MID-SEMESTER REPORT

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EXPERIENTIAL LEARNING CENTER

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Executive Summary

ClostraBio partnered with the Experiential Learning Center (ELC) in order to receive consultation on potential product market paths and strategies for their new treatment process for Inflammatory Bowel Diseases (IBD). ClostraBio is working with a team of eight student consultants who are tasked with completing several objectives. The objectives consist of an of outline of the current market population, identification of competitors, treatment costs, the estimation of a potential product price, and the identification of potential key partners for the company.

In this report, the ELC team have provided a snapshot of the progress made on the objectives. To date the research has included information on market opportunity and product scope of IBD in United States (U.S.). Included in this report is information regarding direct costs of the IBD, information on the market share of different drug groups, names and costs of various direct competitors, and names of various home style remedy indirect competitors.

In addition, the team of consultants has identified potential treatment options considered as competition for ClostraBio, specifically the patients suffering from mild to moderate IBD symptoms. The team of consultants will also explain treatment approaches that are not one of the four primary therapy types and provide cost data relative to treatment types. Lastly, the team has outlined the next steps to be taken over the remaining 6 weeks of the project.

Introduction

Experiential Learning Center

The Experiential Learning Center (ELC) creates unique real-world educational experiences for Northern Illinois University students and provides valuable research, fresh ideas, and recommendations to sponsoring organizations. As of May 2018, the ELC successfully completed over 181 projects for 94 different sponsors.

Successful ELC projects result from the following:

- Committed students
- Dedicated coaches
- Accessible sponsors

Students apply to be on an ELC team and are hand-picked by the team coach. Coaches are tasked with keeping the team on track and serve as a guide. Student teams learn by working through ambiguous situations.

With each project, the students take on the role of a consultant. Project management, communication, presentation, team building, leadership, and technical skills are developed throughout the project experience. With these valuable skills, students are prepared to step into the business world with confidence and knowledge.

ClostraBio

ClostraBio, founded in 2016, is a startup biotechnology company aiming to implement new medications that target Inflammatory Bowel Diseases (IBD) such as; Crohn's Disease (CD) and Ulcerative Colitis (UC), into the market. ClostraBio is confident that its medications and new treatment process can assist in the remission of IBD but would like assistance in gathering market information on IBD treatments.

ClostraBio would like an ELC team to analyze the competitive landscape of IBD treatment therapies and medications, creating a target product profile to help best market medication associated with IBD. This project will include an assessment of the current landscape

of similar medications, market size, market research, and evaluation, price point assessment, and data analytics.

Project Objectives

ClostraBio has set several objectives and deliverables that the ELC team must implement by the end of the 16-week semester. The objectives are as follows;

- Identify immediate market opportunity for ClostraBio medication.
- Identify potential customer population and their treatment costs.
- Identify a potential price estimate for ClostraBio medication.
- Map the competitive landscape of direct and indirect competitors.
- Identify potential key partners.

Project Team

The ClostraBio ELC team is comprised of six undergraduate and two graduate students from Northern Illinois University. The team is led by a faculty coach and a student assistant coach. Each team member was hand selected by the Experiential Learning Center director based on their skillsets, major, and experiences.

Coach
Jason Gorham

Assist. Coach
William Holmes- *Technology Liaison*

Consultant Team
Aditya Amar- *Consultant*

Erick Castillo- *External Communication Liaison, Consultant*

Michael Redwinski- *Internal Communication Liaison, Consultant*

Parth Gandhi- *Consultant*

Rui Zhang- *External Communication Liaison, Consultant*

Shruti Vidya Jituri- *Consultant*

Stephanie Demaria- *Document Manager, Consultant*

Research Progress

Below lists all current progress made on project deliverables. Project deliverables will include data from this report and additional data gathered past this point in the project semester. The team has identified several areas of research in which will require more time before it is substantial enough to base recommendations on, therefore, no project objective deliverables will be marked as complete in this report. Research gathered has been cited in the "Works Cited" section of this report.

Market Opportunity and Product Scope

Prevalence of IBD in United States

The Centers for Disease Control and Prevention (CDC) recently released a new study which estimates IBD prevalence based on 2015 National Health Interview Survey (NHIS). To examine the prevalence of IBD among the nation the noninstitutionalized U.S. adult population was analyzed in this study. The overall estimation of U.S. adults who have received a diagnosis of IBD in 2015 was 3.1 million, or 1.3% of U.S. total adult population. (pg. 1167)

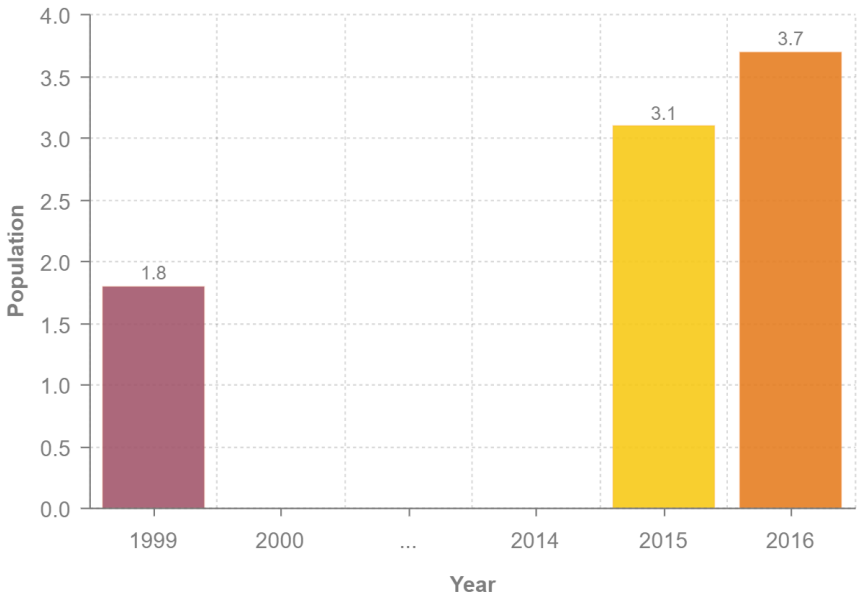
Within this new study, certain characteristics of the patient population stood out. Of the 3.1 million diagnosed, 1.77 million of those were female and 1.31 million were male. The age group of 45-64 had the highest number of cases at 1.26 million whereas the other age groups of 18-24, 25-44, and over 65 had 153,000, 865,000, and 805,000 respectively. Non-Hispanic white patients were the vast majority of cases at 2.34 million when focusing on ethnicity. Lastly, the majority of cases found within the U.S. were focused in the Southern region with 1.18 million cases. Previous IBD prevalence studies using administrative claims data or data collected from limited geographic areas estimated that approximately 1.6 million U.S. adults had IBD. And the most recent study based on large and nationally representative data source was from 1999, estimating that 1.8 million (0.9%) U.S. adults had IBD.

The Clostrabio ELC team extracted the dataset of 2016 NHIS from CDC's website using the similar method to calculate the prevalence of IBD among adults in United States during 2016. The result showed an estimation of 3.7 million (1.5%) U.S. adults were diagnosed with IBD in 2016. Based on the two nationwide studies and the result calculated, the population of

U.S. adults who were diagnosed with IBD almost doubled in 17 years. The growing trend is shown from the results in Figure 1.

Figure1. IBD Prevalence among Adults in U.S. *

(in million)



National Health Interview Survey (2015)
National Health Interview Survey (2016)

The new prevalent estimate of adults who have IBD among U.S. from 2015 NHIS data far exceeds estimates from administrative data. This may not necessarily mean the more targeted patient population studies are invalid since different methods may have different strengths and limitations. It is clear to the ELC team that additional research is required to get better understanding of IBD prevalence in the United States.

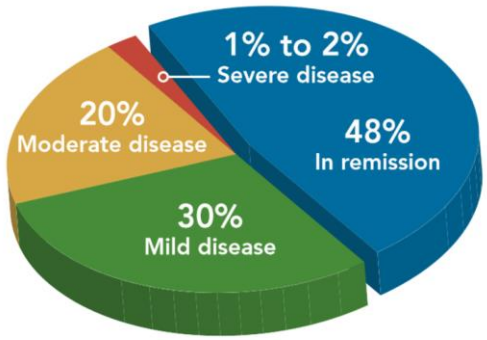
Disease Severity, Progression, and Recurrence

Classifying IBD patients according to disease severity could be critical to identify market opportunities, guide treatment strategy, and manage IBD. However, no formal or consensus definition or classification criteria of mild, moderate, or severe (fulminant) is currently available. Crohn's Disease Activity Index (CDAI) for CD and Mayo Score for UC are used to license biologic agents in clinical trials. But they are rarely used in routine clinical practice since they don't necessarily measure disease severity, which encompasses more than disease activity. According to Dr. Laurent Peyrin-Biroulet (2015), the ideal IBD severity determinants should include clinical symptoms, the impact of the disease on the patients, the patient's quality of life,

the inflammatory burden, the extent of bowel movement, and the location of the problem, as well as the patient's history. (Pg. 474)

Figure 2 shows the breakdown population according to severity level for UC. Almost half of UC patients are in remission for a given year while the sum of the mild and moderate disease population makes up the other half of UC patients. People with severe disease account for just 1% to 2% of the total UC patient population (CCFA. 2014). Based on affected location, UC can be classified into 4 types, ulcerative proctitis, left-sided colitis, extensive colitis, and pan-ulcerative (total) colitis. According to gastroenterologist Todd B. Linder, even though it is good to know which type of disease trends to be more severe, there's no correlation between UC disease type and severity (HealthiNation. 2018). Ulcerative proctitis refers to the type that inflammation just exists in the rectum. There's around 28% to 30% possibility that ulcerative proctitis will progress to left-sided colitis where the inflammation extends as far as a bend in the colon near the spleen. The possibility for ulcerative proctitis directly extends to extensive colitis (which affects most of the colon and rectum) or pan-ulcerative colitis (which affects the whole colon and rectum) is 14% to 16%. And there's 21% to 34% chance for left-sided colitis progress to extensive or pan-ulcerative colitis.

Figure2 Percentage for each severity



For the severity distribution of CD, remission or mild disease is prevalent in 50% of CD patients and the remaining half of the CD population has moderate to severe disease. 20% to 30% CD patients will have non-progressive clinical course while up to 75% will eventually need surgery. After diagnosis, about 30% CD patients will need surgery in 5 years while the percentage will increase to 40% to 55% in 10 years. 30% of those who have already has surgery will experience relapse. (CCFA, 2014; CCFA, 2019; Feuerstein, 2017; Mehta, 2016) Study

shows that patients will spend 24%, 27%, and 41% of the duration of their disease in the state of medical remission, mild disease, and postsurgical remission. The remaining 8% will be allocated to states of severe drug-responsive disease (1%), severe drug-dependent disease (4%), severe drug-refractory disease (2%), and surgery (1%). (Lichtenstein, 2018)

Overview of Economic Burden of IBD

Direct Costs

A study focused on analyzing lifetime healthcare of IBD patients collected data from 78,620 CD and 85,755 UC patients. The result of study is shown in Figure3. For CD patients, the group of age 0-11 had the highest average lifetime cost which was $764,205 while the group of age older than 70 had the lowest lifetime cost at $288,344. Similarly for UC patients, the youngest group had the highest lifetime healthcare cost at $369,955 while the oldest group had the lowest lifetime cost at $132,396. It's clear in the result that the average lifetime cost decreased with age increased and CD patients tend to spend almost as twice as UC patient would spend during the whole life. (Lichtenstein, 2017)

Another study analyzed the average annual cost per patient as well as the cost for the first year after diagnosed. (Table 1) This study shows consistent result with the previous study that younger group tend to spend much more money than older group and patients with CD tend to spend double amount than UC patients. In this study, patients with either CD or UC are in common to spend more than twice in the first year after diagnosed as they do annually during the remaining life. (Baldassano, 2018)

Figure 4 shows the result from another study which analyses the trend of direct cost for CD. This study reflects the recent changes in treatment options. From A, B, D, it appears that the total direct cost, prescription cost, and outpatient cost were increasing over years while the direct cost of patient without CD was remaining the same. However, inpatient cost experienced dramatic increase from 2003 to 2004 and then started decreasing from 2005. As known, one of the best-selling biologics medicine is Humira which was approved to treat CD in 2007. So it's easy to deduce that introduction of new treatment options like biologics is negatively related to

the inpatient costs which means inpatient cost mainly because of hospitalization decreased while patients were have new treatments. (Bounthavong, 2017)

Figure3 Lifetime direct cost per patient

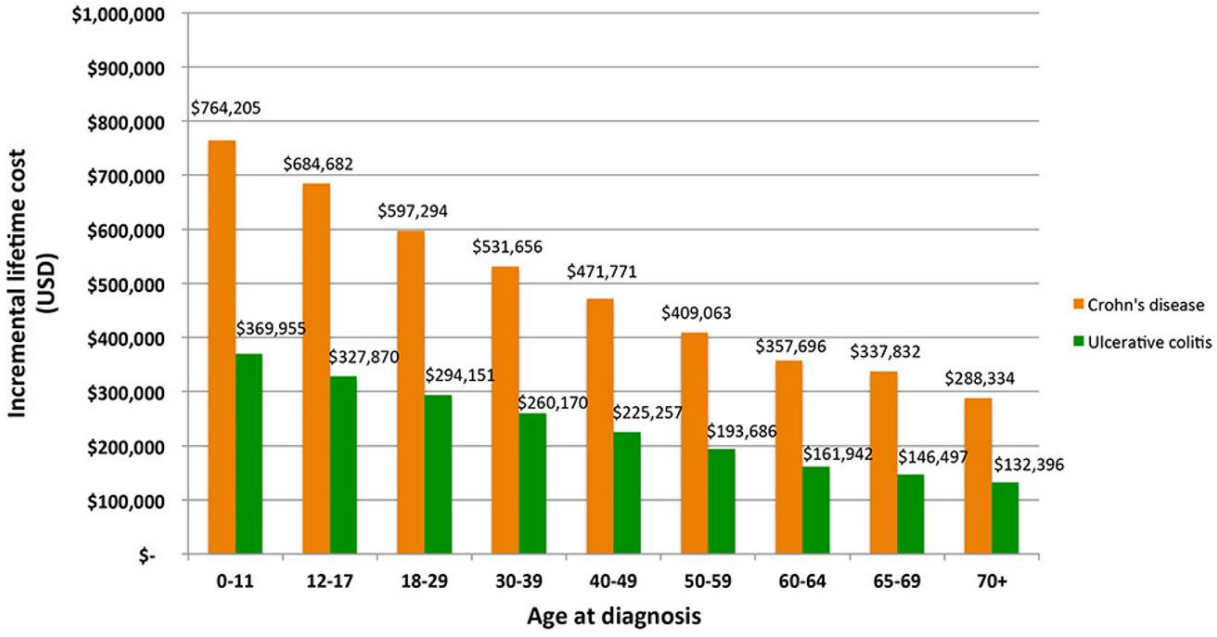
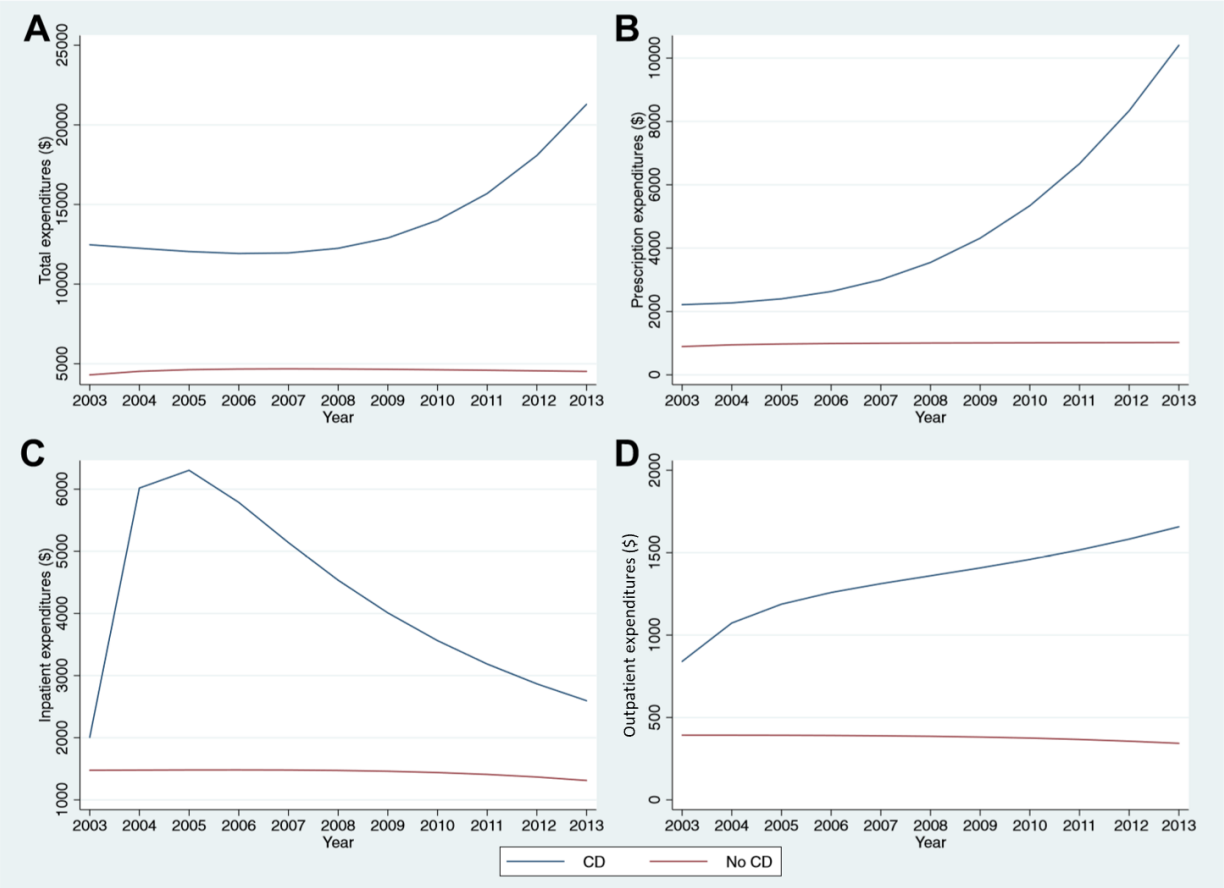


Table1

Average Annual Incremental Cost and Cost for the First Year After Diagnosis for Patients With Crohn's Disease or Ulcerative Colitis, by Age at Diagnosis				
	Crohn's Disease		Ulcerative Colitis	
	Average Incremental Cost			
Age at Diagnosis	Annual	Year 1 After Diagnosis	Annual	Year 1 After Diagnosis
0-11	$22,856	$46,610	$11,032	$29,996
12-17	$21,104	$38,616	$10,113	$23,538
18-29	$18,854	$24,593	$ 9,345	$16,312
30-39	$17,512	$19,625	$ 8,644	$13,243
40-49	$16,431	$18,724	$ 8,014	$12,819
50-59	$15,189	$19,288	$ 7,653	$13,833
60-64	$14,376	$16,421	$ 7,145	$13,192
65-69	$14,525	$21,007	$ 6,930	$ 9,839
70+	$14,276	$14,049	$ 7,224	$10,473

Figure4 Trend of direct costs for CD



Market Shares of IBD Drugs

Research on market shares of current IBD drugs will be important for Clostrabio to gain insights of potential competitors, market opportunities, future market shares, and medication price. Study shows that the proportion of IBD patients using biologics increased while the proportion for 5-ASAs and immunomodulators decreased, only corticosteroids remained the same.

For the medication utilization of CD, biologics started exceeding the utilization of 5-ASAs which was used to be the medication with the highest usage rate (Figure 5). Figure 6 shows the percentage of IBD medication as primary therapy for IBD patients and the market share for each kind of medication. Similar to the IBD medication utilization trend, the patient number choosing biologics as primary medication is increasing over years while the other three kinds were decreasing.

The market share figure shows that biologics medication occupied almost all of the IBD treatment market in 2015 with a continuously growing trend. After breaking down the percentage of IBD medication as primary therapy (Figure 7), it appears that biologics medication is more prevalent in CD market. This also explained the reason why the average direct cost for CD patients could be doubled the direct cost for UC patients. The cost for each kind of medication is clearly shown in Figure 8. The per-member per year (PMPY) costs for biologics and 5-ASAs were increasing while the other two kinds were almost remaining the same. The biologics' PMPY is incredibly higher than the other therapies, explaining the reason why biologics almost occupied all the market share even though its utilization is a little bit than half among all the patients. (Yu 2018)

Figure5 IBD medication utilization trend

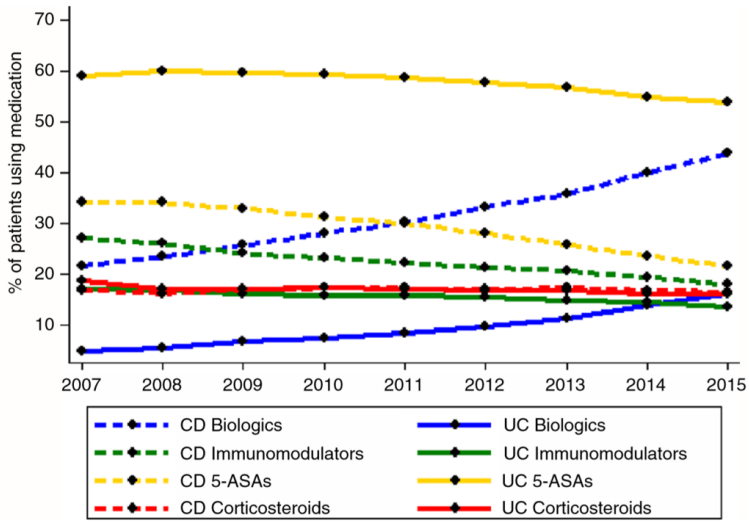


Figure6 Percentage of IBD medication as primary therapy and market share

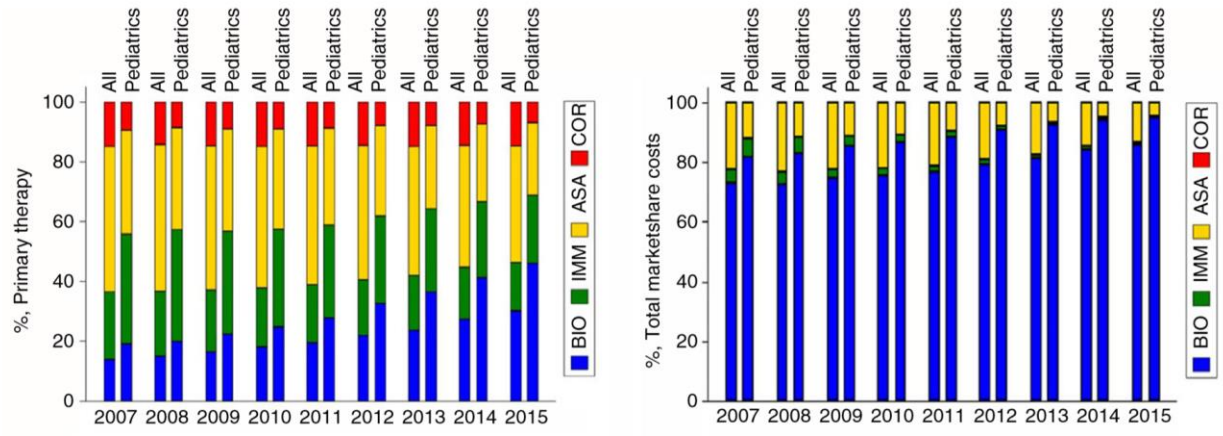


Figure7 Percentage of IBD medication as primary therapy for CD and UC

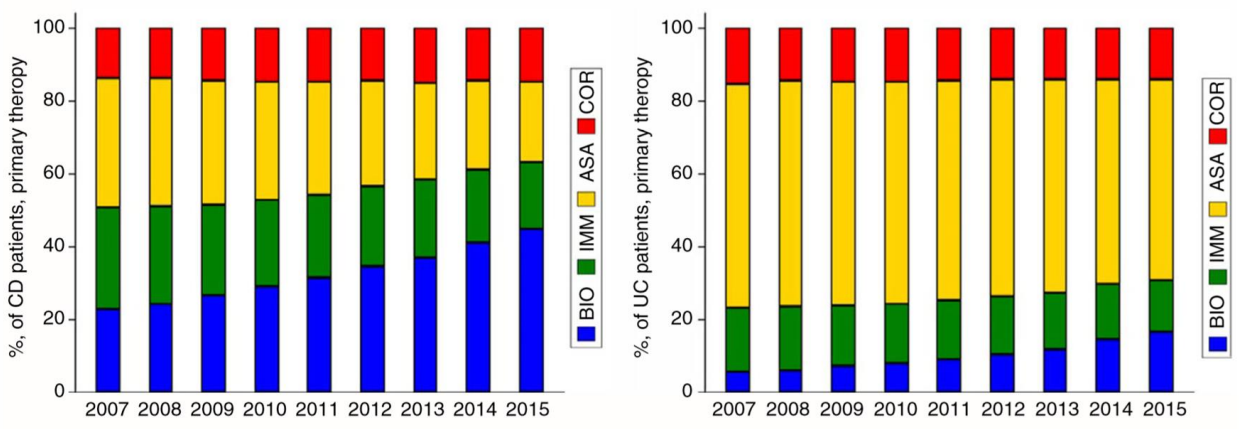
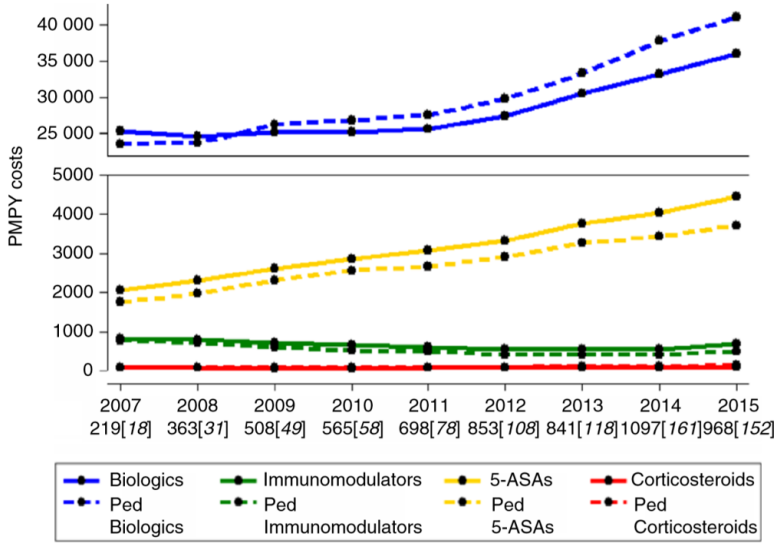


Figure8 IBD medication per-member per year (PMPA) costs



Direct Competitors

The direct competitors are identified as three drug types which fits under mild to moderate level. The three drug types are 5-ASA, Immunomodulators (Immunosuppressants), and corticosteroids, they are from different brand companies, and some are also available in generic form. The medicines under the three drugs types are used to treat Ulcerative Colitis (UC), Crohn's disease (CD), and as well as other several diseases such as cancer, acute lymphoblastic leukemia, autoimmune hepatitis and others.

The 5-ASA drugs are used for mild to moderate Inflammatory Bowel Disease (IBD) as anti-inflammatory drugs as first step in the treatment of ulcerative colitis. The main 5-ASA drugs

are; balsalazide, mesalamine, olsalazine, and sulfasalazine. Balsalazide is commonly used to treat Ulcerative Colitis (UC), it is an anti-inflammatory medication that is released in the large intestine to decrease the inflammation. Mesalamine is commonly used to treat Crohn's disease (CD), and helps to remission Inflammatory Bowel Disease. Olsalazine is used to treat ulcerative colitis, its helps to maintain remission of the disease. Sulfasalazine is commonly used to treat Crohn's disease.

Table 2 shows estimated prices for 5-ASA for a year of treatment per patient using Drugs.com data. These prices are discounted using their prescription program. Retail prices are provided when information is available. The estimated price per year is calculated as follows: **Price of 1-month supply * 12 months**.

Table 2

Drug name	**Brand name**	**Price per year**
Balsalazide - 280 tablets 750 mg per tablet	Colazal	~$6,553.24
Balsalazide (*Generic form*) - 280 tablets 750mg per tablet	Generic	~$602.24 - $1,287.76
Mesalamine- 180 tablets - 800mg per tablet	Asacol HD	~$6,488.68 - $7,101.88
Mesalamine (*Generic form*) - 180 tablets - 800mg per tablet	Asacol HD	~3,945.72 - $4,708.08
Mesalamine-120 tablets- 1.2g per tablet	Lialda	~$3,543.57
Mesalamine (*Generic form*) 30-120 tablets - 1.2g per tablet	Lialda	~$2,945. 39
Olsalazine -100 tablets - 250mg per tablet	Dipentum	~$1,424
Sulfasalazine - 100 tablets - 500mg per tablet	Azulfidine	~ $2,491.20
Sulfasalazine (*Generic form*) - 100 tablets - 500mg per tablet	Azulfidine	~ $382.20 - $393.15

Sulfasalazine - 100 tablets - 500mg per tablet	Sulfazine	~$393.15
Sulfasalazine (*Generic form*) - 100 tablets - 500mg per tablet	Sulfazine	~ $382.20 - $393.15

*Prices above are estimated from Drugs.com

**Prices above are estimated based on a typical prescription prescribed to patient by a doctor, the prescription information is provided by our connection Santesh Shah, pharmacist and Chief Operating Officer (COO) at Greenhill Pharmacy chain based out of Wilmington, Delaware.

The immunosuppressants drugs are used for mild to moderate IBD's to reduce inflammation but they do that by suppressing the immune system response that starts the process of inflammation. The main immunosuppressants drugs are Azathioprine, Mercaptopurine, Methotrexate & Cyclosporine. Azathioprine is used to treat both UC and CD, it's usually used to prevent flares or help the patient cut down on steroids. Mercaptopurine is used to treat CD, and it reduces remission. Methotrexate is used to treat UC, it reduces the body's natural immune response to reduce inflammation. And lastly Cyclosporine is used to suppress the immune system, it helps to decrease inflammation in the digestive tract.

Table 3 below shows the estimated prices of main immunosuppressants drugs for a year of treatment per patient using Drugs.com data. These prices are discounted using their prescription program. Retail prices are provided when information is available. The estimated price per year is calculated as follows:

Price of 1-month supply * 12 months.

Table 3

Drug name	Brand name	Price per year
Azathioprine - 100 tablets - 50mg per tablet	Imuran	~$5,656 - $6,080
Azathioprine -100 tablets (*Generic form*) - 50mg per tablet	Imuran	~$544- $616
Mercaptopurine (*Generic form*) - 25 tablets-	N/A	~$831

50 mg per tablet		
Methotrexate (*Generic form*) - 100 tablets - 2.5mg per tablet	N/A	~$73.47- $230.46
Cyclosporine - 30 tablets - 25mg per tablet	Sandimmune	~$1,479.60
Cyclosporine - 30 tablets - 25mg per tablet	Gengraf	~$446.40
Cyclosporine - 30 tablets- 25mg per tablet	Neoral	~$905.60
Cyclosporine (Generic form) - 30 tablets- 25mg per tablet	N/A	~$446.40 - $918

*The prices above are estimated prices from Drugs.com

**The prices above are estimated prices based on a typical prescription prescribed to patient by a doctor, the prescription information is provided by our connection Santesh Shah, pharmacist and Chief Operating Officer (COO) at Greenhill Pharmacy chain based out of Wilmington, Delaware.

Corticosteroids are a common drug class taken for treatment of mild IBD's. These medications trigger the body to produce more cortisol by the kidneys to help fight inflammation. The common corticosteroids used are Prednisone, Methylprednisolone and Hydrocortisone. Budesonide is another drug that is used for mild to moderate cases of Crohn's disease. For Budesonide, remission induction is not as effective as conventional corticosteroids, however there are less side effects and reduced adrenal suppression associated with taking the drug (Rezaie et al.). The common brand names for Budesonide are Entocort, Uceris, and Pulmicort.

Table 4 shows estimated prices for corticosteroids for a year of treatment per patient using Drugs.com and GoodRx.com data. These prices are discounted using their prescription program. Retail prices are provided when information is available.

Table 4

Drug Name	Brand Name	Price per Year
Prednisone	Deltasone	~$2,062
Prednisone (*Generic form*)	-	~$124
Methylprednisolone	Depo-Medrol, Solu-Medrol	~$900
Methylprednisolone (*Generic form*)	-	~$348
Hydrocortisone	Proctofoam	~$857
Hydrocortisone (*Generic form*)	-	~$660
Budesonide	Entocort	$16,176-$19,452*
Budesonide	Uceris	$21,000-$22,536*
Budesonide	Pulmicort	$3,720-$4,032*
Budesonide (*Generic form*)	-	$900-$1,236*

*Estimated Retail Prices from GoodRx.com and Drugs.com

Indirect Competitors

Current Treatment for IBD

The treatment of IBD starts with the diagnosis, the diagnosis of IBD patients depends on different factors like patient's medical history, endoscopic, radiologic, disease location, area impacted, symptoms like bloody diarrhea etc and severity level. There are several types of drugs which targets inflammatory bowel disease either for specific area or as broadly for reducing or controlling the pain or the remission of it. Below are different medical treatments for treating various IBD's:

- Aminosalicylates (5 ASAs)

- Corticosteroids
- Immunomodulators
- Antibiotics
- Biologic therapies

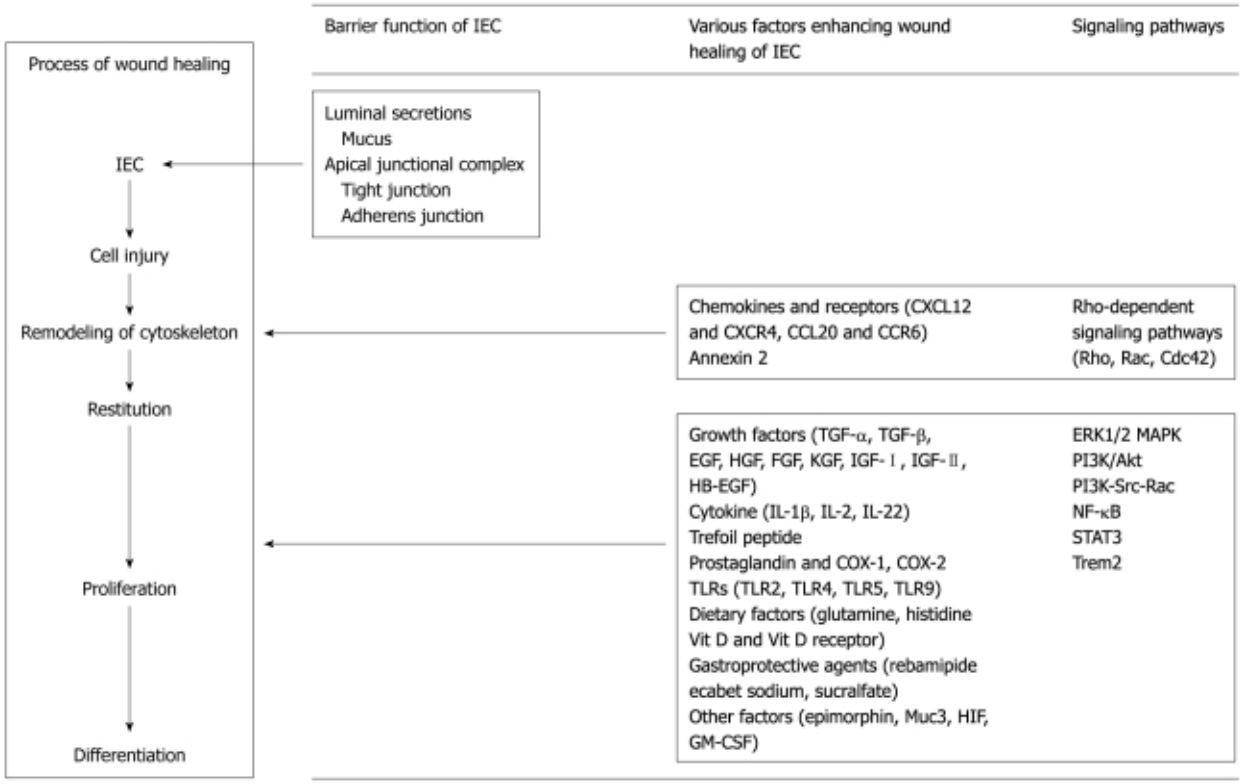
*Some additional patients also require surgery when traditional treatment is not effective

Every drug or treatment listed above currently present has some or the other limitations for treating any Inflammatory Bowel Disease. For example - According to Alternative Medicines as Emerging Therapies for Inflammatory Bowel Diseases, "5-aminosalicylate was a functionally active moiety of prototypical sulfasalazine congener and may block the production of prostaglandins and leukotrienes, inhibiting bacterial peptide-induced neutrophil chemotaxis, scavenging reactive oxygen metabolites, and inhibiting the activation of nuclear factor-B." (Udai and, 2011)

Wound Healing of Intestinal epithelial cells

The disruption of the intestinal barrier function and repeated damage to the patient's intestines are key features of IBD (Iizuka, 2011). Therefore, it is important to discuss ways to improve wound healing as it contributes to therapeutic strategies related to IBD. As stated by Iizuka, "It has been shown that the activation of specific signaling pathways is involved in intestinal epithelial wound repair". For example, HB-EGF enhances wound healing of the intestine in a phosphatidylinositol 3-kinase (PI3K)/Akt- and MAPK/ERK kinase (MEK)/ERK1/2-dependent fashion. Iizuka also states, "the activation of the ERK1/2 MAPK or PI3/Akt pathway plays an important role in the regulation of intestinal epithelial proliferation, survival, and wound healing". It is also suggested by recent studies that nuclear factor (NF)-κB is pro-inflammatory and has a tissue-protective function in IECs (Iizuka, 2011).

Another method to improve wound healing is Trem2 signaling which "promotes efficient wound healing of colonic mucosal injuries by inhibiting cytokines that can enhance M1 macrophage activation, and by promoting cytokines that can promote M2 macrophage activation" (Iizuka, 2011). Below the various factors and signaling pathways of wound healing are illustrated.



Dietary factors can also play an important role in the process of wound healing. As discussed by Iizuka (2011), "Several studies have shown that enteral nutrition with an elemental diet is efficacious in the treatment of CD, especially for maintaining clinical remission or reducing clinical and endoscopic recurrence after resection". Glutamine is a non-essential amino acid that is vital for gut homeostasis and can improve intestinal recovery. For instance, "It was found that pretreatment with oral glutamine prevents mucosal injury and improves intestinal recovery following ischemia-reperfusion injury through the stimulation of cell proliferation rather than the inhibition of cell apoptosis (Iizuka, 2011). Vitamin D deficiency could also have a link to IBD risk and wound healing. The role of vitamin D receptors in mucosal barrier homeostasis was investigated by Kong et al. Iizuka explains the process and results of this study as follows:

> "In this study VDR$^{+/+}$ mice were mostly resistant to 2.5% DSS, but VDR$^{-/-}$mice developed severe colitis, leading to death. They also found severe disruption in the epithelial junctions in VDR$^{-/-}$ mice after DSS treatment. In cell cultures, 1,25-dihydroxy-vitamin D_3 [$1,25(OH)_2D_3$] markedly enhanced tight junctions and stimulated epithelial cell migration *in vitro*. These observations suggest that VDR plays a critical role in

mucosal barrier homeostasis by preserving the integrity of junction complexes and the healing capacity of the colonic epithelium".

Recent studies in the article; Wound healing of intestinal epithelial cells (Lizuka), stated that gastroprotective agents like including ecabet sodium (ES), rebamipid, and sucralfate, have therapeutic effects on IBD and other types of colitis (2011). The agents prevent the delay of wound repair. These studies have suggested the possibility that some gastroprotective agents could be used for the treatment of IBD. The processes and methods associated with wound healing in patients with IBD are indirect competitors because they could greatly impact therapeutic strategies for treating IBD.

Alternative Treatments for IBD

The conventional treatment for Inflammatory bowel disease can reduce the periods of active disease and help in maintaining remission not to happen, but as per the studies these treatments are bringing marginal results for IBD. According to Alternative Medicines as Emerging Therapies for Inflammatory Bowel Diseases (Udai and Dennis), "It is estimated that 40% of IBD patients use some form of megavitamin therapy or herbal/dietary supplement." (2011) There are not side-effects of many herbal therapies used by the IBD patients and which makes it more attractive in patients for using these therapies. Below are the few natural or herbal therapies for IBD

Medicine	Disease	Effects	Remission
Aloe Vera Gel	UC	Improved Histological Score	30%
Wheatgrass Juice	UC/distal	Improved Symptoms	90%
Germinated Barley	UC	Improved diarrhea	-
Curcumin	UC/CD	Lowered CDAI scores and sedimentation rates	90%

Curcumin	UC/CD	Reduced Histological sign of inflammation	-
Rutin	UC	Ameliorates DSS Induced Cells	-
Fresh Pineapple Juice	UC/CD	Ameliorates colitis and colonic neoplaisa	-
Pomegranate	UC	Ameliorates DSS Induced Cells	-
Pomegranate / Metabolite	UC	Reduced DSS inflammation	-
Epiigallocatechin-3 Gallate	UC/CD	Beneficial in Colitis	-
Green Tea Polyphenols	UC	Protect against DSS induced colitis	-
Green Tea Polyphenols	UC/CD	Attenuates colonic injury and inflammation	-
Green Tea Polyphenols	UC/CD	Attenuates colitis	-
Resveratrol	UC/CD	Ameliorates CD	-
Resveratrol	UC	Protect from DSS induced UC	-
Resveratrol	UC/CD	Attenuates colonic inflammation	-
Resveratrol	UC in Rat	Attenuates colonic inflammation	-
Cinnamon extract	UC/CD	Suppress experimental colitis	-
Freeze-Dried Black Raspberry Powder	UC	Potent anti-inflammatory effects	-
American ginseng	UC	Suppress colon cancer associated colitis	-

Ginger Extract	UC/rat	Improved Inflammation	-

From the above table it can be stated that Alternative medicine like aloe vera gel – 30%, wheat grass juice – 90% and Curcumin - 90% helps in remission.
Describing some potent alternative medicine options studied in recent years that mediate IBD stated in the above table.

Curcumin

According to Alternative Medicines as Emerging Therapies for Inflammatory Bowel Diseases (Udai and Dennis), Curcumin, found in plant Curcuma longa, is a natural compound used as a spice in curry powder. The perennial herb has multiple ingredients, including curcuminoids, that have medicinal effects. The curcumin major part is turmeric (diferuloylmethane), which possess both anti-inflammatory and antioxidant properties. Curcumin has been found to inhibit the activation of various transcription factors that play a role in inflammation, cell survival, and angiogenesis. This includes nuclear factor-kappaB (NF-B) and catenin. Curcumin also down regulates COX-2 expression and inhibits expression of cytokines, interlukin-1 beta (IL-1), interlukin-6 (IL-6), and tumor necrosis factor-alpha. (2011)

Green Tea

According to the study above, one of the major polyphenols present in green tea is epigallocatechin-3-gallate, which exhibits antioxidant properties and helps in reducing inflammation. There is substantial evidence which demonstrates that intestinal inflammation is likely to depend at least in part on activation and nuclear translocation of NF-B. More importantly, activated NF-B has been found in colonic epithelium and macrophages from IBD patients. In light of these pharmacological profiles of green tea, its therapeutic effects on experimental colitis are warranted. Several published reports have evaluated the beneficial effects of green tea on experimental models of colitis.

The herbal/natural therapies are always easy to adapt and readily available to common people within their budget. As per the Alternative Medicines as Emerging Therapies for Inflammatory Bowel Diseases it is stated that “Nearly 50% of the IBD patients have tried some

form of alternative medicine." In Other Complementary and Alternative Medicine (CAM) Modalities section of the Alternative Medicines as Emerging Therapies for Inflammatory Bowel Diseases (Udai and Dennis) it is stated that "Boswellia serrta is a traditional Ayurvedic remedy and a component of incense. Many clinical trials of gum resin from Boswellia reported a 70% remission as compared to sulfasalazine." (2011)

Nutrition Deficiency

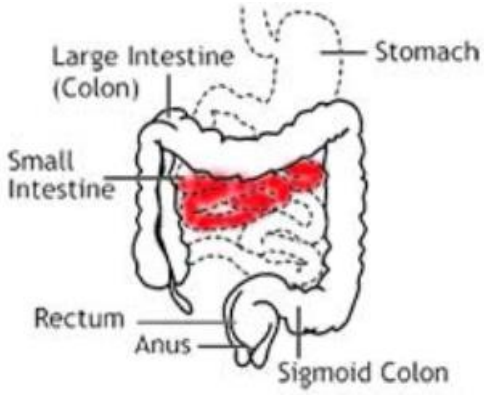
Patients that suffer from IBD also commonly suffer from nutritional deficiency. According to Smith (2012), "Anorexia and weight loss were considered to be defining symptoms of active CD...". Since this is a common problem that people with IBD experience, nutritional supplements can be considered an indirect competitor. The main nutrients that IBD patients need to take supplements for are Iron, Vitamin D, and Zinc (Fritz, 2018). According to Smith (2012), "Iron deficiency is considered the commonest micronutrient deficiency in IBD, and while prospective data are lacking, it has been reported in up to 39% of patients,11 with 65% requiring iron replacement over the course of their disease". This means that Iron nutritional supplements will be the biggest indirect competitor in the nutritional deficiency category. Vitamin D does not seem to be a major issue when it comes to adult IBD patients, but vitamin D deficiency is prevalent in pediatric patients (Fritz, 2018). Fritz states, "Iron deficiency and vitamin D deficiency are common in pediatric patients with IBD". IBD patients, especially pediatric patients, may need to rely on supplements to ensure that their vitamin D levels are not too low.

Also, as stated by Iizuka, "Previous studies have suggested a link between vitamin D deficiency and IBD risk". This risk was demonstrated by studying the vitamin D receptor in mice as was discussed earlier in this report. The final indirect competitor when it comes to nutrients is Zinc. According to Fritz, "Zinc deficiency, while not common, occurs at a higher rate in patients with Crohn's disease than in healthy controls." (2018) So, Zinc deficiency may not be an issue for all IBD patients, but it is definitely relevant when it comes to nutritional deficiency in Crohn's disease.

Small Intestinal Data

Types of Crohn's disease

1. Jejunoileitis



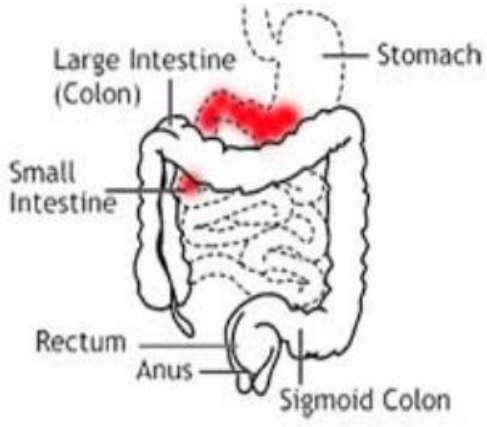
Inflammation is in the middle and end of the small intestine

Symptoms- Cramps after eating, Diarrhea, Abdominal pain, weight loss, Anemia, Fatigue

Complications- nutritional deficiencies, fistulas or inflammatory abscesses in the abdomen, strictures causing blockage in intestines

Percent of Population affected- 20% in children and 4% in adults with Crohn's disease have this type

2. Gastroduodenal



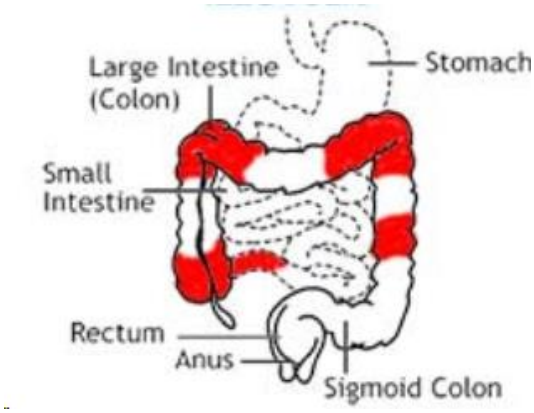
Inflammation to the stomach and duodenum (first part of small intestine)

Symptoms- Loss of appetite, Weight loss, Nausea, Vomiting, Abdominal pain similar to indigestion, Fatigue

Complications- Gastroduodenal strictures and Pancreatitis are most common complication of gastroduodenal crohn's disease. Gastric outlet obstruction causing vomiting, Fistulas, abscess

Percent of Population- 5% of people with Crohn's disease have gastroduodenal Crohn's.

3. Ileocolic



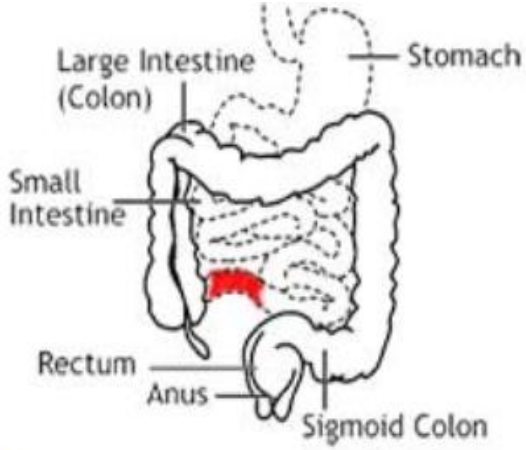
Inflammation is in the colon (Large intestine) and end of small intestine(ileum)

Symptoms- Significant weight loss, diarrhea

Complications- intestinal blockage, fistulas, and Abscesses

Percent of Population- 40-50% of populations is affected by this type of crohn's disease

4. Ileal



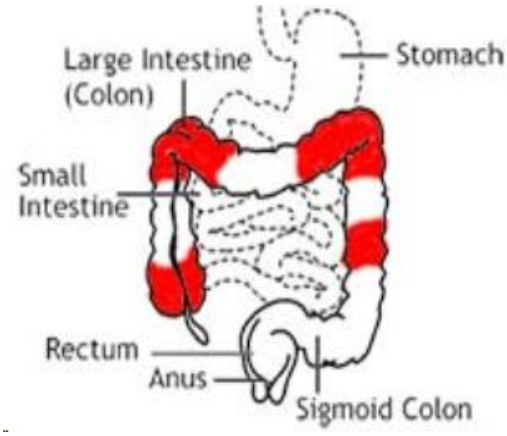
Inflammation is in the ileum (Last part of small intestine)

Symptoms- diarrhea, weight loss, fatigue,

Complications- intestinal blockages, fistulas or inflammatory abscess in right lower part of abdomen

Percent of Population- this type of disease accounts for 30% of cases of crohn's disease

5. Colonic



Inflammation is in some or all parts of colon.

Symptoms- Blood stained diarrhea, Rectal bleeding, Skin lesions, Joint pains, Ulcers, fistulas and abscesses around the anus, Fatigue

Complications- colon cancer, fistulas

Percent of Population- 20% of CD cases are affected in colon. About 30% to 45% of people with crohn’s colitis have granulomas.

Medications

- **Sulfasalazine** (in the doses of 3–6g daily) is effective in treating patients with mild to moderately active colonic CD and/or ileocolonic CD, but not in those with isolated small bowel disease.
    - **Cost** - The price range for Sulfasalazine 500mg is $0.13 - $0.70 per pill or unit. The price for 500mg- (30 to 360 pills) ranges from 1.73 per pill to 0.81 per pill respectively
- Controlled ileal release of **budesonide** at a dosage of 9mg once daily is effective and should be used for induction of symptomatic remission for patients for ileocecal Crohn's disease
    - **Cost -** The price range for Budesonide 3mg is $0.43 - $1.62 per pill or unit.

Recommendation

- Budesonide should not be used to maintain remission of Crohn's disease beyond 4 months. CIR budesonide may be effective for short term relief of mild to moderate CD with patients have disease confined to terminal ileum and right colon.
- Oral corticosteroids are effective and can be used for short-term use in alleviating signs and symptoms of moderate to severely active Crohn's disease. Budesonide (Entocort EC, UCERIS, Budenofalk) - a new steroid targets the end of the small intestine.

Surgery

Even though surgery is a secondary line of treatment, around 90% of patients with Crohn's disease will ultimately require some type of surgical procedure. Procedures can either remove a part of the small intestine (resection) or simply clear an obstruction (strictureplasty). With the removal of a part of the small intestine, patients become more prone to developing short-bowel syndrome, making strictureplasty a preferred alternative. However, some patients may not be eligible to have the procedure done. Lastly, patients may have both types of surgery done at the same time.

Different types of strictureplasty are used for different lengths. For short-segment strictures, less than 5 to 10 cm, the Heineke-Mikulicz strictureplasty remains the procedure of choice. For longer segments, the Finney or Jaboulay methods are often employed.

Series in the Literature Regarding Strictureplasty

Author	Strictureplasties	Follow-up (Months)	Morbidity (%)	Recurrence (%)	Reoperation (%)
Fazio et al[23]	452	36	23	24	15
Serra et al[30]	154	54	19	40	33
Yamamoto et al[31]	285	90	18	54	44
Hurst and Michelassi[32]	109	38	12	22	12
Tonelli and Ficari[33]	174	50	7	44	23
Dietz et al[34]	1124	90	18	37	34
Futami and Arima[35]	293	80	10	n/a	44
Fearnhead et al[36]	479	85	23	n/a	56

Multiple studies have been conducted to measure the efficacy of strictureplasty. The recurrence percentage ranges from 22% to 54%. This gap may be explained by the follow-up difference. Hurst and Michelassi observed 109 strictureplasties, with a recurrence rate of 22% and follow up of 38 months. Yamamoto observed 285 strictureplasties and noted a 54% recurrence rate with a follow up of 90 months. This seems to indicate that recurrence is likely after longer periods.

Tichansky conducted a more comprehensive, meta-analysis where 15 retrospective studies were reviewed. This study included 506 patients that underwent 1,825 strictureplasties. Indications for surgery included recurrent small bowel obstruction (92%), weight loss, chronic pain, fistula, narcotic dependence and gastrointestinal bleeding. Ninety percent of the strictures observed were less than 10 cm in length. Stricture sites included jejuno-ileal, duodenal and anastomotic sites. Fifty-six patients underwent only strictureplasty; the remaining patients underwent strictureplasty along with bowel resection. Heineke-Mikulicz and Finney were the

most common method of strictureplasty, 85 and 13% respectively. Tichansky reported 74 complications in 66 patients for an overall morbidity of 13%. Approximately 25% of patients required reoperation and the overall recurrence rate was 25.5% requiring an additional 132 procedures. From this meta-analysis, Tichansky concluded that strictureplasty for CD is a safe surgical option.

Alternatively, CD is often treated with ileocolic resection, as the ileum is the segment of intestine most often affected. Endoscopically, up to 72% of patients will develop recurrence at the anastomosis site within one year of surgery. As mentioned earlier, the potential for developing short-bowel syndrome increases with each resection.

Next Steps

The ClostraBio ELC team are halfway through the project semester, with the mid-semester presentation on current findings scheduled for March 22nd, 2019. After the mid-semester presentation, the project will be expected to continue for another 5 weeks with the final presentation scheduled for April 26th, 2019. At the point of the final presentation, all objectives and deliverables are expected to be presented on.

Research and suggestions made within this report act as a snapshot of progress made on the project objectives, adjustments and scope may alter based on feedback received from the mid-semester presentation. The team's current plan for the completion of project objectives are as follows:

- Add additional data to direct and indirect costs that can provide ClostraBio with more insight into the competitive landscape.
- Compare recent IBD treatment costs with potential ClostraBio cost savings to determine a ballpark product price.
- Identify potential key partners within ClostraBio's manufacturing, treatment, and distribution processes.
- Identify more data for patients with IBD's afflicting the small intestines. (Population, demographics, etc)

Additionally, the team has identified several industry journals analyzing the landscape of IBD within the U.S. The two most promising journals identified are:

- "Inflammatory Bowel Disease Treatment Market analysis, market size, disease indication analysis, drug class analysis, Distribution Chain analysis, Regional outlook, Competitive strategies, and segment forecasts. 2019 to 2025." (Grand View Research, 2019)
- "Inflammatory Bowel Disease Treatment Market - Global Industry Analysis, Size, Share, Growth, Trends, and Forecast 2017 - 2025" (Transparency: Market Research, 2018)

Both industry journals require the purchase of a license that NIU currently does not have possession of. The ELC department may be able to purchase a user license to acquire both journals, however, it may be more beneficial to ClostraBio for them to purchase the user license themselves. The two journals could be used to support or refute recommendations made by the ELC team at the culmination of the project.

Conclusion

This report represents the current progress the ClostraBio ELC team has made in regard to outlined objectives of the project. Extensive research has been done on the market opportunity and product scope of the IBD industry in the U.S. The current treatment types, costs, and their subsequent economic burden on patients have also been identified, this research will be used to estimate a product price for ClostraBio's offerings.

Furthermore, treatment options dealing with IBD have been separated into either direct competitor or indirect competitor segments depending on their original purpose and treatment map. Research was also conducted on IBD cases affecting the small intestines, this segment was identified as a potential hotspot for the mild-to-moderate IBD patients. Finally, next steps were outlined to show how the teams' research will progress to give a final recommendation to ClostraBio at the culmination of the project.

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