INFLAMMATORY BOWEL DISEASE

A GIVING SMARTER GUIDE

PHILANTHROPY ADVISORY SERVICE
MILKEN INSTITUTE

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Table of Contents

EXECUTIVE SUMMARY

Inflammatory Bowel Disease (IBD) is a collection of diseases, including Crohn's disease and ulcerative colitis, which result in chronic inflammation and damage along the lining and tissues of the digestive tract. The disease greatly affects an individual's quality of life, causing symptomatic fatigue, abdominal pain, diarrhea, bloody stool, nausea, weight loss, with external manifestations such as joint pain, eye irritation, and skin rashes. Current treatments for IBD have allowed patients to better manage disease symptoms, but are limited in their ability to prevent or cure disease.

Patients and individuals at risk for developing IBD face many challenges and critical unmet needs, issues mirrored in the roadblocks facing IBD clinicians and researchers. In December 2015, the Kenneth Rainin Foundation in conjunction with the Milken Institute Philanthropy Advisory Service convened leading academic, clinical, industry, patient, and foundation stakeholders to discuss the state of IBD science and the key challenges impeding research progress. In a new Giving Smarter Guide, the Philanthropy Advisory Service presents the key unmet needs of disease research and recommendations for how strategic philanthropic investments can impact the trajectory of research and better benefit IBD patients and those at risk of developing IBD.

The global burden of IBD is immense, with disease incidence steadily increasing since the 1960s, concomitant with a nation's increasing industrialization and migration toward urban centers. Individuals with IBD face a lifetime of disease symptoms that require constant treatment, resulting in increased medical costs and lost productivity. Furthermore, the chronic nature of IBD can lead to disease-related complications that require surgery, while also increasing the risk for developing colorectal cancer and liver disease.

Currently, there is insufficient research to determine what causes IBD or who will develop this lifelong disease. Although research advancements have led to a broad treatment armamentarium against IBD, clinicians lack the data and tools to predict which patients would best respond to specific therapies. To address these challenges, targeted investments in basic, translational, and clinical IBD research are essential. In this Giving Smarter Guide, we outline the barriers to IBD research progress and the key philanthropic opportunities to better identify and treat persons affected by IBD. These opportunities include:

- Basic and clinical research efforts to assess and validate distinct biochemical, genetic, or molecular characteristics (biomarkers) that will identify individuals at risk for disease development and onset.
- Translational research aimed at developing effective regimens tailored to the individual, from improved delivery of existing drugs, to identification of biomarkers that predict a successful response to potent biologic therapies.
- Interdisciplinary efforts to understand the role of the microbiome in disease etiology, progression, and its potential as a therapeutic intervention.

Readers will be able to use this guide to pinpoint research solutions aligned with their interests. This guide will help to answer the following questions:

- Why should I invest in IBD research?
- What key information should I know about this disease?
- What is the current standard of care and state of IBD research efforts?
- What are the barriers preventing improved diagnosis and treatment?
- How can philanthropy support the translation of innovative basic research into novel treatments?

OVERVIEW

Inflammatory bowel disease (IBD) is a collection of diseases that result in chronic inflammation and damage along the lining and tissues of the digestive tract. An estimated 1.6 million Americans live with IBD, with 70,000 new cases each year. Although IBD can affect persons of any age, disease onset peaks between 15-30 years old, with life-long symptoms that require constant treatment and medication.

The chronic inflammation associated with IBD impacts the surface and integrity of the bowel and, in some cases, leads to a break in the digestive lining. This results in a digestive tract prone to infection, with diminishing ability to adequately process food and waste or absorb water. The disease greatly affects an individual's quality of life, causing symptomatic fatigue, abdominal pain, diarrhea, loss of appetite/weight, and tissue damage along the length of the digestive tract. Current treatments for IBD have allowed patients to better manage disease symptoms, but are limited in their ability to prevent or cure disease.

There is limited understanding of how the disease develops and in whom. Advancements in IBD research have identified a complex interplay between an individual's genetic background, composition of the gut microbial community (microbiome), and environmental triggers that converge and result in the chronically activated immune response that drives disease.

Globally, IBD has been found to affect individuals in industrialized, developed nations, with cases centered in urban areas. The societal burden is immense as patients face a lifetime of lost productivity and treatment. The disease has begun to appear in developing nations, in line with the migration of their populations toward urban centers and with continued industrialization of their economies.

For IBD patients and the multitudes who face an increasing risk of developing the disease, continued support of basic, translational, and clinical IBD research is essential to identify who will develop the disease and how to cure those already living with IBD.

IBD, CROHN'S DISEASE, AND ULCERATIVE COLITIS

IBD patients can be classified into two major clinical subtypes: Crohn's disease (CD) and ulcerative colitis (UC). Although CD and UC share many epidemiologic, immunologic, therapeutic, and clinical features, they are considered to be two distinct subtypes of IBD. The distinction has major implications, because it impacts the choice of medical treatment, timing of surgery, prognosis, and disease course. However, 10-15 percent of patients remain difficult to classify and are diagnosed with indeterminate colitis or IBD unspecified. This report will focus only on the major subtypes of CD and UC.

- **CD** can affect any part of the digestive system and presents as patches of inflammation (skip lesions) that affect sections of the gut. CD ulceration of the digestive lining can extend through the entire depth of the gut tissue.
- **UC** is limited to the rectum and can extend through the entire colon. UC presentation can be described as a continuous stretch of inflammation of the cells lining the colon surface.

HEALTH BURDEN AND PUBLIC POLICY

The early-onset and chronic nature of IBD result in increased indirect and direct medical costs for the affected individual and US healthcare system. These costs involve medical care, treatment, and lost productivity, with a simultaneous impact on an individual's quality of life.

HEALTH BURDEN ON SOCIETY

The societal costs of IBD treatment and medications are immense. In line with the numbers of Americans affected by IBD, visits to outpatient centers (ambulatory care) and hospital visits due to CD and UC have steadily increased since the 1980s (Figure 1).

In 2004 the mean annual direct healthcare costs for **CD** and **UC** patients were estimated to be $8,265 and $5,066 per individual, respectively.

For CD and UC patients, the majority of healthcare costs were for medication (both 35 percent), followed by outpatient services (33 and 28 percent, respectively), then hospitalization (19 and 22 percent, respectively), and finally surgery-related costs (13 and 16 percent, respectively) (Figure 2).

Using lower-end estimates of 436,000 Americans with CD and 512,000 with UC, the estimated annual cost of IBD for the US healthcare system is $6.3 billion dollars: **$3.6 billion for CD** and **$2.7 billion for UC**.

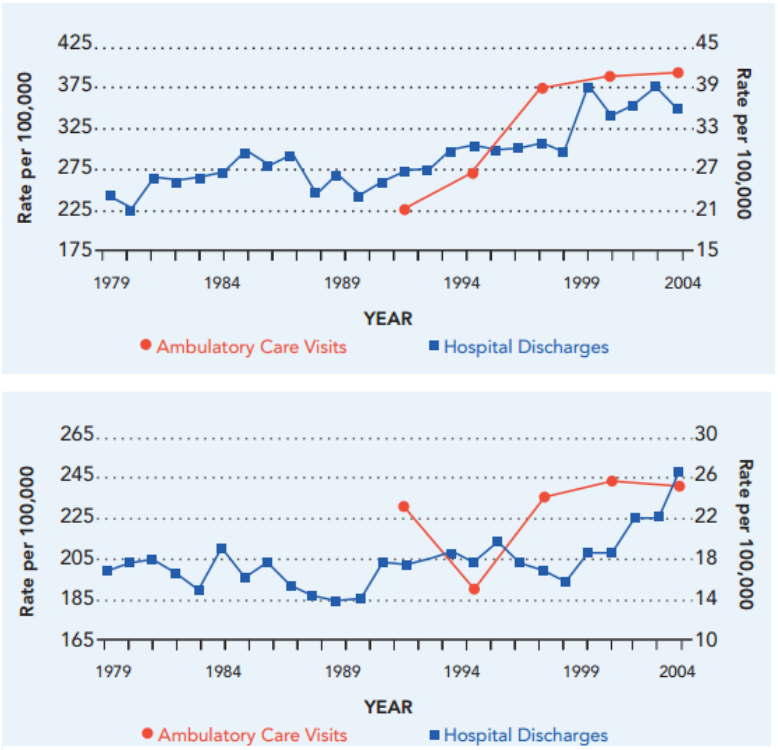

Figure 1: Age-adjusted rates of ambulatory care visits and hospitalizations related to CD (top) and UC (bottom). Results are based on previous reports provided by the National Ambulatory Medical Care, National Hospital Ambulatory Medical Care, and National Hospital Discharge surveys. Images courtesy of CCFA IBD Fact Book.

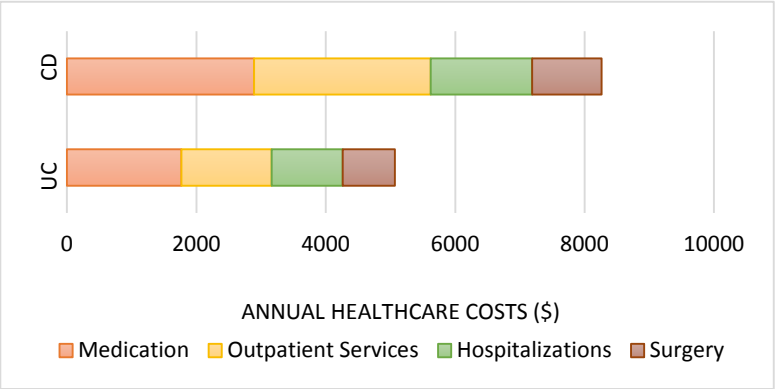

Figure 2: Breakdown of mean annual direct healthcare costs for CD ($8,265/year) and UC ($5,066/year). Data from Kappelman et al. (2008).

HEALTH BURDEN ON THE INDIVIDUAL

Current treatment options allow many IBD patients to live normal, productive lives. However, active periods of the disease (flares) and related complications can greatly affect their quality of life. According to the Crohn's & Colitis Foundation of America's (CCFA) IBD Fact Book:

- A national health survey in 1999 indicated that, in a 1-year timeframe, nearly one-third of symptomatic IBD patients reported being out of the workforce for prolonged periods.
- The chronic nature of IBD can affect the patient's emotional state, because the symptoms during a flare can be unexpected, painful, uncomfortable, and inconvenient.
- IBD patients indicate higher levels of stress, which in and of itself can affect the immune system, thereby prolonging the symptoms of a flare.
- Patients have reported developing depression as a result of their disease, seeking treatment and counseling to improve their well-being and ability to cope with the psychological impacts of IBD.

The chronic nature of IBD can lead to disease-related complications that eventually necessitate surgery.

- Over time, a majority of **CD** patients will require some form of surgery to address disease complications such as scarring and narrowing of a section of the gut (strictures), ulceration of the gut lining that results in a tunnel from one part of the digestive system to another (fistula), and abscess formation, which is a collection of pus in areas such as the abdomen or pelvis. However, surgical treatment is not curative, with disease recurring in a majority percent of patients within 1 year.
- An estimated one-third of **UC** patients who have lived with the disease for more than 30 years will require surgery. Common surgical procedures include removal of the colon and rectum, with the small intestine subsequently attached via a pouch to the anal area. Although generally successful and curative, some patients who undergo this surgery will develop inflammation in the pouch area and, in more severe cases, will require attachment of an external bag to collect fecal waste.

IBD patients also have varying levels of risk for other diseases arising from chronic inflammation.

- Compared to the general population, IBD patients have a slightly higher risk for colorectal cancer (CRC), with risk increasing proportionally to years living with IBD. **UC** patients have a slightly higher risk of developing CRC than do **CD** patients.
- An estimated 1 percent of **CD** patients and 5 percent of **UC** patients may develop primary sclerosing cholangitis (PSC), which is a severe form of scarring of liver bile ducts and can result in liver failure. The connection between IBD and PSC is poorly understood; however, greater than three-quarters of PSC patients have IBD.

LEGISLATIVE ISSUES AND EFFORTS

Ally's Law, also known as The Restroom Access Act: The law is named after Ally Bain from Illinois, who suffered a flare-up of her CD while in a retail store. The restrooms were only for employees, and denial of access led to Ally soiling herself. She met with Illinois legislators, who passed the law passed in 2005, which states that any IBD patient who presents a document signed by a medical professional must be granted access to a toilet facility without delay. As of 2015, 14 states have passed versions of the law; a federal version of the law has not advanced in Congress.

Congressional Crohn's and Colitis Caucus: Formed in 2011, the caucus involves 40 members of the US House of Representatives and Senate. The caucus held an Inaugural Caucus briefing that led to Senate Resolution 199 declaring December 1-7 as Crohn's and Colitis Awareness Week.

EPIDEMIOLOGY

IBD was once a rare disorder, and the numbers of cases only began to rise dramatically during the latter half of the 20th century. Increased disease burden initially occurred in North America and Europe, sometimes at rates that doubled every decade, and in the past two decades has begun to expand into developing countries.

US EPIDEMIOLOGY

IBD is estimated to affect up to 1.6 million persons in the United States. IBD epidemiological studies are difficult to perform and compare because of the gradual onset of the disease, which prevents development of a gold standard for diagnosis. Furthermore, differing assessments of what constitutes CD versus UC make a total breakdown of the two subtypes difficult. Thus, IBD epidemiology is better described by its incidence, or the frequency of new cases over a certain time period.

Although the estimates of individuals affected by CD or UC vary widely by source, it is generally accepted that incidence rates of CD and of UC have steadily increased since the 1970s. These rates are extrapolated from a survey of healthcare records from Olmsted County, Minnesota (Figure 3).

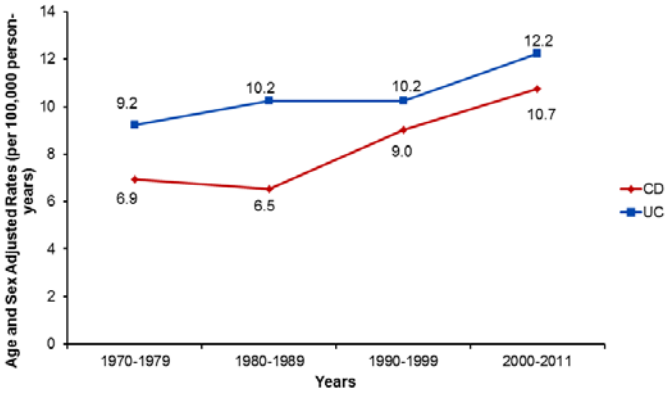

Figure 3: Trends in age- and sex-adjusted incidence rate of CD and UC in Olmsted County, Minnesota, 1970-2011. Image courtesy of Edward V. Loftus, Jr., MD, Mayo Clinic.

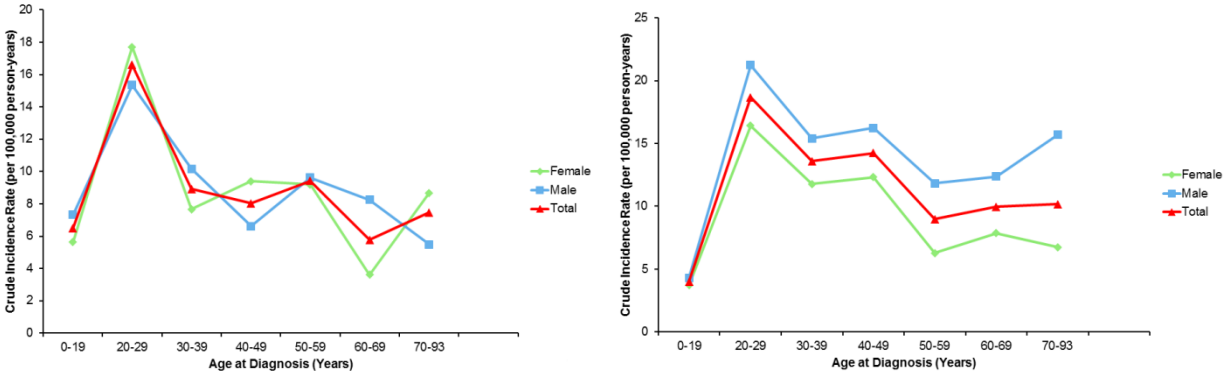

Figure 4: Incidence of CD (left) and UC (right) by age group and gender in Olmsted County, Minnesota (1970-2011). Images courtesy of Edward V. Loftus, Jr., MD, Mayo Clinic.

The Olmsted County study also provides a demographic breakdown of IBD incidence based on age and gender (Figure 4). CD and UC are commonly diagnosed in late adolescence and early adulthood (15-30 years old), but they can be diagnosed across the lifespan. A **CD** diagnosis is slightly more common in women, while an **UC** diagnosis is more common in men.

Globally, the rates of IBD incidence and prevalence (the percentage of the population affected by IBD) follow the increasing trends seen in the United States.

A survey of published **CD** (Figure 5) and **UC** (Figure 6) cases and epidemiological data indicates that, since the 1960s, cases of IBD have continued to increase across the world.

Cases of CD and UC have steadily increased in industrially developed countries with "Westernized" diets and have been concentrated in urban areas. Countries far from the equator have also demonstrated marked increases in incidence and prevalence when compared to those with warmer climates.

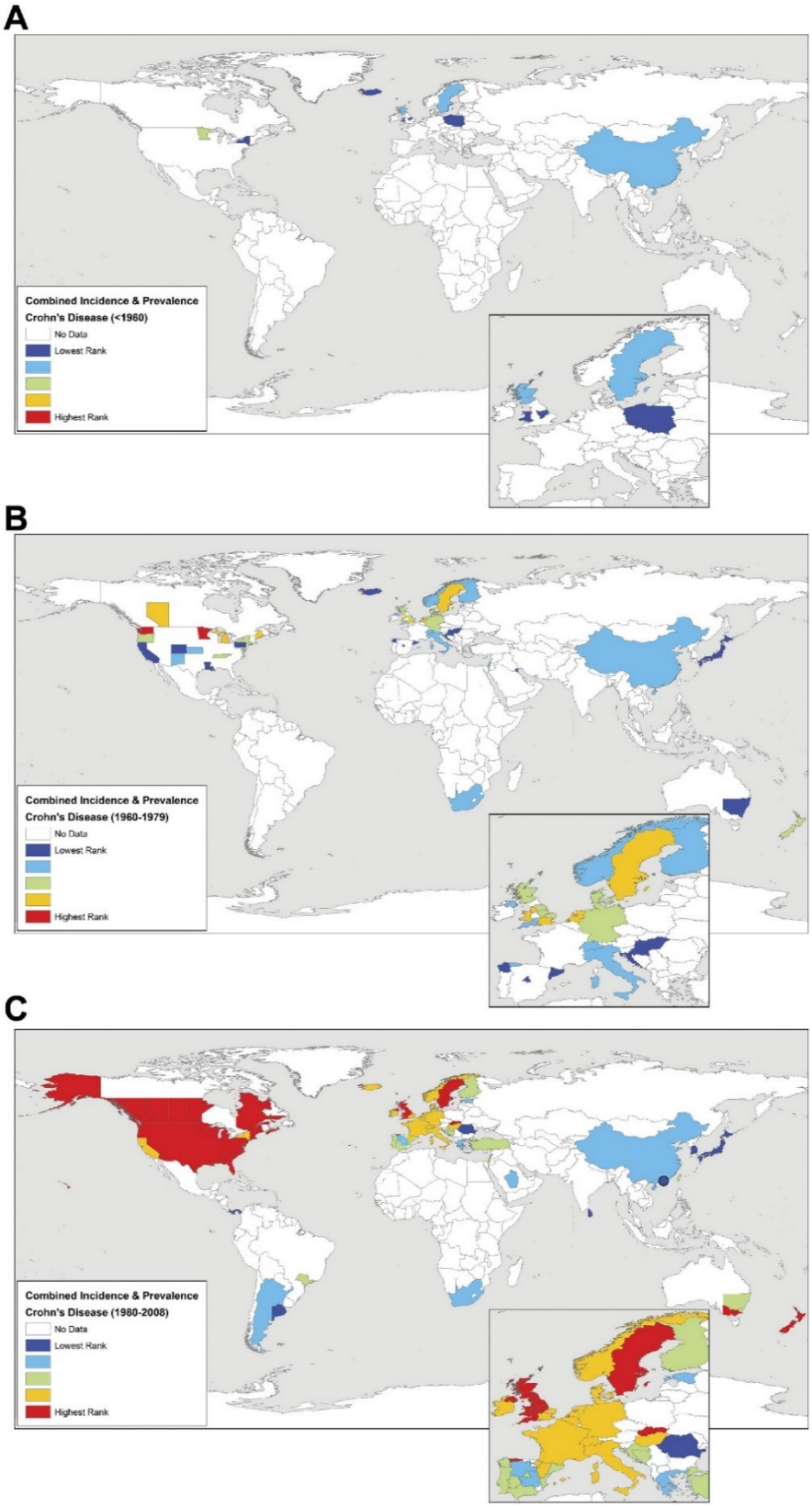

Figure 5: Longitudinal visualization of global combined incidence and prevalence of CD based on reports (A) before 1960, (B) from 1960 to 1979, and (C) from 1980 to 2000. Color legend displays dark-blue→red as low→high incidence/prevalence. Image licensed from Elsevier; Molodecky et al. (2012).

Overall, the global trends of increased industrialization, urban migration, and changing diets portend of new populations that may soon experience increases in IBD incidence and prevalence. These alarming rates underscore the importance and need for research to identify what causes IBD and how to aid the individuals already affected by the disease.

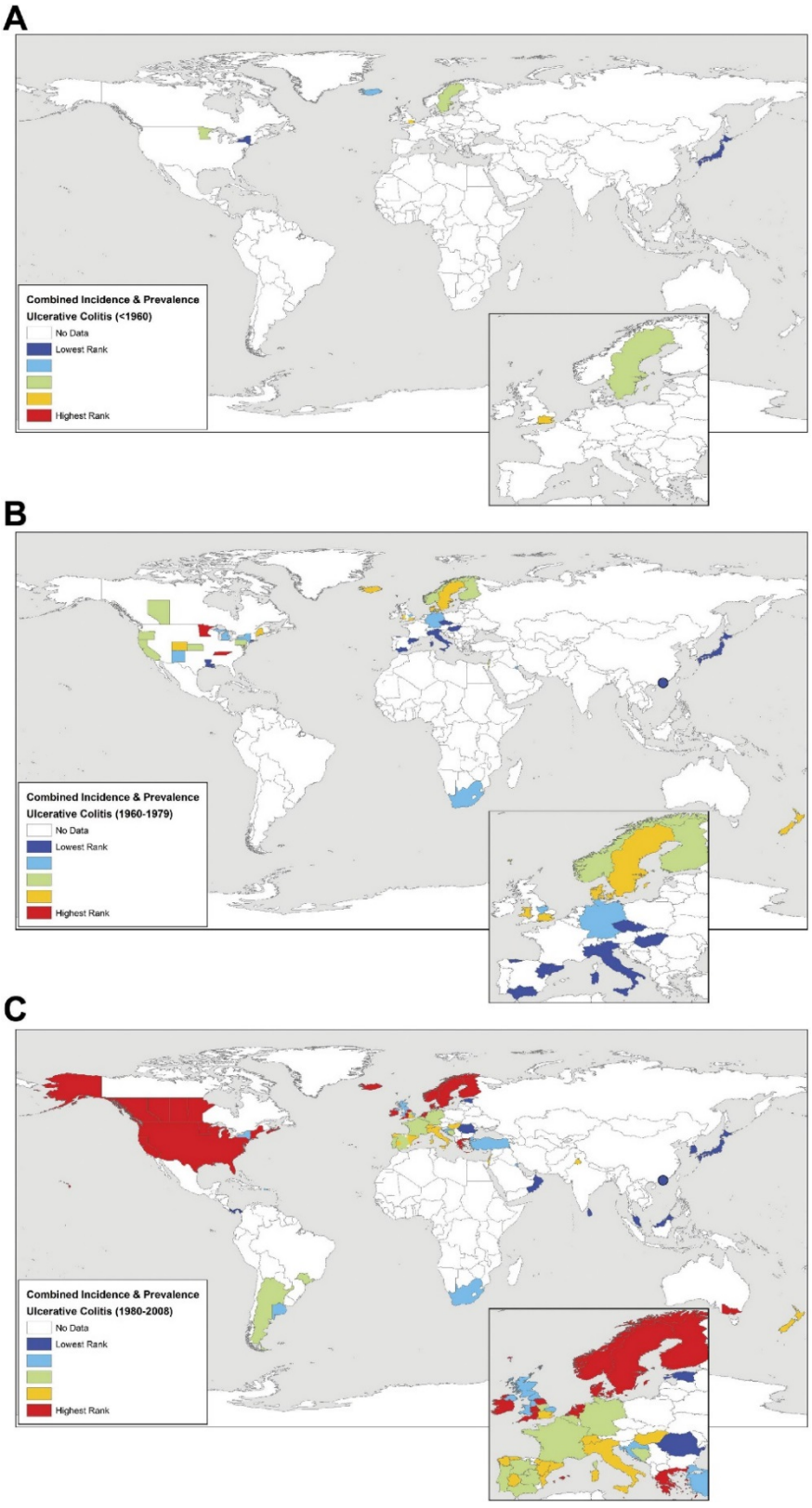

Figure 6: Longitudinal visualization of global combined incidence and prevalence of UC based on reports (A) before 1960, (B) from 1960 to 1979, and (C) from 1980 to 2000. Color legend displays dark-blue→red as low→high incidence/prevalence. Image licensed from Elsevier; Molodecky et al. (2012).

DISEASE DIAGNOSIS, STAGING, AND PROGNOSIS

SIGNS AND SYMPTOMS

Individuals who may be suffering from IBD first present with a range of symptoms such as:

- Abdominal pain and tenderness.
- Anemia (reduced red blood cells).
- Anorexia.
- Dehydration.
- Diarrhea.
- External disease manifestations such as:
    - Joint pain and soreness.
    - Eye irritation.
    - Liver and kidney disease.
    - Rashes on the skin.
- Fatigue.
- Failure to thrive/limited growth.
- Fever.
- Loss of appetite and weight.
- Nausea and vomiting.

Table 1: Key symptomatic differences between **CD and UC.**

Symptom	CD	UC
Blood in stool	Occasional	Very common
Constipation	Uncommon	Very common
Rectal bleeding or anal sores	Common	Rare
Urgent need to evacuate bowels	Occasional	Very common

DIAGNOSIS

To determine whether an individual is suffering from IBD, physicians employ a range of imaging and laboratory tests to diagnose and map the extent of disease. Given the similar clinical manifestations of CD and UC, multiple tests are needed to accurately diagnose between the two subtypes. Diagnosed patients will require regular monitoring because of IBD's chronic and progressive nature.

Biopsy and Tissue Staining: Tissue sampling, or a biopsy, is critical for diagnosing IBD, as well as for differentiating between CD and UC. The collected tissue from a patient undergoes multiples types of staining and imaging procedures to identify the gross cellular features indicative of CD or UC.

- Common features found in **CD** patients include mild-to-severe inflammation and alteration of tissues around the sites of skip lesions and ulcerations. These sites often include inflammation extending below the surface layer of the digestive tissue, described as fissures lined by collected mass of immune cells attempting to wall off the areas of inflammation, or granulomas (Figure 7). Although not present in all patients, granulomas are a hallmark of CD.

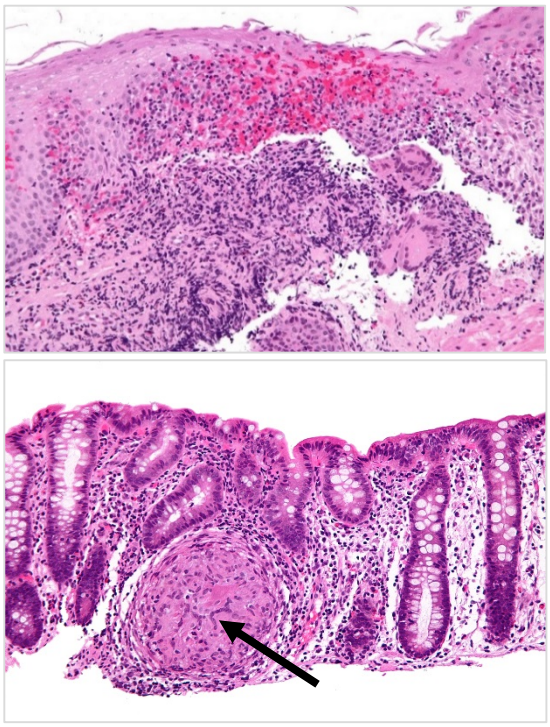

Figure 7: (Top) Biopsy slide of inflamed esophageal tissue from a CD patient. Dark purple dots are immune cells. (Bottom) Biopsy slide from a CD patient's colon, with a large granuloma (arrow). Images from Wikimedia Commons.

- For **UC**, common features include clear alteration of the top layer of the digestive tissue, or mucosal layer. Figure 8 shows the loss of regularity, as well as altered depth and opening of intestinal crypts in UC. The base of the now closed-off crypt is invaded by immune cells turning into crypt abscesses filled with immune and dead cells.

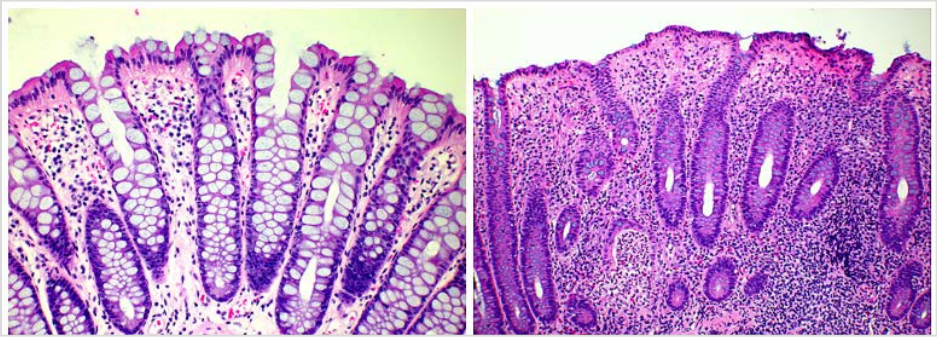

Figure 8: (Left) Biopsy slide of a normal surface layer of the intestine. The clefts along the lining of the intestine are known as crypts. (Right) Biopsy sample of a UC patient's intestinal surface layer. Image courtesy of Stephen B. Hanauer, MD, Northwestern University.

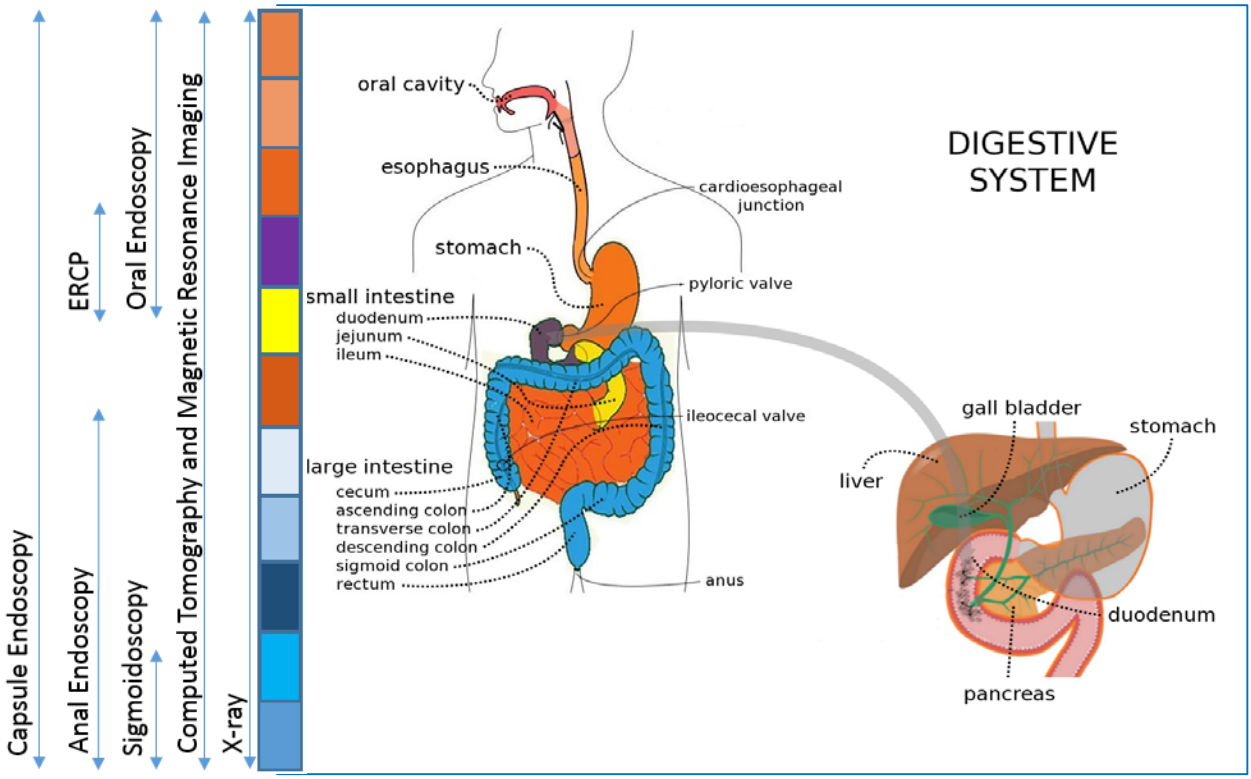

Figure 9: The human digestive system and the range of current imaging modalities. (Right) The digestive system is composed of the oral cavity, esophagus, stomach, small intestine (consisting of the duodenum, jejunum, and ileum), large intestine (consisting of the cecum, ascending, transverse, descending, sigmoid colon, and rectum), and anus. The liver, gall bladder, and pancreas release enzymes and bile into the duodenum. (Left) Following the color scheme of the digestive tract, multiple types of endoscopy and X-rays can image the entire range of the system. Computed tomography, magnetic resonance imaging (MRI), and capsule endoscopy: entire digestive tract. X-ray: small intestine or large intestine. Sigmoidoscopy: rectum→sigmoid colon. Oral endoscopy: oral cavity→duodenum. Anal endoscopy: rectum→ending of the ileum. ERCP (endoscopic retrograde cholangiopancreatography) can image the bile ducts in the liver and the pancreatic ducts to assess PSC development.

Imaging Tools: These techniques visualize sites of inflammation, determine the extent of disease, and further differentiate between a CD or UC diagnosis (Figure 9).

- **UC** is restricted to the large intestine, but **CD** can affect any component of the digestive tract. Thus, imaging tools such as endoscopes are utilized to visualize the surface of the entire digestive tract. Endoscopic procedures involve oral (upper endoscopy) entry or insertion into the rectum (colonoscopy), with the flexible scope able to view accessible regions based on point of entry. Endoscopic advancements also include attachment of an ultrasound probe that allows deeper mapping of an inflamed area.
- Capsule endoscopy involves ingestion of a small capsule fitted with a camera that takes images throughout the entire gut. Images are wirelessly collected via an external receiver, with the capsule exiting as part of a bowel movement 24-48 hours after ingestion.
- An X-ray allows for a quick and easy way to visualize narrowing or blockage of the intestinal system, both of which arise from inflammation and scarring of the digestive tissue. A contrast X-ray involves consumption of a thick liquid before the procedure that heightens the contrast of

the intestine versus the rest of the body. Contrast imaging of the small intestine involves ingestion of the liquid, while imaging of the colon involves an enema of the liquid.

- Computer aided tomography, or CAT scans, takes a series of X-ray slices at different angles throughout the length of the body to generate a cross-sectional image of the digestive tract. Because of the potential of **CD** to penetrate deep into digestive tissues, this diagnostic tool is particularly useful for patients with advanced disease and complications such as:
    - Abscess, a mass filled with pus.
    - Stricture, wherein constant inflammation results in fibrosis, or tissue scarring and narrowing of the affected area (Figure 10).
    - Fistula, progression of an ulcer that results in a tunnel from one part of the digestive system into another, or in some cases to the bladder, vagina, anus, or skin.
- Magnetic resonance imaging (MRI) uses a magnetic field and radio waves to generate detailed images of organs and tissues. For **CD** patients, an MRI is useful in visualizing fistulas in the anal region (perianal) or small intestine.

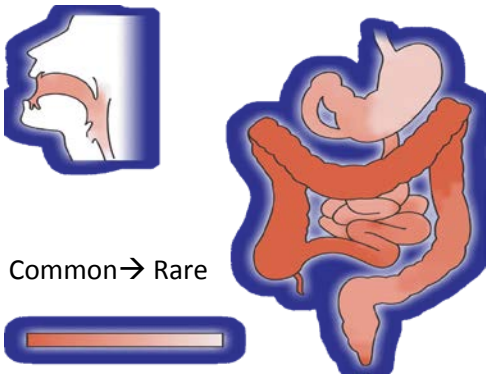

Figure 10: Range and severity of strictures. Although CD can impact any component of the digestive tract, the majority of diagnosed strictures occur in the small intestine and along the colon. Image courtesy of Stephen B. Hanauer, MD, Northwestern University.

Radiological Tool: The following test involves the use of radioactive isotopes or substances.

- Leukocyte scintigraphy, or white blood cell scan, involves attachment of a harmless radioactive substance to a patient's collected white blood cells. This assay takes advantage of the fact that active sites of IBD are highly inflamed and will recruit white blood cells, thereby indicating the affected area of the digestive tract.

Serological Tools: Blood-based, or serological tests, allow for the testing of disease markers that circulate throughout the body. Given the potential of IBD to impact nutrition and anemia, serological tests also allow for assessment of a patient's health and well-being.

- Routine blood tests are not currently used to diagnose a potential IBD patient. However, results from the tests support a potential diagnosis and assist in monitoring disease progression and treatment:
    - Complete blood counts allow for monitoring of potential infections and anemia. A common test to determine the severity of **UC** is the erythrocyte sedimentation rate (ESR), which tests for a nonspecific marker of inflammation.
    - Fecal occult blood test determines whether there is blood in the stool not visible to the eye.
    - Reductions in electrolytes (such as potassium) and vitamin B-12 indicate poor nutritional and mineral uptake by the intestines.
    - Liver function tests screen for liver and bile duct problems, because a small percentage of IBD patients develop PSC.

- Antibody/Biomarker assays are used to monitor disease progression and help to differentiate between CD and UC patients.
    - Anti-Saccharomyces Cerevisiae antibody (ASCA) and perinuclear anti-neutrophil antibody (pANCA) tests can help to distinguish a CD patient from a UC patient: ASCA tests positive for **CD**, while pANCA tests positive for **UC**. These tests, however, are far from definitive because some IBD patients may test positive and/or negative for both.
    - Antibodies to microbial products such as anti-I2, anti-flagellin and anti-OmpC are also considered markers for CD
    - Calprotectin is a biomarker for nonspecific inflammation that may predict disease relapse.
    - C-reactive protein is a biomarker for nonspecific inflammation in the body that may predict patient response to biologic therapies such as infliximab or adalimumab (See Treatment).

Table 2: Summary of CD versus UC Clinical Presentation and Diagnostic Results.

Diagnostic Results	CD	UC
Pathology via biopsy	Full thickness of the digestive tissue, and presence of granulomas	Mucosal layer only and no granulomas
Visualization via endoscopy	Entire digestive system	Colon only
Areas marked by radiological markers	Entire digestive tract	Colon only
	Presence of skip lesions	Continuous distribution across the surface of the mucosal layer
	Fistulae, abscesses, and tissue thickening and hardening	Does not extend below mucosal layer
Biomarker results	ASCA (+), Anti-OmpC (+), Anti-I2 (+), and Anti-flagellin (+),	pANCA (+)

DISEASE CLASSIFICATION AND PROGNOSIS

Classifying and staging IBD enables treating physicians to monitor disease progression and, in some cases, to determine the ideal drug or delivery mechanism for the patient.

CD Classification

The Montreal classification system is used to subclassify the clinical manifestations of CD based on the age of diagnosis, behavior, and location of disease.

- Age:
  - A1<16 years old.
  - A2: Between 17-40 years old.
  - A3: >40 years old.
- Behavior:
  - B1—No strictures or deep ulcerations.
  - B2—Presence of strictures.
  - B3—Presence of deep, penetrating ulcerations.
  - p—Presence of perianal disease (fistulas and deep ulcerations near the anal region).
- Location:
  - L1—Ileal (the final segment of the small intestine). Occurs in about 30 percent of CD cases.
  - L2—Colonic (large intestine-anus). Occurs in about 20 percent of CD cases.
  - L3—Ileocolonic (regions bordering the small and large intestine). Occurs in about 50 percent of CD cases.
  - L4—Upper (digestive regions from the mouth to the jejenum). Occurs in about 5 percent of CD cases.

CD Morbidity and Mortality

In general, CD patients have a life expectancy similar to unaffected individuals, although they have an increased risk of death from complications arising from gastrointestinal (GI) diseases (such as PSC), GI malignancies (such as CRC), and chronic obstructive pulmonary disease.

CD Risk of Relapse and Surgery

- Within the first year of diagnosis, 50 percent of CD patients may experience a disease relapse, with 10 percent of patients experiencing repeated episodes of relapse.
- Most CD patients develop complications (e.g., abscess, strictures, and fistulas) that require surgery, with disease relapse occurring in a high percentage of cases (>90 percent). Five-year intervals for the risk for surgery post diagnosis are described in the Table 3.

Table 3: Risk of Surgery after a CD Diagnosis.

Years post diagnosis	No surgery	1 surgery	2 or more surgeries
5	51%	12%	37%
10	39%	39%	23%
15	30%	34%	36%

- Genetic studies indicate that individuals with mutations in the *NOD2/CARD15* gene are susceptible to early-onset CD. These individuals also have an increased risk of developing strictures in the small intestine, along with a concomitant increase in requiring surgical treatment to remove scarred tissue.

UC Classification

The Montreal disease classification is based on regions of the colon that present disease.

- E1—Ulcerative proctitis, wherein disease is limited to the rectum.
- E2—Left-sided or distal UC, wherein disease extends from the rectum to the region bordering the descending colon and transverse colon.
- E3—Extensive UC or pancolitis, wherein disease extends throughout the large intestine.

UC Morbidity and Mortality

UC patients have life expectancies similar to the general population, but they suffer from increased disease-related mortality such as malnutrition, anemia, and surgical interventions. The most common cause of death for UC patients is toxic megacolon, wherein the colon rapidly widens and becomes thin-walled, resulting in a high risk of tearing. The risk for CRC and other cancers after diagnosis of IBD, is 3-5 percent over time, and is highest in UC patients with longstanding disease and/or pancolitis. All UC patients are encouraged to undergo regular CRC screening and surveillance beyond 8 years post diagnosis.

UC Risk of Relapse and Surgery

- A majority of UC patients experience disease relapse within 2 years post diagnosis. However, rates of relapse differ based on patient age, smoking status, and extent of disease. An estimated 10 percent of UC patients may have only one flare over 25 years, while, in rare situations, patients may experience near-constant disease flares.
- Patients diagnosed with proctitis have the best prognosis, with 70 percent never experiencing extension of disease into other regions of the colon.
- Of patients with pancolitis, 60 percent will eventually require surgical removal of the entire colon (proctocolectomy) and connection of the small intestine to the anus.
- UC-related surgery tends to occur within the first year of diagnosis, with the annual risk of a proctocolectomy dropping to 1 percent after the first year of diagnosis.

DISEASE BIOLOGY AND ETIOLOGY

The human (host) digestive system is composed of cells and tissues that process food and nutrient uptake, as well as the symbiotic bacteria, or commensals, which line the gut. A symbiotic relationship exists between the host and the microbiome, wherein food digested by the former provides nutrients for the latter. On the other hand, the microbiome facilitates digestion of nutrients indigestible by the host, educates the immune system to tolerate commensal microbes, and represses the growth of harmful microorganisms. Although the exact etiology of IBD is not fully understood, research has indicated interplay among genetic predisposition, environmental triggers, microbiome imbalance, and a loss of immune system regulation that culminates in disease.

IBD AND THE HOST INFLAMMATORY RESPONSE

Key Takeaways:

- The host's inflammatory response to the microbiome is influenced by environmental triggers and IBD-susceptibility genes.
- Over 160 genetic regions have been implicated in the development of IBD.
- Having a family member with IBD is the highest risk factor for developing disease.

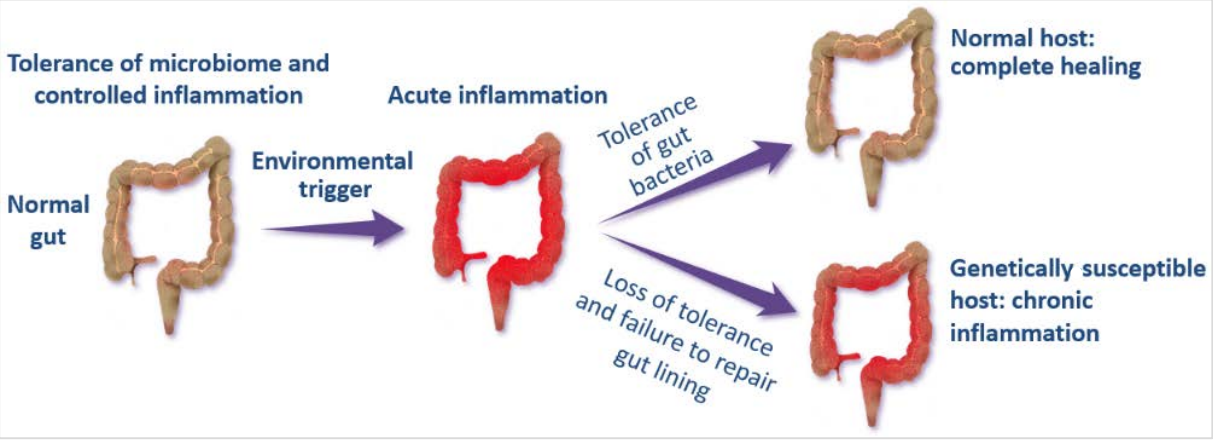

Figure 11: Gut microbiome and host inflammation in a normal host versus an IBD-genetically susceptible host. Modified image with permission © American Gastroenterological Association Institute, Bethesda, MD.

IBD can be described as an abnormal and chronic inflammatory immune response to the microbes that reside in the digestive tract (Figure 11). Within the normal gut, the immune system samples and develops tolerance to the microbiome, resulting in controlled inflammation when it encounters commensal microbes.

Disease onset can begin with an **environmental trigger** such as:

- Acute injury to the gut.
- Appendectomy: increases risk for CD, but lessens risk for UC.
- Switch to a diet rich in sugars and fats.
- Exposure to antibiotics.
- Living in urbanized, developed nations.
- Smoking: worsens course for CD patients, but protects UC patients.

In a normal host, the environmental trigger and ensuing inflammation is promptly down-regulated by the immune system. Inflammation-mediated damage to the gut surface, or mucosal layer, is rapidly repaired with minimal scarring.

However, in a genetically susceptible individual for IBD, the immune response remains abnormally activated and results in inflammatory damage to the mucosal layer. The ensuing damage leads to a leaky intestinal barrier that allows increased microbial invasion, further driving the inflammatory immune response. These individuals subsequently develop an unrestrained inflammatory response, leading to continued tissue destruction and scarring.

Genetic susceptibility to IBD

Deep sequencing of CD and UC patients has led to the identification of over 160 genetic regions that differ from unaffected individuals (Figure 12). The altered regions span a wide range of cellular, metabolic, and immune processes, indicating that IBD cannot be explained by a single gene model. Instead, it is believed that interaction between multiple genetic variants and environmental factors make an individual "susceptible to IBD."

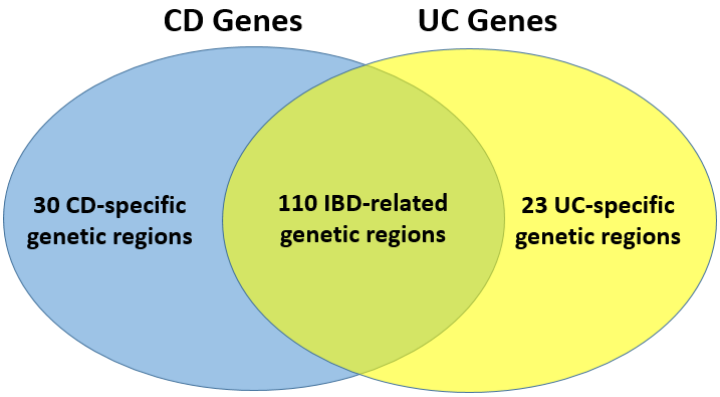

Figure 12: Venn diagram of number of IBD-, CD-, and UC-specific genetic regions. Data obtained from Jostins et al. (2012).

The single greatest genetic risk factor for developing IBD is having an affected family member. Having a first-degree relative with IBD has been shown to correlate to a 5-22 percent chance of developing disease. The level of risk depends on how close the relation is to the affected individual. For example, if one identical twin has IBD, his or her twin has a 50 percent chance of developing disease, while disease concordance between fraternal twins is only 8 percent.

IBD AND MICROBIOME IMBALANCE

Key Takeaways:

- The distribution of bacteria throughout the GI tract varies widely in terms of number and diversity.
- Microbiome imbalance arises when host inflammation suppresses commensal bacteria and allows the growth of pathogenic bacteria.
- It is currently unknown if imbalances in the gut microbiome are causes or consequences of IBD.

The gut microbiome consists of all the microorganisms that coexist with the host (commensals) including bacteria, viruses, worms, parasites, and fungi. The majority of microbiome studies focus on the bacterial component, but this is largely due to our ability to measure the bacterial population and limited ability to measure the other microorganisms. Given the nascence of non-bacterial microbiome research, this report will focus only on the bacterial aspects of the microbiome.

Microbial diversity varies greatly throughout the GI tract, with its level of complexity playing a role in suppressing the growth of pathogenic bacteria. The symbiotic relationship between the host and microbiome is developed by the release of microbial products that educate the immune system as to the types of commensal bacteria in the gut. In response, the immune system learns to recognize commensal bacteria and develops mechanisms that dampen and limit the level of inflammation when exposed to gut microbes.

It is currently unknown whether changes in the microbiome can cause IBD, or whether disease onset results in microbiome imbalance. However, it is well documented that IBD patients with active disease demonstrate drastic changes in microbiome composition. In some patients, microbiome imbalance can result in areas of the gut dominated by 1-2 pathogenic strains.

Causality aside, what ensues during a disease flare is a vicious cycle of microbial imbalance (Figure 13).

- Host inflammation mediates an over-amplified immune response that suppresses the commensal bacteria.
- The resulting hostile environment selects for pathogenic bacteria equipped to grow under highly inflammatory situations.
- Growth of pathogenic bacteria results in further immune activation and propagation of the inflammatory response.

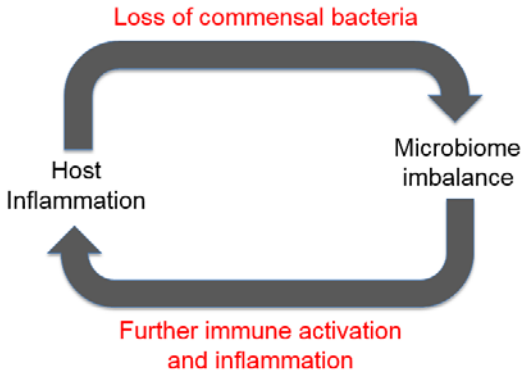

Figure 13: Recurring cycle of IBD pathogenesis. Modified image courtesy of Eugene B. Chang, MD, University of Chicago.

Current research suggests that the highly inflamed and imbalanced state of the gut microbiome is a likely factor behind the limited success of microbiome-focused therapies for IBD patients, as they are unable to break the recurring cycle of IBD pathogenesis.

IBD AND THE MUCOSAL INTERFACE

Key Takeaways:

- The mucosal layer functions as a barrier between the microbiome and the immune system.
- Chronic inflammation ensues when mucosal barrier integrity is lost.
- For patients, healing of the mucosal layer is associated with improved disease management and positive outcomes.

The mucosal layer is composed of mucus and digestive cells known as intestinal epithelial cells (IEC) and forms a sealed barrier between the microbiome and immune cells in the inner tissue of the gut (Figure 14). The region through which food travels and the microbiome is located is known as the gut lumen. The digestive tissue beneath the mucosal layer is known as the lamina propria and houses the immune system's sampling (dendritic cells) and inflammatory response mechanisms (T cells and macrophages). As the initial site of injury for IBD patients, the majority of IBD medications target the cycle of inflammation that occurs at the mucosal layer.

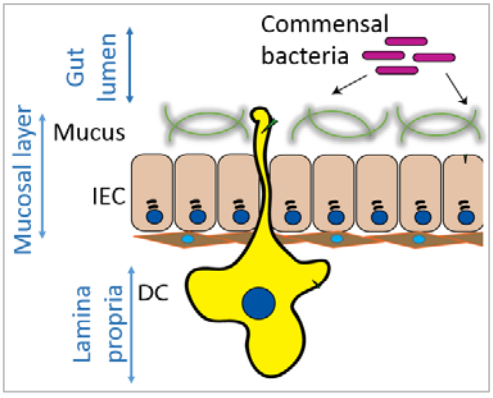

Figure 14: Mucosal interface of the digestive tract. Microbiome sampling by a dendritic cell (DC) is visualized by the cell's extension into the mucus/gut lumen. Image courtesy of Averil Ma, MD, UCSF.

The integrity of the mucosal layer is critical in keeping the microbiome separate from the immune system's inflammatory cells. In a normal host, this balance is maintained by educating the dendritic cells (via the sampling process). By knowing the type of commensal bacteria in the gut lumen, the dendritic cell knows not to cause an overtly inflammatory response to commensals that may pass from the gut lumen.

In an individual with IBD, this careful balance is lost, and the immune system reacts as though the gut was experiencing a massive infection. Through inflammatory white blood cells and molecules (such as TNFα), the immune system initiates a cascade of inflammatory responses to attack all bacteria. However, this response also causes IEC death and subsequent loss of the mucosal layer's integrity. Loss of the barrier allows increased bacterial invasion into the lamina propria, causing further amplification of the immune response, activation of T cells and macrophages, and ultimately chronic inflammation at the mucosal layer (Figure 15).

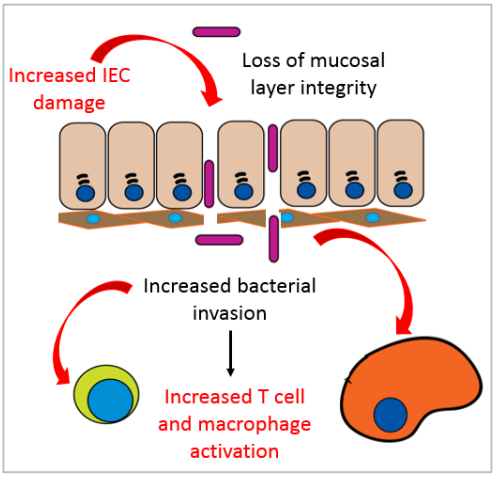

Figure 15: Loss of mucosal layer integrity and chronic inflammation. Events caused by the inflammatory response are in red. T cell, bottom left; macrophage, bottom right. Image courtesy of Averil Ma, MD, UCSF.

Healing of the mucosal layer and reconstitution of IEC are gaining acceptance as measures of disease activity. Beyond indicating a dampened inflammatory response, mucosal healing is also associated with positive outcomes for IBD patients. As a result, IBD clinical studies have begun to use mucosal healing as a clinical trial endpoint.

TREATMENT

OVERVIEW

Given the role of inflammation in IBD, diagnosed patients are treated with medication designed to target general pathways of inflammation.

The goal of IBD treatment is to:

- **Induce remission** (absence of symptoms).
- **Maintain remission** (prevent flare of symptoms).
- **Treat relapse** (return of symptoms).

There are five categories of IBD medications with injection, oral, or anal (i.e., enema, foams) delivery options depending on the site of IBD inflammation. For patients with advanced disease or those who have not responded to therapeutics, surgery at the site of inflammation is a potential treatment. For both CD and UC patients, treatments are based on severity of disease.

CD levels of severity:

- Mild to moderate—Patients experience high fever, and present with abdominal pain, mass or obstructions. Patients can also eat and drink without experiencing dehydration.
- Moderate to severe—Patients do not respond to therapy for mild-to-moderate cases and may experience high fever, dehydration, and weight loss, as well as nausea and vomiting without a clear obstruction of the digestive system.
- Severe to fulminate—Patients experience persistent symptoms despite administration of steroids and may present with high fever, persistent vomiting, obstruction, abdominal tenderness, and abscess formation, as well as weakness and wasting of the body.

UC levels of severity:

- Mild—Patients experience fewer than four stools a day, no or a small amount of blood in stools, and a normal ESR (see Diagnosis).
- Moderate—Patients experience more than four stools a day and a mild elevation of ESR.
- Severe—Patients experience more than six bloody stools a day and may present with fever, rapid heartbeat, anemia, and an elevated ESR.
- Fulminant—Patients experience more than 10 stools a day with continuous bleeding and may present with abdominal tenderness, require transfusions, as well as enlargement of the colon via x-ray.

AMINOSALICYLATES

Mechanism of Action

These anti-inflammatory compounds contain 5-aminosalicyclic acid (5-ASA) and suppress flares by activating cellular receptors highly expressed in surface cells of the colon that contribute to the inflammatory response. ***These drugs are successful in treating mild-to-moderate IBD*.**

Side Effects

Patients who use these drugs may experience side effects such as nausea, vomiting, diarrhea, heartburn, and headaches.

Generic Name	Brand Name	Delivery	Uses	CD Indication	UC Indication
balsalazide	Colazal	Oral or anal	Induction/Maintenance/ Relapse	Yes	Yes
mesalamine	Asacol, Aprisa, Pentasa, Rowasa, Canasa, Lialda	Oral or anal	Same as above	Yes	Yes
olsalazine	Dipentum	Oral or anal	Same as above	No	Yes
sulfasalazine	Azulfidine	Oral or anal	Same as above	No	Yes

CORTICOSTEROIDS

Mechanism of Action

Corticosteroids affect the body's ability to begin and maintain an inflammatory process by suppressing the immune system. Their mechanism of action involves reducing the expression of inflammatory genes. Corticosteroids are most effective as short-term treatments, because of their side effects and known ineffectiveness in healing the mucosal layer and maintaining remission. ***These drugs are successful in treating moderate-to-severe IBD.***

Side Effects

Patients who receive corticosteroids may experience side effects such as weight gain, acne, facial hair, hypertension, diabetes, mood swings, loss of bone mass, and increased risk of infection.

Generic Name	Brand Name	Delivery	Uses	CD Indication	UC Indication
hydrocortisone	Cortef, ProctoFoam-HC	Injection, Oral or anal	Induction/Relapse	Yes	Yes
budesonide	Entocort EC, Uceris	Oral or anal	Same as above	Yes	Yes
methylprednisone	Medrol	Same as above	Same as above	Yes	Yes
prednisone	Deltasone	Same as above	Same as above	Yes	Yes

IMMUNOMODULATORS

Mechanism of Action

These drugs function as molecules that impair the immune response, thereby limiting ongoing inflammation. These drugs encompass multiple mechanisms of action, from preventing activation of immune cells to impairing proliferation of immune cells in response to microbes. ***Immunomodulators are effective therapies for IBD patients who have relapsed with or cannot tolerate 5-ASA therapy, as well as those who have required repeated courses of corticosteroids.***

Side Effects

Common side effects associated with immunomodulators include nausea, vomiting, diarrhea, and a decreased ability to fight infections.

Generic Name	Brand Name	Delivery	Uses	CD Indication	UC Indication
azathioprine	Imuran	Oral	Induction/Maintenance/Relapse	Yes	Yes
6-mercaptopurine	6-MP, Purinethol	Oral	Same as above	Yes	Yes
cyclosporine A	Sandimmune, Neoral	Injection or Oral	Same as above	No	Yes
methotrexate	Rheumatrex, Trexall, Otrexup	Injection or Oral	Same as above	Yes	No
tacrolimus	Prograf	Oral	Same as above	Yes	Yes

BIOLOGICS

Mechanism of Action

The newest class of treatments for IBD, these molecules function as antibodies that suppress the immune system by targeting either the inflammatory molecule tumor necrosis factor (TNF) or by binding to a surface integrin protein present on inflammatory white blood cells (leukocytes). Inhibition of both targets reduces the inflammatory response. ***These treatments have been used on patients with moderate-to-severe IBD who have not responded to conventional treatments.***

Side Effects

Because biologics are delivered by injection, patients may develop redness, itching, bruising, pain, or swelling at the site of injection. Other potential side effects include stomach pain, back pain, rashes, nausea, and increased risk of upper respiratory infections (cough and sore throat).

Generic Name	Brand Name	Delivery	Target	CD Indication	UC Indication
adalimumab	Humira	Injection	Anti-TNF	Yes	Yes
certolizumab pegol	Cimzia	Injection	Anti-TNF	Yes	No
golimumab	Simponi	Injection	Anti-TNF	No	Yes
infliximab	Remicade	Injection	Anti-TNF	Yes	Yes
natalizumab	Tysabri	Injection	Anti-integrin	Yes	No
vedolizumab	Entyvio	Injection	Anti-integrin	Yes	Yes

ANTIBIOTICS

For IBD patients whose sites of inflammation occur in the colon/large intestine and the anus, antibiotics have demonstrated modest effects in inducing and maintaining remission. These treatments include ciprofloxacin (Cipro) and metronidazole (Flagyl) and are successful in treating infections or abscesses that occur at the aforementioned sites.

SURGERY

Given the progressive nature of **CD**, a majority of patients will require some form of surgery. The type of surgery will depend on the site of inflammation, severity of the disease, and the problem creating the need for surgery. Surgery will not cure CD: greater than 90 percent of patients who undergo surgery relapse within the first year after the operation.

Surgical resection for **UC** patients is considered curative for the disease. An estimated 50 percent of surgically resected UC patients may develop pouchitis (inflammation at the site of intestine-anus connection), but the condition is treatable with antibiotics.

CLINICAL PIPELINE

Clinical research is a branch of biomedical research involving human subjects. The goal of clinical research is to evaluate the safety and efficacy of drugs, medical devices, or diagnostics intended for use in humans.

Clinical trials are an important component of clinical research because they are used to evaluate the safety and efficacy of an experimental drug or therapy in human subjects. They can also be used to collect specimens from human subjects for further research.

Importantly, information on potential side effects is gathered during the clinical trial period and weighed against the potential therapeutic benefit of the treatment under investigation. Clinical research is divided into three key phases and is described in Figure 15.

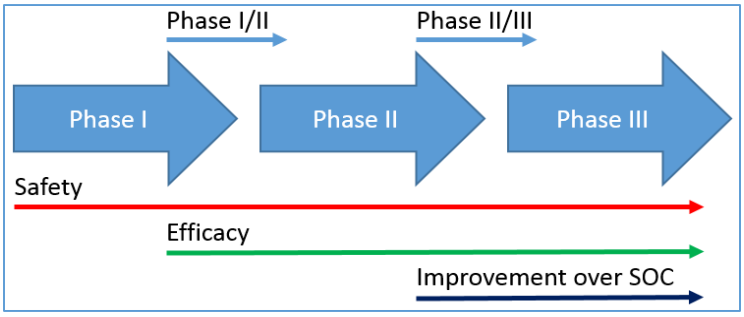

Figure 15: Phases of clinical trials. During **Phase I** studies, researchers test a new drug or treatment for the first time in a small group of people to evaluate its safety, determine a safe dose range, and identify potential side effects. During **Phase II**, proof-of-concept studies are performed as the drug or treatment is given to a larger group of people to assess its efficacy and optimal dose. During **Phase III**, the drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, and assess its impact compared to the current standard of care (SOC). Some clinical studies involve multiple phases to facilitate seamless transition between phases and are written as **Phase I/II** or **Phase II/III**. These designations are also used in adaptive trials, wherein study parameters for the Phase II study are modified with respect to ongoing Phase I trial results, etc.

IBD CLINICAL TRIALS AND INVESTIGATIONAL AGENTS

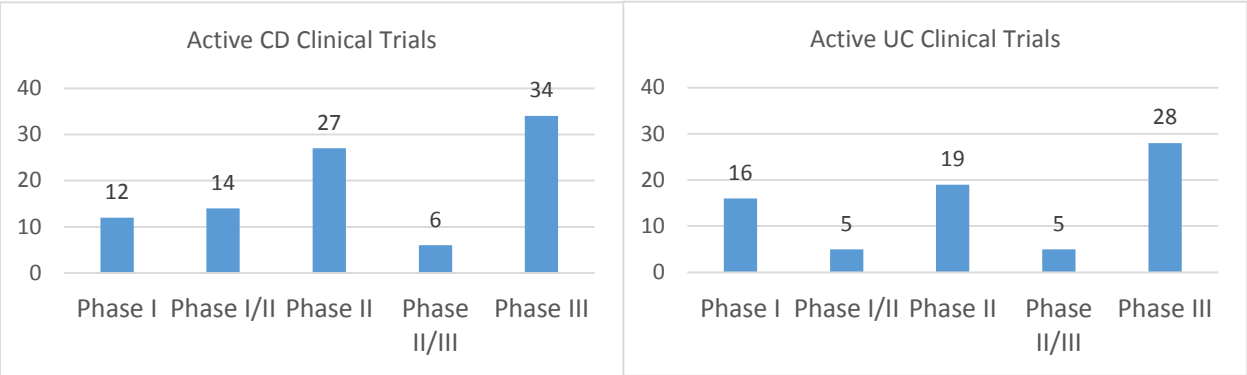

Figure 16: (Left) Active CD clinical trials. (Right) Active UC clinical trials. Data obtained from www.clinicaltrials.gov.

As of March 2016, there were 93 active CD clinical trials and 73 active UC trials (Figure 16). These trials are not mutually exclusive, with multiple trials conducting research in individuals with IBD.

There are currently 95 investigational therapies for IBD. The trial stages and categories of these therapies are visualized in Figure 17.

A large component of the IBD clinical pipeline involves the next generation of, and improved delivery of the five current therapeutic classes: 5-ASA, corticosteroids, immunomodulators, biologics, and combination/delayed release antibiotics.

Novel treatment options include:

- Stem cell therapies that involve transplantation of stem cells onto ulcers and fistulas of CD patients to mediate tissue repair.
- Small molecule inhibitors that mediate suppression of the immune system through novel mechanisms.
- Devices that expand narrowed areas of the digestive tract.
- Devices that modulate activity of the Vagus nerve, which is the nervous system component that mediates the inflammatory response in the gut.

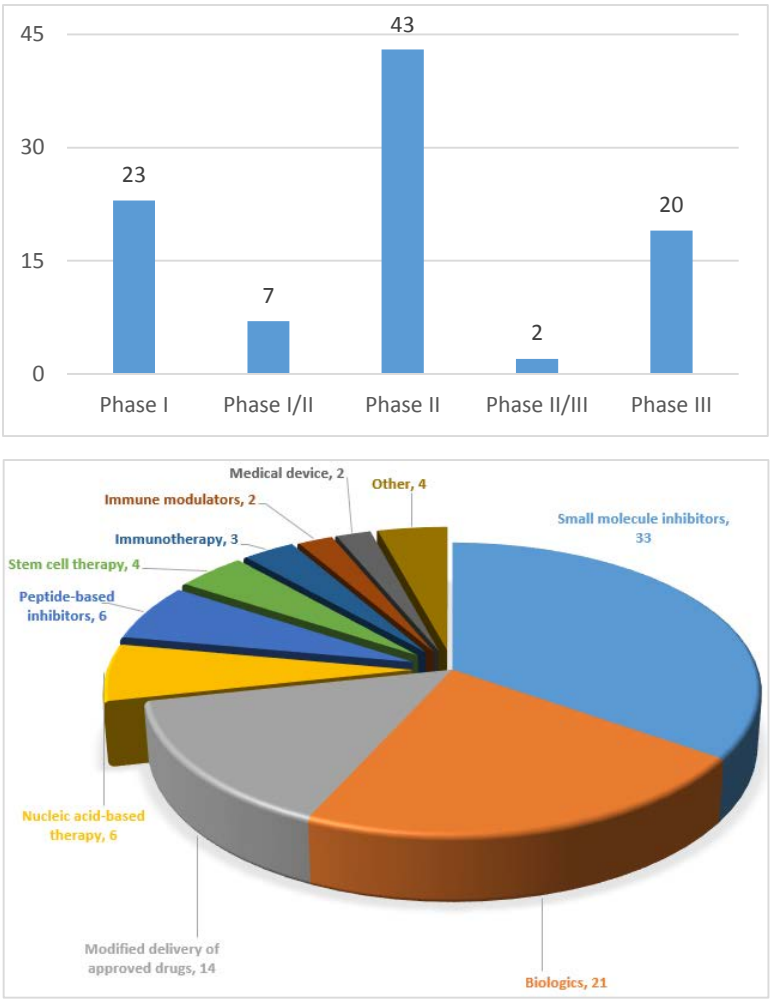

Figure 17: (Top) Distribution of IBD investigational agents based on clinical trial stage. (Bottom) Distribution of IBD investigational agents based on therapeutic modality. FMT and nutrition-based agents/trials are not included in these figures. Data obtained from BioCentury Online Intelligence.

- Fecal microbial transfer (FMT), which involves the implantation of types of bacteria known to alter a patient's microbiome.
- Nutritional supplements that address symptoms of IBD patients as well as modify the gut microbiome.

BARRIERS TO IBD RESEARCH PROGRESS AND KEY PHILANTHROPIC OPPORTUNITIES

Investments in IBD research have led to remarkable advancements in treatments, the tools to explore the relationship between the human gut and the microbiome, and have contributed to the scientific understanding of the immune system. However, key challenges remain in:

- Identifying individuals at risk for disease development and onset.
- Understanding disease etiology and progression.
- Developing effective regimens tailored to the individual.

To address these unmet needs and ultimately benefit IBD patients, the Kenneth Rainin Foundation and the Milken Institute Philanthropy Advisory Service convened academic, clinical, industry, patient advocate, and foundation partners to identify actionable and high-impact philanthropic opportunities.

IBD DIAGNOSIS AND CLINICAL TREATMENT

THE CHALLENGES

Diagnosis—Although patients and clinicians have access to a broad range of medications to treat IBD, the delay between disease onset and diagnosis results in the treatment of patients at a chronic stage of disease.

Predictors of Response—Clinicians lack biomarkers to predict which patients will respond best to current medications and to assess in which patients in remission may stop therapy. This results in a trial-and-error approach to identifying the ideal treatment regimen for patients.

Patient Adherence—Patient adherence to current therapies limits the overall effectiveness of the regimen and management of disease symptoms.

POTENTIAL SOLUTIONS

Diagnosis—Understanding the risk factors for developing IBD as well as how to identify patients before disease onset, or preclinical disease, offers an opportunity to treat patients before they are chronically affected by IBD.

Predictors of Response—Current tools used to assess treatment response and remission maintenance, such as C-reactive protein and calprotectin, are general markers of inflammation that are not specific for IBD.

- Identification of biomarkers that predict which patients would be responsive to biologic therapy allows for earlier administration of these potent treatments. Successful administration of biologics would allow for quicker achievement of remission, while preserving the use of corticosteroids as rescue therapy.
- An active field of research is the identification of biomarkers that predict extended remission to determine when to stop biologic therapy. Understanding the parameters for stopping treatment will improve patient quality of life, while identifying the most accurate trial endpoints for novel treatments and combined regimens.

Patient adherence—Even moderate changes in how patients interact with current therapies can have an outsized impact on the disease management, and reducing a therapy's side effects and toxicity can greatly impact adherence to treatment.

For example, biologics require injections into the blood that then disseminate the treatment throughout the entire body. This requires injection of a large amount of biologics to ensure that a sufficient amount reaches and acts upon the site of inflammation, which increases side effects and the risk of potential toxicity. However, if biologics could be targeted to the site of disease activity, then less biologic would be needed to achieve the same level of effectiveness, thereby reducing side effects and overall toxicity.

EXAMPLES OF CORRESPONDING PHILANTHROPIC OPPORTUNITIES

Diagnosis

- Support research that aims to identify at-risk individuals before disease onset, thereby understanding the environmental factors that trigger development of disease.
- Support efforts to assess the potential of lifestyle changes, such as diet alteration, in populations of at-risk individuals and those with preclinical disease.

Predictors of Response

- Support research to identify biomarkers that predict patient response to treatment, as well as public-private partnerships to overcome the cost of validating and developing clinical guidelines for the use of biomarkers.
- Support patient stratification research to develop a clinically relevant subdivision of IBD patients predictive of response to treatment and maintenance of remission post treatment.

Patient Adherence

- Support research aimed at improving patient adherence by modifying current biologic therapies into long-acting, orally based, and, ideally, as-needed dosing medication.
- Support research to target drugs and biologics to specific sites of inflammation, thereby reducing overall toxicity and increasing treatment effectiveness.

MICROBIOME

THE CHALLENGES

Microbiome research faces multiple, interrelated challenges that limits its current therapeutic potential.

- It is currently unknown whether changes in the microbiome are a cause or consequence of IBD.
- Current methods to collect, process, and assess patient microbiomes lack accuracy, resolution, standardization, and scalability.
- Clinical studies that modify the microbiome (via diet, FMT, and probiotics) have so far been unsuccessful in altering the highly inflammatory and inhospitable environment of active IBD.

POTENTIAL SOLUTIONS

To assess the causal role of the microbiome in IBD, research is needed to determine whether specific bacterial strains can cause IBD. These experiments will explore whether host infection by these strains causes IBD or whether they are already present in the gut and become dominant and pathogenic during IBD development.

Although multiple efforts are under way to understand the role of the microbiome in IBD, the lack of standardization across these efforts stymies the ability to compare results and determine the best research path forward. By facilitating collaboration and standardization, researchers can focus on developing scalable methods of collecting microbiome samples across the entire digestive system—rather than just stool samples—coupled to standardized procedures for storing and processing samples.

Efforts to understand the causal role of the microbiome would also benefit from improvements in sequencing the microbiome. Current methods are able to describe only the family of bacteria present in a sample, with researchers indicating that resolution to the level of bacterial strains is required to understand which strains drive—or possibly protect from—the development of IBD.

Previous efforts to modify the microbiome may have failed because they were tested during a disease flare. In such a situation, the gut is in a highly inflammatory and inhospitable state not conducive to microbiome modification. Patients in remission may be the ideal population in which to explore whether modifying the microbiome can impact the progression IBD.

EXAMPLES OF CORRESPONDING PHILANTHROPIC OPPORTUNITIES

- Support research efforts that will determine whether specific strains of bacteria can cause disease, or whether they arise due to an at-risk individual's genetic predisposition for disease.
- Support research efforts that aim to understand whether the molecules produced by bacteria during disease flares or remission can impact disease progression.
- Support research efforts to identify an elite controller population of IBD patients—individuals that are genetically predisposed for disease, but do not develop IBD, or individuals who have the disease but remain in constant remission. Analysis of these individuals' microbiomes may identify transferable properties to benefit patients with active disease.
- Support development of novel and scalable methods to sample a patient's microbiome, such as capsule collection, to better reflect the geographic diversity of the microbiome.

- Support collaborative efforts to standardize microbiome collection, processing, and scalability for subsequent application in clinical trials.
- Support assay development efforts to improve the resolution of microbial sequencing tools to the bacterial strain level.
- Support efforts to assess whether individuals in remission are the ideal clinical trial population for FMT, diet alteration, and other microbiome-modifying therapies.

HOST IMMUNE SYSTEM AND INFLAMMATION

THE CHALLENGES

Despite the fact that the majority of IBD medications function by dampening the inflammatory immune response, the basic understanding of how the immune system interacts with and responds to the microbiome is limited. Furthermore, the majority of research focuses on the interaction of the mouse immune system with the mouse microbiome, resulting in limited direct applicability for human studies.

POTENTIAL SOLUTIONS

Current research efforts in basic IBD immunology are focused on understanding the role of the multiple classes of cells involved in disease development and remission. For example, advances in understanding these interactions have led to the potent class of biologic therapies, which target specific immune cells and signaling molecules.

Current mouse models have allowed proof-of concept and toxicity studies of the current drugs available to IBD patients. However, development of more specific therapeutic options for IBD patients will require mouse models that more closely replicate human disease.

EXAMPLES OF CORRESPONDING PHILANTHROPIC OPPORTUNITIES

- Support research efforts to dissect the contribution of specific immune cells in IBD flares and remission, in order to identify novel therapeutic targets.
- Support research efforts that delineate how the immune system reacts to known microbes present during active disease to better tailor drugs for IBD patients.
- Support the development of mouse models that interact with the human microbiome, as well as assess and compare current mouse models to determine which models best replicate human disease.
- Support collaborations between IBD researchers and researchers working on other immune-mediated inflammatory diseases—such as multiple sclerosis, rheumatoid arthritis, and psoriasis—to facilitate resource and knowledge sharing.

INTESTINAL EPITHELIAL CELLS AND MUCOSAL HEALING

THE CHALLENGES

Endoscopic confirmation of IEC reconstitution and mucosal healing are key clinical trial endpoints. However, little is known about the processes that govern the healing of ulcerations and inflamed regions. The complexity of IEC research is also affected by the different clinical manifestations of CD (skip lesions and ulcerations) and UC (constant inflammation across the surface of colonic tissue).

POTENTIAL SOLUTIONS

Potent biologic therapy has helped many patients achieve and maintain disease remission; however, how long a patient must be in remission and, similarly, how well his or her IEC and mucosal layer must heal are key research questions that would inform when biologic treatment may be stopped. Identification of a healing biomarker would facilitate this process, because current methods require regular endoscopic procedures.

PHILANTHROPIC OPPORTUNITIES

- Support research efforts to develop standard definitions for IEC reconstitution and mucosal healing, and how they relate to the clinical definition of remission. These efforts would involve long-term patient studies to correlate the extent of mucosal healing with the length of time in remission.
- Support studies to identify biomarkers of IEC and mucosal healing. Identification of a “healing” biomarker would also benefit from guidelines for use in clinical trials and practice.
- Support research efforts that perform *in vitro* IEC studies to better understand the molecular processes that govern healing, as well as small molecule studies to identify novel therapeutic targets.

KEY PHILANTHROPIC FUNDERS OF IBD RESEARCH

There are four primary non-profit organizations that either directly fund research or support researchers. This section provides a brief overview of the grant-making organizations, describing their mission and funding mechanisms.

CROHN'S AND COLITIS FOUNDATION OF AMERICA (CCFA)

MISSION AND BACKGROUND

CCFA's mission is to cure CD and UC and to improve the quality of life of children and adults affected by these diseases. Founded in 1965, CCFA is the largest public charity of IBD research, providing more than $250 million for research.

Financials	FY 2012	FY 2013
Total Revenue	$51.6M	$54.4M
Total Expenses	$51.4M	$53.3M
Research Funding	$16.3M	$16.6M
Research/Expenses Ratio	32%	31%

RESEARCH FUNDING MECHANISMS

Beyond student, postdoctoral, and researcher awards, CCFA funds the following research initiatives:

- IBD Plexus—The goal of the project is to establish an integrated platform that will centralize and aggregate patient information, with linked biological samples, across multiple research efforts. The initiative is designed to speed progress toward precision medicine through novel research, leading to better diagnostics and treatments for CD and UC patients.
- Microbiome Initiative—The goal of the project is to develop greater understanding of the role of gut microbes (e.g., bacteria and viruses that are found normally in the intestines) in digestive health and inflammatory bowel diseases.
- Genetics Initiative—The goal of the project is to better understand the genes and their functions and the chain of biological events that result in IBD (i.e., pathogenesis).
- Pediatric Risk Stratification Initiative—The goal of the project is to identify measurable risk factors (i.e., genetics, microbial, and immunological) for the complications of severe IBD.

CROHN'S AND COLITIS FOUNDATION OF CANADA (CCC)

MISSION AND BACKGROUND

CCC is dedicated to finding cures for CD and UC and to improving the lives of children and adults affected by these chronic conditions. Founded in 1974, CCC is a Canadian national volunteer-based, public charity that has so far invested C$94 million toward IBD research.

Financials (CAD)	FY 2013	FY 2014
Total Revenue	$12.7M	$14.7M
Total Expenses	$7.3M	$9.8M
Research Funding	$5.3M	$7.6M
Research/Expenses Ratio	73%	78%

Research Funding Mechanisms

CCC provides research project grants as well as student, postdoctoral, and researcher awards. A key Foundation initiative is the Genetics, Environmental, Microbial (GEM) project. Launched in 2008, this international study is tracking healthy relatives of people with IBD to better understand how genetic, environmental, and microbial factors are linked to development of the disease.

THE KENNETH RAININ FOUNDATION

The data below is from 2015. For current information about Kenneth Rainin Foundation investments and grant programs visit: krfoundation.org/health

MISSION AND BACKGROUND

The Foundation is a private foundation with the health mission of supporting cutting-edge research projects that are potentially transformative to diagnosing, treating, and curing IBD. Since 2010, the Foundation has provided $8.35 million in research funds to novel basic research projects, with an emphasis on each effort's level of collaboration and innovation.

RESEARCH FUNDING MECHANISMS

The Foundation provides funding to allow researchers with innovative ideas to generate the data required for follow-on funding. Their awards include the following:

Funding Award	# of Grants
Innovator	36
Breakthrough	27
Synergy	5

- Innovator awards provide support for proof-of-concept studies with funding criteria determined by the innovation and scientific merit of the proposed work.
- Breakthrough awards provide longer-term support to existing Innovator Award recipients who have validated their original hypotheses.
- Synergy awards are designed to support discovery-oriented projects that are cross-functional, creative, and feature interdisciplinary collaboration.

THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST

MISSION AND BACKGROUND

The Trust is a private foundation that aspires to improve lives by supporting exceptional nonprofits and mission-aligned organizations in the United States and around the world in health, place-based initiatives, and education and human services. The Trust supports leading research institutions across the globe in an effort to find a cure—and, until then, better treatments—for IBD and Crohn's disease. Since 2009, the Trust has allocated more than $185 million to institutions in the United States, Canada, Europe, and Israel.

RESEARCH FUNDING MECHANISMS

The Trust provides funding in three main areas of IBD research:

Funding Type	# of Grants
Consortia Grants	48
Intramural Grants	12
Trainees, IBD Plexus	12

- Consortia programs that facilitate cross-institute collaborations such as the Sinai-Helmsley Alliance for Research Excellence (SHARE), the CCC GEM Project, CCFA's Microbiome Initiative, and the Very-early Onset IBD Program.
- Intramural awards that support multidisciplinary teams at leading academic centers and institutions such as the Broad Genetics and Exome Projects, the Mount Sinai IBD Center, and the Weizmann Institute of Science in Israel.
- Trainee and Integrated Health Platform awards such as CCFA Research and Training Awards as well as IBD Plexus (see CCFA Initiatives).

CONSORTIA AND STRATEGIC PARTNERSHIPS

Consortia are temporary associations of stakeholders from various sectors—academia, industry, government, and nonprofits—that share resources in order to achieve a common goal. According to *FasterCures'* Consortiapedia Catalogue, a database of biomedical research consortia, six consortia focus on IBD with ongoing efforts in resource building and/or therapeutic development. Patient cohorts are excluded from this analysis.

For a full list, please visit www.consortiapedia.fastercures.org

INTERNATIONAL INFLAMMATORY BOWEL DISEASE GENETICS CONSORTIUM (IIBDGC)

The IIBDGC is a network of researchers working on the genetics of IBD. It has undertaken a number of large-scale genome-wide association studies of CD and UC, which have identified dozens of genomic regions implicated in these diseases. It hopes that this research can be translated into a more complete understanding of the biology of IBD that might lead to improved diagnoses and treatment. To date, the consortium has collected genetic data from more than 37,000 patients with IBD and discovered 71 new genetic associations, bringing the total number of known associations with IBD to 163.

INFLAMMATORY BOWEL DISEASE BIOMARKERS CONSORTIUM (IBD BIOM)

The IBD-BIOM aims to advance the development of early warning diagnostics and molecular biomarker discovery for IBD using integrated "–omics" technologies. The consortium's aim is to discover clinical biomarkers for IBD to enable the early diagnosis of patients with IBD, and point to possible molecular targets for new, improved therapies to alleviate the suffering of IBD patients.

INFLAMMATORY BOWEL DISEASE CHARACTERIZATION BY A MULTI-MODAL INTEGRATED BIOMARKER STUDY CONSORTIUM (IBD-CHARACTER)

The IBD-Character Consortium is a collaborative effort to advance understanding of CD and UC and to increase diagnostic precision in detection of the diseases in their early manifestation. The consortium will generate the largest collection of samples of recently diagnosed, treatment-naïve IBD patients. Genetic modifications and expression, protein markers, gut microbial content, patient genotype for known susceptibility genes, and classical clinical data of the cohort will be extensively characterized to create a molecular snapshot of IBD in its early manifestation. The goal of the effort is to yield a list of biomarkers indicative of disease onset.

COLLABORATIVE CHRONIC CARE NETWORK (C3N)

The C3N aims to design, prototype, optimize, and evaluate a learning health system to improve clinical practice, patient self-management, and disease outcomes of patients with chronic illness. C3N is an open, peer production system that combines the collective input of patients, clinicians, and researchers. It is being developed and tested within the ImproveCareNow Network of 58 pediatric gastroenterology care centers that are actively sharing data to improve the care and outcomes of patients with CD and UC.

STRING OF PEARLS INSTITUTE (SPI)

The SPI is a joint project of the eight university medical centers in the Netherlands. It involves a prospective, disease-specific (including IBD) biobank in which anonymous patients' characteristics are documented and followed over a long period. These data are coupled to a biobank containing patients' biomaterials such as intestinal mucosa, feces, DNA, and serum. In case of approved scientific studies—and after approved protocol—additional samples and materials may be harvested.

MONITORING INNATE IMMUNITY IN ARTHRITIS AND MUCOSAL INFLAMMATION (MIAMI)

The MIAMI consortium (based in Europe) will deliver improved and/or novel methodology for early diagnosis of arthritis and IBD in at-risk populations, who do not currently exhibit clinically relevant conventional indicators. MIAMI will establish a list of biomarkers indicating onset and course of inflammation and will devise potential strategies for therapeutic intervention, including identification of cellular and molecular targets for treatment of the disease.

GLOSSARY

Abscess	A collection of pus, which can occur in the abdomen or pelvis of IBD patients
Anemia	A condition describing insufficient red blood cells, which can lead to fatigue, shortness of breath, and pale skin
Biomarker	A distinct biochemical, genetic, or molecular characteristic that is objectively measured and evaluated as an indicator of a particular biological condition or process
Biopsy	The process of taking a tissue sample in order to examine it more closely
Bowel	The portion of the digestive system below the stomach
Chronic obstructive pulmonary disease	A progressive disease that makes it difficult to breathe due to inflammation in the lungs that result in increased mucus production
Crohn's disease	A subtype of IBD that can affect any part of the digestive system and presents as patches of inflammation (skip lesions) that affect sections of the gut. CD ulceration of the digestive lining can extend through the entire depth of the gut tissue.
Colorectal cancer	A cancer that begins in the colon
Commensals	Symbiotic bacteria that reside in the gut
Dendritic cells	Immune cells that sample antigens throughout the body and process and present them to T cells
Digestive tract	Structures of the body stretching from the mouth to anus
Distal colitis	Ulcerative colitis that extends from the rectum to the transverse colon
Endoscopy	A nonsurgical procedure used to examine a person's digestive tract
Epidemiology	The branch of medicine that deals with the incidence, distribution, and possible control of diseases and other factors relating to health
Flares	Active periods of disease in IBD patients
Fistula	An ulceration of gut tissue that results in a tunnel from one part of the digestive system to another region or tissue
Genotype	Identification of the genes most commonly associated with a disease
Granuloma	A massed collection of immune cells produced in response to inflammation or infection
Gastrointestinal disease	Diseases involving the gastrointestinal tract, namely the esophagus, stomach, small intestine, large intestine and rectum, and the accessory organs of digestion (liver, gallbladder, and pancreas)
Incidence	The occurrence, rate, or frequency of a disease
Inflammation	The process by which the immune system's cells and products protect the body from harmful organisms. It is characterized by injury or destruction of infected tissues and manifests through signs such as pain, heat, swelling, and loss of function
Intestinal crypts	Tubular structures composed of cells that protrude from the inner lining of the intestines and into the walls of the intestines

Intestinal epithelial cells	Cells of the digestive system that take up nutrients from the gut and help form a barrier between the gut lumen and lamina propria
Lamina propria	A thin layer of loose connective tissue that lies beneath the intestinal epithelial cells
Leukocyte	A white blood cell that circulates in the blood and body fluids and is involved in the inflammatory response
Macrophage	A large cell that samples its surroundings—usually in stationary form in the tissues or as a mobile white blood cell around sites of inflammation
Microbiome	The gut microbiome is composed of all the microorganisms that coexist with the host, including bacteria, viruses, worms, parasites, and fungi
Microbiome imbalance	A disease state of reduced microbiome diversity, dominance of pathogenic bacteria, and increased gut inflammation
Mucosal layer	The top layer of the gut composed of mucus and intestinal epithelial cells
Mucosal healing	The process of mucus and intestinal epithelial cell reconstitution
Mucus	A thick protective fluid that lines the digestive tract and lies directly above the intestinal epithelial cells
Pancolitis	Ulcerative colitis that extends throughout the entire colon
Prevalence	The proportion of a population found to have a disease
Primary sclerosing cholangitis (PSC)	A severe form of scarring of the liver bile ducts, which can result in liver failure
Proctitis	Ulcerative colitis that occurs only in the rectum
Proctocolectomy	Surgical removal of the entire colon
Prognosis	The likely course of a disease or ailment
Pouchitis	A disease complication that may arise in patients who undergo a surgical resection that connects the intestine with the anus. The resulting inflammation is treatable with antibiotics
Skip lesion	A wound or site of inflammation that is clearly patchy, which skips areas that remained unharmed
Stricture	Scarring and narrowing of a section of the gut
T cells	Immune cells that play an active role in the immune response, serving as a mediator of the inflammatory response
Toxic megacolon	A complication of ulcerative colitis wherein the colon rapidly widens, becomes thin-walled, and has a high-risk of tearing
TNFα or TNF	Tumor necrosis factor α is a molecule that drives and maintains the inflammatory response mediated by T cells and macrophages
Ulcer/ulceration	A crater-like sore on the gut, wherein the top layers of the tissue have been removed
Ulcerative colitis	A subtype of IBD limited to the rectum that can extend throughout the large intestine/colon. UC presentation can be described as a continuous stretch of inflammation of the cells lining the colon surface.
Vagus nerve	Nerve of the nervous system that mediates the inflammatory response in the gut

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