are female and obese; thirty-five percent have type 2 diabetes, half are hypertensive, and many have metabolic syndrome and insulin resistance syndrome. For all of this, fortunately in the absence of fibrosis and inflammation, consequences are quite limited. When NASH is present, i.e. inflammation with or without fibrosis, the prognosis can be dramatically worsened. Life expectancy is reduced from cardiovascular, malignancy, or liver related sequelae. While perhaps 20% of cases of NAFLD develop non-alcoholic steatohepatitis (NASH), approximately one-third of such NASH patients will develop fibrosis and cirrhosis. Although these numbers may vary approximately six percent of all NAFLD patients will develop cirrhosis. If perhaps sixty million Americans have advanced fatty liver, the numbers suggest that perhaps three million will develop cirrhosis. Currently NASH-related cirrhosis is the third leading cause of liver transplantation. The NASH patient who develops cirrhosis is at risk (2-3% per year) of developing hepatocellular carcinoma. (Spendler, EK, Loomba, R. Mayo Clinic Proc. 90 (9): 1233-1246, 2015).
In order to meet the patient and consider the potential presence of NAFLD and the potential for its more dangerous subset NASH, recognizing the clinical presence of metabolic syndrome and insulin resistance is important. If these metabolic circumstances exist, NASH and its risks are highly likely to be present. While there are limited options for effective care if we just consider the fat in the liver, and if we address the metabolic derangements, we can help patients live longer and live better.

**Characteristics of Metabolic Syndrome**: There are generally accepted parameters which taken in part or together constitute Metabolic Syndrome. 1. Obese or more specifically abdominal obesity. 2. Hypertriglyceridemia. 3. Low HDL. 4. Hypertension. 5. Elevated fasting glucose. Patient must have three of the five criteria for the diagnosis of Metabolic Syndrome. In this condition, the patient is also at higher risk of Insulin Resistance Syndrome.

**Characteristics of Insulin Resistance (IR) Syndrome**: 1. Direct link to hyperlipidemia, CAD, and a reduced response to cardiac intervention. 2. Direct link to diffuse atherosclerosis. 3. IR fat cells do not store triglycerides but release FFA into circulation. 4. IR is present in seventy percent of obese patients. 5. Calculation for Insulin Resistance based upon fasting total insulin and glucose levels. $IR = [(\text{serum insulin}) \times (\text{serum glucose})] / 406$ if $> 3$ IR likely.

I would like to spend some time addressing what may be happening in the liver, what medication trials have shown and what options exist for treatment of NASH. Finally, we will list the current recommendations for treatment and monitoring patients with NAFLD and NASH.

**Peroxisome Proliferator-Activated Receptor System and NASH**
WHAT DO PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS HAVE TO DO WITH NON-ALCOHOLIC FATTY LIVER DISEASE

1. These are nuclear receptors that play a key role in regulation of metabolism
2. They assist in regulation of immune-inflammatory response
3. Stimulating the receptors reduces inflammation in NASH
4. PPARs are prominent in liver and muscle. Stimulating the receptor promotes transcription of proteins that modulate fatty acid transport, and inhibits inflammatory genes in the liver and leads to resolution of steatohepatitis
5. Stimulation of PPARs increases HDL, enhances insulin sensitivity, reduces fat in the liver

PHARMACOLOGIC TREATMENT OF NAFLD/NASH

1. Pioglitazone (ACTOS) – PPARs ligand, weight gain, fractures, chf, Bladder IRIS – insulin resistance intervention after stroke: 24% less stroke/MI at 5 yrs.
2. Vitamin E – bx proven NASH in non-diabetics. Risk of prostate CA, hemor, stroke
4. Statin – Treatment of hyperlipidemia in pts. with NAFLD
6. Elafibranor – PPARs (dual) induces resolution of NASH without worsening fibrosis. (Gastroenterology May 2016.) RCT, favorable SE profile, not FDA approved
RECOMMENDATIONS FOR MANAGEMENT OF NAFLD AND NASH

1. Lifestyle modifications: 5-10% of body weight
2. Assess CV risk factors: lipid profile, fasting glucose, (insulin x glucose)/405 > 3
3. Manage comorbidities: HBP, lipids, search for concurrent cardiac, periphvasc dis.
4. Drugs: steroids, amiodarone, MTX, tamoxifen, estrogens, TCN, valproic acid
5. Labs: US, CBC, lipid and liver panel, INR, creatinine, Hepatitis B and C, PBC, ANA
6. Consider liver bx IF: preliminary evidence of cirrhosis, diabetes, or metabolic synd.
7. Consider pharmacologic therapy if pt. has bx proven NASH without cirrhosis
8. If cirrhosis present, obtain US and AFP every 6 months. EGD to rule out varices.
9. If cirrhosis progresses or patient decompenses, refer to transplant center.
10. Remember: NASH mortality is 10 times that of the general population.

BEDSIDE/CLINIC FIBROSIS CALCULATIONS

AST-Platelet-Ratio Index (APRI): \[
\frac{\text{AST pt/AST unl} \times 100}{\text{Plt Cnt}} > 1 \text{ fibrosis}
\]

Hepatitis C FIB-4 calculation:

\[
\text{FIB-4} = \frac{\text{AGE} \times \text{AST}}{\text{Plt Cnt} \times \text{srtALT}}
\]

- <1.45 90% NPV for fibrosis
- >3.25 65% PPV for fibrosis

70% of patients fall outside this range
86% accuracy for predicting presence or absence of fibrosis.
If result in determinant (30%) proceed to liver biopsy

NAFLD/NASH: Fib-4 calculations:

- <1.3 98% NPV
- >2.6 70% PPV
In gastroenterology, we are frequently faced with managing incurable disease. Such is true for most of medicine. Hepatitis C is one of those uncommon diseases that has moved from observation until death, to inadequate treatment for partial cure, to cure of the disease. All of this has taken place over the past three decades. Hepatitis C is the most common blood-borne viral infection affecting approximately four million Americans. Ten to twenty percent of infected individuals develop cirrhosis and 1-5% may develop hepatocellular carcinoma. Hepatitis C remains the leading cause of liver transplantation and is the leading cause of death in HIV positive patients. While the mortality rate from HIV has continued to fall in the United States over the past fifteen years, the mortality rate for hepatitis C has doubled over the same interval. Mortality among hepatitis C virus infected persons primarily adult ages 55-64 is increasing. For the first time in the United States, in 2007 the number of hepatitis C virus-related deaths exceeded the number of HIV/AIDS-related deaths; this trend has continued. The number of hepatitis C virus-related deaths rose to nearly 20,000 in 2014 and more than half the deaths occurred in person’s ages 55-64 years.

The continuing public health challenge is to increase the proportion of persons tested; and of those who are infected, the related challenge is to increase the proportion referred for treatment. At the present time less than one third of patients with known hepatitis C are referred for care. To address the initial public health challenge the CDC in 2013 recommended one time testing for hepatitis C virus infection among adult born during 1945-1965 (i.e. the baby boomers.) However, not often enough stated is that the prevalence of hepatitis C in the baby boomers is generally flat. Quite the contrary, the number of new cases of hepatitis C is dramatically increasing in the 18-35 age range throughout the United States. It is particularly noteworthy that the incidence of hepatitis C infection parallels the use of narcotics and methamphetamine. Presumably, these drugs are markers for any injectable drug use. This is a significant problem in this state of Montana where methamphetamine use is twice the national average on a population basis. Hence, testing for hepatitis C must be broadened to include not only the baby boomers but also the much younger age groups with risk factors relating to engaging in high-risk drug use.

In daily clinical practice, therefore, it is important to discuss sexual practices, drug use, and other risk factors for hepatitis C in the larger general population beyond baby boomers. For acute infections addressing the 18-35 age groups is particularly important. Risk factors beyond drug use include long-term dialysis, persons with a history of percutaneous exposure in an unregulated healthcare environment (i.e. out of the country, in the United States prior to the 1992 installation of universal precautions in the hospital setting), healthcare workers and public safety workers after needle stick exposure, children born to infected mothers, HIV infection, unexplained chronic liver disease and solid organ donors. Additionally, annual testing for hepatitis C is recommended for persons who inject drugs and for HIV seropositive men who have unprotected sex with men. Periodic testing should be offered to other persons who have ongoing risk factors for exposure to hepatitis C virus who may be currently negative. If a patient tests positive for anti-HCV, current infection should be confirmed by HCV RNA testing. If the latter test is positive, the patient should be informed that he/she has active hepatitis C infection. If the HCV RNA test is negative, the patient should be informed that he/she does not have active hepatitis C viral infection. Of course, the patient will ask if he or she had hepatitis C in the past or if the anti-HCV test is a “false positive.” To make this distinction, the patient should have anti-
HCV testing by an alternative test method. If both the original test and the alternative test for anti-HCV are positive, it is likely that the patient has been exposed to the hepatitis C virus in the past and has cleared the virus leaving only the antibody footprint. This may occur in 10-15% of hepatitis C viral exposure.

Prior to initiation of hepatitis C treatment several factors require assessment in order to choose treatment correctly. These include:

- Hepatitis C virus viral load
- Genotype
- Presence of fibrosis or cirrhosis
- Prior history of treatment
- Current drug and alcohol use
- Co-infection with HIV
- Insurance statuses
- Current medication uses

The current direct acting antivirals (DAA) have a beneficial effect rather independent of the viral load; but patients with viral loads less than six million seem to respond better. Genotype has been important in selecting drug programs but the newest drugs (i.e. combination of sofosbuvir + velpatasvir – commercial name Epclusa) are effective against all genotypes with or without cirrhosis. Other popular combined DAA’s include Harvoni and Viekira Pak. Cost and genotype play a role in the strategic decisions regarding program selection.

Defining the presence and extent of fibrosis and cirrhosis prior to treatment leads to a most important new concept in the management of hepatitis C. It is important to separate in management the approach to the hepatitis C infection and management of the liver disease which may be related solely to hepatitis C or also related to other hepatopathy such as alcohol, iron deposition, fatty liver, nonalcoholic steatohepatitis and autoimmune liver disease. Before treatment begins it is important to know if the patient has fibrosis/cirrhosis. It will impact the selection of the medications and the duration of treatment. Of considerable importance now is the recognition that fibrosis impacts the future of the patient’s health whether they are treated successfully or not. In order to determine the presence or absence of fibrosis, the physical exam is singularly most important. If the patient has florid signs and symptoms of cirrhosis, little more needs to be done. If there is quantification required in this respect perhaps by payors or if more objective support for the presence or absence of fibrosis is desired, there are several correlations that are useful in these situations. The AST to platelet ratio index (APRI) is useful:

\[
\frac{(\text{ASTpt/ASTuLN})/(\text{plt cnt}) \times 100}{\text{value} > 1 \text{ reflects fibrosis}}
\]

This one calculation may not be entirely convincing but addition of an additional test such as the Fib-4 is also quite helpful and worth reporting. Fib-4 calculation:

\[
\frac{(\text{age} \times (\text{AST}))}{(\text{plt cnt} \times (\text{sqrALT}))} = \text{Value} < 1.45 \text{ 90% NPV for advanced fib} \\
\text{Value} > 3.5 \text{ 65% PPV for advanced fib} \\
\text{Values outside this range (30%) ? bx}
\]

In considering liver biopsy the issue again comes up regarding separating the hepatitis virus infection from the current status and future of the liver pathology. While we may be successful in eliminating the virus, newer information provides several warnings. Elimination of the virus does not eliminate the risk for hepatocellular carcinoma. While the risk is reduced by
approximately 80% by virtue of the elimination of the virus, the ongoing risk of hepatocellular cancer relates significantly to the presence or absence of fibrosis/cirrhosis. In specific numbers, patients with viral cure may have an incidence of hepatocellular carcinoma of one per one thousand pt. years; in contrast individuals not achieving viral cure have an incidence of hepatocellular carcinoma of seven per thousand pt. years. If cirrhosis is present, the risk of hepatocellular carcinoma is six per thousand pt. years in the hepatitis viral cure group and twenty-one per thousand pt. years in individuals in whom the virus is not cleared. (Carey, W. HCVnext, 3(12):16-20, 2016.)

The real world of hepatitis C includes the fact that the liver is commonly threatened by more than just the virus. Fatty liver, steatohepatitis, iron overload, and alcoholic hepatitis are commonly present and deserve attention to prevent progressive fibrosis and all the attending consequences. Risk factors also include diabetes mellitus, insulin resistance, and obesity, hepatotoxic drug use (i.e. Tylenol, NSAIDS, illicit drugs, and prescription medications).

The information above indicates that the presence of fibrosis or cirrhosis is a significant tip off that these patients need to be followed closely following successful viral elimination and certainly if cure is not achieved. Currently the best recommendations for follow-up include six-month testing by ultrasound and alpha-fetoprotein (AFP) determination. Interestingly, the former is considered a much more useful test. Some experts do not monitor AFP. While MRI and CT scanning have been used, they do not stand up to standard cost-benefit ratio analysis at the present time. If a nodule is found on ultrasound, it will more often than not be found to be benign. That, however, is the current status of hepatocellular cancer monitoring in the setting of chronic liver disease.

In summary of this issue, screening for hepatoma is based upon ultrasound and alpha-fetoprotein monitoring at six month intervals. It is noteworthy that the hepatitis C viral positive patients are at almost twenty-fold higher risk of hepatocellular carcinoma than patients in whom the virus has been eliminated keeping in mind that this risk is variable if the patient has cirrhosis or stage III fibrosis in which case the risk of hepatocellular carcinoma development is higher. In patients whom there is no fibrosis and viral elimination has been achieved, a much more liberal screening program is satisfactory. Such patient probably could be screened at 2-3 year intervals if at all.

When discussing treatment with DAA it is worth pointing out that we are trying to do more than eliminate the virus. Patients who are successfully treated can expect constitutional improvement particularly in the realm of the most common complaint, specifically fatigue. Additionally, improvement in extrahepatic pathology such as porphyria cutanea tarda, edema, ascites, portal hypertension, esophageal variceal hemorrhage and hepatocellular carcinoma risks can supervene. Good news! Heretofore much less recognized, with successful treatment, fibrosis and cirrhosis are reversible consequences of chronic liver disease particularly hepatitis C. Finally, while early on in the era of DAA, because of cost particularly, there was consideration to stratify patients for whom medications should be made available. As of today that stratification, based upon age, risk, fibrosis, etc. has fallen by the wayside with the scientific consensus that hepatitis C at any age, any symptoms, any fibrosis, is equally worthy of treatment. The older the patient the more rapid the subsequent rate of fibrosis; the younger the patient, the greater the public health risk, etc. The one proviso would be that in patients for whom survival is estimated to be limited, less than one year, based on liver disease or any other comorbidity, treatment with DAA is not likely to be appropriate.
Asymptomatic Pancreatic Cysts Diagnosis and Management

The “big picture” for pancreatic adenocarcinoma remains grim with a five-year survival rate of 6% and median survival time of only 3-6 months. Pancreatic adenocarcinoma accounts for only 2.8% of all new cancers in the US but ranks 4th in annual death rates. Approximately 40,000 deaths occur annually. Unlike the case for breast, colon, prostate and lung cancers for which screening tests are available, there is no recommended screening test for pancreatic cancer. Hence finding an early, potentially curable pancreatic cancer in an asymptomatic individual is largely a matter of chance. There also remains that terrible prospect that pancreatic cancer is de novo a systemic illness (i.e. very early hematogenous spread) at any stage. That notwithstanding, clinicians are faced with making every effort to recognize and remove high risk pre-cancer or very early pancreatic neoplasia if we are to improve survival from pancreatic cancer. This is where the discussion of pancreatic cysts begins.

With the development of CT, MRI, ERCP, and EUS over the past four decades, an optimist could conclude that these modalities have played a role in the improved five-year survival rates for pancreatic adenocarcinoma, specifically from 3% to 6% over as many decades. While there may be some truth to this conclusion, it is also noteworthy that the single most identified risk factor, specifically cigarette smoking, has also decreased over the past four decades. In addition, survival rates for most cancers have improved in the same time frame. However, these sophisticated imaging techniques completed for any reason can identify a high risk lesion. Surgical resection, which itself has dramatically improved in the past quarter century, may save a patient’s life. Perhaps 15% of patients with or without pancreatic-type complaints undergoing an MRI are found to have an “incidental” pancreatic cyst. The risk that a truly incidental cyst found on an MRI is malignant is estimated at be 10-20/100,000.

What do we do with this information? Shall we ignore it all? Do we investigate all cysts in the hope that there is no cancer or that we may find a very early and curable cancer? The American Gastroenterological Association (AGA) Institute Guideline on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts (Gastro. 148:819–822, 2015) offers guidance for clinicians.

In the symptomatic or the at risk patient (i.e. chronic pancreatitis, familial pancreatic cancer and pancreatitis, specific chromosomal disorders associated with pancreatic cancer), clinical judgment, of course, may take precedence over the AGA recommendations applicable only to the asymptomatic patient. Similarly, patients who have a limited lifespan and who may not benefit from surveillance or surgical intervention need separate, judicious consideration.

For most asymptomatic patients found to have a pancreatic cyst size matters. A pancreatic cyst which on cross-sectional imaging measures less than 3 cm in diameter, without any solid components (mural nodules or mass effect beyond the cyst) and without any dilatation of the main pancreatic duct can be judged as low-risk and followed by MRI at one year and then at two year intervals for a total of five years. If no changes are noted during surveillance follow-up, monitoring may be discontinued. A cyst may be considered high risk if two of the three following features are present:
1. Transverse diameter equal to or greater than 3 cm
2. Dilated main pancreatic duct
3. Solid component inside or outside the cyst

If a cyst has two of these three high risk features, evaluation by endoscopic ultrasound plus fine-needle aspiration (EUS/FNA) is recommended as these risk factors are associated with an increased risk of pancreatic malignancy associated with the cystic lesion. EUS has a high sensitivity to define mural nodules, provides a means of safely collecting fluid to assess for mucin, cytology, amylase, and CEA. Cysts without mucin and with a low cyst CEA are low risk for cancer and may be followed if the patient is asymptomatic. If mucin is present and CEA is high, the lesion is a mucinous (pre-malignant) cyst requiring consideration for excision. (Khalid, A. and Brugge, W. ACG Practice Guidelines for the Diagnosis and Management of Neoplastic Pancreatic Cysts. Amer. J Gastro. 102:2339-2349, 2007.)

Most high risk pancreatic cystic lesions are intraductal papillary mucinous neoplasms or IPMN lesions. They may be a main pancreatic duct or side branch variety. The latter is generally a low risk lesion. If the EUS/FNA is negative, the one and two-year follow-up surveillance plan is recommended just as one would do for a low-risk cystic lesion. If during surveillance any of these high risk features develop, additional investigation is warranted. If the EUS/FNA study reveals a positive cytology, cancer is present and surgery warrants consideration if the patient is otherwise suitable for surgical intervention. Significantly, however, if the cytology is negative in the presence of the high risk factors, consideration for surgical intervention is still warranted. The greater the number of factors present, the greater the additive risks for malignancy. Thus despite a low overall risk of cyst-associated cancer, these high risk findings at imagery and EUS–FNA provide the best opportunity to define asymptomatic pancreatic cystic cancer and lead to consideration for life-saving surgical intervention.

The decision to refer a patient for pancreatic surgery assumes that the patient will benefit. In evaluation of all surgical case series of cystic pancreatic neoplasia, only fifteen percent harbored invasive cancer. Approximately the same percentage of IPMN patients undergoing surgery will have worrisome high grade dysplasia (HGD). The patient who has invasive cancer will have an outcome determined by the stage of the malignancy. Determining the surgical benefit in patients with HGD is more difficult as we do not know how many of these patients would have progressed to frank cancer had surgery not been completed. Thus, we cannot know the anti-cancer impact of a given surgery done for reasons of imaging risk factors or HGD. We do know however that pancreatic surgery has a mortality risk of one to two percent, that morbidity may be significant, and that both morbidity and mortality risks increase with age.

For the patient with an asymptomatic pancreatic cyst the clinician must decide the risk of surveillance, the risk of investigation, and the risk of surgery in the effort to protect the patient from death due to pancreatic cancer present or with the very high chance of developing into cancer. We as yet do not have the tools or the data to predict the risk of pancreatic cancer in the future of a patient with a pancreatic cyst. For now we are asked to integrate the specialty society recommendations, an educated patient, common sense, high quality surgical support and some good luck in order to make decisions based on balance between risk of cancer and benefit of resection.
Nicholas V. Costrini, MD, PhD, MBA—Program Director

Gastroenterologist Nicholas Costrini, MD, PhD, MBA, joined Kalispell Gastroenterology in May 2015, and serves as the Program Director of the Digestive Health Institute of Montana. Dr. Costrini earned his PhD in physiology of Marquette University in Milwaukee, Wisconsin, then completed medical school at The Medical College of Wisconsin. He did his residency at Barnes Hospital in St. Louis, Missouri, through the Washington University School of Medicine. He accepted a fellowship in gastroenterology with that institution and followed with a year as chief resident in medicine. He stayed with Washington University as a postdoctoral fellow in biological chemistry and gastrointestinal medicine. He returned to the Medical College of Wisconsin as faculty for several years. He then moved to Savannah, Georgia where he had a private practice for twenty-five years. Before coming to Kalispell, Dr. Costrini directed the Georgia Gastroenterology Group, PC, the largest solo gastrointestinal practice in the South, and was the director of gastroenterology for the Nancy and JC Lewis Cancer and Research Pavilion in Savannah, Georgia. His specialized skills in inflammatory bowel disease, gastrointestinal cancer care, and several disciplines of advanced endoscopy have contributed to his high level of care for patients across the spectrum.

Philip E. Jaffe, MD—Clinic and Endoscopy Director

Gastroenterologist Philip Jaffe, MD, began his practice with Kalispell Gastroenterology in January 2016, and serves as the Director of Clinical and Endoscopy Services. A native of New York, Dr. Jaffe earned his medical degree from Albert Einstein College of Medicine in the Bronx. He completed his internship and residency in internal medicine at the University of Arizona Health Sciences Center in Tucson, and served as chief medical resident. He followed with a two-year fellowship in gastroenterology at that university, then a mini-sabbatical in endoscopic ultrasound at the University of Indiana School of Medicine in Indianapolis. He began professional practice as the medical director of the GI Endoscopy Unit at the Tucson VA Medical Center, then assumed a similar responsibility at the University Medical Center in Tucson. He served in several clinical and academic positions during subsequent years with the University of Arizona Health Sciences Center, the Cleveland Clinic in Naples, Florida, and the University of Connecticut Health Center. Most recently he was medical director of the Digestive Disease Center at Yale New Haven Medical Centers Saint Raphael campus in New Haven, Connecticut and assistant clinical professor at the Yale School of Medicine during that time. In his free time, Dr. Jaffe enjoys traveling, skiing, listening to music, and spending time with his family.
William J. Cobell, MD

Gastroenterologist William Cobell, MD, joined the practice of Kalispell Gastroenterology in July 2014. He is a member of the active medical staff at Kalispell Regional Medical Center and the HealthCenter. In addition to his training in several specialized procedures, he is the Digestive Health Institute’s leader in diagnosis and management of esophageal disease. Dr. Cobell graduated from Montana State University in Bozeman, then completed his medical studies through the University of Utah in Salt Lake City. He carried out his internal medicine residency at the University of Vermont in Burlington, and his gastroenterology fellowship at the University of Missouri in Columbia. He was born in Browning, Montana, and is the son of a backcountry ranger in Glacier National Park. Dr. Cobell and his wife, Kaylene, a native of Bozeman, Montana, have four children. He loves all things outdoors, including skiing, camping, hunting, fishing, and hiking.

Ramon Generoso, MD

Dr. Generoso began caring for patients at Kalispell Gastroenterology in September 2016. He has vast experience in the treatment of gastrointestinal disorders and brings his knowledge to the Flathead community. Dr. Generoso completed his medical degree at the University of the Philippines, and carried out both his internship and residency at New York University, New York. He followed with his fellowship at Yale University School of Medicine, Connecticut. Prior to coming to Kalispell, Dr. Generoso practiced for fifteen years in Connecticut including serving as gastroenterology section chief at Milford Hospital in Milford, Connecticut, and Director of Endoscopy at Yale New Haven Hospital Saint Raphael Campus. He was actively involved in teaching as an Assistant Clinical Professor at Yale School of Medicine. Dr. Generoso also serves on the American College of Gastroenterology’s Minority Affairs and Cultural Diversity Committee. He is board certified in gastroenterology with the American Board of Internal Medicine. His professional interests are in advanced therapeutic and biliary endoscopy, gastrointestinal disorders including acid reflux disease, Barrett’s esophagus, colorectal cancer and hemorrhoidal disease. In his free time, Dr. Generoso enjoys black and white photography, shooting sports, and listening to vinyl.
Craig Harrison, MD

Craig Harrison, MD, is a partner in Kalispell Gastroenterology and a member of the active medical staff at Kalispell Regional Healthcare. He joined Kalispell Gastroenterology in August 1994. Dr. Harrison attended college at Dartmouth in Hanover, New Hampshire, and medical school at the Johns Hopkins University School of Medicine in Baltimore. He completed his internal medicine residency at the University of Utah Affiliated Hospitals in Salt Lake City in 1981 and a fellowship in gastroenterology in 1983. He joined the Rockwood Clinic in Spokane, Washington, for a year. In 1984, Dr. Harrison moved to Boulder, Colorado, where he founded Boulder Valley Gastroenterology. He practiced there until moving to the Flathead Valley in 1994. Dr. Harrison has held academic positions as an instructor in medicine at the University of Utah and a clinical assistant professor of medicine at the University of Colorado. Since joining Kalispell Gastroenterology, Dr. Harrison chaired Kalispell Regional Medical Center’s Department of Medicine and the Ethics Committee, and served as president of the Flathead County Medical Association. He is medical director of the Medical Assistant Program at Flathead Valley Community College. He is married to Dr. Robin Harrison, a general surgeon with Northwest Montana Surgical Associates. They have three children. In his spare time, he enjoys golf, skiing, fly fishing and cycling.

Juergen Johannes Mueller, MD, PhD

Dr. Mueller is the most recent addition to the faculty of the Digestive Health Institute of Montana. He joined the team in the first quarter of 2017. Dr. Mueller received his medical and research training in Munich, Germany, graduating Magna Cum Laude. He moved to the States in 1989 to begin his impressive and contributing career in medicine. He served as Chief Resident in Internal Medicine at Highland General Hospital in Oakland California and completed Gastroenterology Fellowship at California Pacific Medical Center in San Francisco. He joined the Gastroenterology Division of Alameda County Medical Center, Oakland, California and rose to level of Chief of the Division during his eight year tenure there. During that time he also served as Associate Professor of Medicine at the University of California, San Francisco, and Director of the Co-Infection Clinic for Alameda County Medical Center. During that time, he developed a preeminent knowledge and skill in managing complex infectious diseases including HIV, Hepatitis B and C, as well as all forms of acute and chronic liver disease. He later joined the Gastroenterology Division of Trios Medical Group in Kennewick, Washington to serve as the leader in general gastroenterology and diagnosis and management of all forms of liver disease. Dr. Mueller has a strong interest in community medical care and professional medical education.
Howard Lincoln Tice, MD

Gastroenterologists Howard Tice, MD, is a fellowship-trained partner in Kalispell Gastroenterology and is a member of the active medical staff at Kalispell Regional Healthcare. His years of practice in gastroenterology and hepatology provide depth in diagnosis and treatment. Dr. Tice completed his medical degree at the University of South Dakota in Vermillion, and carried out both his internship and residency at the George Washington University Medical Center in Washington, D.C. He followed with a gastroenterology fellowship at the George Washington University Medical Center. Dr. Tice spent the first two decades of his career in private practice; first in Fayetteville, Arkansas, and then in Greenfield, Massachusetts. During two years in Greenfield, he also chaired the Department of Medicine at the Franklin Medical Center. His career experience provides the Digestive Health Institute with a wealth of knowledge to serve physician colleagues and patients.

Shana Carter, ANP

Shana Carter joined the Digestive Health Institute's Cadre of superlative clinicians January 2017. Graduating cum laude, she received her Bachelor of Science degree in Nursing from Montana State University. Thereafter, she obtained her Masters of Science\Family Nurse Practitioner degree from Creighton University in Omaha, Nebraska. She returned to the Flathead Valley and joined the Institute following a distinguished career as an independent clinician in several healthcare systems in Nebraska. She provides that positive, joyful, and talented approach to patient care.
Carrie Ann Thompson, ANP

Carrie Thompson brings twenty-four years of patient-care experience with a focused background in oncology and internal medical skills to the Kalispell Regional Healthcare team. As a Nurse Practitioner, Thompson has had the opportunity to put her exceptional medical skills and kindhearted style to work with patients most recently at the Kalispell Gastroenterology office since July 2016. Carrie holds a Nursing degree with honors from Sir Sandford Flemming College, Ontario, Canada as well as her Bachelor of Health Science in Nursing with distinction from Charles Sturt University in New South Wales, Australia. Subsequently, she earned her Master of Science in Nursing from the University of Nebraska Medical Center in Omaha. Carrie worked as an adult nurse practitioner in Idaho, Wyoming and Montana before moving to Kalispell. She enjoys time with her children and the outdoors.

Tessa Skotnicki, PA

Tessa joined the Digestive Health Institute in May as a certified physician assistant treating patients in the field of gastroenterology. Tessa obtained her Master of Science in Physician Assistant Studies from Alderson Broaddus College in West Virginia. Following her schooling, Tessa worked at Preston Memorial Hospital and Monongalia General Hospital, both in West Virginia. In addition to her background in gastroenterology, Tessa has experience working in emergency medicine, urgent care and outpatient and inpatient settings, where her compassionate bedside manner adds to her clinical capacities. She is no stranger to the Rocky Mountains as she comes to Kalispell from New Mexico, where she put her medical skills to work at an advanced gastroenterology practice. When Tessa in not at the clinic, she enjoys traveling, practicing yoga, hiking and spending time with her family.
**Thomas F. Flass, MD, MS**

Dr. Flass has broad experience in helping build a strong pediatrics program in central and western Montana. He completed his medical degree at the University of Colorado and carried out both his residency and fellowship at the Children’s Hospital of Colorado. Prior to Kalispell, he practiced at the Fortin Pediatric Specialty Clinic with St. Vincent Healthcare in Billings. He also served for five years as director of education and marketing for Vitamin Logic, Inc., and taught and did research in nutrition at Colorado State University. Dr. Flass’ professional interests are nutrition’s effects on health, celiac disease, gluten intolerance, and treating children from infants up to 19 years old. He enjoys spending time with his family in the outdoors, fishing, hiking and skiing.

**Daniel Lustig, MD, MA**

Dr. Lustig joined the practice of Kalispell Gastroenterology in September 2016. With his professional interests, he adds a unique piece to the growing gastroenterology care team at the Kalispell Regional Medical Center. He has been practicing for the past eight years at Mary Bridge Children’s Hospital in Tacoma, Washington. Dr. Lustig earned his medical degree at the University of South Dakota School of Medicine. He completed his residency at Eastern Carolina University Pediatrics/Brody School of Medicine followed by his pediatric gastroenterology fellowship at Vanderbilt Children’s Hospital. Today he is involved with ongoing research in fructose intolerance; his other professional interests are inflammatory bowel disease, motility disorders, eosinophilic esophagitis. Away from the office, Dr. Lustig enjoys spending time with his family while hiking, skiing and fly fishing.

**Kimberly Longcake, ANP**

Advanced Nurse Practitioner, Kimberly Longcake, joined Kalispell Gastroenterology Pediatrics in July 2015. She is based in Helena, Montana, where she provides pediatric gastroenterology outreach services in Great Falls, and Bozeman. She earned her BSN, at Montana State University and her ANP at the University of Alaska. Her professional interests are encopresis and constipation. She and Dr. Thomas Flass have been working together for years to improve access to gastroenterology specialty service for the kids of Montana through the Outreach Program.
Outreach Clinics

**Adult Clinics:**
- Polson (106 Ridgewater Dr.)
- Ronan (107 6th Ave. SW)
- Whitefish (1600 Hospital Way)
- Cut Bank (802 2nd St. E)

**Pediatric Clinics:**
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- Great Falls (1300 28th St. South)
- Bozeman (120 N 19th Ave.)
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