CLOSTRABIO

Northern Illinois University

Experiential Learning Center

Final Project Report

NORTHERN ILLINOIS UNIVERSITY
College of Business

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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 all valuable information gathered from numerous months of research. The research provided includes information on market opportunity and product scope of IBD in United States (U.S.), direct costs of the IBD, information on the market share of different drug groups, names and costs of various direct competitors, names of various home style remedy indirect competitors, IBD treatment drugs in pipeline, and data on IBD patients with the disease in their small intestine.

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 ELC team has also provided several recommendations pertaining to potential target markets and yearly treatment prices for ClostraBio's product. Additions from to this report from the mid-semester report include gathered data and recommendations on; price of biologics therapies, additional data on small intestine, drugs in pipeline by various drug makers, and ClostraBio's product price point. The final recommendations provided acts a culmination of the research completed by the ELC team.

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.

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

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

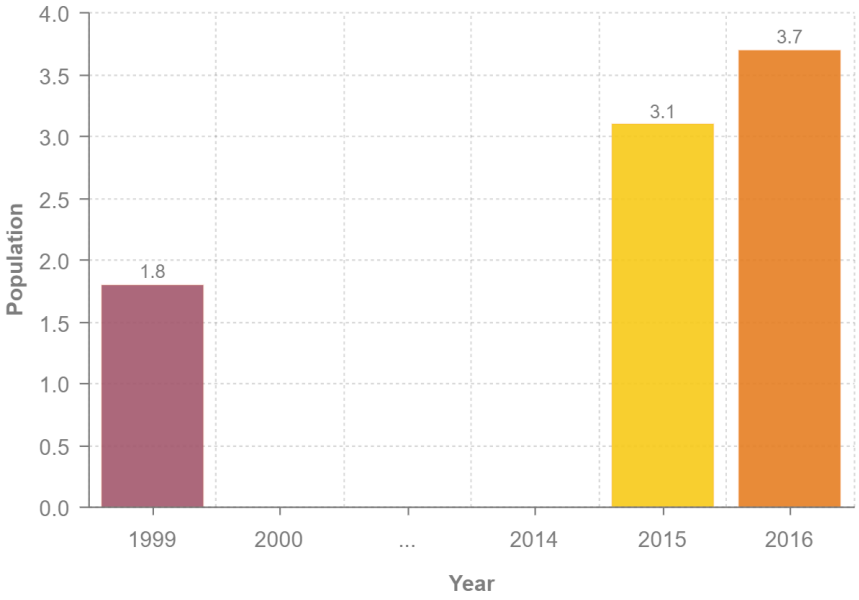
The Centers for Disease Control and Prevention (CDC) recently released a new study which estimates IBD prevalence based on 2015 National Health Interview Survey (NHIS). To examine the prevalence of IBD among the nation the noninstitutionalized U.S. adult population was analyzed in this study. The overall 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.

Figure 1 IBD Prevalence among Adults in U.S. (in million)



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

According to the Crohn's and Colitis Foundation (CCFA), the percentages of CD and UC patients at a given point are about 46.24% and 53.76%. So the estimated number of CD and UC patients in U.S. in 2016 are about 1.7 million and 2 million based on a total IBD population of 3.7 million. 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.

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)

Table 1 shows the breakdown population according to severity level for both UC and CD. Almost half of UC patients are in remission (about 960,000) for a given year while the sum of the mild and moderate disease population makes up the other half of UC patients (about 600,000 for mild and 400,000 for moderate). People with severe disease account for just 1% to 2% (about 40,000) 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%, there is a 21% to 34% chance for left-sided colitis progress to extensive colitis or pan-ulcerative colitis.

Table 1: Prevalence by Severity (in thousands)

IBD 3.7 M	CD (~46.24%) 1,700K	Remission (~60%)	1,020
		Mild (~20%)	340
		Moderate – severe (~20%)	340
	UC (~53.76%) 2,000K	Remission (~48%)	960
		Mild (~30%)	600
		Moderate (~20%)	400
		Severe (~2%)	40

Table 2: Prevalence by CD Type (in thousands)

CD 1,700K	Ileocolitis (~45%)	765
	Ileitis (~26%)	442
	Gastroduodenal (~5%)	85
	Jejunoileitis (~4%)	68
	Crohn's colitis (~20%)	340

For the severity distribution of CD, about 60% of patients (1.02 million) are in remission at a given point. The percentages for mild and moderate to severe are the same at about 20% (340,000) respectively (Project, 2010). Table 2 shows the prevalence breakdown by CD types. Ileocolitis, which affects both large intestine and the end of the small intestine, is the most common type in CD patients, affecting about 45% (765,000) of CD patients. The second largest type of CD is ileitis which only affects small intestine. About 26% (442,000) of CD patients are affected by this type. The type of CD that only affects the large intestine is crohn's colitis which

accounts for 20% (340,000) in CD patients. Gastroduodenal affects the stomach and the first part of small intestine. Jejunoileitis affects the middle and the end of small intestine. These two types appear to have a similar percentage in CD patients which is about 5%. Twenty to thirty percent of CD patients will have non-progressive clinical course while up to seventy five percent will eventually need surgery. After diagnosis, about 30% of CD patients will need surgery in 5 years while 40% to 55% in 10 years. Thirty percent of those who have already has surgery will experience relapse (CCFA, 2014; CCFA, 2019; Feuerstein, 2017; Mehta, 2016).

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 Figure 2. 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 3). 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 likely to spend more than twice the amount of treatment costs in the first year after diagnosed as they do annually during the remaining life. (Baldassano, 2018)

Figure 3 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)

Figure 2: Lifetime Direct Cost per Patient

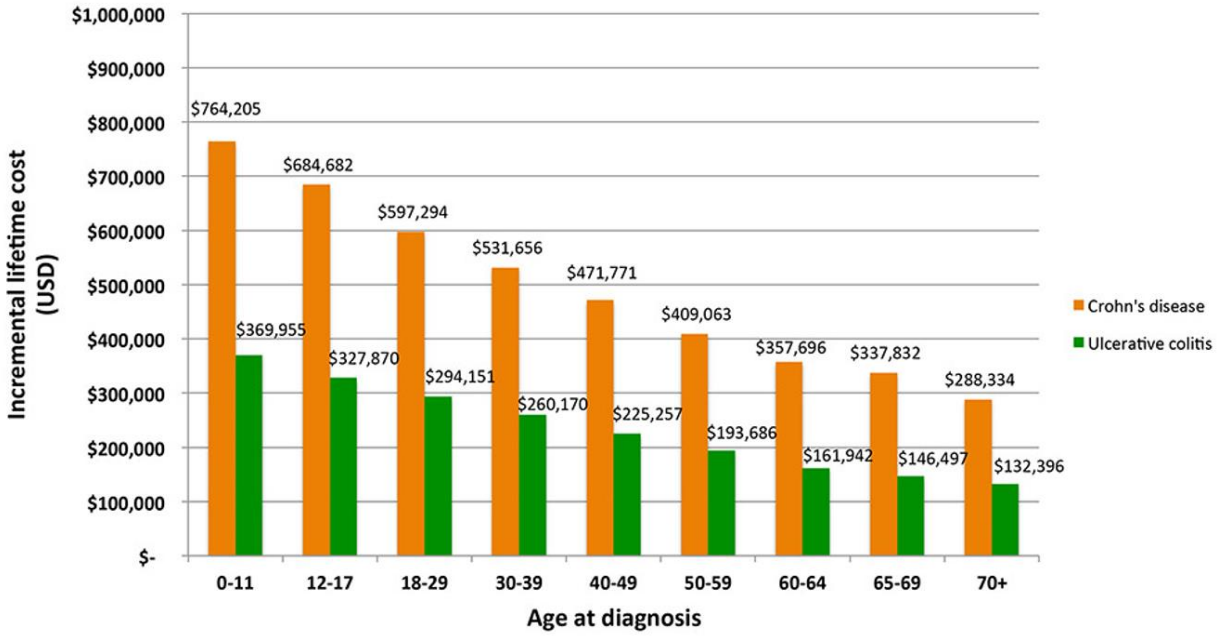
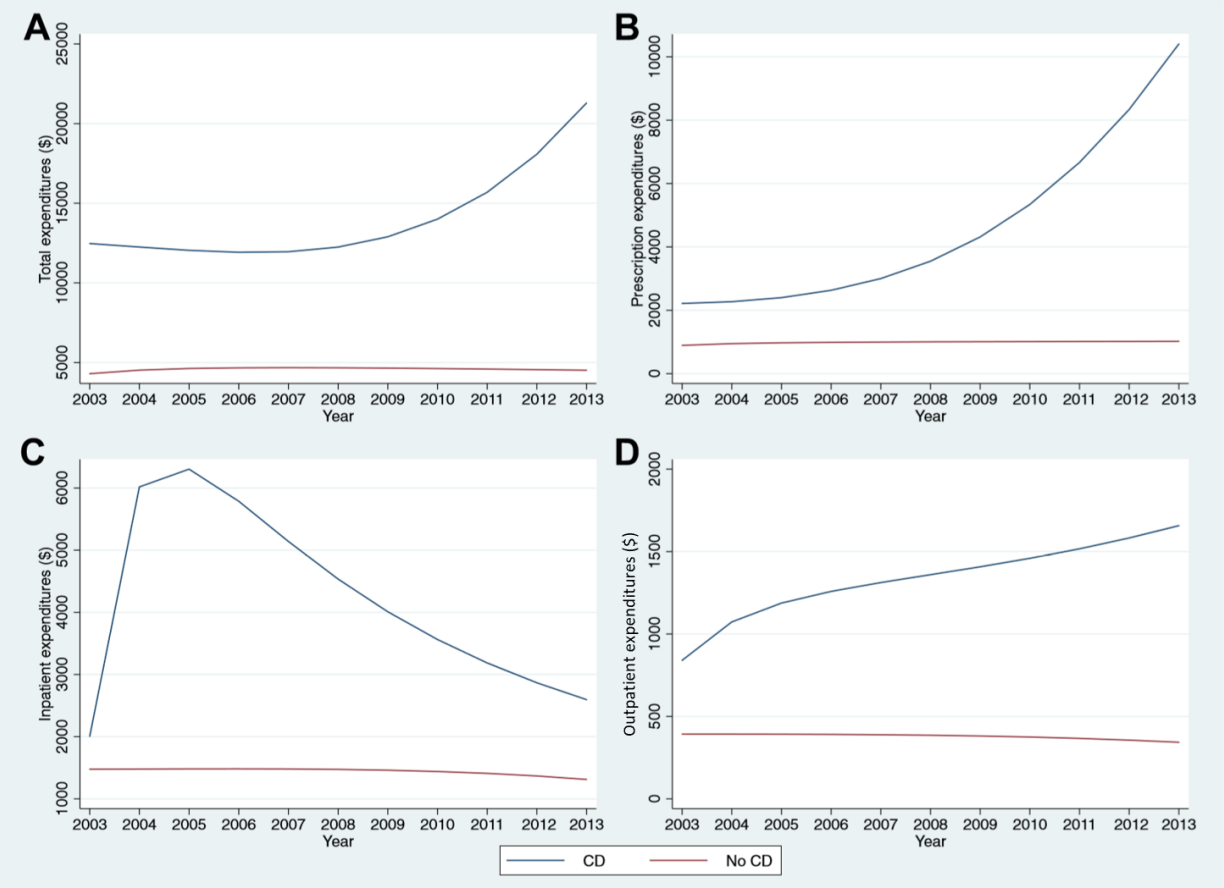


Table 3

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

Figure 3: 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 4). Figure 5 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 6), 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 7. 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)

Figure 4 IBD Medication Utilization Trend

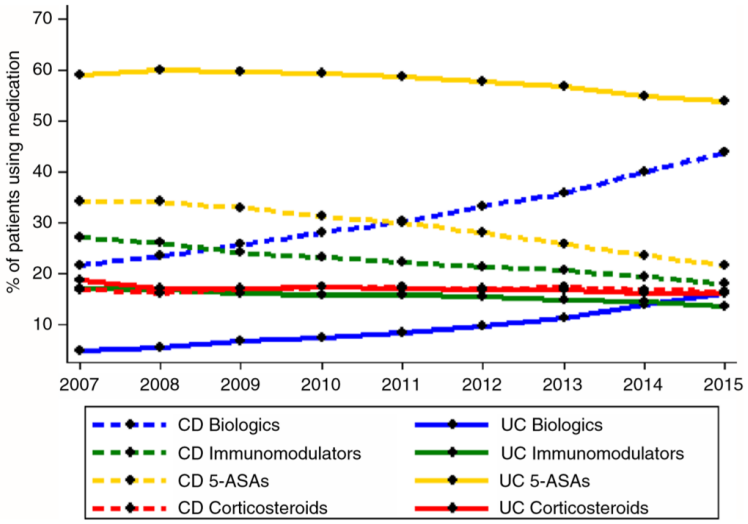


Figure 5 Percentage of IBD Medication as Primary Therapy and Market Share

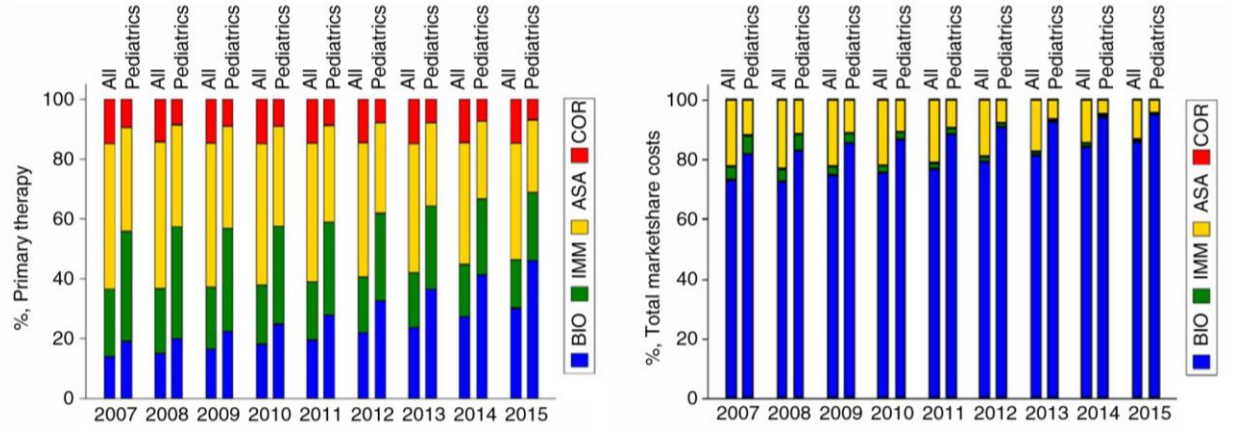


Figure 6 Percentage of IBD Medication as Primary Therapy for CD and UC

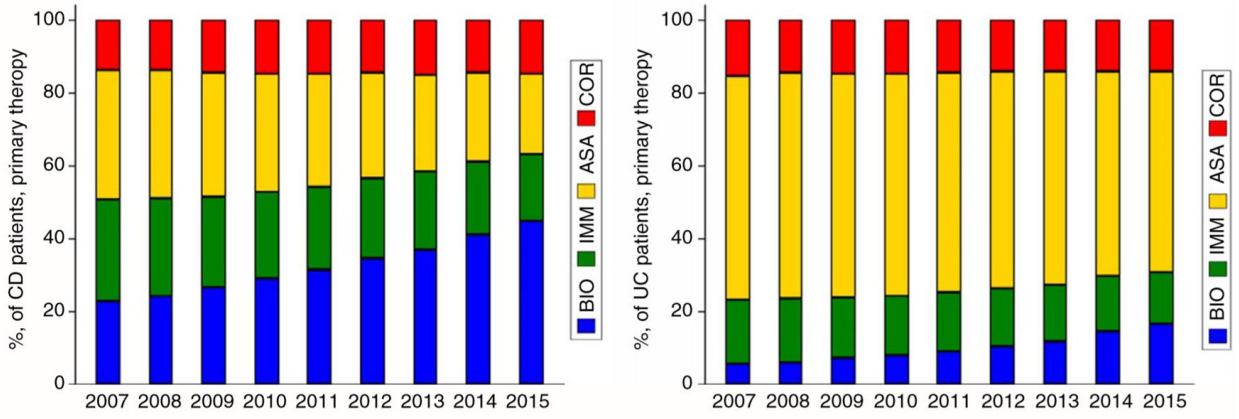
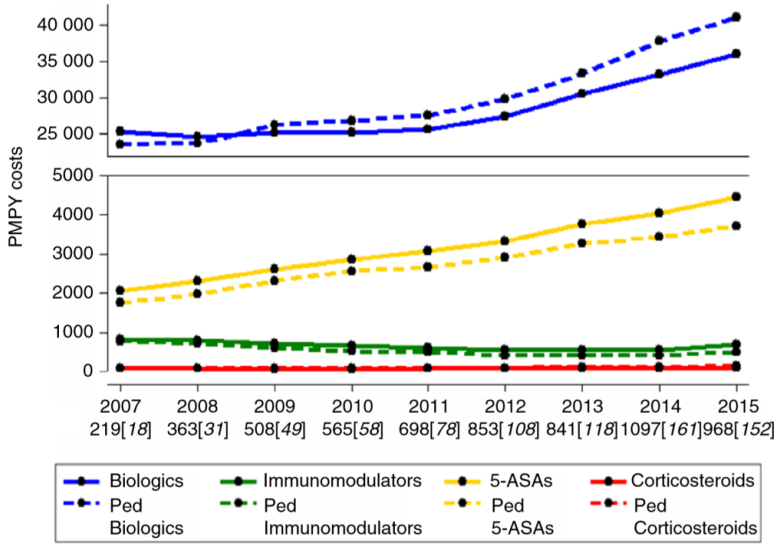


Figure 7 IBD Medication Per Member Per Year (PMPA) costs



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 UC and 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 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 UC it is an anti-inflammatory medication that is released in the large intestine to decrease the inflammation. Mesalamine is commonly used to treat 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 CD.

Table 4 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 4

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 is meant to reduce 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 5 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 5

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- 50 mg per tablet	N/A	~$831
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 fewer 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 6 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 6

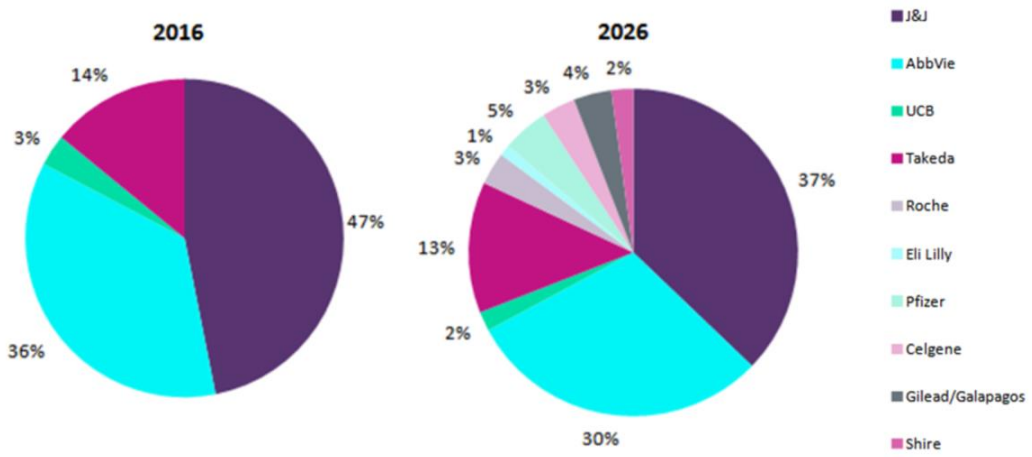
Drug Name	Brand Name	Price per Year
Prednisone	Deltasone	~$2,062
Prednisone (*Generic form*)	-	~$124
Methylprednisolone	Depo-Medrol, Solu-Medrol	~$900
Methylprednisolone (*Generic form*)	-	~$348
Hydrocortisone	Proctofoam	~$857
Hydrocortisone (*Generic form*)	-	~$660
Budesonide	Entocort	$16,176-$19,452*
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

Biologics Therapies

Currently, there are four major companies producing biologics therapy for IBD. It appears that due to the introduction of new drugs, the market shares of current biologics companies will experience decrease in varying degrees. The biologics drugs are used to treat moderate to severe IBD's. Biologics is antibody that works on immune system, it targets certain proteins in the body that causes inflammation. Figure 8 shows market share for biologics in 2016 and 2026.

Figure 8: IBD Companies Sales, 2016 and 2026



Xeljanz is a selective JAK inhibitor used to treat moderate to severe UC, Xeljanz transduce the signals of multiple cytokines involved in immune function. Remicade is a prescription drug used to reduce signs and symptoms of Crohn's disease, and it can also induce and maintain remission in adult patients who hasn't responded well to other therapies. Cimzia is prescription medicine used to treat CD, it works to prevent inflammation that results from overactive immune system. Cimzia is tumor necrosis factor (TNF) blocker used to treat patients with moderate to severe CD. And lastly, Adalimumab (Humira) is prescription medicine used to induce and maintain clinical remissions in patients with moderate to severe Ulcerative Colitis and Crohn's disease. The estimated price per year of biologics is calculated as follows: Price of 1-month supply * 12 months. The data related to these biologics are being stated in Table Pipeline 1 along with the brand name of the medicine.

Table Pipeline 1

Drugs	**Brand Name**	**Price per year**
Xeljanz (5 mg 30 tablets)	Pfizer	~$28,116
Remicade (100 mg 4 vials)	Janssen (Subsidiary of Johnson & Johnson)	~$58,929.60
Cimzia (200 mg 2 syringes kit)	UCB	~$108,530.16
Humira (40 mg 0.4mL 2 Pen)	Abbvie	~$64,922.88

*Price estimates are from drugs.com database.
**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.

Besides current biologics, ELC team also identified several pipelines for IBD treatments. The pipelines are detailed in Table Pipeline 2 where each drug stating the status of the trail along with the disease type and mechanism of the course.

Table Pipeline 2

Drug/ Manufacturer	Status	Regimen	Mechanism	Anticipated Peak Year Sales/Pricing
Ulcerative Colitis				
Kappaproct (Cobitolimod)/InDeX pharmaceuticals	Approved	Rectal (30mg) via colonoscopy with microinjections Up to 3 doses may be given	Balances Th17-TReg cell immune response	$47M in 2022 (5EU); expected to be priced similar to Alicaforsen (Atlantic Healthcare), which is $9,500 per unit
Crohn's Disease				
Vercirnon/ ChemoCentryx	Phase 3	Oral (500mg), once or twice daily	CCR-9 inhibitor	$93.6M in 2022; expected to be priced 35% lower than Humira, which costs $1,350 per 40-mg injection
RHB-104 (95 mg clarithromycin, 45mg rifabutin, 10 mg clofazimine)/ Red Hill Bio	Phase 3	Oral, 5 capsules a day	Anti-Map therapy	Not Available

*Sources located at the end of report

Biologics Therapies for Crohn's Disease :

- Biologic therapies were superior to placebo in inducing remission of active CD and in preventing relapse of quiescent CD.

- Infliximab - given every 8 weeks is effective for maintenance of remission and fistula healing in patients who respond to induction therapy. Similar conclusions were drawn for adalimumab and certolizumab pegol
- The histologic recurrence of CD was observed in only 27.3% of patients treated postoperatively following ileocolonic resection with infliximab versus 84.6% of patients treated with placebo
- Initiation of infliximab therapy within 4 weeks of intestinal surgery for CD is not associated with an increase in postoperative complications.
- Early initiation of infliximab therapy may reduce the recurrence of CD and help eliminate future surgeries in this patient population

The Clostrabio ELC team completed research on risks associated to the IBD treatment medications, which can be summarized in the table below where team have stated each drug type with their side effects:

Table 7: Risks

Medications	Side effects
Corticosteroid	weight gain, osteoporosis, Cushing syndrome, glucose intolerance, glaucoma, and increased risk for infections surgical intervention, increases the risk of perioperative complications after surgery for CD.
Immunomodulators	Spontaneous infection, myelotoxicity, and pneumonitis, organ toxicities
Biologics(Anti-TNF)	reactivation of tuberculosis, increased risk of sepsis and opportunistic infections, and reactivation of hepatitis B

Transmural Healing

Healing of the entire thickness of the intestinal wall of all inflamed segments involved has been proposed as a new treatment in CD. Transmural healing can be achieved in quarter of CD

patients treated with anti-TNF alpha(infliximab and adalimumab). Mucosal healing is good treatment outcome in CD in terms of steroid-free clinical remission, rate of hospitalization and need for surgery, but transmural healing is more robust endpoint associated with better medium and long-term outcomes that mucosal or no healing. Transmural healing is associated with better long-term clinical outcomes than mucosal healing also after discontinuation of biologics.

Table 8: Transmural Healing

Category	Transmural Healing	Mucosal Healing	No Healing
Steroid free clinical remission	95.6%	75%	41%
Rate of hospitalization	8.8%	28.3%	66.6%
Need for surgery	0%	10%	35.5%

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

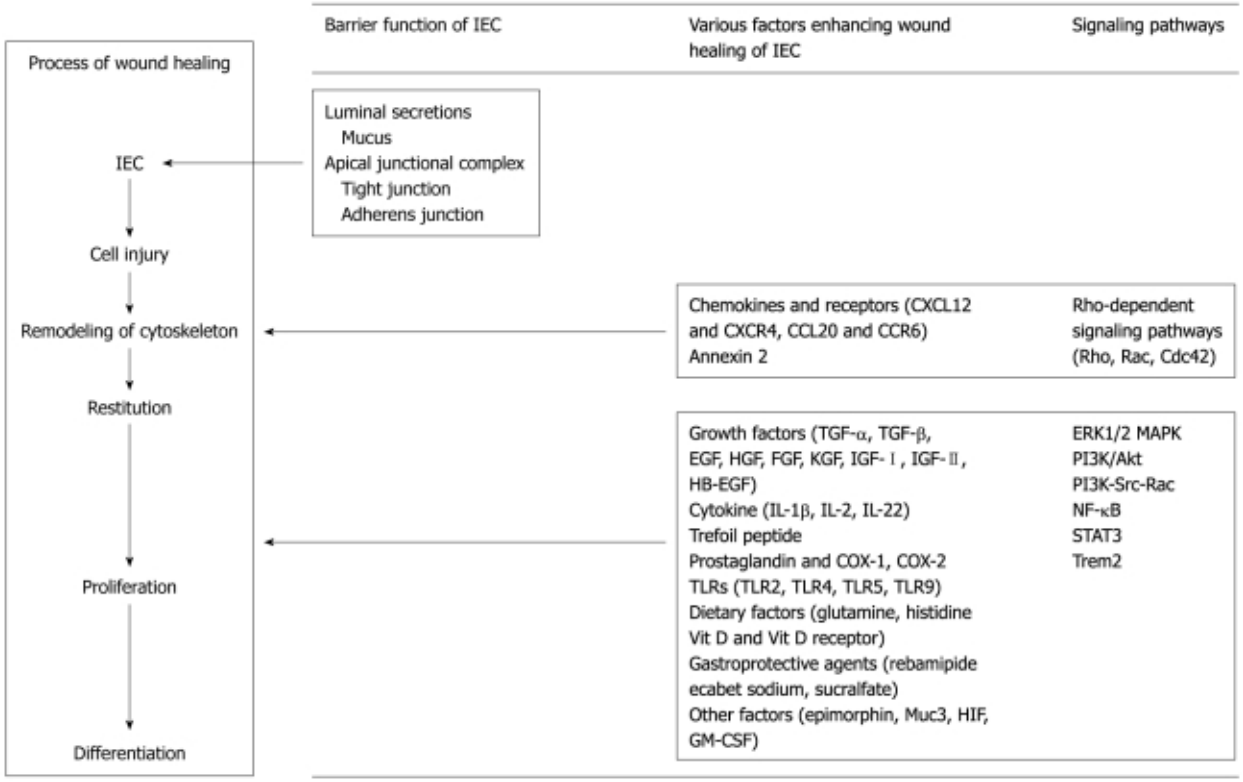
Every drug or treatment listed above currently present has some or the other limitations for treating any Inflammatory Bowel Disease. For example - According to Alternative Medicines as Emerging Therapies for Inflammatory Bowel Diseases, "5-aminosalicylate was a functionally active moiety of prototypical 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.

Figure 9: Wound Healing



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 several natural or herbal therapies for IBD.

Table 9: Natural IBD remedies

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 neoplasia	-
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	-

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 CD.

Vitamins and Minerals in IBD

Vitamin A

Serum retinol concentrations factor is used to identify human being with vitamin A deficiency. For IBD patients by concentrations factor has been diagnosed with deficiency of

vitamin A. According to the Da Rocha et al published case report of retinol deficiency and night blindness in a CD patient with repeated small bowel resections. Normal eyesight was restored by regular Vitamin A administration. The study shows vitamin A deficiency exacerbates inflammation and supplementation offers protection against it. The studies with vitamin A or retinoic acid supplementation are sparse and disappointing. The study tells that no benefit of 50,000 U twice daily in a double-blind study involving 68 CD patients. In another small study by Norrby et al. 150,000 U of vitamin A daily led to no measurable improvement in 8 patients with severe CD.

Vitamin B6

Pyridoxal 5′-phosphate (PLP) is the biologically active form of vitamin B6 . Although severe vitamin B6 deficiency is uncommon, mild insufficiency (plasma PLP <20 nmol/L) is observed in 10–16% of the adult US population. In mammals, food and gut commensal bacteria are the two main sources of vitamin B6. PLP tends to be generally reduced in patients with inflammatory conditions. Restoring normal levels in patients with inflammation requires higher dietary intake. The showed that patients with active CD and UC have significantly lower plasma PLP concentrations than patients with quiescent disease or healthy controls. However, the relationship between inflammation and B6 level is not straightforward. So it can be said that Vitamin B6 can be of help for disease like CD and UC.

Iron

Iron is any important mineral of body and have very important task for example reversible oxygen binding in HB. According to the study, iron deficiency and fatigue in IBD patients with prevalence reported in 36% -76% patient. For IBD patients, the Centers for Disease Control and Prevention recommends 30 mg/day of elemental iron for IDA prophylaxis, and 50–60 mg/day for treatment. However, oral supplementation in IBD may be ineffective in the settings of normocytic anemia of chronic inflammation. It may also be poorly tolerated with adverse effects such as epigastric pain, nausea, flatulence, and diarrhea, which lead to poor adherence to treatment.

High doses and excess of non-absorbed iron in IBD may also be toxic to the epithelium as it undergoes Fenton reaction with hydrogen peroxide and increases inflammatory response. ECCO guidelines recommend intravenous iron to be considered the first line of treatment in patients with clinically active IBD, those with previous intolerances to oral iron, with hemoglobin levels below 10 g/dl, or in patients with documented need for erythropoiesis-stimulating agents.

Vitamin D and Calcium

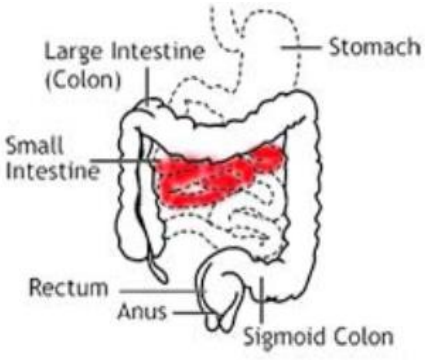
Regulation of calcium homeostasis and bone metabolism are of particular importance in IBD due to immune dysregulation and inflammation-associated loss of bone mineral density prevalent among IBD patients. Vitamin D3 (cholecalciferol) is the natural form of vitamin D active in humans. Among all nutritional deficiencies in IBD, vitamin D3 received the most attention with relatively consistent reports of prevalent deficiency or insufficiency.

The studies above suggested that since cytokines associated with active inflammation, such as IL-1β, IL-6, and TNFα may act synergistically with vitamin D3 to negatively regulate bone turnover, high-dose vitamin D3 supplementation in active IBD may not improve bone density or even lead to a paradoxical BMD loss and that in patients at clear risk of osteopenia or osteoporosis or with proven osteopenia or osteoporosis, vitamin D3 be withheld until remission is achieved. This would also be consistent with vitamin D3 supplementation as means of relapse prevention, which has clinical support in published studies. Although long-term high-dose D3 supplementation has been shown in some studies to significantly reduce disease score in active IBD the effects on the bone are typically not assessed in those inflammation-centric studies.

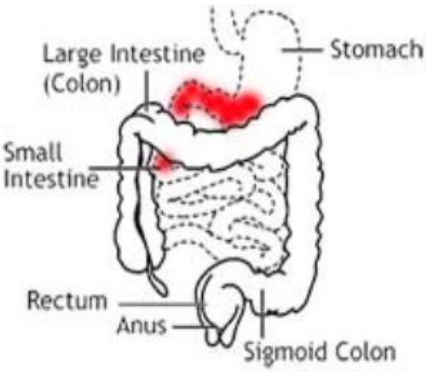
Small Intestinal Data

Types of Crohn's Diseases

1. Jejunoileitis

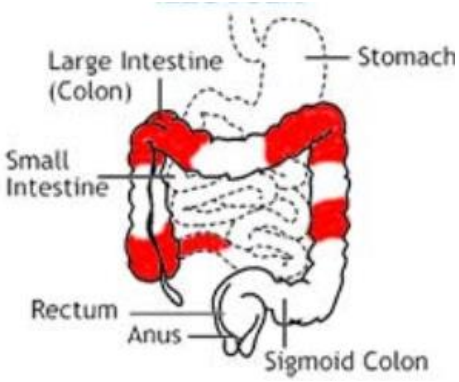
	Inflammation	Middle and end of the small intestine.
	Symptoms	Cramps after eating, Diarrhea, Abdominal pain, weight loss, Anemia, Fatigue.
	Complications	Nutritional deficiencies, fistulas or inflammatory abscesses in the abdomen, strictures causing blockage in intestines.
	Percent of Population affected	20% in children and 4% in adults with CD have this type.

2. Gastroduodenal

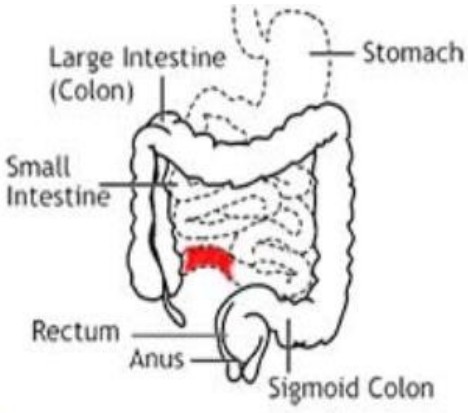
	Inflammation	Stomach and duodenum (first part of small intestine).
	Symptoms	Loss of appetite, Weight loss, Nausea, Vomiting, Abdominal pain similar to indigestion, Fatigue.
	Complications	Gastroduodenal strictures and Pancreatitis are most common complication of gastroduodenal crohn's disease. Gastric outlet obstruction causing vomiting, Fistulas, abscess.

	Percent of Population	5% of people with CD have gastroduodenal Crohn’s.

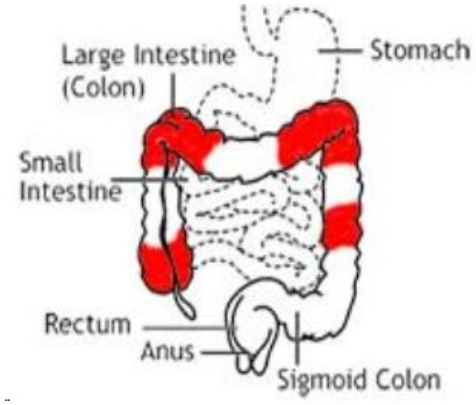
3. Ileocolic

	Inflammation	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	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	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.

Notes:

- 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 CD 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.

Recommendations

Target Market: Small Intestine

Based on research completed, the ELC team believes that targeting the small intestine would be a good opportunity for ClostraBio. Currently, ClostraBio's treatment process prefers to target at the remission-to- moderate severity level of IBD, the most prevalent forms found in the

small intestine. The ELC team has identified that the ClostraBio treatment process would be a feasible replacement for the majority of current treatment types. Biologics, which mainly targets at moderate-to-severe levels of IBD, currently occupies the majority share of that severity threshold and would make it difficult for new competitors to be successful within that market.

Based on 2016 estimates, there are about 3 million out of the total 3.7 million IBD U.S. population with severity between remission-to-moderate, this indicates a huge potential market for ClostraBio to thrive in. About 1.7 million patients in the U.S. have CD and about 80% of CD patients' small intestine are affected by the disease, indicating that about 1.36 million Americans have inflammation in different locations of their small intestine. In addition, the trend of both increasing IBD prevalence and treatment costs makes the disease an explorable market.

From the perspective of surgery, small intestine resection and strictureplasty are the two primary forms of surgeries related to the small intestine, the other form of intestinal surgeries known as colectomy and proctocolectomy, involve resections within the large intestine and colon. Using the FairHealthConsumer.org tool, The ELC team choose three cities from each of the four different regions of the U.S. and calculated the average cost for both of surgery types. Small intestine resection out-of-network cost is about $20,658 and in-network cost are about $8,889. Strictureplasty out-of-network cost is about $8,268 and in-network cost are about $3,449.

A single surgery is typically not enough for patients to be cured of the disease; therefore, patients may need to take several surgeries to maintain their life long-term, increasing treatment costs substantially. As of now there are no long-term treatments available for small intestine IBDs outside of surgery, If indications that ClostraBio's treatment process could control or even reverse the condition of patients so that they don't need surgery, it will be very beneficial for patients and extremely profitable for the company.

Table 10: Surgery cost breakdown per city

City	Region	Small intestine resection		Strictureplasty	
		Out of network	In-Network	Out of network	In-Network
San Antonio, TX	South	$20,069	$7,877	$7,039	$3,030
Nashville, TN	South	$20,568	$8,094	$7,253	$3,126
Matthews, NC	South	$15,062	$9,217	$7,130	$3,196
Springfield, IL	Midwest	$20,653	$9,028	$9,243	$3,751
Chicago, IL	Midwest	$25,129	$10,811	$9,829	$3,320
Carbondale, IL	Midwest	$18,130	$8,395	$6,341	$2,787
San Francisco, CA	West	$21,460	$9,552	$9,986	$3,753
San Diego, CA	West	$20,589	$9,332	$6,447	$3,337
Seattle, WA	West	$18,886	$7,889	$6,628	$3,031
New York, NY	East	$33,080	$11,053	$13,230	$5,653
Washington DC	East	$18,997	$8,933	$7,037	$2,833
Boston, MA	East	$15,268	$6,527	$9,050	$3,573
Average		**$20,658**	**$8,892**	**$8,268**	**$3,449**

Through the entire research process for discovering the small intestine information, the ELC team inferred that studies focusing on small intestine data were not substantial. This inference turned out to become true after several weeks of research by the project team lead to minimal results. The team suggests that there are no substantial studies done on IBD within the

small intestine related to costs, severity, and long-term treatments outside of surgery. The lack of research did greatly hinder the team's projected results; however, it can also be seen as a large potential market for ClostraBio to conduct primary research.

The ELC team also discovered an article by Science Magazine (Kaiko, G) stating that researchers in Washington University School of Medicine in St. Louis found "a unique target that's not an inflammatory molecule, and yet blocking it reduces inflammation and signs of disease, at least in mice." The researchers noticed that a gene called SERPINE-1 and its corresponding protein are "in high levels in inflamed parts of the gut in IBD patients" and "it seems to be highly most highly expressed in people with the most severe disease and those who don't respond to immunosuppressive biologics." The researchers conducted experimentation on mice, when mice with IBD-like symptoms were treated with a compound with called MDI-2268, that blocked the activity of the protein, they fared much better. (2019)

Price Estimate

Determining a specific price for ClostraBio's treatment can be challenging since production and distribution of the treatment is expected to be outsourced to other companies, these third parties will affect profit margins and drive costs up in certain regions. Additionally, the demand for effective drugs to treat CD seems to be fairly inelastic, so that leaves a wide gap for potential prices. However, to be fair to consumers, the ELC team believe that pricing the medicine according to its predicted effectiveness is the way to go. Based on the information provided below, the team suggests a starting retail price of $2,500 per yearly dosage.

In a meta-study conducted by Mao, Hazlewood, Kaplan, Biroulet, and Ananthakrishnan published on Wiley Online Library, concluded that biologics were associated with a significant reduction in hospitalization and surgery for patients with CD and UC. This difference is represented in the charts below. For hospitalization, these are their results:

Pair-wise Comparisons of Treatments for Efficacy in Reducing Crohn's Disease Hospitalization

Comparator / Intervention	Odds ratio (95% credible interval), probability intervention superior to comparator		
	Placebo	Infliximab	Adalimumab
Infliximab	0.44 (0.24–0.76) 99%		
Adalimumab	0.51 (0.23–1.12) 96%	1.14 (0.44–3.18) 37%	
Azathioprine	2.34 (0.64–9.65) 9%	5.34 (1.32–24.85) 99%	4.66 (1.01–24.38) 98%

*Dark grey shading represents comparisons with probability of superiority > 97.5%; light grey shading represents comparisons with probability of superiority between 92% and 97.5%.

Alternatively, for surgery:

Table: Pair-wise Comparisons of Treatments for Efficacy in Reducing Crohn's Disease Surgery

Comparator / Intervention	Odds ratio (95% credible interval), probability intervention superior to comparator			
	Placebo	Infliximab	Adalimumab	Vedolizumab
Infliximab	0.26 (0.10–0.61) 99%			
Adalimumab	0.13 (0.02–0.61) 99%	0.48 (0.06–3.03) 80%		
Vedolizumab	0.43 (0.10–1.91) 88%	1.66 (0.29–9.17) 26%	3.56 (0.38–39.30) 13%	
Azathioprine	0.81 (0.02–36.15) 55%	3.12 (0.09–147.28) 25%	6.81 (0.15–464.57) 15%	1.88 (0.04–105.62) 64%

*Dark grey shading represents comparisons with probability of superiority > 97.5%; light grey shading represents comparisons with probability of superiority between 92% and 97.5%.

Additionally, in “Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease” Colombel JF, Sandborn WJ, Reinish W, found that 56.8% of patients receiving combination therapy (biologic and immunomodulator) were in corticosteroid-free clinical remission at week 26 (primary endpoint), compared to 44.4% receiving infliximab alone and 30% receiving azathioprine alone.

Moreover, the likelihood of these patients requiring surgery also decreases with combined therapies. It is worth noting that this only holds true for combination therapies with biologics involved. In a study designed by Kyung-Jo Kim and Min Seob Kwak, concluded that combination therapy between a 5-ASA and an immunomodulator (6-MP) was not more effective to reduce the need for hospitalization or surgery than either of these alone. The cumulative probabilities of disease-related hospitalization at 5 and 10 years were 52.8% and 91.8% for the 5-ASA + AZA/6-MP and 59.4% and 95.3% for the AZA/6-MP group. However, they did find that early use of these drugs reduced surgical rates.

Given that ClostraBio’s medicine would be used in conjunction with biologic therapy, results may more closely align with those found by Colombel JF. After reviewing these factors, accounting for quality of life, and knowing the average price for immunomodulator is $1,500, the team concluded that a price of around $2,500 a year would be fair.

Conclusion

This report represents the final progress the ClostraBio ELC team has made in regard to outlined objectives of the project and recommendations based on findings. Extensive research has been done on various areas during the 16-week project term. The information on market opportunity and product scope of the IBD industry in the U.S was gathered in which the team identified the total population count and severity types for both the disease (CD and UC), the different severity types were; remission, mild, moderate, and severe. The team further identified alternative treatments for IBD, current treatment costs (direct and indirect cost), and their subsequent economic burden on patients, this research helped the team determine rough estimating price for ClostraBio’s offerings.

Furthermore, the team gathered valuable data about the direct and indirect competitors towards ClostraBio in the IBD market depending on the nature of the competitor and treatment mechanism. The team included pricing details for medications available from 5 ASA's, immunomodulators, corticosteroids, and biologics. The pipeline market for IBD treatment was also touched upon by the team and further detailed in the report where valuable information was collected pertaining to biologics and other important drugs.

Lastly, 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. To conclude, the team administered several recommendations based on the outline research path and our collective interpretation of ClostraBio's feasible next steps. The team hopes that ClostraBio is able to find value in the research gathered and the recommendations suggested.

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