INFLIXIMAB THERAPY FOR INDIVIDUALS WITH CROHN'S DISEASE: ANALYSIS OF HEALTH CARE UTILIZATION AND EXPENDITURES

Patrick D. Meek, Pharm.D., M.S.P.H.,[1] Nilay D. Shah, Ph.D.,[2] Holly K. Van Houten, B.A.,[2] Bora Gumustop, M.D., M.S.P.H.,[3] Marjorie A. Rosenberg, Ph.D.[4]

[1]Department of Pharmacy Practice, and Research Institute for Health Outcomes, Albany College of Pharmacy and Health Sciences, Albany, NY; [2]Division of Health Care Policy and Research, Mayo Clinic, Rochester, MN; [3]Albany Gastroenterology Consultants, Albany, NY; [4]Actuarial Science, Risk Management and Insurance, and Biostatistics and Medical Informatics, School of Business and School of Medicine and Public Health, University of Wisconsin at Madison, Madison, WI

Corresponding author:

Patrick D. Meek, Pharm.D., M.S.P.H., Pharmacy Practice Department, Albany College of Pharmacy and Health Sciences, 106 New Scotland Avenue, Albany, NY 12208-3425, phone: (518) 694-7873, fax: (518) 320-9018, email: patrick.meek@acphs.edu.

Results of this study were presented in part at the 28th Annual Meeting of the Society for Medical Decision Making, October 14, 2006, Cambridge, MA, and the American College of Gastroenterology 2007 Annual Scientific Meeting, October 16, 2007, Philadelphia, PA.

This work was supported in part by a grant titled "Efficacy of Specific Prescription Drugs or Categories of Drugs" from the Society of Actuaries, Schaumburg, IL, and by an intramural grant from the Albany College of Pharmacy and Health Sciences, Albany, NY.

Key words: Private health insurance, hospitalization, emergency department, outpatient office visits, prescription drug, medical expenditure, health care utilization, propensity score

Title: Infliximab Therapy for Individuals with Crohn's Disease: Analysis of Health Care Utilization and Expenditures

ABSTRACT

Objective: To compare health care utilization and expenditures between individuals with Crohn's who had used infliximab and those who had not, with observational data collected during the initial years of availability of the drug.

Data: Claims data from the 1999-2003 Thomson Reuters MarketScan commercial claims and encounters databases. Inpatient, outpatient, and prescription drug claims data of individuals older than 18 years of age with a diagnosis of Crohn's were included.

Methods: We compared results with 2 approaches using a (a) retrospective cohort analysis and (b) 12-month pre-post (before and after infliximab) analysis. Demographic, comorbidity, disease severity characteristics and an infliximab baseline indicator were defined in 1999-2001, and used as covariates in multivariate models to predict health care utilization and expenditures in 2002-2003. Stratified analyses by number of supplied doses were also conducted.

Results: In the cohort analysis, using multivariate models with a propensity score covariate to account for choice of infliximab use, no significant differences in rates of hospitalization (incidence rate ratio [IRR] of 0.82; p=0.183) or emergency visits (IRR of 1.05; p=0.550) were seen. Infliximab was associated with a higher rate of outpatient office visits (IRR of 1.55; p<0.001). Case-mix adjusted mean total expenditures during the 2-year follow-up period were higher for infliximab users than for those who did not receive infliximab ($41,386 versus $21,297, respectively; p<0.001). For the pre-post analysis, we found no differences in mean number of hospitalizations (0.53 versus 0.54 admissions; p=0.84) or length of hospitalization (2.7 versus 3.7 days; p=0.08), or in mean number of emergency visits (0.73 versus 0.79 visits; p=0.60) during the 12-month periods before and after first record of infliximab use. Increases (Δ=difference, post minus pre) were seen in the mean number of outpatient visits (Δ=+2.7 visits; p<0.0001) and mean number of outpatient drug prescriptions (Δ=+5.9 prescriptions; p<0.0001). Infliximab therapy was associated with a mean increase of $18,305 in total 12-month expenditures (p<0.0001).

Conclusion: These results suggest that infliximab therapy is not associated with an overall reduction in direct health care utilization and expenditures when used in actual practice by privately insured individuals with Crohn's.

INTRODUCTION

Infliximab, introduced in 1998, is a biologic drug (of the monoclonal antibody type) that blocks the effects of tumor necrosis factor-α, a substance involved in the promotion of inflammation in Crohn's disease (Crohn's) and other autoimmune diseases. Results of pivotal clinical trials in Crohn's demonstrated that infliximab affected the short and long term outcomes of fistulizing and non-fistulizing disease in individuals failing standard therapies.(20, 37, 41, 42, 48, 49, 54) When used in individuals with moderately severe, complicated, or refractory Crohn's, substantial improvements were seen in clinical status, need for intensive medical management (corticosteroid use, hospitalization and procedures) and quality of life.

Infliximab is integral to the management of approximately 50% of the 650,000 people in the United States diagnosed with Crohn's who are most likely to have a complicated course of disease requiring corticosteroids and/or surgery.(10, 17, 43) Most often, infliximab therapy is directed at ameliorating refractory gastrointestinal symptoms of abdominal pain, chronic diarrhea, and fistula, but increasingly, it is used for maintaining disease remission, treating extraintestinal symptoms, and reducing complications requiring hospitalization and surgery.(44) Recent clinical trial data also suggested that earlier treatment with infliximab and immune modulators (i.e., as first-line therapy before corticosteroid treatment early in the course of disease) may alter the 'natural history' of Crohn's, thereby potentially decreasing the likelihood of overall disease progression during an individual's lifetime.(11, 22, 23) Current practice guidelines (21, 29) however, still recommend infliximab as 'step-up' therapy (i.e., second line, if a person fails to respond to initial therapies) for Crohn's, due in part to continued concerns about safety and cost.(2, 13, 19)

Biologic therapies for Crohn's are expensive ($4,000 to $6,000 per year for episodic induction therapy and $20,000 per year for maintenance treatment) and cost more than non-biologic treatments.(43) Although the effects of infliximab on direct and indirect costs of Crohn's have been studied in post hoc analyses of secondary outcomes of clinical trials (30, 31, 42) or through pre-post comparisons of care provided in academic medical settings,(27, 40) there are virtually no data on how infliximab therapy affected overall health care utilization (i.e., numbers of hospitalizations, emergency visits, office visits) and total expenditures in actual clinical practice across a geographically diverse set of providers, and health care settings. Consequently, a central question (to both clinicians and insurers) remains unanswered whether

the cost of biologic therapy for Crohn's is offset by decreased utilization and cost savings in other areas.(14, 25, 38)

In this article, we present the results of an integrated claims database study of privately insured individuals with Crohn's using data from the initial years of infliximab availability (1999-2003). The primary objective of the study was to compare health care utilization and expenditures between individuals with Crohn's who used infliximab and those who had not. We used two common observational research designs to control for underlying risk and disease severity (the retrospective cohort and pre-post designs). A secondary objective was to evaluate the effects of infliximab in subgroups based on use of infliximab.

METHODS

Data Source and Sample

Data from 52,257 individuals with inflammatory bowel disease were obtained from the MarketScan Commercial Claims and Encounters database (Thomson Reuters, Ann Arbor, Mich.) for calendar years 1999-2003 representing person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services from approximately 45 employers, health plans, government and public organizations.(34) The annual medical databases included private sector health data from approximately 100 payers. Medical and pharmaceutical claims for active employees, early retirees, those who exercised the COBRA option and their dependents insured by employer-sponsored plans across the United States are contained in the Commercial Claims and Encounters database. Using an encrypted unique person identifier contained in each table, paid claims and encounter data were linked to detailed demographic and enrollment information across sites and types of providers, and over time. Encounter records contain detailed utilization and expenditure data representing the service use and cost of billable health care services to the payer. All available records for the 5-year study timeframe (January 1, 1999 to December 31, 2003) were compiled from the following tables: inpatient admission and inpatient service tables (encounter records associated with a hospital admission), outpatient service table (encounter records for services rendered in a doctor's office or other outpatient facility), outpatient pharmaceutical claims table (prescription drug claims), and enrollment summary tables (individual level demographic and insurance coverage information).

To focus on infliximab therapy for adults (aged 18 and over) with Crohn's we identified a subset of 25,739 individuals with a diagnosis of Crohn's between 1999-2003 by locating International Classification of Disease, 9th Edition (ICD-9) codes for Crohn's (ICD-9 = 555.xx [regional enteritis]) in any of the fifteen diagnosis fields within the inpatient admission file, or five diagnosis fields in the outpatient services file.(16) Seventy-six percent of individuals in this cohort had a claim for Crohn's during the 1999-2001 period while the remaining individuals had their first Crohn's-related claim later in the 2002-2003 period.

Infliximab Baseline Indicator

A dichotomous (1 or 0) indicator variable was defined based on the presence or absence of at least one claim for infliximab during the baseline period. The indicator variable was set to "1" for individuals in the intervention (infliximab group) if they had at least one claim for infliximab during 1999-2001, else the baseline indicator variable was set to "0" for individuals in the control group (non-infliximab group). Receipt of infliximab was identified from claims in the outpatient service file (using Healthcare Common Procedure Coding System code, J1745) and the outpatient prescription drug file (using National Drug Code 57894-0030-01). An *index date* was defined for each individual in the infliximab group as the date of the initial infliximab claim during the study period.

To better delineate the use of infliximab therapy for secondary analyses, individuals in the infliximab group were further stratified based on the number of repeat doses, as an indicator of continued treatment.(36, 52) We categorized infliximab users into a 'single-dose treatment subgroup' who had one infliximab dose in 1999-2001 and no repeat doses for the remainder of the study period, and a 'multiple-dose treatment subgroup' who had infliximab in 1999-2001 and at least 1 additional infliximab infusion during the remainder of the study period. Those in the single-dose treatment group received a total of one infliximab dose during the study (baseline) period, and those in the multiple-dose treatment group received at least one dose of infliximab during the baseline period and at least one repeat infliximab infusion at any time during the remainder of the study period.

Outcome Measures

The outcomes of interest in this study were health care utilization and expenditures. Utilization was measured by counting all-cause events (i.e., hospitalizations, emergency visits,

outpatient office visits for any reason). Health care costs (including deductibles, copayments, coinsurance, and coordination-of-benefits payments) were measured in terms of all-cause medical expenditures, all-cause-outpatient prescription drug expenditures, and all-cause total expenditures (i.e., the sum of medical and outpatient prescription drug expenditures). Expenditures were standardized to 2003 U.S. dollars using the medical Consumer Price Index.(56)

Design

Two observational research designs (a retrospective cohort design, and a 12-month pre-post design) were implemented to estimate the impact of infliximab on utilization and expenditures.(7, 18) Using two different observational approaches allowed us to maximize our sample size of infliximab users with a reasonable duration of follow-up for the measurement of outcomes, and compare the results of both analyses in an effort to obtain consistent estimates of the effect of infliximab on the outcome measures of interest.

In the retrospective cohort design, continuously enrolled members were followed from the earliest recorded date in their claims data to the end of the 5-year study timeframe. Each individual's observation period was split into two consecutive time periods based on calendar year; a 3-year 'baseline period' (years 1999-2001) and a 2-year 'measurement period' (years 2002-2003). Infliximab use and baseline characteristics (age, sex, geographic region, comorbidities, and Crohn's-related conditions) were defined during the baseline period and persons were observed for all-cause events and expenditures during the measurement period. Individuals were ineligible for cohort analyses if their infliximab index date occurred during the measurement period, or if their entire observation window transpired within a single time period (i.e., either the baseline or measurement period), thereby precluding the ability to perform analyses over time.

In the pre-post design where persons served as their own controls, only individuals from the infliximab group with at least one year of continuous enrollment before *and* after the index infliximab date were included in the analysis. Fixed (12-month) periods of observation before and after the index date were constructed for each person. The 24-month interval (i.e., 12 months pre- and post-infliximab index date) was selected to maximize the number of treated individuals included in the before and after comparison, while providing a reasonable duration of

follow-up within which a clinical response and change in outcome would be anticipated. By design, individuals were ineligible if their index date occurred in the beginning (i.e., during 1999) or end (i.e., during 2003) of the study timeframe, and if they had less than 12-months of data before and after the first infliximab record for any other reason. Utilization and expenditures before the index date were considered part of the pre-infliximab period, and utilization and expenditures after the index date were considered part of the post-infliximab period. The number of all-cause events and total expenditures were calculated for each individual during the pre-, and post-infliximab periods.

Risk and Propensity Score Adjustment

Two major challenges in observational research are: 1) homogeneity of comparison groups on factors known to influence an outcome of interest and 2) selection bias.(24) Persons with multiple comorbidities, complicated illness, or other significant risk factors generally utilize higher quantities of health care resources and generate higher costs than healthier individuals. Selection bias involves the lack of randomization in assigning individuals to the treatment group and may result in imbalances in important individual characteristics related to the selection of treatment. Ignoring these issues in quasi-experimental research may result in biased estimates of treatment effect. To address these challenges in our cohort study, we used a combination of risk adjustment and propensity score methods to account for baseline differences and improve the comparability of groups in our multivariate analyses.

Risk Adjustment

Risk adjustment methods aim to account for differences in underlying health risks for primary events of interest (e.g., utilization or expenditures), by creating homogeneous groups with respect to relevant characteristics and clinical attributes. To account for differences in underlying risk for future events in our cohort study, we evaluated individuals during the baseline period on demographic, geographic and clinical characteristics, and created a set of risk adjustment variables. Demographic and geographic characteristics included age in years, sex (female), and geographic region (classified as Northeast, Midwest, West, and South). Clinical characteristics included factors *directly* related and *indirectly* related to the principal diagnosis of Crohn's. In contrast to disease states caused by factors directly related to the underlying

inflammatory-mediated pathogenesis of Crohn's, indirectly related factors are disease characteristics not linked to the underlying etiology of the disease.(24)

Factors Directly Related to the Principal Diagnosis (Crohn's Disease Severity Variables)

We included a set of four dichotomous case-mix variables, based on ICD-9-CM codes (see Appendix), that reflect a higher likelihood of adverse outcomes based on expert opinion, conditions with poorer clinical prognosis, or conditions requiring more extensive care: [a] gastrointestinal complications, [b] extraintestinal, [c] debilitating and [d] psychological manifestations of Crohn's. Gastrointestinal complications require additional treatment (with drugs and/or surgery), and may require hospitalization.(28) Extraintestinal manifestations typically occur during periods of active gastrointestinal symptoms and may require additional outpatient care and adjunctive therapy to alleviate symptoms.(28) Individuals with Crohn's are at increased risk for developing debilitating, life threatening infections, and severe immune reactions (septicemia, and systemic inflammatory response syndrome). These persons may require prolonged hospitalization, and closer follow-up.(28) In addition to significant decrements in quality of life, individuals with concurrent psychological symptoms may be more likely to seek additional care.(26)

Factors Indirectly Related to the Principal Diagnosis (Demographic and Comorbidity Variables)

Nine risk adjustment variables were created and used to account for risk associated with underlying chronic diseases other than Crohn's. In addition to age, sex, and geographic region, we developed a set of individual dichotomous variables for 9 comorbidities that were thought to place an individual at higher risk for subsequent events requiring health care, independent of the principal diagnosis of Crohn's.(12, 15, 51) These included cerebrovascular disease, peripheral vascular disease, congestive heart failure, pulmonary disease, peptic ulcer disease, diabetes, liver disease, renal disease, and cancer. [ICD-9 codes provided in Appendix]

We also calculated the Deyo-Charlson adaptation of the Charlson Index as a severity weighted summary of comorbid disease for use in the count models, along with age, sex, and the infliximab baseline indicator variable, to evaluate the relationship between severity of comorbid disease and the likelihood of having zero hospitalizations or emergency room visits.(12) The adapted Charlson Index is a weighted sum of the presence or absence of each of 17 conditions;

each condition is assigned a weight from 1 to 6, with higher weights indicating greater severity. An individual's Charlson Index is the sum of these weights (i.e., the severity weighted sum of disease).(8) Therefore, if a person has no chronic conditions, then the Charlson Index score will be 0. If a person has diabetes, renal disease, and metastatic solid tumor then the Charlson Index score will be 1+2+6=9. The Deyo-Charlson adaptation of the Charlson Index has been shown to perform well in adjusting for comorbidity in claims data.(12) Each condition was identified by the corresponding sets of five-digit ICD-9-CM diagnoses as presented in the appendix. The index score was calculated using ICD-9-CM codes derived from all diagnoses from inpatient, and outpatient records during the baseline period.

Propensity Score Adjustment

Propensity Score Variable

In our study, there was the potential for substantial differences in the distribution of baseline characteristics between infliximab and non-infliximab groups due to selection bias, and each of these factors may have had a strong relationship to the outcomes of interest. Propensity score methods provide a means for adjusting for selection bias in observational studies of causal effects, and serve a separate purpose from risk adjustment, in that these methods adjust for potential confounding not accounted for by the other risk and case-mix variables. In order to adjust for additional confounding due to non-random treatment allocation and to provide a better balance of background disease severity characteristics between groups, a propensity score variable for the likelihood of receiving infliximab was created.(3) We developed the propensity score (39) using logistic regression to assess the likelihood of an individual being treated with infliximab. Seventeen pre-specified candidate variables were included in the propensity score model (i.e., age, sex, region, congestive heart failure, peripheral vascular disease, peptic ulcer disease, diabetes, renal disease, rheumatoid disease, cancer, gastrointestinal complications, extraintestinal, debilitating and psychologic manifestations of Crohn's). The propensity score model estimated the probability that the individual would receive infliximab during 1999-2001 (baseline period). The predictive value of the score (i.e., the predictive ability of the propensity score model to discriminate between infliximab users and non-users) was evaluated using receiver-operator characteristic (ROC) analyses. The c-statistic from ROC analysis was 0.76, indicating good discrimination between infliximab and non-infliximab groups.(6) The

propensity score was also used in supplemental analyses to estimate average treatment effect in subgroups of individuals in the treatment and control groups with similar propensity scores.

Data Analysis

Retrospective Cohort Analysis

In the retrospective cohort analysis, we examined associations between infliximab use in 1999-2001 and utilization and expenditures in 2002-2003 by constructing regression models on the sample of 7,938 individuals with Crohn's. Separate models were estimated for four dependent variables: ([a] number of hospitalizations, [b] number of emergency visits, [c] number of outpatient visits, and [d] expenditures; [total, inpatient, outpatient, prescription drug]) using the infliximab baseline indicator (as the treatment variable), and the set of risk and propensity score adjustment variables (as covariates) to predict aggregate utilization during the measurement period. Because the use of infliximab may have differential effects depending on continued use of the drug, we also examined the effect of use of infliximab separately in the single- and multiple-dose treatment subgroups.

Analysis of health care utilization

Risk and propensity score adjusted utilization models were constructed to compare utilization for those who received infliximab therapy to those who did not. We used zero-inflated Poisson count models to analyze dependent variables (i.e., hospitalizations, and emergency visits) with a non-trivial number of zeros and positive skewness of non-zero outcomes among infliximab utilizers.(32) Negative binomial (NB) count models were used to analyze dependent variables (i.e., outpatient visits) when more favorable as compared to Poisson regression.(55)

Analysis of total medical expenditures

Expenditures were calculated separately for inpatient services, outpatient services, and outpatient prescription drugs. We calculated total expenditures as a sum of expenditures for hospital stays, outpatient services, and outpatient prescription drugs. Based on distributional assumptions of the data, we utilized a generalized linear model (GLM) model with a gamma distributional assumption to compare expenditures for those who received infliximab therapy to

those who did not.(9, 33) The Gamma GLM was supported by the results of a modified Park test as a diagnostic test for an appropriate variance function.(35)

Pre-post Analysis

In the pre-post analysis, we compared utilization and expenditures for the year before versus the year after starting infliximab. These analyses used the individual as their own control. We report results from a sample of 396 continuously enrolled persons from the full sample of infliximab users. Counts of hospitalizations, emergency department, physician office visits and total expenditures were compared between the pre- and post-infliximab periods. The mean number of hospitalizations, emergency visits, outpatient visits, and total expenditures during a fixed, 12-month period preceding infliximab therapy were compared with the mean values during a 12-month period after this date using paired t-tests. We also examined the effect of follow-up doses of infliximab by repeating the pre-post analysis in two subgroups: those receiving only a single infusion of infliximab, and those who received multiple infliximab doses infusions.

Supplemental Analysis

In addition, a matched propensity score sample was used in a supplemental analysis for each outcome event (i.e., hospitalizations, emergency visits, and outpatient office visits). In contrast to the use of the propensity score as a covariate in standard regression, where the goal is to adjust for a summary measure that reflects the likelihood of receiving treatment, the use of the propensity score matching is more likely to produce analyses that are robust to model misspecification. A nearest-neighbor matching approach was used for matching on propensity score. This method randomly orders individuals in the treatment and control groups based on propensity score, and then selects the first treated individual with the closest propensity score to form a matched pair with an individual in the control group. The treatment effect, in terms of health care utilization and expenditures, is calculated as the difference in adjusted mean between the infliximab and non-infliximab group.(4). A disadvantage of propensity score matching is the need for a relatively large sample size to avoid substantial imbalance of covariates.(57)

RESULTS

A flow chart showing the results of the sample selection process is provided in Figure 1. Of the 52,257 individuals identified in the original data query using Crohn's and non-Crohn's ICD-9 codes, 7,938 individuals with Crohn's were included in the retrospective cohort analyses and 396 infliximab users were included in the pre-post analyses.

Baseline Characteristics

Table 1 shows differences in population characteristics for the 7,938 individuals included in the retrospective cohort. Characteristics of individuals included in the pre-post analysis were similar to the group of individuals receiving infliximab in the cohort analysis, and are not shown in the table. Of the 7,938 in the cohort analysis, 181 received infliximab during the baseline period. The mean age is 45.5 for the non-infliximab group, and 42.1 for the infliximab group ($p<0.0001$), and both groups were similar in terms of sex (57% and 56% female, respectively; $p=0.896$). Those in the infliximab group are less likely to live in the Northeast (12% versus 24%; $p<0.0001$), Midwest (17% versus 28%; $p<0.001$), and West (1% versus 5%; $p=0.027$), and more likely to live in the South (70% versus 43%; $p<0.0001$). Regarding comorbidity, infliximab, users were more likely to have rheumatoid disease (7.7% versus 1.8%; $p<0.0001$), a finding that is consistent with infliximab indications (i.e., infliximab received FDA approval in July 2000 for treatment of rheumatoid arthritis). All other listed comorbidities were found in similar percentages between groups.

In terms of disease severity, approximately 60% and 72% of infliximab users have a Crohn's complication or extraintestinal manifestation of Crohn's, respectively, compared to 32% and 61% of the non-infliximab group ($p<0.0001$, and $p=0.005$, respectively). The infliximab and non-infliximab groups are similar in terms of debilitating (e.g., septicemia, shock) and psychological manifestations (e.g., anxiety, adjustment reaction, transient mental condition) of Crohn's. Concurrent therapies for Crohn's are more common in the infliximab group, compared to the non-infliximab group (54% and 11% [$p<0.0001$], 69% and 39% [$p<0.0001$], and 52% and 31% [$p<0.0001$]) for immune modulator, corticosteroid, and mesalamine therapies, respectively. These findings indicate that infliximab users have a higher burden of illness from Crohn's compared to the non-infliximab group. We adjusted for baseline differences in our analyses by including comorbidity and disease severity variables in the models.

Infliximab Use Patterns

Patterns of infliximab use are shown in Table 2 for individuals in the retrospective cohort (top section of Table 2), and pre-post analysis (bottom section of Table 2). One-hundred and eighty-one (14.4% of infliximab users from the original sample) received at least one infusion during the baseline period and were included in the retrospective cohort analysis. Forty-three (23.8%) of these 181 individuals received just one dose of infliximab throughout the entire study period (and were grouped into the single-dose treatment subgroup) while the remaining 138 (76.2%) individuals received multiple infusions over the course of the study (and were grouped into the multiple-dose treatment subgroup). The number of repeat doses received by infliximab users in the retrospective cohort analysis during the baseline and measurement periods is shown in Table 2. It is important to note that very few individuals in the retrospective cohort analysis received full dose maintenance therapy (i.e., one dose every 6-8 weeks).

For the pre-post design, a total of 396 individuals (31.4% of infliximab users from the original sample) met inclusion criteria for the pre-post analysis (i.e., they received at least one dose of infliximab, and were continuously enrolled for a 12-month period of observation before and after the initial infliximab dose). The total number of doses of infliximab received by individuals in the pre-post analysis is shown in Table 2. Eighty-eight of 396 individuals (22%) received a single infusion (and were grouped into the single-dose treatment subgroup), and 308 of 396 (78%) received multiple infusions during the 12-month post-period (and were grouped into the multiple-dose treatment subgroup). One-hundred and fifty-two (38%) individuals received between 5 to 10 doses, or approximately what would be expected if patients were receiving full dose maintenance therapy.

Health Care Utilization and Expenditures

Table 3 presents the results of the case-mix adjusted analyses of health care utilization and expenditures. The main variable (infliximab) is listed at the top of the table and covariates are grouped into the following categories: demographics, geographic region, comorbidities and disease severity characteristics, and propensity score. Incidence rate ratios are provided for each variable in the count portion of the models to show the relationship of each covariate to numbers of hospitalizations [model 1], numbers of emergency visits [model 2] and numbers of outpatient office visits [model 3] in 2002-2003. Incidence rate ratios are calculated from the count models

by exponentiation of the regression coefficients. An incidence rate ratio provides a measure of treatment effect in terms of the relative rate of events per unit of time between treated and untreated persons (i.e., the factor change in expected utilization in 2002-2003 for infliximab users relative to the non-infliximab group). Regression coefficients are also presented in Table 3 for the expenditure model (model 4) and are interpreted as the change in direction of expenditures associated with a given covariate. The predicted case-mix and propensity score adjusted differences in health care utilization and expenditures by treatment group using propensity score adjustment (as covariate), and propensity score matching (supplemental analysis) in the overall and stratified groups are provided in Table 4.

Retrospective Cohort Analysis

Infliximab

Based on models 1 and 2 shown in Table 3, the adjusted rates of hospitalization (IRR = 0.82, p=0.183) and emergency visits (IRR = 1.05, p=0.55) in 2002-2003 with infliximab use in 1999-2001 were no different, relative to those not receiving infliximab. However, the adjusted rate of outpatient office visits (model 3) was greater (IRR = 1.55, p<0.001) relative to the non-infliximab group. Total expenditures (model 4) in 2002-2003 for individuals using infliximab in 1999-2001 were also greater (regression-coefficient=0.707, p<0.001) relative to the non-infliximab group. Controlling for demographic characteristics, geographic region, comorbidities, and disease severity characteristics, the predicted biennial hospitalization rates for the measurement period for the infliximab and non-infliximab groups were 0.55 and 0.41 admissions, for the infliximab and non-infliximab groups, respectively (Table 4). The predicted biennial rates of emergency visits during the measurement period for the infliximab and non-infliximab groups, respectively were 0.98 and 0.90 visits (Table 4). The predicted rate of outpatient office visits for the measurement period for the infliximab and non-infliximab groups were 18.7 and 12.1 visits, respectively (Table 4). The predicted case-mix adjusted mean total expenditures (Table 4) for the two-year period were $41,386 for infliximab users, and $21,297 among those who did not receive infliximab in the baseline period (1999-2001), a difference of $20,089 (p<0.001).

In subgroup analyses (multivariate regression models not shown), there were no differences in the adjusted rates of hospitalization (IRR = 1.35, p=0.265), emergency visits

(IRR = 1.50, p=0.391), or outpatient office visits (IRR = 1.11, p=0.434) in 2002-2003 with single-dose treatment in 1999-2001, relative to those not receiving infliximab. For the multiple-dose treatment subgroup, the adjusted rates of hospitalization (IRR = 0.67, p=0.090), and emergency visits (IRR = 0.93, p=0.784) were also no different compared to the non-infliximab group. However, the adjusted rate of outpatient office visits (IRR = 1.72, p<0.001) and total expenditures (regression-coefficient=0.731, p<0.001) were greater with the multiple-dose treatment in 1999-2001, relative to the non-infliximab group. Controlling for demographic characteristics, geographic region, comorbidities, and disease severity characteristics, the predicted number of outpatient office visits during the measurement period for the multiple-dose treatment subgroup and non-infliximab groups were 20.8 and 12.1 visits, a difference of 8.7 visits (95% CI = 6.2 to 10.8 visits), for the multiple-dose treatment subgroup and non-infliximab groups, respectively (Table 4). The predicted case-mix adjusted mean total expenditures (Table 4) for the two-year period were $45,049 for the multiple-dose treatment subgroup, and $21,321 among those who did not receive infliximab in the baseline period (1999-2001), a difference of +$23,728 (95% CI = $19,128 to $28,328).

Covariates

In terms of demographic and geographic factors (Table 3), females had a lower rate of hospital admission than males (incidence rate ratio [IRR] = 0.83, p<0.001). Increasing age by 1 year was related to a 1.4% (IRR = 0.986, p<0.001) decrease in the rate of hospitalization, a 2.0% (IRR = 0.98, p<0.001) decrease in the rate of emergency visits, and a 0.6% (IRR = 1.006, p<0.001) increase in the rate of outpatient office visits. There were no differences in hospitalization rates between geographic regions, although living in the Midwest was associated with a lower rate of hospitalization of bordering statistical significance (IRR=0.91, p=0.063) compared to the Northeast. Living in the Midwest was associated with a significantly lower rate of emergency (IRR = 0.90, p<0.01) and outpatient office visits (IRR = 0.94, p<0.05) compared to the Northeast. Living in the South was associated with higher total expenditures (regression-coefficient = 0.166, p<0.001) compared to the Northeast.

In terms of comorbidity and disease severity characteristics (Table 3), the following conditions were associated with an increased rate of hospitalizations, emergency visits, outpatient office visits, and total expenditures (with a p<0.05): congestive heart failure,

cerebrovascular disease, chronic pulmonary disease, peptic ulcer disease, diabetes, renal disease, cancer, Crohn's related gastrointestinal complications, extraintestinal, debilitating, psychological manifestations. Peripheral vascular disease, and end-stage liver disease were not associated with the rate of hospitalization, however these conditions were associated with increased rates of emergency visits, outpatient office visits, and total expenditures (with a $p<0.05$). The propensity score (i.e., the predicted probability of receiving infliximab during 1999-2001) was not associated with significant differences in hospitalization rates, outpatient office visit rates or expenditures. Increasing the propensity score by 1 unit was related to a 0.4% (IRR = 1.004, $p<0.001$) increase in the rate of emergency visits.

Pre-post Analysis

Results of the analysis of health care utilization during the 12-month period before and after infliximab therapy are shown in Table 5. There were no differences in mean number (0.53 versus 0.54 visits, p=0.84) or length of hospitalizations (2.7 versus 3.7 days, p=0.08), or mean number of emergency department (0.73 versus 0.79 visits, p=0.60), for the pre- and post-periods, respectively. However, when comparing the pre-infliximab period to the post-infliximab period, there was an increase in mean number of outpatient office visits (Δ=+2.7 visits, $p<0.0001$), and an increase in mean number of outpatient drug prescriptions (Δ=+5.9 prescriptions, p=<0.0001) after infliximab therapy. Mean total expenditures were also higher during the 12-month post-infliximab period by +$18,305 ($p<0.0001$), with an increase in expenditures for inpatient services (Δ=+$4,028, p=0.022), outpatient services (Δ=+$13,043, $p<0.0001$) and outpatient prescription drugs (Δ=+$1,234, $p<0.0001$).

In subgroup analyses, the average pre-post changes in number of hospitalizations, length of hospitalization, and number of emergency visits were +0.27 visits (p=0.08), +3.4 days (p=0.05), and +0.42 visits (p=0.16), respectively for individuals in the single dose treatment subgroup. For patients in the multiple dose treatment subgroup, the average pre-post changes in number of hospitalizations, length of hospitalization, and number of emergency visits were -0.06 visits (p=0.35), +0.40 days (p=0.50), and -0.06 visits (p=0.54), respectively. Increases in mean number of outpatient visits (+2.4 visits [p=0.008], and +2.8 visits [$p<0.0001$]) and mean number of outpatient drug prescriptions (+6.2 prescriptions [p=0.006], and +5.8 prescriptions [$p<0.0001$]) from the pre- to post-infliximab periods, were seen for both the single and multiple-

dose subgroups, respectively. These findings are also consistent with the findings of the overall group.

Consistent findings were also noted to those seen in the overall group in terms of expenditures, for the single-dose treatment subgroup, increases were noted in inpatient (Δ=+$11,549, p=0.015), outpatient service (+$3,662, p=0.001), and outpatient prescription drug expenditures (+$960, p<0.0001), and total expenditures (+16,172, p=0.002). For the multiple-dose treatment subgroup, increases were also noted for each component of expenditures (Δ=+$15,723 [p<0.0001] for outpatient services, Δ=+$3,662 [p=0.001], and Δ=+$1,312 [p<0.0001] for outpatient prescription drug) except inpatient hospitalization expenditures where there was no difference between the pre-, and post-infliximab periods. Total expenditures increased by +$18,915 (p<0.0001) in the multiple-dose treatment subgroup from the pre- to the post-infliximab periods.

In the overall, single- and multiple-dose treatment subgroups, the findings of the pre-post analysis were consistent with the results of the case-mix-adjusted retrospective cohort models presented earlier (Table 3). For the multiple-dose subgroup, the differences in expenditures seemed more consolidated in the outpatient setting, while expenditures for the single-dose group seemed to be consolidated in the inpatient setting.

Supplemental Propensity Score Matched Analysis

Results of the supplemental analyses using propensity score matching are presented in Table 4 (column 4). The conclusions of the supplemental propensity score matched analysis agree with the conclusions based on the case mix and propensity score adjusted approach, with minor differences. In contrast to the findings from the primary (retrospective cohort, and pre-post) analyses, there were numeric differences in the predicted rates of hospitalization (i.e., -0.06 for the overall group, -0.04 for the multiple-dose subgroup), and emergency visits (i.e., +0.13 visits for the multiple dose subgroup), however none of these difference were statistically significant. Regarding outpatient visits, the findings from the primary (case mix and propensity score adjusted analyses) were both numerically and statistically consistent with the findings from the supplemental propensity score matched analyses, showing +6.8 and +7.5 more outpatient office visits among those in the overall, and multiple-dose treatment groups, respectively

compared with the non-infliximab group, and no difference in outpatient office visits for the single-dose treatment group compared to the non-infliximab group.

DISCUSSION

The retrospective cohort and pre-post studies used administrative data from privately insured individuals with Crohn's to examine utilization associated with infliximab use in actual clinical practice. In this study, infliximab was not associated with a reduction in health care utilization and expenditures. There were no changes in average annual number of hospitalizations, and average annual number of visits to an emergency department. Infliximab therapy was associated with a modest increase in the average number of outpatient visits, and an increase of $18,000 in total expenditures after infliximab therapy. The reason for this cannot be directly determined from our study; however, it seems unlikely that it is mainly due to differences in Crohn's severity since similar increases were seen in both the retrospective cohort, and pre-post analyses.

In general, individuals with Crohn's require monitoring (with regularly scheduled blood tests) every 8-12 weeks. In our study, the predicted number of visits by individuals with Crohn's who did not receive infliximab was 12.1 visits over the course of the 2-year measurement period, which is approximately what is expected for this group. If compliance with infliximab, which is infused in physician offices, encouraged patients to be more compliant with their schedule of physician office visits, then this would explain the higher rate of office visits seen in this group. Additional monitoring for infliximab toxicity (e.g., infection screening, exploring neurological side effects, avoiding use in individuals with heart failure or chronic infections) may be necessary and would explain the increase in outpatient office care.(13)

There are several strengths to our study. To our knowledge, this is the first study to examine health care utilization and expenditures associated with infliximab therapy using a sample of individuals with Crohn's from a large, geographically diverse administrative database. The study combined information from inpatient, outpatient, and prescription drug data sources to evaluate the association of infliximab with study outcomes in actual practice. Using a database like this avoids biases that may be seen in single-center studies, and in strictly controlled clinical trials. We also used a variety of analytic approaches to address potential limitations in our methods. Although it is not possible in non-experimental research to be certain that unmeasured

case-mix and severity is not confounding observed associations, the increased utilization and expenditures associated with infliximab therapy reported in this article were robust to a variety of analytic approaches, were adjusted by a detailed case-mix and propensity score method, and were consistent between retrospective cohort and pre-post analyses.

These findings also make clinical sense. The greater complexity of infliximab therapy (an infused therapy), compared with taking a pill, would be expected to lead to some increase in visits for the purpose of infusing the therapy. Similarly, additional visits for monitoring infliximab safety and response are generally considered necessary for safe and effective infliximab management. Because some evidence suggests that routine monitoring of infliximab therapy may be beneficial in managing Crohn's, the higher costs for those receiving infliximab therapy may be striking, but are expected and appropriate. However since the data only extends over a couple of years and in the early days after its introduction, its long-term effect is not immediately evident, and further research to evaluate the future costs of Crohn's disease is necessary. Use of infliximab may reduce hospitalizations over an extended period by changing the course of the disease. Likewise, we were not able to evaluate the impact of infliximab on two dimensions that contribute significantly to the overall societal costs of Crohn's: quality of life and productivity at school or work.(58)

Caution should be used in generalizing our results to other settings. The sample may differ in several ways from the overall Crohn's population. Our study was conducted in a privately insured population. All persons were employed or dependents of an employed individual; few were poor, disabled, or elderly and none were uninsured. Although we used administrative data, which is generally considered to be a reliable source for assessing health care utilization and expenditures, some measures could potentially suffer from biased reporting. Also, those included in the study tended to be younger and have more visits and may differ from non-participants in other important ways. We compared mean utilization and expenditures (rather than median) in our pre-post analyses using paired t-tests. Distributions for the mean utilization or mean expenditures were higher than the respective median within either the infliximab or non-infliximab groups for most outcomes. Still, the analyses of utilization and expenditures from the cohort and pre-post analyses yielded very similar results, adding further support for our findings.

How important are the increases in utilization and expenditures associated with infliximab therapy? The addition of several visits per year for several tens of thousands of people nationwide cannot be taken lightly, but, of course, these costs must be weighed against the expected long-term benefits of reducing Crohn's complications. For those whose disease was initially poorly controlled (and therefore who are at highest risk of debilitating disease consequences), improvements in symptom control would be expected to result in substantial long-term benefits, including improved quality of life, enhanced productivity, and possible future cost savings, in this high-risk group. Also, the timeframe of the study was during the early years of infliximab availability. Crohn's management strategies have evolved since its release in 1998 and have become more sophisticated in terms of the recommendations for the optimal concurrent use with other therapies.(29)

For those diagnosed more recently, different outcomes may be seen. Expanded indications for maintenance therapy arising from the 2004 ACCENT II trial, and discoveries of other biologic medications (e.g., adalimumab, certolizumab) were not available at the time of our study and few individuals were receiving infliximab as maintenance therapy. Perhaps these newer treatment regimens, and adjunctive agents can help caregivers achieve better disease control in their patients than observed in our study.(45-47, 50, 53) Additional research is needed to evaluate the relationship between the new treatment alternatives for Crohn's disease and health care utilization and expenditures. The methods used in this study can be used as a foundation for future research.

Figure 1. Flow chart describing sample identification, starting from the 52,257 individuals identified with ICD-9 codes for inflammatory bowel disease from January 1, 1999 to December 31, 2003.

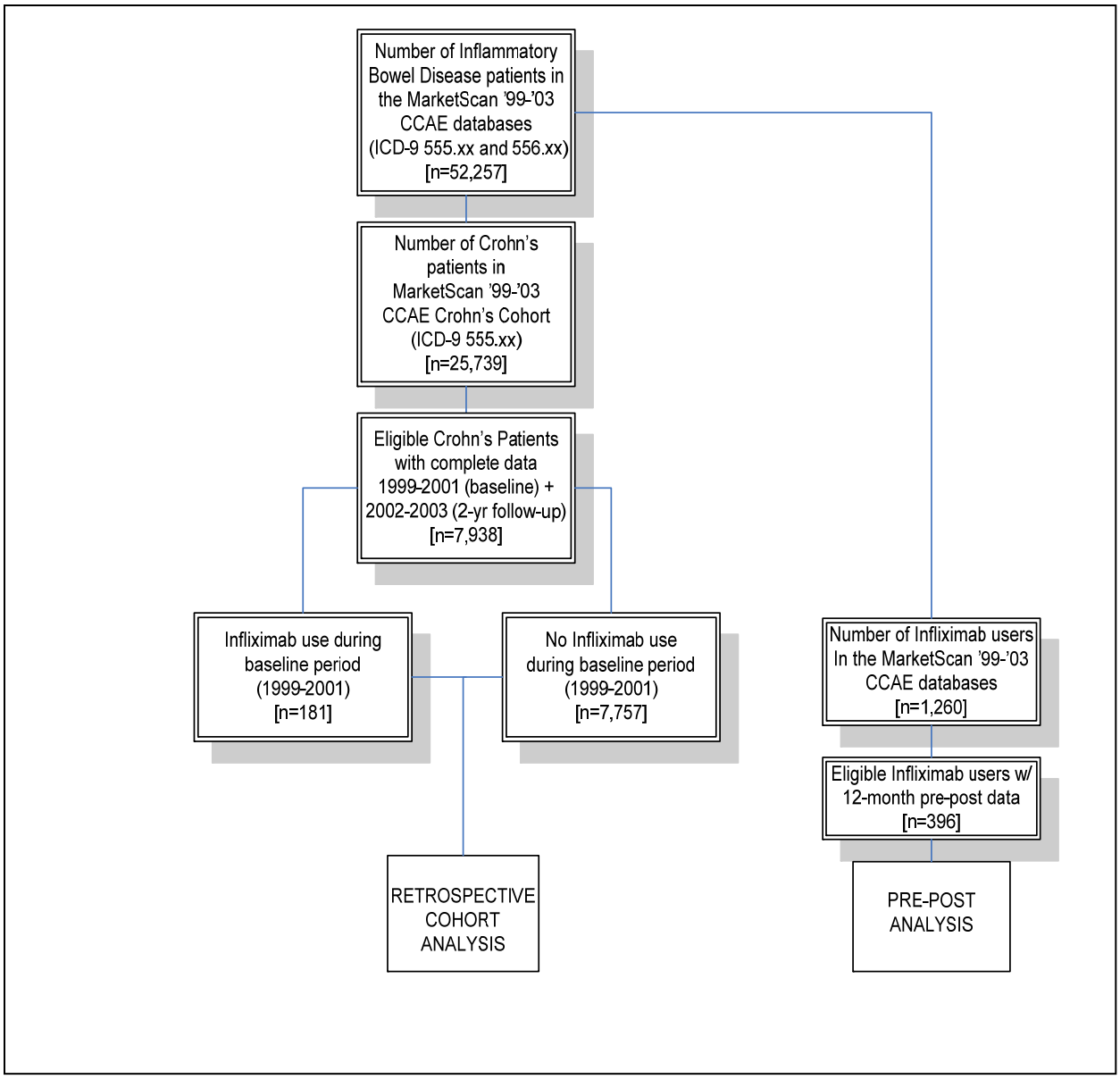

Table 1. Characteristics of individuals in the retrospective cohort analysis.[a]

Characteristic	Overall (n=7,938)	Non-infliximab (n=7,757)	Infliximab (n=181)	P-Value
Demographics				
Age±Std.Dev.	45.5±10.9	45.5±10.9	42.1±12.3	<0.0001
Female (percent)	57%	57%	56%	0.896
Geographic Region (percent)				
Northeast	24%	24%	12%	<0.0001
Midwest	28%	28%	17%	<0.001
South	44%	43%	70%	<0.0001
West	4.5%	5%	1%	0.027
Comorbidities (percent)				
Congestive heart failure	2.3%	2.3%	0.6%	0.112
Peripheral vascular disease	1.8%	1.8%	2.8%	0.310
Cerebrovascular disease	2.0%	2.0%	3.9%	0.079
Chronic pulmonary disease	6.8%	6.9%	6.1%	0.668
Peptic ulcer disease	1.1%	1.1%	0.6%	0.462
End-stage liver disease	0.71%	0.68%	1.1%	0.523
Diabetes	7.3%	7.3%	6.1%	0.520
Renal disease	1.2%	1.2%	1.1%	0.933
Rheumatoid disease	1.9%	1.8%	7.7%	<0.0001
Cancer	5.3%	5.4%	3.3%	0.220
Deyo-Charlson Index (severity weighted sum of diseases, mean±Std.Dev.)	0.45±1.13	0.46±1.13	0.39±0.72	0.396
Disease Severity Characteristics (percent)				
Crohn's related complications	32%	32%	60%	<0.0001
Extraintestinal manifestations	62%	61%	72%	0.005
Debilitating manifestations	1.6%	1.6%	3.3%	0.072
Psychological complications	14%	14%	14%	0.853
Drug Treatment (percent)				
Immune Modulator Therapy	12%	11%	54%	<0.0001
Corticosteroid Therapy	40%	39%	69%	<0.0001
Mesalamine (5-ASA) Therapy	32%	31%	52%	<0.0001

Note: Continuous variable reported as mean±standard deviation, while dichotomous variables are reported as percent with condition or characteristic.

[a] Characteristics of individuals in the pre-post analysis (N=396, data not shown) were similar to the overall group of infliximab users in the cohort analysis (N=181)

Table 2. Infliximab use by individuals in the retrospective cohort [top], and pre-post analyses [bottom].

Infliximab use during the *baseline* period (1999-2001) by individuals in the retrospective cohort analysis	Infliximab use during the *measurement* period (2002-2003) by individuals in the retrospective cohort analysis [n=181] No. (%) of individuals*				
	Number of repeat doses				
	None	**1 dose**	**2-4 doses**	**5-10 doses**	**>10 doses**
Infliximab (1 dose) [n=61]	43 (23.8%)	2 (1.1%)	5 (2.8%)	8 (4.4%)	3 (1.7%)
Infliximab (2-4 doses) [n=84]	34 (18.8%)	6 (3.3%)	14 (7.7%)	23 (12.7%)	7 (3.9%)
Infliximab (5-10 doses) [n=36]	6 (3.3%)	4 (2.2%)	5 (2.8%)	12 (6.6%)	9 (5.0%)

	Infliximab use by individuals in the pre-post analysis [n=396] No. (%) of individuals*				
Total number of doses	**None**	**1 dose**	**2-4 doses**	**5-10 doses**	**>10 doses**
	----	88 (22%)	156 (39%)	152 (38%)	0 (0%)

*Individuals receiving multiple infusions are shown in the shaded cells for the retrospective cohort (n=138, shaded cells at top) and for pre-post analysis (n=308, shaded cells at bottom).

Table 3. Statistical association of infliximab use with health care utilization and expenditures [overall population] (in 2002-2003).

	[Model 1]		[Model 2]		[Model 3]		[Model 4]	
	Hospitalizations (propensity score adjusted ZIP)	p-value	Emergency Visits (propensity score adjusted ZIP)	p-value	Outpatient Office Visits (propensity score adjusted NB)	p-value	Total Expenditure (GLM)	p-value
	Incidence Rate Ratio (SE) **n=7,938**		**Incidence Rate Ratio (SE)** **n=7,938**		**Incidence Rate Ratio (SE)** **n=7,938**		**Regression coefficients (SE)** **n=7,938**	
Infliximab use in 99-01	0.82 (0.12)	0.183	1.05 (0.09)	0.550	1.55 (0.10)	<0.001	0.707 (0.139)	<0.001
Infliximab use in 99-01 (inflate)	0.35 (0.36)	0.003	0.93 (0.17)	0.683				
Demographics								
Age	0.99 (0.01)	<0.001	0.98 (0.01)	<0.001	1.01 (0.01)	<0.001	0.002 (0.002)	0.149
Age (inflate) †	1.00 (0.01)	0.767	1.00 (0.01)	0.709				
Female	0.83 (0.04)	<0.001	1.03 (0.03)	0.311	1.22 (0.02)	<0.001	0.01 (0.034)	0.766
Female (inflate)	0. 60 (0.08)	<0.001	0.84 (0.06)	0.004				
Geographic region								
Northeast (Reference)	(Reference)	----	(Reference)	----	(Reference)	----	(Reference)	----
Midwest	0.91 (0.05)	0.063	0.90 (0.03)	0.002	0.94 (0.02)	0.014	0.03 (0.05)	0.532
South	1.01 (0.05)	0.773	1.00 (0.03)	0.934	1.03 (0.02)	0.162	0.17 (0.04)	<0.001
West	0.86 (0.09)	0.125	0.95 (0.06)	0.448	1.05 (0.05)	0.234	0.15 (0.09)	0.073
Comorbidities								
Congestive heart failure	1.51 (0.11)	<0.001	1.29 (0.07)	<0.001	1.33 (0.08)	<0.001	0.57 (0.11)	<0.001
Peripheral vascular disease	1.07 (0. 10)	0.471	1.37 (0.08)	<0.001	1.26 (0.08)	<0.001	0.46 (0.13)	<0.001
Cerebrovascular disease	1.43 (0.11)	<0.001	1.33 (0.07)	<0.001	1.42 (0.08)	<0.001	0.55 (0.12)	<0.001
Chronic pulmonary disease	1.34 (0.07)	<0.001	1. 60 (0.06)	<0.001	1.55 (0.05)	<0.001	0.47 (0.07)	<0.001
Peptic ulcer disease	1.89 (0.21)	<0.001	1.21 (0.10)	0.024	1.48 (0.12)	<0.001	0.55 (0.16)	<0.001
End-stage liver disease	1.19 (0.16)	0.192	1.32 (0.13)	0.007	1.30 (0.13)	0.009	0.83 (0.20)	<0.001
Diabetes	1.26 (0.07)	<0.001	1.39 (0.05)	<0.001	1.45 (0.05)	<0.001	0.38 (0.07)	<0.001
Renal disease	1.99 (0.16)	<0.001	1.60 (0.10)	<0.001	1.28 (0.10)	0.001	1.15 (0.16)	<0.001
Cancer	1.30 (0.08)	<0.001	1.12 (0.06)	0.021	1.57 (0.06)	<0.001	0.88 (0.07)	<0.001
Deyo-Charlson Index (severity weighted sum of diseases) (inflate) †	0.62 (0.04)	<0.001	0.75 (0.04)	<0.001				
Disease severity characteristics								
Crohn's related complications	1.41 (0.06)	<0.001	1.19 (0.03)	<0.001	1.08 (0.02)	<0.001	0.20 (0.04)	<0.001
Extraintestinal manifestations	1.50 (0.07)	<0.001	1.68 (0.05)	<0.001	1.50 (0.03)	<0.001	0.41 (0.04)	<0.001
Debilitating manifestations	1.65 (0.12)	<0.001	1.40 (0.08)	<0.001	1.25 (0.08)	0.001	0.76 (0.13)	<0.001
Psychological manifestations	1.39 (0.07)	<0.001	1.44 (0.04)	<0.001	1.26 (0.03)	<0.001	0.31 (0.05)	<0.001
Propensity score	1.00 (0.01)	0.232	1.00 (0.01)	<0.001	1.00 (0.01)	0.060	-0.01 (0.01)	0.265

Notes: Zero-inflated Poisson (ZIP), negative binomial (NB) regressions, generalized linear model (GLM) using a gamma response probability with a log link function are performed. Incidence rate ratios are presented for NB, and ZIP regressions, and regression coefficient estimates are presented for generalized linear regressions. Corresponding standard errors reported in parentheses. Two-tailed t-tests and one-tailed chi square tests are applied to the estimated coefficients and model specification statistics (i.e., LR and Voung). †Indicates which variables were used as continuous covariates (predictor variables) in the ZIP regression model analyses. Variables in the inflated portion of the model are marked as "(inflate)."

Table 4. Predicted case-mix and propensity score adjusted health care utilization and expenditures over the 2-year measurement period (2002-2003) by treatment group (Propensity score abbreviated as PS).

	Infliximab	**Non-infliximab (N=7,757)**	**Difference (Infliximab minus Non-infliximab)**	**Difference (Infliximab minus Non-infliximab)**
Predicted 2002-2003 utilization in Crohn's sample (age ≤ 18)	Predicted Rate[c] (PS as covariate) [1]	Predicted Rate[c] (PS as covariate) [2]	Predicted difference[c] (p-value) (PS as covariate) [3]	Average effect of treatment on the treated[d] (p-value) (PS matched) [4]
Hospitalizations				
Overall group (N=181)	0.55	0.41	+0.14 (p=0.183)	-0.06 (p=0.621)
Single-dose treatment group[a]	0.85	0.41	+0.44 (p=0.265)	+0.47 (p=0.150)
Multiple-dose treatment group[b]	0.47	0.41	+0.06 (p=0.090)	-0.04 (p=0.856)
Emergency visits				
Overall group (N=181)	0.98	0.90	+0.08 (p=0.550)	+0.22 (p=0.352)
Single-dose treatment group[a]	1.40	0.90	+0.50 (p=0.391)	+1.39 (p=0.166)
Multiple-dose treatment group[b]	0.88	0.90	-0.02 (p=0.784)	+0.13 (p=0.742)
Outpatient visits				
Overall group (N=181)	18.7	12.1	+6.6 (p<0.001)	+6.8 (p<0.0001)
Single-dose treatment group[a]	13.4	12.1	+1.3 (p=0.434)	+4.8 (p=0.058)
Multiple-dose treatment group[b]	20.8	12.1	+8.7 (p<0.001)	+7.5 (p<0.0001)
Total Expenditures (2003USD)				
Overall group (N=181)	$41,386	$21,297	+$20,089 (p=<0.001)	+$19,012 (p<0.0001)
Single-dose treatment group[a]	$28,243	$21,349	+$6,894 (p=0.470)	+$9,243 (p=0.054)
Multiple-dose treatment group[b]	$45,049	$21,321	+$23,728 (p<0.001)	+$16,446 (p<0.0001)

[a]N=43 infliximab users in single-dose treatment group;

[b]N=138 infliximab users in multiple-dose treatment group;

[c]Bootstrapped values (predicted rate) holding demographics, geographic region, comorbidity, disease severity, and propensity score at their estimation sample mean; bootstrapped 95% confidence interval; p-value from multivariate regression or generalized linear model

[d]ATT calculated based on nearest neighbor matching method described by Becker(ref. 4); bootstrapped 95% confidence intervals; p-value from paired t-test; USD = U.S. dollars

Table 5. Unadjusted Health care utilization 12-months before and after infliximab.

	Infliximab			
	12-months Pre-infliximab (Mean)	12-months Post-infliximab (Mean)	Pre-post change (Δ) (Mean ± SEM)	P-value[c]
Utilization (#/year):				
Number of hospitalizations				
Overall group (N=396)	0.53	0.54	+0.01 ± 0.06	0.84
Single-dose group[a]	0.49	0.76	+0.27 ± 0.16	0.08
Multiple-dose group[b]	0.54	0.48	-0.06 ± 0.07	0.35
Length of stay (days)				
Overall group (N=396)	2.7	3.7	+1.0 ± 0.60	0.08
Single-dose group[a]	2.7	6.1	+3.4 ± 1.7	0.05
Multiple-dose group[b]	2.6	3.0	+0.4 ± 0.60	0.50
Number of emergency visits				
Overall group (N=396)	0.73	0.79	+0.05 ± 0.09	0.60
Single-dose group[a]	0.76	1.2	+0.42 ± 0.30	0.16
Multiple-dose group[b]	0.73	0.67	-0.06 ± 0.09	0.54
Number of outpatient visits				
Overall group (N=396)	10.5	13.3	+2.7 ± 0.35	<0.0001
Single-dose group[a]	9.6	12.0	+2.4 ± 0.88	0.008
Multiple-dose group[b]	10.9	13.7	+2.8 ± 0.37	<0.0001
Number of prescriptions				
Overall group (N=396)	33.1	39.0	+5.9 ± 1.1	<0.0001
Single-dose group[a]	29.6	35.8	+6.2 ± 2.2	0.006
Multiple-dose group[b]	34.1	39.9	+5.8 ± 1.3	<0.0001
Medical expenditures (2003 USD/year):				
Inpatient services				
Overall group (N=396)	$5,334	$9,362	+$4,028 ± $1,746	0.022
Single-dose group[a]	$4,555	$16,104	+$11,549 ± $4,650	0.015
Multiple-dose group[b]	$5,556	$7,436	+$1,879 ± $1,795	0.300
Outpatient services[d]				
Overall group (N=396)	$7,406	$20,449	+$13,043 ± $867	<0.0001
Single-dose group[a]	$7,318	$10,981	+$3,662 ± $1,066	0.001
Multiple-dose group[b]	$7,431	$23,154	+$15,723 ± $1,019	<0.0001
Outpatient prescription drug				
Overall group (N=396)	$2,540	$3,774	+$1,234 ± $190	<0.0001
Single-dose group[a]	$2,417	$3,377	+$960 ± $196	<0.0001
Multiple-dose group[b]	$2,575	$3,887	+$1,312 ± $236	<0.0001
Total Expenditures				
Overall group (N=396)	$15,279	$33,585	+$18,305 ± $2,056	<0.0001
Single-dose group[a]	$14,290	$30,462	+$16,172 ± 5,070	0.002
Multiple-dose group[b]	$15,562	$34,477	+$18,915 ± $2,203	<0.0001

[a]N=88 infliximab users in single-dose treatment group;

[b]N=308 infliximab users in multiple-dose treatment group;

[c]P-value for pre-post change (Δ = post- minus pre-) from 2-tailed paired t-test;(refs. 1, 5)

[d]outpatient costs include hospital and clinical outpatient costs;

USD = U.S. dollars

REFERENCES

1. Altman DG, Bland JM. Measurement in Medicine: The Analysis of Method Comparison Studies. *The Statistician*. 1983;32(3):307-317.
2. Altschuler A, Collins B, Lewis JD, et al. Gastroenterologists' attitudes and self-reported practices regarding inflammatory bowel disease. *Inflamm Bowel Dis*. 2008;14(7):992-9.
3. Austin PC, Mamdani MM. A comparison of propensity score methods: a case-study estimating the effectiveness of post-AMI statin use. *Stat Med*. 2006;25(12):2084-106.
4. Becker SO, Ichino A. Estimation of average treatment effects based on propensity scores. *The Stata Journal*. 2002;2(4):358-377.
5. Bradley EL, Blackwood LG. Comparing Paired Data: A Simultaneous Test for Means and Variances. *The American Statistician*. 1989;43(4):234-235.
6. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T. Variable selection for propensity score models. *Am J Epidemiol*. 2006;163(12):1149-56.
7. Campbell DT, Stanley JC, Gage NL. *Experimental and quasi-experimental designs for research* Chicago: R. McNally; 1966.
8. Charlson M, Pompei P, Ales K, McKenzie C. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis*. 1987;40(5):373-83.
9. Cook RD, Weisberg S. Diagnostics for heteroscedasticity in regression. *Biometrika*. 1983;70(1):1.
10. Cosnes J, Nion-Larmurier I, Beaugerie L, Afchain P, Tiret E, Gendre JP. Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. *Gut*. 2005;54(2):237-41.
11. D'Haens G, Baert F, van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet*. 2008;371(9613):660-7.
12. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-9.
13. DHaens G. Risks and benefits of biologic therapy for inflammatory bowel diseases. *Gut*. 2007;56(5):725-32.
14. Dove H, Duncan I. (Society of Actuaries). An introduction to care management interventions and their implications for actuaries - Paper 1: Programs and Interventions. 2004 August 10, 2004.
15. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care*. 1998;36(1):8-27.
16. Farrokhyar F, McHugh K, Irvine EJ. Self-reported awareness and use of the International Classification of Diseases coding of inflammatory bowel disease services by Ontario physicians. *Can J Gastroenterol*. 2002;16(8):519-26.

17. Faubion WA, Jr., Loftus EV, Jr., Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology*. 2001;121(2):255-60.

18. Grimes DA, Schulz KF. Cohort studies: marching towards outcomes. *Lancet*. 2002;359(9303):341-5.

19. Hanauer SB. Clinical perspectives in Crohn's disease. Turning traditional treatment strategies on their heads: current evidence for "step-up" versus "top-down". *Rev Gastroenterol Disord*. 2007;7 Suppl 2:S17-22.

20. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359(9317):1541-9.

21. Hanauer SB, Sandborn W. Management of Crohn's disease in adults. *Am J Gastroenterol*. 2001;96(3):635-43.

22. Hommes D, Baert F, Van Assche G. The ideal management of Crohn's disease: top down versus step up strategies, a randomized controlled trial. *Gastroenterology*. 2006;130:A108.

23. Hommes D, Baert F, Van Assche G, et al. Management of recent onset Crohn's disease: A controlled, randomized trial comparing step-up and top-down therapy. *Gastroenterology*. 2005(128(Suppl 2)):A577.

24. Iezzoni LI. *Risk adjustment for measuring health care outcomes*. 3rd ed. Chicago: Health Administration Press; 2003.

25. Iglehart JK. Biotech drugs come of age; policymakers take notice. *Health Aff (Millwood)*. 2006;25(5):1202-3.

26. Janke KH, Klump B, Gregor M, Meisner C, Haeuser W. Determinants of life satisfaction in inflammatory bowel disease. *Inflamm Bowel Dis*. 2005;11(3):272-86.

27. Jewell DP, Satsangi J, Lobo A, et al. Infliximab use in Crohn's disease: impact on health care resources in the UK. *Eur J Gastroenterol Hepatol*. 2005;17(10):1047-52.

28. Kasper DL, Harrison TR. *Harrison's principles of internal medicine*. 16th ed New York: McGraw-Hill, Medical Pub. Division; 2005.

29. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W. American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology*. 2006;130(3):935-9.

30. Lichtenstein GR, Yan S, Bala M, Blank M, Sands BE. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. *Gastroenterology*. 2005;128(4):862-9.

31. Lichtenstein GR, Yan S, Bala M, Hanauer S. Remission in patients with Crohn's disease is associated with improvement in employment and quality of life and a decrease in hospitalizations and surgeries. *Am J Gastroenterol*. 2004;99(1):91-6.

32. Long JS, Freese J. *Regression models for categorical dependent variables using Stata* College Station, Tex.: Stata Press; 2006.

33. Manning WG, Mullahy J. Estimating log models: to transform or not to transform? *J Health Econ*. 2001;20(4):461-94.

34. MarketScan® Research Databases, Ann Arbor, MI: Thomson Reuters Healthcare (Thomson Reuters, Inc.); 2004.

35. Park R. Estimation with heteroscedastic error terms. *Econometrica*. 1966;34(4):888.

36. Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. *Value Health*. 2007;10(1):3-12.

37. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med*. 1999;340(18):1398-405.

38. Robinson JC. Insurers' strategies for managing the use and cost of biopharmaceuticals. *Health Aff (Millwood)*. 2006;25(5):1205-17.

39. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies of causal effects. *Biometrics*. 1983;70(1):41-55.

40. Rubenstein JH, Chong RY, Cohen RD. Infliximab decreases resource use among patients with Crohn's disease. *J Clin Gastroenterol*. 2002;35(2):151-6.

41. Rutgeerts P, D'Haens G, Targan S, et al. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology*. 1999;117(4):761-9.

42. Rutgeerts P, Feagan BG, Lichtenstein GR, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology*. 2004;126(2):402-13.

43. Rutgeerts P, Van Assche G, Vermeire S. Optimizing anti-TNF treatment in inflammatory bowel disease. *Gastroenterology*. 2004;126(6):1593-610.

44. Rutgeerts P, Van Assche G, Vermeire S. Review article: Infliximab therapy for inflammatory bowel disease--seven years on. *Aliment Pharmacol Ther*. 2006;23(4):451-63.

45. Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med*. 2007;357(3):228-38.

46. Sandborn WJ, Hanauer SB, Rutgeerts PJ, et al. Adalimumab for Maintenance Treatment of Crohn's Disease: Results of the CLASSIC II Trial. *Gut*. 2007.

47. Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med*. 2007;146(12):829-38.

48. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med*. 2004;350(9):876-85.

49. Sands BE, Blank MA, Patel K, van Deventer SJ. Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II Study. *Clin Gastroenterol Hepatol*. 2004;2(10):912-20.

50. Schreiber S, Khaliq-Kareemi M, Lawrance IC, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med*. 2007;357(3):239-50.

51. Southern DA, Quan H, Ghali WA. Comparison of the Elixhauser and Charlson/Deyo methods of comorbidity measurement in administrative data. *Med Care*. 2004;42(4):355-360.

52. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol*. 1997;50(1):105-16.

53. Targan SR, Feagan BG, Fedorak RN, et al. Natalizumab for the treatment of active Crohn's disease: results of the ENCORE Trial. *Gastroenterology*. 2007;132(5):1672-83.

54. Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med*. 1997;337(15):1029-35.

55. Vuong QH. Likelihood ratio tests for model selection and non-nested hypotheses. *Econometrica*. 1989;57(307-333).

56. Consumer Price Indexes. U.S. Department of Labor, Bureau of Labor Statistics, Division of Consumer Prices and Price Indexes; 2007. Available at: http://www.bls.gov/cpi/home.htm (accessed March 5, 2007).

57. Zhao Z. Using matching to estimate treatment effects: data requirements, matching metrics, and monte carlo evidence. *The Review of Economics and Statistics*. 2004;86(1):91-107.

58. Zisman TL, Cohen RD. Pharmacoeconomics and quality of life of current and emerging biologic therapies for inflammatory bowel disease. *Curr Treat Options Gastroenterol*. 2007;10(3):185-94.

Appendix: Risk and Case-mix Adjustment Variables

Risk Adjustment and Case-Mix Variables

Nine risk adjustment and four case-mix variables were created and used in multivariate models to account for differences in underlying risk associated with underlying chronic diseases, and manifestations of Crohn's disease. The nine risk adjustment variables were: congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, peptic ulcer disease, end-stage liver disease, diabetes, renal disease, and cancer (see table of ICD-9-CM codes). The four case-mix variables were: gastrointestinal complications, extraintestinal manifestations, debilitating manifestations, and psychological manifestations.

Appendix Table A2-1. ICD-9-CM Codes for Risk Adjustment and Case-mix Variables:

ICD–9–CM Diagnosis Code	Disease
	RISK ADJUSTMENT VARIABLES
Congestive Heart Failure	
402	Hypertensive heart disease
428	Heart failure
Peripheral vascular disease	
440*	Atherosclerosis
441*, 442*	Aortic aneurysm and dissection, Other aneurysm
443*	Other peripheral vascular disease
785.4	Gangrene
V434	Blood Vessel Replacement NEC
Cerebrovascular disease	
430*, 431*, 432*	Subarachnoid hemorrhage, Intracerebral hemorrhage, Other and unspecified intracranial hemorrhage
433*, 434*	Occlusion and stenosis of precerebral arteries, Occlusion of cerebral arteries
435*	Transient cerebral ischemia
436*	Acute, but ill-defined, cerebrovascular disease
437*	Other and ill-defined cerebrovascular disease

ICD–9–CM Diagnosis Code	Disease
438*	Late effects of cerebrovascular disease
Chronic pulmonary disease	
491*, 492*, 493*	Chronic bronchitis, Emphysema, Asthma
494*, 495*	Bronchiectasis, and Extrinsic allergic alveolitis
496*	Chronic airway obstruction, NEC
500*, 501*	Coal workers' pneumoconiosis, and Asbestosis
502*, 503*	Pneumoconiosis due to other silica or silicates, or due to other inorganic dust
504*, 505*	Pneumonopathy due to inhalation of other dust, and Pneumoconiosis, unspecified
506	Respiratory conditions due to chemical fumes and vapors
506.4	Chronic respiratory conditions due to fumes and vapors
Peptic ulcer disease	
531*, 532*, 533*, 534*	Gastric ulcer, Duodenal ulcer, Peptic ulcer, site unspecified, and Gastrojejunal ulcer
Mild Liver Disease	
571.2	Alcoholic cirrhosis of liver
571.4 – 571.6	Chronic hepatitis, Cirrhosis of liver without mention of alcohol, Biliary cirrhosis
End-stage liver disease	
452*	Portal vein thrombosis
453.0*	Budd-Chiari syndrome
456.0*, 456.1*	Esophageal varices with, and without mention of bleeding
456.21	Esophageal varices in diseases classified elsewhere, without mention of bleeding
572.2, 572.3	Hepatic coma, and Portal hypertension

ICD–9–CM Diagnosis Code	Disease
572.4	Hepatorenal syndrome
572.5, 572.6, 572.7, 572.8	Other sequelae of chronic liver disease
Diabetes (with and without chronic complications)	
250*	Diabetes mellitus
250.1	Diabetes with ketoacidosis
250.2	Diabetes with hyperosmolarity
250.3	Diabetes with other coma
250.4	Diabetes with renal manifestations
250.5	Diabetes with ophthalmic manifestations
250.6	Diabetes with neurological manifestations
250.7	Diabetes with peripheral circulatory disorders
250.8	Diabetes with other specified manifestations
250.9	Diabetes with unspecified complication
Renal disease	
582	Chronic glomerulonephritis
583.1 – 583.7	Nephritis and nephropathy, not specified as acute or chronic
585*	Chronic kidney disease (CKD)
586*	Renal failure, unspecified
588*	Disorders resulting from impaired renal function
Rheumatoid disease	
710.0	Systemic lupus erythematosus
710.1	Systemic sclerosis
710.4	Polymyositis
714.0	Rheumatoid arthritis

ICD–9–CM Diagnosis Code	Disease
714.1	Felty's syndrome (Rheumatoid arthritis with splenoadenomegaly and leucopenia)
714.2	Other rheumatoid arthritis with visceral or systemic involvement
714.81	Rheumatoid lung
725*	Polymyalgia rheumatica
Cancer (Any Malignancy or Metastatic Solid Tumor)	
140*	Malignant neoplasm of lip
150*	Malignant neoplasm of esophagus
160*	Malignant neoplasm of nasal cavities, middle ear, and accessory sinuses
170*	Malignant neoplasm of bone and articular cartilage
171*	Malignant neoplasm of connective and other soft tissue
172*	Malignant melanoma of skin
174 – 195.8	Other malignant neoplasms
200*	Lymphosarcoma and reticulosarcoma
201*	Hodgkin's disease
202*	Other malignant neoplasms of lymphoid and histiocytic tissue
203*	Multiple myeloma and immunoproliferative neoplasms
204*, 205*	Lymphoid leukemia, Myeloid leukemia
206*, 207*, 208*	Monocytic leukemia, Other specified leukemia, Leukemia of unspecified cell type
196*	Secondary and unspecified malignant neoplasm of lymph nodes
197 – 197.8, 197.9*	Secondary malignant neoplasm of respiratory and digestive systems
198 – 198.1, 198.3 – 198.9	Secondary malignant neoplasm of other specified sites
199.0	Malignant neoplasm without specification of site

ICD–9–CM Diagnosis Code	Disease
Myocardial Infarction	
410*	Acute myocardial infarction
412*	Old myocardial infarction
Dementia	
290.0	Dementias
331.0	Other cerebral degenerations
Hemiplegia / Paraplegia	
342*	Hemiplegia and hemiparesis
344 – 344.9	Other paralytic syndromes, Paraplegia, Diplegia of upper limbs, Monoplegia of lower and/or upper limb, Unspecified monoplegia, Cauda equina syndrome, Other specified paralytic syndromes, Paralysis, unspecified
AIDS	
042 - 044	Human immunodeficiency virus [HIV] disease
ICD–9–CM Diagnosis Code	Disease
CASE MIX ADJUSTMENT VARIABLES	
Gastrointestinal Complications	
537.3	Duodenal obstruction NEC
560.89	Intestinal obstruct NEC
560.9	Intestinal obstruct NOS
565*	Anal fissure & fistula*
566	Anal & rectal abscess
567.2	Suppurative peritonitis NEC
567.8	Peritonitis NEC
567.9	Peritonitis NOS
569.3	Rectal & anal hemorrhage
569.41	Rectal & anal ulcer

ICD–9–CM Diagnosis Code	Disease
569.5	Intestinal abscess
569.81	Fistula of intestine, excluding rectum and anus
569.82	Ulceration of intestine
569.83	Perforation of intestine
578.1	Blood in stool
578.9	Gastrointestinal hemorrhage NOS
579	Intestinal malabsorption
579.3	Intestinal postoperative nonabsorption
579.8	Intestinal malabsorption NEC
579.9	Intestinal malabsorption NOS
593.82	Ureteral fistula
596.1	Intestinovesical fistula
599.1	Ureteral fistula
616.4	Abscess of vulva NEC
619.1	Digest-genital tract fistula, female
682	Other cellulitis/abscess
Extraintestinal Manifestations	
260	Kwashiorkor
261	Nutritional marasmus
262	Other severe malnutrition
263*	Malnutrition
264*	Vitamin A deficiency*
265*	Thiamine/niacin deficiency*
266	B-complex deficiencies*

ICD–9–CM Diagnosis Code	Disease
267	Ascorbic acid deficiency
268*	Vitamin D deficiency*
268	Rickets, active
269	Deficiency of Vitamin K
280*	Iron deficiency anemias*
281*	Other deficiency anemia*
285*	Anemia NEC/NOS*
360.12	Panuveitis
364*	Iris/ciliary body disorders*
379*	Scleritis/episcleritis*
686.01	Pyoderma gangrenosum
707.8, 707.9	Chronic skin ulcer NEC
714*	Rheumatoid arthritis*
716.4*	Transient arthropathy*
716.5*	Polyarthritis NOS*
718.5*	Ankylosis of joint*
719*	Effusion of joint*
720*	Inflammatory spondylopathies*
721	Spondylosis and allied disorders
724*	Spinal stenosis NEC*
725	Polymyalgia rheumatica
727*	Synovitis/tenosynovitis*
728	Disorders of muscle/ligament/fascia

ICD–9–CM Diagnosis Code	Disease
729	Rheumatism NOS
731.2	Hypertrophic osteoarthropathy
781.5	Clubbing of fingers
695.2	Erythema nodosum
Debilitating Manifestations	
038*	Septicemia*
785.5*	Shock without trauma*
995.92, 996.64 and 999.3	Systemic inflammatory response syndrome
Psychological Manifestations	
293	Transient mental disorders due to conditions classified elsewhere
300*	Anxiety states*
309*	Adjustment reaction*

Appendix Table A2-2. Drug Codes for Treatment of Crohn's

Drug Name	NDC or J-Code Drug Code		
Antibiotic Drug Codes			
amoxicillin/clavulanate	00029607112	54569012100	55175122305
	00029607212	54569012101	55175122307
	00029607347	54569012103	55175174500
	00029607447	54569013601	55175185000
	00029607527	54569013603	55175602001
	00029607531	54569013700	55289024015
	00029608012	54569014201	55289024215
	00029608027	54569029800	55289024221
	00029608031	54569029801	55289029615
	00029608522	54569101900	58016010610
	00029608523	54569195900	58016010612
	00029608539	54569195901	58016010614
	00029608612	54569195903	58016010615
	00029608621	54569195905	58016010620
	00029608729	54569195906	58016010630
	00029608739	54569196200	58016010700
	00029608751	54569196201	58016010708
	00029609022	54569196202	58016010710
	00029609023	54569196203	58016010712
	00029609039	54569432500	58016010714
	00029609229	54569433700	58016010715
	00029609239	54569433800	58016010720
	00029609251	54569435200	58016010730
	00403035730	54569435300	58016013420
	00403035918	54569445800	58016013430
	00403036118	54868019902	58016100805
	00403036318	54868019903	58016100975
	00403036518	54868020001	58016101105
	00403036718	54868038700	58016101201
	00403036921	54868038701	58016178010
	00403036930	54868038702	58016178014
	00403518318	54868038703	58016178015
	52959002115	54868038800	58016178020
	52959002120	54868038801	58016178030
	52959002121	54868038802	58016183712
	52959002130	54868038804	58016183715
	52959002230	54868038805	58016183730
	52959034309	55175121900	60346007403
	52959034315	55175121901	60346007409
	52959034321	55175121905	60346007415
	52959034330	55175122000	60346007421
	52959047030	55175122001	60346008244
	52959047810	55175122002	60346036403
	52959101200	55175122005	60346036409
	52959101201	55175122105	60346036415
	52959143100	55175122107	60346036421
	54569011700	55175122201	60346036444
	54569012000	55175122202	60346059021
ciprofloxacin	00026851106	54569172303	58016011615
	00026851248	54569172304	58016011620
	00026851251	54569172305	58016011630

Drug Name	NDC or J-Code Drug Code		
	00026851348	54569172306	58016011640
	00026851351	54868093900	58016011700
	00026851448	54868093901	58016011704
	00026851450	54868093902	58016011708
	00026852736	54868093903	58016011710
	00026852763	54868093905	58016011712
	00026855136	54868093906	58016011714
	00026855236	54868099000	58016011715
	00026855336	54868099001	58016011720
	00026855463	54868099002	58016011730
	00026856220	54868118401	58016011750
	00026856464	54868118402	58016011800
	00026856665	54868118403	58016011810
	00403060102	55175189501	58016011812
	00403060110	55175189502	58016011814
	00403060114	55175189504	58016011815
	00403060130	55175189506	58016011820
	00403302720	55175189600	58016011830
	00403351114	55175189601	58016011850
	00403351120	55175189602	60346003106
	52959003606	55175189604	60346003110
	52959003610	55175189606	60346003114
	52959003614	55175189702	60346003120
	52959003615	55289037106	60346003125
	52959003620	55289037110	60346003130
	52959003714	55289037114	60346003144
	52959003720	55289037179	60346003199
	54569164800	55289045906	60346043306
	54569164803	55289045910	60346043310
	54569164804	55289045912	60346043314
	54569164805	55289045914	60346043315
	54569164807	58016011600	60346043320
	54569172300	58016011610	60346043344
	54569172301	58016011612	60346043399
	54569172302	58016011614	
metronidazole	00025182131	00536403201	49884009510
	00025182134	00536403202	49884011401
	00025182150	00536403205	49884011403
	00025182151	00536403301	49884011404
	00025183131	00536403332	49884011405
	00025183134	00603464021	50111033301
	00025183141	00603464024	50111033302
	00025183150	00603464028	50111033306
	00025183155	00603464121	50111033401
	00025194234	00603464128	50111033402
	00025194250	00615157601	51079012219
	00025196130	00615157605	51079012220
	00062157001	00615157613	51079012619
	00062157101	00615157615	51079012620
	00074121711	00615157622	52555009501
	00074781124	00615157628	52555009502
	00074781137	00615157713	52555009505
	00093085101	00641233741	52555011401
	00093085105	00641233761	53489013501

Drug Name	NDC or J-Code Drug Code		
	00093085152	00677069001	53489013503
	00093085205	00677069003	53489013601
	00093085253	00677081601	55829036410
	00172297160	00686012220	55829036510
	00172297165	00686012620	56126009511
	00172297170	00781174201	57480043201
	00172297180	00781174205	57480043301
	00172300748	00781174213	58016012900
	00172300760	00781174225	58016012905
	00182133001	00781174701	58016012908
	00182133002	00781174713	58016012909
	00182133005	00814481014	58016012910
	00182133089	00814481022	58016012912
	00182151701	00814481514	58016012914
	00182151789	00814481522	58016012920
	00185055101	00839641506	58016012921
	00185055105	00839641509	58016012925
	00185055152	00839662004	58016012928
	00185055501	00839662006	58016012930
	00228225810	00839662012	58016072500
	00264553532	00904145340	58016072504
	00338105548	00904145360	58016072507
	00349236301	00904145361	58016072508
	00349236305	00904145370	58016072509
	00349236325	00904269460	58016072510
	00349238301	00904269461	58016072512
	00349238305	00905180410	58016072514
	00364059501	00905184724	58016072515
	00364059504	17236030301	58016072518
	00364059590	17236030328	58016072520
	00364068750	17236030404	58016072521
	00364068790	17236030414	58016072524
	00405467701	49884009501	58016072528
	00405467704	49884009504	58016072530
	00405467801	49884009505	60429012914
Corticosteroid Drug Codes			
hydrocortisone	00006061968	00223788005	00904267460
	00006062568	00223789302	00904780631
	00006751903	00223789402	10956067301
	00006763304	00223789908	23317051124
	00006763310	00245011112	38245016812
	00009001201	00245011224	38245016837
	00009003101	00254840006	42037013212
	00009004401	00254840015	42037013250
	00009014201	00364242312	45802028703
	00009082501	00364242324	45802072530
	00009090013	00364662454	45802072531
	00009090015	00402005110	51079065571
	00009090020	00403029818	51301056712
	00009090908	00463103710	52735076281
	00009090909	00472051112	53265076112
	00009090916	00472051124	58016202301
	00009091205	00496085904	58016300401
	00009092003	00501420307	58298015012

Drug Name	NDC or J-Code Drug Code		
	00026500512	00536120070	58298015024
	00032190473	00536140601	58298015050
	00032190482	00536140612	58634002401
	00071172607	00536391301	58634002501
	00071172613	00573283010	58634002801
	00071313113	00574202001	58634003601
	00074567102	00574202007	58634003602
	00074567202	00574709012	59741030112
	00074567304	00603812711	59741030124
	00074567408	00603812718	59741030149
	00083570096	00677007601	59741030150
	00091069520	00677027821	60258050112
	00093916871	00677137712	61570002512
	00115368501	00686050312	61570002525
	00115368502	00713025747	61570002801
	00115368503	00713050301	61570007001
	00143125401	00713050312	61570017261
	00143125425	00713050324	61570017262
	00144065413	00781770032	61570030361
	00144065424	00781770040	61570030362
	00182703811	00814373514	61570031311
	00182703816	00839136506	62174009182
	00223106301	00839517630	63304040501
	00223106302	00839760312	63304040701
	00223555501	00904016012	63304040812
	00223555512	00904016060	65144031000
	J1700	J1710	J1720
methylprednisolone	00009002201	00182106862	00603459315
	00009004902	00182313162	00603459321
	00009005602	00182313262	00615253501
	00009005603	00223816001	00615253510
	00009005604	00223816102	00615253521
	00009005605	00223816203	00641250641
	00009007301	00223816510	00677049220
	00009007302	00223816605	00677056501
	00009011312	00223816705	00677056513
	00009011313	00259038805	00677063120
	00009011319	00314084075	00677153820
	00009015501	00314084175	00677153920
	00009017601	00314084270	00781140201
	00009019009	00349827901	00781140207
	00009019010	00349827921	00781305075
	00009019016	00364046701	00781306075
	00009027401	00364046721	00814478038
	00009028002	00364306446	00814478040
	00009028003	00364306451	00814478114
	00009028032	00364306453	00814478121
	00009028033	00364306454	00814478238
	00009028051	00364306546	00839620025
	00009028052	00364306551	00839620125
	00009030602	00364306553	00839622406
	00009030610	00364674854	00839622458
	00009030612	00402106810	00839794625
	00009069801	00402106905	00839794630

Drug Name	NDC or J-Code Drug Code		
	00009075801	00402106910	00839794725
	00009076502	00402107005	00904089705
	00009079601	00405466601	00904217519
	00009088701	00405466621	00904217560
	00009307301	00418640105	11845012019
	00009307302	00418650105	44437019705
	00009307303	00456484005	51285030102
	00009338901	00456488005	51285030121
	00009347501	00463110505	52349010705
	00009347502	00536403601	52544079001
	00009347503	00536403644	52544079021
	00074560144	00536534065	52584019605
	00074560344	00536534070	52584019705
	00074563004	00536535165	56126032611
	00074563108	00536537070	58016200401
	00074568401	00536538065	59762332701
	00074568502	00536538565	59762332702
	00182105001	00588536175	62269035121
	00182105003	00588536475	62269035124
	00182106762		
	J1020	J1030	J1040
	J2920	J2930	J7509
prednisolone	00006757201	00403240784	17022263807
	00006757203	00403240788	17022265903
	00006757702	00405482301	17022265907
	00006757703	00451150008	25332003110
	00093611816	00451150016	25332006205
	00093611887	00451220104	25332012103
	00115428001	00456092410	43797002712
	00115428003	00463101930	52349010810
	00182093966	00463102010	52544052016
	00217840408	00536434610	52544052038
	00217841008	00536640070	52637032510
	00223151201	00536640075	53014025001
	00223151202	00536640570	54569216100
	00223534610	00536640575	54569401200
	00223834510	00588535270	54569401201
	00223834530	00677011601	54569401202
	00223834630	00677011610	54569480700
	00259031010	00677029423	55175184203
	00314069530	00684011510	55175184206
	00314069570	00781154001	55289095202
	00314069670	00814625014	55289095204
	00314069770	00814625030	55553024910
	00364021701	00814625546	58016067300
	00364021702	00814626046	58016067312
	00364662656	00839507606	58016067324
	00364662754	00839507616	58016067348
	00364662756	00839512036	58016414401
	00378342524	00839561736	58441112505
	00378342548	00879080108	59196001024
	00402007330	00879080116	59196001048
	00402024910	00904215560	59439045502

Drug Name	NDC or J-Code Drug Code		
	00402024930	00904215580	
	J1690	J2640 J7510	J2650
prednisone	00009003201	00364021801	51079002219
	00009004501	00364021802	51079002220
	00009004502	00364021890	51079003219
	00009004504	00364044201	51079003220
	00009004505	00364044202	51079003319
	00009004516	00364044205	51079003320
	00009016501	00364044290	52544079701
	00009016502	00364046101	52544083010
	00009016503	00364046102	52544083101
	00009019301	00364046105	52544083110
	00009019302	00364046190	52544083201
	00009019303	00403196518	52544083205
	00009038801	00403196718	53489013801
	00032280801	00405482801	53489013810
	00032280810	00405482803	53489013850
	00032281001	00405482901	53489013901
	00032281010	00405482902	53489013905
	00032281201	00405482903	53489013910
	00032281210	00405483001	53489014001
	00032281401	00405483002	53489014005
	00032281410	00451120104	53489014010
	00032281601	00451120108	54569033107
	00054372144	00536432410	54569330202
	00054372250	00536432450	54569379800
	00054372263	00536432501	54569384700
	00054472825	00536432510	54868323400
	00054472831	00536432601	55175276601
	00054472925	00536432605	55175276608
	00054472929	00536432610	55829042210
	00054473025	00536432801	55829042310
	00054473029	00603533215	55829042410
	00054473325	00603533221	57480035101
	00054474125	00603533231	57480035201
	00054474131	00603533232	57480047201
	00054474225	00603533315	58016021600
	00054872216	00603533321	58016021612
	00054872425	00603533331	58016021614
	00054872525	00603533332	58016021615
	00054872625	00603533421	58016021620
	00054872925	00603533432	58016021621
	00054873925	00615053613	58016021624
	00054874025	00677011701	58016021628
	00085084303	00677011710	58016021630
	00115429401	00677042701	58016021632
	00115429403	00677042705	58016021640
	00131222881	00677042710	58016021650
	00143147301	00677069801	58016021660
	00143147310	00677069805	58016021700
	00143147325	00677069810	58016021710
	00143147501	00686002220	58016021715

Drug Name	NDC or J-Code Drug Code		
	00143147510	00686003220	58016021716
	00143147525	00781145001	58016021718
	00143147701	00781145013	58016021720
	00143147705	00781148501	58016021721
	00143147710	00781149501	58016021722
	00143147725	00781149510	58016021724
	00143148125	00781149513	58016021728
	00182020110	00781150001	58016021730
	00182020189	00781150010	58016021740
	00182108601	00814628514	58016021760
	00182108610	00814628530	58016021800
	00182108689	00814628814	58016021820
	00182133401	00814628828	58016021821
	00182133410	00814629014	58016021824
	00182133489	00814629028	58016021830
	00223151501	00839151706	58016021833
	00223151502	00839151712	58016021836
	00223151601	00839152006	58016021840
	00228233696	00839152012	58016021850
	00228233710	00839152016	58016021855
	00228233750	00839514306	58016021860
	00228233810	00839514316	58016032020
	00228233850	00839514358	60904028620
	00254509413	00904052760	61392040830
	00254509423	00904214060	61392040831
	00259036421	00904214061	61392040832
	00259038948	00904214080	61392040839
	00259039021	00904214160	61392040851
	00259039148	00904214161	61392040854
	00259040049	00904214180	61392040860
	00302550001	00904215719	61392040890
	00339529312	00904215746	61392041730
	00339529512	00904215752	61392041731
	00339529612	00904215760	61392041732
	00339577512	00904215761	61392041739
	00339577712	00904215780	61392041751
	00349893310	11845017804	61392041754
	00349893401	11845017904	61392041760
	00349893405	11845018001	61392041790
	00349893501	11845018004	
		J6506	
		J7506	
Immune Modulator Drug Codes			
azathioprine	00054408425		00378100501
	00054808425		00781105901
	00081059756		55390060020
	00173059755		60976059755
	00173059871		60976059871
	J7500		J7501
cyclosporine	00074646332	00078024215	50111090943
	00074647932	00078024615	50111092043
	00078010901	00078024815	54569256300
	00078011022	00078027422	54569287200

Drug Name	NDC or J-Code Drug Code		
	00078024015	00185093230	55390012210
	00078024115	00185093330	62053053905
		J7502	
		J7503	
mercaptopurine		00173080725	
		00173080765	
methotrexate	00005450704	00405464336	55390003310
	00005450705	00536399801	55390003410
	00005450707	00536399836	58406067103
	00005450709	00555057202	58406067105
	00005450723	00555057235	58406067301
	00005450791	00555057245	58406068114
	00013226691	00555057246	58406068117
	00013227691	00555057247	58406068312
	00013228691	00555057248	58406068315
	00013229691	00555057249	58406068316
	00054455015	00603449921	58406068318
	00054455025	00677161001	59911587401
	00054855003	00781107601	61703040707
	00054855005	00781107636	61703040732
	00054855006	00839790506	61703040804
	00054855007	00904174960	61703040807
	00054855010	00904174973	61703040813
	00054855025	51079067005	61703040832
	00182153901	51079067086	63323012102
	00182153995	51079067087	63323012104
	00205533798	51079067088	63323012108
	00364249901	51079067089	63323012110
	00364249936	55390003110	63323012302
	00378001401	55390003210	63323012310
	00405464301		
	J8610	J9250	J9260
mycophenolate	00004025901		00004026043
	00004025943		00004026129
	00004026001		00004029809
		J7517	
Mesalamine Codes			
Mesalamine (5-ASA)	00032192482	00088201080	00574725003
	00032192824	00088201090	54092018980
	00032192846	00149075202	54092018981
	00088201046		