GROUP-BASED TRAJECTORY MODELING FOR LONGITUDINAL DATA OF HEALTHCARE FINANCIAL CHARGES IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

by

Jianfei Jiang

B.S., Lanzhou University, China, 1995

Ph.D., Shanghai Institute of Materia Medica, Chinese Academy of Sciences, China, 2000

Submitted to the Graduate Faculty of

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2015

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

This thesis was presented

by

Jianfei Jiang

It was defended on

June 5, 2015

and approved by

Thesis Advisor:

Chung-Chou H. Chang, PhD, Professor
Department of Biostatistics, Medicine
Graduate School of Public Health, School of Medicine
University of Pittsburgh

Committee Members:

David G. Binion, MD, Professor
Department of Medicine
School of Medicine
University of Pittsburgh

Gong Tang, PhD, Associate Professor
Department of Biostatistics
Graduate School of Public Health
University of Pittsburgh

Chung-Chou H. Chang, PhD

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ABSTRACT

Inflammatory bowel disease (IBD) is a heterogeneous group of lifelong chronic inflammatory diseases with variable and unpredictable disease courses which often require significant healthcare expenditures. There exists no uniform severity measure to capture the activity and the healthcare utilization of the disease. This study seeks to identify disease trajectories for the IBD patients based on their annual financial healthcare charges over time. We performed a longitudinal study of annual financial charges using a consented, prospective, natural history registry of 2,400 IBD patients at the University of Pittsburgh Medical Center from 2009 to 2013. The annual charges were calculated as the sum of inpatient admission charges and professional service charges, with ($Charge_F$) or without ($Charge_R$) biological medicine charges. Patients who completed a five-year follow-up were included in the study. The continuous financial charges were first categorized into sections of different price range, and then the data was fitted with a latent group-based zero-inflated Poisson model to identify different homogeneous trajectory patterns of financial charges. We identified six distinct trajectory groups of total annual charges obtained from each of the two calculation methods ($Charge_F$ and $Charge_R$). We further compared between these trajectories for patient characteristics, disease activity indices (Harvey-Bradshaw Index and ulcerative colitis activity

index), disease activity markers (high-sensitivity C-reactive protein and erythrocyte sedimentation rate), health-related quality of life index (short inflammatory bowel disease questionnaire, SIBDQ), healthcare utilization (emergency department, hospitalization, and surgery), and corticosteroid prescriptions.

We concluded that the healthcare financial charge could be a novel and uniform metric to evaluate the disease severity and the response of IBD patients to treatments. The present study is the first of its kind using latent group-based trajectory modeling of financial charges to identify distinct subsets of IBD patients with their response to treatments. The model could be used to determine the genetic, environmental, and other factors that influence disease severity and the patient's response to medical therapies. It will provide important information for the development of personalized or precision medical interventions for IBD patients and the reduction of their health care cost.

Public Health Relevance:

This study proposed a new metric which could be an accurate reflection of classic disease activity parameters, biochemical markers of inflammation, disease activity indices, and health-related quality of life in a cohort of patients with inflammatory bowel disease. The model developed would be of great significance to exploring the risk factors that influence the response to medical interventions. It will provide important information for the development of personalized or precision medical interventions for patients with inflammatory bowel disease and the reduction of their health care cost.

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PREFACE

This work would not have been possible without the advice and support of many people. First, I wish to express my deepest thanks to my thesis advisor, Professor Chung-Chou H. Chang, for her excellent guidance from the beginning to the completion of this thesis. She was always so patient and inspirational, and willing to take time to add new ideas to my project, teaching me analytical techniques, and giving me invaluable comments and suggestions to the thesis. Secondly, I am extremely grateful to Dr. David G. Binion, who provided me with the dataset, clinical knowledge, idea development and support that were indispensable to the completion of this study. Finally, I would like to express my sincere gratitude to Dr. Gong Tang for his invaluable support and intellectual guidance.

I am also indebted to Dr. Benjamin Click, for his extraordinary help with the medical terms, data analysis, and manuscript writing. I would like to extend my thanks to all the faculty and staff members in the Department of Biostatistics, and School of Public Health for all the helps I received throughout my MS program. I would also like to thank all my colleagues of the Department of Environmental and Occupational Health for creating a friendly and supportive environment. A special thank goes to Dr. Valerian E. Kagan for his encouragement and inspiration.

Finally, I thank my wife, Qing Zhao, and my boys, Peter Jiang and Paul Jiang, for their love, inspiration, and support throughout all of my endeavors.

NOMENCLATURE

AvePP, Average Posterior Probability

BIC, Bayesian Information Criteria

BMI, Body Mass Index

CD, Crohn's Disease

ED, Emergency Department

ESR, Erythrocyte Sedimentation Rate

HBI, Harvey Bradshaw Index

hsCRP, high-sensitivity C-reactivity Protein

IBD, Inflammatory Bowel Disease

MLE, Maximum Likelihood Estimator

OCC, Odds of Correction Classification

SIBDQ, Short Inflammatory Bowel Disease Questionnaire

UC, Ulcerative Colitis

UCAI, Ulcerative Colitis Activity Index

ZIP, Zero-Inflated-Poisson

1.0 INTRODUCTION

Inflammatory bowel disease (IBD) is a heterogeneous group of chronic inflammatory disorders affecting the gastrointestinal tract as a result of the interaction of genetic variations, environmental influences, intestinal microbiota alterations, and disturbances in the innate and adaptive immune response (Brant, 2011; McGovern et al., 2001; Triantafillidis et al., 2011). IBD including ulcerative colitis (UC) and Crohn's disease (CD) often experience intermittent episodes of active disease alternating with variable periods of remission. The majority of IBD patients require hospitalization and surgery at some point in life and their response to treatments varies and is largely unpredictable, which often results in large financial costs (Cohen et al., 2000; Silverstein et al., 1999). Recent estimates placed the total annual cost of CD in the US at $15.5 billion (Yu et al., 2008) and of UC at $14.9 billion (Cohen et al., 2010). Small groups of patients contribute disproportionately to healthcare expenditures and a minority of patients is responsible for over 50% of total costs of care. These patients often require repeat admissions and surgeries for refractory inflammation, complications of IBD, chronic pain, or psychosomatic issues(Click et al., 2015).

To date, the genetics, environmental, and other factors that influence the response of patients to therapy are still poorly understood. Attempts at prognostication of disease trajectory and response to treatments have largely failed. Furthermore, research and clinical care for the IBD has been hampered by lack of a uniform severity metric that encompasses the longitudinal

pattern of disease. Most measures of disease activity and endoscopic scores only capture a single point in time. A recently published CD metric, the Lemann index, was the first attempt at capturing the cumulative burden of disease over time (Pariente et al., 2011; Pariente et al., 2015). Unfortunately, the Lemann index was considered cumbersome and requires advanced imaging to calculate a score. For lack of a standardized severity measure, clinicians often rely upon a combination of patient-reported symptoms and physician global assessment, endoscopic or radiographic activity, and biochemical inflammatory markers to define disease activity. These measures capture only direct results of gastrointestinal inflammation and fail to account for patient perception and experience of the disease. Consequently, researchers have utilized measures of healthcare utilization including hospitalizations, emergency department (ED) visits, surgical requirement, and advanced medical therapy to evaluate both disease and patient activity. While these measures are routinely available and comparable across institutions, they fail to differentiate the severity across patients.

We propose a unique phenotypic metric which encompasses disease activity, healthcare utilization, and patient disease experience – healthcare financial charges – to define distinct subgroups of the IBD patients. We hypothesized that financial charges would be an accurate reflection of classic disease activity parameters, biochemical markers of inflammation, disease activity indices, and health-related quality of life in a cohort of IBD patients. Using group-based trajectory models, which are increasingly popular in clinical research to assess the heterogeneity in response to medical interventions, we attempted to classify patients into different subpopulations according to their 5-year longitudinal trajectory patterns of financial charges collected from 2009 to 2013. The modeling was performed using the SAS macro *Proc Traj*. We examined and compared characteristics of the patients among these subpopulations.

2.0 METHODS

2.1 STUDY POPULATION

A natural history registry maintained at the University of Pittsburgh Medical Center (UPMC) for adult IBD patients (≥ 18 years old) prospectively recruited were used in this study. The IBD registry encompasses highly detailed, prospectively collected demographic, phenotypic, clinical, radiographic, and biochemical data on over 2,400 IBD patients. Both established and new patients (patient has not been admitted at UPMC before) were eligible for inclusion. Patients were eligible for inclusion if they were seen in the outpatient clinic between 2009 and 2013, had at least five years of follow up defined by medical charges, and were diagnosed with IBD (CD, UC, or IBD unclassified [IBD-U]). Patients were excluded if they were not diagnosed with IBD, did not have a clinical encounter between 2009 and 2013, or did not have financial charge data available.

Baseline patient demographics were collected at the initial clinical encounter during the study period, and these included age, gender, body mass index (BMI), smoking status, and medical comorbidities (psychiatric disease including anxiety and/or depression, hypertension, hyperlipidemia, coronary artery disease, and diabetes mellitus). Comorbidities were defined by the ICD-9 code or physician reported problems listed in the electronic medical record (EMR). Disease characteristics determined at the first clinical and endoscopic encounter included disease

type (CD, UC, or IBD-U), duration of disease, anatomic location, and behavior according to the Montreal Classification (Silverberg et al., 2005), and history of prior IBD surgeries.

Disease activity was prospectively assessed at each clinical encounter using the Harvey-Bradshaw Index (HBI) for CD(Harvey and Bradshaw, 1980), ulcerative colitis activity index (UCAI) for UC(Kozarek et al., 1989), as well as high-sensitivity C-reactive protein (hsCRP) and erythrocyte sedimentation rate (ESR) elevation defined by local laboratory normal values (CRP: ≥0.74 mg/dl; ESR: >40 mm/hr). Mean annual values were created for disease activity indices and any elevated biochemical inflammatory marker during a year was dichotomized as normal or abnormal for the year. Health-related quality of life was also prospectively collected at each clinical encounter using the validated short inflammatory bowel disease questionnaire (SIBDQ). Healthcare utilization parameters included emergency department (ED) use, hospital admission for any indication, IBD-related surgery verified by review of operative report, outpatient clinic appointments, and telephone encounters.

2.2 FINANCIAL CHARGE DATA

Financial charge data for patients in the IBD registry during 2009-2013 was obtained through the Center for Assistance in Research using the EMR, an information technology support group at the UPMC. Charge data was obtained for all healthcare services (i.e. not limited to gastrointestinal care) including inpatient and outpatient services at the UPMC (>20 hospitals and >500 outpatient clinics) for all patients in the IBD registry. The charges associated with outpatient medications were not included in the initial charge data. Given that the majority of medication charges accrue from biologic agents, we elected to impute biologic therapy charges

using Medicare maximal allowance charge data 2009-2013 (available at http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/index.html). If charge data was missing for a year but there were charges in the surrounding years, the missing data was assumed to be zero. If there was missing data for more than one consecutive year or missing data occurred on the initial or last year of the study period, it was left as missing. Charges were organized by total annual charge amounts for each year. We computed trajectory modeling using two models. For the full model ($Charge_F$), the total annual charges were calculated as the sum of impatient admission charges ("hospital"), professional service charges (surgery and related fees, endoscopies, radiology, pathology, laboratory testing, diagnostic test or procedures) and biological medicine charges. In the reduced model ($Charge_R$), imputed charges of biologic agents were not included.

2.3 ANALYSIS PROCEDURE

Group-based trajectory modeling has been designed to classify a population into distinct subgroups based on the patterns of one or several measurements taken over time. The model assumes that the population is composed of a mixture of *j* underlying trajectory groups such that $P(Y_i) = \sum_j \pi_j P^j(Y_i)$ (Jones et al., 2001), where $P^j(Y_i)$ is the probability of outcome Y_i given individual *i* in group *j*, and π_j is the probability of group *j*. It is further assumed that (Nielsen et al., 2014), conditional on individual *i* being in group *j*, Y_i are independent for different time *t* so that

$$P(Y_i) = \sum_j \pi_j \prod_t P^j(Y_i)$$

In the present study, we used SAS 9.4 software and the SAS macro *Proc Traj* (http://www.andrew.cmu.edu/user/bjones/) to analyze the patterns of annual charges (from 2009-2013) in patients with IBD. In order to fit the healthcare financial charges to an appropriate latent group-based trajectory model, the continuous financial charges were converted to categorical variables, and zero-inflated Poisson model were fitted to the categorical charge data. This model assume that if individual *i* belongs to class *j*, then the distribution of categorical financial charge is a mixture of a Poisson distribution with an excess probability of zero charges (period of remission). Hence, financial charge Y_i at time *t* conditional on individual *i* being in class *j* following distribution (Lambert, 1992; Nielsen et al., 2014)

$$(Y_{it}|individual\ i\ in\ class\ j) \sim (1\text{-}\phi_t^j)\text{Poisson}\ (\lambda_t^j) + \phi_t^j \delta_0$$

where ϕ_t^j is the probability of having in zero charge at time *t*, λ_t^j is the expected categorical financial charge at time *t*, and δ_0 is a point-mass at zero.

The probability mass function of the categorical financial charge Y_{it}, therefore, has the following form

$$P(Y_{it} = y_{it}|individual\ i\ is\ in\ class\ j)$$

$$= \begin{cases} (1-\phi_t^j)e^{-\lambda_t^j} + \phi_t^j & y_{it} = 0 \\ (1-\phi_t^j)\frac{e^{-\lambda_t^j}(\lambda_t^j)^{y_{it}}}{y_{it}!} & y_{it} > 0 \end{cases}$$

where parameters ϕ_t^j is the probability of having zero charge, and λ_t^j is the expected categorical categorical financial charge for individual *i* in group *j* at time *t*.

This equation provides the estimated mean or expected value, μ_t^j, of the categorical charge Y_{it} at time *t* of an individual *i* being in group *j*, where

$\mu_t^j = E(Y_{it}|individual\ i\ in\ class\ j) = (1-\phi_t^j)\lambda_t^j$. Note that

The expected categorical financial charge λ_t^j are modeled (Nielsen et al., 2014) by either the quadratic predictor functions:

$$\log(\lambda_t^j)=\beta_{0j} + \beta_{1j}t + \beta_{2j}t^2$$

or the cubic predictor functions:

$$\log(\lambda_t^j)=\beta_{0j} + \beta_{1j}t + \beta_{2j}t^2 + \beta_{3j}t^3$$

where for each group *j*, the unknown values β_{ij} are needed to be estimated.

Probabilities ϕ_t^j model the amount of zero inflation, that is, the excess probability of individual *i* having in a no charge. They are modeled by predictor functions given as either a logit-linear function (Nielsen et al., 2014):

$$\text{logit}(\phi_t^j)= \log(\frac{\phi_t^j}{1-\phi_t^j})=\alpha_{0j} + \alpha_{1j}\text{t}$$

or a logit-quadratic function:

$$\text{logit}(\phi_t^j)= \log(\frac{\phi_t^j}{1-\phi_t^j})=\alpha_{0j} + \alpha_{1j}\text{t} + \alpha_{2j}t^2$$

or a form that is proportional to $\log(\phi_t^j)$ as in the zero-inflated Poisson model with parameter τ of Lambert (Lambert, 1992):

$$\text{logit}(\phi_t^j)= \log(\frac{\phi_t^j}{1-\phi_t^j})=-\tau_j \log(\lambda_t^j)$$

where α_{ij} and τ_j are unknown values to be estimated.

Combining these equations, the overall likelihood function is given by

$$L_k(\theta)=\prod_{i=1}^{N}\sum_{j=1}^{J} p_j \prod_t^T[(1-\Phi_t^j)e^{-\lambda_t^j}\frac{(\lambda_t^j)^{y_{it}}}{y_{it}!} + \Phi_t^j I\,(y_{it}=0)]$$

where θ is a vector of all the unknown parameters (Nielsen et al., 2014).

2.3.1 Model selection

The model selection procedure with *Proc Traj* is an iterative model-fitting and decision process that requires both statistical and subjective determinations. We followed a two-stage model selection process as suggested by Nagin (Nagin, 2005) that the number of trajectory groups will be determined in the first stage and the best polynomial trajectory function (constant, linear, quadratic, or cubic) will be determined and the Bayesian Information Criteria (BIC) value will then be calculated in the second stage.

BIC is calculated as in equation: $\text{BIC} = \log(L) - 0.5k\log(N)$

Where L is the value of the model's maximum likelihood, N is the sample size, and k refers to the number of parameters in the model.

In SAS output, two values of the BIC are calculated based on: 1) the number of subjects, and 2) the total number of observations across time. The true BIC lies within these two BIC values. We started by determining the best one-group model and then increased the number of groups one by one until the maximum logical number of groups was reached or the BIC value started to rise. In the final step, we selected the final best model that has the lowest absolute BIC value (Roeder et al., 1999). Other factors in making such selection were clinical knowledge and reasonable judgment (e.g., group size is reasonably large, >5%) (Nagin, 2005) and ΔBIC which is the difference of BICs between two models with different numbers of trajectory groups ($\Delta\text{BIC}=\Delta\text{BIC}_{complex} - \Delta\text{BIC}_{null}$). In accordance with recommendations of Jones *et al.*(Jones et al., 2001), 2ΔBIC larger than 10 is considered a strong evidence in favor of the model with a larger number of BIC.

2.3.2 Model adequacy assessment

The model adequacy was assessed using several diagnostics suggested by Nagin (2005). The first one is based on the average posterior probability (AvePP) calculated for each trajectory group. The minimum rule-of thumb, according to Nagin, is that AvePP should be at least 0.7 for all the trajectory groups. The second diagnostic static odds of a correct classification (OCC) for each trajectory group is defined by OCC = [(AvePP/(1-AvePP)] / [π/(1- π)], where π is the estimated group probability. The numerator of OCC is the odds of a correct classification into the corresponding trajectory group on the basis of the maximum probability classification rule. The denominator of OCC, $\frac{\pi}{1-\pi}$ is the odds of correct classification based on the random assignment, with the probability of assignment to this group equals the estimated group membership. An OCC value greater than 5.0 for all trajectory groups indicates that the model has high assignment accuracy. The third diagnostic is based on the estimated group probability (π) versus the proportion ($P = \frac{n}{N}$) of the sample assigned to the group. If individuals are assigned to groups with perfect certainty, P and π become identical. Therefore, the model adequacy can be evaluated by determining whether values P and π are reasonably close. Finally, the precision of the estimated group memberships can be evaluated using confidence intervals. A narrow confidence interval means that the probability is accurately estimated. However, there are no formal criteria for determining when a confidence interval is sufficiently narrow to be considered accurate for the estimate.

2.4 ETHICAL CONSIDERATIONS

Enrollment in and use of the IBD registry (Protocol #0309054) as well as the current registry analysis (Protocol #15050428) were approved by the Institutional Review Board at University of Pittsburgh.

3.0 RESULTS

3.1 GROUP-BASED TRAJECTORY MODELING OF LONGITUDINAL HEALTHCARE FINANCIAL CHARGES WITH BIOLOGICAL MEDICINE CHARGES EXCLUDED

3.1.1 Descriptive analysis

There was financial charge data of 2,204 IBD patients in the registry. The analysis included a total of 1,600 IBD patients (mean ± SD age: 47.0 ± 15.7 years, 53.4% female) with 5-year complete financial charges. The vast majority of the patients were white (96.8%), 60% of patients were married, and nearly 50% patients had full-time jobs (**Table 1**).

As shown in **Table 2**, the total annual charges ($Charge_R$, including 'hospital' and 'professional service' charge) for IBD patients are highly skewed. The spending on health care services is highly concentrated among small proportion of patients with very high usage (**Figure 1**). For instance, 9.6% of patients had 80% of health care expenditure in 2009, and the lower 50% of patients had $0.75 million of health care compared to $35 million in total. Because there were many low charges, no transformation could bring annual charges to approximately a normal distribution.

Table 1. Demographic statistics for the population studied.

Categorical	Coding	n	Percent
Sex missing=63	1=Male	716	46.6
	2=Female	821	53.4
Race missing=80	1=White	1,472	96.8
	2=Others	48	3.2
Marital missing=371	1=Single	427	34.7
	2=Married	740	60.2
	3=Divorced	62	5.1
Employment missing=79	1=Full time	746	49.1
	2=Unemployed	285	18.7
	3=Retired	144	9.5
	4=Part time	37	2.4
	5=Student	118	7.8
	6=Unknown	191	12.6
Continuous	**Min/max**	**n**	**Mean (SD)**
Age (in years) missing=63	18/96	1,537	47.0(15.7)

Table 2. Descriptive statistics for Charge$_R$* from 2009 to 2013.

Years	Minimum	25th percentile	Mean	Median	75th percentile	Maximum
2009	0	658	22,345	2,551	5,708	1,884,564
2010	0	338	23,489	2,361	5,265	1,390,001
2011	0	363	19,712	2,338	5318	1,509,565
2012	0	320	26,285	2,350	5,178	2,839,320
2013	0	429	22,694	2,293	5,197	2,103,697

*Charge$_R$ presented is in the US dollars.

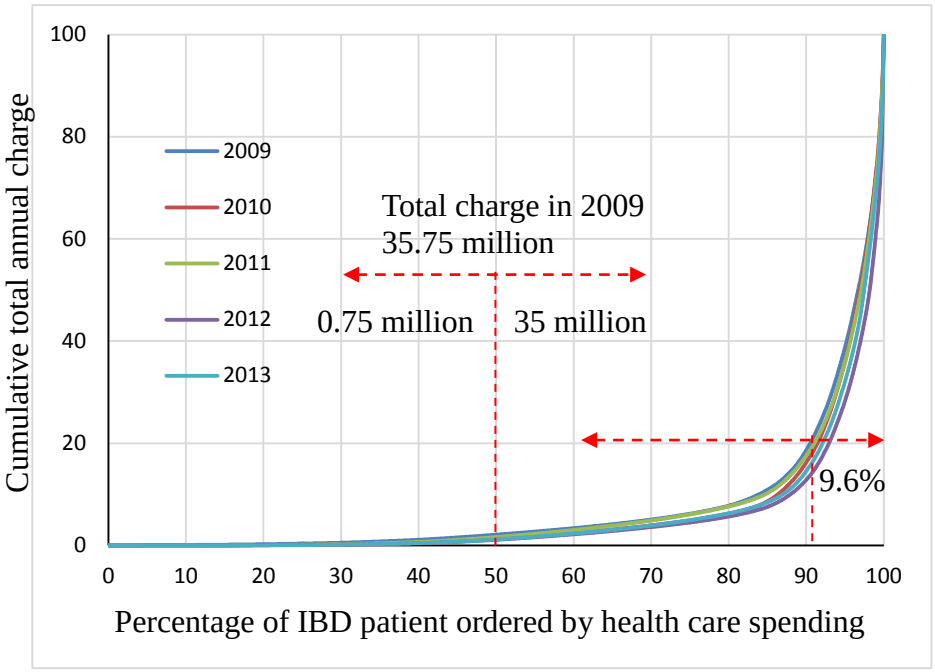


Figure 1. Cumulative distribution of total annual financial charges (Charge$_R$) from 2009 to 2013.

The *Proc Traj* provides options for modeling three different distributions (censored normal, Zero-Inflated Poisson, and logistic model). In order to fit the data to an appropriate group-based trajectory model via *Proc Traj*, we converted the continuous charges into 41 categorical groups using the cut points described in **Table 3**. **Figure 2** shows the distribution of new categorical Charge$_R$. The new categorical annual charges were also highly skewed. The individual trend lines plotted with the categorical annual charges for the first 5 patients are presented in **figure 3.** The ZIP model of *Proc Traj* was appropriate for the analysis since the count data were employed for the new categorical financial charges.

Table 3. Conversion of continuous financial charges to categorical variables.

Categorical Variable values	Cut points	Categorical Variable values	Cut points	Categorical Variable values	Cut points	Categorical Variable values	Cut points
0	0						
1	<=1000	**11**	<=15000	**21**	<=50000	**31**	<=180000
2	<=2000	**12**	<=18000	**22**	<=55000	**32**	<=200000
3	<=3000	**13**	<=21000	**23**	<=60000	**33**	<=250000
4	<=4000	**14**	<=24000	**24**	<=70000	**34**	<=300000
5	<=5000	**15**	<=27000	**25**	<=80000	**35**	<=350000
6	<=6000	**16**	<=30000	**26**	<=90000	**36**	<=400000
7	<=7500	**17**	<=33000	**27**	<=100000	**37**	<=450000
8	<=9000	**18**	<=36000	**28**	<=120000	**38**	<=500000
9	<=10500	**19**	<=40000	**29**	<=140000	**39**	<=1000000
10	<=12000	**20**	<=45000	**30**	<=160000	**40**	>1,000,000

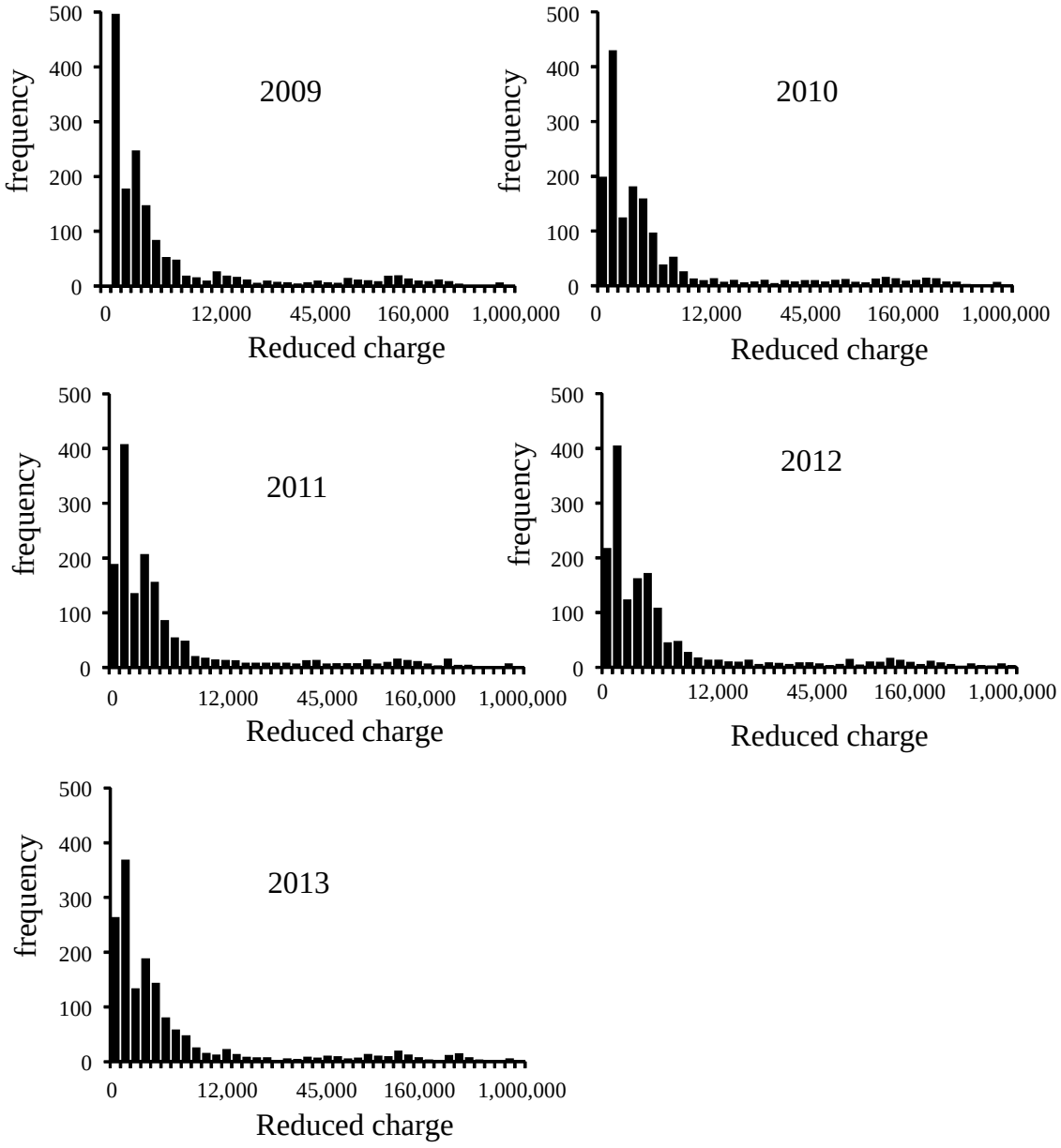


Figure 2. Frequency distribution of categorical annual charges ($Charge_R$) from 2009 to 2013.

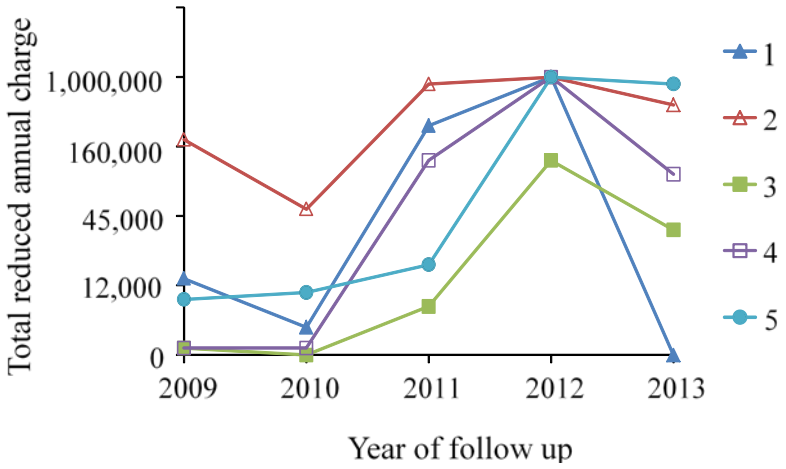


Figure 3. Categorical Charge$_R$ trend lines from 2009 to 2013 for the first 5 IBD patients.

3.1.2 Trajectory model development using ZIP model with Charge$_R$

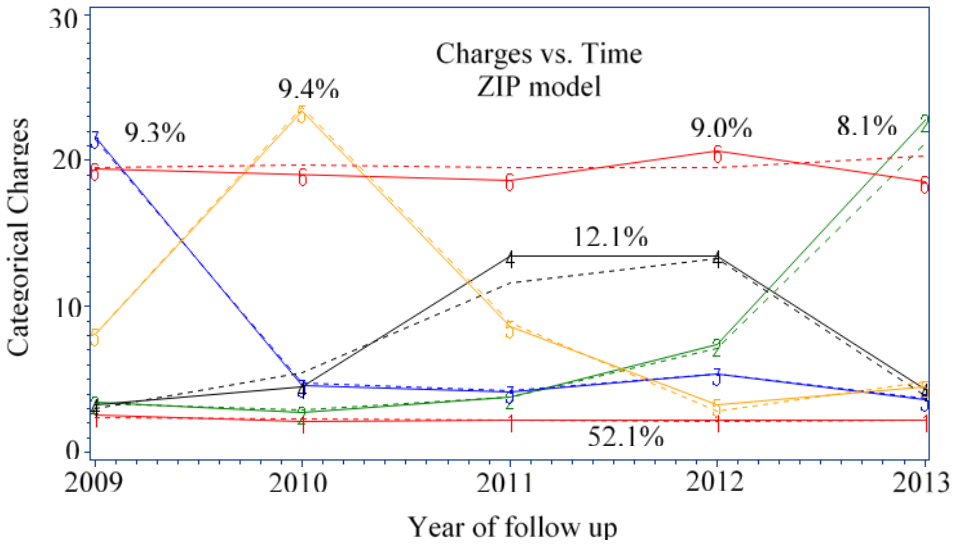
In selecting the optimum number of groups, the most common approach is to optimize the BIC by computing the corresponding maximum likelihood estimator (MLE) using the *Proc Traj* procedure (Jones and Nagin, 2007; Jones et al., 2001). Here we found that the BIC monotonically increased when more groups were added (**Table 4**). Thus, BIC alone is not useful in identifying the best model (Eggleston et al., 2004; Nagin, 2005). It has been suggested that subject-specific judgement should be combined with BIC to decide the group number (Blokland et al., 2005; Loughran and Nagin, 2006; Nagin and Odgers, 2010). By examining models ranging from 1 to 8 groups, we noticed that the additional groups in the 7- and 8-group models offered no extra explanation power clinically when compared with the 6-group model. Together with other criteria such as reasonable sample size for each group membership (>5%), we decided to use the 6-group model since it provided the similar intuition with less complexity.

The 6-group model was then refined until the highest polynomial's coefficient for each trajectory group was significantly different from 0. Our final model had a flat line for group 1, one quadratic order for group 2, three cubic orders for the groups 3, 4 and 5, and a linear order for the 6th group (**Table 4**). The BIC value for this model was -27029.93 (N=1600), and the best fit among all the other 6-group models had different polynomial's coefficients (**Figure 4**).

Table 4. Comparison of BICs from selected ZIP models fitted using Charge$_R$.

No. of Groups	Order*	Iorder*	BIC^1 (N=1,600)	BIC^2 (N=8,000)
1	2	2	-44608.52	-44613.35
2	2 2	2	-34503.79	-34511.83
3	2 2 2	2	-32042.06	-32053.32
4	2 2 2 2	2	-29630.29	-29644.78
5	2 2 2 2 2	2	-28319.80	-28337.51
6	2 2 2 2 2 2	2	-28274.48	-28295.40
7	2 2 2 2 2 2 2	2	-27736.07	-27760.21
8	2 2 2 2 2 2 2 2	2	-26730.99	-26758.35
6	**0 2 3 3 3 1**	**2**	**-27029.93**	**-27050.85**

*Order: Polynomial (0=intercept, 1=linear, 2=quadratic, 3=cubic) for each group; Iorder: Polynomial (0=intercept, 1=linear, or 2=quadratic) zero inflation probability logit for each group. BIC^1 relates to the overall sample size and BIC^2 related to the subject sample size.



The average data is represented by the solid lines and the predicted trajectories are represented by the dashed lines.

Figure 4. Graphical output from *Proc Traj* showing a six-group of the categorical annual Charge$_R$ trend patterns in IBD patients.

Using the maximum probability rule, the majority of the patients (52.1%) were located in group 1 consisting of individuals who consistently incurred low charges during the follow up time (**Figure 4**). These patients were presumed to have no new active symptoms and remained stable for years. Group 2 (8.1%) had low charge in 2009 with a slight increase in the next 3 years, suggesting that the patients in this group were developing active symptoms and requiring healthcare expenditures during that period of time. The largest increase in the expenses occurred in 2013. Longer observation time would be needed to evaluate the potential benefit effects of the interventions. Patients in groups 3 (9.3%) and group 5 (9.4%) all responded very effectively to treatments received, as the financial charges in all subsequent years were dropped remarkably to low level. Patients in group 4 (12.1%) started to develop active symptoms in 2010, after two years of moderate medical interventions in 2011 and 2012, charge$_R$ dropped to a low level in 2013. Among all the groups, group 6 (9.0%) had the highest basal level of charges in 2009.

Importantly, the cost of medical services for this group of patients remained at high level over 5 years. Patients in group 6 likely had severe disease and poor response to medical and surgical treatments. Therefore, future studies to identify genetic and environmental risk factors associated with the poor outcome of this group of patients will be particularly important for the development of novel therapeutic strategies and the reduction of healthcare utilization.

3.1.3 Evaluating the fit of the model

The fit of the model was evaluated using several diagnostics suggested by Nagin (Nagin, 2005), and the results are presented in **Table 5**. The lowest average posterior probability was 0.950, far greater than the recommended value of 0.7. Furthermore, the lowest value for the OCC was 59.2, which was also much larger than the recommendation of 10 as a general guideline. The data indicate that the model assigned patients to different trajectory groups with very high certainty. In addition, the probability of group membership (π) and the proportion assigned to each group using the maximum probability rule (P), are almost identical for each group. Finally, the 95% confidences of the estimated group memberships (π_j) were also relatively narrow for each group; less than 0.025 plus or minus π_j.

Table 5. Diagnostics of model (fitted using Charge$_R$) performance.

Trajectory Group	Group Membership π	N	AvePP*	OCCj*	*P**	95% Confidence Interval
1	0.521	838	0.985	59.2	0.524	(0.496, 0.546)
2	0.081	128	0.961	279.4	0.08	(0.067, 0.095)
3	0.093	149	0.950	185.4	0.093	(0.078, 0.108)
4	0.121	193	0.956	159.7	0.121	(0.104, 0.138)
5	0.094	150	0.964	257.5	0.094	(0.079, 0.109)
6	0.09	142	0.981	522.5	0.089	(0.075, 0.105)

*AvePP, average AvePP, average Posterior Probability; OCC, odds of correct classification;
P, actual proportion of subjects assigned to each trajectory group using the maximum probability rule.

3.1.4 Demographic and comorbidity characteristics among the identified trajectory groups

Extensive demographic and clinical data collected from 1537 (96.1%) patients were analyzed. There were no significant difference in age, gender and marital status among the charge trajectory groups. The chi-squared test demonstrated a statistically significant difference in employment status in the distribution of charge trajectory groups ($p<0.01$) (**Table 6**). The unemployment rates were higher in Groups 3 and 6.

No significant association between BMI and trajectory membership was observed. There was significantly more comorbid anxiety and/or depression ($p<0.0001$), diabetes mellitus ($p=0.003$), and hypertension ($p<0.0001$) in Groups 5 and 6 as compared to other groups. Groups 5 and 6 also had significantly more CD ($p<0.0001$), perianal disease ($p=0.002$), and more extensive UC ($p<0.0001$) as compared to the other groups. Patients in Group 6 also had significantly more prior IBD surgery ($p<0.0001$) (**Table 6**).

Table 6. Patients characteristics for each financial charge trajectory subgroup.

Trajectory Group	1	2	3	4	5	6	*P* value
No., %	794 (51.7)	121 (7.9)	146 (9.5)	186 (12.1)	149 (9.7)	141 (9.2)	--
Female %	400 (50.4)	62 (51.2)	80 (54.8)	108 (58.1)	91 (61.1)	80 (56.7)	0.11*
Age, median (IQR)	46 (24)	46 (25)	43.5 (27)	43.5 (24)	46 (23)	46 (27)	0.95†
BMI, median (IQR)	25.6 (6.3)	25.9 (8.4)	24.8 (6.8)	26.5 (8.6)	25.7 (7.5)	26.2 (8.2)	0.38†
Smoking Status, %							0.08*
Never	554 (74.0)	95 (79.2)	105 (75.0)	129 (70.9)	103 (70.1)	85 (61.2)	
Former	143 (19.1)	19 (15.8)	27 (19.3)	44 (24.2)	36 (24.5)	41 (29.5)	
Current	52 (6.9)	6 (5.0)	8 (5.7)	9 (5.0)	8 (5.4)	13 (9.4)	
Comorbid, %							
Psychiatric	160 (20.2)	25 (20.7)	36 (24.7)	49 (26.3)	57 (38.3)	51 (36.2)	<0.0001*
DM	34 (4.3)	7 (5.8)	8 (5.5)	11 (5.9)	17 (11.4)	16 (11.3)	0.003*
HLD	81 (10.2)	12 (9.9)	20 (13.7)	22 (11.8)	20 (13.4)	21 (14.9)	0.45*
HTN	138 (17.4)	23 (19.0)	26 (17.8)	44 (23.7)	45 (30.2)	47 (33.3)	<0.0001*
CAD	11 (1.4)	1 (0.8)	4 (2.7)	3 (1.6)	6 (4.0)	6 (4.3)	0.09*
Thyroid Disorder	51 (6.4)	6 (5.0)	15 (10.3)	5 (2.7)	10 (6.7)	10 (7.1)	0.12*
Marital Status, %							0.30*
Single	222 (34.8)	28 (33.7)	47 (37.6)	48 (33.8)	40 (31.5)	42 (36.8)	
Married	390 (61.1)	49 (59.0)	75 (60.0)	84 (59.2)	81 (63.8)	61 (53.5)	
Divorced	26 (4.1)	6 (7.2)	3 (2.4)	10 (7.0)	6 (4.7)	11 (9.7)	
Employment Status, %							<0.0001*
Full Time	396 (49.7)	65 (44.3)	65 (42.1)	101 (56.6)	67 (51.9)	52 (44.2)	
Unemployed	111 (13.9)	23 (21.5)	29 (28.3)	36 (16.6)	43 (17.3)	43 (26.7)	
Retired	61 (10.0)	10 (9.4)	21 (8.6)	22 (7.2)	9 (12.2)	21 (9.7)	
Part Time	21 (2.7)	3 (2.5)	4 (2.7)	3 (1.6)	3 (2.0)	3 (2.1)	
Student	64 (8.2)	8 (6.6)	9 (6.2)	13 (7.0)	11 (7.4)	13 (9.2)	
Other	125 (16.1)	12 (10.0)	18 (12.3)	11 (5.9)	16 (10.7)	9 (6.4)	
Disease, %							<0.0001*
CD	405 (51.0)	70 (57.9)	87 (59.6)	110 (59.1)	111 (74.5)	93 (66.0)	
UC	343 (43.2)	47 (38.8)	52 (35.6)	65 (34.9)	34 (22.8)	42 (29.8)	
IBD-U	43 (5.4)	1 (0.8)	6 (4.1)	9 (4.8)	4 (2.7)	5 (3.5)	
Duration, years median (IQR)	13.5 (12)	14 (20)	12 (11)	14 (14)	13 (12)	14 (12.5)	0.30*
CD Location‡, %							0.55*
Ileal	103 (27.1)	21 (31.8)	21 (25.3)	33 (32.4)	32 (29.9)	26 (28.6)	0.82*
Colonic	78 (20.5)	7 (10.6)	19 (22.9)	18 (17.6)	26 (24.3)	14 (15.4)	0.22*
Ileocolonic	198 (52.1)	38 (57.6)	43 (51.8)	49 (48.0)	48 (44.9)	51 (56.0)	0.79*
Upper	16 (4.2)	2 (3.0)	3 (3.6)	4 (3.9)	5 (4.7)	8 (8.8)	0.55*
Perianal‡, %	69 (17.4)	4 (5.8)	20 (23.3)	18 (17.1)	32 (29.1)	21 (22.6)	0.002*
CD Behavior‡, %							0.27*
Inflammatory	160 (45.1)	33 (50.8)	25 (30.9)	45 (45.0)	37 (35.6)	37 (40.2)	0.15*
Stricturing	108 (30.4)	22 (33.8)	30 (37.0)	32 (32.0)	35 (33.7)	30 (32.6)	0.70*
Penetrating	87 (24.5)	10 (15.4)	26 (32.1)	23 (23.0)	32 (30.8)	25 (27.2)	0.13*
UC Extent ‡, %							0.01*
Proctitis	20 (7.0)	4 (9.5)	2 (4.2)	6 (10.9)	1 (4.2)	1 (2.6)	0.52*
Left-Sided	104 (36.4)	15 (35.7)	17 (35.4)	23 (41.8)	5 (20.8)	3 (7.7)	0.002*
Extensive	162 (56.6)	23 (54.8)	29 (60.4)	26 (47.3)	18 (75.0)	35 (89.7)	<0.0001*
Prior IBD Surgery, %	253 (31.9)	49 (40.5)	50 (34.2)	64 (34.4)	62 (41.6)	74 (52.5)	<0.0001*

BMI: body mass index; DM: diabetes mellitus; HTN: hypertension; HLD: hyperlipidemia; CAD: coronary artery disease; CD: Crohn's disease; UC: ulcerative colitis; IBD-U: inflammatory bowel disease unclassified

* Chi-squared test; †median test.

‡Location data missing in 47 CD patients; perianal disease data missing in 16 CD patients; Behavior data missing in 79 CD patients; and Extent data missing in 89 UC patients.

3.1.5 Disease activity and quality of life analysis based on trajectory group memberships

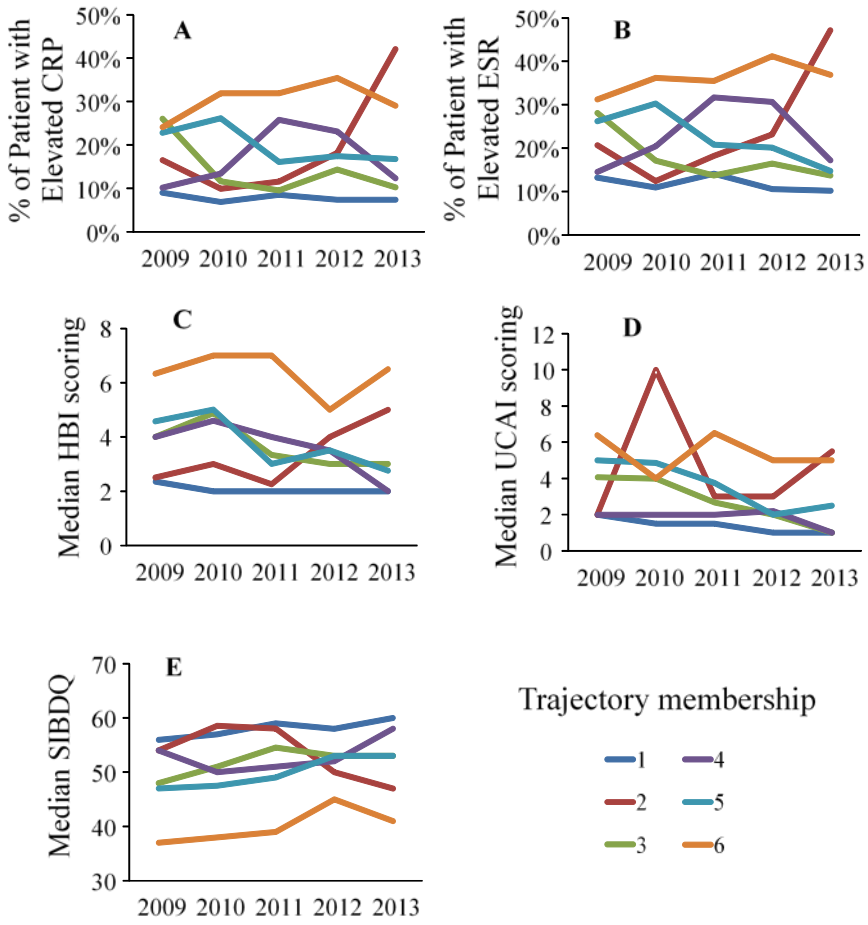


Figure 5. Inflammatory biomarkers, IBD disease activity indices and health related quality of life in trajectory groups.

To assess whether the financial charge data accurately reflect the IBD disease activity, we first evaluated hsCRP and ESR, two biomarkers of inflammation, for each trajectory group and plot the proportion of patients with elevated maker against time (Figure 5 A, B). Annual trend patterns of elevated hsCRP and ESR mirrored group trajectory over the five-year period. Group 6 patients with persistently high $charge_R$ also had increased annual elevated hsCRP and ESR

patterns as compared to the other groups. Group 6 also had the highest proportion of hsCRP elevation (72.3%) and ESR (79.4%) over the five-year period. Conversely, patients with consistently low $charge_R$ (Group 1) had the lowest rates of abnormal hsCRP and ESR both annually and over the five-year period (24.7% and 34.1% respectively). Examining those groups with fluctuation in their charge patterns (Groups 2-5), the timing of hsCRP and ESR elevation was reflected in simultaneous elevated charge patterns.

Similarly, annual patterns of disease activity indices were markedly similar to the patterns of charges. Median annual values of HBI and UCAI were reflected in the group trajectory membership (Figure 5C and D) as patients in Group 6 displayed a persistently elevated median HBI, reflective active disease, over the five years as compared to peers. On the other hand, patients in Group 1 had decreased median HBI and UCAI as compared to other groups. Similar to biochemical markers of inflammation, temporal variations in charges were well reflected in patterns of disease activity indices.

The health-related quality of life measured by SIBDQ revealed an inverse and temporal association with the charge group status (Figure 5E). Patients in Group 6, with persistently high charges demonstrated consistently low SIBDQ scores denoting a lower quality of life. Conversely, patients in Group 1 with perpetually low charges demonstrated a higher quality of life annually over the five-year period as compared to the other groups. Temporal trends in charges in Groups 2-5 were mirrored by deterioration or improvement in SIBDQ at the respective time points.

3.1.6 Healthcare utilization analysis among identified trajectory groups

Annuals rates of emergency department (ED) usage, inpatient hospitalizations, and IBD-related surgeries were each well reflected by the financial charge group status (**Figure 6**). Group 6 had consistently higher annual rates of ED usage and hospitalization as compared to other groups, and Group 1 patients had the lowest annual rates of ED usage and hospitalization. Furthermore, Group 6 had the highest overall proportion of patients who utilized the ED (95.0%), experienced hospitalization (97.2%), or underwent IBD-related surgery (64.5%) over the five years. On the other hand, Group 1 had the lowest five-year rates of ED use (21.0%), hospitalization (5.5%), and surgery (2.0%). Similar to other parameters, temporal trends in healthcare utilization were almost identically mirrored in the charge group membership for Groups 2-5.

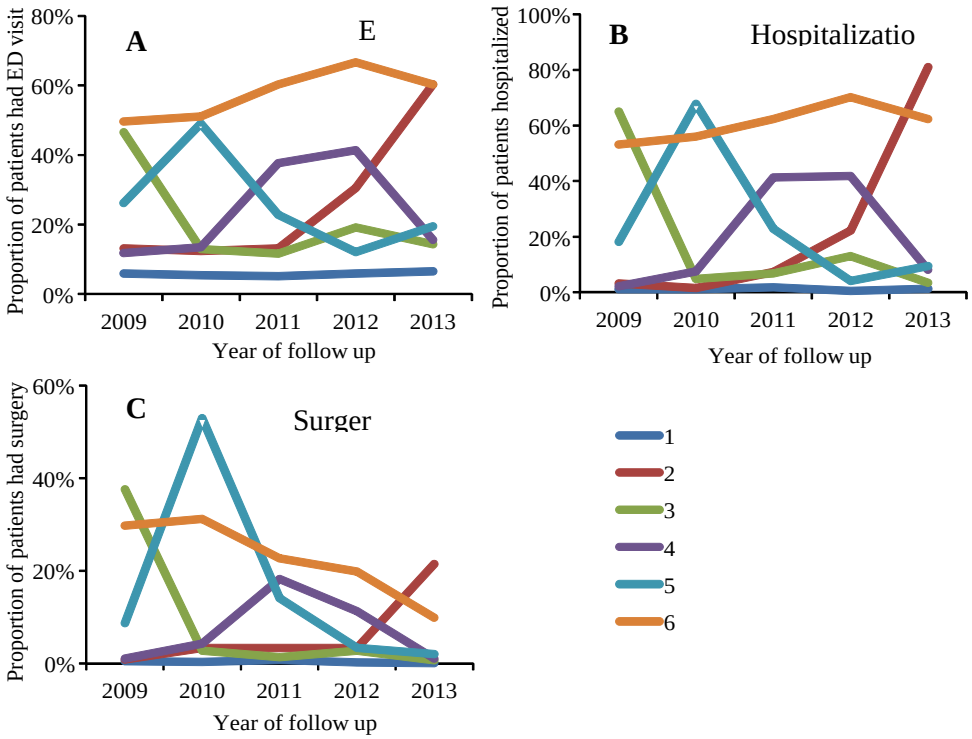


Figure 6. Healthcare utilization in established trajectory groups.

3.1.7 Corticosteroid requirement based on trajectory group memberships

Corticosteroids are used to treat acute (sudden onset and/or short duration) flare-ups. The use of corticosteroids over the five-year period also correlated to charge group membership (**Figure 7**). Group 6 had the highest rates of corticosteroid use for all years except for year 5 when Group 2 overtook in rates of steroids use and the total charges. Over the five-year period, Group 6 had the highest proportion of patients receiving corticosteroids (70.9%). Group 1 had a persistently low rate of corticosteroid use and lowest cumulative steroid exposure (29.6%) while Groups 2-5 had variations in their corticosteroid prescriptions reflected by simultaneous fluctuation in their charge trajectory.

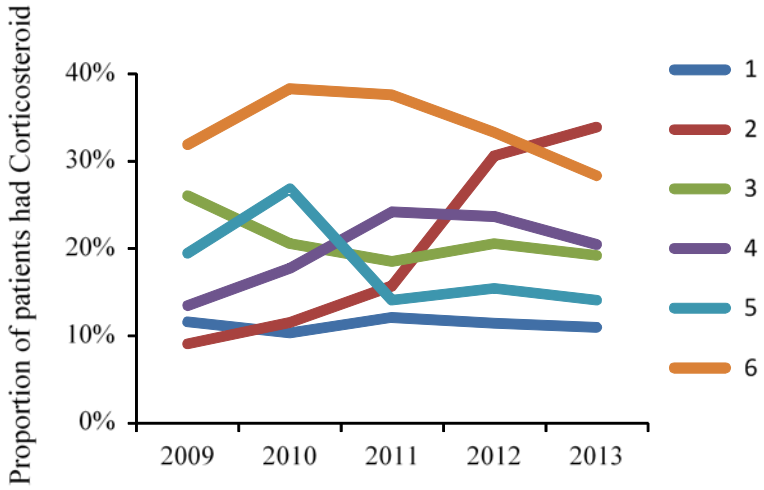


Figure 7. Corticosteroid requirement in among established trajectory groups.

3.2 GROUP-BASED TRAJECTORY MODELING OF LONGITUDINAL HEALTHCARE FINANCIAL CHARGES WITH BIOLOGICAL MEDICINE CHARGES.

Although the exact causes of IBD are unknown, genetic, environmental, and immune response factors have been proposed. Among those, the immune system plays a major role in the development of active disease. Recently, a variety of biological therapies have been developed for the treatment of IBD. These medications have changed the way physicians treat IBD patients. The medications, however, are very expensive, with treatment costs ranging from US$3,000 to $8,000 per infusion. In order to get a more complete estimation of disease severity using medical cost, we re-calculated the total annual charge ($Charge_F$) using "hospital" charges, "professional service" charges and imputed biological medicine charges (**Table 7**). Similar to $Charge_R$, the distributions of $Charge_F$ were also highly skewed. Around 12.5% patients had 80% of health care expenditure in 2009, and the lower 50% patient had $0.86 million of health care cost as compared to $40.14 million in total (**Figure 8**). Similarly, the continuous $Charge_F$ were converted to categorical variables in order to use the appropriate model via *Proc Traj*. **Figure 9** demonstrated the frequency distribution of the categorical charge variables. The individual $Charge_R$ trend patterns for the first 5 patients are shown in **Figure 10**.

Table 7. Descriptive statistics for Charge$_F$ * from 2009 to 2013.

Years	Minimum	25th percentile	Mean	Median	75th percentile	Maximum
2009	0	771	25,087	2,827	15,270	1,908,866
2010	0	383	25,875	2,618	9,207	1,390,001
2011	0	410	22,510	2,710	13,170	1,534,226
2012	0	447	30,355	3,373	20,156	2,839,320
2013	0	429	27,317	3,262	20,396	2,103,697

*Charge$_F$ presented is in the US dollars.

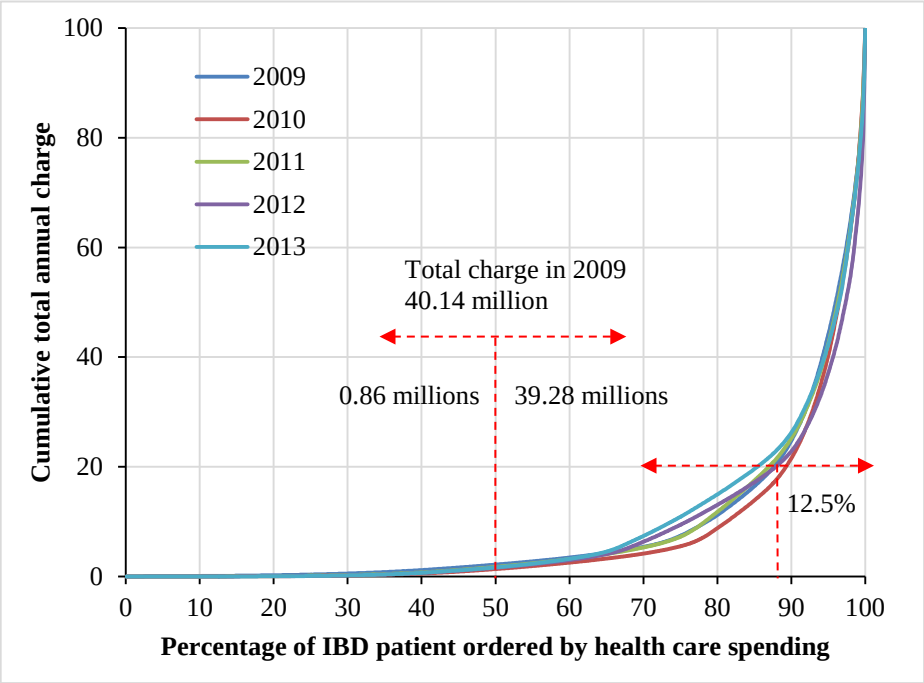


Figure 8. Cumulative distribution of total annual financial charges (Charge$_F$) from 2009 to 2013.

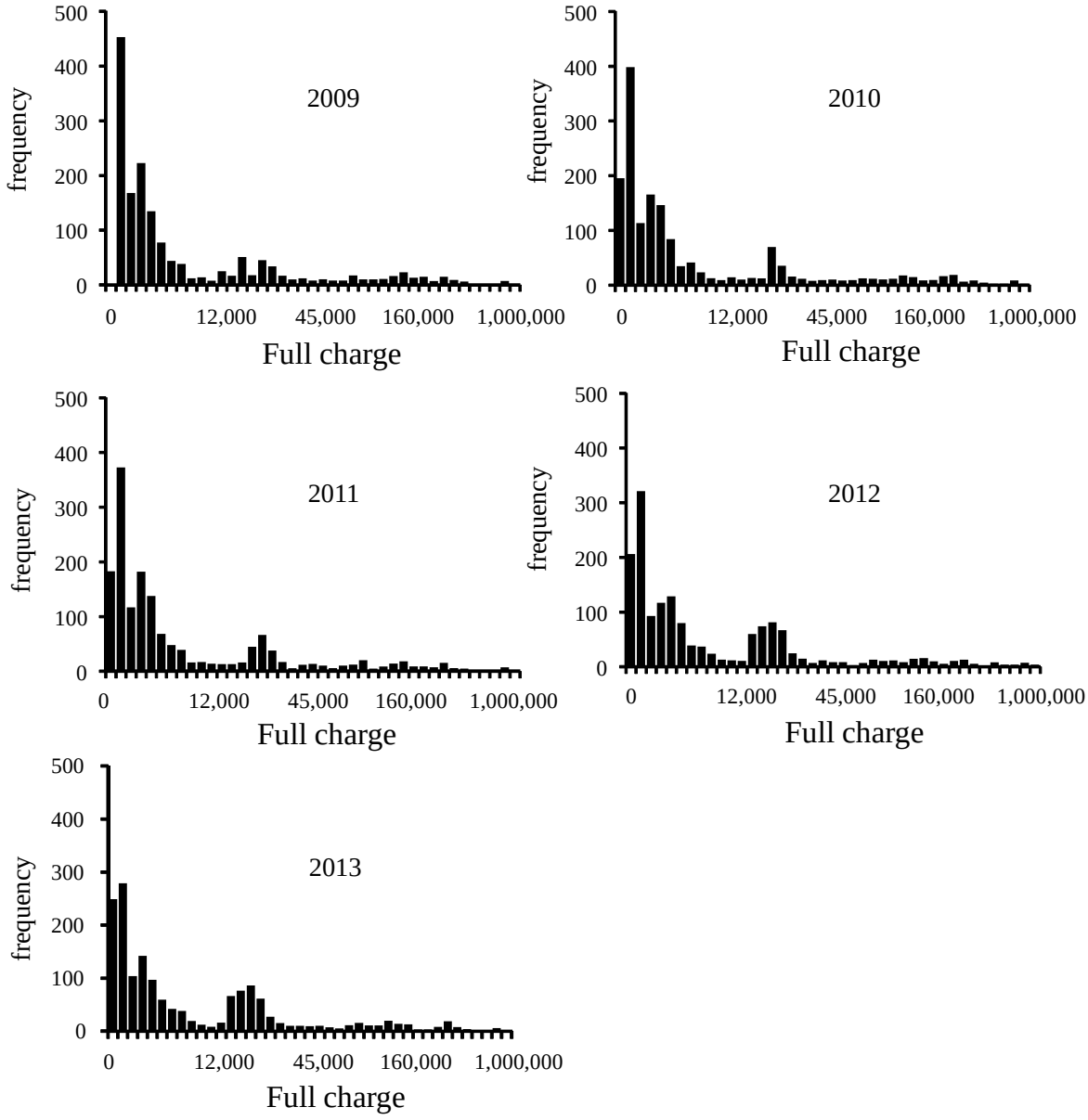


Figure 9. Frequency distribution of categorical annual charges ($Charge_R$) from 2009 to 2013.

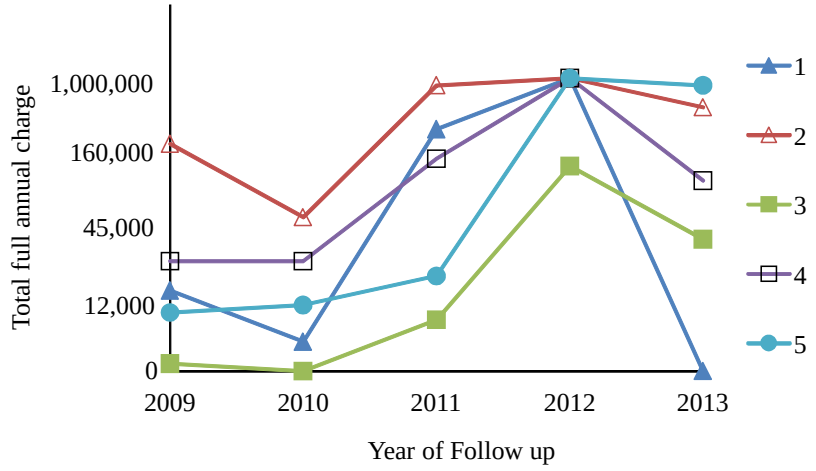


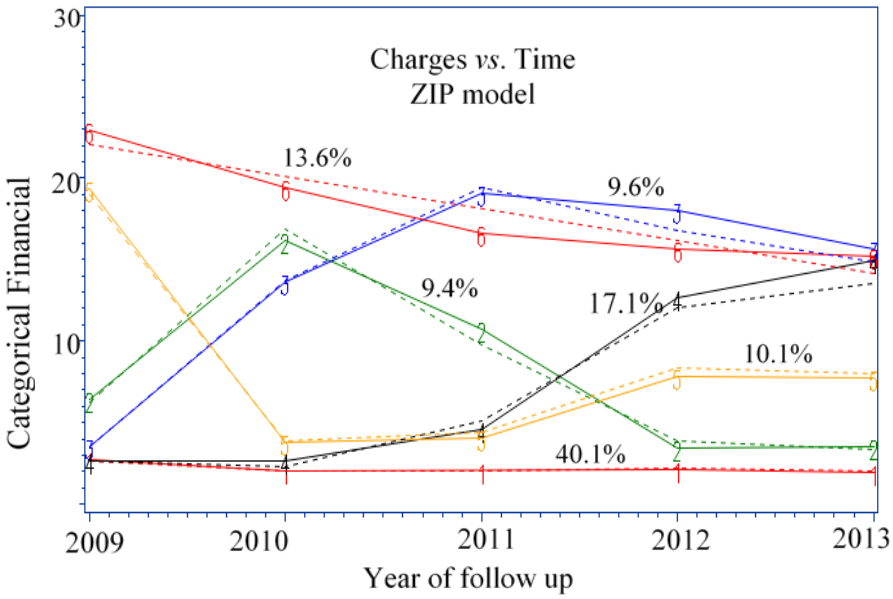
Figure 10. Annual financial charge data using Charge$_F$ (with different symbols) from 2009 to 2013 (connected in line) for the first 5 IBD patients.

Using the same model development strategy mentioned in **3.1.2**, we set the optimum trajectory group number to 6, which provided sufficient explanatory power with less complex (**Table 8**). The highest polynomial's coefficient for each trajectory group was then refined for the best fit. Our final model had cubic orders for the first 5 groups, and a linear order for the 6th group (**Table 8**). The BIC value for this model was -28596.7 (N=1600), and the best fit among all the other 6-group models had different polynomial's coefficients.

Table 8. Comparison of BICs from ZIP models fitted using Charge$_F$.

No. of Groups	Order*	Iorder*	BIC^1 (N=1600)	BIC^2 (N=8000)
1	2	2	-46132.03	-46136.86
2	2 2	2	-35295.62	-35303.67
3	2 2 2	2	-32210.58	-32221.85
4	2 2 2 2	2	-30625.99	-30640.48
5	2 2 2 2 2	2	-29682.82	-29700.53
6	2 2 2 2 2 2	2	-29022.17	-29043.10
7	2 2 2 2 2 2 2	2	-28596.01	-28620.16
8	2 2 2 2 2 2 2 2	2	-28217.32	-28244.68
6	**3 3 3 3 3 1**	1	**-28596.7**	**-28620.09**

*Order: Polynomial (0=intercept, 1=linear, 2=quadratic, 3=cubic) for each group; Iorder: Polynomial (0=intercept, 1=linear, or 2=quadratic) zero inflation probability logit for each group. BIC^1 relates to the overall sample size and BIC^2 related to the subject sample size.



The average data is represented by the solid lines and the predicted trajectories are represented by the dashed lines.

Figure 11. Graphical output from Proc Traj showing a six-group of the categorical annual ChargeF trend patterns in IBD patients.

Using the maximum probability rule, around 40.1% patients were assigned to Group 1 which presumably consisted of individuals who had no active symptoms and remained stable from 2009 to 2013 (**Figure 11**). Group 2 (9.4%) had active symptoms in 2009 and 2010, and responded well to the medical interventions, as the healthcare charge dropped to low levels in 2012 and 2013. Group 3 (9.6%) has low basal charge in 2009, which markedly increased in the next 2 years and remained high afterward. This suggests that patients in Group 3 developed active symptom during the follow-up time, and they did not response well to the medical interventions. Future studies will be necessary for this sub-group of patients to identify the factors that are responsible for the high expenditure. Group 4 was estimated to comprise 17.1 % of total sample population. Patients in this group were developing active symptoms from 2009 to 2013 as reflected by the increasing financial charges, and longer observation time will be needed

to evaluate the potential benefit effects of the interventions. Patients in Group 5 (10.1%) had active symptoms in 2009, and have undergone extensive medical cares as reflected by the high finance charges. As for those patients in Group 2, this population also responded very well to the therapies because the charges dropped sharply to low levels in the subsequent years. The charges, however, bounced back to low-medium level in 2012 and 2013. In the trajectory models developed using $charge_R$, a portion of patients (Group 6, 13.6%) did not response well to the medical intervention, and the $Charge_F$ remained at high level during 5 years (**Figure 11**).

The diagnostic analysis(Nagin, 2005) revealed a good capability of the trajectory model in estimating group memberships and assigning patients among the groups. **Table 9** presented the appropriateness of the model assessed with four diagnostics standard. The lowest average posterior probability was 0.950, and the lowest value for the OCC was 59.2, far greater than the recommended values of 0.7 and 10, respectively. Furthermore, the estimated probability of group membership and the proportion of the patients assigned to each group are almost identical. Finally, the 95% confidences of the estimated group memberships were also reasonably narrow for each group; less than 0.025 plus or minus π_j.

Table 9. Model diagnostics for data using $Charge_F$.

Trajectory Group	Group Membership π	95% Confidence Interval	n	AvePP*	OCC*	*P**
1	0.401	(0.386, 0.426)	640	0.989	126.1	0.4
2	0.094	(0.079, 0.109)	152	0.953	195.8	0.095
3	0.096	(0.080, 0.111)	152	0.952	186.2	0.095
4	0.171	(0.151, 0.191)	275	0.958	110.5	0.172
5	0.101	(0.085, 0.117)	163	0.946	154.6	0.102
6	0.136	(0.119, 0.153)	218	0.971	214.9	0.136

*AvePP, average Posterior Probability; OCC, odds of correct classification;
P, actual proportion of subjects assigned to each trajectory group using the maximum probability rule.

4.0 DISCUSSION

Through the use of group-based trajectory modeling we have identified distinct patterns of healthcare charges that are reflective of variations of disease activity, quality of life, healthcare utilization, and medication requirement for patients followed over a five-year time period. To our knowledge this is the first use of group-based trajectory modeling in financial data for an IBD patient population to reflect all-encompassing patterns of both the disease activity and patient experience of the disease.

In this study, we first identified six distinct subgroups of patients by annual patterns of reduced healthcare charges (without biological medicine charge). The patterns could be summarized as persistently high (Group 6), chronically low (Group 1), and those with temporal variation (Groups 2-5). Demographic characteristics with significant variation among the established trajectory groups included CD (vs. UC or IBD-U), perianal involvement, extensive UC (vs. left-sided or proctitis), history of prior IBD surgery, comorbidities including psychiatric illness, diabetes mellitus, hypertension, as well as being unemployed. These demographic and disease associations are consistent with the previous studies. Several studies have demonstrated that CD to be in general more costly than UC (Yu et al., 2008) and that patients with more severe disease (perianal or extensive UC) carry a larger financial burden than those with mild or more limited disease (Feagan et al., 2000; Hillson et al., 2008; Silverstein et al., 1999). Furthermore, unemployment may simply be a reflection of patient disability secondary to severe IBD thus

leading to higher expenses (Ananthakrishnan et al., 2008). Similarly, the presence of multiple comorbid conditions has been shown to be associated with patients who utilize healthcare disproportionately (Gawande; Hempstead et al., 2014).

The trajectory patterns are slightly different when the biological charges were included in the total annual charges, in particular, when we compare groups 2 and 3 with groups 4 and 5 developed with reduced charges. Clearly, a portion of the patients in group 3 in the full charge model were able to maintain remission under the biological therapy. Similarly, the bounce of financial charge in group 2 in 2012 and 2013 in the full charge model were likely due to the biological charges, indicating that some patients were able to achieve and maintain remission after the surgical care with the help of biological medicine.

While some might view the reduced charge as a misrepresentation of the true costs of IBD patients, we believe it is a more realistic reflection of disease activity, healthcare utilization, and patient experience of disease. This could be exemplified by a patient in complete remission being maintained on an expensive biologic agent having roughly the same financial expenditures as a patient hospitalized and underwent a surgical resection for active disease. The financial charge alone could not differentiate these two disparate situations in term of disease processes and patient experiences as the two situations carry roughly the same expense. Thus, we elected to perform a sensitivity analysis of models with and without biologic charges.

We further demonstrated that patterns of healthcare spending generated by group-based trajectory modeling are reflective of multiple dimensions of the chronic disease experience. First, patient patterns in spending are reflective of patterns in acute disease activity as measured by both patient-reported measures (HBI, UCAI) and biochemical markers of inflammation (hsCRP, ESR), and patients with the most persistently high or low financial charge totals also had the

most extreme measures of the disease activity. Secondly, patterns in spending echo healthcare utilization measures such as ED use, hospitalization, and surgery. The interpretation of this association, however, should be cautioned for likely collinearity, as these parameters produce a financial charge inherently. The trends in financial charges were also adequately reflective of the need for corticosteroid, a mainstay in the treatment for acute attacks of moderate to severe disease. Finally, financial charges were reflected by changes in quality of life of the IBD patients. Together, these trends suggest that financial charges can be an adequate and sensitive measure of disease activities, healthcare utilization, medication requirement, and quality of life, and may serve as and uniform gold standard for IBD disease severity.

Like all other studies in the field, this one is also not free from limitations. First, conversion of continuous financial charges to categorical charges, regardless of how you do it, results in loss of power in the subsequent statistical hypothesis testing (Aiken and West, 1991). These categories were not divided equally in this study. There are no good reasons in general to justify why the financial charge should be categorized as it was. Therefore, effect of using of different cutting points on trajectory groups should be examined in the future. Second, the process of enrollment in the IBD registry and back-filling of data to 2009 allows for bias if patients were seen in another capacity at the UPMC but outside of gastroenterological care prior to enrollment in the IBD registry. This would result in financial charges while not receiving focused IBD care and thus may not accurately reflect the impact or their IBD course. We were not able to identify the first visit date at the IBD clinic to minimize this bias. We attempted to control for this possible confounding as we only included patients with five-year follow up, and excluded patients if charges in the first year were missing. Third, the use of observational data limits the data available for collection and analysis. There were a proportion of patients with missing

clinical data (n=63) as well as missing Montreal classification characterization (location n=47, perianal n=16, behavior n=79, extent n=89). We included these patients in the trajectory model development to avoid reduction in power and increase of variability. The missing data, however, is a potential source of bias when we compare the patients characteristics based on the established group memberships. In addition, patients with missing financial charge at 2009 or 2013, or with missing data for more than one consecutive year were excluded from the model analysis. For those patients with charge data missing for a year but had charges in the surrounding years, we empirically set their missing charge to zero. Clearly, these techniques of handling of missing data may lead to both bias and loss of power. A sensitivity analysis should be considered in the future study. Furthermore, though this was a temporal analysis of healthcare financial charges, disease and clinical parameters, certain variables that temporally vary were only available in a static measure (e.g. smoking). These dynamic changes may have influenced the progression of the disease. Lastly, the present study was a single institutional study at a tertiary referral center and thus the findings may not yet be generalizable to other populations or centers.

Despite the potential limitations mentioned above, there are major strengths in this study. The use of a highly detailed observational natural history registry in a large cohort of IBD patients provides an accurate reflection of real-life clinical care in a tertiary center. This study is a multi-year longitudinal evaluation allowing for temporal variation in disease course in response to medical interventions. The association of financial charges to classic measures of disease activity, quality of life, healthcare utilization, and medication requirement implies that financial healthcare expenditures are perhaps the best all-encompassing measure of disease burden (both from an activity standpoint and a patient's perspective) in the IBD. Thus, we believe that

financial burden can be used as a surrogate outcome measure to reflect a general global assessment of patient status.

In conclusion, group-based trajectory modeling of financial charges in the IBD patients allows for identification of patient subgroups that mirrors overall disease course. Financial charges represent a novel and unique means of agnostic phenotyping in IBD. Combined with multinomial logistic regression, the trajectory model could also be used to determine the genetic and environmental factors that influence the responses of patients to the healthcare strategies. Further studies to quantify and clarify the effects of various clinical interventions on financial charges are needed to determine what treatment strategies are effective in subgroups of patients.

APPENDIX A. SAS CODE AND OUTPUT

A.1 SAS CODE FOR THE REDUCED CHARGE MODEL

```
/*import data set from excel file*/
proc import datafile = 'C:\mysas\Nobio040215_5yrs.xlsx'
DBMS = EXCEL OUT = mysas.Nobio_5;
GETNAMES=YES;
MIXED=NO;
SCANTEXT=YES;
USEDATE=YES;
SCANTIME=YES;
run;


/*convert continuous charges to categorical charges*/
Data Nobio_5;
       set mysas.Nobio_5;


              if c1=0                then cc1=0;
              else if c1<=1000     then cc1=1;
              else if c1<=2000     then cc1=2;
              else if c1<=3000     then cc1=3;
              else if c1<=4000     then cc1=4;
              else if c1<=5000     then cc1=5;
              else if c1<=6000     then cc1=6;
              else if c1<=7500     then cc1=7;
              else if c1<=9000     then cc1=8;
              else if c1<=10500    then cc1=9;
              else if c1<=12000    then cc1=10;
              else if c1<=15000    then cc1=11;
              else if c1<=18000    then cc1=12;
              else if c1<=21000    then cc1=13;
              else if c1<=24000    then cc1=14;
              else if c1<=27000    then cc1=15;
              else if c1<=30000    then cc1=16;
              else if c1<=33000    then cc1=17;
              else if c1<=36000    then cc1=18;
              else if c1<=40000    then cc1=19;
              else if c1<=45000    then cc1=20;
              else if c1<=50000    then cc1=21;
              else if c1<=55000    then cc1=22;
              else if c1<=60000    then cc1=23;
              else if c1<=70000    then cc1=24;
              else if c1<=80000    then cc1=25;
              else if c1<=90000    then cc1=26;
              else if c1<=100000   then cc1=27;
              else if c1<=120000   then cc1=28;
              else if c1<=140000   then cc1=29;
```

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                else if c1<=160000   then cc1=30;
                else if c1<=180000   then cc1=31;
                else if c1<=200000   then cc1=32;
                else if c1<=250000   then cc1=33;
                else if c1<=300000   then cc1=34;
                else if c1<=350000   then cc1=35;
                else if c1<=400000   then cc1=36;
                else if c1<=450000   then cc1=37;
                else if c1<=500000   then cc1=38;
                else if c1<=1000000  then cc1=39;
                else cc1=40;


                if c2=0                 then cc2=0;
                else if c2<=1000     then cc2=1;
                else if c2<=2000     then cc2=2;
                else if c2<=3000     then cc2=3;
                else if c2<=4000     then cc2=4;
                else if c2<=5000     then cc2=5;
                else if c2<=6000     then cc2=6;
                else if c2<=7500     then cc2=7;
                else if c2<=9000     then cc2=8;
                else if c2<=10500    then cc2=9;
                else if c2<=12000    then cc2=10;
                else if c2<=15000    then cc2=11;
                else if c2<=18000    then cc2=12;
                else if c2<=21000    then cc2=13;
                else if c2<=24000    then cc2=14;
                else if c2<=27000    then cc2=15;
                else if c2<=30000    then cc2=16;
                else if c2<=33000    then cc2=17;
                else if c2<=36000    then cc2=18;
                else if c2<=40000    then cc2=19;
                else if c2<=45000    then cc2=20;
                else if c2<=50000    then cc2=21;
                else if c2<=55000    then cc2=22;
                else if c2<=60000    then cc2=23;
                else if c2<=70000    then cc2=24;
                else if c2<=80000    then cc2=25;
                else if c2<=90000    then cc2=26;
                else if c2<=100000   then cc2=27;
                else if c2<=120000   then cc2=28;
                else if c2<=140000   then cc2=29;
                else if c2<=160000   then cc2=30;
                else if c2<=180000   then cc2=31;
                else if c2<=200000   then cc2=32;
                else if c2<=250000   then cc2=33;
                else if c2<=300000   then cc2=34;
                else if c2<=350000   then cc2=35;
                else if c2<=400000   then cc2=36;
                else if c2<=450000   then cc2=37;
                else if c2<=500000   then cc2=38;
                else if c2<=1000000  then cc2=39;
                else cc2=40;

if c3=0          then cc3=0;
                else if c3<=1000     then cc3=1;
                else if c3<=2000     then cc3=2;
                else if c3<=3000     then cc3=3;
                else if c3<=4000     then cc3=4;
                else if c3<=5000     then cc3=5;
                else if c3<=6000     then cc3=6;
                else if c3<=7500     then cc3=7;
                else if c3<=9000     then cc3=8;
                else if c3<=10500    then cc3=9;
                else if c3<=12000    then cc3=10;
                else if c3<=15000    then cc3=11;
                else if c3<=18000    then cc3=12;
                else if c3<=21000    then cc3=13;
                else if c3<=24000    then cc3=14;
                else if c3<=27000    then cc3=15;
```

```
                else if c3<=30000    then cc3=16;
                else if c3<=33000    then cc3=17;
                else if c3<=36000    then cc3=18;
                else if c3<=40000    then cc3=19;
                else if c3<=45000    then cc3=20;
                else if c3<=50000    then cc3=21;
                else if c3<=55000    then cc3=22;
                else if c3<=60000    then cc3=23;
                else if c3<=70000    then cc3=24;
                else if c3<=80000    then cc3=25;
                else if c3<=90000    then cc3=26;
                else if c3<=100000   then cc3=27;
                else if c3<=120000   then cc3=28;
                else if c3<=140000   then cc3=29;
                else if c3<=160000   then cc3=30;
                else if c3<=180000   then cc3=31;
                else if c3<=200000   then cc3=32;
                else if c3<=250000   then cc3=33;
                else if c3<=300000   then cc3=34;
                else if c3<=350000   then cc3=35;
                else if c3<=400000   then cc3=36;
                else if c3<=450000   then cc3=37;
                else if c3<=500000   then cc3=38;
                else if c3<=1000000  then cc3=39;
                else cc3=40;

if c4=0                 then cc4=0;
                else if c4<=1000     then cc4=1;
                else if c4<=2000     then cc4=2;
                else if c4<=3000     then cc4=3;
                else if c4<=4000     then cc4=4;
                else if c4<=5000     then cc4=5;
                else if c4<=6000     then cc4=6;
                else if c4<=7500     then cc4=7;
                else if c4<=9000     then cc4=8;
                else if c4<=10500    then cc4=9;
                else if c4<=12000    then cc4=10;
                else if c4<=15000    then cc4=11;
                else if c4<=18000    then cc4=12;
                else if c4<=21000    then cc4=13;
                else if c4<=24000    then cc4=14;
                else if c4<=27000    then cc4=15;
                else if c4<=30000    then cc4=16;
                else if c4<=33000    then cc4=17;
                else if c4<=36000    then cc4=18;
                else if c4<=40000    then cc4=19;
                else if c4<=45000    then cc4=20;
                else if c4<=50000    then cc4=21;
                else if c4<=55000    then cc4=22;
                else if c4<=60000    then cc4=23;
                else if c4<=70000    then cc4=24;
                else if c4<=80000    then cc4=25;
                else if c4<=90000    then cc4=26;
                else if c4<=100000   then cc4=27;
                else if c4<=120000   then cc4=28;
                else if c4<=140000   then cc4=29;
                else if c4<=160000   then cc4=30;
                else if c4<=180000   then cc4=31;
                else if c4<=200000   then cc4=32;
                else if c4<=250000   then cc4=33;
                else if c4<=300000   then cc4=34;
                else if c4<=350000   then cc4=35;
                else if c4<=400000   then cc4=36;
                else if c4<=450000   then cc4=37;
                else if c4<=500000   then cc4=38;
                else if c4<=1000000  then cc4=39;
                else cc4=40;

if c5=0          then cc5=0;
                else if c5<=1000     then cc5=1;
                else if c5<=2000     then cc5=2;
```

```
                else if c5<=3000     then cc5=3;
                else if c5<=4000     then cc5=4;
                else if c5<=5000     then cc5=5;
                else if c5<=6000     then cc5=6;
                else if c5<=7500     then cc5=7;
                else if c5<=9000     then cc5=8;
                else if c5<=10500    then cc5=9;
                else if c5<=12000    then cc5=10;
                else if c5<=15000    then cc5=11;
                else if c5<=18000    then cc5=12;
                else if c5<=21000    then cc5=13;
                else if c5<=24000    then cc5=14;
                else if c5<=27000    then cc5=15;
                else if c5<=30000    then cc5=16;
                else if c5<=33000    then cc5=17;
                else if c5<=36000    then cc5=18;
                else if c5<=40000    then cc5=19;
                else if c5<=45000    then cc5=20;
                else if c5<=50000    then cc5=21;
                else if c5<=55000    then cc5=22;
                else if c5<=60000    then cc5=23;
                else if c5<=70000    then cc5=24;
                else if c5<=80000    then cc5=25;
                else if c5<=90000    then cc5=26;
                else if c5<=100000   then cc5=27;
                else if c5<=120000   then cc5=28;
                else if c5<=140000   then cc5=29;
                else if c5<=160000   then cc5=30;
                else if c5<=180000   then cc5=31;
                else if c5<=200000   then cc5=32;
                else if c5<=250000   then cc5=33;
                else if c5<=300000   then cc5=34;
                else if c5<=350000   then cc5=35;
                else if c5<=400000   then cc5=36;
                else if c5<=450000   then cc5=37;
                else if c5<=500000   then cc5=38;
                else if c5<=1000000  then cc5=39;
                else cc5=40;
        run;

/*Frequency distribution of categorical charges*/
proc sgplot data=Nobio_5;
vbar cc1;
run;
proc sgplot data=Nobio_5;
vbar cc2;
run;
proc sgplot data=Nobio_5;
vbar cc3;
run;
proc sgplot data=Nobio_5;
vbar cc4;
run;
proc sgplot data=Nobio_5;
vbar cc5;
run;

/*obtain descriptive statistics for total annual charge*/
proc univariate data=Nobio_5;
var total2009 total2010 total2011 total2012 total2013;
        histogram total2009 total2010 total2011 total2012 total2013;
run;

/*group based trajectory analysis, final model*/
PROC TRAJ DATA=Nobio_5 OUTPLOT=OP OUTSTAT=OS OUT=OF OUTEST=OE ITDETAIL;
    ID ID; VAR cc1-cc5; INDEP T1-T5;
    MODEL ZIP; NGROUPS 6; ORDER 0 2 3 3 3 1; IORDER 2;
RUN;

%TRAJPLOT(OP,OS,'Charges vs. Time','ZIP Model','charges','Time, Year')
```

A.2 SAS OUTPUT FOR THE FINAL ZIP MODEL USING REDUCED FINANCIAL CHARGE

Maximum Likelihood Estimates
Model: Zero Inflated Poisson (ZIP)

Group	Parameter	Estimate	Standard Error	T for H0: Parameter=0	Prob > |T|
1	Intercept	0.88201	0.01331	66.248	0.0000
2	Intercept	1.73373	0.11212	15.463	0.0000
	Linear	-0.70612	0.07817	-9.033	0.0000
	Quadratic	0.19844	0.01204	16.483	0.0000
3	Intercept	7.00765	0.22136	31.657	0.0000
	Linear	-5.50242	0.32160	-17.110	0.0000
	Quadratic	1.74314	0.12021	14.501	0.0000
	Cubic	-0.17330	0.01325	-13.076	0.0000
4	Intercept	1.40392	0.18163	7.729	0.0000
	Linear	-1.03631	0.21533	-4.813	0.0000
	Quadratic	0.86111	0.07645	11.263	0.0000
	Cubic	-0.13019	0.00838	-15.534	0.0000
5	Intercept	-2.87687	0.24584	-11.702	0.0000
	Linear	7.53492	0.28196	26.723	0.0000
	Quadratic	-2.86484	0.10206	-28.069	0.0000
	Cubic	0.30810	0.01131	27.242	0.0000
6	Intercept	2.94690	0.02407	122.408	0.0000
	Linear	0.03498	0.00746	4.687	0.0000
	Alpha0	-6.23055	0.43051	-14.473	0.0000
	Alpha1	1.88658	0.26125	7.221	0.0000
	Alpha2	-0.21336	0.03800	-5.615	0.0000
	Group membership				
1	(%)	52.10149	1.29442	40.251	0.0000
2	(%)	8.06928	0.72653	11.107	0.0000
3	(%)	9.34635	0.78552	11.898	0.0000
4	(%)	12.12111	0.88423	13.708	0.0000
5	(%)	9.35572	0.76501	12.230	0.0000
6	(%)	9.00605	0.74000	12.170	0.0000

BIC=-27050.85 (N=8000) BIC=-27029.93 (N=1600) AIC=-26960.02 L=-26934.02

A.3 SAS CODE FOR THE FULL FINANCIAL CHARGE MODEL

```
/*group based trajectory analysis using full charge, final model*/
PROC TRAJ DATA=sortID_5 OUTPLOT=OP OUTSTAT=OS OUT=OF OUTEST=OE ITDETAIL;
    ID ID; VAR cc1-cc5; INDEP T1-T5;
    MODEL ZIP; NGROUPS 6; ORDER 3 3 3 3 3 1; IORDER 1;
RUN;

%TRAJPLOT(OP,OS,'Charges vs. Time','ZIP Model','charges','Time, Year')
```

A.4 SAS OUTPUT FOR THE FINAL ZIP MODEL USING FULL FINANCIAL CHARGE

Maximum Likelihood Estimates
Model: Zero Inflated Poisson (ZIP)

Group	Parameter	Estimate	Standard Error	T for H0: Parameter=0	Prob > |T|
1	Intercept	1.74982	0.14155	12.361	0.0000
	Linear	-1.06537	0.18872	-5.645	0.0000
	Quadratic	0.34698	0.07081	4.900	0.0000
	Cubic	-0.03416	0.00789	-4.329	0.0000
2	Intercept	-1.86553	0.18598	-10.031	0.0000
	Linear	5.45221	0.22333	24.413	0.0000
	Quadratic	-1.93518	0.08525	-22.699	0.0000
	Cubic	0.19464	0.00979	19.878	0.0000
3	Intercept	-1.61189	0.21033	-7.663	0.0000
	Linear	3.83442	0.23018	16.659	0.0000
	Quadratic	-1.02615	0.07815	-13.131	0.0000
	Cubic	0.08743	0.00817	10.701	0.0000
4	Intercept	2.82371	0.21867	12.913	0.0000
	Linear	-2.97808	0.26665	-11.168	0.0000
	Quadratic	1.27351	0.08986	14.172	0.0000
	Cubic	-0.13623	0.00907	-15.023	0.0000
5	Intercept	7.47794	0.19880	37.615	0.0000
	Linear	-6.37780	0.28656	-22.256	0.0000
	Quadratic	2.06293	0.10650	19.370	0.0000
	Cubic	-0.19957	0.01152	-17.318	0.0000
6	Intercept	3.19755	0.01948	164.104	0.0000
	Linear	-0.08302	0.00673	-12.335	0.0000
	Alpha0	-4.47524	0.18692	-23.942	0.0000
	Alpha1	0.50738	0.04554	11.141	0.0000
	Group membership				
1	(%)	40.11527	1.25678	31.919	0.0000
2	(%)	9.44210	0.77658	12.159	0.0000
3	(%)	9.56050	0.79306	12.055	0.0000
4	(%)	17.14981	1.00953	16.988	0.0000
5	(%)	10.12066	0.79872	12.671	0.0000
6	(%)	13.61167	0.89121	15.273	0.0000

BIC=-28620.09 (N=8000) BIC=-28596.75 (N=1600) AIC=-28518.77 L=-28489.77

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