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REAL-WORLD UTILIZATION AND EXPENDITURE OF TOP-DOWN AND STEP-UP THERAPY IN INFLAMMATORY BOWEL DISEASE

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REAL-WORLD UTILIZATION AND EXPENDITURE OF TOP-DOWN AND STEP-UP THERAPY IN INFLAMMATORY BOWEL DISEASE

BY

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ABSTRACT

Introduction

Inflammatory bowel disease (IBD) describes gastrointestinal inflammatory diseases Crohn's disease (CD) and ulcerative colitis (UC). The inflammation associated with CD can penetrate deep layers of gastrointestinal tissue anywhere along the gastrointestinal tract. Pharmaceutical therapy options for CD include aminosalicylates, corticosteroids, antimicrobials, immunomodulators, and biologics. The step-up (SU) treatment strategy for CD begins with anti-inflammatory agents (aminosalicylates, corticosteroids, and antimicrobials), and progresses to immunomodulators and biologics if disease control is not achieved. Conversely, with top-down (TD) therapy strategy, patients initiate CD medication treatment with immunomodulators and biologics and use anti-inflammatory agents as second-line options. Presently, limited evidence exists characterizing the utilization and short-term costs related to SU and TD therapy in CD.

Objective

The objective of this thesis research was to observe patient/disease characteristics in patients initiating CD pharmaceutical treatment with SU and TD therapy, and to examine predictors of increased first-year healthcare expenditures in a real-world setting.

Methods

This was a retrospective, cohort analysis of Optum's de-identified Clinformatics® Data Mart Database examining patients with CD who were newly initiated on medication therapy from 2010 to 2018. Patients with CD were identified as having two International Classification of Diseases (ICD) codes for CD that were at least 30 days apart. The first CD-ICD code was considered the index diagnosis date. The SU and TD cohorts were defined based on medications for CD dispensed in the 60-day exposure period after the index diagnosis date. We examined 365 days prior to the index diagnosis to exclude patients not newly initiated on therapy, and 365 days after the exposure period to examine costs. We conducted a descriptive analysis comparing the SU and TD cohorts and used t-tests, chi-squared tests, and analyses of variance (ANOVA) to test the statistical significance of group differences. Predictors of per-patient average adjusted CD-specific healthcare cost were estimated using a generalized linear model.

Results

We identified 3,157 patients newly initiating medication therapy for CD, with 2,392 patients in the SU cohort and 765 patients in the TD cohort. The SU cohort consisted of a larger proportion of females than the TD cohort (55.02%, 49.67%, respectively, $p=0.0009$) and the mean age in the SU cohort was higher than the TD cohort (48.9 years, 39.8 years, respectively, $p<0.001$). SU therapy was the dominant treatment strategy utilized each year of our study period, but the proportion of TD therapy utilized increased over time from 17% in 2011 to 31% in 2017 ($p<0.0001$). Furthermore, the TD strategy was associated with

higher overall and CD-specific costs in the follow-up period ($p<0.0001$) compared to the SU cohort. Treatment strategy, age group, disease location, GI-related hospitalization prior to diagnosis, payer, and diagnosis year were significant predictors of CD direct healthcare costs in the generalized linear model. Patients initiating CD medication treatment with TD therapy had a follow-up adjusted average per-patient CD-specific direct healthcare cost of 149.78% ($1,230.26) higher than patients who initiated with SU therapy.

Discussion and Conclusion

To our knowledge, this is the first study to use a large administrative claims database to compare the utilization and first-year healthcare expenditure among patients initiating medication therapy for CD with either SU or TD approach. We found that while the SU approach was the dominant treatment strategy, the proportion of TD therapy utilization increased over time. Furthermore, TD was associated with a higher overall and CD-specific cost in the year following treatment initiation. Further research is needed to determine the long-term overall healthcare costs associated with these strategies.

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PREFACE

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CHAPTER 1

INTRODUCTION

Inflammatory bowel disease (IBD) is a gastrointestinal inflammatory disease, characterized by relapsing intestinal inflammation and tissue damage. In the gastrointestinal tract, the immune system normally plays an important role in combating pathogenic bacteria or viruses ingested. In patients with IBD, however, the immune system response is exaggerated and causes damage to the gastrointestinal tissue. This damage further triggers an inflammatory response of the immune system to repair the tissue, leading to a chronic cycle of damage and inflammation in the gastrointestinal tissue.[1,2] IBD describes two chronic inflammatory gastrointestinal conditions, Crohn's disease (CD) and ulcerative colitis (UC). CD can affect any part of the gastrointestinal tract (from mouth to anus), most commonly the small and large intestines. Unlike the continuous nature of UC, CD occurs in patches along the gastrointestinal tract and penetrates the deep layers of gastrointestinal tissue. Common symptoms of CD include persistent diarrhea, abdominal pain, gastrointestinal bleeding/bloody stools, weight loss, malnutrition, and fatigue.[1-2] Irritable bowel syndrome (IBS), though similar to IBD in symptoms, is not associated with inflammation and damage to the gastrointestinal tissue.[2]

Approximately 3 million US adults (1.3% of the US adult population) reported a diagnosis of IBD (CD or UC) in the 2015 National Health Interview Survey (NHIS).[3,4] The prevalence of both CD and UC was higher in adults ≥45

years of age and among non-Hispanic whites.[4] Furthermore, the adjusted incidence of CD was estimated at 10.7 cases (95% CI: 9.1, 12.3) per 100,000 person-years using Rochester Epidemiology Project data from 2000 to 2010; the estimated adjusted prevalence of CD on January 1, 2011 was 246.7 cases (95% CI: 221.7, 271.8) per 100,000 persons.[5] CD has a bimodal distribution for age of onset, with ages 20-35 and 50-65 having the highest incidence rates.[5-8] Rates of CD-related hospitalizations (CD listed as primary diagnosis) increased from 44.2 per 100,000 US population in 2003 to 59.7 per 100,000 in 2013, based on an analysis of the Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS) data from 2003 to 2013.[9] Among the CD-related hospitalizations in 2013, colorectal resection occurred in 12.8% of hospitalizations, small bowel resections occurred in 3.9% of hospitalizations, and fistula repairs occurred in 2.0 % of hospitalizations.[9]

Medication Therapy Guidelines and Recommendations

Medication therapy options for CD include aminosalicylates, corticosteroids, antimicrobials, immunomodulators, and biologics (see Table 1 for CD-indicated medications).[10-14] Aminosalicylate agents are anti-inflammatory agents that can be taken orally or topically (suppositories or enemas). Corticosteroids suppress the immune system systematically, and are generally not recommended for long-term daily therapy.[1,10-14] Antimicrobial agents, specifically metronidazole and ciprofloxacin, are indicated as anti-inflammatory agents that eliminate bacterial overgrowth and associated antigenic triggers to decrease inflammation, but have limited evidence of benefit over placebo in CD.[10-14]

Immunomodulator/antimetabolite agents, specifically thiopurines, and methotrexate, are systemic therapies indicated for CD to decrease immune system and inflammation activity. Lastly, biologic agents indicated for CD have immunomodulatory mechanisms of action, such as tumor necrosis factor (TNF)-alpha inhibitors, Janus Kinase (JAK) inhibitors, adhesion inhibitors, and interleukin (IL)-23 inhibitors.[1,10-14]

Guideline recommendations for treating CD include lifestyle changes, medication therapy, and surgery.[10-14] Medication therapy goals for CD are to induce and maintain remission of the inflammatory processes, achieve mucosal healing, control symptoms, and prevent complications of CD such as strictures and fistulas.[10-11] Recommendations for initial medication therapy in CD differ based on the severity of disease presentation and risk of developing complications.[10-14] For mild disease, the American College of Gastroenterology (ACG) and American Gastroenterological Association (AGA) recommends medication therapy with either mesalamine, sulfasalazine, budesonide and/or antibiotics.[10-14] The ACG 2009 guidelines recommended mesalamine, sulfasalazine, or metronidazole, but note that mesalamine and metronidazole have weaker evidence.[10] The ACG 2018 guidelines recommend sulfasalazine and budesonide for initial treatment of mild/moderate CD, and state mesalamine, ciprofloxacin, and metronidazole are not recommended for induction treatment in mild/moderate disease for most patients due to limited evidence of benefit.[11] The AGA guidelines recommend budesonide or prednisone with optional azathioprine treatment for mild/low-risk disease.[12-14]

For moderate/severe CD, corticosteroids may be utilized to attain initial disease control and induce remission, but are not recommended for long-term therapy.[10-14] The AGA defines moderately severe CD as disease requiring systemic corticosteroids for symptom control.[12-14] The ACG and AGA guidelines recommend using aminosalicylates, immunomodulators, and/or biologic agents as medication therapy to maintain remission for moderate/severe CD. Per the ACG 2009 guidelines, azathioprine and 6-mercaptopurine were recommended to maintain a steroid-induced remission, and methotrexate was recommended for steroid-dependent and steroid-refractory CD.[10] The 2009 ACG guidelines recommended anti-TNF monoclonal therapy only in patients who fail therapy with corticosteroids or immunosuppressive agents. The 2018 ACG guidelines similarly recommend immunosuppressive agents as initial therapy, but also endorse anti-TNF therapy, anti-integrin therapy (vedolizumab), and natalizumab therapy as the first medication treatment option or in patients unresponsive to corticosteroids and immunomodulators; ustekinumab is recommended only for patients failing corticosteroids, thiopurines, methotrexate, or anti-TNF inhibitors.[11] The AGA guidelines recommend anti-TNF inhibitors over thiopurine monotherapy in patients with moderately severe Crohn's disease "despite standard therapies."[12-14]

Top-Down and Step-Up Treatment Sequencing

Traditionally, treatment for CD begins with anti-inflammatory agents (aminosalicylates, corticosteroids, and antimicrobials), and progresses to immunomodulatory agents and biologics if disease control is not achieved. This

treatment sequence has been termed step-up (SU) therapy.[1,15-18] Of note, step therapy, while similar to step-up therapy in choice of medication order, is guided by managing medication costs for payers and may require patients to fail lower-costing anti-inflammatory agents before trying higher-costing biologic agents. As the development and approval of biologics and immunomodulating agents increases for CD, clinical experts are investigating and, in some instances, recommending early-biologic or top-down (TD) therapy sequences for certain patients and disease severities.[11-14] With TD treatment sequencing, patients receive the traditionally advanced therapies, such as biologics and immunomodulators, as their initially prescribed therapy and use anti-inflammatory agents (aminosalicylates, corticosteroids, and antimicrobials) as a secondary therapy, if needed.[1,15-18]

The use of TD therapy in Crohn's disease has been debated for over a decade.[19] While evidence exists showing an association between TD therapy and disease control, reduced relapses, and symptom improvements in CD, clinical experts hesitate to embrace widespread TD therapy use because of the risks associated with TD therapy, the lack of definitive evidence that TD therapy modifies the clinical course of disease, and the costs attributed with TD medication.[20-27] The adverse reactions of the immunomodulators indicated for CD include increased risk of infection, hepatitis, bone marrow suppression, pancreatitis, and lymphoma.[24,28,29] The biologics indicated for CD are associated with an increased risk of infection, malignancy, demyelinating disorders, autoimmunity, and worsening of congestive heart failure.[23-26]

Conversely, anti-inflammatory agents (aminosalicylates, corticosteroids, and antimicrobials) are considered less toxic and have favorable safety profiles compared to TD therapies.[24] Additionally, the efficacy of the TD therapies were demonstrated using surrogate endpoints (mucosal healing and symptom control) to represent decreased intestinal inflammation and associated complications (ulcerations, bleeding, fistula formation, and fibrosis).[24] However, these surrogate endpoints may be too short-term to account for complications of CD that evolve over a patient's lifetime.[21,27] In rheumatoid arthritis, TD therapy is a widely accepted treatment pattern supported by radiographic evidence of prevention or decreased progression of joint erosion, which modifies the course of the disease.[27,30] Experts have postulated that TD therapy may not have demonstrated disease modification in CD, and speculated a disconnect between the mucosal healing endpoint and symptom control.[24,27,31] Furthermore, in terms of cost, the prices and medication-associated healthcare utilization related to TD therapy may have substantial budget implications for payers, meanwhile SU therapies have generic options and are generally less costly.[32]

The economic value of medication therapy and controlling inflammation in CD is reflected in costs of hospital/emergency department utilization, outpatient healthcare visits, and surgical procedures over the patient's lifetime.[33,34] Though short-term costs incurred from medications and associated healthcare utilization can be substantial, the expected decreased healthcare utilization over the patient's lifetime may ultimately yield cost-savings for the healthcare system.[33-37] However, since a single payer typically does not cover a patient for the

entirety of a patient's lifetime, an individual payer may not realize the long-term economic benefits associated with utilizing expensive, aggressive therapies early in a patient's disease course.

Economic evaluation studies comparing SU to TD therapy in CD showed that cost-effectiveness was not observed in short time horizons (less than 5 years) or in all disease severities; moderate/severe CD has a greater potential for decreased healthcare utilization in the long-term (5 years) with early aggressive medication therapy to attain remission compared to mild disease.[36,37] To our knowledge, no study has examined the first-year healthcare expenditure among patients initiating medication therapy for CD with either a SU or TD therapy in a large administrative claims database. These short-term costs are important for payers to understand when creating coverage policies for optimal healthcare resource utilization.

Objective

The goal of this thesis research was to examine utilization patterns and short-term healthcare expenditures associated with initiating medication therapy for CD with either SU or TD therapy in a real-world setting. This research ascertained how often and in which patient/disease characteristics CD pharmaceutical treatment was initiated with either SU or TD therapy. Furthermore, this research examined the difference in the average per-patient healthcare expenditure in the first year following medication initiation with SU or TD therapy, adjusting for demographic and clinical factors.

CHAPTER 2

REVIEW OF LITERATURE

Evidence Assessing Top-Down Therapy in Crohn's Disease

The TOP-DOWN trial was an open-label, randomized clinical trial of early immunosuppression therapy compared to conventional management in patients with CD in Europe from May 2001 to January 2004. Patients aged 16-75 years who had been diagnosed with CD within 4 years of the study period and who were not exposed to corticosteroids, antimetabolites, or biological agents prior to entering the study were included. In the early immunosuppression therapy cohort, 65 patients with CD received infliximab and azathioprine as initial pharmaceutical therapy. Conversely, 64 patients with CD in the conventional management cohort received methylprednisolone or budesonide for induction therapy. This trial was the first to show that medication therapy with early immunosuppressive agents achieved remission in more patients at 26 and 52 weeks after therapy initiation than conventional therapy for CD. The absolute difference in remission rates between immunosuppression and conventional therapy was 24.1% (39/65 [60%] and 23/64 [35.9%], respectively, p=0.0062) at 26 weeks, and 19.3% (40/65 [61.5%] and 27/64 [42.2%], respectively, p=0.0278) at 52 weeks.[38]

Hoekman et al. conducted a follow-up retrospective chart review of patients enrolled in the TOP-DOWN trial[38], to compare long-term outcomes of SU and TD therapy. After the 2-year TOP-DOWN trial, patients were treated by their

physicians, therefore the cohort assignment for this follow-up study was based on intent-to-treat from the original study. After a median follow-up of 8 years, the researchers found clinical remission rates of 70% and 73% in the SU and TD cohorts, respectively, (p=0.85). Furthermore, the median time to flare was shorter in the SU cohort than the TD cohort (five semesters, nine semesters, respectively, p=0.01). The researchers also found no significant difference between the SU and TD cohorts for time to CD hospitalization (13 semesters, 14 semesters, respectively, p=0.30) and time to CD surgery (14 semesters, 15 semesters, respectively, p=0.25).[39]

The REACT trial was a cluster randomized controlled trial conducted from 2010 to 2013 in Belgium and Canada, comparing early combined immunosuppression (with a TNF antagonist plus antimetabolite) to conventional management in patients with CD. After 12 months, the researchers found no statistically significant difference in remission rates and adverse-medication reaction occurrences between the early combined immunosuppression cohort and the conventional therapy cohort (adjusted difference in remission rates: 2.5% [p=0.5169]). Early combined immunosuppressive therapy was, however, associated with lower adverse outcomes such as surgery, hospitalization, and serious disease complications (HR: 0.73, 95% CI:0.62,0.86).[40]

In a prospective, interventional, controlled study, researchers administered either infliximab plus azathioprine or prednisone plus azathioprine to patients with moderate to severe active CD naïve to treatment. After 30 weeks, the deep remission rates, time to clinical remission, and clinical remission rates were

compared between groups. Of the 38 participants in the infliximab plus azathioprine group, 44.7% achieved deep remission, compared to 17.9% (out of 39 patients) in the prednisone plus azathioprine group (p=0.011). The median time to clinical remission was 6.8 weeks for the infliximab plus azathioprine group and 14.2 weeks for the prednisone plus azathioprine group (p=0.009). Additionally, the clinical remission rates in the infliximab plus azathioprine group were higher than the prednisone plus azathioprine group at 30 weeks (68.4%, 43.6%, respectively, $p<0.05$).[41]

A prospective, observational study examined bowel damage in patients with early CD at high risk for disabling disease receiving either SU, TD, or accelerated SU (AC) therapy, which was initial therapy with an immunomodulator. The researchers examined rates of mucosal healing, described as the absence of ulcerations in patients having ulcerations at baseline. After 36 months, the rates of mucosal healing were 78.8%, 39.9%, and 42.2% for the TD, AC, and SU cohorts, respectively (p=0.001). The researchers also found non-statistically significant differences between the TD, AC, and SU cohorts at 60 months for surgery-free rates (83.2%, 82.5%, 60.3%, respectively, p=0.16) and hospitalization-free rates (63.9%, 67.8%, 57.4%, respectively, p=0.58).[42]

A real-world analysis of PharMetrics administrative claims data from January 2000 through January 2009 determined if a TD treatment approach with an anti-TNF medication was associated with improved clinical outcomes. The researchers identified three cohorts, a SU cohort consisting of patients

initiating medication therapy with an aminosalicylate or corticosteroid, an immunosuppressive therapy cohort consisting of patients initiating medication therapy with a thiopurine or methotrexate, and a TD cohort consisting of patients initiating medication therapy with an anti-TNF medication. The researchers found early treatment with an anti-TNF medication was associated with lower concomitant use of corticosteroids ($p<0.05$), lower rates of medication regimen alterations/discontinuations ($p<0.05$), and CD-related surgeries ($p<0.05$) compared to the SU and immunosuppressive therapy cohorts.[43]

A systematic review of studies examining the clinical effectiveness of TD therapy in patients with CD published before July 2017 was conducted by Tsui et al. The researchers identified 19 studies evaluating early biologic and/or immunomodulator use. The compiled evidence showed a clinical benefit of early combined therapy for CD when biologics and immunomodulators were prescribed together; however, biologic therapy and immunomodulator therapy separately did not have consistent evidence of efficacy or benefit over SU therapy. The results of this systematic review showed that while TD therapy showed promise in achieving remission and reducing complications, additional research to understand the pathophysiology of CD is required to guide personalized medication therapy and identify patients who will benefit most from TD therapy.[44]

A systematic review and meta-analysis conducted by Ungaro et al. examined the efficacy and safety of top-down, early biologic therapy strategies in Crohn's disease. Studies were included in the analysis if patients were

initiated on biologic therapy within two years of CD diagnosis in the study or if early biologic was compared to conventional therapy in the study. The researchers identified 47 studies, including observational studies , retrospective cohort studies, and one cost-effectiveness study. The meta-analysis found that early biologic therapy was associated with higher rates of clinical remission (OR 2.10 [95% CI: 1.69,2.60], n=2763, p<0.00001), lower rates of relapse (OR 0.31 [95% CI: 0.14,0.68], n=596, p=0.003) and higher rates of mucosal healing (OR 2.37 [95% CI: 1.78,3.16], n=994, p<0.00001) compared to SU or late conventional management. The identified cost-effectiveness study conducted by Beilman et al. is discussed in the "Cost-Effectiveness and Economic Analyses" section of this thesis (page 14).[45]

Cost of Crohn's Disease

According to an analysis using Optum Research Data for the years 2007 to 2016, the estimated inflation-adjusted mean annual direct healthcare cost for patients with IBD was $22,987. The patients with CD had a higher average all-cause total cost of care compared to patients with UC. The estimated mean annual healthcare cost for patients without IBD was $6,956. The authors speculate the increased cost in IBD patients compared to controls may be due to higher healthcare utilization, out-of-pocket expenditure, and productivity loss associated with IBD.[46]

In a Truven Health MarketScan database analysis from 2008 to 2015, researchers designed a Markov model to estimate the overall lifetime healthcare costs for patients with CD and UC. The researchers found the lifetime total cost

for a patient with CD was $622,056, which included outpatient ($273,056), inpatient ($164,298), pharmacy ($163,722), and emergency department ($20,979) costs. The lifetime healthcare costs varied by age of diagnosis.[35]

The medical care financial burden of CD was assessed prospectively and observationally in a cohort of patients with CD from the natural history registry of IBD patients at the University of Pittsburgh Medical Center from 2009 to 2013. The median charge per patient for the 5-year follow-up period was $116,838 (IQR: $45,643 – $240,398). Hospitalizations were associated with 67% of total charges and anti-TNF therapy accounted for 15.2% of total charges.[33]

A systematic review of studies examining the cost of CD in Western industrialized countries found the inflation-adjusted direct medical per-patient per-year costs for CD was $18,022-18,932 in the United States and €2,898-6,960 in European countries. Hospitalizations contributed 53-66% of the direct medical costs per patient, on average. Indirect costs accounted for 28% of total costs in the United States and 64-69% in Europe.[34]

Cost-Effectiveness Economic Analyses of Step-Up and Top-Down Therapy

A study conducted using data from the Italian Healthcare System published in 2013 examined the cost-effectiveness of initial CD treatment with infliximab by calculating the incremental cost-utility ratio (ICUR) between SU and TD cohorts. Utility scores, based on mean Crohn's Disease Activity Index (CDAI) scores, were used to calculate quality-adjusted life-years (QALYs). Costs were determined from the third-party payer (Italian Healthcare System) perspective, including inpatient, outpatient, follow-up, medication, and surgery costs. The

model time horizon was five years. The researchers found that TD therapy had a quality-adjusted life expectancy 0.14 QALYs higher than the SU therapy cohort (3.90 QALYs, 3.76 QALYs, respectively). Furthermore, the cost of medication therapy for TD was €14,631 and for SU was €15,404. Therefore, TD therapy was dominant in the cost-effectiveness analysis because it was associated with an improvement in quality of life and a cost-saving of €773 over five years. Sensitivity analysis results maintained the dominance of TD therapy in varying discount rates, surgery rates, relapse rates, and surgery costs. As the cost of infliximab increased and the time horizon of the model decreased (less than 5 years), TD therapy was no longer dominant, but the ICUR calculated was under €100,000/QALY for all scenarios.[36] The willingness to pay thresholds in Europe ranges from €20,000 to €80,000 per QALY.[47] The generalizability of these results to the United States is limited by differing government regulations and lower medication prices in Italy.[48]

Beilman et al. assessed the lifetime cost-effectiveness of early (within 2 years) compared to late (greater than 2 years) anti-TNF therapy initiation in CD. The disease progression after initiating an anti-TNF therapy was simulated in a Canadian CD cohort using a Markov model. Costs were derived from the Alberta Ministry of Health. The researchers found early initiation with infliximab or adalimumab in CD yielded an additional 0.72 and 0.54 QALYs, respectively, and a saving of $50,418 and $43,969, respectively, compared to late initiation. Therefore, the authors concluded early initiation with infliximab or adalimumab (anti-TNF therapies) within two years of CD diagnosis was associated with

increased QALYs and cost-saving opportunities compared to initiation after two years.[49] The results of this study may not generalize to the United States, given the difference in healthcare systems and costs between the United States and Canada.[48]

A systematic review of economic evaluations published before March 2017 was conducted to assess the cost-effectiveness of treatment strategies for both UC and CD. The researchers found biologic therapies (infliximab and adalimumab) were associated with improved outcomes but were not cost-effective for all patients and disease severities in CD. Initial and induction medication therapy with biologics was cost-effective compared to standard care for patients with moderate or severe CD but was not cost-effective in CD refractory to conventional medication therapy and post-surgically induced remission.[37]

Real-World Evidence of Step-Up and Top-Down Utilization

Siegel et al. conducted a retrospective, observational study of the Truven Health MarketScan Commercial and Medicare Database to examine treatment pathways for adult patients with CD and UC from 2008 to 2016. The researchers identified both incident and prevalent disease and examined treatment patterns. Treatment for CD was most commonly initiated with either corticosteroid monotherapy (42%) or 5-aminosalicylic acid monotherapy (35%). Biologic therapy was used as initial therapy in less than 5% of CD patients, with adalimumab monotherapy (0.5%) and infliximab monotherapy (0.3%) as the most common biologic regimens for initial treatment. Furthermore,19% of

patients with CD had a treatment pathway including biologics in the follow-up period (ending in 2016) compared to 81% of patients who did not have exposure to a biologic during the study.[50]

Another Truven MarketScan Database analysis was conducted by Yu et al. to examine the utilization trends, relative market share, and costs of maintenance medication therapy for IBD patients from 2007 to 2015. Over time, the number of biologics used in the CD cohort increased from 21.8% in 2007 to 43.8% in 2015. Conversely, the use of immunomodulators and 5-aminosalicylic acid decreased from 2007 to 2015 (27.2% to 18.0%; 34.1% to 21.6%, respectively). The average per-member-per-year expenditure for patients with IBD (CD and UC) taking a biologic was $25,275 in 2007 and $36,051 in 2015.[51]

Rubin et al. conducted a Market Scan Commercial Claims and Encounters (CCAE) database analysis to assess continuity of initial therapy prescribed for CD and UC and associated costs from 2006 to 2010. The researchers identified patients on suboptimal treatment based on rates of treatment discontinuation, interruption, upward/downward titration, switching, and augmentation. In the CD cohort, 47.2% of patients were initiated on therapy with 5-aminosalicylic acid, 39.8% with corticosteroids, 8.2% with immunomodulators, and 4.9% with biologics. The all-cause and IBD-specific costs associated with suboptimal treatment were higher when compared to patients with optimal therapy in the CD cohort ($73,367, $32,213, respectively).[52]

Siegel et al., Yu et al., and Rubin et al., examined the utilization of SU and TD treatment sequences in different settings, and with different objectives. Siegel et al. reported treatment initiation and follow-up patterns, but did not examine costs or stratify by year. Yu et al. examined the utilization and costs of biologics compared to other therapies in IBD, but did not specifically assess therapy choice among newly diagnosed patients. Rubin et al. examined treatment initiation patterns in CD and UC, and reported first-year costs associated with optimal and suboptimal treatment, but did not examine the costs by treatment initiation pattern. Therefore, we identified a gap in the literature, as to our knowledge no prior study has determined the first-year healthcare expenditure in patients newly initiating therapy for CD with either SU or TD treatment sequences.

CHAPTER 3

METHODOLOGY

This study analyzed the prescribing trends and associated costs for patients initiating CD medication therapy. A descriptive analysis compared the demographic and disease characteristics of patients receiving SU or TD therapy. Then, a predictive model was executed to identify if SU or TD therapy, among other variables, was associated with higher direct healthcare costs in CD.

Study Design and Data Source

We conducted a retrospective, cohort analysis of Optum's de-identified Clinformatics® Data Mart Database (Optum Inc., Eden Prairie, MN) examining patients newly diagnosed and initiated on pharmaceutical therapy for CD from 2010 to 2018. Given the resources available for this research, a retrospective cohort study was the best option to investigate the research questions using data for patients across the US over eight years. The cohorts were identified based on treatment sequence (SU or TD), from a population of patients initiated on medication therapy for CD. Patients were followed for one year after medication initiation to ascertain cost and healthcare utilization outcomes.

Optum's de-identified Clinformatics® Data Mart is an administrative health claims database from a national insurer. The database contains detailed, de-identified, longitudinal administrative claims, including pharmacy, medical, laboratory, and inpatient data. Optum's de-identified Clinformatics® Data Mart

was selected as the data source for this research to accomplish the objective of examining real-world evidence in a large sample size.

Study Population

The study population consisted of adults newly initiated on medication therapy for CD. Patients were included in the study population if they had at least two International Classification of Diseases (ICD) codes for CD based on the method described by McAuliffe et al. (see Table 2 and Table 3 for ICD codes).[53-58] Patients with CD were identified as having at least two diagnosis codes for CD in any setting at least 30 days apart within the follow-up period and having a one-year period prior to index diagnosis without either a CD-indicated therapy dispensed or a CD ICD code present. The index diagnosis date was defined as the first diagnosis code appearing on a patient's claims record.

Patients with CD newly initiated on medication therapy were identified using prescriptions dispensed from claims data. The medication exposure period was the 60-day period following index diagnosis. Patients with a CD-indicated medication dispensed during the exposure period without any CD-indicated medication dispensed in the one-year pre-diagnosis period were considered newly initiated on pharmaceutical therapy for CD. Each patient was followed for 365 days after the 60-day medication exposure period to determine cost and healthcare utilization. Please see Figure 1 for a study schematic diagram.

Algorithm to Identify Patients with CD in Claims Data (Inclusion)

Multiple algorithms to identify CD in administrative claims data have been described in the literature. A review by Ye et al. describes three algorithms to identify patients with IBD and CD using claims data and compares the obtained cohort of each.[53] The first algorithm, initially described by Herrinton et al, identified patients with CD as having at least two CD diagnosis codes within any 30-month period.[53,59] The McAuliffe et al. algorithm identified patients with CD as having at least two CD diagnosis codes at least 30 days apart in any time, setting, or diagnosis location for the study period.[53,54] Lastly, Rezaie et al. described an algorithm identifying patients with CD in claims data by having ≥2 hospitalizations, ≥4 physician office visits, or ≥2 ambulatory care visits with a diagnosis code for CD in a 2-year period.[53,60] The positive predictive values (PPV) of the Herrinton et al. algorithm was 81% and 84% when validated with different electronic medical health records and corresponding claims data, respectively.[59] The Rezaie et al. algorithm had a PPV of 97.4% when validated with single-payer health records from one Canadian province.[60] The McAuliffe et al. algorithm was not validated by chart review but was developed to refine upon the Herrinton et al. algorithm.[53] Ye et al. implemented all three algorithms on Clinformatics® Data Mart data (CDM; Optum, Eden Prairie, MN, USA) and compared the cohorts identified by each algorithm. The Herrinton et al. algorithm yielded a CD cohort size of N=124,899, the McAuliffe et al. algorithm yielded a CD cohort of size N=108,100, and the Rezaie et al. algorithm yielded a cohort of N=70,919. Ye et al. concluded that all three algorithms have strengths and weaknesses in identifying patients with CD, and the choice of

algorithm should be based on the research question.[53] The McAuliffe et al. algorithm, requiring at least two CD diagnosis codes at least 30 days apart, features methodology and temporal relationships recommended for identifying patients with chronic disease in administrative healthcare data.[61] The 30-day separation of diagnosis codes may help to rule out misdiagnoses and misclassifications associated with assigning multiple diagnoses at initial presentation.[53] Therefore, the McAuliffe et al. algorithm was chosen for this research.[54]

Exclusion

Patients were excluded from the identified CD cohort based on age, missing data, enrollment in the healthcare plan, and comorbidities. Patients less than 18 years of age at the date of index diagnosis were excluded. We also excluded patients without linked prescriptions dispensed data or who did not have any CD-indicated medication dispensed in the 60-day exposure period. Furthermore, patients without full enrollment in the healthcare plan for the 790-day study period or whose pre-index or follow-up periods fell outside 2010 to 2018 were excluded. Lastly, we excluded patients who had at least two ICD-codes on different dates for at least one comorbidity treated with a biologic also indicated for CD (ankylosing spondylitis, Behçet's disease, hidradenitis, Kawasaki disease, multiple sclerosis, non-radiographic axial spondyloarthritis, psoriasis, rheumatoid arthritis, ulcerative colitis, and uveitis; see Table 4 for excluded comorbidities and ICD codes).[62]

SU and TD Cohort Definition

Among the cohort of patients newly initiated on medication therapy for CD, patients were further classified into the SU or TD cohorts based on the initial therapy prescribed (see Figure 2 for a visual diagram). The initial prescribed therapy was determined based on the medications dispensed during the 60-day exposure period after the diagnosis date. If a patient's initial dispensed therapy was an anti-inflammatory medication (aminosalicylate, corticosteroid, or antimicrobial) within the 60 days following initial diagnosis and without an immunomodulator/biologic agent, the patient was assigned to the SU cohort. For steroid and antibiotic medications dispensed in the 60-day exposure period, we required the days supplied to be greater than or equal to 15 days, to exclude short-term use for other indications, such as acute illness. A patient with initial dispensed therapy of an immunomodulator and/or biologic was included in the TD cohort. If a patient had both an immunomodulator/biologic and long-term anti-inflammatory medication dispensed in the exposure period, we included them in the TD cohort (see Table 5 for medications used to categorize the SU and TD cohorts).

Independent Variables of Interest

Variables of interest included patient demographic and clinical characteristics. Demographics included patient age at index diagnosis, sex, geographic location, payer type, and diagnosis year. Geographic location was determined by a variable in the data dividing the country into 9 regions: East North Central, East South Central, Middle Atlantic, Mountain, New England,

Pacific, South Atlantic, West North Central, and West South Central. Payer type was subdivided into commercial, Medicare for patients less than 65 years, and Medicare for patients 65 years or older. The diagnosis year variable was derived from the date of index diagnosis, and was used to identify trends in SU and TD utilization by year.

Clinical variables included disease location in the GI tract, comorbidities, GI-related hospitalizations prior to diagnosis, and CD-related surgical procedures performed in the 60 days following diagnosis. Disease location was determined based on the CD ICD codes, which are subdivided into disease of the small intestine (ICD9/10: 555.0, K50.0), large intestine (ICD9/10: 555.1, K50.1), small and large intestine (ICD9/10: 555.2 K50.8), and unspecified (ICD9/10: 555.9, K50.9). If the index diagnosis indicated a location in the gastrointestinal tract of “unspecified,” we then looked at the diagnoses during the 60-day exposure period to determine if a disease location was specified by the subsequent ICD10 codes. Comorbidities were quantified using the Elixhauser index, which generates a diagnosis-derived score weighting a patient’s comorbidities.[63,64] The Elixhauser index was calculated using all diagnosis codes present in the pre-diagnosis period. Prior GI-related hospitalization was coded as a binary variable, and patients with one or more GI-related hospitalization in the one-year pre-diagnosis period were recorded as patients with a prior hospitalization. GI-related hospitalizations were defined as having a discharge diagnosis of colonic conditions including indeterminate colitis (ICD9/10: 558.9/K52.3), noninfective gastroenteritis (ICD9/10:

558.9/K52.9), diverticular disease of the colon (ICD9/10: 562.12/K57.3), enterocolitis due to Clostridium difficile (ICD9/10: 008.45/A04.7), and unspecified origin of gastroenteritis and colitis (ICD9/10: 009.1/A09.9), as described by Stepaniuk et al.[65] We also included hospitalizations for stricture/obstruction (ICD9/10: 560.9/K56.6), fistulas (ICD9/10: 569.81/K63.2), abscesses (ICD9/10: 569.5/K63.0), and ulcers (ICD9/10: 569.82/K63.3), which are described as complications of CD, in the GI-related hospitalization definition.[10-14] Lastly, we examined CD-related surgical procedures performed within the 60 days following the index diagnosis as a binary variable. CD-related surgical procedures were identified using ICD procedure codes for enterostomy (including colostomy and ileostomy), small bowel resection, colorectal resection, local excision of large intestine lesion, and other bowel surgeries, as defined by Long et al.[62]

Disease Severity

An IBD severity index that can be used to gauge IBD severity using claims data was developed and validated in a retrospective cohort study using Optum Clinformatics, IMS PharMetrics, and Truven MarketScan databases from 2013 to 2017. The researchers developed a logistic regression model to identify variables predictive of severe CD or UC, defined by frequency of IBD-related hospitalizations and surgeries (colectomy or bowel resection). The factors identified as predictive of disease severity in CD were female sex, higher frequency of comorbidities (measured with the Charlson Comorbidity Index), renal comorbidities, anemia, weight loss, IV corticosteroid use, prior GI-related

ED visit and/or hospitalization, intestinal fistula, intestinal stricture, disease location, and time from diagnosis to first biologic therapy.[66] The authors describe a severity score calculation based on assigned risk indexes for each variable predictive of severe disease. We were able to create comparable variables for gender, comorbidity frequency (Elixhauser Index), disease location, GI-related hospitalizations prior to diagnosis, and CD-related surgical procedures performed within the 60 days following the index diagnosis. We looked at these severity variables separately, instead of applying the risk index factors and deriving a severity score because our data source did not include all of the relevant variables presented in the validated method described by Chen et al.[66]

Cost and Utilization

The cost and utilization variables were calculated in the one-year follow-up period following the 60-day medication exposure period after the index diagnosis (Figure 1). Both overall any-cause costs and CD-related costs were calculated. Overall any-cause costs included healthcare expenditures of any type, encompassing all pharmacy, outpatient healthcare, laboratory testing, imaging, and hospitalization/emergency department utilization costs. CD-related costs were calculated as the sum of prescriptions dispensed for CD-indicated therapies as well as medical visits and hospitalizations with a primary diagnosis of CD in the follow-up period. CD-related costs in the follow-up period were further split into pharmacy and healthcare costs, with pharmacy including only medication-related costs, and healthcare costs including outpatient

healthcare visits, laboratory tests, imaging, and hospitalization/emergency department utilization in the follow-up period. Costs were inflation adjusted to the 2017 USD ($) value using the Personal Health Care Expenditure deflator.[67,68]

Overall CD-specific utilization was calculated as a sum of healthcare visits, including outpatient appointments, laboratory tests, imaging, hospitalization/emergency department use with CD as the primary diagnosis, and prescriptions dispensed for CD-indicated therapies in the follow-up period. CD-specific utilization was also subdivided into medication and healthcare utilization, with medication utilization representing the number of total prescriptions dispensed for any CD-indicated medication, and healthcare utilization representing the number of healthcare visits in the follow-up period.

Cost Analysis

The objective of the cost analysis was to determine if TD therapy is associated with higher mean per patient total first-year direct healthcare costs compared to SU therapy, and to identify predictors of overall direct disease-specific healthcare costs in newly treated patients with CD. To achieve this objective, we developed a generalized linear model with the primary independent variable of treatment sequence (SU or TD). Covariates included sex, age group, disease location, geographic location, payer, Elixhauser index, GI-related hospitalizations prior to diagnosis, CD-related surgical procedures performed within the 60 days following the index diagnosis, and diagnosis year. The dependent variable was direct first-year CD-specific healthcare costs,

which represented the overall CD-specific cost minus the costs of CD medications. We did not include CD medication costs in the cost analysis because TD therapy is associated with higher costing therapies, and the goal of our analysis was to examine disease cost, not treatment cost.

Statistical Analysis

A descriptive analysis at the patient-level categorized by treatment sequence (SU or TD) was conducted for all independent variables. Results were reported using descriptive statistics and significance was tested using t-tests for continuous variables and chi-squared tests for categorical variables. Similarly, the mean CD-specific healthcare costs were reported for each independent variable. T-test and analysis of variance (ANOVA) were used to assess the significance of the mean CD-specific healthcare costs in the CD cohort, and pairwise comparisons were performed for multilevel variables, with significance assessed at the 5% alpha level.

A generalized linear model with a gamma distribution and log link function was used to estimate the differences in per-patient average adjusted CD-specific healthcare costs for potential predictor covariates. Skewness and kurtosis were assessed for the CD-specific healthcare cost distribution, and a modified Park test was used to determine that a gamma distribution was the best choice for modeling the CD-specific healthcare cost data. The generalized linear model was optimized with manual backward elimination, and significance was assessed using chi squared tests of the difference in Akaike information criterion (AIC). Non-significant variables were removed from the model to

enhance fit. The model was considered optimized when all included variables had either at least one statistically significant strata or were considered clinically relevant irrespective of significance, and removing additional variables did not result in a statistically significant decrease in AIC. Beta estimates were exponentiated to derive adjusted odds ratios, standard errors, and 95% confidence intervals. The estimates presented represent the percentage difference in cost for a particular level of a variable when other independent variables are at their reference level. Results with a p-value less than or equal to 0.05 were discussed. All statistical analyses were performed using SAS version 9.4 statistical analysis software (SAS Institute, Cary, NC).

The data obtained from the Optum® Clinformatics™ database for this study were stored on URI's secure server. The study proposal was submitted and considered exempt by the IRB and Research and Development Committee at URI (Reference Number 1666706) and appropriate training was completed.

CHAPTER 4

FINDINGS

Population & Cohort Results

We identified 183,452 patients with an ICD-diagnosis code for CD among the over 52 million commercial enrollees in Optum's de-identified Clinformatics® Data Mart Database. Of the 183,452 patients, 95,549 had two ICD diagnosis codes for CD at least 30 days apart. Based on the patient's age at initial diagnosis, 4,710 patients were excluded for having an age less than 18 years. Of the resulting 90,839 adult patients in the cohort, prescription information indicating a dispensing of a CD-indicated medication was available for 70,408 patients. Next, 31,201 patients were identified as initiating pharmaceutical therapy, because there was a CD-indicated medication dispensed in the 60-day exposure period without a dispense in the one-year pre-diagnosis period. Of the 31,201 patients, 3,884 individuals had enrollment for the 790-day study period. Lastly, 727 patients were excluded for having at least one comorbidity treated with biologics also indicated for CD. The final cohort of adult patients newly initiated on medication therapy for CD with full enrollment was 3,157 patients. The SU cohort consisted of 2,392 patients and the TD cohort consisted of 765 patients. Please see Figure 3 for a population flow diagram.

Descriptive Characteristics

The descriptive characteristics are presented in Table 6. The total cohort was 53.72% female and the mean age was 46.69 years (SD: 18.86 years).

Additionally, 1,085 (34.37%) of patients had disease in the small intestine, 719 (22.77%) in the large intestine, 902 (28.57%) in both the small and large intestine, and 451 (14.29%) in an unspecified location. For payer type, 2,444 patients (77.42%) of the total CD cohort were enrolled in commercial insurance, 112 (3.55%) in Medicare and under 65 years of age, and 601 (19.04%) in Medicare and 65 years of age or older. Of the total CD cohort, 916 patients (29.01%) had an Elixhauser index of zero, 1,273 patients (40.32%) had an Elixhauser index of 1-2, and 968 patients (30.66%) had an Elixhauser index greater than 3. Furthermore, 278 patients (8.81%) of the total CD cohort had an GI-related hospitalization in the year prior to the index diagnosis date. Lastly, 1,858 patients (58.85%) had at least one CD-related surgical procedure performed within 60 days following the index diagnosis.

In the follow-up period, the overall all-cause average per-patient inflation-adjusted cost in the study population was $38,887 (SD: $83,818), the average per-patient CD-specific total cost was $16,830 (SD: $28,305), the average per-patient CD-specific healthcare cost was $6,321 (SD: $19,627), and the average per-patient CD-specific medication cost was $10,414 (SD: $16,216). Additionally, in the follow-up period, the average CD-specific healthcare utilization was 8.34 visits (SD: 11.27) per patient, and the average CD-specific medication utilization was 8.08 prescriptions dispensed (SD: 6.84) per patient. The cost and utilization results are presented in Table 7.

The SU cohort consisted of a slightly larger proportion of females than the TD cohort (55.02%, 49.67%, respectively, p=0.0099). The mean age in the SU

cohort was 48.92 years (SD: 18.90), which was higher than the mean age of 39.72 years (16.69) in the TD cohort ($p<0.0001$). When age was divided into four age groups, a larger proportion of patients in the SU cohort were categorized in the older age groups, and a larger proportion of patients in the TD cohort were in the younger age groups (chi-squared $p<0.0001$, see Table 6 for proportions and Figure 4 for a visual of the age distribution in the SU and TD cohorts).

The unadjusted results also indicated that the SU cohort had a larger percentage of patients with disease in either the small or large intestine and the TD cohort had a larger percentage of patients with disease located in both the small and large intestine, or an unspecified location (chi-squared $p<0.0001$). For geographic location, a larger proportion of patients in the SU cohort were located in either the Middle Atlantic, Mountain, Pacific, or South Atlantic region, a larger proportion of patients in the TD cohort located in the East North Central and West North Central regions, and a similar proportion of patients between the SU and TD cohorts located in the East South Central, New England, and West South Central regions (chi-squared $p<0.0001$). Furthermore, more patients in the TD cohort had commercial insurance, and more patients in the SU cohort had Medicare (for patients both <65 and ≥65 years of age; chi-squared $p<0.0001$). The mean Elixhauser index was higher in the SU cohort compared to the TD cohort (2.2 [SD: 2.50], 1.65 [2.11], respectively, $p<0.0001$). When categorized by an Elixhauser index of 0, 1-2, or >3, the TD cohort had a larger percentage of patients with a score of 0 (32.68%, SU: 27.84%) or 1-2

(45.62%, 38.63%), while the SU cohort had a larger percentage of patients with scores >3 (33.53%, TD: 21.70%, chi-squared p<0.0001). We also found that the frequency of TD utilization increased over time (chi-squared p<0.0001, see Table 6 for proportions and Figure 5 for a visual of SU and TD utilization over time).

The bivariate average overall all-cause cost, CD-specific total cost, CD-specific healthcare costs, and CD-specific medication costs over the follow-up period were significantly different between the SU and TD cohort, with TD having higher costs in all categories (p<0.0001). Similarly, average utilization over the one-year follow-up period in the TD cohort compared to SU cohort was significantly higher (p<0.0001) in the for CD-specific healthcare (TD: 14.35, SU: 6.42 visits) and medication utilization (TD: 11.53, SU: 6.97 prescriptions dispensed). See Figure 6 for a visual of cost and utilization by CD, SU, and TD cohorts.

The mean CD-specific healthcare costs are reported for each independent variable in Table 8. Since the distribution of CD-specific healthcare costs was right skewed (skew: 4.43) with a platykurtic distribution (kurtosis: 28.05), the standard deviations are larger than the means. The mean CD-specific healthcare cost was not significantly different between females and males (p=0.8557), geographic locations (p=0.9542), Elixhauser indexes (p=0.5287), diagnosis year (p=0.0741, see Figure 7) and between those who had and did not have a CD-related surgical procedure performed within the 60 days following index diagnosis(p=0.0603) in the CD-cohort (study population). The

average follow-up disease-specific healthcare costs were statistically significantly different between commercial, Medicare and under 65 years of age, and Medicare and 65 years of age or older (p=0.0006), with commercial having a higher mean CD-specific healthcare cost (commercial: $7,021, Medicare age <65: $2,188 Medicare age≥65: $4,246, based on Tukey follow-up test). The CD-specific healthcare cost was also significantly different between the age groups (p<0.0001), and based on a Tukey follow-up test, the youngest age groups (aged 18-29 years) had a significantly higher mean cost. The mean CD-specific healthcare cost was also significantly different by disease location, with all pairwise comparisons being significant except the large intestine and unspecific location comparison (small intestine: $7,071 large intestine:$3,450, both small and large intestine: $10,050, unspecified location: $1,637). Lastly, patients having a GI-related hospitalization prior to diagnosis had a significantly higher mean CD-specific healthcare cost compared to patients not hospitalized prior to diagnosis ($10,143, $5,952, respectively).

Linear Regression Findings

We conducted a generalized linear model to observe predictors of CD-specific healthcare cost in patients with CD. The geographic location variable was statistically nonsignificant and removed to enhance the fit of the model. Though the gender, Elixhauser index, and CD-related surgical procedure variables were non-significant, eliminating these variables from the model did not produce a statistically significantly better fitting model, based on a chi-squared test, and these variables were retained due to their clinical relevance.

The results of the model with geographic location removed are presented in Table 9, and the full model results are presented in Table 10.

In the optimized generalized linear model with a gamma distribution and log link, treatment strategy, age group, disease location, GI-related hospitalization prior to diagnosis, payer, and diagnosis year were significant predictors of first-year adjusted average per-patient CD-specific direct healthcare cost. CD treatment initiated with TD therapy had a first-year adjusted average per-patient CD-specific direct healthcare cost that was 149.78% ($1,230.26) higher than initiation with SU therapy. Furthermore, compared to patients older than 65 years, those aged 18-29, 30-44, and 45-64 years had an increased first-year adjusted average per-patient CD-specific direct healthcare cost of 269.91% ($2,217.05), 137.76% ($1,131.57), 85.63% ($703.38), respectively. CD located in the small intestine or both the small and large intestine had a 99.43% ($816.72) or 207.04% ($1,700.59) higher first-year adjusted average per-patient CD-specific direct healthcare cost, respectively, than CD located in the large intestine. Conversely, CD of unspecified location was associated with a 57.38% ($471.30) lower first-year adjusted average per-patient CD-specific direct healthcare cost than CD located in the large intestine. Patients with a GI-related hospitalization in the pre-diagnosis period had a 179.69% ($1,475.93) higher first-year adjusted average per-patient CD-specific direct healthcare cost than those not hospitalized in the pre-diagnosis period. Patients aged less than 65 years using Medicare had a first-year adjusted average per-patient CD-specific direct healthcare cost of 58.95% ($484.22) lower than patients using

commercial insurance. Lastly, compared to 2011, the first-year adjusted average per-patient CD-specific direct healthcare cost was 36.48% ($299.64), 73.93% ($607.28), and 37.85% ($310.90) higher in 2013, 2014, and 2016, respectively.

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CHAPTER 5

DISCUSSION AND CONCLUSION

This study attempted to fill a gap in the literature by examining SU and TD therapy utilization and short-term expenditures in patients newly initiated on medication therapy for CD in a real-world setting using a large administrative claims database. We described trends overtime and stratified by demographic and clinical variables to examine SU and TD therapy usage patterns in an observational data setting. We also used a generalized linear model to illuminate factors predictive of higher first-year healthcare expenditures in patients newly initiated with medication therapy for CD. We found that a larger proportion of patients were initiated on SU therapy compared to TD therapy during the 2010 to 2018 study period, but over time, the proportion of patients initiated on TD therapy increased. In our study the TD cohort also had a lower mean age, higher frequency of commercial insurance, and higher proportion of disease manifesting in both the small and large intestine. Our disease-specific healthcare cost model showed that TD therapy was associated with a higher mean cost compared to SU therapy. Other factors we identified as predictive of a higher CD-specific healthcare cost were age, disease location, and having a GI-related hospitalization prior to diagnosis. These findings can inform payer decisions, pharmaceutical policies, and guideline recommendations.

Our analysis revealed that in a population of patients newly diagnosed with CD, SU was more commonly utilized than TD (75.8%, 24.2% respectively). The

frequency of TD therapy utilization among the patients initiated on medication therapy for CD increased over time from 17% in 2011 to 31% in 2018. (Figure 5). This trend may be attributed to the increased availability of and provider/patient familiarity with biologic agents during the study timeframe. In 2014, vedolizumab was FDA approved for the treatment of UC and CD.[69,70] Additionally, in 2014 the indications of adalimumab were expanded to include CD.[69,71] In 2016, the indications for ustekinumab were expanded to include CD.[69,72] Biosimilars for infliximab were also approved during the study period, with Inflectra in 2016, and Renflexis and Ixifi in 2017.[69,73-75] The approval of these products, in addition to publications of research examining therapy sequencing, may have influenced the increased utilization of TD therapy in later years of our study. Additionally, we noted a spike in CD-specific healthcare expenditure in 2014 (Figure 7), which may be related to the adalimumab and vedolizumab approval in 2014 and/or the Affordable Care Act health insurance exchanges opening during that year.[69-72,76]

Overall all-cause cost, CD-specific total cost, CD-specific healthcare cost, and CD-specific medication costs were higher in the TD cohort compared to the SU cohort. The predictive analysis showed that TD therapy was associated with an increased average per-patient CD-specific healthcare cost in the one-year follow-up period compared to SU therapy (OR: 2.50, 95%CI: [2.12,2.95]). In the short term, medication prices and adverse events associated with TD therapy can result in increased prescriber visits, hospitalizations, and cost.[22-25,29,30] Our analysis confirmed that the expenditure and frequency of healthcare utilization

was higher in the TD compared to the SU cohort. The TD cohort had a higher average cost for CD-indicated medications dispensed and a higher average disease-specific healthcare utilization in the follow-up period.

Ascertaining disease severity from claims data is challenging due to limited patient-specific symptom and pathophysiology data. In our model, diagnosis location, GI-related hospitalizations prior to diagnosis, and CD-related surgical procedures performed within the 60 days following the index diagnosis were indicators of disease severity. Disease location, determined by ICD codes, had a significant relationship with treatment strategy (chi-squared $p<0.0001$), with the SU cohort having a larger percentage of patients with disease in either the small or large intestine and the TD cohort having a larger percentage of patients with disease located in the small and large intestine. CD located in the small intestine or in both the small and large intestine was associated with a higher cost than disease in the large intestine (OR: 1.99 [1.66,2.40], 3.07 [2.53,3.72], respectively). In a retrospective analysis examining factors associated with severe disease in claims data, disease located in the ileum, ileum/colon, and unspecified were associated with increased severity of disease, characterized by increased hospitalizations and surgeries, compared to disease in the colon.[66] Our results emulate this finding by suggesting that disease location in the ileum and ileum/colon were associated with a higher first-year healthcare cost, with disease in the colon as the reference.

Furthermore, though a similar frequency of patients had a GI-related hospitalization in the pre-CD diagnosis period in the SU cohort (9.03%) and TD

cohort (8.10%), patients who had a GI-related hospitalization prior to CD-diagnosis had a higher average healthcare cost than those without a GI-related hospitalization prior to CD diagnosis (OR: 2.80 [2.18,3.63]). Therefore, the hospitalization prior to diagnosis could be indicative of severe disease or inflammation activity prior to diagnosis. A prior study examining severity of CD suggest patients with a GI-related hospitalization prior to IBD diagnosis have an increased risk of hospitalizations and surgeries after diagnosis, which could be an indicator for severe CD.[66] We also observed that 61.43% of the TD cohort and 58.03% of the SU cohort had at least one CD-related surgical procedure performed within the 60 days following index diagnosis. These procedures are typically reserved for severe disease.[10-14] However, the healthcare costs for patients having procedures within 60-days of diagnosis were not significantly higher than those who did not have a procedure in our linear model (OR: 0.91 [0.78,1.05]).

Our analysis showed that TD treatment was more frequent as an initial therapy sequence for CD in the younger age groups, while SU treatment was more frequently initiated in the older age groups (Figure 4). These results are similar to an analysis of the Winnipeg Regional Health Authority (WRHA), a Canadian health region hospitalization discharge database examining the clinical course, presentation, and management of older and younger patients hospitalized with IBD. The researchers found that older patients were prescribed aminosalicylates more often (61%, 43%, respectively, p=0.04) and biologics less often (6%, 21%; respectively, p=0.016) than younger patients.

The researchers also conducted a logistic regression analysis to identify predictors of immunomodulator or biologic use, and found that the only significant predictor was age (OR of young compared to age 65 or older: 2.47 [95% CI: 1.21, 5.05]).[65]

In our cost predictive model, younger age groups were associated with higher average per-patient CD-specific healthcare cost in the follow-up period; the 18-29 aged group had the highest odds of increased adjusted CD-specific healthcare cost, followed by the 30-44 aged group and the 45-65 aged group (OR: 3.70 [2.22,5.84], 2.38 [1.43,3.73], 1.86 [1.13,2.89], respectively). This finding aligns with the findings of a study examining risk factors that may predict TD therapy use among 207 patients with CD in China. The authors conducted two logistic regression models, varying the independent variables of site of diagnosis and steroid requirements for flare/exacerbation, to predict which risk factors were associated with developing a disabling disease. Based on the logistic model that most matches the ICD9/10 codes for site of diagnosis, the authors found age at diagnosis below 40 years was a significant predictor of developing disabling CD with a 5-year timeframe. The non-significant risk factors were site of disease at diagnosis, systemic manifestations at diagnosis, perianal disease at diagnosis, steroid requirements for first flare, sex, previous appendectomy, and smoking status at diagnosis.[77] While the authors did not report findings related to expenditure, their results may be similar to the findings of our study, assuming severe disease leads to higher healthcare expenditure. Aside from the relationship between age and severity of disease established by

previous studies, we question if disease presentation, medication burden/therapy interactions, insurance, and expected life expectancy might be influencing the age effect we observed with a higher frequency of TD use and a higher average per-patient CD-specific healthcare cost in younger patients.

Our study also showed that the TD cohort had a larger proportion of commercial insurance utilization than the SU cohort, and patients with commercial insurance had a higher CD-specific healthcare cost than patients with Medicare (both <65 and ≥65 years of age). This finding may be related to commercial and Medicare coverage policies for biologics. While we were unable to examine past coverage policies for the CD-indicated biologics, we examined the current (2021) commercial coverage policies for certolizumab pegol, infliximab, natalizumab, ustekinumab, and vedolizumab; we were unable to locate publicly available policies for adalimumab. Certolizumab pegol and infliximab coverage required a history of failing medication therapy with corticosteroids, 6-mercaptopurine, azathioprine, and/or methotrexate.[78,79] Natalizumab required a history of inadequate response to both conventional therapies (SU therapies) and inadequate response to TNF-alpha inhibitors for coverage.[80] Ustekinumab and vedolizumab did not have a requirement of failing a non-biologic therapy prior to initiating pharmaceutical therapy for CD.[81,82] Based on a current medication formulary, the biologic agents indicated for CD were tier 2 or greater, while the small molecule medications, including aminosalicylates and immunomodulators were tier 1.[83] Therefore, payer type may influence the ease and affordability of obtaining SU or TD medication.

Furthermore, our finding of a higher frequency of commercial insurance in the TD cohort may be influenced by the difference in out-of-pocket costs between commercial and Medicare insurance. Medicare Part D has a 25% cost sharing for most medications and is associated with coverage gaps (the doughnut hole) requiring even higher cost sharing. The cost sharing and coverage gaps vary between commercial payer plans but tend to be favorable compared to Medicare. Patients having to pay large out-of-pocket co-payments for their medications may request the SU therapies due to affordability.

As more therapies being developed and approved for CD fall into the biologic, specialty, and/or high-cost categories, the prescription spending for payers and the healthcare system will likely increase for CD.[32] Insurance companies, managed care organizations, and payers use methods, such as prior authorizations, formularies, quantity limits, and co-payments, to control prescription costs and utilization for certain, usually expensive, medications.[32] Payers face the challenge of balancing potential long-term cost-effectiveness with short-term high prescription medication costs. Factors such as the severity of disease and the potential length of time a patient is on the higher-costing medication therapies are important for payers to consider when judging the value of higher-cost TD therapies compared to SU therapies in patients initiating treatment for CD. Ultimately, SU and TD therapy options both have positives and negatives that must be weighted based on patient-specific factors to determine which treatment plan provides patients the best efficacy and minimizes exposure to unnecessary risk.

The patient and disease characteristics we identified as significant in SU and TD utilization and expenditure can inform future studies, payer decisions, and pharmaceutical therapy recommendations to identify patients who may receive TD therapy or have a higher expenditure. While the benefits of TD therapy have been studied and postulated in a clinical trial setting[38-45], limited evidence exists that examines the use and short-term costs associated with SU and TD therapy in a real-world setting. Our research illuminates real-world trends in SU and TD therapy use and examines the characteristics of patients receiving either SU and TD therapy in the United States. Further research is needed to determine the long-term overall healthcare costs associated with SU and TD treatment strategies in a real-world setting.

The design and data available for this study introduced inherent limitations worth acknowledging. The data source used for this analysis does not have specific information describing the severity of the disease, which is a factor that influences the choice of initial medication therapy. Our analysis did include disease location, GI-related hospitalizations prior to diagnosis, and CD-related surgical procedures performed within the 60 days following the index diagnosis , which can be indicators of increased disease severity. However, we were unable to account for symptom burden, mucosal tissue damage, and other indicators of disease severity.[10-14,66] Additionally, while pharmacy claims data provides detailed information on medication names, doses, and dispense dates, pharmacy claims data only captures medications charged to the health plan. Thus, medications distributed through specialty channels that bypass

community pharmacies may not have been recorded in the database used for our analysis. Furthermore, we only assessed initial therapy dispensed in the 60 days after index diagnosis and did not account for therapy switching or adherence during the follow-up period. Prescriber bias may be present in this study. Each prescriber may have a different preference for TD or SU therapy, which will influence prescribing practices. Misdiagnosis and reporting bias may also be present in this study as a result of relying on ICD coding to determine CD diagnosis and index diagnosis date. Lastly, we only address short-term costs among newly treated patients with CD in this study, therefore the results may not be generalizable to longer-term costs (over one year) or patients with prevalent disease.

We examined the utilization and expenditure of SU and TD treatment strategies in patients initiating medication therapy for CD in a real-world setting. We found the proportion of TD therapy utilization increased each year of our study period. Furthermore, TD was associated with a higher overall and CD-specific cost in a one-year period following the CD diagnosis and medication exposure. Our predictive model showed that treatment strategy, age group, disease location, GI-related hospitalization prior to diagnosis, payer, and diagnosis year were significant predictors of CD direct healthcare costs. These findings can be used to inform pharmaceutical policy and provide a basis for further research to understand the real-world outcomes associated with SU and TD therapy.

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APPENDIX 1: TABLES

Table 1: Medications Indicated for Crohn's Disease[10-14]

Medication Class	Medication Name	Mechanism of Action
Aminosalicylates	Balsalazide (Colazal™)	Anti-inflammatory, 5-Aminosalicylate (5-ASA) precursor
	Mesalamine (Oral = Pentasa™, Asacol™) (Rectal = Rowasa™)	Anti-inflammatory, 5-Aminosalicylate (5-ASA) precursor
	Olsalazine (Dipentum™)	Anti-inflammatory, 5-Aminosalicylate (5-ASA) precursor
	Sulfasalazine	Anti-inflammatory, 5-Aminosalicylate (5-ASA) precursor
Corticosteroids	Budesonide	Glucocorticoid
	Betamethasone	Glucocorticoid
	Cortisone	Glucocorticoid/Mineralocorticoid
	Dexamethasone	Glucocorticoid
	Hydrocortisone	Glucocorticoid
	Methylprednisolone	Glucocorticoid
	Prednisone	Glucocorticoid
	Prednisolone	Glucocorticoid
	Triamcinolone	Glucocorticoid
Anti-microbial	Metronidazole (Flagyl™)	Antibiotic Nitroimidazole Agent
	Ciprofloxacin (Cipro™)	Antibiotic Fluoroquinolone Agent
Immunomodulators	Azathioprine	Purine Synthesis Inhibitor
	Cyclosporine	Calcineurin Inhibitor
	Mercaptopurine (6-MP)	Purine Analog, Antimetabolite
	Methotrexate	Folic Acid Analog
	Tacrolimus	Calcineurin Inhibitor
Biologic	Adalimumab (Humira™)	Tumor Necrosis Factor (TNF)-α Inhibitor
	Certolizumab pegol (Cimzia™)	Tumor Necrosis Factor (TNF)-α Inhibitor
	Infliximab (Remicade™)	Tumor Necrosis Factor (TNF)-α Inhibitor
	Natalizumab (Tysabri™)	Adhesion Molecule Inhibitors
	Ustekinumab (Stelara™)	Interleukin-23 (IL-23) Inhibitor
	Vedolizumab (Entyvio™)	Adhesion Molecule Inhibitors

Table 2: Crohn's Disease International Classification of Disease (ICD) 10/9 Codes[55-58]

ICD-10: K50.xxx	**ICD-9: 555.xx**
K50.0: Crohn's disease of small intestine	555.0: Regional enteritis of small intestine
K50.1: Crohn's disease of large intestine	555.1: Regional colitis of large intestine
K50.8: Crohn's disease of small and large intestine	555.2: Regional enteritis of small intestine with large intestine
K50.9: Crohn's disease, unspecified	555.9: Regional enteritis of unspecified site

ICD = International Classification of Diseases

Table 3: International Classification of Disease (ICD)-10 Codes and Comparable ICD-9 Codes with Descriptions for Crohn's Disease[55-58]

ICD10	ICD10 Code Description	ICD9	ICD9 Code Description
K5000	Crohn's disease of small intestine without complications	5550	Regional enteritis of small intestine
K50011	Crohn's disease of small intestine with rectal bleeding	5550	Regional enteritis of small intestine
K50012	Crohn's disease of small intestine with intestinal obstruction	5550	Regional enteritis of small intestine
K50013	Crohn's disease of small intestine with fistula	5550	Regional enteritis of small intestine
K50014	Crohn's disease of small intestine with abscess	5550	Regional enteritis of small intestine
K50018	Crohn's disease of small intestine with other complication	5550	Regional enteritis of small intestine
K50019	Crohn's disease of small intestine with unspecified complications	5550	Regional enteritis of small intestine
K5010	Crohn's disease of large intestine without complications	5551	Regional enteritis of large intestine
K50111	Crohn's disease of large intestine with rectal bleeding	5551	Regional enteritis of large intestine
K50112	Crohn's disease of large intestine with intestinal obstruction	5551	Regional enteritis of large intestine
K50113	Crohn's disease of large intestine with fistula	5551	Regional enteritis of large intestine
K50114	Crohn's disease of large intestine with abscess	5551	Regional enteritis of large intestine
K50118	Crohn's disease of large intestine with other complication	5551	Regional enteritis of large intestine
K50119	Crohn's disease of large intestine with unspecified complications	5551	Regional enteritis of large intestine
K5080	Crohn's disease of both small and large intestine without complications	5552	Regional enteritis of small intestine with large intestine
K50811	Crohn's disease of both small and large intestine with rectal bleeding	5552	Regional enteritis of small intestine with large intestine
K50812	Crohn's disease of both small and large intestine with intestinal obstruction	5552	Regional enteritis of small intestine with large intestine
K50813	Crohn's disease of both small and large intestine with fistula	5552	Regional enteritis of small intestine with large intestine
K50814	Crohn's disease of both small and large intestine with abscess	5552	Regional enteritis of small intestine with large intestine
K50818	Crohn's disease of both small and large intestine with other complication	5552	Regional enteritis of small intestine with large intestine
K50819	Crohn's disease of both small and large intestine with unspecified complications	5552	Regional enteritis of small intestine with large intestine
K5090	Crohn's disease, unspecified, without complications	5559	Regional enteritis of unspecified site
K50911	Crohn's disease, unspecified, with rectal bleeding	5559	Regional enteritis of unspecified site
K50912	Crohn's disease, unspecified, with intestinal obstruction	5559	Regional enteritis of unspecified site
K50913	Crohn's disease, unspecified, with fistula	5559	Regional enteritis of unspecified site
K50914	Crohn's disease, unspecified, with abscess	5559	Regional enteritis of unspecified site
K50918	Crohn's disease, unspecified, with other complication	5559	Regional enteritis of unspecified site
K50919	Crohn's disease, unspecified, with unspecified complications	5559	Regional enteritis of unspecified site

Table 4: Comorbidities Treated with Biologics that are Indicated for Crohn's Disease and Associated International Classification of Disease (ICD) 10/9 Codes[62,84-86]

Comorbidity	ICD10	ICD9
Ankylosing Spondylitis	M45.0, M45.1, M45.2, M45.3, M45.4, M45.5, M45.6, M45.7, M45.8, M45.9	720.0
Behçet's Disease	M35.2	711.20, 711.21, 711.22, 711.23, 711.24, 711.25, 711.26, 711.27, 711.28, 711.29, 136.1
Hidradenitis Suppurativa	L73.2	705.83
Kawasaki Disease	M30.3	446.1
Multiple Sclerosis	G35	340
Non-Radiographic Axial Spondyloarthritis	M46.80, M46.81, M46.82, M46.83, M46.84, M46.85, M46.86, M46.87, M46.88, M46.89	720.89
Psoriasis	L40.0, L40.1, L402, L403, L404, L4050, L4051, L4052, L4053, L4054, L4059, L408, L409	696.0, 696.1
Psoriatic Arthritis		
Juvenile Idiopathic Arthritis, Polyarticular Juvenile Idiopathic Arthritis, Rheumatoid Arthritis	M05.20, M05.211, M05.212, M05.219, M05.221, M05.222, M05.229, M05.231, M05.232, M05.239, M05.241, M05.242, M05.249, M05.251, M05.252, M05.259, M05.261, M05.262, M05.269, M05.271, M05.272, M05.279, M05.29, M05.30, M05.311, M05.312, M05.319, M05.321, M05.322, M05.329, M05.331, M05.332, M05.339, M05.341, M05.342, M05.349, M05.351, M05.352, M05.359, M05.361, M05.362, M05.369, M05.371, M05.372, M05.379, M05.39, M05.40, M05.411, M05.412, M05.419, M05.421, M05.422, M05.429, M05.431, M05.432, M05.439, M05.441, M05.442, M05.449, M05.451, M05.452, M05.459, M05.461, M05.462, M05.469, M05.471, M05.472, M05.479, M05.49, M05.50, M05.511, M05.512, M05.519, M05.521, M05.522, M05.529, M05.531, M05.532, M05.539, M05.541, M05.542, M05.549, M05.551, M05.552, M05.559, M05.561, M05.562, M05.569, M05.571, M05.572, M05.579, M05.59, M05.60, M05.611, M05.612, M05.619, M05.621, M05.622, M05.629, M05.631, M05.632, M05.639, M05.641, M05.642, M05.649, M05.651, M05.652, M05.659, M05.661, M05.662, M05.669, M05.671, M05.672, M05.679, M05.69, M05.70, M05.711, M05.712, M05.719, M05.721, M05.722, M05.729, M05.731, M05.732, M05.739, M05.741, M05.742, M05.749, M05.751, M05.752, M05.759, M05.761, M05.762, M05.769, M05.771, M05.772, M05.779, M05.79, M05.7A, M05.80, M05.811, M05.812, M05.819, M05.821, M05.822, M05.829, M05.831, M05.832, M05.839, M05.841, M05.842, M05.849, M05.851, M05.852, M05.859, M05.861, M05.862, M05.869, M05.871, M05.872, M05.879, M05.89, M05.8A, M05.9, M06.00, M06.011, M06.012, M06.019, M06.021, M06.022, M06.029, M06.031, M06.032, M06.039, M06.041, M06.042, M06.049, M06.051, M06.052, M06.059, M06.061, M06.062, M06.069, M06.071, M06.072, M06.079, M06.08, M06.09, M06.0A, M06.1, M06.20, M06.211, M06.212, M06.219, M06.221, M06.222, M06.229, M06.231, M06.232, M06.239, M06.241, M06.242, M06.249,	714.0, 714.2, 714.30, 714.31, 714.32, 714.33, 714.9

Table 4 Continued

Comorbidity	ICD10	ICD9
Juvenile Idiopathic Arthritis, Polyarticular Juvenile Idiopathic Arthritis, Rheumatoid Arthritis	M06.251, M06.252, M06.259, M06.261, M06.262, M06.269, M06.271, M06.272, M06.279, M06.28, M06.29, M06.30, M06.311, M06.312, M06.319, M06.321, M06.322, M06.329, M06.331, M06.332, M06.339, M06.341, M06.342, M06.349, M06.351, M06.352, M06.359, M06.361, M06.362, M06.369, M06.371, M06.372, M06.379, M06.38, M06.39, M06.4, M06.80, M06.811, M06.812, M06.819, M06.821, M06.822, M06.829, M06.831, M06.832, M06.839, M06.841, M06.842, M06.849, M06.851, M06.852, M06.859, M06.861, M06.862, M06.869, M06.871, M06.872, M06.879, M06.88, M06.89, M06.8A, M06.9, M08.00, M08.011, M08.012, M08.019, M08.021, M08.022, M08.029, M08.031, M08.032, M08.039, M08.041, M08.042, M08.049, M08.051, M08.052, M08.059, M08.061, M08.062, M08.069, M08.071, M08.072, M08.079, M08.08, M08.09, M08.0A, M08.1, M08.20, M08.211, M08.212, M08.219, M08.221, M08.222, M08.229, M08.231, M08.232, M08.239, M08.241, M08.242, M08.249, M08.251, M08.252, M08.259, M08.261, M08.262, M08.269, M08.271, M08.272, M08.279, M08.28, M08.29, M08.2A, M08.3, M08.40, M08.411, M08.412, M08.419, M08.421, M08.422, M08.429, M08.431, M08.432, M08.439, M08.441, M08.442, M08.449, M08.451, M08.452, M08.459, M08.461, M08.462, M08.469, M08.471, M08.472, M08.479, M08.48, M08.4A, M08.80, M08.811, M08.812, M08.819, M08.821, M08.822, M08.829, M08.831, M08.832, M08.839, M08.841, M08.842, M08.849, M08.851, M08.852, M08.859, M08.861, M08.862, M08.869, M08.871, M08.872, M08.879, M08.88, M08.89, M08.90, M08.911, M08.912, M08.919, M08.921, M08.922, M08.929, M08.931, M08.932, M08.939, M08.941, M08.942, M08.949, M08.951, M08.952, M08.959, M08.961, M08.962, M08.969, M08.971, M08.972, M08.979, M08.98, M08.99, M08.9A	714.0, 714.2, 714.30, 714.31, 714.32, 714.33, 714.9
Ulcerative Colitis	K51.00, K51.011, K51.012, K51.013, K51.014, K51.018, K51.019, K51.20, K51.211, K51.212, K51.213, K51.214, K51.218, K51.219, K51.30 , K51.311, K51.312, K51.313, K51.314, K51.318, K51.319, K51.40, K51.411, K51.412, K51.413, K51.414, K51.418, K51.419, K51.50 , K51.511, K51.512, K51.513, K51.514, K51.518, K51.519, K51.80 , K51.811, K51.812, K51.813, K51.814, K51.818, K51.819, K51.90 , K51.911, K51.912, K51.913, K51.914, K51.918, K51.919	556.0, 556.1, 556.2, 556.3, 556.4, 556.5, 556.6, 556.8, 556.9
Uveitis	H20.9	364.11, 364.3

Table 5: Crohn's Disease-Indicated Medications Used to Categorize Step-Up and Top-Down Cohorts[1,11-18]

SU Medications	TD Medications
Aminosalicylates	**Immunomodulators**
Balsalazide Mesalamine Olsalazine Sulfasalazine	Azathioprine Cyclosporine Mercaptopurine Methotrexate Tacrolimus
Corticosteroids	**Biologics**
Budesonide Betamethasone Cortisone Dexamethasone Hydrocortisone Methylprednisolone Prednisone Prednisolone Triamcinolone	Adalimumab Certolizumab pegol Infliximab Natalizumab Ustekinumab Vedolizumab
Antimicrobial	
Ciprofloxacin Metronidazole	

Table 6: Crohn's Disease, Step-Up, and Top-Down Cohort Baseline Characteristics

	CD Cohort (Study Population)	**SU Cohort**	**TD Cohort**	**Significance (Ha: SU≠TD)**
n (%)	3,157	2,392 (75.77)	765 (24.23)	
Sex				
Female (n, %)	1,696 (53.72)	1,316 (55.02)	380 (49.67)	p=0.0099
Age at Diagnosis				
Age, Years (mean, SD)	46.69 (18.86)	48.92 (18.90)	39.72 (16.96)	p<0.0001
Age: 18-29 years (n, %)	737 (23.34)	460 (19.23)	277 (36.21)	p<0.0001
Age: 30-44 years	797 (25.25)	585 (24.46)	212 (27.71)	
Age: 45-64 years	948 (30.03)	755 (31.56)	193 (25.23)	
Age: ≥ 65 years	675 (21.38)	592 (24.75)	83 (10.85)	
Disease Location (ICD 9/10 Code) at Diagnosis				
Small Intestine (555.0, K50.0) (n,%)	1,085 (34.37)	832 (34.78)	253 (33.07)	p<0.0001
Large Intestine (555.1, K50.1)	719 (22.77)	585 (24.46)	134 (17.52)	
Small and Large Intestine (555.2 K50.8)	902 (28.57)	601 (25.13)	301 (39.35)	
Unspecified (555.9, K50.9)	451 (14.29)	374 (15.64)	77 (10.07)	
Geographic Location				
East North Central (n, %)	567 (17.96)	403 (16.85)	164 (21.44)	p<0.0001
East South Central	96 (3.04)	72 (3.01)	24 (3.14)	
Middle Atlantic	218 (6.91)	173 (7.23)	45 (5.88)	
Mountain	287 (9.09)	227 (9.49)	60 (7.84)	
New England	145 (4.59)	114 (4.77)	31 (4.05)	
Pacific	339 (10.74)	266 (11.12)	73 (9.54)	
South Atlantic	782 (24.77)	624 (26.09)	158 (20.65)	
West North Central	352 (11.15)	231 (9.66)	121 (15.82)	
West South Central	371 (11.75)	282 (11.79)	89 (11.63)	
Payer				
Commercial (n, %)	2,444 (77.42)	1,770 (74.00)	674 (88.10)	p<0.0001
Medicare, Age < 65 (n, %)	112 (3.55)	91 (3.80)	21 (2.75)	
Medicare, Age ≥ 65 (n, %)	601 (19.04)	531 (22.20)	70 (9.15)	
Elixhauser Index (based on pre-CD-diagnosis period)				
Score (mean, SD)	2.10 (2.42)	2.24 (2.50)	1.65 (2.11)	p**<0.0001**
Score: 0 (n, %)	916 (29.01)	666 (27.84)	250 (32.68)	p<0.0001
Score: 1-2 (n, %)	1,273 (40.32)	924 (38.63)	349 (45.62)	
Score: >3 (n, %)	968 (30.66)	802 (33.53)	166 (21.70)	
GI-Related Hospitalization Prior to Diagnosis				
Prior Hospitalization (n, %)	278 (8.81)	216 (9.03)	62 (8.10)	p=0.4317
CD-Related Surgical Procedures Performed Within 60 Days Following Index Diagnosis				
Procedure Performed (n, %)	1,858 (58.85)	1,388 (58.03)	470 (61.43)	p=0.0951
Diagnosis Year				
2011	588 (18.63)	489 (20.44)	99 (12.94)	p<0.0001
2012	524 (16.60)	415 (17.35)	109 (14.25)	
2013	469 (14.86)	352 (14.72)	117 (15.29)	
2014	357 (11.31)	258 (10.79)	99 (12.94)	
2015	399 (12.64)	294 (12.29)	105 (13.73)	
2016	438 (13.87)	321 (13.42)	117 (15.29)	
2017	382 (12.10)	263 (10.99)	119 (15.56)	

CD = Crohn's Disease; SU = Step-Up Therapy; TD = Top-Down Therapy; ICD = International Classification of Diseases; SD = Standard Deviation

Significance assessed with t-test and chi-squared tests comparing the SU and TD cohorts for each variable.

Table 7: Crohn's Disease, Step-Up, and Top-Down Cohort Cost and Utilization Results Measured in the Follow-Up Period

	CD Cohort (Study Population)	**SU Cohort**	**TD Cohort**	**Significance** (Ha: SU ≠ TD)
Cost (based on follow-up period)				
Overall All-cause Cost (mean $, SD)	38,887 (83,818)	34,898 (88,168)	51,359 (66,988)	p<0.0001
CD-Specific Total Cost (mean $, SD)	16,830 (28,305)	11,765 (24,752)	32,664 (32,570)	p<0.0001
CD-Specific Healthcare Costs (mean $, SD)	6,321 (19,627)	4,616 (16,731)	11,653 (26,031)	p<0.0001
CD-Specific Medication Costs (mean $, SD)	10,414 (16,216)	7,025 (12,560)	21,011 (21,074)	p<0.0001
Utilization (based on follow-up period)				
CD-Specific Total Utilization (mean, SD)	16.19 (14.78)	13.27 (13.23)	25.33 (15.63)	p<0.0001
CD-Specific Healthcare Utilization (mean, SD)	8.34 (11.27)	6.42 (9.92)	14.35 (12.99)	p<0.0001
CD-Specific Medication Utilization (mean, SD)	8.08 (6.84)	6.97 (6.34)	11.53 (7.18)	p<0.0001

CD = Crohn's Disease; SU = Step-Up Therapy; TD = Top-Down Therapy; SD = Standard Deviation
Significance assessed with t-tests comparing the SU and TD cohorts for each variable.
Costs were standardized to the 2017 dollar using the Personal Health Care Expenditure deflator

Overall All-cause Cost: healthcare expenditures for any indication, encompassing all pharmacy, outpatient healthcare, laboratory testing, imaging, and hospitalization/emergency department costs.

CD-Specific Total Cost/Utilization: sum of cost/prescriptions dispensed for CD-indicated therapies and cost/utilization of medical visits and hospitalizations with a primary diagnosis of CD in the follow-up period.

CD-Specific Healthcare Cost/Utilization: Cost relating to/number of healthcare visits, including outpatient appointments, laboratory tests, imaging, hospitalization/emergency department use, with CD as the primary diagnosis

CD-Specific Medication Cost/Utilization: Cost relating to/number of prescriptions dispensed for CD-indicated medications.

Table 8:Direct, Per-Patient Average Disease-Specific Healthcare Costs for the Crohn's Disease, Step-Up, and Top-Down Cohorts

	CD Cohort (n=3,157)			SU Cohort (n=2,392)		TD Cohort (n=765)	
	n	Average Cost (SD)	p-value*	n	Average Cost (SD)	n	Average Cost (SD)
Sex							
Female	1,696	6,380 (20,724)	p=0.8557	1,316	4,909 (18,075)	380	11,477 (27,454)
Male	1,461	6,253 (18,277)		1,076	4,258 (14,924)	385	11,828 (24,582)
Age at Diagnosis							
Age: 18-29 years	737	10,869 (25,457)	p<0.0001	460	7,364 (18,919)	277	16,688 (32,840)
Age: 30-44 years	797	6,318 (18,609)		585	5,327 (17,748)	212	9,050 (20,599)
Age: 45-64 years	948	4,325 (13,718)		755	3,146 (10,696)	193	8,937 (21,263)
Age: ≥ 65 years	675	4,164 (19,745)		592	3,652 (19,678)	83	7,819 (19,952)
Disease Location (ICD 9/10 Code)							
Small Intestine	1,085	7,071 (21,609)	p<0.0001	832	5,079 (16,692)	253	13,625 (32,150)
Large Intestine	719	3,450 (12,589)		585	2,771 (11,602)	134	6,413 (15,928)
Small and Large Intestine	902	10,050 (24,579)		601	8,147 (23,835)	301	13,849 (25,620)
Unspecified	451	1,637 (7,071)		374	799 (2,923)	77	5,712 (15,292)
Location							
East North Central	567	6,432 (17,974)	p=0.9542	403	4,431 (13,699)	164	11,350 (24,995)
East South Central	96	5,590 (18,319)		72	4,287 (15,322)	24	9,502 (25,300)
Middle Atlantic	218	7,361 (19,851)		173	4,016 (12,943)	45	20,221 (32,793)
Mountain	287	5,812 (17,578)		227	4,344 (15,102)	60	11,367 (24,177)
New England	145	5,680 (13,828)		114	3,297 (11,139)	31	14,446 (18,693)
Pacific	339	5,401 (17,543)		266	3,820 (14,429)	73	11,161 (25,210)
South Atlantic	782	6,172 (18,316)		624	5,094 (16,227)	158	10,431 (24,516)
West North Central	352	6,804 (20,632)		231	5,580 (22,047)	121	9,141 (17,467)
West South Central	371	7,072 (27,664)		282	4,988 (23,177)	89	13,673 (38,005)
Payer							
Commercial	2,444	7,021 (19,777)	p=0.0006	1,770	5,015 (15,838)	674	12,289 (26,873)
Medicare, Age < 65	112	2,188 (6,060)		91	1,705 (4,464)	21	4,281 (10,414)
Medicare, Age ≥ 65	601	4,246 (20,429)		531	3,784 (20,482)	70	7,748 (19,812)
Elixhauser Index (based on pre-CD-diagnosis period)							
Score: 0	916	6,759 (20,125)	p=0.5287	666	4,440 (14,836)	250	12,934 (29,116)
Score: 1-2	1,273	6,431 (18,428)		924	5,503 (16,382)	349	10,078 (22,608)
Score: <3	968	5,764 (20,659)		802	4,258 (18,526)	166	13,037 (27,763)
GI-Related Hospitalization Prior to Diagnosis							
Prior Hospitalization	278	10,143 (25,660)	p=0.0007	216	10,019 (27,290)	62	10,574 (19,097)
No Prior Hospitalization	2,879	5,952 (18,908)		2,176	4,080 (15,196)	703	11,749 (26,565)
CD-Related Surgical Procedures Performed Within 60 Days Following Index Diagnosis							
Procedure Performed	1,858	6,870 (20,083)	p=0.0603	1,388	5,034 (17,437)	470	12,292 (25,658)
No Procedure Performed	1,299	5,536 (18,936)		1,004	4,308 (15,693)	295	10,637 (26,630)
Diagnosis Year							
2011	588	4,871 (19,281)	p=0.0741	489	3,341 (11,906)	99	12,429 (38,100)
2012	524	5,272 (15,661)		415	4,290 (14,822)	109	9,013 (18,100)
2013	469	6,619 (21,098)		352	5,694 (20,139)	117	9,401 (23,626)
2014	357	8,132 (21,537)		258	5,422 (17,782)	99	15,192 (28,037)
2015	399	6,219 (16,356)		294	3,901 (13,422)	105	12,712 (21,413)
2016	438	8,086 (25,513)		321	6,419 (24,390)	117	12,658 (27,970)
2017	382	6,019 (16,239)		263	3,867 (12,304)	119	10,775 (21,958)

CD = Crohn's Disease; SU = Step-Up Therapy; TD = Top-Down Therapy; ICD = International Classification of Diseases; SD = Standard Deviation

Crohn's Disease-Specific Healthcare Costs was used for calculations, which represents all medical costs, without medication costs.

*Significance assessed with t-tests and analysis of variance (ANOVA) tests for variation between levels of the variables in the CD cohort (study population).

Table 9:Results of Optimized General Linear Model Predicting Factors Associated with Direct Crohn's Disease-Specific Healthcare Expenditure

	Adjusted Ratio§	SE	Adjusted Ratio 95% CI*	Adjusted Costs ($)	% Difference in Cost*‡
Intercept	821.39	1.30	(498.35, 1419.70)		
Therapy Strategy					
TD	2.50	1.09	(2.12, 2.95)	2,051.65	149.78%
SU	Reference				
Sex					
Female	1.15	1.08	(1.00, 1.32)	943.79	14.90%
Male	Reference				
Age Group					
Age: 18-29 years	3.70	1.28	(2.22, 5.84)	3,038.44	269.91%
Age: 30-44 years	2.38	1.27	(1.43, 3.73)	1,952.96	137.76%
Age: 45-64 years	1.86	1.27	(1.13, 2.89)	1,524.77	85.63%
Age: ≥ 65 years	Reference				
Disease Location (ICD 9/10 Code)					
Small Intestine (555.0, K50.0)	1.99	1.10	(1.66, 2.40)	1,638.11	99.43%
Large Intestine (555.1, K50.1)	Reference				
Small and Large Intestine (555.2 K50.8)	3.07	1.10	(2.53, 3.72)	2,521.98	207.04%
Unspecified (555.9, K50.9)	0.43	1.13	(0.34, 0.54)	350.09	-57.38%
Payer					
Commercial	Reference				
Medicare, Age < 65	0.41	1.22	(0.28, 0.62)	337.17	-58.95%
Medicare, Age ≥ 65	1.45	1.27	(0.88, 2.27)	1,190.82	44.98%
Elixhauser Index					
Score: 0	Reference				
Score: 1-2	1.00	1.09	(0.83, 1.19)	817.70	-0.45%
Score: ≤ 3	1.06	1.11	(0.86, 1.31)	868.88	5.78%
GI-Related Hospitalization Prior to Diagnosis					
Prior Hospitalization	2.80	1.14	(2.18, 3.63)	2,297.32	179.69%
No Prior Hospitalization	Reference				
CD-Related Surgical Procedures Performed Within 60 Days Following Index Diagnosis					
Procedure Performed	0.91	1.08	(0.78, 1.05)	748.37	-8.89%
No Procedure Performed	Reference				
Diagnosis Year					
2011	Reference				
2012	0.90	1.13	(0.71, 1.14)	739.52	-9.97%
2013	1.36	1.13	(1.07, 1.74)	1,121.03	36.48%
2014	1.74	1.14	(1.34, 2.27)	1,428.67	73.93%
2015	1.10	1.14	(0.86, 1.41)	901.00	9.69%
2016	1.38	1.13	(1.08, 1.76)	1,132.29	37.85%
2017	0.84	1.14	(0.66, 1.09)	692.36	-15.71%

CD = Crohn's Disease; SU = Step-Up Therapy; TD = Top-Down Therapy; ICD = International Classification of Diseases; SD = Standard Deviation

Dependent Variable: Crohn's Disease-Specific Healthcare Costs, which represents all medical costs, without medication costs.

§:Adjusted exponentiated β Coefficient exponentiated

*: Adjusted exponentiated values

‡: Percentage change in cost when all other independent variables are at the reference level.

Table 10: Results of Full General Linear Model Predicting Factors Associated with Direct Crohn's Disease-Specific Healthcare Expenditure

	Adjusted-Ratio§	SE	Adjusted Ratio 95% CI*	Adjusted Costs ($)	% Difference in Cost*‡
Intercept	859.37	1.33	(500.50, 1539.33)		
Therapy Strategy					
TD	2.52	1.09	(2.14, 2.98)	2,164.40	151.86%
SU	Reference				
Sex					
Female	1.13	1.08	(0.98, 1.31)	0,972.53	13.17%
Male	Reference				
Age Group					
Age: 18-29 years	3.56	1.28	(2.13, 5.66)	3,060.70	256.16%
Age: 30-44 years	2.25	1.28	(1.35, 3.55)	1,934.69	125.13%
Age: 45-64 years	1.80	1.27	(1.09, 2.82)	1,550.29	80.40%
Age: ≥ 65 years	Reference				
Disease Location (ICD 9/10 Code)					
Small Intestine (555.0, K50.0)	2.01	1.10	(1.67, 2.42)	1,726.76	100.93%
Large Intestine (555.1, K50.1)	Reference				
Small and Large Intestine (555.2 K50.8)	3.19	1.10	(2.62, 3.87)	2,739.69	218.80%
Unspecified (555.9, K50.9)	0.44	1.13	(0.34, 0.56)	373.98	-56.48%
Location					
East North Central	0.87	1.14	(0.67, 1.13)	751.82	-12.51%
East South Central	0.97	1.26	(0.63, 1.55)	833.56	-3.00%
Middle Atlantic	0.98	1.19	(0.70, 1.38)	843.20	-1.88%
Mountain	1.07	1.17	(0.79, 1.45)	917.36	6.75%
New England	0.71	1.21	(0.49, 1.05)	613.14	-28.65%
Pacific	0.83	1.16	(0.62, 1.11)	712.73	-17.06%
South Atlantic	1.10	1.13	(0.86, 1.41)	946.91	10.19%
West North Central	1.04	1.16	(0.78, 1.36)	891.05	3.69%
West South Central	Reference				
Payer					
Commercial	Reference				
Medicare, Age < 65	0.43	1.22	(0.30, 0.65)	370.55	-56.88%
Medicare, Age ≥ 65	1.44	1.28	(0.87, 2.27)	1,240.91	44.40%
Elixhauser Index					
Score: 0	Reference				
Score: 1-2	1.00	1.09	(0.84, 1.19)	0,856.03	-0.39%
Score: <3	1.01	1.12	(0.82, 1.26)	0,870.35	1.28%
GI-Related Hospitalization Prior to Diagnosis					
Prior Hospitalization	2.83	1.14	(2.21, 3.68)	2,434.51	183.29%
No Prior Hospitalization	Reference				
CD-Related Surgical Procedures Performed Within 60 Days Following Index Diagnosis					
Procedure Performed	0.94	1.08	(0.81,1.09)	804.56	-6.38%
No Procedure Performed	Reference				
Diagnosis Year					
2011	Reference				
2012	0.87	1.13	(0.68, 1.10)	744.04	-13.42%
2013	1.37	1.13	(1.07, 1.76)	1,179.80	37.29%
2014	1.72	1.14	(1.32, 2.25)	1,481.19	72.36%
2015	1.07	1.14	(0.83, 1.38)	920.76	7.14%
2016	1.40	1.14	(1.09, 1.80)	1,203.39	40.03%
2017	0.84	1.14	(0.65, 1.09)	722.70	-15.90%

CD = Crohn's Disease; SU = Step-Up Therapy; TD = Top-Down Therapy; ICD = International Classification of Diseases; SD = Standard Deviation

Dependent Variable: Crohn's Disease-Specific Healthcare Costs, which represents all medical costs, without medication costs.

§:Adjusted exponentiated β Coefficient exponentiated

*: Adjusted exponentiated values

‡: Percentage change in cost when all other independent variables are at the reference level.

APPENDIX 2: FIGURES

Figure 1: Study Schematic

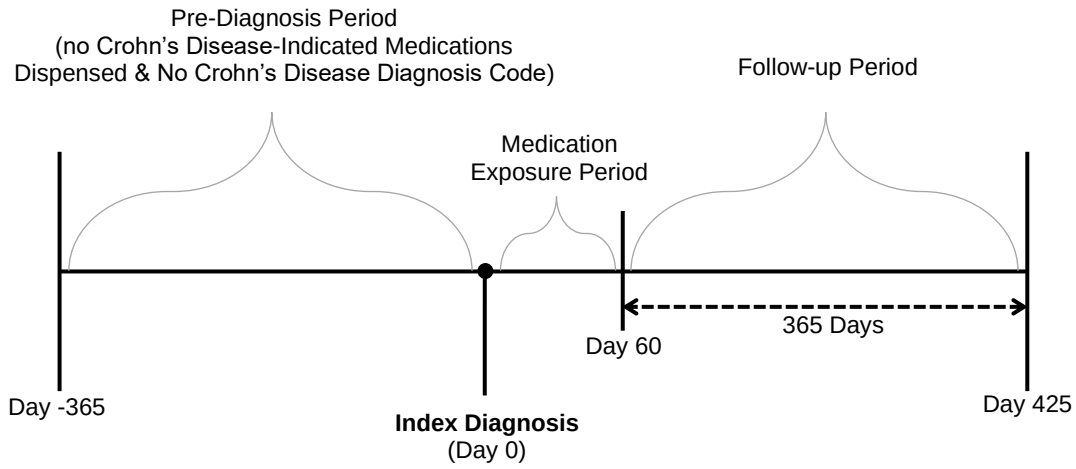
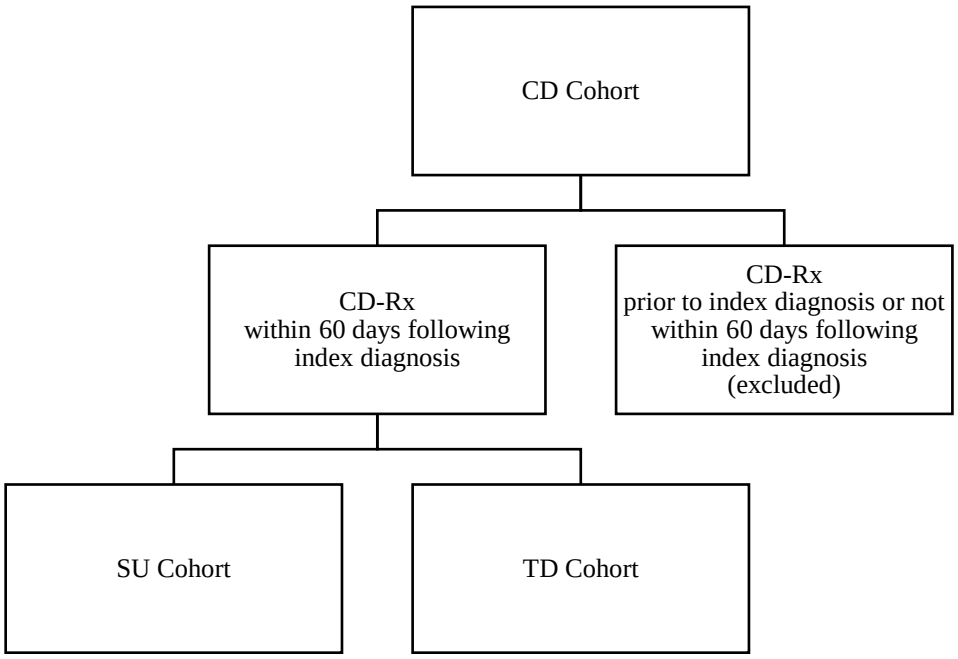


Figure 2: Step-Up and Top-Down Cohort Selection Method



CD: Crohn's Disease; SU: Step-Up Therapy; TD: Top-down Therapy; Rx: Prescription Dispensed

Figure 3: Population Flow Diagram

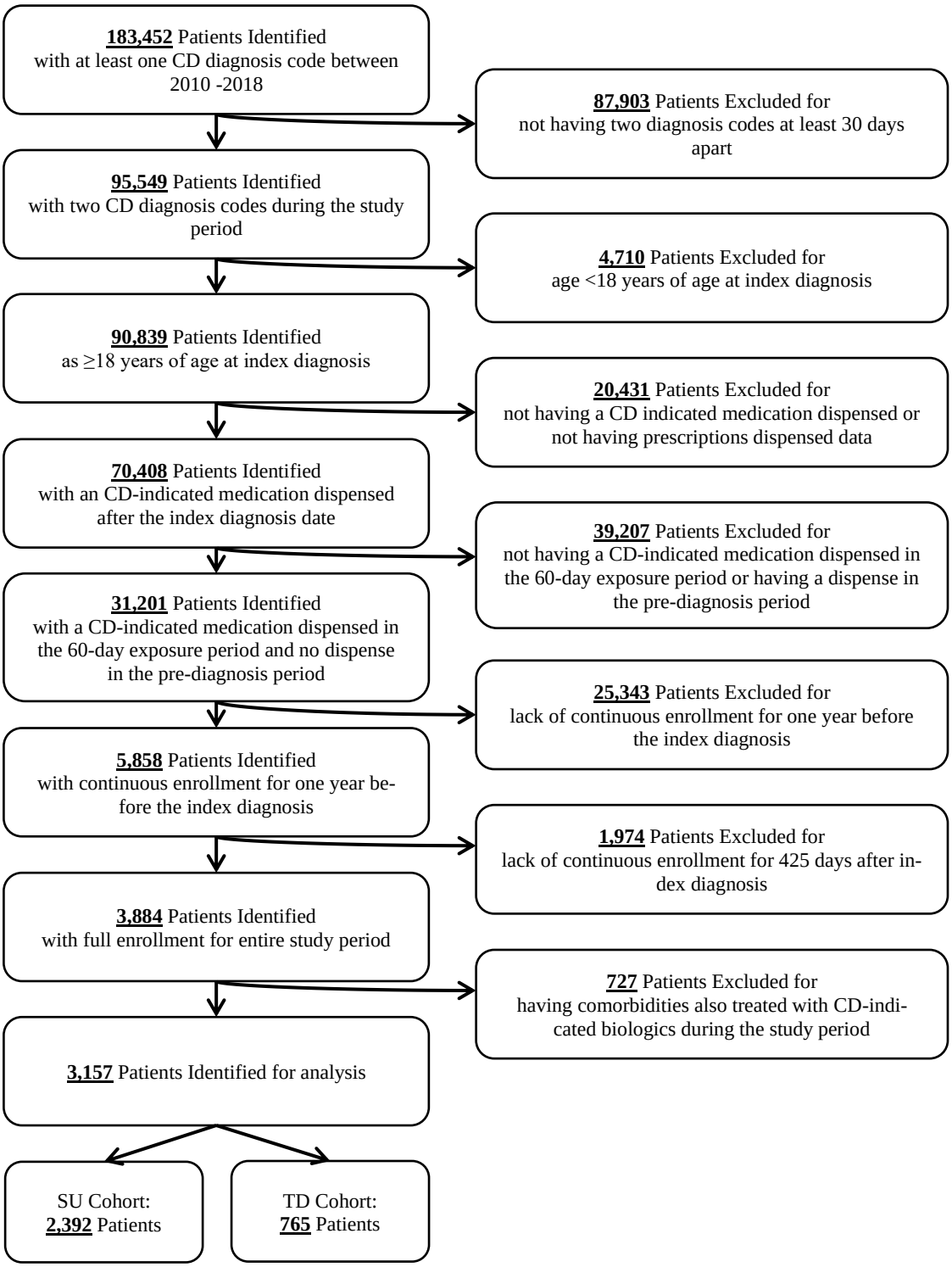


Figure 4: Percentage of Age Groups in Step-Up and Top-Down Cohorts

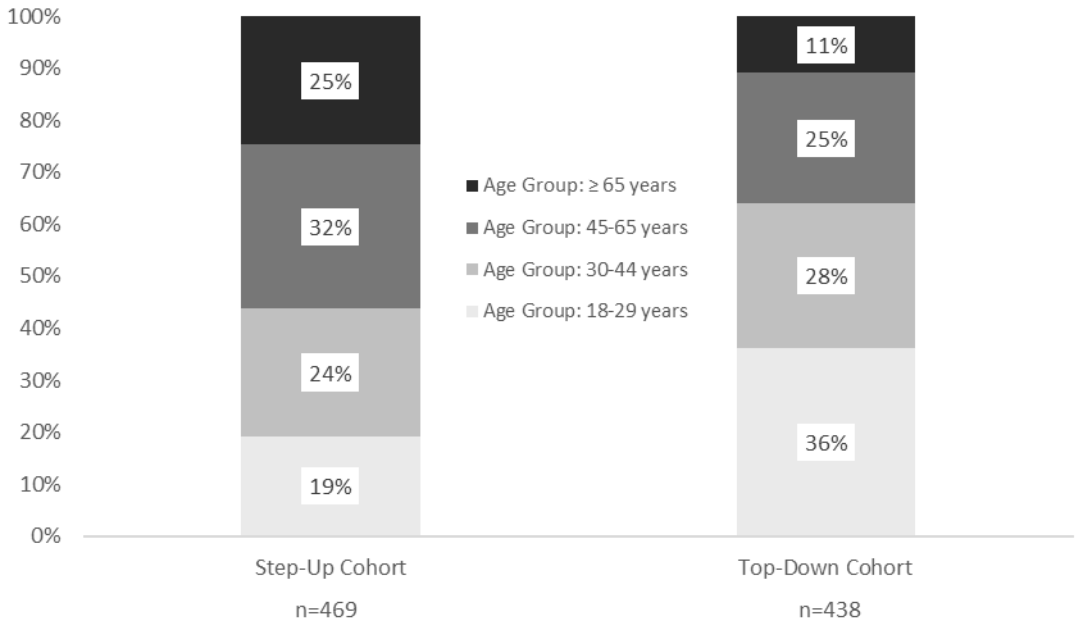


Figure 5: Percentage of Step-Up and Top-Down Therapy Initiated by Year

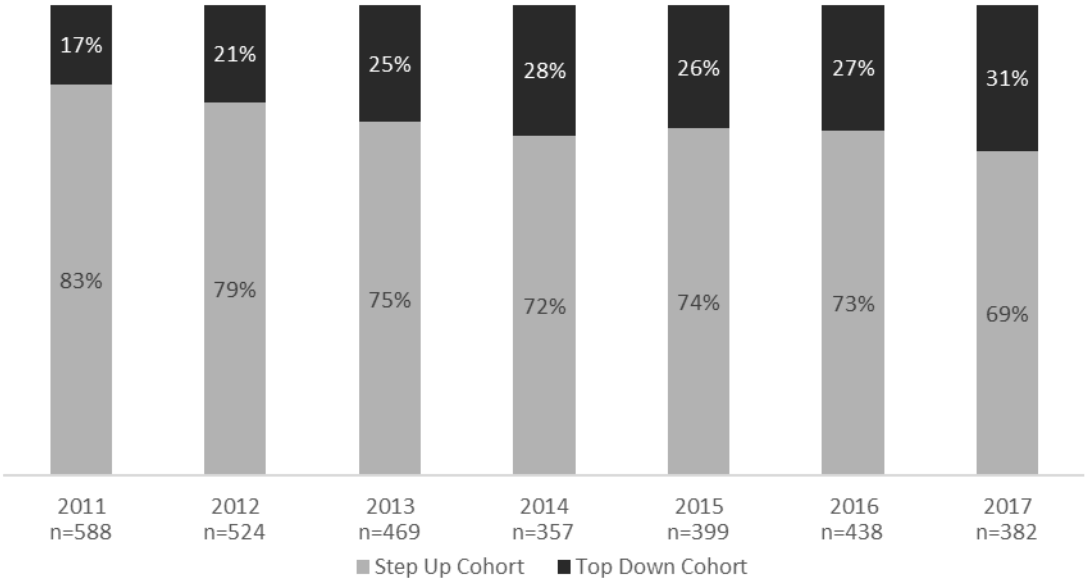


Figure 6A: Cost Variable Distributions for Study Cohorts

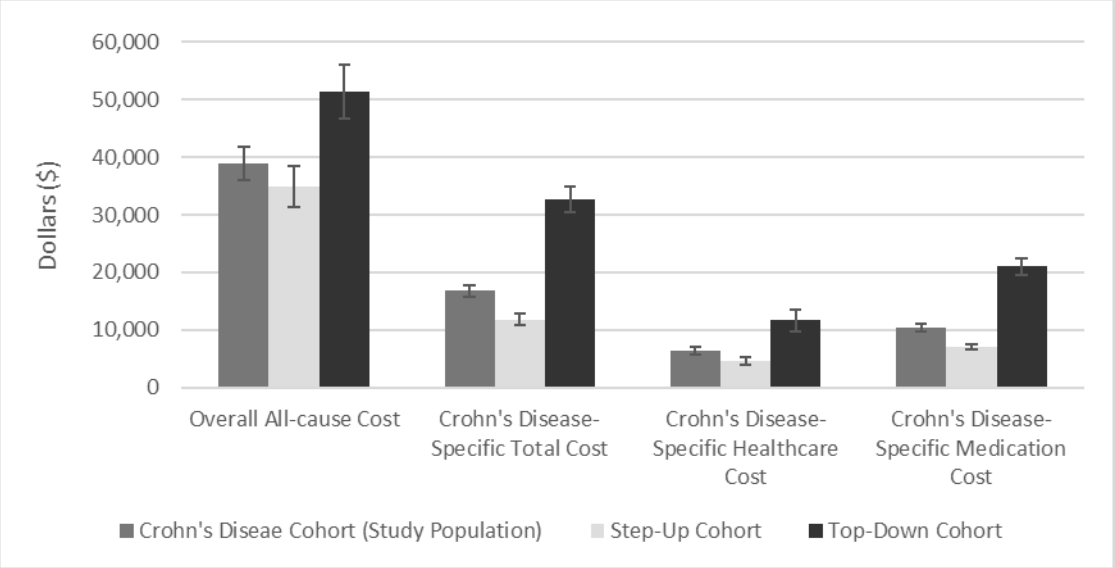


Figure 6B: Utilization Variable Distributions for Study Cohorts

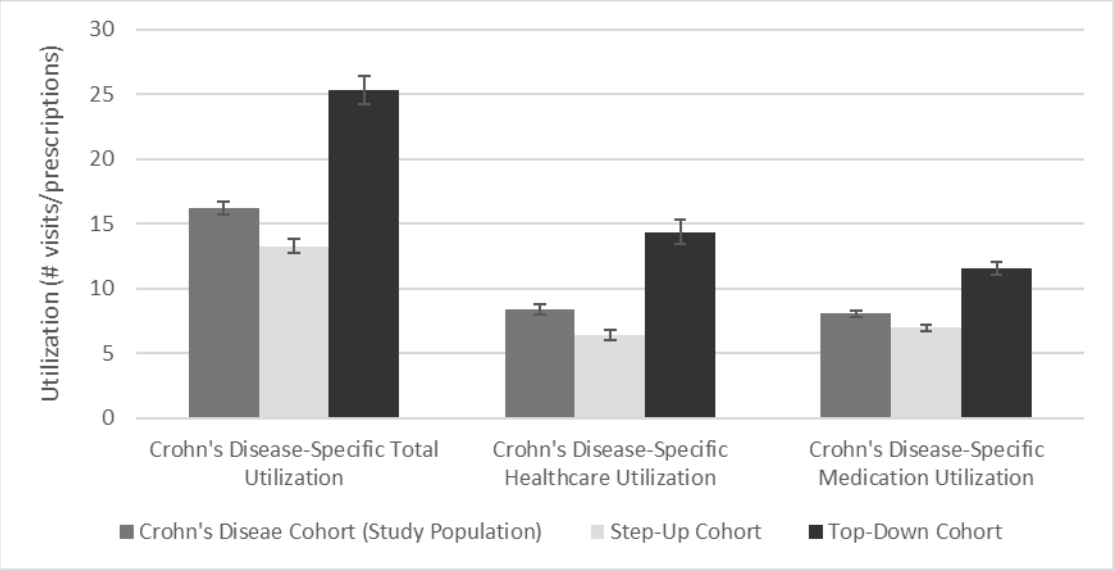
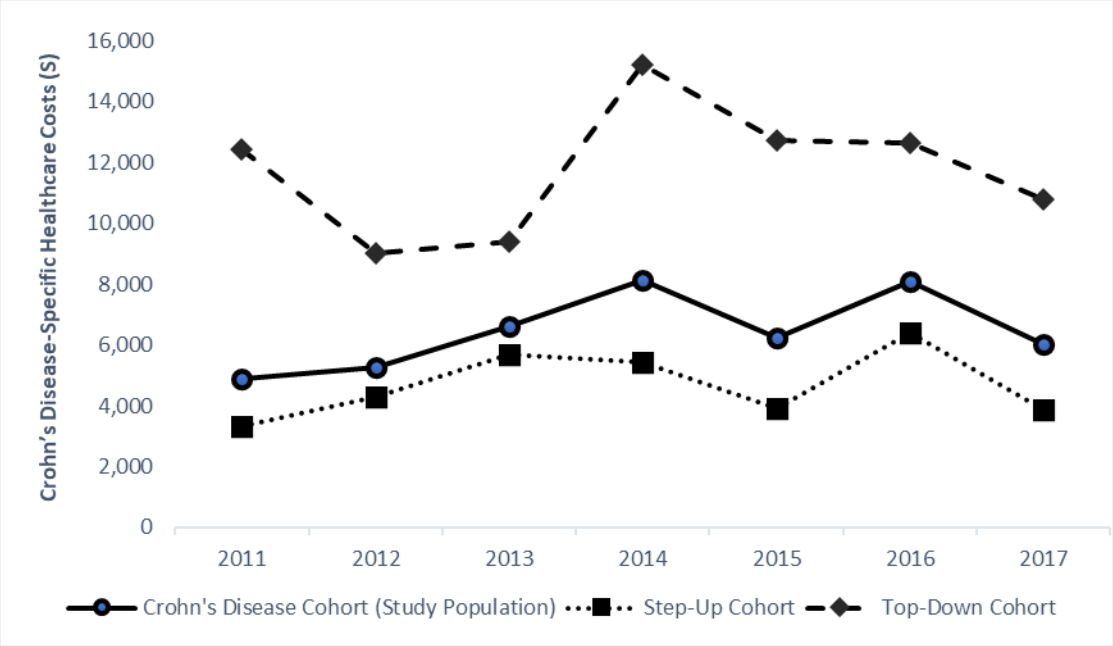


Figure 7: Disease-Specific Healthcare Cost by Year/Over Time for the Crohn's Disease, Step-Up, and Top-Down Cohorts



Note: Crohn's Disease-Specific Healthcare Costs is graphed, which represents all medical costs, without medication

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