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Serologic, Genetic, and Clinical Associations with Increased Healthcare Resource Utilization in IBD

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Abstract

Background—Inflammatory bowel diseases (IBD) are associated with significant morbidity and economic burden. The highly variable course of IBD creates a need for accurate predictors of clinical outcomes and health resource utilization (HRU) to guide treatment decisions early in the disease course.

Objective—We aimed to identify clinical, serologic and/or genetic markers associated with inpatient resource utilization in patients with ulcerative colitis (UC) and Crohn's disease (CD).

Methods—Patients with IBD with available genetic and serologic data who had at least one emergency department (ED) visit or hospitalization in a 3 year period were included. The primary outcome measure was HRU, which was measured by the All-Patient-Refined Diagnosis-Related-Group classification system. Univariate and multivariate linear and logistic regression models were used to identify clinical, serologic and genetic associations with HRU.

Results—A total of 858 patients (562 CD) were included. Anti-CBir1 seropositivity (p= 0.002, ES: 0.762 [95% CI 0.512 to 1.012]) and low socioeconomic status (SES) (p= 0.005, ES: 1.620 [95% CI 1.091 to 2.149]) were independently associated with higher HRU. CD status (p= 0.006, ES: −0.701 [95% CI −0.959 to −0.443]) was independently associated with lower inpatient HRU.

Conclusions—Anti-CBir1 antibody seropositivity, UC status, and low SES were independently associated with higher inpatient HRU in a cohort of IBD patients who required at least one ED visit or hospitalization. If verified by future studies, anti-CBir1 antibody status may be a useful biomarker of HRU when formulating management strategies to reduce disease complications and resource utilization.

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Keywords

Inflammatory bowel disease; Crohn's Disease; Ulcerative Colitis; Healthcare resource utilization

INTRODUCTION

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is an immune-mediated condition driven by chronic inflammation of the intestinal mucosa. It is characterized by a highly variable clinical course associated with periods of remission and severe relapses. Approximately 1.4 million people are currently affected by IBD in the United States (US).[1] In North America, the prevalence of CD ranges from 26 to 199 cases per 100,000 persons and for UC ranges from 37 to 246 cases per 100,000 persons.[1]

Most commonly diagnosed in late adolescence and early adulthood, IBD is an incurable disease that commits patients to lifelong medical care that often results in substantial medical expenses. In 2004, the mean annual treatment cost was $8265 per patient for CD and $5066 per patient for UC in the US. The total annual disease-attributable direct cost of IBD in the US is estimated to be $6.3 billion ($3.6 billion for CD and $2.7 billion for UC).[2] The majority of costs occur during the first year of diagnosis.[3–5] Surgery and hospitalizations were previously the primary drivers of cost but have recently taken a smaller role since the introduction of biologic agents.[2,6] In 2014, anti-Tumor Necrosis Factor (TNF) agents accounted for 64.1% of healthcare costs in CD and 31.4% in UC while hospitalizations and surgeries accounted for 19% and <1%, respectively, in CD and 23% and 1.4%, respectively, in UC.[7] It is unclear from published data whether anti-TNF use in IBD is associated with overall increases or decreases in healthcare expenditures when factoring the expense of therapy against the potential cost savings associated with reduced rates of hospitalizations and surgery.[8–10]

Therefore, IBD has a profound economic burden that will likely continue to grow. With ever-increasing pressures to reduce medical healthcare expenses, identifying patients at risk of increased healthcare resource utilization (HRU) is a potential strategy to reduce healthcare expenditures and improve outcomes by developing individualized management strategies. HRU is a measure of the amount or cost of utilized health services[11] In CD, younger age, fistulizing disease, use of biologics, disease activity, socioeconomic status, disease duration, gender, and previous need for steroid therapy are all associated with increased HRU.[2,12,13] In UC, disease severity, use of biologics, C-reactive protein levels, age, gender, and smoking status are associated with increased HRU.[12,14]

Although many clinical predictors of increased HRU have been identified, genetic and serologic predictors of HRU in IBD have not been well described or systematically investigated. One study has suggested that the *NOD2/CARD15* mutation Gly908Arg and ASCA seropositivity are associated with longer duration of surgical hospitalizations and higher surgical hospitalization costs in CD.[15] However, the study was limited to only CD patients and only analyzed for the presence of *NOD2/CARD15* mutations and ASCA. Thus, we aimed to expand upon these findings by identifying genetic and/or serologic markers

associated with hospital-based resource utilization using a retrospective cohort design that included both CD and UC patients.

METHODS

Subjects

We conducted a retrospective cohort study using subjects from the Cedars-Sinai Medical Center (CSMC) MIRIAD Research Repository (IRB #3358) who had at least one hospital admission or emergency department (ED) visit between 12/22/2011 and 12/31/2014. The CSMC IBD MIRIAD Research Repository contains clinical (demographics, disease phenotype, hospitalization history), serologic, and genetic data on 5,756 consented IBD patients prospectively followed at the CSMC IBD Center.

Healthcare Resource Utilization: Primary and Secondary Outcomes

Our primary inpatient HRU outcome measure was defined using the All-Patient-Refined Diagnosis-Related-Group (APR-DRG) classification system, which calculates national relative inpatient cost-weights based on co-morbidities, age, procedures, and principal diagnosis.[16]. We used the APR-DRG grouper[16] to identify the cost-weight for each inpatient hospitalization and recorded the sum of all APR-DRG cost-weights. Secondary outcomes included number of ED visits, hospital days, number of hospitalizations, number of medical admissions, and number of surgical admissions. A surgical admission was defined as a hospitalization that required an operation, which included elective, and urgent operations.

Clinical and Serological Phenotyping

Demographic data (age, sex, self-reported race, self-reported ethnicity, and insurance coverage) were obtained from the medical center's data warehouse. Patients' insurance coverage was identified as Dual Eligible if they were insured by both Medicare and Medi-Cal (California's Medicaid program) at time of first encounter, and being Dual Eligible was used as a proxy for low socioeconomic status.[17] IBD-associated serologies (anti–*Saccharomyces cerevisiae* antibodies [ASCA IgG and IgA], anti-nuclear cytoplasmic antibody [ANCA], anti-flagellin [anti-CBir1], and anti–outer membrane porin C [anti-OmpC]) were measured by enzyme-linked immunosorbent assay separately for UC and CD and with UC and CD as a combined IBD cohort.[18] In addition to individual qualitative and quantitative serologic correlations, quartile sums using ASCA, anti-CBir-1, and anti-OmpC were also assessed.

Genotyping

Genotyping of IBD-susceptibly genes[19–21] was performed at CSMC using Illumina Infinium ImmunoChip-v1 array as previously described.[19] Genotype determinations (allele calls) were made using GenomeStudio version 2011.1 with Genotyping Module Version 1.9.4. single nucleotide polymorphism (SNP)s underwent methodological review and were evaluated using several SNP statistic parameters, including SNP call frequency, cluster separation, replicate and heritability error rates, heterozygous excess, theta mean and deviation, and R intensity mean. Raw genotyping intensities were visually examined to ensure accurate allele-calling for reported SNPs. The average genotyping rate across all

samples that passed genotyping QC was 99.82%. Approximately 2% samples were genotyped in replicate (with both inter- and intra-plate replicates) and yielded >99.9% concordance for genotypes called.

Statistical Analysis

Univariate Analysis—The Wilcoxon test was used to evaluate differences between CD and UC patients in regard to primary and secondary HRU outcomes. A threshold of $p \leq 0.05$ was considered statistically significant. Associations with demographic characteristics, clinical factors, and serology were assessed using a linear regression model, with adjustment for age and gender when available. A permutation test for statistical significance was performed for all analyses to control for skewed distribution of the outcome variables. Given the number of clinical and demographic factors evaluated, a nominal threshold of $p \leq 0.01$ was considered statistically significant.

Genetic Analysis—The association between HRU and single SNPs was evaluated with linear regression model using PLINK, a whole genome association analysis toolset.[22,23] A nominal level of significance of $p \leq 0.05$ for the known IBD loci and $p \leq 1.0 \times 10\text{E-}5$ for the other SNPs in ImmunoChip was specified. Principle components from population stratification analysis were included to control for potential confounding, and a permutation test was performed in all analyses.[24]

Multivariate Analysis—Demographic, clinical, and serologic factors associated with HRU were included in the multivariate analysis using linear regression. A permutation test was performed for all analyses to control for the impact of the skewed distribution of the outcome variables. A level of $p \leq 0.01$ in the joint model was considered statistically significant.

Ethical Considerations

The study was approved by the Cedars-Sinai Medical Center Institutional Review Board (IRB# 42132, #3358). All subjects provided written informed consent upon enrollment into the MIRIAD registry.

RESULTS

Clinical Associations

A total of 858 patients met inclusion criteria, including 562 CD patients and 296 UC patients. Females represented 50.6% of patients. The average age was 41.1 years (Table 1). Average disease duration was 13.46 years. Dual Eligible status represented 5% of patients.

Compared to UC, patients with CD had significantly lower HRU (p=0.043, effect size (ES): −0.183 [95% CI −1.017 to −0.098]), fewer hospitalizations (p=0.0007, ES: −0.193 [95% CI −0.724 to −0.086]), fewer hospital days (p=0.004, ES: 0.217–0.217 [95% CI −5.036 to 0.847]), and fewer surgical admissions (p=0.027, ES: −0.292 [95% CI −0.437 to −0.134]).

In UC, current age had no significant association with HRU. In CD, older current age was significantly associated with higher HRU (p=0.005, ES: 0.021 [95% CI 0.006 to 0.035]),

more hospital days (p=0.006, ES: 0.090 [95% CI 0.026 to 0.154]), and more medical admissions (p=0.009, ES: 0.011 [95% CI 0.002 to 0.020]). When both CD and UC were analyzed as one single IBD cohort, older current age was significantly associated with higher HRU (p=0.007, ES 0.016 [95% CI 0.004 to 0.028]) and more hospital days (p=0.007, ES: 0.073 [95% CI 0.020 to 0.126]).

In UC, Dual Eligible status was significantly associated with higher HRU (p=0.0006, ES: 3.060 [95% CI 2.180 to 3.940]), more hospital days (p= 0.002, ES: 12.980 [95% CI 8.910 to 17.050]), more ED visits (p=0.00008, ES: 1.040 [95% CI 0.78 to 1.3]) and more hospitalizations (p=0.004, ES: 1.810 [95% CI 1.180 to 2.440]). In CD, Dual Eligible status was associated with more ED visits (p=0.007, ES: 0.650 [95% CI 0.410 to 0.890]). In the IBD cohort overall, Dual Eligible status was significantly associated with higher HRU (p=0.0009, ES: 1.630 [95% CI 1.140 to 2.120]), more hospital days (p=0.0007, ES: 7.420 [95% CI 5.230 to 9.610]), more ED visits (p=0.000005, ES: 0.801[95% CI 0.630 to 0.990]), and more hospitalizations (p=0.004, ES: 0.980 [95% CI 0.640 to 1.320]).

Finally, in UC, disease duration was not associated with HRU, but longer disease duration was associated with fewer surgical admissions (p=0.043, ES: −0.014 [95% CI −0.021 to −0.007]). In CD and the IBD cohort overall, disease duration was not associated with HRU or any secondary outcomes.

Serologic Associations

In UC, anti-Cbir1 antibody seropositivity (p=0.003, ES 1.865 [CI 95% 0.710 to 3.020]) and quantitative increased anti-Cbir1 antibody levels (p=0.005, ES 0.009 [CI 95% 0.020 to 0.052]) were significantly associated with higher HRU. Furthermore, anti-CBir1 antibody seropositivity (p=0.009, ES 7.538 [95% CI 2.000 to 13.076]) was associated with significantly more hospital days. In CD, anti-Cbir1 antibody seropositivity (p=0.09), and quantitative increased anti-Cbir1 antibody (p=0.02) were not significantly associated with HRU or any of the secondary outcomes. In the IBD cohort overall, anti-Cbir1 antibody seropositivity (p=0.010, ES: 0.574 [CI 95% 0.109–1.040]) and quantitative increased anti-Cbir1 antibody levels (p=0.002, ES: 0.009 [CI 95% 0.003–0.014]) were significantly associated with higher HRU. Other IBD-associated serologies including anti-OmpC antibody and pANCA were not associated with HRU or any of the secondary outcomes. Serological quartile sums were not associated with resource utilization.

Genetic Associations

Five hundred and twenty-five patients were included in the genetic analysis. Several IBD-susceptibility loci met the predetermined nominal level of significance of association of p<5× 10E-5 with HRU, including loci containing *ICOSLG, BACH2, ORMDL3, BCMS, EDIL3,* and *HLA-B/HLA-C*. Similarly, seven known IBD susceptibility SNPs met the nominal level of significance of association with HRU (Table 2). SNPs associated with *NOD2/CARD15* mutations were not significantly associated with HRU. Composite gene risk scores were not associated with HRU.[25]

Multivariate analysis

A multivariate analysis of the most significant variables, including anti-Cbir1 antibody seropositivity, age, Dual Eligible status, and diagnosis of CD, was conducted (Table 3). Anti-CBir1 antibody seropositivity remained significantly associated with higher HRU (p= 0.002, ES: 0.762 [95% CI 0.512 to 1.012]) and an increased number of hospital days (p = 0.005, ES: 3.142 [95% CI 2.039 to 4.245]). Older current age was no longer significantly associated with HRU or the other secondary outcomes. Dual Eligible status remained significantly associated with higher HRU (p= 0.005, ES: 1.620 [95% CI 1.091 to 2.149]), greater number of hospital days (p= 0.001, ES: 8.751 [95% CI 6.415 to 11.087]), greater number of ED visits (p= 0.0003, ES: 0.906 [95% CI 0.720 to 1.092]), and greater number of hospitalizations (p= 0.007, ES: 1.080 [95% CI 0.712 to 1.448]). Finally, CD had significantly lower HRU than UC (p= 0.006, ES: −0.701 [95% CI −0.959 to −0.443]), fewer hospital days (p= 0.001, ES: −3.733 [95% CI −4.873 to −2.593]), fewer hospitalizations (p= 0.007, ES: −0.486 [95% CI −0.663 to −0.303]) and fewer surgical admissions (p= 0.00002, ES:−0.371 [95% CI −0.452 to −0.290]).

DISCUSSION

The current estimated annual cost of treating IBD is $6.3 billion in the US, and costs are rising despite advancements in treatments.[2,8,10,26] The ability to identify patients at risk of higher HRU could create an opportunity to reduce healthcare expenditures by individualizing management strategies in order to reduce disease complications, hospitalizations, and surgeries. We were able to both confirm a few known clinical associations with HRU and describe novel serologic and genetic associations with HRU.

Although several clinical features have previously been associated with higher HRU, data on predictive biomarkers is lacking. In a smaller cohort of CD patients, the *NOD2/CARD15* mutation Gly908Arg and ASCA seropositivity were associated with higher surgical hospitalization costs and longer surgical hospitalization duration, but we were unable to replicate these findings.[15] In a multivariable analysis, important factors predictive of HRU included anti-CBir1 antibody status, CD status, and socioeconomic status. Furthermore, we identified several genes which met nominal levels of significance that are potentially predictive of HRU.

Anti-Cbir1 antibody is a serologic marker more commonly known to be associated with CD.[27,28] Found on the *Clostridium* species, CBir1 flagellin activates NF-κb through interactions with TLR5 and, subsequently, induces many proinflammatory cytokines.[29,30] Anti-CBir1 antibody has been associated with more complicated and aggressive Crohn's disease phenotypes, including small bowel, penetrating, and fibrostenosing disease.[28,31,32] These patients often experience severe disease complications, requiring multiple surgeries and expensive pharmacologic therapies.

Even after controlling for CD status in the multivariable analysis, we found that anti-CBir1 antibody remained significantly associated with increased HRU. Furthermore, anti-CBir1 seropositivity and quantitative increased levels of anti-CBir1 were significantly associated with increased inpatient HRU in the UC cohort. This potentially suggests that anti-Cbir1

antibody is associated with a unique subset of UC patients who require more aggressive therapy. One subset of UC patients in which anti-CBir1 antibody may have a potential role in HRU is UC patients status post ileal pouch anal anastomosis (IPAA). Studies have suggested that UC patients with anti-CBir1 seropositivity are at higher risk of developing pouchitis after IPAA. Fleshner, et al. demonstrated that preoperative anti-CBir1 seropositivity is associated with an increased incidence of acute pouchitis in patients who have low-level pANCA expression. Preoperative anti-CBir1 seropositivity is also associated with an increased incidence of chronic pouchitis in patients who have high-level pANCA expression.[33] Moreover, anti-CBir1 seropositivity is associated with infliximab use in pouchitis.[34] Finally, anti-CBir1 seropositivity has been suggested to be an independent risk factor for developing CD-like pouchitis, which eventually requires treatment with immunomodulators and biologics in 23%–45% of patients.[35–38]

The existing data thus suggest that anti-CBir1 antibody may represent a population of both UC and CD patients who are at risk for developing severe and complicated disease and may theoretically require more healthcare resources to manage such as hospitalizations, outpatient visits, surgeries, and aggressive pharmacologic therapy. Our study contributes to the literature by demonstrating that anti-CBir1 antibody is associated with increased inpatient HRU in a large cohort of IBD patients independent of diagnosis. While prospective studies are needed to confirm these findings, our results suggest that IBD patients with anti-CBir1 antibody seropositivity warrant careful consideration for more aggressive therapy and closer monitoring early in the disease course.

In addition to serologic biomarkers, we found clinical factors associated with inpatient HRU. In the literature, CD is a well-established predictor of resource utilization and is associated with higher hospitalization costs, more hospitalizations, and more bowel resections than UC.[8–10] In fact, rates of hospitalizations have increased in CD but have remained stable in UC. On the other hand, CD is associated with shorter hospital stays than UC.[8] In our cohort, we confirmed CD was associated with shorter hospital stays, but it was associated with lower overall inpatient HRU and fewer surgical admissions. There may be several explanations to reconcile this discrepancy. The observed differences may be a consequence of varying length of follow-up. We collected data within a three-year period, and the higher number of surgical admissions observed in UC likely reflects the multiple operations required to complete an IPAA. Thus, CD patients may require more surgical interventions throughout their disease course, but UC patients are more likely to require more surgeries within a short period of time immediately following their initial operation to complete their IPAA. Also, while most studies included only surgeries involving bowel resections or surgical admissions with a primary discharge diagnosis of UC or CD, our data included all inpatient surgeries, such as extra-intestinal surgeries that may or may not be related to IBD. It is possible that UC patients require more surgeries for extra-intestinal complications than CD patients. To our knowledge, this topic has not been well studied and may warrant further investigation in future studies. Overall, UC patients tended to have longer hospital stays and potentially utilize more inpatient resources, which are likely surgery related. Further studies are needed to confirm this and identify major drivers of inpatient HRU in UC patients compared to CD patients.

Socioeconomic status (SES), which is widely represented by Dual Eligible status in the literature, is also a well-described driver of HRU.[17] Socioeconomic status is associated with disparities in health services delivery for numerous chronic diseases, and low SES is a well-described risk factor for poor health outcomes and higher HRU.[17,39–41] In IBD, low SES is also associated with increased healthcare costs including higher hospitalization rates, ED visits, and inpatient mortality,[13,42,43] although low SES has not been shown to influence surgery rates.[42–44] Similarly, we found that low SES was associated with higher HRU, longer hospital stays, more hospitalizations, and more ED visits. These findings may have several possible explanations. While lower SES may theoretically be associated with disease severity or phenotype, one study in CD did not find that association.[42] Medication adherence may play a role, but studies have not found a clear association between SES and medication adherence in IBD.[42,45] Finally, our findings may indicate a shortcoming in outpatient healthcare. Low income patients have higher rates of potentially preventable hospitalizations. [46] Therefore, patients of lower SES may lack access to critical resources needed for a timely diagnosis and experience delayed care that might have prevented disease complications. This could result in more frequent, and possibly preventable, hospitalizations, especially during an active flare, and eventually lead to surgery due to poorly controlled disease. Ultimately, patients of low SES may represent a more vulnerable patient population in IBD that requires more attention and support throughout their disease course. Further investigation is required to identify interventions that can help reduce disease complications and HRU in low SES patients with IBD.

In the general population, older age is a known predictor of increased HRU.[47,48] However, in the IBD population, aging has not been shown to significantly influence IBD-associated direct healthcare costs.[49] In fact, higher HRU is observed in pediatric IBD patients.[2,4] In our cohort, younger age was not associated with HRU. This discrepancy is likely a consequence of the majority of our cohort being composed of adults.

Finally, we found several genes that met nominal level of significance that are potentially predictive of increased HRU. Future studies with larger cohorts are needed to further clarify the role of genetic predictors of HRU in IBD.

Our study has several limitations, including its retrospective design. Furthermore, we were unable to control for IBD versus non-IBD related visits, different disease phenotypes within CD and UC, and known clinical features associated with increased HRU such as disease severity. Future studies should control for these variables. Finally, our cohort only included patients with at least one ED visit or hospitalization but did not include patients who were well-maintained as outpatients. Thus, our findings may not be applicable to the general IBD population and warrant careful interpretation. On the other hand, strengths include a novel perspective in IBD management and a relatively large sample size for genetic and serologic analysis. Our findings can form the basis of future studies to establish the predictive value of anti-CBir1 antibody status and genetics for HRU in IBD patients.

In conclusion, we have demonstrated that anti-CBir1 antibody seropositivity, ulcerative colitis, and low SES are independently associated with higher inpatient HRU in a cohort of IBD patients who required at least one ED visit or hospitalization. These findings suggest

that anti-CBir1 antibody may play an important role in UC in addition to its known role in CD. Our findings also suggest that anti-CBir1 antibody seropositivity may be helpful for identifying patients at risk for increased HRU. If verified by future studies, clinicians may consider routinely screening for anti-CBir1 antibody for prognostic information as well as informing management strategies early in the disease course to reduce financial burden.

References

1. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology. 2004; 126:1504–17. [PubMed: 15168363]
2. Kappelman MD, Rifas-Shiman SL, Porter CQ, et al. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. Gastroenterology. 2008; 135:1907–13. [PubMed: 18854185]
3. Burisch J, Vardi H, Pedersen N, et al. Costs and resource utilization for diagnosis and treatment during the initial year in a European inflammatory bowel disease inception cohort: an ECCO-EpiCom Study. Inflamm Bowel Dis. 2015; 21:121–31. [PubMed: 25437816]
4. Bernstein CN, Longobardi T, Finlayson G, Blanchard JF. Direct medical cost of managing IBD patients: a Canadian population-based study. Inflamm Bowel Dis. 2012; 18:1498–508. [PubMed: 22109958]
5. Odes S, Vardi H, Friger M, et al. Cost analysis and cost determinants in a European inflammatory bowel disease inception cohort with 10 years of follow-up evaluation. Gastroenterology. 2006; 131:719–28. [PubMed: 16952541]
6. Saro C, da la Coba C, Casado MA, Morales JM, Otero B. Resource use in patients with Crohn's disease treated with infliximab. Aliment Pharmacol Ther. 2007; 26:1313–23. [PubMed: 17850419]
7. van der Valk ME, Mangen MJ, Leenders M, et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFalpha therapy: results from the COIN study. Gut. 2014; 63:72–9. [PubMed: 23135759]
8. Bewtra M, Su C, Lewis JD. Trends in hospitalization rates for inflammatory bowel disease in the United States. Clin Gastroenterol Hepatol. 2007; 5:597–601. [PubMed: 17382602]
9. Nguyen GC, Tuskey A, Dassopoulos T, Harris ML, Brant SR. Rising hospitalization rates for inflammatory bowel disease in the United States between 1998 and 2004. Inflamm Bowel Dis. 2007; 13:1529–35. [PubMed: 17828784]
10. Xu J, Tang M, Shen J. Trends and Factors Affecting Hospitalization Costs in Patients with Inflammatory Bowel Disease: A Two-Center Study over the Past Decade. Gastroenterol Res Pract. 2013; 2013:267630. [PubMed: 24307891]
11. Agency for Healthcare Research and Quality; 2014. Part III. Introduction to Resource Use/ Efficiency Measures. (Accessed at http://www.ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/perfmeasguide/perfmeaspt3.html.)
12. Sulz MC, Siebert U, Arvandi M, et al. Predictors for hospitalization and outpatient visits in patients with inflammatory bowel disease: results from the Swiss Inflammatory Bowel Disease Cohort Study. Eur J Gastroenterol Hepatol. 2013; 25:790–7. [PubMed: 23571609]
13. Greenberg D, Schwartz D, Vardi H, et al. Health-Related Utility Weights in a Cohort of Real-World Crohn's Disease Patients. J Crohns Colitis. 2015; 9:1138–45. [PubMed: 26374662]
14. Bodger K, Yen L, Szende A, et al. Medical resource utilization and associated costs in patients with ulcerative colitis in the UK: a chart review analysis. Eur J Gastroenterol Hepatol. 2014; 26:213–21. [PubMed: 24145865]
15. Odes S, Friger M, Vardi H, et al. Role of ASCA and the NOD2/CARD15 mutation Gly908Arg in predicting increased surgical costs in Crohn's disease patients: a project of the European Collaborative Study Group on Inflammatory Bowel Disease. Inflamm Bowel Dis. 2007; 13:874–81. [PubMed: 17278126]
16. Averill R, Goldfield N, Hughes J, et al. What are APR-DRGs? An Introduction to Severity of Illness and Risk of Mortality Adjustment Methodology. 3M Health Information Systems. 2003

17. Samson LW, Finegold K, Ahmed A, Jensen M, Filice CE, Joynt KE. Examining Measures of Income and Poverty in Medicare Administrative Data. Med Care. 2016
18. Mow WS, Vasiliauskas EA, Lin YC, et al. Association of antibody responses to microbial antigens and complications of small bowel Crohn's disease. Gastroenterology. 2004; 126:414–24. [PubMed: 14762777]
19. Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature. 2012; 491:119–24. [PubMed: 23128233]
20. Liu JZ, van Sommeren S, Huang H, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. Nat Genet. 2015; 47:979–86. [PubMed: 26192919]
21. Huang H, Fang M, Jostins L, et al. Association mapping of inflammatory bowel disease loci to single variant resolution. 2015 In Print.
22. Purcell, S. PLINK V1.07.
23. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007; 81:559–75. [PubMed: 17701901]
24. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet. 2006; 38:904–9. [PubMed: 16862161]
25. Cleynen I, Boucher G, Jostins L, et al. Inherited determinants of Crohn's disease and ulcerative colitis phenotypes: a genetic association study. Lancet. 2016; 387:156–67. [PubMed: 26490195]
26. Coward S, Heitman SJ, Clement F, et al. Ulcerative colitis-associated hospitalization costs: a population-based study. Can J Gastroenterol Hepatol. 2015; 29:357–62. [PubMed: 26079072]
27. Lodes MJ, Cong Y, Elson CO, et al. Bacterial flagellin is a dominant antigen in Crohn disease. J Clin Invest. 2004; 113:1296–306. [PubMed: 15124021]
28. Targan SR, Landers CJ, Yang H, et al. Antibodies to CBir1 flagellin define a unique response that is associated independently with complicated Crohn's disease. Gastroenterology. 2005; 128:2020–8. [PubMed: 15940634]
29. Hayashi F, Smith KD, Ozinsky A, et al. The innate immune response to bacterial flagellin is mediated by Toll-like receptor 5. Nature. 2001; 410:1099–103. [PubMed: 11323673]
30. Means TK, Hayashi F, Smith KD, Aderem A, Luster AD. The Toll-like receptor 5 stimulus bacterial flagellin induces maturation and chemokine production in human dendritic cells. J Immunol. 2003; 170:5165–75. [PubMed: 12734364]
31. Dubinsky MC, Lin YC, Dutridge D, et al. Serum immune responses predict rapid disease progression among children with Crohn's disease: immune responses predict disease progression. Am J Gastroenterol. 2006; 101:360–7. [PubMed: 16454844]
32. Papadakis KA, Yang H, Ippoliti A, et al. Anti-flagellin (CBir1) phenotypic and genetic Crohn's disease associations. Inflamm Bowel Dis. 2007; 13:524–30. [PubMed: 17260364]
33. Fleshner P, Ippoliti A, Dubinsky M, et al. Both preoperative perinuclear antineutrophil cytoplasmic antibody and anti-CBir1 expression in ulcerative colitis patients influence pouchitis development after ileal pouch-anal anastomosis. Clin Gastroenterol Hepatol. 2008; 6:561–8. [PubMed: 18378498]
34. Kelly OB, Rosenberg M, Tyler AD, et al. Infliximab to Treat Refractory Inflammation After Pelvic Pouch Surgery for Ulcerative Colitis. J Crohns Colitis. 2016; 10:410–7. [PubMed: 26721938]
35. Coukos JA, Howard LA, Weinberg JM, Becker JM, Stucchi AF, Farraye FA. ASCA IgG and CBir antibodies are associated with the development of Crohn's disease and fistulae following ileal pouch-anal anastomosis. Dig Dis Sci. 2012; 57:1544–53. [PubMed: 22311367]
36. Truta B, Li DX, Mahadevan U, et al. Serologic markers associated with development of Crohn's disease after ileal pouch anal anastomosis for ulcerative colitis. Dig Dis Sci. 2014; 59:135–45. [PubMed: 24091907]
37. Tyler AD, Milgrom R, Xu W, et al. Antimicrobial antibodies are associated with a Crohn's disease-like phenotype after ileal pouch-anal anastomosis. Clin Gastroenterol Hepatol. 2012; 10:507–12 e1. [PubMed: 21963956]

38. Shen B, Remzi FH, Brzezinski A, et al. Risk factors for pouch failure in patients with different phenotypes of Crohn's disease of the pouch. Inflamm Bowel Dis. 2008; 14:942–8. [PubMed: 18300279]
39. Fiscella K, Franks P, Gold MR, Clancy CM. Inequality in quality: addressing socioeconomic, racial, and ethnic disparities in health care. JAMA. 2000; 283:2579–84. [PubMed: 10815125]
40. Epstein AM, Stern RS, Weissman JS. Do the poor cost more? A multihospital study of patients' socioeconomic status and use of hospital resources. N Engl J Med. 1990; 322:1122–8. [PubMed: 2108331]
41. Mustard CA, Frohlich N. Socioeconomic status and the health of the population. Med Care. 1995; 33:DS43–54. [PubMed: 7500669]
42. Nahon S, Lahmek P, Macaigne G, et al. Socioeconomic deprivation does not influence the severity of Crohn's disease: Results of a prospective multicenter study. Inflamm Bowel Dis. 2009; 15:594–8. [PubMed: 19085998]
43. Nguyen GC, Bayless TM, Powe NR, Laveist TA, Brant SR. Race and health insurance are predictors of hospitalized Crohn's disease patients undergoing bowel resection. Inflamm Bowel Dis. 2007; 13:1408–16. [PubMed: 17567876]
44. Nguyen GC, Laveist TA, Gearhart S, Bayless TM, Brant SR. Racial and geographic variations in colectomy rates among hospitalized ulcerative colitis patients. Clin Gastroenterol Hepatol. 2006; 4:1507–13. [PubMed: 17162242]
45. Nguyen GC, LaVeist TA, Harris ML, Datta LW, Bayless TM, Brant SR. Patient trust-in-physician and race are predictors of adherence to medical management in inflammatory bowel disease. Inflamm Bowel Dis. 2009; 15:1233–9. [PubMed: 19177509]
46. Billings J, Zeitel L, Lukomnik J, Carey TS, Blank AE, Newman L. Impact of socioeconomic status on hospital use in New York City. Health Aff (Millwood). 1993; 12:162–73.
47. Demers M. Factors explaining the increase in cost for physician care in Quebec's elderly population. CMAJ. 1996; 155:1555–60. [PubMed: 8956832]
48. Barer ML, Pulcins IR, Evans RG, Hertzman C, Lomas J, Anderson GM. Trends in use of medical services by the elderly in British Columbia. CMAJ. 1989; 141:39–45. [PubMed: 2731101]
49. van der Have M, Mangen MJ, van der Valk ME, et al. Effect of aging on healthcare costs of inflammatory bowel disease: a glimpse into the future. Inflamm Bowel Dis. 2014; 20:637–45. [PubMed: 24518606]

Table 1

Demographic characteristics of study cohort

	All Patients
Number	858
Current Age (years), mean (SD)	44.3 (18.3)
Current Age (years), range	13–96
Current Age (years), median	41
Sex (% female)	50.6
Self-Reported Race (%)	
Caucasian	88.0
African American	6.2
Asian	2.8
Other	3.0
Self-Reported Ethnicity (%)	
Hispanic	6.6
Non-Hispanic	93.2
N/A	0.1
Disease (%)	
Crohn's Disease	65.5
Ulcerative Colitis	34.5
Disease Duration (years), mean (SD)	13.46 (11.9)
Dual Eligible Status * **(%)**	4.8

* Dual eligible = receiving benefits from both Medicare and Medicaid

Table 2

Seven known IBD susceptibility SNPs associated with higher total inpatient resource utilization

SNP	Candidate Locus	*p*-value	Effect Size (95% CI)
rs11742570	*PTGER4*	0.004	0.53 (0.20–0.85)
rs2072711	*NCF4*	0.003	0.67 (0.25–1.09)
rs2457996	*CXCL5*	0.0007	0.93 (0.42–1.45)
rs6920220	*TNFAIP3*	0.003	1.22 (0.45–1.99)
rs7554511	*C1orf106*	0.003	0.59 (0.16–1.023)
rs7725339	*IL12B*	0.005	0.55 (0.16–0.93)
rs7746082	*PRDM1*	0.002	0.54 (0.21–0.88)

Table 3

Univariate Analysis of Clinical Factors Associated with higher inpatient HRU in IBD patients

Clinical Factors	***p*-value**	**Effect Size (95% CI)**
Current Age (years)	0.007	0.016 [0.004 to 0.028])
Sex	NS	-
Race		
Caucasian	NS	-
African American	NS	-
Asian	NS	-
Other	NS	-
Ethnicity		
Hispanic	NS	-
Non-Hispanic	NS	-
Diagnosis		
Ulcerative colitis	Reference	-
Crohn's Disease	0.043	−0.183 [−1.017 to −0.098]
Disease Duration (years)	NS	-
Dual Eligible Status	0.0009	1.630 [1.140 to 2.120]

Table 4

Univariate Analysis of Serologic Associations with higher inpatient HRU in IBD patients based on Seropositivity

Serology	*p*-value	Effect Size (95% CI)
Anti-CBir1	0.010	0.574 [0.109–1.040]
Anti-OmpC	NS	-
Anti-I2	NS	-
ASCA	NS	-
ANCA	NS	-

Table 5

Multivariate Analysis of Clinical and Serologic markers associated with higher inpatient HRU

Serologic/Clinical Marker	*p*-value	Effect Size (95% CI)
Anti-Cbir1 Seropositivity	0.002	0.762 (0.512–1.012)
Crohn's Disease	0.006	−0.701 (−0.959 – −0.443)
Dual Insurance Status	0.005	1.620 (1.091–2.149)
Age (years)	0.256	-