# Dipeptidyl Peptidase-4 Inhibitors and Risk of Inflammatory Bowel Disease among Patients with Type 2 Diabetes Mellitus

MarketScan Commercial Claims and Encounters Database, 2007-2015

Medicare Fee-for-Service Claims Database, 20% Random Sample, 2007-2015

Study Protocol, Oct 22, 2018

Notes:

- We have started analyzing data at the time of protocol submission.

## 1. Background

Dipeptidyl peptidase-4 inhibitors (DPP4i), a class of second-line glucose lowering drugs, have been shown to reduce haemoglobin A1c (HbA1c) by 0.5-1.0%, with few adverse side effects and neutral weight loss, by means of decreasing the degradation of the glucagon-like peptide (GLP)-1 and prolonging the insulinotropic effect (1,2). However, DPP4i have recently been linked to an increased risk of inflammatory bowel disease (IBD), a family of immunologically mediated disorders consisting of two main idiopathic pathologies – Crohn's disease (CD) and ulcerative colitis (UC) – that cause chronic inflammation of the gastrointestinal tract (3). A recent cohort study performed in the British Clinical Practice Research Datalink (CPRD) demonstrated that the use of DPP4i was associated with an increased risk of IBD (hazard ratio 1.75, 95% CI 1.22 to 2.49) during a median follow-up of 3.6 years (4).

DPP-4, also known as the cell surface antigen CD26, have a costimulatory function in the immune response (5). However, the underlying mechanism of the effect of DPP-4 on immune diseases such as IBD is still unclear. Current evidence suggests that DPP-4 exert complex and potentially conflicting biological effects on the development of IBD (6). On one hand, studies in mice have shown that DPP4i have a proliferative effect on the colonic epithelium and a minimal effect in the amelioration of colitis to decrease both disease activity and disease severity, indicating potential clinical application of this novel drug class for IBD (7,8). On the other hand, studies have indicated that lower concentrations of DPP-4 have been detected in tissue and plasma from patients with IBD than healthy controls, suggesting that lower DPP-4 concentrations may be inversely associated with increased IBD activity (9-11).

Epidemiological studies can provide real-world evidence on drug safety and assist clinicians and policymakers to make informed decisions that will improve health care at both the

individual and population levels (12,13). Various study designs have been developed to assess drug safety and effectiveness, including the prevalent user design (14), the new user design (14), and the prevalent new user design (15). Among them, the active comparator, new user (ACNU) design is the most influential methodological study design. The new-user design helps to avoid many time-related biases introduced when including prevalent drug users in cohort studies (16) (Appendix 1). The magnitude of the risks and benefits of drugs often vary over time after the start of treatment, which introduces bias in prevalent user designs. Another difficulty in the analysis of prevalent user designs stems from the fact that disease risk factors can be affected by the treatment itself. In a new user design, this difficulty is addressed by measuring potential confounders at baseline, prior to treatment initiation. Using an active comparator will help to mitigate bias by restricting the study to patients with an indication for treatment and without contraindications such as frailty (16). Although the benefits of the new user design are attractive and well understood, such designs are often not employed because of the logistical complexities of identifying new users and because of the loss of sample size and statistical power that result from excluding prevalent users. However, the Center for Pharmacoepidemiology at the University of North Carolina at Chapel Hill is a recognized academic leader in the development and implementation of pharmacoepidemiology methods and has extensive institutional experience with implementing the ACNU design in large administrative databases.

To our knowledge, there has been little research assessing the risk of IBD among patients with Type 2 diabetes mellitus (T2D) treated with DPP4i, using large, real-world patient populations. Therefore, we aim to conduct a cohort study, using an ACNU design, to assess whether new use of DPP4i is associated with an increased risk of IBD compared to new use of other therapeutic alternatives, in two large, US-based administrative claims databases.

## 2. Objectives

**Aim**: To evaluate the association between the initiation of DPP4i versus the initiation of clinically relevant second-line glucose lowering therapies (thiazolidinediones and sulfonylureas) and the short-term risk of IBD, based on an ACNU study design.

## 3. Study design

We will implement an ACNU design [16]. The new user component aims to eliminate time-related biases by restricting the analysis to patients under observation at the start of the treatment. The active comparator component will help to balance the baseline risk of IBD between comparison groups, and provides indirect control for diabetes severity. Therefore, such a design can be used to examine the IBD risk associated with DPP4i use, rather than the underlying diabetes.

## 4. Data Sources

- Truven Analytics IBM® Watson Health MarketScan® Commercial Claims and Encounters Database, 2007-2015
- Medicare Fee-for-Service (FFS) Database (Parts A, B, and D), 20% random sample, 2007-2015

## 5. Study Population/Inclusion and exclusion criteria

1. MarketScan enrollees 18-64 years of age, or Medicare FFS enrollees $\geqslant$65 years of age.

2. The base population for the analysis will consist of all beneficiaries with $\geqslant$1 prescription dispensing claim for a DPP4i or an active comparator drug between January 01, 2007 and

September 30, 2015. We will first conduct the study through Sept 30, 2015 and consider adding 2016 data (and ICD-10 conversion) based on timing of availability of data.

*We will exclude the following patients:*

1. To ensure new use of either DPP4i or an active comparator drug, we will exclude all individuals who do not have at least **12 months** of continuous enrollment (inpatient, outpatient, and prescription coverage) in the appropriate insurance database prior to the first prescription dispensing claim (12-month baseline period), during which no use of any of the study drugs is detected.
2. Patients with the following conditions in the 12-month baseline period will be excluded, to remove patients from the study cohort who may have pre-existing IBD:
    1) previous diagnosis of IBD (CD, UC)**;**
    2) history of diverticulitis, ischemic colitis, pseudomembranous colitis, unspecific colitis;
    3) prior exposure to IBD treatments [17,18], including 5-aminosalicylic acid (5-ASA), anti-tumor necrosis factor (anti-TNF), enteral budesonide (we did not exclude patients who used other corticosteroids due to their wide indications for use), and immunosuppressive or immunoregulatory agents (azathioprine, mercaptopurine, methotrexate, and intravenous cyclosporine);
    4) previous colectomy, ileostomy, ostomy supplies;
    5) prior colonoscopy or sigmoidoscopy before age 50 (MarketScan only). This exclusion was implemented to exclude patients who were more likely to be receiving early colonoscopy for possible IBD related diseases, since the 2016 US Preventive Services

Task Force guidelines recommend colonoscopy for colorectal cancer only for individuals aged 50-75 [19];

6) (*DPP4i vs. TZD comparison only*) patients with a diagnosis of congestive heart failure (CHF) in the 12 months prior to the first eligible prescription, as initiation of TZDs is contraindicated in patients with CHF [16].

## 6. Exposure and comparisons

Exposure will be defined by at least **two** same-drug class prescription dispensing claims of either a DPP4i or an active comparator drug between January 1, 2007 and Mar 31, 2015 identified using National Drug Codes (NDCs). The second prescription will serve as the index date for the analysis. Patients will be required to fill a second prescription of the same drug within (days' supply + 90 days) of index date. This is to increase the probability that the new users are actually started on the therapy.

**Table 1**. DPP4i and active comparator drugs.

| Comparisons | Index Drug: generic (ATC* code) | Comparator Drug |
|---|---|---|
| I | DPP-4i: Sitagliptin (A10BH01) ), Saxagliptin (A10BH03), Linagliptin (A10BH05), Alogliptin (A10BH04) | Sulfonylureas (glyburide, glipizide, glimepiride). |
| II | DPP-4i: Sitagliptin (A10BH01) ), Saxagliptin (A10BH03), Linagliptin (A10BH05), Alogliptin (A10BH04) | Thiazolidinediones (pioglitazone, rosiglitazone) |

ATC, Anatomical Therapeutic Chemical.

## 7. Outcome

The primary outcome of interest is incident IBD. We are aiming for an algorithm with high specificity so as to minimize the potential for bias of ratio measures [20]. The IBD outcome will

be defined by the first IBD diagnosis (*International Classification of Disease, 9th edition, Clinical Modification* (ICD-9-CM) codes 555.x and 556.x) (17,18) during follow-up which is preceded by a colonoscopy/sigmoidoscopy and biopsy within 30 days **before** diagnosis, and followed by a prescription claim for IBD medication treatment within 30 days **after** diagnosis (Figure 1). The date of IBD diagnosis will be considered as the event date. To quantify the potential for time-related biases that may result from using the IBD diagnosis date as the event date, we will perform an ancillary analysis using the date of IBD treatment as the event date (also described in sensitivity analysis below). We will identify colonoscopy, sigmoidoscopy, and biopsy using ICD-9-CM and Current Procedural Terminology (CPT) codes (Supplementary Table 1) and IBD treatment using NDCs and Healthcare Common Procedure Coding System (HCPCS) codes for drug infusion (Supplementary Table 2). Secondary outcomes include incident CD and UC, respectively, which will be identified by the first diagnosis for CD or UC, respectively, with a colonoscopy/sigmoidoscopy and biopsy within 30 days **before** diagnosis and an IBD treatment within 30 days **after** diagnosis.

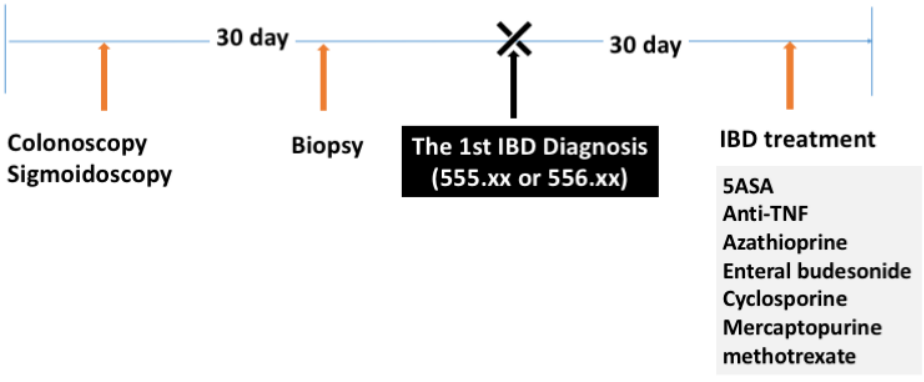


Figure 1. Outcome algorithm. For primary analysis, the date of IBD diagnosis will be considered as the event date. We will perform a sensitivity analysis using the date of IBD treatment as the event date, to account for possible time-related biases in the primary analysis definition.

**8. Follow-up**

Patients will be followed after the second prescription (cohort entry date) until treatment status change in the form of either index drug class discontinuation, or switching to or addition of a drug from the comparator drug class (Figure 2). Treatment discontinuation will be defined as no refill within a period equal to the prescribed days' supply of the last filled prescription plus a 90-day grace period; patients not refilling a prescription of the same drug class will be censored at the end of the 90-day grace period. Treatment switch or augmentation will be defined by a prescription claim for a comparator drug within a period equal to the prescribed days' supply of the last filled prescription plus a 90-day grace period; censoring will occur on the date of the comparator drug fill.

Because we assume that the clinical diagnosis of IBD is not made immediately after symptom onset (24), we will start follow-up for the outcome 180 days after the second prescription (latency period) and exclude patients with the outcome within 180 days after their second prescription. Similarly, follow-up for IBD events will continue 180 days (the "carry-over" period) after treatment changes or discontinuation.

In the primary as-treated analysis (Supplementary Figure 1), follow-up will start 180 days (induction period) after the cohort entry date (the second eligible prescription) and end at the earliest of the following events: 1) 180 days after treatment discontinuation (the days' supply of the last filled prescription plus a 90-day grace period), 180 days after treatment switching or augmenting (adding DPP4i to the comparator drug class or vice versa); 2) the end of an individual's insurance enrollment period in the MarketScan database, or the end of enrollment for Medicare parts A, B or D for Medicare beneficiaries; 3) death (for Medicare beneficiaries only); 4) administrative study end (September 30, 2015); or 5) observation of an incident IBD event, per

the definition above. We will use the first incident IBD event date during follow-up to define the outcome date.

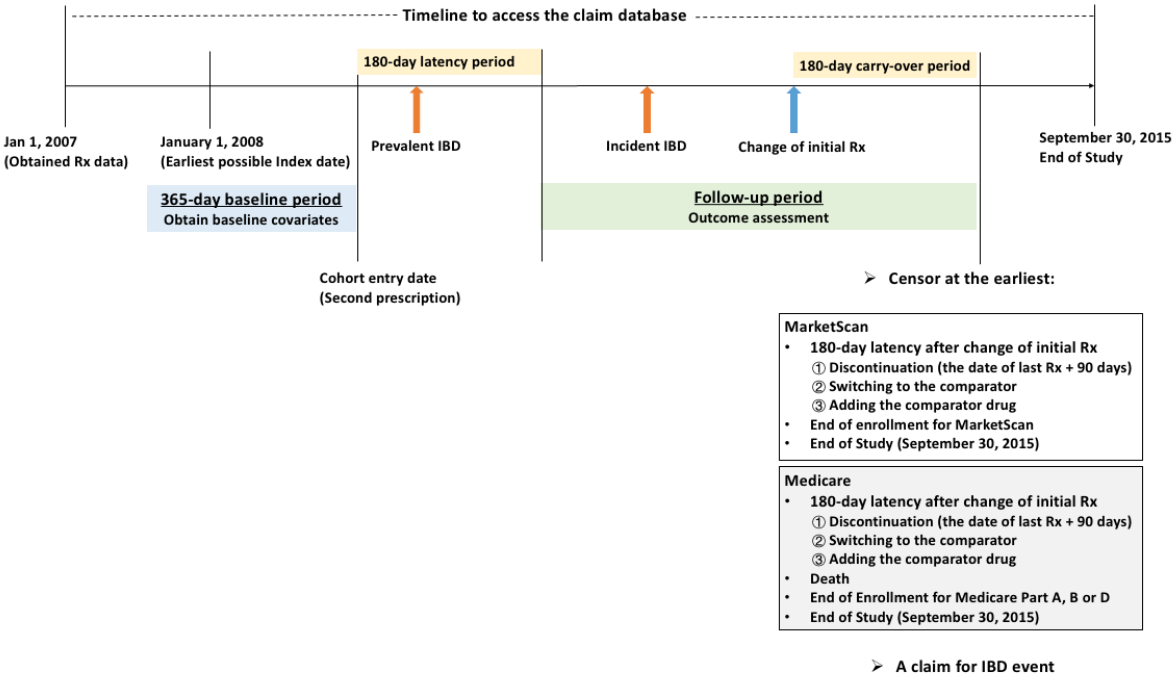


**Figure 2. Overview of study design and new user cohort for as treated analysis.** Rx, prescription. We assume that the clinical diagnosis of IBD is not made immediately after symptom onset, we will start follow-up for the outcome 180 days after the second prescription (latency period) and exclude patients with the outcome within 180 days after their second prescription. We allow patients with discontinuation, switching, or addition of a drug from comparator within 180 days after their second prescription to contribute to the person-time. Similarly, follow-up for IBD events will continue 180 days (the "carry-over" period) after treatment changes.

## 9. Covariates

Baseline covariates will be measured in the **12 months** prior to index date. We have the following types of covariates (3, 17, 25):

1) Demographics: age, gender, race (for Medicare beneficiaries only), calendar year, low income subsidy (for Medicare beneficiaries only);
2) Diabetes comorbidities: retinopathy, nephropathy, neuropathy;
3) Pre-existing autoimmune comorbidities: psoriasis, systemic vasculitis, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, celiac disease;
4) Gastroenterological diseases: diseases of esophagus, stomach, and duodenum, appendicitis, hernia of abdominal cavity, noninfective enteritis and colitis, other disease of intestines and peritoneum, other diseases of digestive system;
5) Cardiovascular comorbidities: hypertension, dyslipidemia, coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure;
6) Other health comorbidity: chronic obstructive pulmonary disease, depression, cancer, chronic kidney disease;
7) Diabetic medication use: metformin, SU, TZD, DPP4i, Glucagon-like peptide-1 receptor agonist, long acting insulin, alpha glucosidase inhibitor, meglitinide;
8) Other medication use: angiotensin-converting-enzyme inhibitor, angiotensin receptor blockers, beta-blockers, calcium channel blockers, statins, loop diuretics, other diuretics;
9) Use of medications that may induce IBD (Supplementary table 3);
10) Measures of healthcare utilization: hyperglycemia diagnosis, hospitalization due to diabetes, emergency department visit due to diabetes, physician encounters, gastroenterologist encounters, emergency department visit, flu shot, smoking, and

appendectomy.

**10. Statistical analysis**

The active comparator, new user study design tends to synchronize patients with respect to diabetes severity and duration. We will assess this balance by looking at the crude distribution of claims data based covariates across treatment cohorts. We will then use propensity scores to remove remaining imbalances in measured potential confounders between study cohorts. Our primary aim is to identify active comparator drug initiators that will allow us to estimate what would have happened to the actual DPP4i initiators if they had, contrary to the fact, not initiated DPP4i. To achieve this goal, we will estimate the average treatment effect in the treated (ATT) by reweighting the comparator drug initiators by the propensity score odds (PS/(1-PS)), i.e. standardized mortality/morbidity ratio (SMR) weights (20). We will estimate and compare the cumulative incidence of both primary and secondary outcomes for each study cohort using weighted Kaplan-Meier methods. Crude and adjusted hazard ratios (HRs) for both primary and secondary outcomes will be estimated using weighted Cox proportional hazards models, controlling for age, sex, as well as any potential confounders that remain unbalanced after propensity score implementation.

If the estimates in MarketScan and Medicare are compatible, we will perform a meta-analysis using random-effects models with inverse variance weighting and the DerSimonian and Laird method (21) to pool both estimates from MarketScan and Medicare data; fixed effects model will be used for sensitivity analysis. The between-database heterogeneity will assess using $I^2$ statistics (22), which represent the proportion of the total variance in the meta-analysis that is attributed to between-database heterogeneity. We considered $I^2$ >75% as high heterogeneity thus

will not report pooled HR and only report HR from the two databases separately as estimates are not compatible.

We will stratify analysis by age at cohort entry (<50 and ≥50 years in MarketScan and <75 and ≥75 in Medicare) and sex. To assess whether the risk varies with duration of use, we will estimate separate HRs for the first 12 months, and after 12 months of follow-up. Additionally, we will evaluate whether the risk of IBD varies across patients with and without pre-existing autoimmune disease and gastroenterological disease at cohort entry, since patients with pre-existing conditions tend to have more frequent encounters with the healthcare system and may have higher chance for IBD detection and diagnosis. Finally, we will estimate IBD risk for each individual DPP4i agent (Sitagliptin, Saxagliptin, linagliptin, alogliptin).

## 11. Sensitivity analyses

To examine the robustness of our primary results to changes in study population and condition definitions, we plan to perform the following sensitivity analyses based on our primary analysis (as treated, follow-up starts from second prescription, 180-day latency period) unless stated otherwise:

1) We will repeat the analyses changing latency and carry-over periods from 180 days to 0 days, 90 days, and 365 days. We will similarly assess our secondary outcomes, CD and UC, respectively, using different latency and carry-over periods (0 day, 90 days and 365 days).
2) We will perform an analysis based on initial treatment (IT) (Supplementary Figure 2), ignoring censoring for treatment changes during follow-up. This approach mimics the intention-to-treat analysis in a randomized trial. In this IT analysis, follow-up starts 180 days after the second prescription (latency period) after excluding patients with the

outcome within 180 days after their second prescription, and follow-up is terminated at the earliest of the following events: 3 years after drug initiation; death (for Medicare beneficiaries); the end of insurance enrolment for MarketScan or the end of enrolment in Medicare Parts A, B or D for Medicare beneficiaries; end of study (September 30, 2015); or an incident IBD event.

3) We will require only one study drug prescription in the exposure definition, and use the first prescription as cohort entry date, i.e., follow-up starts on 180 days (latency period) after the first prescription and ends on 180 days (carry-over effect) after treatment change.
4) We will modify our primary outcome to
    a. Use the date of IBD treatment instead of the date of IBD diagnosis as event date, to quantify the potential for time related bias in our primary outcome definition.
    b. Remove the biopsy requirement, as some colonoscopy codes already include biopsy (i.e., outcome defined as: the date of first IBD diagnosis with a colonoscopy/sigmoidoscopy within 30 days prior and an IBD treatment within 30 days after).
    c. We also will modify our primary outcome to remove both colonoscopy/sigmoidoscopy and biopsy requirements (i.e., outcome defined as: the date of first IBD diagnosis with an IBD treatment claims within 30 days after).
    d. We will use an outcome definition adapted from a previously validated definition (29), that defines IBD patients as those with at least three health care contacts, on different days within 90 days, with an ICD-9 diagnosis code for CD (555.xx) or UC (556.xx). The third diagnosis date will be considered as the event date.
5) We will relax our exclusion criteria to include additional patients with 1) prior use of the

abovementioned IBD treatments except 5-ASA and enteral budesonide (as other treatments may be indicated for other autoimmune diseases); 2) prior partial colectomy, colostomy, ileostomy, and ostomy supplies (we will continue to exclude patients with total colectomy); and 3) MarketScan patients who received colonoscopy/sigmoidoscopy prior to age 50.

6) We will additionally censor patients when they receive medications that could potentially induce or progress IBD (30) (Supplementary Table 3).
7) We will conduct analysis using multivariable-adjusted Cox regression in place of SMR-weighted Cox regression.
8) We will identify patients who originally qualified for Medicare due to end stage renal disease and disability. Given the large prevalence of diabetes in the ESRD population and the high risk of mortality, we will exclude such patients.

All database-specific analyses described above will be performed with SAS version 9.4 and meta-analyses will be conducted using STATA version 14.0.

## 12. Sample size calculation

In this large retrospective cohort study based on administrative healthcare claims data, we will include all beneficiaries meeting our inclusion criteria in both the MarketScan and 20% random sample of all fee-for-service Medicare beneficiaries. Because we plan to include all available eligible patients in both databases, we therefore did not perform a sample size calculation to determine the minimum-required study population. We calculate the power of this study as a function of hazard ratio (31) with a two-sided alpha of 0.05, given the conditions listed in Table 2a below. In addition, we will perform a meta-analysis of both estimates from MarketScan and Medicare data, which will increase the power of our analysis.

Table 2a. Parameter values for sample size calculation.

| Parameter | Value | |
|---|---|---|
| Cohorts | DPP4i vs SU | DPP4i vs TZD |
| Alpha | 0.05 | 0.05 |
| Group allocation proportion | 0.4 vs 0.6 | 0.7 vs 0.3 |
| Total N | 362442 | 205752 |
| % loss to follow-up | 0 | 0 |
| Follow-up (years) | 2 | 2 |
| 2-year cumulative incidence rate for control* | 34.5 cases/100,000 person-year | 34.5 cases/100,000 person-year |
| Range for hazard ratio | 1.0-2.0 | 1.0-2.0 |
| Comparison Method | Log-Rank Test | Log-Rank Test |

*Assuming the incidence rate of SU and TZD group is equal to the incidence rate of other oral antidiabetic drugs (except DPP4i) in the study by Abrahami et al (4).

Table 2b. Calculated power for different hazard ratios.

| Hazard ratio | Power | |
|---|---|---|
| | DPP4i vs SU | DPP4i vs TZD |
| 1.0 | 0.05 | 0.05 |
| 1.2 | 0.192 | 0.123 |
| 1.4 | 0.541 | 0.334 |
| 1.6 | 0.840 | 0.608 |
| 1.8 | 0.965 | 0.828 |
| 2.0 | 0.995 | 0.944 |

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## Appendix 1 - New User Algorithm

Definitions/Conventions

Washout Period (WP) = minimum length of time that a patient must be drug-free prior to becoming eligible for the new user cohort
Grace Period (GP) = maximum length of time that a user can go after the last prescription date plus the days supply without a drug before being considered discontinued from drug use
Days Supply (DS) = assumed (or imputed) number of days supply to use as Days Supply when true value is unknown (usually 30 days)

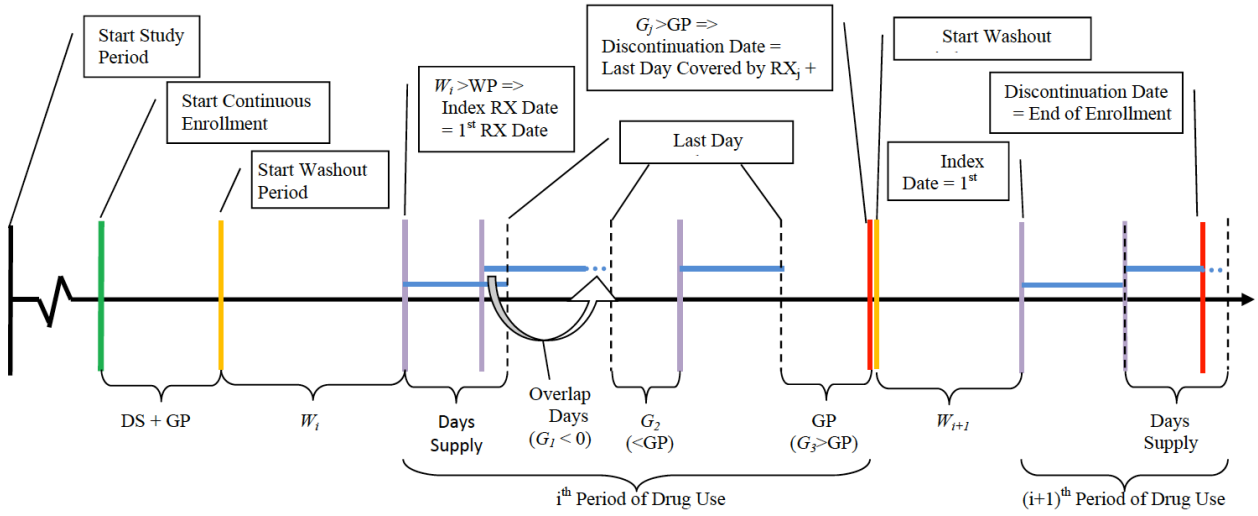
Wi = Days since start of washout period prior to 1st RX fill of ith period of use for patient
Gj = Days from last day covered by the jth RX fill to the (j+1)th RX fill date

Cohort Eligibility

If W1 > WP then patient's period of drug use is eligible for the new user cohort.
If Wi > WP and i>1 then patient's ith period of drug use is eligible for new user cohort IFF the analysis allows for previous users to become new users.

Drug Discontinuation/Censor Date

If Gj > GP then the patient is considered discontinued from drug use on the last day covered by the jth RX fill + GP
If (End of Enrollment) – GP < (Last Day Covered by an RX Fill) then the patient is censored at End of Enrollment



Algorithm

1. Set (Last Day Covered) = (Start of Continuous Enrollment) + (Days Supply) + (Grace Period).

2. Set (Index Date) = (1st RX Fill Date following Start of Continuous Enrollment).

3. Let W = (Index Date) – (Last Day Covered). If W > (Washout Period) then flag the period of drug use as eligible for the new user cohort.

4. Let G = (RX Fill Date) – (Previous Last Day Covered). Sequentially cycle through the subsequent prescription claims for the patient, applying the appropriate step below, until (Discontinuation Date) is set:

a. If G > (Grace Period) then set (Discontinuation Date) = max(Previous Last Day Covered, RX Fill Date) + (Days Supply) + (Grace Period).

b. If G <= (Grace Period) then set (Last Day Covered) = max(Previous Last Day Covered, RX Fill Date) + (Days Supply). If (Last Day Covered) + (Grace Period) > (End of Continuous Enrollment) and the patient has no additional RX claims with (RX Fill Date) <= (End of Continuous Enrollment), then set (Discontinuation Date) = (End of Continuous Enrollment). Otherwise, repeat Step 3 for the next prescription.

5. If the record was flagged for inclusion in the new user cohort in Step 3, output the record containing Index Date and Discontinuation Date3.

6. Set (Index Date) = (1st RX Fill Date following Discontinuation Date).

a. If the patient is continuously enrolled from (Discontinuation Date) to (Index Date), set (Last Day Covered) = (Discontinuation Date).

b. If the patient has a gap in enrollment between (Discontinuation Date) and (Index Date), then set (Last Day Covered) = (Start of Next Period of Continuous Enrollment) + (Days Supply) + (Grace Period) and set (Index Date) = (1st RX Fill Date following Start of Next Period Continuous
Enrollment).

7. Repeat Steps 3-7 for the patient's remaining RX fills.

**Supplementary Table 1. Codes used for outcome definition and key covariates.**

| **Primary and secondary outcome** | **ICD-9 Codes** |
|---|---|
| Inflammatory bowel disease (including Crohn's disease and Ulcerative colitis) | 555.0, 555.1, 555.2, 555.9, 556.0, 556.1, 556.2, 556.4, 556.8, 556.9 |
| Crohn's disease | 555.0, 555.1, 555.2, 555.9 |
| Ulcerative colitis | 556.0, 556.1, 556.2, 556.4, 556.8, 556.9 |
| **Other specific gastroenterological diseases** | **ICD-9 Codes** |
| Diverticulitis | 562.01, 562.03, 562.11, 562.13 |
| Ischemic colitis | 557.0, 557.1, 557.9 |
| Pseudomembranous colitis | 008.45 |
| Unspecific colitis | 558.9 |
| **Other gastroenterological disease categories** | **ICD-9 Codes** |
| Diseases Of Esophagus, Stomach, And Duodenum | 530 - 539 |
| Appendicitis | 540 - 543 |
| Hernia Of Abdominal Cavity | 550 - 553 |
| Noninfective Enteritis And Colitis | 555 - 558 |
| Other Diseases Of Intestines And Peritoneum | 560 - 569 |
| Other Diseases Of Digestive System | 570 - 579 |
| **Procedures for endoscopy and biopsy** | **CPT Codes** |
| Colorectal cancer screening | G0104, G0105, G0106, G0120, G0121 |
| Colonoscopy | 44388, 44390, 44391, 44393, 44394, 44397, 44401, 44402, 44403, 44404, 44405, 44406, 45355, 45378, 45379, 45381, 45382, 45383, 45385, 45386, 45387, 45388, 45389, 45390, 45391, 45393, 45398, |
| Colonoscopy involving biopsy | 44389, 44392, 44407, 45380, 45384, 45392 |
| Sigmoidoscopy | 45300, 45302, 45303, 45307, 45309, 45310, 45317, 45320, 45321, 45327 45330, 45332, 45334, 45335, 45338, 45339, 45340, 45341, 45345, 45346, 45347, 45349, 45350, G6022, G6023, |

| | |
|---|---|
| Sigmoidoscopy involving biopsy | 45305, 45308,<br>45315,<br>45331, 45333, 45336<br>45342, |
| Biopsy | 88300, 88302, 88304, 88305, 88307, 88309 |
| **Procedures for endoscopy and biopsy** | **ICD 9 procedure code** |
| Colonoscopy | 4523 |
| Colonoscopy involving biopsy | 4525 |
| Sigmoidoscopy | 4524, 4821, 4822, 4823 |
| Screening | 4521, 4522, 4543 |
| Biopsy | 4824, 4825, 4826 |
| **Procedures for colectomy, colostomy, ileostomy, and ostomy supplies** | **CPT Codes** |
| Partial colectomy | 44140, 44141, 44143, 44144, 44145, 44146,<br>44147,<br>44160,<br>44204, 44205, 44206, 44207, 44208 |
| Total colectomy | 44150, 44151, 44155, 44156, 44157, 44158,<br>44210, 44211, 44212 |
| Colostomy | 44188, 44206, 44208, 50810, 57307 |
| Ileostomy | 44186, 44187, 44136 |
| Ostomy supplies | A4331, A4357,<br>A4361, A4362, A4363, A4364, A4366, A4367,<br>A4368, A4369,<br>A4371, A4372, A4373, A4375, A4376, A4377,<br>A4378, A4379,<br>A4380, A4381, A4382, A4383, A4384, A4385,<br>A4386, A4387, A4388, A4389,<br>A4390,<br>A4402, A4404, A4405, A4406, A4407, A4408,<br>A4409,<br>A4410, A4411, A4412, A4413, A4414, A4415,<br>A4416, A4417, A4418, A4419,<br>A4420, A4421, A4422, A4423, A4424, A4425,<br>A4426, A4427, A4428 A4429,<br>A4430, A4431, A4432, A4433, A4434, A4435,<br>A4450, A4452, A4455, A4456,<br>A5051, A5052, A5053, A5054, A5055, A5056,<br>A5057, |

| | |
|---|---|
| | A5061, A5062, A5063,<br>A5071, A5072, A5073,<br>A5081, A5082, A5083,<br>A5093,<br>A5102,<br>A5120, A5121, A5122, A5126,<br>A5131,<br>A6216,<br>A9270 |
| **Procedures for colectomy, colostomy, ileostomy, and ostomy supplies** | **ICD9 procedure Codes** |
| Total colectomy | 4581, 4582, 4583 |

**Supplementary Table 2. Medications considered as inflammatory bowel disease therapy*.**

| Class | Medications |
|---|---|
| 5-Aminosalicylic Acid (5-ASA) | Sulfasalazine |
| | Mesalazine |
| | Olsalazine |
| | Balsalazide |
| Anti-Tumor Necrosis Factor (anti-TNF) | Infliximab |
| | Adalimumab |
| | Certolizumab pegol |
| | Natalizumab |
| | Vedolizumab |
| | Golimumab |
| | Ustekinumab |
| Corticosteroid† | Enteral budesonide |
| Immunosuppressive and immunoregulatory agents | Azathioprine |
| | Mercaptopurine |
| | Methotrexate |
| | Intravenous cyclosporine |

*Due to the wide indications, antibiotics are not considered as therapy to treat inflammatory bowel disease.

†Due to the wide indications, only enteral budesonide is considered as the corticosteroid therapy to treat inflammatory bowel disease.

**Reference**


1. Podolsky DK. Inflammatory Bowel Disease. *N Engl J Med* 2002 Aug 8;347(6):417-29
2. Feuerstein JD, Nguyen GC, Kupfer SS et al. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology 2017 Sep;153(3):827-834.

**Supplementary Table 3. Drugs that may induce inflammatory bowel disease[1].**

| Drug |
|---|
| Oral contraceptives |
| Hormonal replacement therapy |
| Aspirin |
| Nonsteroidal Anti-inflammatory Drugs (NSAIDs) |
| Isotretinoin |
| Mycophenolate mofetil |
| Etanercept |
| Ipilimumab |
| Rituximab |

**Reference**

Dubeau M-F, Lacucci M, Beck PL, et al. Drug-indcued inflammatory bowel disease and IBD-like conditions. Inflamm Bowel Dis 2013 Feb;19(2):445-56.