USING REAL-WOLRD HEALTHCARE DATA TO DEFINE AND PREVENT COMPLICATIONS IN INFLAMMATORY BOWEL DISEASE

by

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USING REAL-WOLRD HEALTHCARE DATA TO DEFINE AND PREVENT COMPLICATIONS IN INFLAMMATORY BOWEL DISEASE

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Inflammatory bowel disease (IBD) is a collection of chronic, immune mediated disorders of the gastrointestinal track, characterized by relapsing and remitting disease activity. Despite our growing understanding of risk factors associated with developing disease, we still lack understanding of the impact of disease complications and how to best avoid complications with preventive care. Two known complications of IBD include the increased predisposition to *Clostridium difficile* infection and the increased risk of non-melanoma and melanoma skin cancers. This thesis aims to (1) define the long-term impact of *Clostridium difficile* infection on IBD patients after accounting for patients' inherent risk of infection, (2) evaluate the rate at which IBD patients access dermatologic preventive care for skin cancer screening, and (3) model the cost-effectiveness of melanoma screening strategies in the IBD patient population.

We found that *Clostridium difficile* infection was significantly associated with more steroid and antibiotic exposure, elevated inflammatory markers, increased disease activity, worse quality of life, and increased healthcare utilization in the year of infection. During the year after infection, patients in the *Clostridium difficile* group continued to have increased exposure to *Clostridium difficile* targeted antibiotics and other systemic antibiotics, while having more clinic visits, telephone encounters, and a five-fold increase in healthcare charges.

We determined that 21% of IBD patients utilized dermatology from 2010-2016, and 2.6% of patients had at least one total body exam for skin cancer screening. Between 8% and 11% of patients recommended by gastroenterology preventive care guidelines visited dermatology each

year, suggesting only a small proportion of IBD patients recommended for screening obtain dermatologic care.

Finally, we used a Markov model to estimate intervention costs and effectiveness of melanoma screening in the IBD population. We found screening for melanoma in IBD patients was more effective, but expensive. Among model variations, screening every other year was the most cost-effective strategy.

In conclusion, the dissertation reveals the long-term impact of infection among IBD patients, the underutilization of dermatologic preventive care, and provides a cost effectiveness model to inform the development of skin cancer screening programs in IBD.

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PREFACE

I would like to begin this document by sharing that this work did not happen in isolation. The work is a product of thoughtful mentorship, collaboration, feedback, and support from my committee and others. Upon joining the University of Pittsburgh Medical Scientist Training Program, I was interested in pursuing patient centered, translational research. During my interview I met Dr. David Binion, who has a particular way of inspiring trainees to take on complex research challenges. He instills independence and confidence in his trainees, encouraging them to work outside their comfort zone. Without his mentorship, this work and other projects would not have come to fruition. It has been an honor to be a part of his team.

I want to recognize and acknowledge the important contributions of Drs. Ben Click and Claudia Ramos-Rivers who work closely with Dr. Binion. They have guided my research through thoughtful consideration of data, multiple rounds of paper revisions, and more. Much of this work would not have been driven to the stages it has reached without their guidance.

To the members of my committee: your expertise, feedback and overall support have been critical to research progress and my personal growth over the last year. I cannot begin to thank you for your contributions to this work, and the new techniques and information I continue to learn from you. I have been fortunate to have a thoughtful and invested committee to enhance my training and resulting research.

I also would like to thank my family, including the never-ending support from my parents who encouraged me to follow my academic dreams, even as I left Wisconsin. They have made endless trips to Pittsburgh to help us with moving, childcare, and house projects which afforded me so much more time to dedicate to scholarly work. To my brother and his legacy – although he never understood why I liked school so much, he taught me how to work hard while truly enjoying life. His memory keeps me grounded in what is genuinely important, and for that I am forever grateful. Finally, I would like to thank my husband, Paul, and my son, Drew, for their unwavering support and encouragement. Pursing medical and graduate school has been a journey in which you have both unselfishly joined. The memories of my graduate school years will include the rigor of education, but also the happiness of our wedding, the many sleepless nights as new parents, and the pleasure of watching my newborn grow into a young boy. You have made life and learning so enjoyable, and for this – I thank you with my whole heart.

1.0 INTRODUCTION

1.1 INFLAMMATORY BOWEL DISEASE (IBD)

1.1.1 Epidemiology of IBD

The inflammatory bowel diseases (IBDs), consisting primarily of Crohn's disease (CD) and ulcerative colitis (UC), are complex immune-mediated disorders of the gastrointestinal tract affecting over 3 million people in Europe and North America with an increasing incidence of 39.4 cases per 100,000 person years in North America.[1–3] IBD is associated with increased morbidity and mortality, resulting in $6.3 billion in direct healthcare costs.[4,5] Although the etiology of IBD is unknown, complex interactions between diet, environment and the immune system of a genetically susceptible host are thought to contribute to the development and natural history of IBD.[6]

1.1.2 Complications of IBD

There are a number of known complications of IBD, including gastrointestinal infection, malnutrition, extraintestinal manifestations of disease, increased risk of intestinal and extraintestinal malignancy, and side effects attributed to medication exposures.[7–10] IBD is frequently associated with a multitude of psychiatric comorbidities of disease including poor

quality of life, depression, and anxiety.[11] Abdominal pain contributes further to psychiatric complexities of IBD, as many patients rely on pain management to cope with their symptoms.[12–14] Throughout our work we have discovered that complications of disease, especially psychiatric complications and pain, are associated with increased financial healthcare charges, which contribute to the overall cost burden of IBD.[15–17] Understanding the natural history of complications and implementing strategies to prevent IBD related complications has the potential to reduce overall cost of care while positively impacting patient care and wellbeing.

1.1.2.1 Clostridium difficile infection

The enteric pathogen *Clostridium difficile* has become an increasingly challenging and costly complication in IBD. Unfortunately, the incidence of *Clostridium difficile* infection (CDI) in IBD is increasing.[18] CDI in IBD is associated with increased healthcare charges and longer hospital stays.[19,20] While traditional risk factors of antibiotic exposure and healthcare contact contribute to the development of CDI, recent studies have suggested that IBD patients themselves are at an increased risk for primary CDI, and have a significantly greater chance of developing recurrent CDI compared to the general population.[21,22] It is hypothesized that the increased risk of initial infection and recurrent CDI in IBD is related to disease inflammation, dysregulated immune system, and gut microbiome dysbiosis.[23]

Despite our growing appreciation of the severity of CDI in IBD, there is still much that we do not know. It is unknown how the natural history of disease changes after infection, and if there are long-term effects on healthcare utilization. We also assume from the literature that CDI results in increased healthcare utilization, but the quantification of these changes in the year after infection is not clearly defined, as appropriate controls for these studies have been limited.

1.1.2.2 Extraintestinal manifestations

In addition to infectious complications of IBD, many patients experience extraintestinal manifestations of IBD. It is estimated that 40% of patients will experience extraintestinal manifestations, with complications of the skin being one of the most common.[24] Between 22-75% of CD patients, and 5-11% of UC patients are thought to have mucocutaneous findings that are associated with IBD.[25] There is a range of cutaneous findings associated with IBD. Certain cutaneous findings are related to disease severity and IBD pathophysiology including pyoderma gangrenosum and oral aphthous ulcers, while others are more generally associated with IBD including erythema nodosum and psoriasis.[25] Finally, there are cutaneous complications of IBD that are due to adverse reactions of medications including shingles and generalized rash.[8] Despite the high percentage of patients that are likely to experience dermatologic problems, it is uncertain how many IBD patients are actively seeking dermatologic care, and for what reasons.

1.1.2.3 Skin Cancer

A subset of skin complications in IBD includes the increased risk of melanoma and non-melanoma skin cancers (NMSC).[26–28] IBD is associated with a 37% increase in the risk of melanoma, a figured which is thought to be independent of medication exposure.[26] There are also studies that suggest medication exposures may increase the risk of melanoma even further among IBD patients exposed to biologics.[28–30] An estimate of the incidence rate ratio for NMSC in IBD compared to controls is 1.64 (95% CI: 1.51-1.78).[27] Medication exposures, especially thiopurines, are thought to contribute to the burden of NMSC in IBD.[31] Interestingly, many gastroenterologists surveyed were unaware of the risk of NMSC and its association with medication exposures.[32] This suggests that patients may need to self-advocate for skin cancer screening and dermatologic care. However, is unknown how many IBD patients undergo skin

cancer screening though a total body skin exam. It is also unknown if the proportion of patients who obtain skin cancer screening aligns with medication exposures and age as recommended by the current IBD specific preventive care guidelines.

Finally, a handful of studies over the last two decades have evaluated the cost-effectiveness of melanoma screening programs.[33–36] Annual population-wide screening is likely cost prohibitive due to low prevalence of melanoma, and may result in unnecessary morbidity from screening in low risk persons. Previous cost effectiveness studies agree that screening high-risk patients, in contrast to the entire population, for melanoma may be the most cost-effective strategy. However, the cost effectiveness of melanoma screening has not been evaluated in the IBD population. Additionally, the published cost effectiveness studies model screening strategies that may be difficult to translate to IBD patients, including primary care based screening and within a clinical trial.[35,36] Therefore, it is still uncertain of how the cost-effectiveness of screening by a dermatologist translates to IBD patients with intermediate risk.

1.2 STATEMENT OF PROBLEM AND MAJOR QUESTIONS

There are many complications of IBD that are not sufficiently addressed in the literature. We will begin by outlining the methodology of generating large, real-world observational data from the electronic medical record to facilitate in-depth patient phenotyping in IBD. The methodology and data generated from the IBD research registry are used to support the clinical questions addressed in the first two dissertation subprojects.

As incidence and awareness of CDI in IBD are increasing, we are beginning to understand some of the risk factors associated with infection. However, we are still uncertain

how patients' natural history of disease is modified after infection. We will address this gap in the literature in our first dissertation sub-project by generated a propensity matched control cohort to which we can compare IBD patients with CDI before, during, and after infection.

There has also been a growth in our understanding of the extraintestinal manifestations of disease, and the increased risk of dermatologic malignancies in IBD. However, it is unclear how physician preventive care guidelines translate into patterns of dermatologic care. The second sub-project in this dissertation aims to understand the rates of and reasons fore dermatologic care among IBD patients with an emphasis on skin cancer screening.

Finally, while guidelines recommending skin cancer screening among IBD patients exist in the literature, these have not been broadly implemented in clinical care. Therefore, we will use Markov models to evaluate the cost-effectiveness of melanoma screening in IBD patients in the last sub-project of the dissertation.

2.0 IBD RESEARCH REGISTRY METHODOLOGY

Adapted with permission from publication in *Digestive Diseases & Sciences*:

Development of an Inflammatory Bowel Disease Research Registry Derived from Observational Electronic Health Record Data for Comprehensive Clinical Phenotyping

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2.1 INTRODUCTION

Inflammatory bowel disease (IBD) consists of two main entities: Crohn's disease (CD) and ulcerative colitis (UC). IBD is estimated to affect up to two million Americans, with an increasing annual incidence of 39.4 cases per 100,000 person years in North America.[2] CD and UC result in morbidity, disability, and heightened mortality, generating approximately $6.3 billion in direct healthcare costs and an additional $3.6 billion in indirect costs due to loss of productivity.[4,5,37] The clinical course of IBD is variable and often unpredictable. IBD severity ranges from mild symptoms to severely debilitating disease. Therefore, IBD encompasses a large spectrum of severity, disease duration, disease course, and complexity of disease-related extra-intestinal manifestations. This heterogeneity of disease over time and across individuals significantly limits our ability to translate results from randomized controlled clinical trials into clinical practice.[38] For example, the effectiveness of therapeutic drugs varies over time within individuals, and across individuals with different degrees of IBD severity.[39–41]

Given our incomplete understanding of disease heterogeneity, and the inherent limitations of clinical efficacy studies in IBD, we sought to define clinical subtypes of disease by examining disease course patterns and the effectiveness of medical therapy in a tertiary care clinic. To this end, we developed a research registry of IBD patients at UPMC. The aims of the IBD research registry are to: (1) organize clinical information and define the natural history of IBD; (2) develop a research platform for association studies and the delineation of clinical phenotypes; and (3) examine effectiveness and quality of care measures in the setting of IBD. We propose that a database using prospective observational health record data will support and facilitate natural history, disease phenotyping, and effectiveness research in chronic illness. This

manuscript details the design, development, challenges faced, and implementation of the IBD research registry at a large tertiary care center in the US.

2.2 METHODS

2.2.1 Registry Setting

The IBD research registry is an IRB-approved patient registry maintained at UPMC in Pittsburgh, PA. The registry was created in 2001 by a gastroenterologist who is also the Principal Investigator (MR). The Principal Investigator originally began enrolling IBD patients in the National Institutes of Digestive, Diabetes and Kidney Disease genetics consortium and used the registry in parallel to prospectively consent all IBD patients visiting the UPMC Digestive Disorder Center. The rationale for the initial development of the registry was to gather clinical data for IBD patients who were participating in the genetic discovery arm of the consortium. The registry was initially managed as a research tool, outside of the daily clinical practice and clinician access. In 2008, an initiative was formed to incorporate observational healthcare data into the registry. To achieve this goal, the registry was moved into an electronic, Health Insurance Portability and Accountability Act (HIPAA) secure environment that could be readily accessed by gastroenterologists, support staff, and IRB-approved research collaborators. Concurrently, UPMC introduced an outpatient electronic health record system (EpicCare, Epic Systems, Verona, WI, USA) for all affiliated sites in the UPMC system, which includes over 20 hospitals and 500 clinics across Western Pennsylvania. This system-wide electronic medical record allowed all clinical data across numerous healthcare facilities to be captured.

2.2.2 Registry Enrollment

The target population for the registry is adult IBD patients, 18 years of age and older. This population is derived from patients presenting to the Digestive Disorders Center at UPMC, a tertiary care clinic with physicians with IBD expertise. Recruitment for the IBD research registry is ongoing and in perpetuity. As a part of the initial clinic visit, all patients are provided a consent form with a description of the IBD registry. All IBD physicians and their staff are co-investigators on the registry. At the time of the clinic visit, the registry is explained to the patient by a co-investigator and the patient has the opportunity to ask questions. The patient may choose to sign the registry consent during the clinic visit, may decline enrollment in the registry or may elect to take the consent with them to review further and ask additional questions. The consent form describes the participation risks including the most significant potential risk of a breach of confidentiality. Within the consent form, we request access to medical records for research purposes and the ability to approach enrolled patients for future research studies, both of which are critical for ongoing research and recruitment. The consent form does not have a menu of options to avoid unnecessary complexity. Any new research initiatives that would like to link data to the UPMC IBD Registry, or request biological samples, require a separate consent. Patients may withdraw from the registry at any point, and these procedures are outlined in the consent. Patients are also offered the opportunity to participate in the registry during follow-up care. Participation in the registry is optional and all patients receive the same clinical care whether they are included in the registry or not.

2.2.3 Registry Design and Measures

Variables imported into the IBD research registry are generated as a part of routine outpatient clinical care. Data extraction from the electronic medical record (EMR) for the purpose of the IBD registry has been occurring since 2009. Clinical data for patients enrolled in the registry are systematically exported from the EMR through the Center for Assistance in Research using eRecord at the University of Pittsburgh, an information technology support group. Data is retrieved from the EMR biannually, categorized according to clinical domain (medications, radiology, laboratories, etc.), and delivered electronically to the registry research team. Automated and manual data transformations are used to separate all values into domain-specific data-sets. Clinical events are categorized as binary (categorical) outcomes (0,1) for initial statistical analyses. Laboratory values are imported as raw numbers and are further defined as normal or abnormal (0,1). Annual dichotomous patterns for clinical events, medication prescriptions, and abnormal laboratory values are created. The exact dates of these data points are also preserved for time-to-event analyses. All data are stored behind the HIPPA-compliant, password-protected UPMC firewall, in a secure environment; only accessible by co-investigators listed on the IRB approval who have completed appropriate human subjects research training. Master data lists are password-protected and archived for data integrity.

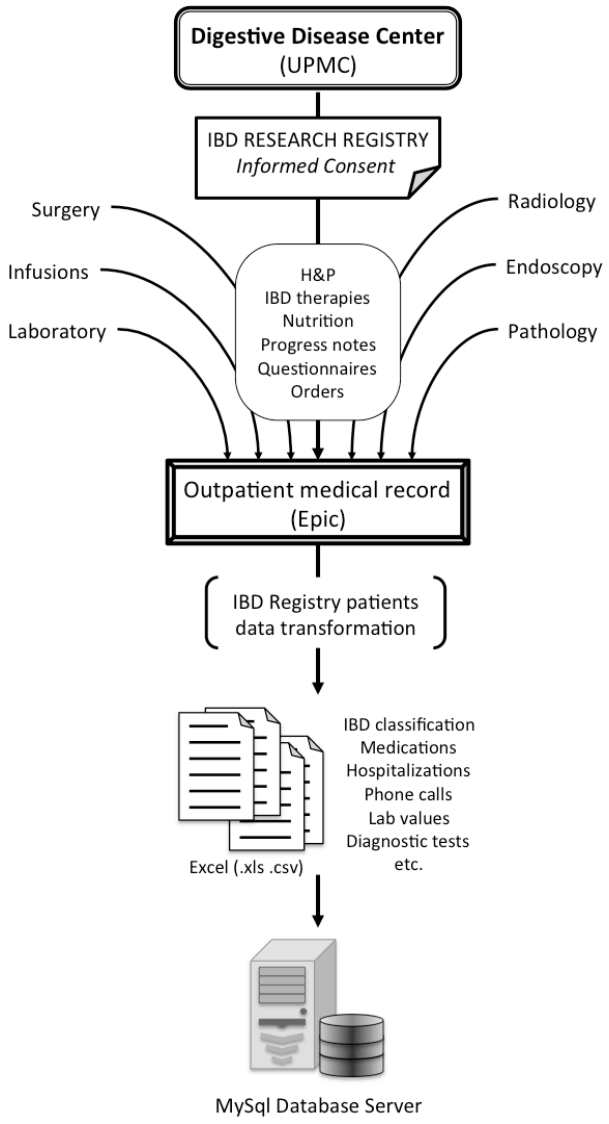

Figure 1. Flow diagram of inflammatory bowel disease research registry

Abbreviations: IBD – Inflammatory bowel disease, H&P – History and physical

In order to provide access to the data for research collaborators, and to enable advanced data analysis, the data is completely de-identified and imported into a relational database or statistical package. The de-identification process creates unique identifiers for each record and generates a patient lookup list used to link the original data structure. This lookup list is stored

behind the UPMC firewall, and patient identifiers are separated from the data. The relational database is deployed on a secure HIPAA-compliant server accessible via a virtual private network by co-investigators listed on the IRB approval. The de-identification process also allows for collaboration with outside institutions if multi-site collaborations arise.

Table 1. Measurements collected in the inflammatory bowel disease research registry

- **Patient demographics**
- **Disease related information**
  - Age at diagnosis
  - Disease duration
  - Disease localization according to Montreal classification
  - Disease phenotype according to Montreal classification
  - Patient questionnaires
    - SIBDQ
    - HBI
    - UCAI
  - Endoscopic data
  - Pathology (surgical and procedural)
  - Radiological data
  - Comorbidities – ICD9 codes
- **Laboratory**
  - Standardized IBD lab panel
  - Fecal microbial testing including *Clostridium difficile*
- **Medications**
  - IBD related prescriptions
  - Other prescriptions
- **Healthcare Utilization**
  - IBD clinic visits
  - Emergency department visits
  - Hospital admissions
  - Telephone encounters
  - Radiology
  - Surgical procedures
  - Total charges for healthcare services

Variables collected include demographic information (**Table 1**) and initial IBD classification of CD or UC. Related comorbidities are recorded through the use of administrative International Classification of Diseases, Ninth Revision and Tenth Revision (ICD-9, ICD-10) codes and EMR problem lists. Laboratories, vitals and objective data collected and entered into the EMR during the patient visit are organized by subject and visit date. Healthcare utilization measures include telephone encounters, emergency department visits, IBD clinic visits, hospital admissions, endoscopic and radiologic procedures, and surgeries. Financial healthcare charges are also organized by year. Medication data includes prescriptions for biologics, immunomodulators, steroids, 5-aminosalicylates and iron supplementation for each calendar year. Data on psychiatric and opiate pain medications are also collected as markers comorbid. Additional medications that are not part of routine IBD care can be retrieved using search algorithms.

As a part of the standardized visit in the UPMC Digestive Disorders Center, each patient is asked to complete health related questionnaires, such as the published version of the Short Inflammatory Bowel Disease Questionnaire (SIBDQ), the Harvey-Bradshaw Index for CD (HBI), and an ulcerative colitis activity index (UCAI) for UC.[42–44] The questionnaires are administered at every visit to inform clinical care, regardless of a patient's registry inclusion status. Patients complete hard copies of the questionnaires in their clinic room. Individual component sub-scores and total scores for each visit are recorded in the EMR by clinic support staff and are available for export into the registry. These standardized clinical measures allow prospective measurements of patient-reported disease clinical activity and health-related quality of life.

The outpatient EMR has many standard data entry fields, which can be exported in collaboration with the Center for Assistance in Research using eRecord at the University of Pittsburgh. When research projects would benefit from the addition of a variable that is collected in clinical care, we can make additional data extraction requests for retrieval of this data. One example would be family history of IBD and other co-existent diseases. This data is routinely collected at patient visits and was not originally a part of the initial pre-specified registry dataset. Requesting new information allows the research team the ability to create and manipulate new variables and populations of interest as new research questions arise.

In addition to data collected in standard data entry fields, the outpatient record contains health information that is not standardized in the patient chart. This valuable information appears in patient discharge summaries, surgical notes, endoscopic reports, pathology reports, clinic notes, and other free text entry fields. Text data from free entry fields is exported into the IBD research registry in de-identified ASCII text files, which allows for the use of natural language processing toolkit and the R Project for Statistical Computing for analysis and retrieval of textual information from free text files.[45,46] We recently began work on implementing a combination of Apache openNLP natural language toolkit and Apache cTakes natural language processing (NLP) system for extraction of information from clinical free-text to improve the processing of natural language text.[47,48] There are several major challenges to extracting meaningful information from free text data, such as pathology or endoscopy reports. These challenges include lack of structure in the narrative, multiple spellings and synonyms for terms of interest, as well as issues with context negation. For example, when extracting presence or absence of *Clostridium difficile* from pathology reports, 16 different spellings for "*Clostridium difficile*" were found. In order to address these issues, we began to use NOBLE tools developed at the

University of Pittsburgh Department of Biomedical Informatics to create dictionaries and ontologies for terms of interest.[49] Furthermore, NOBLE tools have built-in NLP support for identifying context negation, helping resolve issues with false positive term identification. While this approach is still in its development phases, we have been validating its accuracy with manual search and classification of terms of interest.

2.2.4 Quality Assurance

The IBD clinic has a standardized intake visit and also standard lab panels which help facilitate more uniform data capture. Many of these uniform datasets and data capture strategies are utilized at the goodwill of clinicians. Our clinicians are not incentivized to use certain notes or pre-populated laboratory order sets. Data quality and integrity is monitored by manual review after data export. Data validation occurs at the extreme values of each measure. For example, a patient weight is verified if the value does not fall within a pre-specified data validation range. Random manual EMR verification ("spot checking") is also performed on each data set to ensure accuracy. Data linkage and matching is performed using unique patient identifiers. Missing data is imputed using the medical record, and manual data extraction from the EMR is performed on a case-by-case basis.

2.2.5 Registry Team

The registry is coordinated by an analytical research scientist who processes data extraction requests and organizes master files. We have found that having a dedicated staff member has revitalized the UPMC IBD Registry. The staff analytical research scientist allocates

duplicate data appropriately to active researchers, preserving data integrity of the master files. Trained clinical personnel consent individuals to join the registry. Hard copies of disease activity indices and quality of life metrics are completed by patients in their clinic rooms, and entered into the official medical record by clinical support staff. All other research related operations, including the data entry of research questionnaires, are assigned to the primary investigator on each IRB approved sub-study. We also receive information technology assistance from the Center for Assistance in Research using eRecord at the University of Pittsburgh, and data science collaborators from University of Pittsburgh, School of Information Sciences.

2.2.6 Ethical Considerations

The research registry is an IRB approved protocol (Protocol # 0309054), open for continuous enrollment and undergoes renewal as dictated by IRB regulations. All subsequent data linkage protocols and research questions involving the database require separate IRB approval to ensure the protection of human subjects. Subjects are able to withdraw from the IRB research registry at any time with a written request to the principal investigator.

2.3 RESULTS

The initial registry cohort, in collaboration with other NIDDK genetics consortium institutions, has been an instrumental part of published genome wide association studies and other genetic discoveries in IBD.[6,50] With ongoing enrollment, the registry continued to grow after the revitalization initiative in 2008, and currently includes over 2,565 patients participating

in the IBD research registry **(Table 2)**. Using annual visit trends, we estimate that approximately 70% of the IBD patients in our clinic are actively participating in the registry. Each newly consented registry participant provides us with new data going forward, but also all retrospective data contained in their outpatient EMR from 2009 to the time of the data pull. This allows for backfilling of the data for each new registry member while avoiding manual chart review. IBD registry participants represent over 700 unique zip codes and represent a wide geographic area **(Table 2)**. The median age is 43.8 years, and the vast majority of participants are Caucasian, while just under half the participants report full time employment **(Table 2)**.

Table 2. Inflammatory bowel disease research registry demographics

IBD Registry Participants (n)	2565
Age*, years (median, IQR)	43.8 (32.9-57.6)
Race, n (%)	
Black	60 (2.3)
White	2390 (93.2)
Other	8 (0.3)
Not specified	107 (4.2)
Living Status (n, % alive)	2500 (97.5)
Number of Zip Codes	748
Employment Status, n (%)	
Full time	1184 (46.2)
Part time	59 (2.3)
Self employed	60 (2.3)
Student	190 (7.4)
Retired	206 (8.0)
Not employed	460 (17.9)
Not specified	403 (15.7)

*Age calculated as of October 1, 2015; IQR: interquartile range

Disease related information is a critical component of the registry with nearly 90% of IBD registry participants having defined disease phenotype based on Montreal Classification **(Table 3)**.[51] The average disease duration is 17.4 years and 22% of patients have had a history of IBD-related surgery prior to 2009 **(Table 3)**. Nearly half of the participants have CD **(Table 3)**.

Table 3. Inflammatory bowel disease research registry disease information

	Total, (%)
Disease classification, n (%)	
Crohn's disease	1313 (51.2)
Ulcerative colitis	910 (35.5)
Indeterminate colitis	7 (0.3)
IBD - Unclassified	190 (7.41)
Disease duration, median (IQR)	15.0, (10-22)
Patients with Montreal Classification, n (%)	2238 (87.3)
Patients with history of IBD surgery, n (%)	563 (22.0)
IBD questionnaires (n; median, IQR)	
SIBDQ	9905 52 (40-61)
HBI	10446 4.84 (0-55)
UCAI	10446 2.0 (0-6.0)

Abbreviations: IQR – interquartile range, IBD – Inflammatory bowel disease, SIBDQ – Short inflammatory bowel disease questionnaire[42], HBI – Harvey Bradshaw Index[43], UCAI – Ulcerative colitis activity index[44].

The effort to achieve our primary aim to organize prospectively collected, longitudinal clinical information has resulted in over 500 gigabytes of temporally organized data. We have organized over 1.3 million laboratory values and 124,658 prescriptions since 2009 **(Table 4)**.

Routinely collected utilization measures, including office visits, telephone calls, surgeries, hospitalizations, emergency room visits and radiologic or endoscopic procedures have been organized by year **(Table 4)**. We have organized over $310 million of total financial healthcare charges incurred by patients in the IBD registry and are exploring financial charge data as a new phenotype of disease severity **(Table 4)**.

Table 4. Inflammatory bowel disease research registry total number of measurements

	Total Number Organized
Laboratory values	1,308,993
Clinic visits	36,747
Telephone encounters	645,888
Emergency room visits	7,378
Hospital admissions	3,508
Endoscopies	8,472
Surgeries	1,304
Radiology (n)	
CT	7,716
MRI	2,585
X-ray	10,569
Comorbidities*	2,152
Prescriptions	
Biologics†	5,976
Immunomodulators	6,897
Systemic steroids	6,867
5-ASA	4,652
Other	100,236
Total charges organized ($)	$310.3 Million

Abbreviations: 5-ASA - 5-aminosalicyclic acid medications.

* Based on the International Classification of Diseases, Ninth Revision (ICD-9) codes contained in patient specific problem lists.

† Biologics included anti-tumor necrosis factor agents (Infliximab, Adalimumab, Certolizumab pegol)

Our second aim was to develop a research platform for the definition of clinical phenotypes. The data has resulted in multiple clinical phenotypes that have been published and are associated with increased levels of healthcare utilization or predictive of poor disease outcomes **(Table 5)**. These phenotypes include patients with high volume telephone calls, persistent or recurrent anemia, CRP elevations and peripheral eosinophilia.[52–56] We developed a set of tools written in Python programming language to search unstructured text data and identify patients with features of interests. These features included presence of granulomas on pathology reports, as well as presence or absence of *Clostridium difficile* in endoscopy reports, both of which have resulted in meaningful subgroups for analysis.[57,58] Projects are underway to link the clinical phenotypes to genotype signatures and utilize genetic data to understand the relationship of drug metabolism polymorphisms and patient data in our population.

Table 5. Example clinical phenotypes explored using the inflammatory bowel disease research registry

Phenotypes	**Risk of adverse health outcome**
Silent Crohn's disease: CRP elevation without clinical symptoms[53]	Increased risk and rate of hospitalization
Persistent/recurrent anemia[54]	Associated with increased healthcare utilization
High telephone encounters[52]	Increased risk of hospitalization and/or emergency room use
Peripheral eosinophilia[55,56]	Increased patient charges and healthcare utilization
Obesity in IBD[59]	Use of lower dosing of IBD related medications
Long-term lipid profiles in IBD[60]	Dyslipidemia is associated with more severe disease
High healthcare utilization in IBD[15]	Associated with unemployment, psychiatric disease, narcotic use, and medical comorbidities.

Abbreviations: CRP – C reactive protein; IBD – Inflammatory bowel disease

Finally, we have overcome numerous challenges during the development and implementation of a longitudinal natural history database (**Table 6**). An ongoing challenge is the quantification of patient follow-up. With natural history data it is difficult to distinguish whether a patient did not have an endoscopy because they were lost to follow up, or if they are feeling well and did not require endoscopic evaluation. To ensure patients in hypothesis driven studies resulting from registry data are only included if they are active in our practice, we organize outpatient EMR encounters to quantify a patient's telephone activity, email exchanges, clinic visits, or emergency department use in a calendar year. This data is the backbone of all inclusion and exclusion criteria for multi-year studies, and is not routinely accessible in registries unlinked from the EMR or cohorts based off of administrative datasets.

Table 6. Challenges and solutions in creating and maintaining a registry

Challenges	**Solutions**
Data extraction from the electronic medical record	Active and ongoing partnerships with outpatient medical record support teams at our local institution. Our local partners facilitate data transfer requests.
Standardization of data capture	Patient encounters are standardized, regardless of inclusion in the registry. There are standard laboratory orders and questionnaires.
Quantification of patient follow up	Participants are considered "active" if they had at least one phone call or office visit in the calendar year.
Complex longitudinal data	Initially, patient data is organized by calendar year. Time stamped data is available for more complex longitudinal data analyses, and time to event analyses.
Historical data on newly consented registry participants	Each data extraction from the electronic medical record provides historical data on each patient from 2009 to date of extraction. This overcomes the problem of manual filling of historical data as in other non-electronic medical record derived registries.
Recruitment and retention	All clinic physicians are actively recruiting IBD patients to join the registry. By utilizing the electronic medical record as a data source we greatly reduce participant burden and increase retention. Physician and staff data entry burden is also minimized.

Another facet of data organization that commonly accompanies longitudinal data is the identification of study observation intervals. To address this, we prospectively lock our data on a calendar year basis. This strategy allows for cross sectional association studies to be repeated on each annually locked dataset and provides internal validation for the evaluation of trends over time. Previous studies from our group have employed the data to generate prediction models in with data from one calendar year, and perform a validation of the prediction model in subsequent years.[15] The annual trend data is the primary way in which data is curated; however, all raw data from the EMR is maintained in a time stamped manner that allows for a granular approach if any particular study requires individual data elements.

2.4 DISCUSSION

This paper outlines the design, development, challenges and implementation of an IBD research registry at a tertiary care center. We describe successful implementation of an IBD research registry generated from the outpatient medical record and linked surveys related to patient reported disease activity and quality of life. Given that the majority of IBD patients are managed in the outpatient setting, the outpatient registry allows for the examination of real world IBD subgroups, treatment patterns, disease trajectories, and clinical effectiveness in a large IBD cohort.

We have made it a research priority to define clinical subtypes of disease that relate to poor health outcomes, and have demonstrated that routinely collected patient care data overtime can be organized to provide the framework for such studies. The use of routinely collected observational patient data from the EMR allows for rapid implementation of research findings at other institutions.[61] Many studies use point measurements of disease activity indices, quality of life scores or biomarkers, but with the registry's data we are able to evaluate patterns of these markers and trends over time which probably reflects disease severity with better accuracy. Additionally, we are capturing healthcare data from real world patients and clinical practice, which has been advocated by the Institute of Medicine to facilitate rapid comparative effectiveness research.[62] These large datasets include patients that would be excluded from participation in randomized, controlled clinical trials due to comorbid illness or complex disease history.[38] Thus, research findings generated from the IBD research registry are a closer reflection on real world IBD compared to highly controlled trials.

Registries have been used in the setting of other chronic disorders and rare diseases.[63–67] Despite the utility of research registries in the setting of chronic disorders, there is a lack of

publications outlining registry development and implementation of longitudinal medical records data, especially in the setting of IBD. Others have described methods of patient identification using the medical record, however this approach generates administrative data without the ability to contact individuals for current and future study recruitment.[68,69] The EMR derived registry approach allows identification of patients with unique clinical signatures that may benefit from enrollment in research trials. For example, we are in the process of recruiting patients to a microbiome research trial based on the extremes of documented gastrointestinal infection, which is phenotype data generated from the research registry. Additionally, while we have not yet actively pursued these studies, registries can facilitate linkage with other state and national databases to enrich the data. Furthermore, using a registry approach we are able to validate variables that appear inaccurate and fill in any missing data using the EMR. Generating the majority of the data from the EMR also avoids data entry burnout that can restrict the potential of registries distinct from the EMR. EMR data pulls also facilitate effortless, unbiased back filling of clinical care data that is not routinely available with prospective registries distinct from the EMR.

We have linked the data in the IBD research registry to a variety of validated healthcare questionnaires in order to quantify comorbidities in our clinic population. Over time we have collected data using an autonomic dysfunction screening questionnaire (COMPASS-31), persistent stress questionnaire, an intake depression screen, and a fiber and fat dietary intake questionnaire.[70–72] Introducing clinical questionnaires into the routine clinical workflow and linking the results of these questionnaires to patient data in the registry has resulted in studies aimed to validate these questionnaires that have not been used previously in the setting of IBD.

Finally, we now have the infrastructure required to examine effectiveness and quality of care measures in the setting of IBD, with the development of this registry. New research is focusing on the evaluation of the effectiveness of biologic therapies within our patient cohort. We are also dedicating research efforts on quality of care metrics including the management of surveillance colonoscopies in patients with colonic IBD, infection rates, medication exposure, and the frequency and outcomes related to micronutrient repletion.[73,74] Furthermore, the infrastructure currently afforded by this registry allows application of machine learning algorithms to discover patterns in the data. We in the process of testing statistical models that could be used to predict poor health outcomes, and are developing exploratory data visualization systems to allow clinicians and researchers to observe patient trends over time and rapidly identify clinical events of interest.

In comparison to other population-based cohorts, the EMR based registry approach has some advantages. We have learned a great deal from Olmsted County to advance our understanding of prevalence and incidence of IBD over time.[75] However, the linked census and healthcare data is based primarily from diagnosis codes, and achieving data granularity requires retrospective chart examination. It is also often cited that, a large percentage of Olmsted County inhabitants are also working in healthcare and are highly educated which may make natural history findings less generalizable to the larger US population.[75] The Ocean State Crohn's and Colitis Registry (OSCCAR), is another registry of a multi-center population that recruited incident cases of IBD in Rhode Island up to 6 months from initial diagnosis.[76] OSCCAR follows patients prospectively at predetermined intervals and has collected extremely valuable data on health outcomes, quality of life, and disease activity while having the added benefit biological sample collection. While time intervals are consistent across patients these intervals and requires

dedicated study personnel to prospectively monitor patients and schedule follow up. Patients in the UPMC IBD registry do not need to engage in research outside of their routine clinical care, which greatly reduces the burden of research on both the participant and research staff. Although the UPMC IBD registry does not capture data at predetermined time points, our aim is to capture real-world healthcare utilization data on a patient level, as they require care for worsening disease.

Research registries from Canada have also contributed to our understanding of IBD. The Alberta IBD Consortium recently published an influential study on IBD phenotypes and medical outcomes using their registry.[77] This study employed intensive manual chart review by two independent data abstractors with clinical expertise. In the context of our registry, the EMR data abstraction methods at the Center for Assistance in Research using eRecord at the University of Pittsburgh at UPMC are automated and uniformly applied to all registry participants and may reduce errors associated with manual data extraction and interpretation. The Manitoba IBD research group has also been influential in advancing our understanding of IBD.[78] The Manitoba group maintains an open enrollment IBD registry and cohort studies that follow recently diagnosed IBD patients.[79] In addition to registry data, Manitoba's IBD related epidemiologic studies are strengthened by large administrative datasets that capture universal care. The lack of universal care systems in the United States requires creative solutions to track health outcome and healthcare utilization data on the majority of our patients. We have detailed one solution to this problem through the use of a commonly employed outpatient EMR to serve as the basis of real-world data in a longitudinal IBD research registry.

Despite successful implementation of the IBD research registry, this methodology has limitations. The registry is housed at a tertiary care center and may selectively capture highly

severe disease. Even with this potential bias, IBD patients in our registry are similar to IBD patients seen at other centers, in that they experience unpredictable flares with the clinical goal of controlling symptoms and restoring quality of life. Additionally, outpatient data is collected from UPMC satellite clinics and allows us to capture routine care that occurs in the community setting outside the walls of our tertiary care center. We are also limited in the breadth and accuracy of observational data as it is entered into the EMR. To address this, we validate data at the extremes to confirm any potential outliers in an effort to improve data accuracy. This limitation applies to all forms of research utilizing the EMR as a source of real world data. Finally, with observational and interventional research studies there is participation bias of subjects who join the registry. We are unable to capture the healthcare states and reasons why persons decline participation in the registry.

We have detailed the methods to develop, implement and utilize a research registry in the setting of IBD and ways in which we have overcome challenges associated with real world, longitudinal data. Future and current studies utilizing the research registry will be focused on better defining IBD phenotypes in an effort to uncover clinical pathways that can be targeted for treatment. These studies are designed to bring the practice of Gastroenterology and IBD clinical management closer to the ultimate goal of personalized medicine.

3.0 THE LASTING IMPACT OF CLOSTRIDIUM DIFFICILE INFECTION IN INFLAMMATORY BOWEL DISEASE: A PROPENSITY-SCORE MATCHED ANALYSIS

Adapted from manuscript accepted to *Inflammatory Bowel Diseases*:

The lasting impact of Clostridium difficile infection in inflammatory bowel disease: a propensity score matched analysis

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3.1 INTRODUCTION

Clostridium difficile is a Gram-positive, anaerobic, spore-forming bacilli and the etiological agent of antibiotic associated pseudomembranous colitis. Common risk factors for community or hospital acquired *C. difficile* infection (CDI) are comorbid diseases and exposure to any class of antibiotics.[21,80] Comorbid inflammatory bowel disease (IBD) is considered the most significant risk factor for the acquisition of CDI in the community setting.[21] Previous research has shown that the likelihood of infection is increased by many factors including, but not limited to, healthcare system contact, nutritional deficiencies, and antibiotic exposure.[80–83] CDI is an increasingly prevalent infectious complication in the IBD patient population.[23,84,85] CDI in IBD patients is associated with higher rates of hospitalization, surgery, longer hospital stays, increased healthcare charges, and, most importantly, an increased mortality.[18,20]

Much of what is known about CDI in IBD has been derived from large national databases and administrative healthcare data. These data have provided information about increased risks of mortality and colectomy in IBD patients with CDI and how these risks have increased over time.[18,86] However, many of the findings were derived from retrospective samples and administrative data, and are unable to account for a patient's inherent risk of CDI or their disease severity prior to infection.[87]

We are unaware of any studies that have used a propensity score matching approach to generate a control cohort that has similar risk factors of developing CDI in the year prior to infection. Our primary aim was to determine the impact of CDI on biomarkers of IBD severity, healthcare utilization, and patient reported outcomes compared to a matched cohort based on known risk factors for infection. Our secondary aim was to investigate if changes of healthcare utilization patterns continued into the year following infection. We hypothesized that CDI would

negatively impact patient outcomes in the acute period of infection and in the long-term follow up period.

3.2 MATERIALS, METHODS AND DESIGN

3.2.1 Study design and participants

This study was conducted as a part of the UPMC IBD research registry, which has been previously described in detail.[88] Briefly, IBD patients are consented and enrolled in a prospective, longitudinal, natural history registry, which organizes real world patient care data from 2009 to the present time. All data from the registry is derived from the electronic medical record and systematically processed and transformed for research.

In this study, we included all IBD patients in the UPMC IBD registry with a definite diagnosis based on standard criteria of ulcerative colitis (UC) or Crohn's disease (CD) for our selection of cases and controls. CDI was defined as any patient with a confirmed molecular laboratory diagnosis of *Clostridium difficile* from 2010 to 2014 calendar years. All confirmed molecular diagnoses were assumed to have infection. Participants with CDI also had to have clinical follow up, defined as at least one clinic visit or telephone encounter in the gastroenterology clinic over the calendar year, in the year prior to infection in order to meet inclusion criteria. Controls were selected from the remaining IBD registry participants without a history of CDI.

IBD patients in both the case and control groups were excluded if they had unclassified IBD or undefined disease type. To allow capture of data from the year before and year after CDI,

IBD patients with CDI occurring in 2009 or 2015 were excluded. CDI cases were also excluded if they did not have clinical follow up in the year prior to infection. We did not exclude controls who had been tested for infection, or CDI positive participants who had multiple or relapsing infections, as this is a feature of CDI in IBD patients.[22] The CDI positive cohort includes IBD patients with single and multiple positive tests for CDI documented in the medical record.

3.2.2 Data collection and organization

All data are prospectively collected as a part of routine healthcare visits in any UPMC affiliated hospital or clinic (comprising over 20 hospitals and 500 clinics).[88] All IBD related healthcare utilization including clinic visits, telephone encounters, hospitalizations, emergency room (ER) visits, and IBD related surgeries were derived from the IBD registry and temporally organized by calendar year. Healthcare utilization was also quantified by financial charges, which includes charge data for all healthcare services including, but not limited to, gastrointestinal care. Financial charges include both inpatient and outpatient charges, but do not include pharmacy charges as prescription charges independent of the UPMC system. Labs were ordered as a part of routine care as deemed appropriate by providers, therefore, laboratory biomarkers, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and vitamin D and B-12 deficiencies were organized by calendar year and dichotomized as normal or abnormal based on local laboratory standards. All outpatient electronic prescriptions were organized annually for each patient. Patients were designated as having exposure to the medication if they had one or more prescriptions within the calendar year. Antibiotics only included systemic exposure. Systemic antibiotics with the exception of vancomycin and fidaxomicin were analyzed as a separate category. Within the systemic antibiotics category we

looked at the subgroup of patients prescribed metronidazole, as it is indicated in the setting of CDI. However, vancomycin and fidaxomicin were analyzed alone as a separate antibiotics category, as their primary indications are for CDI.

Patient reported disease activity and quality of life (QOL) metrics were collected during clinical visits to the UPMC Digestive Disorders Clinic as a part of routine care, and entered into the electronic medical record. QOL was measured by the Short Inflammatory Bowel Disease Questionnaire (SIBDQ).[42] Disease activity was measured by the Harvey Bradshaw Index (HBI) for CD and Ulcerative Colitis Activity Index (UCAI) for UC.[43,44] "Active disease" was defined as annual mean UCAI score ≥4 or annual mean HBI scores ≥5 during the study period. Disease phenotypic characterization was performed in both CD and UC patients using the Montreal Classification at initial presentation.[51]

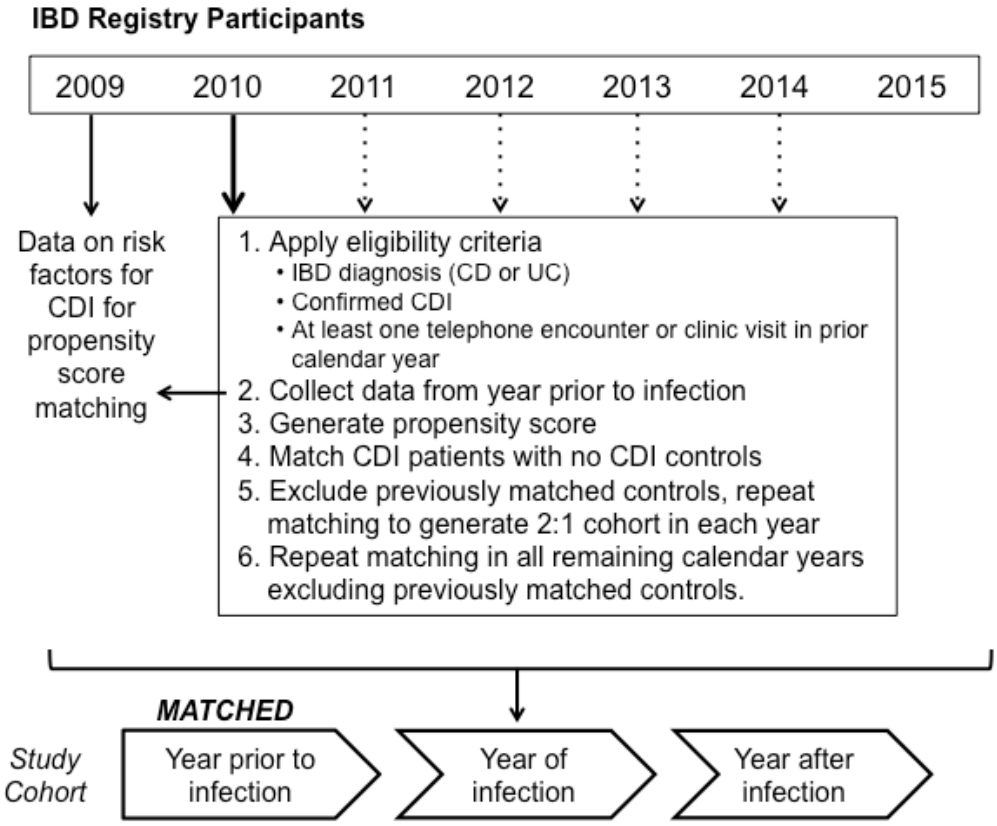

Figure 2. Schematic of propensity score matching.

Repeated nearest neighbor propensity score matching by year without replacement.

3.2.3 Propensity score matching

To build a comparable control cohort at baseline we utilized nearest neighbor propensity score matching.[89] We generated the propensity score for CDI with the covariates listed in **Table 7**, using logistic regression. The propensity score is considered the calculated "likelihood" of infection given a patient's particular set of covariates.[90] All covariates were chosen from hypothesis driven clinical parameters that may influence a patient's risk for CDI. Most importantly we included all encounters with the healthcare system and antibiotic exposures in the

year prior to infection, which have been implicated in risk for infection.[80,81] We also included all antibiotic exposures in the year prior to infection, age, and vitamin D deficiency, all which have been linked to risk of infection.[23,83] Patients were matched using the protocol outlined in **Figure 2**, which features a rolling propensity score matching process over time beginning with study participants who had their first CDI event in 2010. Matching was done without replacement to build a 1:2 (cases:controls) cohort. Any controls matched to cases in previous years were excluded from any subsequent control population selection pool. Covariate balance in the year prior to infection was examined following matching.

Table 7. Variables included in each propensity score model

Propensity Score Model Covariates	**Variable type**
Demographics and disease characteristics	
Age	Continuous
Gender	Dichotomous
Disease type (ulcerative colitis vs. Crohn's disease)	Dichotomous
Years of disease	Continuous*
Colonic disease by Montreal Classification[51]	Dichotomous*
Follow up during the year of infection	Dichotomous
Medication exposure in the year prior to infection	
Biologics	Dichotomous
Immunomodulators	Dichotomous
Prednisone	Dichotomous
5-aminosalicylic acid	Dichotomous
Proton pump inhibitor	Dichotomous
Any systemic antibiotic exposure	Dichotomous
Number of systemic antibiotic exposures	Continuous
Clostridium difficile associated antibiotic exposure†	Dichotomous
Biomarkers of disease severity in the year prior to infection	

Abnormal C-reactive protein	Dichotomous
Abnormal erythrocyte sedimentation rate	Dichotomous
Low vitamin D (<40 ng/mL)	Dichotomous
Low vitamin B12 (<300 pg/mL)	Dichotomous
Healthcare utilization and healthcare contacts in the year prior to infection	
Clinic visits	Continuous
Number of emergency room visits	Continuous
Number of hospital admissions	Continuous
Number of surgeries	Continuous
Number of endoscopies	Continuous
Number of radiologic procedures[§]	Continuous

* Any missing values were matched with dummy variables to characterize missing values.
[†] *Clostridium difficile* associated antibiotics include vancomycin and fidaxomicin.
[‡] Having been tested for *Clostridium difficile* was removed from all propensity score models due to perfect prediction of cases.
[§] Radiologic procedures include all computerized tomography and magnetic resonance imaging scans, ultrasounds, and X-rays.

3.2.4 Statistical analysis

We used chi-square analyses for categorical variables, Student's t-test for normally distributed continuous variables, and the Wilcoxon rank-sum test for nonparametric continuous variables to assess differences and balance between groups at baseline. To account for matching, outcomes in the year of infection and year after infection were assessed using conditional logistic regression for binary outcomes, and fixed effects regression for continuous variables. Counts of healthcare utilization (hospitalizations, ER visits, telephone calls, clinic visits, radiologic procedures, endoscopies) were initially evaluated using fixed effects Poisson regression and significance was ultimately reported using conditional negative binomial regression due to over dispersion of zeros. Financial charges were transformed to natural log for normality prior to

regression. All statistical tests were evaluated with an alpha = 0.05, and were completed in StataSE (v.14, StataCorp, College Station, TX).

3.2.5 Ethical Considerations

All participants were enrolled in the IBD Research Registry using informed consent. The IBD Research Registry (Protocol #0309054) and the current analysis (Protocol #15010214) were both approved by the University of Pittsburgh Institutional Review Board. All authors had access to the study data and reviewed and approved the final manuscript.

3.3 RESULTS

A total of 198 patients (66 CDI, 132 matched controls) were included (56.6% female; 60.1% CD, 39.9% UC) (**Table 8**). Infection and control groups did not significantly differ in terms of baseline disease characteristics in the year prior to infection for all available metrics (**Table 9**). Study groups did not differ in regard to contact with the healthcare system including hospitalizations, ER visits, endoscopies, radiologic studies, clinic visits, and total financial charges. Additionally, the groups did not differ in terms of the proportion of patients who were exposed to antibiotics or the number of times they were prescribed antibiotics (**Table 9**).

Table 8. Baseline demographics of inflammatory bowel disease patients included in the study

		Infection Status		
	Total Study Population n= 198	*Clostridium difficile* positive n= 66	Controls n= 132	p-value
Age (mean years ± SD)*	45.4 ± 15.2	44.3 ± 14.8	45.9 ± 15.5	0.486
Female, (n, %)	112 (56.6)	34 (51.5)	78 (59.1)	0.311
Race/Ethnicity, (n, %)				
Caucasian	190 (96.5)	62 (93.9)	128 (97.7)	0.249
Black	6 (3.1)	3 (4.6)	3 (2.3)	
Other or unknown	1 (0.5)	1 (1.5)	0 (0.0)	
Hispanic/Latino	0 (0.0)	0 (0.0)	0 (0.0)	1.00
Marital Status, (n, %)				
Married or significant other	120 (60.6)	41 (62.1)	79 (59.9)	0.447
Single	58 (29.3)	21 (31.8)	37 (28.0)	
Divorced, widowed, separated	17 (8.6)	4 (6.1)	13 (9.9)	
Unknown	3 (1.5)	0 (0.0)	3 (2.3)	
Employment status (n, %)				
Full time or self-employed	103 (52.0)	36 (54.6)	67 (50.8)	0.937
Full time student	12 (6.1)	5 (7.6)	7 (5.3)	
Part-time	7 (3.5)	2 (3.0)	5 (3.8)	
Retired	17 (8.6)	6 (9.1)	11 (8.3)	
Not employed	43 (21.7)	13 (19.7)	30 (22.7)	
Unknown	16 (8.1)	4 (6.1)	12 (9.1)	

SD - standard deviation; *Age of study participants as of January 1, 2015.

Table 9. Baseline disease characteristics from the year prior to infection

		Infection Status		
	Total n= 198	CDI positive n= 66	Controls n= 132	p-value
Disease category (n, %)				
Crohn's disease	119 (60.1)	41 (62.1)	78 (59.1)	0.681
Ulcerative colitis	79 (39.9)	25 (37.9)	54 (40.9)	
Disease characteristics[51]				
Crohn's disease location, n=98				
Ileal (L1)	26 (26.5)	7 (20.6)	19 (29.7)	0.331
Colonic (L2)	31 (31.6)	9 (26.5)	22 (34.4)	0.423
Ileocolonic (L3)	44 (44.9)	18 (52.9)	26 (40.6)	0.243
Upper GI (L4)	4 (4.1)	3 (8.8)	1 (1.6)	0.084
Crohn's disease behavior, n=98				
Inflammatory (B1)	50 (51.0)	14 (41.2)	36 (56.3)	0.155
Stricturing (B2)	38 (38.8)	17 (50.0)	21 (32.8)	0.096
Penetrating (B3)	20 (20.4)	7 (20.6)	13 (20.3)	0.974
Perianal disease, n=98	21 (21.4)	6 (17.7)	15 (23.4)	0.506
Ulcerative colitis extent, n=68				
Proctitis (E1)	4 (5.9)	2 (9.5)	2 (4.3)	0.394
Left-Sided (E2)	18 (26.5)	4 (19.1)	14 (29.8)	0.354
Extensive (E3)	49 (72.1)	17 (81.0)	32 (68.1)	0.275
History of IBD related surgery*	62 (31.3)	18 (27.3)	44 (33.3)	0.386
Biomarkers of severity (n, %)[†]				
Elevated CRP	89 (45.0)	30 (45.5)	59 (44.7)	0.920
Elevated ESR	70 (35.4)	24 (36.4)	46 (34.9)	0.833
Low Vitamin D (<40 ng/mL)	88 (44.4)	31 (47.0)	57 (43.2)	0.613
Low B-12 (<300 pg/mL)	37 (18.69)	12 (18.2)	25 (18.9)	0.897
Medication use (n, %)[†]				
Immunomodulators	45 (22.7)	15 (22.7)	30 (22.7)	1.00
Biologics	66 (33.3)	23 (34.9)	43 (32.6)	0.749
Systemic steroids	81 (40.9)	132 (43.9)	52 (39.4)	0.540
5-aminosalicylic acids	55 (27.8)	16 (24.2)	39 (29.6)	0.432
Systemic Antibiotics	107 (54.0)	37 (56.1)	70 (53.0)	0.687
Metronidazole	44 (22.2)	14 (21.2)	30 (22.7)	0.809
Vancomycin	35 (17.7)	11 (16.7)	24 (18.2)	0.792
Average Total SIBDQ, n=145 (median, [IQR])	46 [21.5]	45.7 [18.8]	47 [21.7]	0.273
Disease activity metrics (median, [IQR])				
HBI, n=96	5.0 [6.1]	5.0 [9.5]	5.0 [4.7]	0.860

UCAI, n=61	5.0 [8.0]	6.5 [10.0]	4.2 [8.0]	0.147
Healthcare utilization, (median, [IQR])				
Emergency room visits	0.0 [2.0]	1.0 [3.0]	0.0 [2]	0.075
Hospitalizations	0.0 [2.0]	0.0 [2.0]	0.0 [2.0]	0.427
Surgeries, (n, %)	29 (14.7)	10 (15.2)	19 (14.4)	0.887
Radiologic studies	2.0 [6.0]	3.0 [5.0]	2.0 [6.0]	0.332
Clinic visits	2.0 [3.0]	2.0 [3.0]	2.0 [2.0]	0.172
Telephone calls	5.0 [7.0]	5.0 [8.0]	5.0 [7.0]	0.792
Financial charges ($)	6984.75 [118713.10]	14462.00 [125282.00]	5990.00 [112014.30]	0.290

Abbreviations: SIBDQ, short inflammatory bowel disease questionnaire; IBD, inflammatory bowel disease; GI, gastrointestinal; IQR, interquartile range; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HBI, Harvey-Bradshaw Index; UCAI, ulcerative colitis activity index.

* History of any gastrointestinal surgery prior to 2009.

† Immunomodulators include 6-mercaptopurine, azathioprine, methotrexate. Biologics include anti-tumor necrosis factor agents (infliximab, adalimumab, and certolizumab), anti-integrin therapy (vedolizumab and natalizumab). Biologics include all anti-tumor necrosis factor agents and anti-integrin therapies. Systemic antibiotics include all systemic antibiotic exposure, excluding vancomycin and fidaxomicin.

3.3.1 Year of infection

In the year of CDI, follow up occurred in 93.4% (n=185) of the cohort, and rates of follow up did not differ between infection and control groups (95.5% CDI vs. 92.4% controls). Having CDI was significantly associated with increased medication exposure including steroids (49.2% CDI vs. 28.7% controls, p=0.005) systemic antibiotics (excluding vancomycin) (90.5% CDI vs. 50.8% controls, p<0.001), and vancomycin exposure (73.0% CDI vs. 12.3% controls, p<0.001) (**Table 10**). Neither group had any exposure to fidaxomicin or fecal microbiota transplantation. The CDI group also had a greater total number of antibiotic prescriptions (median: 3 CDI vs. 1 controls, p<0.001). The two groups did not differ in their exposure to 5-aminosalicylic acids, immunomodulators, or biologic medications (**Table 10**).

Infection was also significantly associated with elevated inflammatory biomarkers including CRP (58.7% CDI vs. 32.0% controls, p=0.002) and ESR (41.3% CDI vs. 18.0% controls, p=0.002), low vitamin D (p=0.001), and low vitamin B-12 (p=0.02) (**Table 10**). Using patient reported metrics, infection was associated with lower QOL scores (p=0.003) and self reported active disease (p=0.02) (**Table 10**).

Table 10. Disease severity, medication exposure and healthcare utilization from the year of *Clostridium difficile* infection

		Infection Status		
	Total n=185	CDI positive n=63	Controls n=122	p-value
Medication use (n, %)[†]				
Immunomodulators	45 (24.3)	13 (20.6)	32 (26.2)	0.399
Biologics	54 (29.2)	19 (30.2)	35 (28.7)	0.812
Systemic steroids	66 (35.7)	31 (49.2)	35 (28.7)	**0.005**
5-aminosalicylic acids	41 (22.2)	17 (27.0)	24 (19.7)	0.355
Systemic antibiotics	119 (64.3)	57 (90.5)	62 (50.8)	**<0.001**
Metronidazole	48 (26.0)	27 (42.9)	21 (17.2)	**<0.001**
Vancomycin	61 (33.0)	46 (73.0)	15 (12.3)	**<0.001**
Biomarkers of severity (n, %)				
Elevated CRP	76 (40.1)	37 (58.7)	39 (32.0)	**0.002**
Elevated ESR	49 (26.0)	26 (41.3)	22 (18.0)	**0.002**
Low Vitamin D (<25 ng/mL)	42 (22.7)	24 (38.1)	18 (14.8)	**0.001**
Low Vitamin D (<40 ng/mL)	96 (50.3)	42 (66.7)	51 (41.8)	**0.001**
Low B-12 (<300 pg/mL)	21 (11.4)	11 (17.5)	10 (8.2)	**0.027**
Average Total SIBDQ, n=130 (median, [IQR])	48.3 [20.3]	43.2 [19.9]	53.5 [22.0]	**0.003**
Active disease (n, %)*	65 (48.9)	33 (63.5)	32 (39.5)	**0.016**
Disease activity metrics, (median, [IQR])				
Harvey-Bradshaw Index, n=92	3.5 [5.6]	5.5 [6.5]	2.5 [5.0]	**0.006**
UCAI, n=51	5.0 [7.0]	6.2 [7.0]	4.0 [6.0]	0.960
Healthcare utilization, (median, [IQR])				
Emergency room visits	0.0 [1.0]	0.0 [4.0]	0.0 [1.0]	**<0.001**
Hospitalizations	0.0 [1.0]	1.0 [4.0]	0.0 [1.0]	**<0.001**
Surgeries, (n, %)	18 (9.73)	6 (9.52)	12 (9.84)	1.00

Radiologic Procedures	1.0 [4.0]	2.0 [5.0]	1.0 [3.0]	**<0.001**
Endoscopies	1.0 [1.0]	1.0 [1.0]	1.0 [1.0]	**<0.001**
Clinic visits	2.0 [3.0]	3.0 [3.0]	2.0 [2.0]	**<0.001**
Telephone calls	5.0 [8.0]	9.0 [12.0]	3.0 [7.0]	**<0.001**
Financial charges ($)	6805.00 [94059.00]	28433.88 [149294.70]	4989.00 [65498.25]	**<0.001**

P-values are bolded if significant, <0.05.
Abbreviations: SIBDQ – short inflammatory bowel disease questionnaire; IBD – inflammatory bowel disease; GI – gastrointestinal; IQR – interquartile range; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; UCAI – ulcerative colitis activity index.
*Active disease defined as annual mean ulcerative colitis activity index score ≥4 or annual mean Harvey-Bradshaw Index scores ≥5 during the study period.
† Immunomodulators include 6-mercaptopurine, azathioprine, methotrexate. Biologics include anti-tumor necrosis factor agents (infliximab, adalimumab, and certolizumab), anti-integrin therapy (vedolizumab and natalizumab). Biologics include all anti-tumor necrosis factor agents and anti-integrin therapies. Systemic antibiotics include all systemic antibiotic exposure, excluding vancomycin and fidaxomicin.

Patients with CDI experienced significantly increased healthcare utilization across all measured metrics except the proportion of patients requiring surgery during the year of infection (**Table 10**). Those with CDI had an increased number of radiographic studies, endoscopies, clinic visits, and telephone encounters (all p<0.001). They also had more unplanned care including ER visits (mean: 3.7 CDI vs. 1.1 controls, p<0.001) and hospitalization (mean: 2.2 CDI vs. 0.8 controls, p<0.001). Patients with CDI had increased financial healthcare charges in the year of infection (p<0.001) (**Table 10**).

3.3.2 Year after infection

In the year after infection, follow up occurred in 77.8% (n=154) of the original study group. The CDI group includes patients with single or multiple positive tests for CDI. CDI patients were significantly more likely to follow up in the year after infection (CDI 90.9%; controls 71.2%) compared to controls (p=0.003), (**Table 11**).

Those with prior CDI continued to have increased exposure to vancomycin ($p<0.001$) and other systemic antibiotics ($p=0.02$). Neither group had any exposure to fidaxomicin or fecal microbiota transplantation in the year after infection. All other medication exposures including biologics, systemic steroids, immunomodulators, and 5-aminosalicyclic acid agents did not differ between groups, although exposure to systemic steroids nearly met significance ($p=0.07$) (**Table 11**). In the year following infection, CDI patients continued to have more clinic visits ($p=0.02$), and telephone encounters ($p=0.001$). CDI patients also had significantly more financial healthcare charges in the year after infection (median $51,146.00 CDI vs. $8,120.50 controls, $p=0.003$). However, patient reported disease activity, QOL ($p=0.08$), and biomarkers of severity including ESR and CRP were not significantly different between the two groups. Other metrics of healthcare utilization including radiologic studies, endoscopy, surgery, hospitalizations, and ER visits were not significantly different (**Table 11**).

Table 11. Risk of future disease severity and healthcare utilization in the year after infection

		Infection Status		
	Total n=154	CDI Positive n=60	Controls n=94	p-value
Follow up year after infection, n (%)	154 (77.8)	60 (90.9)	94 (71.2)	0.003
Biomarkers of Severity				
Elevated CRP	45 (29.2)	18 (30.0)	27 28.7)	0.797
Elevated ESR	36 (23.4)	16 (26.7)	20 (21.3)	0.328
Medications† n (%)				
Biologics, n (%)	49 (31.8)	23 (38.3)	26 (27.7)	0.260
Immunomodulators	49 (31.8)	16 (26.7)	33 (35.1)	0.487
Prednisone	48 (31.2)	23 (38.3)	25 (26.6)	0.067
5-aminosalicylic acids	34 (22.1)	15 (25.0)	19 (20.2)	0.490
Systemic antibiotics	81 (52.6)	39 (65.0)	42 (44.7)	**0.023**
Metronidazole	22 (14.3)	8 (13.3)	14 (14.9)	0.931
Vancomycin	34 (22.1)	23 (38.3)	11 (11.7)	**0.001**
Average Total SIBDQ, n=102 (median, [IQR])	49.8 [19.0]	47.0 [22.0]	51.5 [19.5]	0.078
Disease activity, (median, [IQR])				
HBI (Crohn's disease), n=73	3.7 [6.0]	4.0 [6.0]	3.0 [5.0]	0.698
UCAI (Ulcerative colitis), n=39	2.0 [5.0]	3.3 [5.0]	2.0 [5.8]	0.931
Healthcare utilization, (median [IQR])				
Telephone calls	4.0 [7.0]	5.5 [8.5]	3.0 [5.0]	**0.001**
Office visits	2.0 [2.0]	2.0 [3.0]	1.0 [1.0]	**0.023**
Radiologic procedures	1.0 [4.0]	1.0 [7.0]	1.0 [4.0]	0.552
Endoscopies	1.0 [1.0]	1.0 [1.0]	1.0 [1.0]	0.874
Surgery, n (%)	8 (5.2)	4 (6.7)	4 (4.3)	0.778
Hospitalizations	0.0 [1.0]	0.0 [2.0]	0.0 [0.0]	0.400
Emergency room visits	0.0 [2.0]	0.0 [3.0]	0.0 [1.0]	0.087
Financial charges ($)	11309.00 [98577.50]	51146.00 [182517.00]	8120.50 [63850.25]	**0.001**

Bolded p-values are statistically significant ($p<0.05$)

Abbreviations: SIBDQ, short inflammatory bowel disease questionnaire; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HBI, Harvey Bradshaw Index; UCAI, Ulcerative colitis activity index; IQR, interquartile range

† Immunomodulators include 6-mercaptopurine, azathioprine, methotrexate. Biologics include anti-tumor necrosis factor agents (infliximab, adalimumab, and certolizumab), anti-integrin therapy (vedolizumab and natalizumab). Biologics include all anti-tumor necrosis factor agents and anti-integrin therapies. Systemic antibiotics include all systemic antibiotic exposure, excluding vancomycin and fidaxomicin.

3.3.3 Year after infection, excluding patients with multiple infections

Of the 60 CDI patients who had follow up in the year after infection, there were 18 patients (30%) who had more than one CDI infection documented with molecular testing during their participation in the UPMC IBD research registry. We performed a subgroup analysis of the patients who followed up the year after infection and did not have multiple documented infections (n=136: 42 CDI, 94 controls). When patients who had more than one documented CDI were excluded, we observed that higher exposure to vancomycin in the CDI group remained significant (33.3% CDI vs. 11.7% controls, p=0.03) in the year after infection. Meanwhile, the exposure to all other classes of antibiotics was no longer significantly different (p=0.64) between the two groups.

After excluding those with multiple CDI, we observed that the number of clinic visits (median [IQR]: 2 [3] CDI vs. 1 [1] controls) between groups is no longer significantly different (p=0.18), but CDI patients continued have significantly more telephone encounters (median [IQR]: 5 [8] CDI vs. 3 [5.5] controls, p=0.04) in the year after infection. CDI patients also continued to have significantly more healthcare related charges (median [IQR]: $40,865.25 [$149,684.90] CDI vs. $7,775.08 [$74,816.48] controls, p=0.018), after excluding patients with multiple positive CDI molecular tests.

3.4 DISCUSSION

In this propensity score matched analysis of CDI patients compared to controls, participants were matched on risk factors for *Clostridium difficile* in the year prior to infection. While groups did not differ at in any measured metrics at baseline, those who developed CDI in the following year demonstrated significantly increased biomarkers of inflammation (CRP and ESR), increased patient reported metrics of disease severity, increased medication exposure, decreased QOL, and significantly increased inpatient and outpatient healthcare utilization compared to controls. Interestingly, the increase in healthcare utilization and antibiotic exposure extended into the year after infection for patients with CDI. Differences in QOL just failed to reach statistical significance in the year after infection. This could be due to the statistically lower follow up in the control group in the year after infection. The poor follow up in the control group results in fewer QOL scores completed from patients who are likely feeling well. Overall, the findings suggest CDI has a lasting and measureable impact on IBD patients beyond the acute care period.

Previous research has shown that CDI in IBD is associated with systemic inflammation and disease activity, which we validated in this propensity matched cohort study.[91,92] In addition to association with measures of disease severity, we observed that patients with CDI were more frequently prescribed and exposed to systemic steroids during the year of infection. This could be due to worsening of symptoms initially thought to be a flare of IBD and may have been attributable to infection, or CDI that precipitates an IBD flare. These data highlight the difficulty of diagnosis and importance of proper management of CDI in the setting of IBD, as both infection and disease flare present with similar symptoms of elevated inflammatory biomarkers and diarrhea.

A recent meta-analysis demonstrated that CDI is a significant risk factor for colectomy in patients with IBD.[86] Our study failed to find differences in the proportion of patients requiring surgery in the year of infection and the year after. This could be due to the baseline matching, which selected for a severe disease cohort from the outset, placing both groups at higher risk for surgery than the general IBD population. This is supported by the fact that a third of patients had a history IBD related surgery prior to study enrollment, and around 15% of patients had surgery in the year prior to infection. In the year of infection approximately 9% of patients had an IBD related surgery, and this was similar between groups. Other reasons for the lack of surgical endpoints in this study includes the relatively small cohort of patients, and that we did not exclude patients who had prior surgery or colectomy.

In this study, we included participants who had multiple positive molecular tests for CDI. Recurrent infection is a significant and important feature of CDI in the setting of IBD that we hoped to characterize with longitudinal observational data. Additionally, many IBD patients are treated empirically without repeat molecular testing due to the high likelihood that persistent symptoms represent CDI recurrence in the setting of IBD. Similar to other studies, we observed approximately one-third of patients experience repeat infection confirmed with molecular testing.[22] To ensure that patients with documented recurrent infection were not influencing the results of the statistically significant parameters, we repeated the analysis excluding this fraction of patients and found similar significant results in relation to increased vancomycin antibiotic exposure, increased telephone encounters possibly due to continuing empiric therapy, and increased financial charges which serves as an all-encompassing healthcare utilization metric. However, the differences in the number of clinic visits were no longer statistically significant.

This study was performed at a tertiary care center, and therefore may not be generalizable to patients in the community setting. However, the UPMC IBD Registry collects all data from the electronic medical record, which includes over 22 different hospitals and 500 clinics in the surrounding community. This analysis is restricted to only those patients who are enrolled in the UPMC IBD Research registry, and is therefore subject to participation bias. Given the strict inclusion criteria of requiring clinical follow-up in the year *prior* to infection, we may have missed valuable data on patients initially presenting to our tertiary care clinic for worsening disease that could be attributed to CDI, or were diagnosed with CDI on their first visit to the Digestive Disorders Center. We recognize that there is a testing bias, as only those initially tested for CDI due to clinical suspicion were included in our CDI cohort. Choice of methodology for testing was not standardized among providers and not captured in the registry data; therefore, we do not have detailed data regarding colonization as compared to infection. The size of our cohort is also relatively small, including only 66 patients with CDI; therefore, some of our measured outcomes in the year after infection may have lacked statistical power due to low sample size. Despite the small size of our study cohort, we were able to observe highly significant differences between the matched groups in the year of infection and the year after infection.

This is the first propensity score matched analysis of a CDI cohort in the setting of IBD. This approach helps to alleviate many of the caveats associated with a random sample, as those who have a history of infection may be inherently different due to risk factors associated with infection. These data are prospectively derived from the electronic medical record and represents real world care of IBD patients, as it is not collected under the standardized setting of a clinical trial. The analysis of real world data brings us closer to understanding typical care patterns and the true IBD patient experience of CDI.

In conclusion, CDI negatively impacts the clinical course of IBD in the year of infection, and also has lasting and measurable effects. CDI results in increased IBD activity, elevated biomarkers of inflammation, poor health- related QOL, and increased healthcare utilization during the year of infection, some of which extends into the year after infection. Given the dramatic impact of CDI on IBD, future studies evaluating treatment strategies of CDI in IBD are needed.

4.0 LOW RATES OF DERMATOLOGIC CARE AND SKIN CANCER SCREENING AMONG INFLAMMATORY BOWEL DISEASE PATIENTS

Adapted from manuscript under submission:

Low rates of dermatologic care and skin cancer screening among inflammatory bowel disease patients

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4.1 INTRODUCTION

Inflammatory bowel disease (IBD) is a complex immune mediated disorder including Crohn's disease (CD) and ulcerative colitis (UC).[1] Extraintestinal manifestations of IBD occur in up to 50% patients and can involve almost every organ system.[8,93,94] Dermatologic complications are one of the most common.[24] Between 22-75% of CD patients, and 5-11% of UC patients are thought to have mucocutaneous findings associated with IBD.[25]

There is a range of associated cutaneous findings in IBD. Certain cutaneous manifestations mirror disease activity, while others occur at random.[94,95] Hallmark dermatologic manifestations of IBD include pyoderma gangrenosum, and erythema nodosum, both of which are reactive skin lesions.[94] Medication exposures can increase the risk of cutaneous findings in IBD including adverse psoriaform skin lesions in patients receiving anti-tumor necrosis factor (anti-TNF) therapy.[8,96] Melanoma and non-melanoma skin cancer (NMSC) risk are increased in IBD.[9,26,97] While there are studies suggesting biologics may further increase the risk of melanoma in immunosuppressed populations, including IBD,[28–30] the American College of Gastroenterology (ACG) preventive care guidelines for IBD patients suggest melanoma screening skin exams for UC and CD patients, independent of biologic therapy.[98] There are also data to support the increased risk of NMSC among IBD patients on immunomodulator therapy;[27,28,31,99–101] therefore, the ACG guidelines similarly recommend patients on thiopurines (6-mercaptopurine or azathioprine) obtain a skin cancer-screening exam due to increased risk of NMSC.[98] Finally, the Crohn's and Colitis Foundation (CCFA) preventive guidelines suggest anyone on systemic immunosuppression (azathioprine, 6-mercaptopurine, methotrexate, anti-TNFs, anti-IL-12/23) undergo annual skin cancer screening.[98]

Total body skin exams to detect skin cancer remain relatively infrequent among the general population in the United States. Studies estimate only 8-15% of the general population report having a recent skin exam by a physician.[102,103] These estimates may not reflect the rates of preventive care skin exams among IBD patients who are recommended for screening and frequently obtain coordinated care from specialists. Despite the extensive literature outlining the comorbid skin conditions associated with disease activity, heightened risk of skin cancer, and the high percentage of patients that are likely to experience dermatologic problems, it is uncertain how many IBD patients are actively seeking dermatologic care, and for what reasons. The aims of this study were to define the rate of dermatologic care in IBD patients, identify the reasons for dermatology visits with a focus on skin cancer screening, and determine factors associated with dermatology use.

4.2 METHODS

4.2.1 Study population

This study was conducted at a single tertiary referral center. All subjects included in this study are a part of the University of Pittsburgh Medical Center (UPMC) IBD research registry. The data collection methods and variables associated with the registry have been previously described in detail.[88] Briefly, clinical care data from the outpatient electronic medical record are prospectively collected, exported and organized for the purposes of research. The registry captures outpatient encounters across all specialties that utilize the outpatient electronic medical record within the UPMC healthcare system. Encounter specific data, including primary diagnosis

codes, are also curated and organized at the visit and patient level. Registry participants were eligible for inclusion in this study if they were consented and enrolled in the UPMC IBD research registry, had a confirmed diagnosis of CD or UC, using standard diagnostic criteria, and had at least one in-person clinic visit in the digestive clinic from 2010-2016. Patients were excluded from this study if they did not have an established diagnosis of IBD, or they were not seen in the digestive clinic at any point between 2010-2016.

4.2.2 Clinical data collection

4.2.2.1 IBD related clinical information

IBD specific clinical data include disease type (CD or UC), duration of the disease, and extent and behavior at diagnosis using the Montreal classification.[51] Medication exposures were assessed using prescriptions and categorized as exposure per year. Medication categories consisted of immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), biologics (anti-TNF, anti-interleukin-12/23, and anti-integrin), 5-aminosalyslyic acid agents, systemic steroids, and topical steroids. Healthcare utilization was quantified using the total number of emergency room (ER) visits, hospital admissions, IBD clinic visits, telephone calls, and the need for an IBD-related surgery over the study period. We dichotomized certain healthcare utilization metrics as "ever occurring" over the study period for meaningful interpretation (surgery, hospitalization, and ER visit).

We assessed biomarkers of inflammation including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). ESR and CRP were transformed into annual dichotomous variables if they were elevated using local laboratory reference values, and were determined as "ever-abnormal" over the study period. Disease-related clinical activity scores were

prospectively collected at outpatient visits using the Harvey-Bradshaw Index (HBI) for CD and ulcerative colitis activity index (UCAI) for UC.[43,44] Active disease was defined as mean UCAI score ≥4 or mean HBI scores ≥5 during the study period. The short inflammatory bowel disease questionnaire (SIBDQ) was collected at outpatient visits to estimate participants' health-related quality of life.[42] Mean disease activity and quality of life scores were calculated over the entire study period.

4.2.2.2 Dermatology utilization data

From those eligible for the study, we captured all patient encounters (clinic visits, procedural visits, emails, and telephone encounters) that were completed at a dermatology clinic or were associated with a dermatology practice group in the UPMC system from 2010-2016. We organized in-person dermatology patient encounters (clinic visits and procedural visits) by year and further classified reasons for care into categories (**Appendix A, Table 19**). The grouping was based on clinical indications as defined by primary diagnosis codes associated with each visit or procedure. A practicing dermatologist (LF) verified the final categories. We then determined the frequency of dermatology care by indication for each calendar year and overall from 2010-2016.

To determine the proportion of patients actively seeking dermatologic care, we divided the number of IBD patients with dermatologic visits (clinic or procedural) by the number of IBD patients with clinical follow up in the digestive clinic. Clinical follow up was used to estimate of the number of IBD patients actively seeking gastrointestinal/specialty care, and defined as any clinic visit within a calendar year. We excluded telephone calls as a source of clinical follow up as we assumed only in-person visits or procedures would provide appropriate interaction time between provider and patient to discuss preventive care guidelines.

To determine the proportion of patients obtaining skin cancer screening as their primary reason for visiting dermatology, we considered any outpatient visit or procedure involving the primary diagnosis codes within the category of "screening", outlined in **Appendix A, Table 19,** as involving screening for skin malignancy. We used this proxy as a conservative estimate of skin cancer screening including only total body skin exams in which clinicians screened for skin cancer, so the results were not inflated due to incidental findings of skin cancers or spot checks that occur during other visits, such as a follow up visit for psoriasis or dermatitis. Prior validation of this approach within our health system found this ICD9/ICD10 classification methodology may miss approximately 20% of total body skin exams (data unpublished), which we explored in sensitivity analyses. From this definition of total body skin exams, we determined the number of unique individuals with skin cancer screening during the calendar year and calculated the proportion of patients with screening compared to the number of patients at the IBD clinic and each particular high-risk subgroup.

4.2.3 Definition of high-risk subgroups for skin cancer screening

Given the preventive care guidelines in IBD, we evaluated how many patients were recommended for screening each year according to ACG or CCFA guidelines.[98,104] The ACG recommends all UC and CD patients undergo skin cancer screening for melanoma regardless of medication exposures, which we considered to be all patients with in-person follow up in the digestive clinic.[98] The ACG also recommends patients on thiopurines undergo screening for NMSC, particularly those over age 50.[98] This population was defined as any patient within the digestive clinic cohort with 6-mercaptopurine or azathioprine exposure (prescription), who was over 50 years old as of January 1st of the associated calendar year. Finally, the CCFA

recommends annual screening for skin cancer for all IBD patients on any immunosuppression.[104] This population was defined as any patient within the digestive clinic cohort exposed to azathioprine, 6-mercaptopurine, methotrexate, anti-TNFs, ant-integrin, and/or anti-interleukin-12/23 agents within the calendar year. Within each of the defined high-risk subgroups we determined the proportion of patients who were seen by dermatology, and those with primary diagnosis codes indicating skin cancer screening as the primary reason for their visit.

4.2.4 Capturing skin cancer diagnoses

IBD patients with concurrent diagnosis of melanoma and NMSC were identified through primary visit diagnoses codes at dermatology visits and/or pathology diagnoses of melanoma, squamous cell carcinoma, or basal cell carcinoma. All skin cancer diagnoses identified through medical records and pathology data extraction were confirmed using manual chart review.

4.2.5 Statistical analysis

Descriptive statistics of IBD patients with and without a history of dermatologic care were calculated as means and standard deviations for normally distributed variables, and median and interquartile range for nonparametric variables. Categorical variables and the fraction of patients obtaining care were presented as proportions. Proportions were averaged over seven years and reported with the 95% confidence interval. Incidence rates of melanoma and NMSC were calculated as the number of cases per total person-years of in-person follow up in the digestive clinic. To compare between dermatology and no-dermatology groups we used the Student's t-test for normally distributed continuous variables, the Wilcoxon rank-sum test for

non-parametric continuous variables, and categorical variables were compared between groups using the Chi-squared test. To evaluate IBD factors associated with dermatologic care we used univariable and multivariable logistic regression analysis. Hypothesis driven covariates, and those p-value <0.10 on univariable analysis were included in multivariable logistic regression models. All statistical tests used an alpha <0.05.

4.2.6 Ethical considerations

The UPMC IBD research registry (Protocol # 0309054) and this particular study (Protocol #PRO17040311) were approved by the University of Pittsburgh Institutional Review Board.

4.3 RESULTS

4.3.1 Study cohort

There were 2127 IBD patients in the IBD registry from 2010-2016 that were eligible for this study and evaluated for the use of dermatologic care. Of these, 452 (21.3%) IBD patients obtained dermatologic care from January 1, 2010 – December 31, 2016. The majority of IBD patients seeking dermatologic care were female (55.5%), with a mean age of 46.1 ± 14.9 years (**Table 12**). Over half of the patients were employed, married, were Caucasian, and 21% of patients were active smokers (**Table 12**). Five percent of the cohort had a family history of skin

cancer (NMSC and/or melanoma), which was significantly increased in the cohort using dermatology (18.1% vs. 1.9%) (**Table 12**).

Table 12. Dermatology study cohort demographics

		Dermatology utilization		
	Total n= 2,127	Dermatology n= 452	No Dermatology n= 1675	p-value
Age (mean years ± SD)*	46.1 ± 15.3	46.1 ± 14.9	46.1 ± 15.4	0.981
Female, n (%)	1,108 (52.1)	251 (55.5)	857 (51.2)	0.099
Race/Ethnicity, n (%)				
Caucasian	1989 (94.3)	423 (93.8)	1,566 (94.4)	0.109
Black	51 (2.4)	14 (3.1)	37 (2.2)	
Other, unknown, or not specified	62 (2.9)	10 (2.2)	52 (3.1)	
Hispanic/Latino	8 (0.4)	4 (0.9)	4 (0.2)	
Marital Status, n (%)				
Married	1,180 (55.5)	252 (55.8)	928 (55.5)	0.131
Single	739 (34.8)	166 (36.7)	573 (34.3)	
Divorced, widowed, separated	175 (8.2)	32 (7.1)	143 (8.6)	
Unknown	31 (1.5)	2 (0.4)	29 (1.73)	
Employment status (n, %)				
Full time or self-employed	1080 (51.2)	251 (55.5)	829 (50.1)	**0.001**
Full or part time student	161 (7.6)	39 (8.6)	122 (7.4)	
Part-time	50 (2.4)	13 (2.9)	37 (2.2)	
Retired	173 (8.2)	36 (8.0)	137 (8.3)	
Not employed	401 (19.0)	87 (19.3)	314 (19.0)	
Unknown	243 (11.5)	26 (5.6)	217 (13.1)	
Smoking status (n, %)				
Current use	452 (21.4)	98 (21.7)	354 (21.3)	0.983
Former use	406 (19.2)	86 (19.0)	320 (19.3)	
Never	1,256 (59.4)	268 (59.3)	988 (59.5)	
Family history of skin cancer (n, %)	114 (5.5)	82 (18.1)	32 (1.9)	**<0.001**

4.3.2 Dermatology healthcare utilization

The 452 IBD patients were responsible for 1633 dermatology office visits, 278 procedural visits, 1108 telephone encounters, and 127 patient emails between the years 2010 and 2016. Patients ranged from 1 to 44 procedure or office visits over the study period, with a median of 2 total visits over the 7-year study period. The study participant with 44 in-person visits was being actively treated for vitiligo, which resulted in frequent treatments and follow up. Among the patients who saw dermatology, median number of dermatology visits per patient in a single calendar year was 1.0 visit.

4.3.3 Indications for dermatologic care

The indications for care, as determined by primary diagnosis codes, remained relatively consistent each year (**Appendix A, Table 20**). The most frequent indication for office or procedure visits each year was “contact dermatitis or dermatitis”. While other indications fluctuated slightly from year to year, the top categories included: contact dermatitis; acneiform eruptions; neoplasm of uncertain behavior or unspecified; benign neoplasm; actinic keratosis and solar skin aging; and psoriasis (**Appendix A, Table 20**). We also evaluated the percentage of patients seeking care for known extraintestinal manifestations of IBD including primary diagnosis codes of pyoderma gangrenosum, erythema nodosum, hidradenitis suppurativa, and IBD (details in **Appendix A, Table 19**). The proportion of dermatologic visits in the IBD

category varied between a minimum of 1.1% to a maximum of 10.3% of all dermatologic visits by IBD patients per year, averaging a total of 4.1% (95%CI: 1.23-6.9) of visits per year.

4.3.4 Annual rate of dermatology use in IBD patients

The proportion of IBD patients seeking dermatologic care compared to those with an in-person visit in the IBD clinic ranged from 3.6% – 10.8%, with an average of 8.3%, over the seven-year study period (**Figure 3, Table 13**). Similar trends were observed in the CCFA and ACG high-risk subgroups (**Figure 3**), with 8.6% and 10.9% of patients visiting dermatology each year, respectively (**Table 13**).

Table 13. Proportion of inflammatory bowel disease patients with dermatologic care and skin cancer screening per year

	Mean	**95% CI**
Total IBD patients (n=2127)		
IBD Patients with dermatologic visit per year, (n) *	132.7	[101.3, 164.1]
IBD Patients with TBSE, (n) †	12.4	[6.8, 18.1]
IBD patients with digestive visit, (n)	1089.4	[951.6, 12227.3]
Proportion with dermatologic visit (%)*	8.3	[6.1, 10.6]
Proportion with TBSE (%)†	0.9	[0.3, 1.4]
IBD patients under CCFA recommendations, (n)	809.9	[692.3, 927.4]
Proportion with dermatologic visit (%)*	8.6	[6.5, 10.7]
Proportion with TBSE (%)†	0.8	[0.4, 1.1]
IBD patients under ACG recommendations, (n)	110.6	[97.9, 123.2]
Proportion with dermatologic visit (%)*	10.9	[7.1, 14.6]
Proportion with TBSE (%)†	2.5	[0.4, 4.6]

Table 14. Clinical characteristics of inflammatory bowel disease patients with and without a dermatologic visit

		Dermatology Utilization		
	Total	Dermatology	No Derm	p-value
	n= 2,127	n= 452	n= 1675	
Disease category (n, %)				
Crohn's disease	1,341 (63.1)	291 (64.4)	1,050 (62.7)	0.508
Ulcerative colitis	786 (36.9)	161 (35.6)	635 (37.3)	
Years of disease, (mean ± SD) n=1440	18.9 ± 10.3	20.0 ± 11.5	18.6 ± 10.0	**0.037**
Disease characteristics				
Crohn's disease location, n=1,67				
Ileal (L1)	316 (29.6)	65 (27.0)	251 (30.4)	0.307
Colonic (L2)	217 (20.3)	45 (18.7)	172 (20.8)	0.465
Ileocolonic (L3)	535 (50.2)	127 (52.7)	408 (49.5)	0.376
Upper GI (L4)	43 (4.0)	11 (4.6)	32 (3.9)	0.632
Crohn's disease behavior				
Inflammatory (B1)	456 (42.8)	112 (46.5)	344 (41.7)	0.187
Stricturing (B2)	408 (38.2)	83 (34.4)	325 (39.4)	0.168
Penetrating (B3)	239 (22.4)	51 (21.2)	188 (22.8)	0.600
Perianal disease	193 (18.1)	48 (19.9)	145 (17.6)	0.402
Ulcerative colitis extent, n=607				
Proctitis (E1)	47 (7.7)	9 (7.1)	38 (7.9)	0.777
Left-Sided (E2)	199 (32.8)	39 (31.0)	160 (33.3)	0.623
Extensive (E3)	351 (57.8)	77 (61.1)	274 (57.0)	0.401
Biomarkers (n, %)				
Elevated CRP, n=1,925	1,063 (55.2)	249 (59.4)	814 (54.1)	**0.050**
Elevated ESR, n=1,916	816 (42.6)	208 (49.6)	608 (40.6)	**0.001**
Medication use (n, %)[†]				
Biologics	935 (44.0)	245 (54.2)	690 (41.2)	**<0.001**
Any immunomodulator	1,177 (55.3)	265 (58.6)	912 (54.5)	0.113
Thiopurines (6MP + AZA)	947 (44.5)	199 (44.0)	748 (44.7)	0.811
Methotrexate	326 (15.3)	98 (21.7)	228 (13.6)	**<0.001**
5-aminosalicylic acids	1,109 (52.1)	244 (54.0)	865 (51.6)	0.377
Systemic steroids	1,200 (56.4)	319 (70.6)	881 (52.6)	**<0.001**
Topical steroids	457 (21.5)	277 (61.3)	180 (10.8)	**<0.001**
Average total SIBDQ, n=1951 (median, IQR)	54.0 [16.9]	54.3 [14.9]	54.0 [17.7]	0.719
Active disease, n=1,906 (n, %)	652 (34.2)	135 (32.9)	517 (34.6)	0.537
Healthcare utilization				
Emergency room visit, (n, %)	1,137 (53.5)	315 (69.7)	822 (49.1)	**<0.001**
Hospitalization, (n, %)	1,075 (50.5)	261 (57.7)	814 (48.6)	**0.001**
IBD related surgery, (n, %)	396 (18.6)	92 (20.4)	304 (18.2)	0.285
Digestive clinic visits, (median, IQR)	6.0 [7.0]	7.0 [9.0]	5.0 [6.0]	**<0.001**
Digestive clinic telephone encounters, (median, IQR)	13.0 [19.0]	17.0 [27.0]	12.0 [18.0]	**<0.001**

4.3.5 IBD characteristics associated with dermatology utilization

The majority of the study cohort had CD (63.1%). Increased disease duration was associated with dermatologic care (**Table 14**). There were no differences in disease location, behavior, extent, or perianal disease between the two groups. Those with dermatology care were more likely to ever have elevated serum markers of inflammation including ESR and CRP (**Table 14**). Medications exposures associated with dermatologic care included biologics, methotrexate, systemic and topical steroids (all $p<0.001$), but not thiopurines. Quality of life scores and active disease status was not different between groups. However, a larger proportion of patients with dermatology use was hospitalized or used the ER over the study period (all $p<0.01$). Dermatology use was associated with an increased number of digestive telephone encounters and digestive clinic visits ($p<0.001$) (**Table 14**).

After adjusting for covariates, factors that remained significantly associated with dermatology utilization were employment status, family history of skin cancer, longer disease duration, systemic steroids, any emergency room use, and increasing number of IBD related clinic visits (**Table 15**). Elevated CRP was negatively associated with dermatology use (**Table 15**). We did not adjust for topical steroid use, as this is likely an outcome of visiting dermatology.

Table 15. Multivariate logistic regression of factors associated with dermatology utilization

	Adjusted Odds Ratio	95% CI	*p-value*
Dermatology utilization*			
Female	1.01	[0.74 – 1.4]	0.964
Employment status			**0.012**†
Full time or self employed	*Reference*		
Not employed	0.85	[0.55 – 1.30]	0.451
Part time	1.24	[0.48 – 3.21]	0.656
Full or part time student	1.84	[1.09 – 3.11]	0.023
Retired	0.80	[0.45 – 1.43]	0.395
Unknown	0.47	[0.25 – 0.86]	0.015
Family history of skin cancer	13.22	[7.31 – 23.9]	**<0.001**
Years of disease	1.02	[1.01 – 1.04]	**0.003**
Abnormal CRP	0.62	[0.42 – 0.89]	**0.011**
Abnormal ESR	1.33	[0.93 – 1.91]	0.123
Exposure to biologics	1.18	[0.85 – 1.63]	0.317
Exposure to methotrexate	1.28	[0.84 – 1.95]	0.249
Exposure to systemic steroids	1.68	[1.19 – 2.37]	**0.003**
Emergency room visit	2.31	[1.60 – 3.33]	**<0.001**
Hospitalization	0.71	[0.49 – 1.04]	0.077
Total digestive clinic visits	1.06	[1.02 – 1.09]	**<0.001**
Total digestive telephone encounters	1.00	[1.00 – 1.01]	0.487

4.3.6 Skin cancer screening

A total of 55 (2.59%) IBD patients in the cohort had a dermatology visit for a total body skin exam at least once over the study period. Of those with a clinic visit at the digestive clinic, the proportion of patients undergoing skin cancer screening with dermatology ranged from 0.2 – 2.1% of patients per year (**Table 13**). We also evaluated the percentage of IBD patients who

were recommended for preventive care screening by the CCFA and ACG (**Figure 3**). The CCFA cohort was larger and 0.8% of this group received a total body skin exam per year (**Figure 3, Table 13**). Of the ACG recommended patients, an average of 2.2% received skin cancer screening per year (**Figure 3, Table 13**). Given the limitations of the methodology of identifying total body skin exams, these may be underestimated by approximately 20%, which would suggest 1.1% of the IBD patients, 0.9% of the CCFA and 2.7% of the ACG groups likely underwent skin cancer screening by a dermatologist.

We determined the number of patients with primary care visits each year in an attempt to account for abbreviated skin cancer screenings and found an average of 8.7% (95% CI: 8.0% - 9.3%) of IBD patients visited a primary care office within the health system each year.

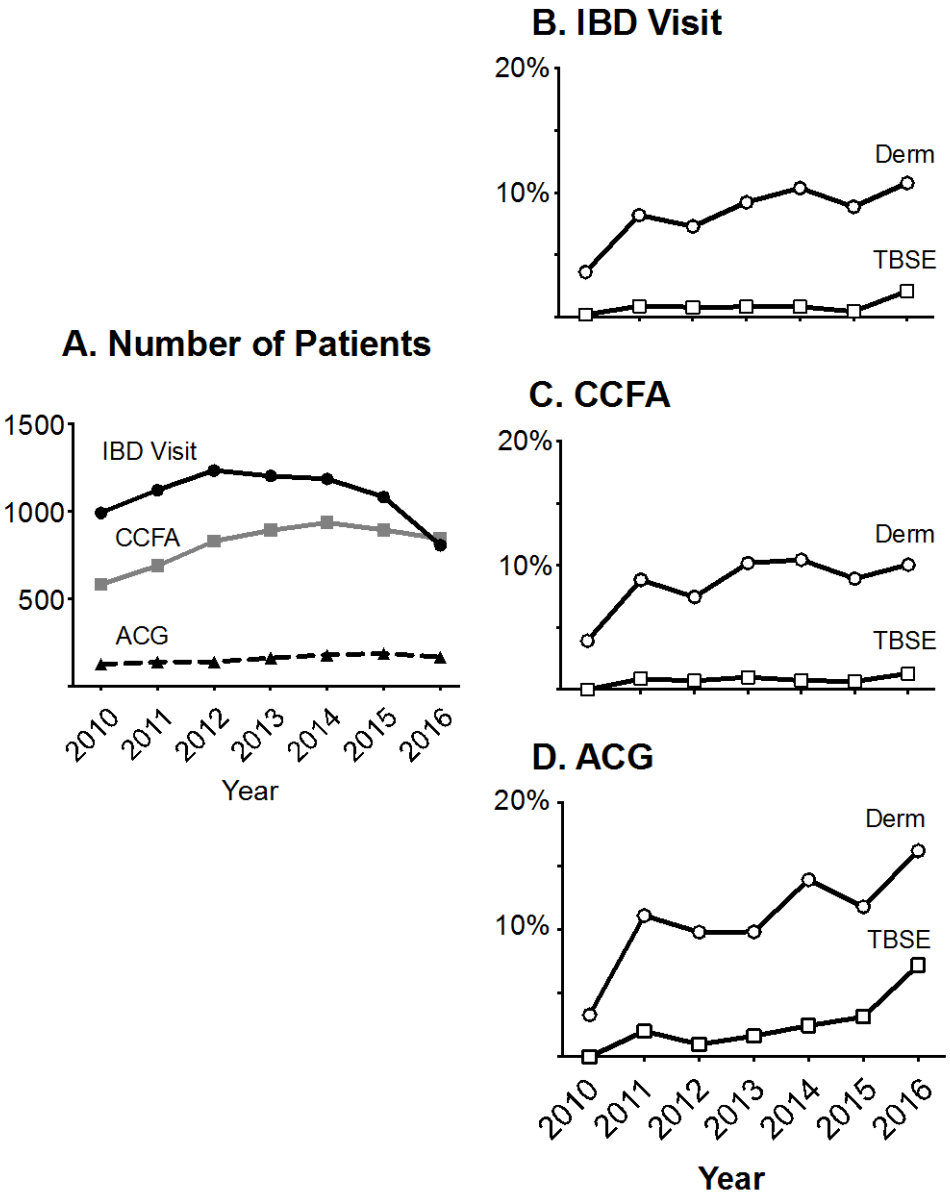

Figure 3. Proportion of patients with inflammatory bowel disease who visited dermatology

(A) Total number of unique patients in each category (IBD clinic visit, CCFA guidelines, ACG guidelines, per year. (B – D) The proportion of patients with a dermatologic clinic or procedural visit within the calendar year, and the proportion of patients with a total body skin exam for skin cancer screening per year.

ACG, American College of Gastroenterology; CCFA, Crohn's and Colitis Foundation; IBD, inflammatory bowel disease; TBSE, total body skin examination

4.3.7 Skin cancer diagnoses

Using pathology reports and dermatology clinic and procedure visit diagnoses, there were a total of 12 (0.56%) patients with cutaneous squamous cell carcinoma, 15 patients (0.71%) with basal cell carcinoma, and 5 patients (0.24%) with melanoma diagnosed between the years 2010 – 2016. Overall, in our IBD cohort, the incidence of NMSC was 35.4 /10,000 [95%CI: 23.3 – 51.5]. There were also, five patients with melanoma, with an incidence of 6.56 / 10,000 [95%CI: 2.1 – 15.3]. Of the five IBD patients diagnosed, the stages of melanoma ranged from in-situ melanoma (n=1, 20%) to stage IV metastatic melanoma (n=2, 40%). The remaining two intermediate melanomas were stage I with Breslow depths of 0.25mm and 0.45mm. The patients diagnosed with stage IV metastatic melanoma were ages 63 and 81, and both passed away within the study period.

4.4 DISCUSSION

In this observational study we used a multiyear, prospectively collected dataset to evaluate the dermatologic care patterns of IBD patients. We discovered 21.3% of patients saw dermatology and only 2.6% of our study population was screened for skin cancer at least once over the study period. Approximately, 8% of IBD patients seek care from a dermatologist or dermatology clinic each year. While there is a wealth of literature dedicated to the dermatologic complications of IBD including increased non-melanoma and melanoma skin cancer risk,[26–28,101] few IBD patients in this study sought dermatologic consultation and fewer obtained skin cancer screening.

These findings are similar to other studies examining preventive care habits in IBD patients, including cervical cancer screening, which found preventive care fell below recommended guidelines.[105,106] In a recent study, only 11% of IBD patients within the Veterans Health Administration dataset obtained dermatologic care over a 10-year study period.[105] This is less than our study showing 21.3% of patients over 7 years visited dermatology. However, there are likely inherent differences between our study population and veterans, including gender, which may impact risk for skin cancers and overall dermatology utilization.

We also compared our findings of low dermatology utilization to those in the solid organ transplant population who also have prolonged exposure to immunosuppressive medications.[107,108] A questionnaire study estimated around 14% of solid organ transplant patients have regular dermatologic skin care, which is higher than our observed 8% among IBD patients.[109] This same study suggested over half of transplant patients would be interested in skin cancer screening by a dermatologist.[109] While there are models incorporating total body skin exams for transplant patients, the adoption of formal skin surveillance varies among transplant clinics.[110,111] Interestingly, a qualitative study suggested that kidney transplant recipients were aware of their increased risk of skin malignancy, but expressed uncertainty regarding cancer screening recommendations, and expected guidance on screening from a health professional.[112,113] Additionally, patients and were most concerned about acute healthcare problems concerning their transplant.[112] These thoughts and attitudes may apply to the IBD patient population, but the extent to which these themes apply is unknown.[9,114]

We found that exposure to biologics was associated with dermatology use. A recent study suggested nearly a third of IBD patients initiating anti-TNF agents experience skin lesions, which provides rationale to why biologic use is associated with dermatologic care on univariable

analysis.[96] Biologics may also be used to treat certain dermatologic manifestations. Interestingly, exposure to thiopurines was not associated with dermatologic use. Thiopurines are frequently associated with increased risk of skin malignancy.[27,100,101] This finding may suggest while evidence and guidelines are available, the translation and implementation of these data into the practice of increased dermatologic care and skin cancer surveillance is lacking.

After adjusting for significant factors, family history of skin cancer remained strongly associated with dermatology use, which may imply a heightened awareness to the risk of skin cancer in these patients. However, this likely represents an information bias as the intake process of a dermatologic visit includes standard questions about family history of skin cancer, and this information may not be routinely obtained in primary care or gastroenterology visits. Systemic steroid use also remained significant, which may reflect side effects of steroid use, underlying IBD severity, or treatment of dermatologic conditions that require immunosuppression. Interestingly, increasing numbers of digestive visits and increasing disease duration of IBD are associated with dermatology use. These variables indirectly represent face time with a gastroenterology practitioner and suggest that preventive care guidelines may be discussed more frequently as time with gastroenterology providers increases.

The low proportion of patients obtaining dermatologic care potentially contributed to the lower incidence of NMSC in our patient population which was significantly lower than published NMSC incidence rates in IBD of 73.3 per 10,000.[27] There may be a subset of IBD patients with NMSC that is currently undiagnosed. Interestingly, our IBD cohort had similar incidence of melanoma compared to recent population based estimates of melanoma in IBD (2.0 to 6.1/10,000).[26,28] However, these were surprisingly advanced melanomas with two patients

diagnosed with metastatic disease. Improvement of access to screening and dermatology can help facilitate early detection of thinner melanomas.[115]

Limitations of this study include that it was based at a single tertiary care center and may not be representative of other populations or other geographic regions, given that sun exposure and skin cancer awareness may vary with climate. The IBD population may also have more severe disease at baseline given the referral center. This study was also completely dependent on electronic coding and ICD codes which have many limitations and likely oversimplify the patient encounter. This study spanned seven years, but we do not capture any preventive care occurring prior to 2010 and the utilization of the electronic medical record.

This study does not include dermatologic care obtained through local private practice clinics not linked to the UPMC outpatient medical record which limits the true estimation of dermatologic care obtained. However, our dataset captures all outpatient care in any UPMC affiliated hospital or clinic (comprising over 20 hospitals and 500 clinics), and UPMC dermatology provides a large proportion of care for the area. We also do not capture total body skin exams that occur in the primary care office using this study design. We evaluated the number of patients with primary care visits within the health system each year in an attempt to account for primary care screenings and found an <10% of IBD patients visited a UPMC affiliated primary care office each year. While this is likely an underestimation, given we do not capture private practitioners, literature suggests only 15-31% of PCP visits include a skin examination.[116,117] This study required consented enrollment in a prospective IBD research registry, which is subject to participant bias, as those who volunteer for the registry may not be representative of all IBD patients. Despite these limitations, even if the potentially missing IBD

patients obtaining of dermatology care were included, still suggest only a minority of the recommended patients are obtaining skin cancer screening.

A notable strength of this study is the use of a longitudinal multiyear dataset to evaluate care patterns over time. This approach overcomes biases associated with a pure cross-sectional analysis and provides an annual internal validation of our findings. As such, we observed that the trends of dermatologic care utilization and skin cancer screening were relatively stable over time. This analysis captures real world care patterns. The IBD registry is a not an interventional study and thus is not subject to changes in patient or provider behavior due to being observed.

In conclusion, this study highlights the low skin cancer surveillance in a tertiary referral IBD population, and suggests the need to understand patient and provider awareness and attitudes toward guidelines for screening and dermatology involvement and in comprehensive IBD care. Despite the high prevalence of skin complications, and the increased risk of skin cancers, IBD patients rarely seek dermatologic care and skin cancer screening.

5.0 COST-EFFECTIVENESS OF MELANOMA SCREENING IN INFLAMMATORY BOWEL DISEASE

Adapted from manuscript under submission:

Cost-Effectiveness of Melanoma Screening in Inflammatory Bowel Disease

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5.1 INTRODUCTION

Inflammatory bowel disease (IBD) is a collection of immune mediated disorders of the gastrointestinal tract including Crohn's disease and ulcerative colitis. It is estimated that 40% of patients will experience extraintestinal manifestations of IBD, with skin complications being one of the most common.[24] IBD skin complications include an increased risk of melanoma and non-melanoma skin cancers.[26–28] Overall, IBD is associated with a 33% increase in melanoma risk.[26] While the etiology of the increased susceptibility is not fully known, evidence suggests medication exposures and disease related inflammation may contribute to the elevated risk of skin malignancy.[31]

Currently, there are no clear recommendations for melanoma screening in the general United States (US) population. In 2009 and again in 2016, the US Preventive Services Task Force report did not recommend routine skin cancer screening, citing lack of evidence of anticipated harms and benefits with screening.[118,119] Since the initial 2009 recommendations, some evidence in favor of skin cancer screening and associated reduced mortality has evolved. Research studies suggest that melanoma awareness and screening are associated with increased melanoma diagnoses, thinner melanomas, and a reduction in melanoma related mortality.[120–122] However, these studies were primarily performed in large population based cohorts, and do not provide specific information about high-risk populations, such as IBD. IBD specific guidelines encourage patient awareness, self skin exams, and referral of patients for a skin examination by a physician.[98] The American College of Gastroenterology (ACG) preventive medicine guidelines for IBD patients suggest an annual melanoma screening skin exam, independent of biologic therapy.[98] It is also recommended that patients on immunomodulators (6-mercaptopurine or

azathioprine) also obtain a skin cancer-screening exam due to an increased risk of non-melanoma skin cancers.[98]

A handful of studies over the last two decades have evaluated the cost-effectiveness of national melanoma screening programs.[33] Overall, these studies suggest that annual population-wide screening is cost prohibitive and may result in unnecessary morbidity from screening in low risk persons. However, the studies generally agree that screening patients at higher risk of melanoma (i.e. siblings of persons with melanoma) are cost-effective strategies.[33] Despite the published studies evaluating population based screening, it is uncertain how this translates to IBD patients with increased risk of skin cancers.

Our primary aims were to determine the costs and effectiveness of the guideline recommended annual melanoma screening in the IBD population, and two alternative strategies of screening every other year and once at age 50. We also sought to determine the variables that most influence the cost-effectiveness of screening and their respective thresholds to optimize a cost-effective pragmatic approach to melanoma screening for IBD patients.

5.2 MATERIALS AND METHODS

5.2.1 Model Structure and Perspective

Using TreeAge Healthcare Pro 2015 software (TreeAge Software Inc., Williamstown, MA), we created a Markov state-transition model to evaluate the cost-effectiveness of skin cancer screening by a dermatologist compared to routine background screening. Screening for melanoma occurs from ages 40 - 80. We used a six-month cycle length over a lifetime horizon.

All costs were measured in US Dollars and adjusted to the equivalent 2016 dollar using the Consumer Price Index inflation calculator.[123] Effectiveness was measured in quality adjusted life years (QALYs). Future costs and QALYs were discounted at 3% per year. Our primary measured outcomes of the model were costs and effectiveness. Our predetermined willingness-to-pay (WTP) threshold was set at $100,000/QALY, based on contemporary US benchmarks.[124]

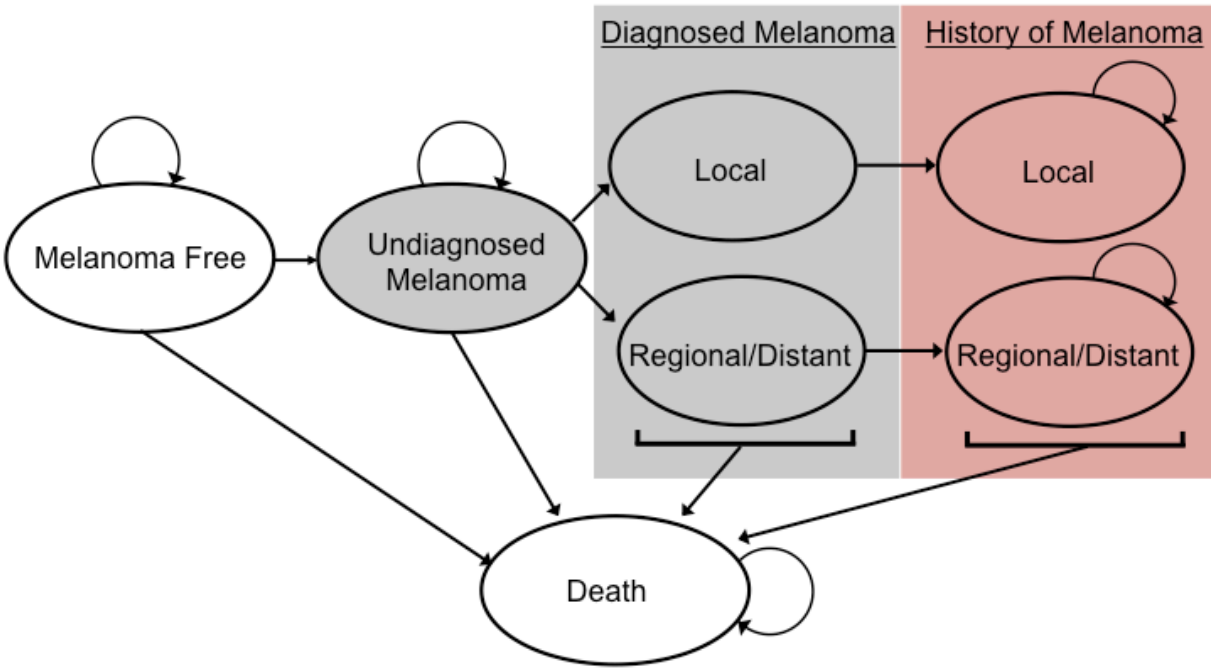

Figure 4. Markov state transition model

Health states included in model with shaded health states indicating the presence of melanoma, or history of melanoma.

5.2.2 Model Cohort

Our hypothetical cohort included adult IBD patients of average disease severity. IBD patients remained melanoma free and acquired melanoma based on published incidence rates that reflected their increased melanoma risk due to IBD.[26] Once patients developed melanoma, they

transitioned to an undiagnosed melanoma state (**Figure 4**). Patients with undiagnosed melanoma subsequently either had it detected by a physician or remained in the undiagnosed melanoma state (**Figure 4**). Melanoma detection rates for dermatologists and PCPs were obtained from published literature (**Table 16**). Once diagnosed, patients were classified as having local (Stage 1 or 2) or regional/distant (Stage 3 or 4) melanoma.[125] After the melanoma diagnosis, patients became melanoma survivors or died. Melanoma survivors entered a melanoma surveillance program of total body skin exams every six months, and had an increased likelihood of developing a second primary melanoma, which was influenced by age.[126]

Melanoma incidence and survival statistics were obtained from the Surveillance, Epidemiology, and End Results (SEER) database.[127] Patients with melanoma, regardless of diagnostic status, had higher mortality according to disease stage than did patients who were melanoma free. Age and gender specific US life tables determined survival estimates in the melanoma-free population and background mortality.[128]

5.2.3 Model Assumptions

In order to model melanoma screening in IBD patients, we made a number of assumptions. We assumed all IBD patients had the same average relative risk of melanoma. We did not model differences in IBD disease severity or exposure to IBD therapies. There is primary literature suggesting anti-tumor necrosis factor (anti-TNF) exposure increases melanoma risk in IBD and in other populations routinely exposed to biologics.[28,29] However, our base case relative risk of melanoma in the IBD population did not incorporate any additional risk of exposure to biologic therapy, as the recent meta-analysis from which it was derived did not provide definitive evidence regarding therapeutic influences on melanoma risk in IBD.[26] Given the ongoing

uncertainty of this parameter, relative risk of melanoma was varied over plausible ranges in sensitivity analyses. We assumed adherence to annual skin cancer screening would be similar to overall adherence to IBD-related appointments and medical therapy, which was derived from the literature (**Table 16**).

Localized melanomas are defined as one category within the SEER database. We assumed that approximately 75% of diagnosed melanomas confined locally would be stage 1 melanomas (tumor thickness <1.0mm and/or between 1.01-2.0mm without ulceration), and the other 25% stage 2 melanomas (tumor thickness between 1.01-2.00mm with ulceration, or any tumor >2.01mm without nodal involvement regardless of thickness).[125] We assumed that 10% of all undetected local melanomas would transition to regional/distant melanoma in the following year based on expert opinion and consistency with previous melanoma screening cost-effectiveness analyses.[34] Additionally, while melanoma screening programs are likely to detect NMSCs, including basal cell carcinoma and squamous cell carcinoma, we did not include this detection in our model as this analysis has been shown to be cost-effective in Crohn's disease patients previously.[129]

Table 16. Model probabilities, costs, and utilities

	Base Case	Monte-Carlo Distribution		Distribution	Reference
		Low Value	High Value		
Probabilities (%)					
Background skin cancer screening	10	0.9	24.5	Beta	[102,103,130]
Annual screening adherence	82.6	63.3	95.4	Beta	[131,132]
Screening adherence with history of melanoma	96.0	90.7	99.4	Beta	[133]
Dermatologist sensitivity	89.0	66.1	99.0	Beta	[134]
PCP sensitivity	80.0	67.9	91.6	Beta	[134]
Melanoma: Stage I or II (Local)	84.0	68.8	94.4	Beta	[127]
Local melanoma, Dermatologist screened	91.7	75.9	98.1	Beta	[135]
Local melanoma, PCP screened	83.4	72.3	91.3	Beta	[135]
Melanoma: Stage III	8.9	7.3	10.9	Beta	[127]
Melanoma: Stage IV	3.8	2.2	5.7	Beta	[127]
Progression: local to distant melanoma	10.0	3.4	20.5	Beta	Expert opinion[34]
Costs ($)					
Skin cancer screening exam	108.85	37.15	264.97	Gamma	[136]
Melanoma diagnosis/biopsy	104.55	41.75	200.90	Gamma	[136]
Melanoma: Stage I or II (Local)	4,027.20	1,267.06	9,926.75	Gamma	[137]
Melanoma: Stage III	13,646.81	7,845.79	20,753.99	Gamma	[137]
Melanoma: Stage IV	27,237.19	9,108.28	20,753.99	Gamma	[137]
Utilities					
Inflammatory bowel disease	0.800	0.670	0.899	Beta	[138]
Active melanoma diagnosis					
Melanoma: Stage I	0.93	0.791	0.992	Beta	[139]
Melanoma: Stage II	0.92	0.681	0.998	Beta	[139]
Melanoma: Stage III	0.72	0.533	0.853	Beta	[139]
Melanoma: Stage IV	0.58	0.418	0.736	Beta	[139]
History of melanoma					
Melanoma: Stage III	0.94	0.812	0.996	Beta	[139]
Melanoma: Stage IV	0.50	0.319	0.697	Beta	[139]
Other parameters					
Relative risk of melanoma in IBD	1.33	1.0	2.95	Log normal	[26]

NNB – Dermatologist	17.4	9.86	26.3	Gamma	[140]
NNB – PCP	32.8	24.15	42.25	Gamma	[140]

PCP – primary care physician; IBD – inflammatory bowel disease; NNB – number needed to biopsy to diagnosis one melanoma

5.2.4 Costs and Effectiveness

Cost estimates associated with melanoma screening and treatment were obtained from published literature and US databases, as were utilities for IBD and stages of melanoma (**Table 1**). Medicare physician fee schedules were used to estimate the costs associated with a screening visit and skin biopsy.[136] Effectiveness was measured in QALYs. QALYs of average IBD and melanoma health states were derived from published literature (**Table 16**), and were adjusted by age.[141] Age based utility from 40-54 years old was 0.92, from 55-64 years was 0.88, and for 65+ years was 0.84.[141]

5.2.5 Screening Strategies

The base case skin cancer screening strategy included an annual total body skin exam by a dermatologist. This screening program began at age 40 years and continued until death or 80 years of age. This was compared to background rates of skin cancer screening by primary care practitioners which were estimated through published literature.[102,103,130] Background screening was not dependent on age and continued until death in both strategies. We also evaluated alternative screening strategies to reduce the overall screening intensity on IBD patients including screening every other year and screening once at age 50. All other model parameters remained the same during the evaluation of the alternative frequency screening strategies.

5.2.6 Cost-Effectiveness Analysis

A series of one-way sensitivity analyses were performed to determine the variables that most influence the incremental cost effectiveness ratio (ICER), defined as the change in cost over the change in effectiveness. Variables were evaluated over plausible ranges, and guided by available published literature. We used deterministic sensitivity analyses to define parameter thresholds at WTP levels of $100,00/QALY and $150,00/QALY. We employed probabilistic sensitivity analysis simultaneously sampling parameter distributions over 10,000 trials, to determine the percent of model iterations favoring screening at predetermined WTP levels. We used beta distributions for probabilities and utility values, and gamma distributions for cost parameters and number needed to biopsy variables (**Table 16**).[142] Relative risk for melanoma was modeled using a log-normal distribution.[142]

5.3 RESULTS

5.3.1 Base-Case Analysis & Screening Strategies

In the IBD population, annual melanoma screening by a dermatologist cost $1961 per person compared to background screening which was $81 per person (**Table 17**). Annual screening was more effective, gaining an additional 9.2 QALYs per 1000 persons. The resulting ICER for the base case analysis was $203,400/QALY (**Table 17**). We also evaluated screening every other year from ages 40 to 80 years old. In this scenario, screening costs an average of $999 per person, while background screening costs remained the same at $81 per person.

Incremental effectiveness decreased to 6.4 QALYs per 1000 persons resulting in an ICER of $143,959/QALY. Finally, screening for melanoma once at age 50 resulted in lower screening costs, lower incremental effectiveness of screening of only 0.4 QALYs per 1000 persons, and a lower ICER as compared to the base case (**Table 17**). However, the ICER of the strategy to screen once at age 50 was $153,518/QALY, and was dominated by the strategy of screening every other year (**Table 17**).

Table 17. Cost effectiveness analysis results

	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Incremental cost-effectiveness ratio
No screening/ background	$81	-	16.5924	-	-
Base case: annual screening	$1961	$1880	16.6017	0.0092	$203,400 /QALY
Screening every other year	$999	$918	16.5988	0.0064	$143,959 /QALY
Screening once at age 50	$148	$66	16.5928	0.0004	$153,518 /QALY

All three evaluated scenarios did not meet the WTP threshold of $100,000/QALY gained. Therefore, melanoma screening is not strictly cost-effective or the preferred strategy as compared to background levels of skin cancer screening. However, given the three tested strategies, the most cost-effective approach is screening every other year with an ICER of $143,959/QALY, which is lower than screening annually and screening once at age 50.

Table 18. One-way sensitivity analyses

			Resulting ICER		Willingness to pay threshold	
	Base case	Range	Low value	High value	$100,000 / QALY	$150,000 / QALY
Base case: annual screening						
Progression percentage	10%	2% – 15%	$382,815	$181,799	n/a*	n/a*
Relative risk of melanoma in IBD	1.33	1.0 – 4.0	$268,394	$72,356	2.81	1.83
Cost of melanoma screening	$108.85	$25 - $200	$46.383	$374,088	$53.63	$80.33
Alternative strategy: screening every other year						
Progression percentage	10%	2% – 15%	$231,734	$142,307	n/a	8.15%
Relative risk of melanoma in IBD	1.33	1.0 – 4.0	$189,560	$52,255	1.95	1.27
Cost of melanoma screening	$108.85	$25 - $200	$33,023	$264,554	$75.62	$113.42

ICER – incremental cost effectiveness ratio; IBD – inflammatory bowel disease; QALY – quality adjusted life year
* Value outside of plausible range given specified willingness to pay threshold.

5.3.2 One-Way Sensitivity Analyses

5.3.2.1 Percent progression from local to regional melanoma

The percent of patients progressing from local to regional disease over time is unknown and our value was based on previously published models for consistency. Given this uncertainty, we performed one-way sensitivity analysis on this parameter from 2% progression to 15% progression in the base case annual melanoma screening scenario. Despite varying the parameter from 2-15%, there was no value that satisfied WTP cutoffs of $100,000 or $150,000/QALY. As the progression percentage increased, the ICER decreased from $382,815/QALY at 2% progression to $181,799/QALY at the highest estimate of 15% progression (**Table 18**).

When we repeated this one-way sensitivity analysis in the favored strategy of screening every other year, we obtained similar results. As the progression percentage increased, the ICER decreased from $231,734/QALY at 2% progression to $142,307/QALY at the highest estimate of 15% progression (**Table 18**).

At low progression percentages, screening every other year is the clearly preferred strategy (>$150,00/QALY difference) as compared to screening annually. While at higher progression percentages the differential in the ICERs of the two strategies of screening annually or every other year is smaller (approximately $40,000) (**Table 18**).

5.3.2.2 Relative risk of melanoma in IBD

There is relative uncertainty in the increased melanoma risk in IBD patients. We used a conservative estimate of a relative risk (1.33) derived from a meta-analysis.[26] In our one-way sensitivity analyses we evaluated relative risks between 1.0 and 4.0. In the base case strategy of screening every year, the ICER is less than $100,00/QALY if the relative risk of melanoma in IBD patients is greater than 2.81 (**Table 18**). The ICER is less than $150,000/QALY if the relative risk of melanoma in IBD is less than 1.83 (**Table 18**).

We performed the same sensitivity analysis of the relative risk of melanoma in the favored strategy of screening every other year. Results of one-way threshold analysis for this strategy were similar. When screening every other year, the ICER remains less than $100,000/QALY as long as the relative risk of melanoma in IBD patients is greater than 1.95 (**Table 18**). The ICER remains less than $150,000/QALY as long as the relative risk of melanoma in IBD is less than 1.27, which is slightly less than the base case parameter (**Table 18**).

5.3.2.3 Cost of melanoma screening by a dermatologist

Melanoma screening cost significantly influenced results. The base case cost of screening was $108.85.[136] We varied this cost in one-way sensitivity analysis from $25 to $200 in the annual screening strategy. To maintain an ICER under a WTP threshold of $100,000/QALY, screening cost must remain less than $53.63 per exam (**Table 18**). When we repeated the one-way sensitivity analysis in the more favored strategy of screening every other year, screening costs needed to remain less than under $75.62 per screen to result in an ICER less than $100,000/QALY gained (**Table 18**).

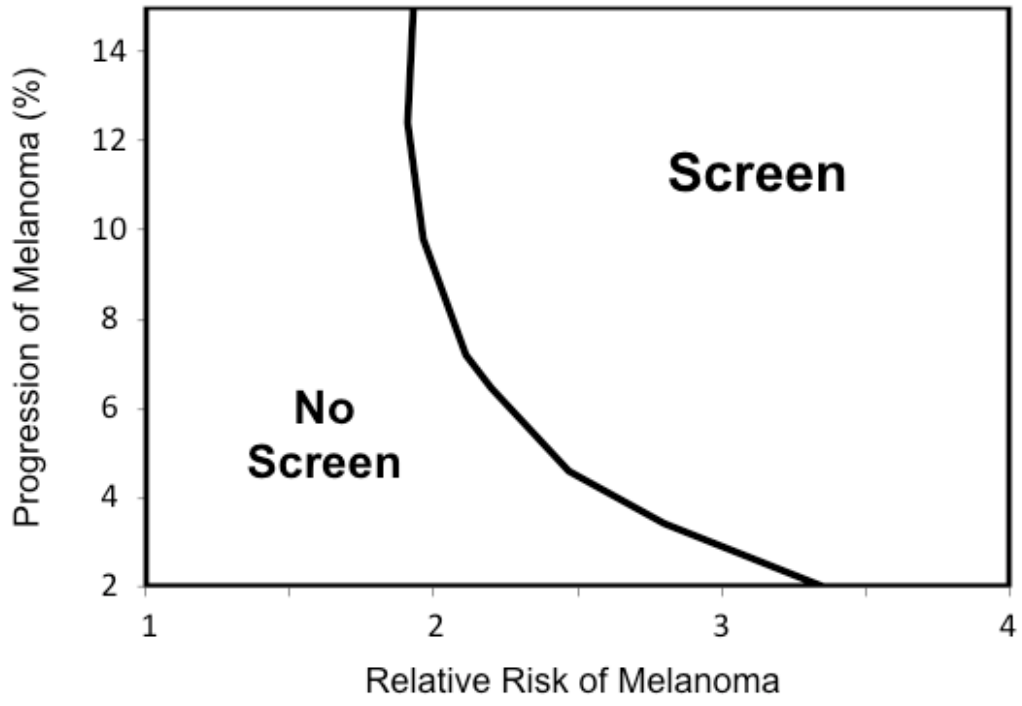

Figure 5. Two-way sensitivity analysis

Two-way sensitivity analysis of the progression percentage of melanoma (y-axis), and the relative risk of melanoma in inflammatory bowel disease patients (x-axis). Separation plane is a willingness to pay threshold of $100,000/QALY. Preferred strategy (screening every other year or no screening) is labeled in each respective area.

5.3.3 Two-way sensitivity analysis

While not strictly cost effective compared to our WTP threshold, screening every other year was the preferred strategy as compared to the base case and guideline recommendations of screening annually. One-way sensitivity analyses demonstrated that the relative risk of melanoma and the percent progression from local to regional disease have an important influence on the ICER (**Table 18**). We performed two-way sensitivity analyses on these parameters, varying them simultaneously, as they are both uncertain characteristics of melanoma, which may be different in the setting of IBD. Two-way sensitivity analysis was performed for the screening strategy of every other year (**Figure 5**). Screening every other year is favored at higher relative risks and increased probabilities of melanoma progression, as indicated in **Figure 5**.

5.3.4 Probabilistic Sensitivity Analyses

We evaluated the screening every other year strategy using probabilistic sensitivity analysis over 10,000 trials. Screening every other year was cost effective in 17.4% of model iterations at a WTP threshold of $100,000/QALY. At a WTP threshold of $150,000/QALY, screening every other year was cost effective in 44.8% of iterations (**Figure 6**).

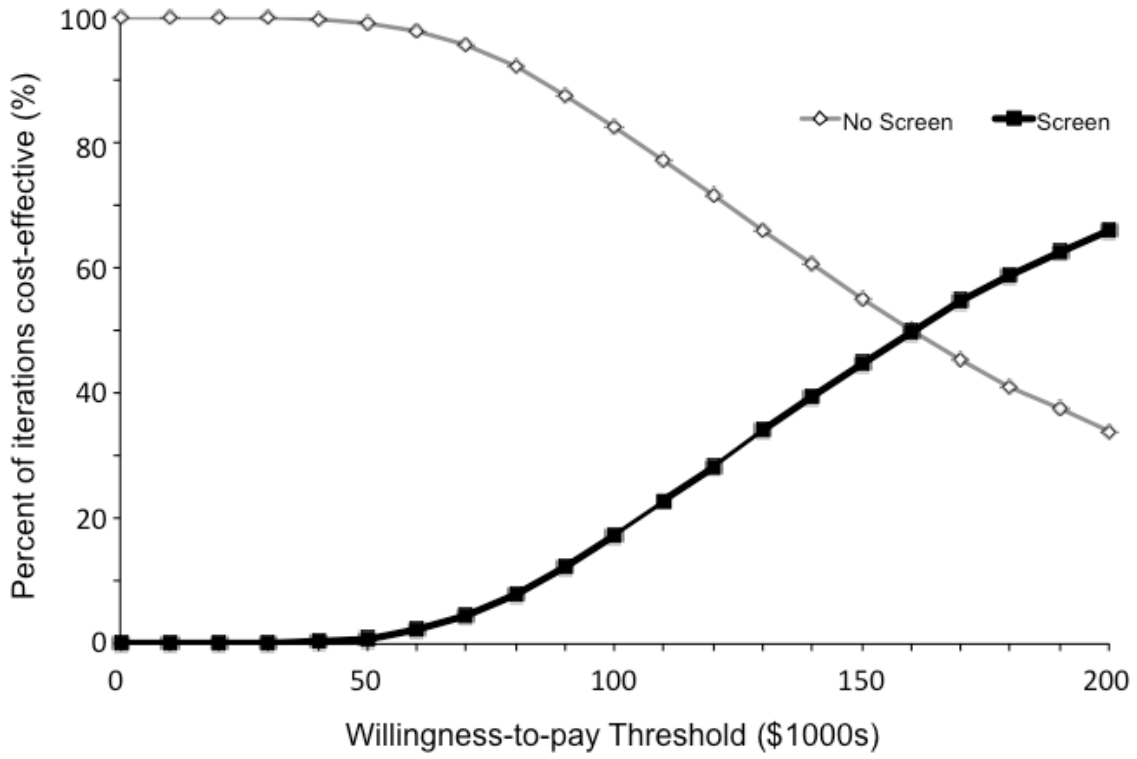

Figure 6. Probabilistic sensitivity analysis

Cost-effectiveness acceptability curves show the likelihood that melanoma screening (black square) and no screening (open circle) are considered cost-effective over a range of willingness-to-pay thresholds when parameters are simultaneously varied over their distributions.

5.4 DISCUSSION

Screening for melanoma in IBD patients was effective but expensive. With a WTP threshold of $100,000/QALY in place, screening for melanoma in the IBD population was not cost-effective. Compared to background rates of skin exams by PCPs, dermatology based screening for melanoma in IBD patients was more effective, but substantially more expensive. Of the three strategies examined, screening for melanoma every other year was the preferred

strategy. Screening every other year was more cost effective, under the $100,000/QALY threshold, than screening once at age 50 or screening annually.

Our one-way sensitivity analyses suggest that the cost-effectiveness of melanoma screening depends on the percent of melanomas that progress from local to regional disease. This finding is consistent with previous models of melanoma screening in the general population.[34] Interestingly, this variable is difficult to define and currently unknown. Our chosen estimate was based on previous models and was not IBD specific. IBD specific estimates of this parameter may influence the overall cost-effectiveness of melanoma screening programs.

The relative risk of melanoma was also varied in sensitivity analyses. Of the papers included in the systematic review from which the base case relative risk of 1.33 was derived, the relative risk of melanoma ranged from 0.70 to 5.41.[26] However, the majority of relative risk estimates of melanoma in IBD were between 1.00 and 2.00.[26] Additionally, while not statistically different between groups, Crohn's disease patients had an increased incidence of melanoma compared to ulcerative colitis, with a relative risk of 1.51 and 1.23, respectively.[26] This suggests initially targeting screening to Crohn's disease patients could be one way to stratify patients who are higher risk.

There are also studies suggesting medication exposures can increase risk of melanoma in immunosuppressed populations including IBD.[28,29,99] Long, et al reported an increase in melanoma in IBD over time, which paralleled the increase in biologic use in years 1997 – 2009.[28] Additionally, subgroup analyses suggested patients with long-term duration of anti-TNF biologics demonstrated increased odds of melanoma compared to those with short-term use.[28] While these findings require validation, duration of immunosuppression and exposure to

biologics could be used to target dermatologic screening to IBD patients at highest risk of melanoma making screening more cost-effective.

In this study, our WTP threshold was set at $100,000/ QALY gained. However, the selection of WTP thresholds remain somewhat arbitrary for programs evaluated in the United States. Therefore, our results should be taken in context given WTP thresholds are often predetermined cutoffs and do not accurately translate to programmatic decisions or justify implementation. It is often recommended to evaluate programs upon a continuum of WTP thresholds from $50,000 to $200,000/ QALY.[124] The preferred strategy of screening every other year has an ICER of $143,959/ QALY, which fits comfortably in the suggested range of evaluation. However, screening every year for melanoma is at the high end of the range of WTP thresholds, slightly above $200,000/ QALY. While our current preventive care guidelines in IBD recommend annual screening, screening every other year may present an opportunity to modify of our approach of preventive skin cancer screenings by dermatologists. Other potential modifications may include, but are not limited to, partnering with dermatology in new holistic care models including IBD medical homes, incorporating teledermatology to increase patient access to dermatologic care, as well as increasing the focus on primary prevention and education about skin cancer to improve early self detection in IBD patients.[143,144]

Our analysis is limited as data are derived from multiple sources, each associated with their own inherent biases. Additionally, there are unknown parameters and remaining uncertainty in parameters relating specifically to the risk and behavior of melanoma in IBD patients. We also did not include NMSC in our model. IBD patients are at an increased risk of NMSC and it is more prevalent than melanoma, however, it is rarely fatal.[27,28] NMSC is similarly discovered through total body skin exams, and the detection of NMSC would add costs as well as benefits.

A recent paper by Okafor, et al, suggests screening for NMSC in patients with Crohn's disease is cost effective. They found screening all Crohn's disease patients annually was the most cost-effective strategy, with every other year screening as the second best strategy.[129] The addition of NMSC screening may improve the ICER of this study, however we sought to specifically model melanoma, and the additional costs and benefits of NMSC detection is outside the scope of this analysis.

While current preventive care guidelines exist to promote annual skin exams in IBD, it is uncertain how frequently IBD patients currently obtain skin cancer screening. Our estimates of background screening were derived from the general population, which is likely an underestimation as IBD patients generally have increased healthcare contact. However, this data on physician and patient adherence to skin cancer screening guidelines in the IBD population is unknown. Proper estimates of background screening in IBD will further clarify the potential benefits of a melanoma screening program and strengthen our analysis.

In summary, compared to background primary care exams, screening annually for melanoma in IBD patients was more effective, but more expensive. Screening for melanoma every other year by a dermatologist was the preferred strategy. Future research evaluating the risk and behavior of melanoma in IBD, including determining therapies most associated with increased risk of melanoma, is needed to clearly define the costs and benefits of melanoma screening. While research is ongoing, primary prevention of skin cancers through counseling on sun protection remains of utmost importance among IBD patients. Presently, targeting IBD patients at the highest risk of developing melanoma, such as those with certain medication exposures or a family history of skin cancer, for dermatologic exams will assist in designing the most cost-effective approach to melanoma screening in IBD.

6.0 CONCLUSIONS

In the first chapter of the dissertation, we described the methodology of generating large observational datasets from the electronic medical record, and how these can be used to discover and refine patient phenotypes in IBD. We outlined challenges to abstracting real-world data, and how these have been overcome with a systematic and efficient approach in the IBD research registry. The IBD research registry served as a critical data source for the first two research questions addressed in this dissertation and many other projects outside the scope of this work.

In the second chapter we generated a propensity matched cohort of IBD patients through which we could define the long-term impact of *Clostridium difficile* infection. Propensity matching allowed us to account for the measurable differences between IBD patients who are likely to get infection and those who are not. We matched based on variables that are associated with an increased risk of infection, including antibiotic and healthcare exposure. This methodology overcomes many of the difficulties of using a random sample as a comparison group. The resulting matched groups were similar in all measurable outcomes in the year prior to infection. We found that *Clostridium difficile* infection was significantly associated with more steroid and antibiotic exposure, elevated inflammatory markers, increased disease activity, worse quality of life, and increased healthcare utilization in the year of infection. During the year after infection, patients in the *Clostridium difficile* group continued to have increased exposure to *Clostridium difficile* targeted antibiotics and other systemic antibiotics, while having more clinic

visits, telephone encounters, and a five-fold increase in healthcare charges. These findings suggest that infection is associated with a measurable impact on healthcare utilization beyond one year. This includes both financial measures of healthcare utilization (healthcare charges), and non-cost generating measures (telephone calls), both of which are important to the total time and cost investment of taking care of patients.

In the third dissertation chapter we evaluated the overall utilization of dermatology care among IBD patients in the research registry. We determined that 21% of IBD patients utilized dermatology from 2010-2016, and 2.6% of patients had a total body exam for skin cancer screening at least once over the same time frame. Each year, between 8% and 11% of patients recommended by gastroenterology preventive care guidelines visited dermatology for any indication. When we look at skin cancer screening specifically, only 0.8% to 2.5% of patients on average obtained a total body skin exam. These trends did not vary by different guideline recommendations, which stratify patients by medication exposures, nor did they vary over time. Overall, these findings suggest only a small proportion of IBD patients recommended for screening obtains dermatologic care for any indication. Additionally, the data imply that IBD patients are not screened according to medication exposures that introduce additional skin cancer risk.

In the fourth project included in this dissertation, we used a Markov model to estimate intervention costs and effectiveness of melanoma screening in the IBD population. This model was generated in response to known guidelines that recommend screening for melanoma among IBD patients regardless of medication exposure. The data from the prior dissertation project suggest that patients are not obtaining screening, but we wanted to model the scenario that screening by a dermatologist was available to all IBD patients annually. This screen strategy was

compared to the background rates of skin cancer screening in the general population, performed by a primary care practitioner. Utilizing the cost effectiveness model we found screening for melanoma in IBD patients was more effective but also expensive. Among model variations, screening every other year was the most cost-effective strategy at $143,959 per quality adjusted life year gained. This strategy fits within cost effectiveness thresholds for the United States and may be an alternative approach to skin cancer screening by dermatologists in the IBD population.

In conclusion, the included studies reveal the methodology of research data derived from the electronic medical record, the long-term impact of infection among IBD patients, the underutilization of dermatologic preventive care, and provide a cost effectiveness model to inform the development of skin cancer screening programs in IBD.

7.0 FUTURE DIRECTIONS

Despite the work presented here many questions remain and deserve further investigation. Importantly, what can we do to reduce the impact of *Clostridium difficile* infection among IBD patients? There are new therapies available and in development that may be more effective at reducing recurrent infection.[145] It is natural to wonder how this would modify the long-term impact of infection in IBD patients. There have also been cost effectiveness studies evaluating different treatment approaches in *Clostridium difficile* infection.[146] However, these studies do not incorporate the cost figures we generated using a propensity matched cohort, nor are they specific to IBD. The financial impact that extends into the year after infection may be an important addition to such models. One could use the data presented here to evaluate the cost effectiveness of newer, more expensive therapeutics in the setting of IBD and *Clostridium difficile* infection, as compared to standard treatment regimens.

In our second research project, we discovered only a small proportion of patients are seeking dermatologic care, which leads into the next question of…why? Through the multivariable analyses we determined there are a few factors associated with dermatologic use including family history of skin cancer and overall opportunities or face time for referral (clinic visits and emergency room utilization). However, using our methodology, the only aspects of care that we are able to objectively quantify are embedded in the electronic medical record. There are likely many reasons why patients do not seek or obtain skin cancer screening that are

difficult to measure without further investigation including patient and provider attitudes, knowledge, and barriers and facilitators of seeking care. These unanswered questions lend themselves to a qualitative study of both patients and providers that aims to understand each group's thoughts, experiences and attitudes on the involvement of dermatology in all-encompassing IBD care.

After we understand the barriers and facilitators to dermatologic care in IBD we can best approach implementation of preventive screening. This pairs with the findings from our cost effectiveness study, which suggest a different screening interval from what is currently recommended may be the most cost effective approach to melanoma prevention in IBD patients. This study also raises a number of other ideas which may increase the efficiency of screening, including screening high-risk patients to reduce costs associated with a screening program. Additional studies to clarify how current and historical medication exposures and how the duration of exposures impact skin cancer risk in IBD patients are of the utmost importance. Developing a skin cancer risk stratification system among IBD patients is an important future endeavor which may increase the efficiency of skin cancer screening in IBD.

Finally, as skin screening programs are implemented, it is critical to evaluate the implementation for continual quality improvement, acceptance, and to assess their performance. We lack an understanding of how skin cancer screening in IBD patients impacts clinical outcomes and quality of life. While this would be a large undertaking, the evidence would be extremely valuable to support current practices and guidelines.

APPENDIX A

DERMATOLOGY VISIT CATAGORIES AND ANNUAL TRENDS OF VISIT INDICIATIONS

This appendix contains two large tables referenced in Chapter 5. Low rates of dermatologic care and skin cancer screening among inflammatory bowel disease patients.

Table 19. Categories of dermatology care and associated ICD9 and ICD10 codes

Categories: Primary Diagnosis Codes		
Acneiform eruptions	**ICD 9**	**ICD 10**
Acne	706.1	L70.9
Acne rosacea	695.3	L71.9
Acne, unspecified acne type	706.1	L70.9
Acne scarring	709.2	L73.0
Acne vulgaris	706.1	L70.0
Acneiform eruption	692.9	L30.9
Cystic acne	706.1	L70.0
Demodex acne	706.1	L70.8
Nodulocystic acne	706.1	L70.8
Other acne	706.1	L70.8
Inflammatory papule	709.8	R23.8
Dilated pore of Winer of back	706.1	L70.8
Infestation by demodex folliculorum	133.8	B88.0
Rosacea	695.3	L71.9
Actinic keratoses and solar skin aging	**ICD 9**	**ICD 10**

Actinic keratoses	702	L57.0
Actinic keratosis	702	L57.0
Actinic keratosis of left cheek	702	L57.0
Actinic keratosis of scalp	702	L57.0
AK (actinic keratosis)	702	L57.0
Intrinsic aging of facial skin	701.8	R23.8
Solar lentigo	709.09	L81.4
Solar aging of skin	692.74	
Sun-damaged skin	692.79	L57.8
Solar keratosis	702	L57.0, X32.XXXA
Contact Dermatitis or Dermatitis	**ICD 9**	**ICD 10**
Allergic contact dermatitis	692.9	L23.9
Allergic contact dermatitis due to metals	692.83	L23.0
Allergic contact dermatitis due to other agents	692.89	L23.89
Allergic contact dermatitis, unspecified trigger	692.9	L23.9
Atopic dermatitis, unspecified type	691.8	L20.9
Chondrodermatitis nodularis chronica helicis	380	H61.009
Chondrodermatitis nodularis helicis	380	H61.009
Contact dermatitis	692.9	L25.9
Contact dermatitis and other eczema due to other chemical products	692.4	L25.3
Contact dermatitis and other eczema, due to unspecified cause	692.9	L25.9
Contact dermatitis due to chemicals	692.4	L25.3
Contact dermatitis due to cosmetics, unspecified contact dermatitis type	692.81	L25.0
Dermatitis	692.9	L30.9
Dermatitis, unspecified	692.9	L30.9
Dermatitis due to cosmetics	692.81	L25.0
Dermatitis due to metals	692.83	L23.0
Chronic dermatitis of hands	692.9	L30.9
Hand dermatitis	692.9	L30.9
Irritant contact dermatitis	692.9	L24.9
Irritant contact dermatitis due to chemical	692.4	L24.5
Irritant contact dermatitis due to other agents	692.89	L24.89
Irritant dermatitis	692.9	L24.9
Dyshidrosis	705.81	L30.1
Dyshidrotic hand dermatitis	705.81	L30.1
Dyshidrotic eczema	705.81	L30.1
Nummular eczema	692.9	L30.0

Eczema	692.9	L30.9
Eczema, unspecified type	692.9	L30.9
Eczematous dermatitis	692.9	L30.9
Other eczema		L30.8
Jacquet's dermatitis	691	L22
Atopic dermatitis	691.8	L20.9
Flexural atopic dermatitis	691.8	L20.89
Papular atopic dermatitis	691.8	L20.89
Perianal dermatitis	692.9	L30.9
Stasis dermatitis	454.1	I83.10
Stasis dermatitis of both legs	454.1	I83.11, I83.12
Stoma dermatitis	692.9	L30.9
Seborrhea	706.3	L21.9
Seborrheic dermatitis	690.1	L21.9
Perioral dermatitis	695.3	L71.0
Periorificial dermatitis	695.3	L71.0
Peristomal dermatitis	692.9	L30.9
Other atopic dermatitis	691.8	L20.89
Other atopic dermatitis and related conditions	691.8	L20.89
Other dermatitis due to solar radiation	692.79	L57.8
Superficial perivascular dermatitis	692.89	L30.8
Palisaded neutrophilic and granulomatous dermatitis	692.9	L25.9
Hair Loss or growth	**ICD 9**	**ICD 10**
Alopecia	704	L65.9
Alopecia areata	704.01	L63.9
Alopecia, scarring	704.09	L66.9
Alopecia, unspecified	704	L65.9
Hair loss	704	L65.9
Lichen planopilaris	697	L66.1
Lichen plano-pilaris	697	L66.1
Male pattern alopecia	704.09	L64.9
Scarring alopecia	704.09	L66.9
Telogen effluvium	704.02	L65.0
Hirsutism	704.1	L68.0
Benign Neoplasm	**ICD 9**	**ICD 10**
Benign neoplasm groin skin	216.5	D23.5
Benign neoplasm of other specified sites of skin	216.8	D23.9
Benign neoplasm of skin	216.9	D23.9
Benign neoplasm of skin of cheek	216.3	D23.39

Benign neoplasm of skin of lower limb, including hip	216.7	D23.70
Benign neoplasm of skin of other and unspecified parts of face	216.3	D23.30
Benign neoplasm of skin of trunk, except scrotum	216.5	D23.5
Benign neoplasm of skin of upper limb, including shoulder	216.6	D23.60
Benign neoplasm of skin, site unspecified	216.9	D23.9
Benign neoplasm of skin of right lower extremity	216.7	D23.71
Benign neoplasm of skin of upper limb, including shoulder, unspecified laterality	216.6	D23.60
Angioma	228	D18.00
CNH (chondrodermatitis nodularis helicis)	380	H61.009
Cherry angioma	448.1	I78.1
Dermatofibroma	216.9	D23.9
Inflamed skin tag	701.9, 686.9	L91.8
Skin tag	701.9	L91.8
Sebaceous hyperplasia	706.8	L73.8
Fordyce spots	750.26	Q38.6
Lentigines	709.09	L81.4
Lentigo	709.09	L81.4
DSAP (disseminated superficial actinic porokeratosis)	692.75	L56.5
Lesion of nose	478.19	J34.89
Porokeratosis	757.39	Q82.8
Seborrheic keratoses	**ICD 9**	**ICD 10**
Seborrheic keratoses	702.19	L82.1
Seborrheic keratoses, inflamed	702.11	L82.0
Seborrheic keratosis	702.19	L82.1
Seborrheic keratosis, inflamed	702.11	L82.0
Inflamed seborrheic keratosis	702.11	L82.0
Other seborrheic keratosis	702.19	L82.1
Stucco keratosis	701.1	L85.1
Nevus	**ICD 9**	**ICD 10**
Atypical nevus	216.9	D22.9
Atypical nevus of back	216.5	D22.5
Atypical nevus of upper back excluding scapular region	216.5	D22.5
Dermal nevus of face	216.3	D23.30
Dermal nevus of scalp	216.4	D22.4
Dysplastic nevus	216.9	D23.9
Dysplastic nevus of trunk	216.5	D22.5
Dysplastic nevus of lower extremity, left	216.7	D23.72

Irritated nevus of cheek	216.3	D22.39
Irritated nevus	216.9	D22.9
Irritated nevus of neck	216.4	D22.4
Intradermal melanocytic nevus	216.9	D22.9
Melanocytic nevi of trunk	216.5	D22.5
Melanocytic nevus	216.9	D22.9
Multiple melanocytic nevi	216.9	D22.9
Multiple melanocytic nevus	216.9	D22.9
Multiple benign melanocytic nevi	216.9	D22.9
Multiple benign nevi	216.9	D22.9
Multiple nevi	216.9	D22.9
Nevus	216.9	D22.9
Nevus of multiple sites	216.9	D22.9
Longitudinal melanonychia	703.8	L60.8
Inflammatory bowel diseases, pyoderma, erythema nodosum, hidradenitis	**ICD 9**	**ICD 10**
Crohn disease(Notable Code)	555.9	K50.90
Crohn's disease of both small and large intestine without complication(Notable Code)	555.2	K50.80
Crohn's disease(Notable Code)	555.9	K50.90
Regional enteritis of small intestine with large intestine(Notable Code)	555.2	K50.80
Ulcerative colitis(Notable Code)	556.9	K51.90
Pyoderma gangrenosa	686.01	L88
Pyoderma gangrenosum	686.01	L88
Pyostomatitis vegetans	528.09	K12.1
Erythema nodosum	695.2	L52
Parastomal pyoderma gangrenosum	686.01	L88
Hydradenitis	705.83	L73.2
Hidradenitis	705.83	L73.2
Hidradenitis suppurativa	705.83	L73.2
Cyst, carbuncle or furuncle	**ICD 9**	**ICD 10**
Cyst	IMO0001	
Cyst of lip	528.5	K13.0
Cyst of skin	706.2	L72.9
EIC (epidermal inclusion cyst)	706.2	L72.0
Epidermal inclusion cyst	706.2	L72.0
Epidermal cyst	706.2	L72.0
Subcutaneous nodule	782.2	R22.9
Sebaceous cyst	706.2	L72.3

Carbuncle and furuncle of leg, except foot	680.6	L02.429
Furuncle	680.9	L02.92
Furunculosis	680.9	L02.92
Pilar cyst	704.41	L72.11
Infection (bacterial, fungal, viral) or infestation	**ICD 9**	**ICD 10**
Abscess	682.9	L02.91
Abscess of buttock, left	682.5	L02.31
Pustule	686.9	L08.9
Dermatophytosis of foot	110.4	B35.3
Dermatophytosis of groin and perianal area	110.3	B35.6
Dermatophytosis of nail	110.1	B35.1
Dermatophytosis of the body	110.5	B35.4
Disseminated superficial actinic porokeratosis	692.75	L56.5
Deep seated dermatophytosis	110.6	B35.8
Tinea	110.9	B35.9
Tinea manuum	110.2	B35.2
Tinea corporis	110.5	B35.4
Tinea versicolor	111	B36.0
Pitted keratolysis	695.89	L98.8
Pityriasis versicolor	111	B36.0
Onychodystrophy	703.8	L60.3
Onychomycosis	110.1	B35.1
Intertrigo	695.89	L30.4
Unspecified local infection of skin and subcutaneous tissue	686.9	L08.9
Cellulitis and abscess of unspecified site	682.9	L03.90, L02.91
Impetigo	684	L01.00
Staph skin infection	686.9, 041.10	L08.9, B95.8
Other postoperative infection	998.59	T81.4XXA
Thrush	112	B37.0
Erythrasma	39	L08.1
Scabies	133	B86
Molluscum contagiosum	78	B08.1
Herpes labialis	54.9	B00.1
Herpes simplex	54.9	B00.9
Herpes zoster	53.9	B02.9
Shingles	53.9	B02.9
Zoster	53.9	B02.9

Vascular, connective tissue, or granulomatous	ICD 9	ICD 10
Unspecified venous (peripheral) insufficiency	459.81	I87.2
Vasculitis of skin	709.1	L95.9
Vasculitis(Notable Code)	447.6	I77.6
Connective tissue disease(Notable Code)	710.9	M35.9
Connective tissue disease, undifferentiated(Notable Code)	710.9	M35.9
Cutaneous lupus erythematosus	695.4	L93.2
Allergic purpura(Notable Code)	287	D69.0
Atrophie blanche	701.3	L90.8
Henoch-Schonlein purpura(Notable Code)	287	D69.0
HSP (Henoch Schonlein purpura)(Notable Code)	287	D69.0
Purpura(Notable Code)	287.2	D69.2
Capillaritis	448.9	I78.8
Morphea en coup de sabre	701	L94.0
Localized morphea	701	L94.0
Raynaud's syndrome	443	I73.00
Hemangioma of skin and subcutaneous tissue	228.01	D18.01
Leukocytoclastic vasculitis(Notable Code)	446.29	M31.0
Facial telangiectasia	448.9	I78.1
Pyogenic granuloma	686.1	L98.0
Majocchi's granuloma	110.6	B35.8
Granulation tissue of skin	701.5	L92.9
Granuloma annulare	695.89	L92.0
Folliculitis	**ICD 9**	**ICD 10**
Folliculitis	704.8	L73.9
Pseudofolliculitis	704.8	L73.8
Pseudofolliculitis barbae	704.8	L73.1
Pseudofolliculitis of the beard	704.8	L73.1
Pityrosporum folliculitis	704.8	L73.8
Screening	**ICD 9**	**ICD 10**
Screening for malignant neoplasm of skin	V76.43	Z12.83
Screening for malignant neoplasm of the skin	V76.43	Z12.83
Screening for skin cancer	V76.43	Z12.83
Screening, malignant neoplasm, skin	V76.43	Z12.83
Screening exam for skin cancer	V76.43	Z12.83
Personal history of malignant melanoma of skin	V10.82	Z85.820
Personal history of other malignant neoplasm of skin	V10.83	Z85.828
Personal history of skin cancer	V10.83	Z85.828

History of squamous cell carcinoma in situ	V10.89	Z86.008
Hx of squamous cell carcinoma of skin	V10.83	Z85.828
History of basal cell carcinoma	V10.83	
History of basal cell cancer	V10.83	Z85.828
Hx of atypical nevus	V13.3	Z87.2
History of squamous cell carcinoma of skin	V10.83	Z85.828
Family history of melanoma	V16.8	Z80.8
Skin exam, screening for cancer	V76.43	Z12.83
Skin cancer screening	V76.43	Z12.83
Encounter for screening for malignant neoplasm of skin	V76.43	Z12.83
Basal cell carcinoma	**ICD 9**	**ICD 10**
Basal cell carcinoma	173.91	C44.91
Basal cell carcinoma of back	173.51	C44.519
Basal cell carcinoma of brow	173.31	C44.319
Basal cell carcinoma of chest wall	173.51	C44.519
Basal cell carcinoma of eyebrow	173.31	C44.319
Basal cell carcinoma of face	173.31	C44.310
Basal cell carcinoma of left cheek	173.31	C44.319
Basal cell carcinoma of nose	173.31	C44.311
Basal cell carcinoma of right forehead	173.31	C44.319
Basal cell carcinoma of right temple region	173.31	C44.319
Basal cell carcinoma of skin of other and unspecified parts of face	173.31	C44.319
Basal cell carcinoma of skin of trunk	173.51	C44.519
Basal cell carcinoma of skin, site unspecified	173.91	C44.91
BCC (basal cell carcinoma of skin)	173.91	C44.91
BCC (basal cell carcinoma), face	173.31	C44.310
BCC (basal cell carcinoma), trunk	173.51	C44.519
Recurrent basal cell carcinoma of ear	173.21	C44.211
Squamous cell carcinoma	**ICD 9**	**ICD 10**
Squamous cell carcinoma in situ	234.9	D09.9
Squamous cell carcinoma in situ of skin	232.9	D04.9
Squamous cell carcinoma in situ of skin of deltoid region	232.6	D04.60
Squamous cell carcinoma in situ of skin of right cheek	232.3	D04.39
Squamous cell carcinoma of back	173.52	C44.529
Squamous cell carcinoma of skin of arm	173.62	C44.621
Squamous cell carcinoma of skin of left upper limb, including shoulder	173.62	C44.629
Squamous cell carcinoma skin right ear and external	173.22	C44.222

auricular canal		
Squamous cell carcinoma, leg, right	173.72	C44.722
Squamous cell carcinoma, scalp/neck	173.42	C44.42
Squamous cell skin cancer	173.92	C44.92
Squamous cell carcinoma in situ of skin of chest	232.5	D04.5
Squamous cell carcinoma in situ of skin of face	232.3	D04.30
Squamous cell carcinoma in situ of skin of forehead	232.3	D04.39
Squamous cell carcinoma in situ of skin of left cheek	232.3	D04.39
Squamous cell carcinoma in situ of skin of left forearm	232.6	D04.62
Squamous cell carcinoma in situ of skin of neck	232.4	D04.4
Squamous cell carcinoma of dorsum of right hand	173.62	C44.622
Squamous cell carcinoma of left lower leg	173.72	C44.729
SCC (squamous cell carcinoma), eyelid, right	173.12	C44.122
SCC (squamous cell carcinoma)	173.92	C44.92
SCC (squamous cell carcinoma), arm	173.62	C44.621
SCC (squamous cell carcinoma), leg	173.72	C44.721
Melanoma	**ICD 9**	**ICD 10**
Melanoma in situ of back(Notable Code)	172.5	D03.59
Melanoma of groin(Notable Code)	172.5	C43.59
Melanoma of skin(Notable Code)	172.9	C43.9
Neoplasm of uncertain behavior or unspecified	**ICD 9**	**ICD 10**
Neoplasm of skin	239.2	D49.2
Neoplasm of uncertain behavior	238.9	D48.9
Neoplasm of uncertain behavior of back	238.8	D48.7
Neoplasm of uncertain behavior of skin	238.2	D48.5
Neoplasm of uncertain behavior of skin of chest	238.2	D48.5
Neoplasm of uncertain behavior of skin of forehead	238.2	D48.5
Neoplasm of unspecified nature of bone, soft tissue, and skin	239.2	D49.2
Carcinoma in situ of eyelid, including canthus	232.1	D04.10
Other and unspecified malignant neoplasm of scalp and skin of neck	173.4	
Other and unspecified malignant neoplasm of skin of other and unspecified parts of face	173.3	
Carcinoma in situ of skin of other and unspecified parts of face	232.3	D04.39
Unspecified malignant neoplasm of skin of lip	173	C44.00
Unspecified malignant neoplasm of skin of other and unspecified parts of face	173.3	C44.300
Other malignant neoplasm of skin of lower limb,	173.7	

including hip		
Other malignant neoplasm of skin of trunk, except scrotum	173.5	
Psoriasis	**ICD 9**	**ICD 10**
Arthritis with psoriasis(Notable Code)	696	L40.50
Guttate psoriasis	696.1	L40.4
Psoriasiform dermatitis	696.8	L30.8
Psoriasis	696.1	L40.9
Psoriasis and similar disorder	696.1	L40.8
Sebopsoriasis	692.9	L30.9
Other psoriasis	696.1	L40.8
Plantar pustulosis	696.1	L40.8
Ulcer, erosion, fissure, or wound	**ICD 9**	**ICD 10**
Decubitus ulcer, buttock, left, stage I	707.05, 707.21	L89.321
Decubitus ulcer, stage 1	707.00, 707.21	L89.91
Stage 1 decubitus ulcer	707.00, 707.21	L89.91
Ulcer of perianal area(Notable Code)	707.8	L98.499
Ulcer(Notable Code)	707.9	L98.499
Ulcer, skin, non-healing(Notable Code)	707.9	L98.499
Ulceration(Notable Code)	707.9	L98.499
Ulcer of left lower leg, with fat layer exposed(Notable Code)	707.1	L97.922
Ulcer, skin, chronic, limited to breakdown of skin(Notable Code)	707.9	L98.491
Ulcer, skin, non-healing, limited to breakdown of skin(Notable Code)	707.9	L98.491
Skin ulceration, with fat layer exposed(Notable Code)	707.9	L98.492
Chronic ulcer of left lower extremity with fat layer exposed(Notable Code)	707.1	L97.922
Chronic ulcer of leg, left, limited to breakdown of skin(Notable Code)	707.1	L97.921
Stomal ulcer	534.9	K28.9
Skin fissures	709.8	R23.4
Skin erosion(Notable Code)	709.9	L98.9
Parastomal ulcer of enterostomy	534.9	
Peristomal skin breakdown(Notable Code)	707.9	L98.499
Oral aphthae	528.2	K12.0
Perleche	686.8	K13.0

Angular cheilitis	528.5	K13.0
Warts	**ICD 9**	**ICD 10**
Condyloma	78.11	A63.0
Condyloma acuminata	78.11	A63.0
Condyloma acuminatum	78.11	A63.0
Common wart	78.19	B07.8
Plantar wart	78.12	B07.0
Plantar wart, right foot	78.12	B07.0
Plantar warts	78.12	B07.0
Flat wart	78.19	B07.8
Mosaic wart	78.19	B07.8
Subungual warts	78.1	B07.9
Verruca	78.1	B07.9
Verruca plana	78.19	B07.8
Verruca plantaris	78.12	B07.0
Verruca vulgaris	78.1	B07.9
Viral wart	78.1	B07.9
Viral warts	78.1	B07.9
Viral warts due to HPV	078.19, 079.4	B07.9
Viral warts, unspecified	78.1	B07.9
Viral warts, unspecified type	78.1	B07.9
Wart	78.1	B07.9
Wart viral	78.1	B07.9
Warts	78.1	B07.9
Other viral warts	78.19	B07.8
Other specified viral warts	78.19	B07.8
Follow up visit	**ICD 9**	**ICD 10**
Follow-up examination, following unspecified surgery	V67.00	Z09
Visit for suture removal	V58.32	Z48.02
Visit for wound check	V58.89	Z51.89
Suture check	V58.49	Z48.89
Postop check	V67.00	Z09
Postoperative examination	V67.00	Z09
Postoperative follow-up	V67.00	Z09
Encounter for long-term (current) use of other medications	V58.69	Z79.899
Pregnancy examination or test, negative result	V72.41	Z32.02
Research study patient	V70.7	Z00.6

Vitiligo & skin pigmentation	**ICD 9**	**ICD 10**
Vitiligo	709.01	L80
Dyspigmentation	709	L81.9
Post-inflammatory hyperpigmentation	709	L81.0
Hyperpigmentation of skin	709	L81.9
Dyschromia	709	L81.9
Dyschromia, unspecified	709	L81.9
Other dyschromia	709.09	L81.9
Melasma	709.09	L81.1
Rash, puritis or scratching	**ICD 9**	**ICD 10**
Unspecified pruritic disorder	698.9	L29.9
Excoriation	919.8	T14.8
Rash	782.1	R21
Rash and other nonspecific skin eruption	782.1	R21
Generalized pruritus	698.9	L29.9
Grover's disease	702.8	L11.1
Pruritus ani	698	L29.0
Prurigo nodularis	698.3	L28.1
Prurigo	698.2	L28.2
Urticaria	708.9	L50.9
Urticaria, unspecified	708.9	L50.9
Multiple excoriations	919.8	T14.8
Neurotic excoriations	698.4	L98.1
Dermal hypersensitivity reaction	692.9	L23.9
Dermatographism	708.3	L50.3
Other specified urticaria	708.8	L50.8
Insect bite	919.4, E906.4	W57.XXXA
Other, multiple, and unspecified sites, insect bite, nonvenomous, without mention of infection	919.4	
Papular urticaria	698.2	L28.2
Morbilliform rash	782.1	R21
Perianal irritation	698	L29.0
Drug related	**ICD 9**	**ICD 10**
Long term use of drug	V58.69	Z79.899
Drug rash	693	L27.0
Drug eruption	693	L27.0
Phototoxic drug eruption	692.72, E947.9	L56.0

Other	ICD 9	ICD 10
Dysesthesia	782	R20.8
Erythromelalgia(Notable Code)	443.82	I73.81
Neutrophilic dermatosis	695.89	L98.2
Erythema ab igne	949.1	L59.0
Hyperhidrosis	705.21	L74.519
Primary focal hyperhidrosis	705.21	L74.519
Generalized hyperhidrosis	780.8	R61
Unspecified disorder of skin and subcutaneous tissue	709.9	L98.9
Unspecified hypertrophic and atrophic condition of skin	701.9	L91.9, L90.9
Other specified congenital anomaly of skin	757.39	Q82.8
Other specified disease of hair and hair follicles	704.8	L73.8
Other specified disorder of skin	709.8	L98.8
Other specified erythematous condition(695.89)	695.89	
Other specified hypertrophic and atrophic condition of skin	701.8	L91.8, L90.8
Dupuytren's contracture of both hands	728.6	M72.0
Facial swelling	784.2	R22.0
Scrotal edema	608.86	N50.89
Dry skin, skin peeling, scar or callous	**ICD 9**	**ICD 10**
Wrinkles	701.8	L90.8
Facial rhytids	701.8	L90.8
Xerosis cutis	706.8	L85.3
Xerosis of skin	706.8	L85.3
Dry skin	701.1	L85.3
Hypertrophic scar of skin	701.4	L91.0
Keloid	701.4	L91.0
Scar	709.2	L90.5
Scar condition and fibrosis of skin	709.2	L90.5
Scars	709.2	L90.5
Keratolysis exfoliativa	757.39	Q82.9
Callus of foot	700	L84
Corns and callosities	700	L84
Lichen planus	697	L43.9
Lichenification and lichen simplex chronicus	698.3	L28.0

Abbreviations: ICD9 - International Classification of Diseases, Ninth Revision; ICD10 – International Classification of Disease, Tenth Revision

Table 20. Top five reasons for dermatologic care from IBD patients over the study period according to primary diagnosis code

2010 (n=89 visits)	**n (%)***
1. Contact Dermatitis or Dermatitis	24 (27.0)
2. Neoplasm of uncertain behavior or unspecified	20 (22.5)
3. Acneiform eruptions	8 (9.0)
4. Benign neoplasm	6 (6.7)
4. Hair loss or growth	6 (6.7)
4. Warts	6 (6.7)
2011 (n=261 visits)	
1. Contact dermatitis or dermatitis	76 (29.1)
2. Acneiform eruptions	43 (16.5)
3. Neoplasm of uncertain behavior or unspecified	24 (9.2)
4. Benign neoplasm	15 (5.8)
5. Actinic keratoses and solar skin aging	14 (5.4)
5. Other	14 (5.4)
2012 (n=256 visits)	
1. Contact dermatitis or dermatitis	42 (16.4)
2. Acneiform eruptions	25 (9.8)
3. Psoriasis	20 (7.8)
4. Neoplasm of uncertain behavior or unspecified	19 (7.4)
5. Benign neoplasm	17 (6.6)
2013 (n=368 visits)	
1. Contact dermatitis or dermatitis	62 (16.9)
2. Vitiligo	41 (11.1)
3. Acneiform eruptions	34 (9.2)
4. Psoriasis	34 (9.2)
5. Benign neoplasm	25 (6.8)
2014 (n=298 visits)	
1. Contact dermatitis or dermatitis	40 (12.5)
2. IBD, pyoderma gangrenosum, hidradenitis suppurativa	33 (10.3)
3. Acneiform eruptions	32 (10.0)
4. Warts	28 (8.7)
5. Benign neoplasm	18 (5.6)
2015 (n=298)	
1. Contact dermatitis or dermatitis	41 (13.8)
2. Acneiform eruptions	32 (10.7)
3. Actinic keratoses and solar skin aging	22 (7.4)
4. Neoplasm of uncertain behavior or unspecified	21 (7.1)
5. Warts	19 (6.4)
2016 (n=313 visits)	

1. Contact dermatitis or dermatitis	46 (14.7)
2. Screening	24 (7.7)
2. Neoplasm of uncertain behavior or unspecified	24 (7.4)
4. Nevus	23 (7.4)
5. Acneiform eruptions	22 (7.0)
5. Actinic keratoses and solar skin aging	22 (7.0)
Total 2010 – 2016 (n=1906 visits)	
1. Contact dermatitis or dermatitis	331 (17.4)
2. Acneiform eruptions	196 (10.3)
3. Neoplasm of uncertain behavior or unspecified	144 (7.6)
4. Benign neoplasm	107 (5.6)
5. Actinic keratoses and solar skin aging	103 (5.4)
5. Psoriasis	103 (5.4)

Abbreviations: IBD – inflammatory bowel disease

*Percentage of total dermatologic visits made by inflammatory bowel disease patients over each calendar year.

BIBLIOGRAPHY

1. Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med 2009;361(21):2066–78.
2. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;142(1):46–54.e42; quiz e30.
3. Burisch J, Munkholm P. Inflammatory bowel disease epidemiology. Curr Opin Gastroenterol 2013;29(4):357–62.
4. 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(6):1907–13.
5. Bernstein CN, Nugent Z, Targownik LE, Singh H, Lix LM. Predictors and risks for death in a population-based study of persons with IBD in Manitoba. Gut 2015;64(9):1403–11.
6. Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature 2012;491(7422):119–24.
7. Magro F, Peyrin-Biroulet L, Sokol H, et al. Extra-intestinal malignancies in inflammatory bowel disease: results of the 3rd ECCO Pathogenesis Scientific Workshop (III). J Crohns Colitis 2014;8(1):31–44.
8. Harbord M, Annese V, Vavricka SR, et al. The First European Evidence-based Consensus

on Extra-intestinal Manifestations in Inflammatory Bowel Disease. J Crohns Colitis 2016;10(3):239–54.

9. Kappelman MD, Farkas DK, Long MD, et al. Risk of cancer in patients with inflammatory bowel diseases: a nationwide population-based cohort study with 30 years of follow-up evaluation. Clin Gastroenterol Hepatol 2014;12(2):265–73.e1.

10. Ananthakrishnan AN, McGinley EL. Infection-related hospitalizations are associated with increased mortality in patients with inflammatory bowel diseases. J Crohns Colitis 2013;7(2):107–12.

11. Faust AH, Halpern LF, Danoff-Burg S, Cross RK. Psychosocial factors contributing to inflammatory bowel disease activity and health-related quality of life. Gastroenterol Hepatol (N Y) 2012;8(3):173–81.

12. Coates MD, Lahoti M, Binion DG, Szigethy EM, Regueiro MD, Bielefeldt K. Abdominal pain in ulcerative colitis. Inflamm Bowel Dis 2013;19(10):2207–14.

13. Targownik LE, Nugent Z, Singh H, Bugden S, Bernstein CN. The prevalence and predictors of opioid use in inflammatory bowel disease: a population-based analysis. Am J Gastroenterol 2014;109(10):1613–20.

14. Bielefeldt K, Davis B, Binion DG. Pain and inflammatory bowel disease. Inflamm Bowel Dis 2009;15(5):778–88.

15. Click B, Ramos Rivers C, Koutroubakis IE, et al. Demographic and Clinical Predictors of High Healthcare Use in Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis 2016;22(6):1442–9.

16. Jiang J, Click B, Anderson AM, et al. Group-Based Trajectory Modeling of Healthcare Financial Charges in Inflammatory Bowel Disease: A Comprehensive Phenotype. Clin

Transl Gastroenterol 2016;7(7):e181.

17. Limsrivilai J, Stidham RW, Govani SM, Waljee AK, Huang W, Higgins PD. Factors That Predict High Health Care Utilization and Costs for Patients With Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol 2017;15(3):385–392.e2.

18. Ananthakrishnan AN, McGinley EL, Saeian K, Binion DG. Temporal trends in disease outcomes related to Clostridium difficile infection in patients with inflammatory bowel disease. Inflamm Bowel Dis 2011;17(4):976–83.

19. Nguyen GC, Kaplan GG, Harris ML, Brant SR. A national survey of the prevalence and impact of Clostridium difficile infection among hospitalized inflammatory bowel disease patients. Am J Gastroenterol 2008;103(6):1443–50.

20. Ananthakrishnan AN, McGinley EL, Binion DG. Excess hospitalisation burden associated with Clostridium difficile in patients with inflammatory bowel disease. Gut 2008;57(2):205–10.

21. Furuya-Kanamori L, Stone JC, Clark J, et al. Comorbidities, Exposure to Medications, and the Risk of Community-Acquired Clostridium difficile Infection: a systematic review and meta-analysis. Infect Control Hosp Epidemiol 2015;36(2):132–41.

22. Razik R, Rumman A, Bahreini Z, McGeer A, Nguyen GC. Recurrence of Clostridium difficile Infection in Patients with Inflammatory Bowel Disease: The RECIDIVISM Study. Am J Gastroenterol 2016;111(8):1141–6.

23. Rao K, Higgins PD. Epidemiology, Diagnosis, and Management of Clostridium difficile Infection in Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis 2016;22(7):1744–54.

24. Huang BL, Chandra S, Shih DQ. Skin manifestations of inflammatory bowel disease.

Front Physiol 2012;3:13.

25. Marzano AV, Borghi A, Stadnicki A, Crosti C, Cugno M. Cutaneous manifestations in patients with inflammatory bowel diseases: pathophysiology, clinical features, and therapy. Inflamm Bowel Dis 2014;20(1):213–27.

26. Singh S, Nagpal SJ, Murad MH, et al. Inflammatory bowel disease is associated with an increased risk of melanoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2014;12(2):210–8.

27. Long MD, Herfarth HH, Pipkin CA, Porter CQ, Sandler RS, Kappelman MD. Increased risk for non-melanoma skin cancer in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2010;8(3):268–74.

28. Long MD, Martin CF, Pipkin CA, Herfarth HH, Sandler RS, Kappelman MD. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. Gastroenterology 2012;143(2):390–399.e1.

29. Mariette X, Matucci-Cerinic M, Pavelka K, et al. Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. Ann Rheum Dis 2011;70(11):1895–904.

30. McKenna MR, Stobaugh DJ, Deepak P. Melanoma and non-melanoma skin cancer in inflammatory bowel disease patients following tumor necrosis factor-α inhibitor monotherapy and in combination with thiopurines: analysis of the Food and Drug Administration Adverse Event Reporting System. J Gastrointestin Liver Dis 2014;23(3):267–71.

31. Abbas AM, Almukhtar RM, Loftus EV, Lichtenstein GR, Khan N. Risk of melanoma and non-melanoma skin cancer in ulcerative colitis patients treated with thiopurines: a

nationwide retrospective cohort. Am J Gastroenterol 2014;109(11):1781–93.

32. De Luca JF, Severino R, Lee YS, Johnson D. Dermatologist and gastroenterologist awareness of the potential of immunosuppressants used to treat inflammatory bowel disease to cause non-melanoma skin cancer. Int J Dermatol 2013;52(8):955–9.

33. Gordon LG, Rowell D. Health system costs of skin cancer and cost-effectiveness of skin cancer prevention and screening: a systematic review. Eur J Cancer Prev 2015;24(2):141–9.

34. Losina E, Walensky RP, Geller A, et al. Visual screening for malignant melanoma: a cost-effectiveness analysis. Arch Dermatol 2007;143(1):21–8.

35. Girgis A, Clarke P, Burton RC, Sanson-Fisher RW. Screening for melanoma by primary health care physicians: a cost-effectiveness analysis. J Med Screen 1996;3(1):47–53.

36. Pil L, Hoorens I, Vossaert K, et al. Cost-effectiveness and Budget Effect Analysis of a Population-Based Skin Cancer Screening. JAMA dermatology 2016;

37. Longobardi T, Jacobs P, Bernstein CN. Work losses related to inflammatory bowel disease in the United States: results from the National Health Interview Survey. Am J Gastroenterol 2003;98(5):1064–72.

38. Ha C, Ullman TA, Siegel CA, Kornbluth A. Patients enrolled in randomized controlled trials do not represent the inflammatory bowel disease patient population. Clin Gastroenterol Hepatol 2012;10(9):1002–7; quiz e78.

39. Gonzaga JE, Ananthakrishnan AN, Issa M, et al. Durability of infliximab in Crohn's disease: a single-center experience. Inflamm Bowel Dis 2009;15(12):1837–43.

40. Chaparro M, Panes J, García V, et al. Long-term durability of infliximab treatment in Crohn's disease and efficacy of dose "escalation" in patients losing response. J Clin

Gastroenterol 2011;45(2):113–8.

41. Chaparro M, Panés J, García V, et al. Long-term durability of response to adalimumab in Crohn's disease. Inflamm Bowel Dis 2012;18(4):685–90.

42. Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. Am J Gastroenterol 1996;91(8):1571–8.

43. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. The Lancet 1980;1(8167):514.

44. Kozarek RA, Patterson DJ, Gelfand MD, Botoman VA, Ball TJ, Wilske KR. Methotrexate induces clinical and histologic remission in patients with refractory inflammatory bowel disease. Ann Intern Med 1989;110(5):353–6.

45. R Core Team. R: A language and environment for statistical computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2013 [cited 2015 Oct 12]. Available from: http://www.R-project.org

46. Natural Language Toolkit. [cited 2016 May 22];Available from: http://www.nltk.org/

47. The Apache Software Foundation. openNLP. [cited 2016 May 22];Available from: https://opennlp.apache.org/

48. The Apache Software Foundation. Apache cTAKES™ - clinical Text Analysis Knowledge Extraction System. [cited 2016 Aug 1];Available from: http://ctakes.apache.org/

49. Tseytlin E, Mitchell K, Legowski E, Corrigan J, Chavan G, Jacobson RS. NOBLE - Flexible concept recognition for large-scale biomedical natural language processing.

BMC Bioinformatics 2016;17:32.

50. Duerr RH, Taylor KD, Brant SR, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science 2006;314(5804):1461–3.

51. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005;19 Suppl A:5A–36A.

52. Ramos-Rivers C, Regueiro M, Vargas EJ, et al. Association between telephone activity and features of patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2014;12(6):986–94.e1.

53. Click B, Vargas EJ, Anderson AM, et al. Silent Crohn's Disease: Asymptomatic Patients with Elevated C-reactive Protein Are at Risk for Subsequent Hospitalization. Inflamm Bowel Dis 2015;21(10):2254–61.

54. Koutroubakis IE, Ramos-Rivers C, Regueiro M, et al. Persistent or Recurrent Anemia Is Associated With Severe and Disabling Inflammatory Bowel Disease. Clin Gastroenterol Hepatol 2015;13(10):1760–6.

55. Click BH, Machicado JD, Rivers CR, et al. Su1334 Eosinophilia in Patients With Inflammatory Bowel Disease Is Independently Associated With Increased Healthcare Expenditures: A Prospective 5-Year Experience. Gastroenterology 2015;148(4):S–477–S–478.

56. Machicado JD, Kabbani T, Rivers CR, et al. Sa1187 Peripheral Blood Eosinophilia in Patients With Inflammatory Bowel Disease Is Associated With Worse Outcomes: A 5-Year Prospective Study. Gastroenterology 2015;148(4):S–251.

57. Johnson C, Hartman DJ, Rivers CR, et al. Sa1876 Do Epithelioid Granulomas Function As a Biomarker of Severity in Crohn's Disease? Analysis of a Prospective Six-Year Natural History Registry. Gastroenterology 2016;150(4):S387–S388.

58. Anderson AJ, Rivers CR, Click BH, et al. Su1810 Clostridium difficile Infection in Inflammatory Bowel Disease Predicts Future Healthcare Utilization. Gastroenterology 2016;150(4):S559.

59. Seminerio JL, Koutroubakis IE, Ramos-Rivers C, et al. Impact of Obesity on the Management and Clinical Course of Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis 2015;21(12):2857–63.

60. Koutroumpakis E, Ramos-Rivers C, Regueiro M, et al. Association Between Long-Term Lipid Profiles and Disease Severity in a Large Cohort of Patients with Inflammatory Bowel Disease. Dig Dis Sci 2016;61(3):865–71.

61. Atreja A, Achkar JP, Jain AK, Harris CM, Lashner BA. Using technology to promote gastrointestinal outcomes research: a case for electronic health records. Am J Gastroenterol 2008;103(9):2171–8.

62. Sox HC, Greenfield S. Comparative effectiveness research: a report from the Institute of Medicine. Ann Intern Med 2009;151(3):203–5.

63. Ali UA, Issa Y, van Goor H, et al. Dutch Chronic Pancreatitis Registry (CARE): design and rationale of a nationwide prospective evaluation and follow-up. Pancreatology 2015;15(1):46–52.

64. Howes N, Lerch MM, Greenhalf W, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clin Gastroenterol Hepatol 2004;2(3):252–61.

65. Hye RJ, Inui TS, Anthony FF, et al. A multiregional registry experience using an

electronic medical record to optimize data capture for longitudinal outcomes in endovascular abdominal aortic aneurysm repair. J Vasc Surg 2015;61(5):1160–6.

66. Schmitt-Egenolf M. PsoReg--the Swedish registry for systemic psoriasis treatment. The registry's design and objectives. Dermatology (Basel) 2007;214(2):112–7.

67. Papp KA, Strober B, Augustin M, et al. PSOLAR: design, utility, and preliminary results of a prospective, international, disease-based registry of patients with psoriasis who are receiving, or are candidates for, conventional systemic treatments or biologic agents. J Drugs Dermatol 2012;11(10):1210–7.

68. Liao KP, Ananthakrishnan AN, Kumar V, et al. Methods to Develop an Electronic Medical Record Phenotype Algorithm to Compare the Risk of Coronary Artery Disease across 3 Chronic Disease Cohorts. PLoS ONE 2015;10(8):e0136651.

69. Ananthakrishnan AN, Cagan A, Cai T, et al. Identification of Nonresponse to Treatment Using Narrative Data in an Electronic Health Record Inflammatory Bowel Disease Cohort. Inflamm Bowel Dis 2016;22(1):151–8.

70. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983;24(4):385–96.

71. Sletten DM, Suarez GA, Low PA, Mandrekar J, Singer W. COMPASS 31: a refined and abbreviated Composite Autonomic Symptom Score. Mayo Clin Proc 2012;87(12):1196–201.

72. Hamilton CM, Strader LC, Pratt JG, et al. The PhenX Toolkit: get the most from your measures. Am J Epidemiol 2011;174(3):253–60.

73. Kabbani TA, Koutroubakis IE, Schoen RE, et al. Association of Vitamin D Level With Clinical Status in Inflammatory Bowel Disease: A 5-Year Longitudinal Study. Am J

Gastroenterol 2016;111(5):712–9.

74. Hashash JG, Chintamaneni P, Ramos Rivers CM, et al. Patterns of Antibiotic Exposure and Clinical Disease Activity in Inflammatory Bowel Disease: A 4-year Prospective Study. Inflamm Bowel Dis 2015;21(11):2576–82.

75. Loftus CG, Loftus EV, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000. Inflamm Bowel Dis 2007;13(3):254–61.

76. Sands BE, LeLeiko N, Shah SA, Bright R, Grabert S. OSCCAR: Ocean State Crohn's and Colitis Area Registry. Med Health R I 2009;92(3):82–5, 88.

77. Moran GW, Dubeau MF, Kaplan GG, et al. Phenotypic features of Crohn's disease associated with failure of medical treatment. Clin Gastroenterol Hepatol 2014;12(3):434–42.e1.

78. Bernstein CN, Blanchard JF, Rawsthorne P, Wajda A. Epidemiology of Crohn's disease and ulcerative colitis in a central Canadian province: a population-based study. Am J Epidemiol 1999;149(10):916–24.

79. Leslie WD, Miller N, Rogala L, Bernstein CN. Vitamin D status and bone density in recently diagnosed inflammatory bowel disease: the Manitoba IBD Cohort Study. Am J Gastroenterol 2008;103(6):1451–9.

80. Ananthakrishnan AN. Clostridium difficile infection: epidemiology, risk factors and management. Nat Rev Gastroenterol Hepatol 2011;8(1):17–26.

81. Stoica O, Trifan A, Cojocariu C, Gîrleanu I, Maxim R, Stanciu MC. Incidence and risk factors of Clostridium difficile infection in patients with inflammatory bowel disease. Rev Med Chir Soc Med Nat Iasi 2015;119(1):81–6.

82. Ramos-Martínez A, Ortiz-Balbuena J, Curto-García I, et al. Risk factors for Clostridium difficile diarrhea in patients with inflammatory bowel disease. Rev Esp Enferm Dig 2015;107(1):4–8.

83. Ananthakrishnan AN, Cagan A, Gainer VS, et al. Higher plasma vitamin D is associated with reduced risk of Clostridium difficile infection in patients with inflammatory bowel diseases. Aliment Pharmacol Ther 2014;39(10):1136–42.

84. Hourigan SK, Oliva-Hemker M, Hutfless S. The prevalence of Clostridium difficile infection in pediatric and adult patients with inflammatory bowel disease. Dig Dis Sci 2014;59(9):2222–7.

85. Issa M, Vijayapal A, Graham MB, et al. Impact of Clostridium difficile on inflammatory bowel disease. Clin Gastroenterol Hepatol 2007;5(3):345–51.

86. Chen Y, Furuya-Kanamori L, Doi SA, Ananthakrishnan AN, Kirk M. Clostridium difficile Infection and Risk of Colectomy in Patients with Inflammatory Bowel Disease: A Bias-adjusted Meta-analysis. Inflamm Bowel Dis 2017;23(2):200–7.

87. Trifan A, Stanciu C, Stoica O, Girleanu I, Cojocariu C. Impact of Clostridium difficile infection on inflammatory bowel disease outcome: a review. World J Gastroenterol 2014;20(33):11736–42.

88. Anderson AJ, Click B, Ramos-Rivers C, et al. Development of an Inflammatory Bowel Disease Research Registry Derived from Observational Electronic Health Record Data for Comprehensive Clinical Phenotyping. Dig Dis Sci 2016;61(11):3236–45.

89. Lee J, Little TD. A practical guide to propensity score analysis for applied clinical research. Behav Res Ther 2017;

90. Rosenbaum PR, Rubin DB. The Central Role of the Propensity Score in Observational

Studies for Causal Effects. Biometrika 1983;70(1):41.

91. Rao K, Erb-Downward JR, Walk ST, et al. The systemic inflammatory response to Clostridium difficile infection. PLoS ONE 2014;9(3):e92578.

92. Czepiel J, Biesiada G, Brzozowski T, et al. The role of local and systemic cytokines in patients infected with Clostridium difficile. J Physiol Pharmacol 2014;65(5):695–703.

93. Trikudanathan G, Venkatesh PG, Navaneethan U. Diagnosis and therapeutic management of extra-intestinal manifestations of inflammatory bowel disease. Drugs 2012;72(18):2333–49.

94. Hagen JW, Swoger JM, Grandinetti LM. Cutaneous manifestations of crohn disease. Dermatol Clin 2015;33(3):417–31.

95. Weizman A, Huang B, Berel D, et al. Clinical, serologic, and genetic factors associated with pyoderma gangrenosum and erythema nodosum in inflammatory bowel disease patients. Inflamm Bowel Dis 2014;20(3):525–33.

96. Cleynen I, Van Moerkercke W, Billiet T, et al. Characteristics of Skin Lesions Associated With Anti-Tumor Necrosis Factor Therapy in Patients With Inflammatory Bowel Disease: A Cohort Study. Ann Intern Med 2016;164(1):10–22.

97. Pedersen N, Duricova D, Elkjaer M, Gamborg M, Munkholm P, Jess T. Risk of extra-intestinal cancer in inflammatory bowel disease: meta-analysis of population-based cohort studies. Am J Gastroenterol 2010;105(7):1480–7.

98. Farraye FA, Melmed GY, Lichtenstein GR, Kane SV. ACG clinical guideline: preventive care in inflammatory bowel disease. Am J Gastroenterol 2017;112(2):241–58.

99. Jensen P, Hansen S, Møller B, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. J Am Acad Dermatol

1999;40(2 Pt 1):177–86.

100. Scott FI, Mamtani R, Brensinger CM, et al. Risk of nonmelanoma skin cancer associated with the use of immunosuppressant and biologic agents in patients with a history of autoimmune disease and nonmelanoma skin cancer. JAMA dermatology 2016;152(2):164–72.

101. Clowry J, Sheridan J, Healy R, et al. Increased non-melanoma skin cancer risk in young patients with inflammatory bowel disease on immunomodulatory therapy: a retrospective single-centre cohort study. J Eur Acad Dermatol Venereol 2017;

102. Saraiya M, Hall HI, Thompson T, et al. Skin cancer screening among U.S. adults from 1992, 1998, and 2000 National Health Interview Surveys. Prev Med 2004;39(2):308–14.

103. Coups EJ, Geller AC, Weinstock MA, Heckman CJ, Manne SL. Prevalence and correlates of skin cancer screening among middle-aged and older white adults in the United States. Am J Med 2010;123(5):439–45.

104. Crohn's and Colitis Foundation Professional Education Committee Sub Group. CCFA Health Maintenance Checklist for Adult IBD Patients. 2017;

105. Pandey N, Herrera HH, Johnson CM, MacCarthy AA, Copeland LA. Preventative care for patients with inflammatory bowel disease in the Veterans Health Administration. Medicine 2016;95(27):e4012.

106. Long MD, Porter CQ, Sandler RS, Kappelman MD. Suboptimal rates of cervical testing among women with inflammatory bowel disease. Clin Gastroenterol Hepatol 2009;7(5):549–53.

107. Lindelöf B, Sigurgeirsson B, Gäbel H, Stern RS. Incidence of skin cancer in 5356 patients following organ transplantation. Br J Dermatol 2000;143(3):513–9.

108. Robbins HA, Clarke CA, Arron ST, et al. Melanoma Risk and Survival among Organ Transplant Recipients. J Invest Dermatol 2015;135(11):2657–65.

109. Cowen EW, Billingsley EM. Awareness of skin cancer by kidney transplant patients. J Am Acad Dermatol 1999;40(5 Pt 1):697–701.

110. Ali FR, Samarasinghe V, Russell SA, Lear JT. Increasing capacity for skin surveillance in a transplant review clinic. Transplantation 2014;97(8):e48–e50.

111. Lloyd A, Klintmalm G, Qin H, Menter A. Skin cancer evaluation in transplant patients: a physician opinion survey with recommendations. Clin Transplant 2015;29(2):110–7.

112. Williams NC, Tong A, Howard K, Chapman JR, Craig JC, Wong G. Knowledge, beliefs and attitudes of kidney transplant recipients regarding their risk of cancer. Nephrology (Carlton) 2012;17(3):300–6.

113. Wisgerhof HC, van der Geest LG, de Fijter JW, et al. Incidence of cancer in kidney-transplant recipients: a long-term cohort study in a single center. Cancer Epidemiol 2011;35(2):105–11.

114. Jess T, Horváth-Puhó E, Fallingborg J, Rasmussen HH, Jacobsen BA. Cancer risk in inflammatory bowel disease according to patient phenotype and treatment: a Danish population-based cohort study. Am J Gastroenterol 2013;108(12):1869–76.

115. Cheng MY, Moreau JF, McGuire ST, Ho J, Ferris LK. Melanoma depth in patients with an established dermatologist. J Am Acad Dermatol 2014;70(5):841–6.

116. Kirsner RS, Muhkerjee S, Federman DG. Skin cancer screening in primary care: prevalence and barriers. J Am Acad Dermatol 1999;41(4):564–6.

117. Oliveria SA, Christos PJ, Marghoob AA, Halpern AC. Skin cancer screening and prevention in the primary care setting: national ambulatory medical care survey 1997. J

Gen Intern Med 2001;16(5):297–301.

118. U.S. Preventive Services Task Force. Screening for skin cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2009;150(3):188–93.

119. US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, et al. Screening for skin cancer: US preventive services task force recommendation statement. JAMA 2016;316(4):429–35.

120. Waldmann A, Nolte S, Weinstock MA, et al. Skin cancer screening participation and impact on melanoma incidence in Germany--an observational study on incidence trends in regions with and without population-based screening. Br J Cancer 2012;106(5):970–4.

121. Katalinic A, Waldmann A, Weinstock MA, et al. Does skin cancer screening save lives?: an observational study comparing trends in melanoma mortality in regions with and without screening. Cancer 2012;118(21):5395–402.

122. Makin JK, Warne CD, Dobbinson SJ, Wakefield MA, Hill DJ. Population and age-group trends in weekend sun protection and sunburn over two decades of the SunSmart programme in Melbourne, Australia. Br J Dermatol 2013;168(1):154–61.

123. U.S. Bureau of Labor Statistics. CPI Inflation Calculator [Internet]. Consumer Price Index Inflation Calculator. [cited 2016 Oct 19];Available from: http://www.bls.gov/data/inflation_calculator.htm

124. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold. N Engl J Med 2014;371(9):796–7.

125. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009;27(36):6199–206.

126. DiFronzo LA, Wanek LA, Elashoff R, Morton DL. Increased incidence of second primary

melanoma in patients with a previous cutaneous melanoma. Ann Surg Oncol 1999;6(7):705–11.

127. National Cancer Institute. Melanoma of the Skin - SEER Stat Fact Sheets [Internet]. Surveillance, Epidemiology, and End Results (SEER) Program. 2014 [cited 2016 Mar 6];Available from: http://seer.cancer.gov/statfacts/html/melan.html

128. Arias E. United States life tables, 2008. Natl Vital Stat Rep 2012;61(3):1–63.

129. Okafor PN, Stallwood CG, Nguyen L, et al. Cost-effectiveness of nonmelanoma skin cancer screening in Crohn's disease patients. Inflamm Bowel Dis 2013;19(13):2787–95.

130. LeBlanc WG, Vidal L, Kirsner RS, et al. Reported skin cancer screening of US adult workers. J Am Acad Dermatol 2008;59(1):55–63.

131. Tabibian A, Tabibian JH, Beckman LJ, Raffals LL, Papadakis KA, Kane SV. Predictors of health-related quality of life and adherence in Crohn's disease and ulcerative colitis: implications for clinical management. Dig Dis Sci 2015;60(5):1366–74.

132. Zelante A, De Giorgi A, Borgoni R, Trevisani L, Gallerani M. Adherence to medical treatment in inflammatory bowel disease patients. Minerva Gastroenterol Dietol 2014;60(4):269–74.

133. Livingstone E, Krajewski C, Eigentler TK, et al. Prospective evaluation of follow-up in melanoma patients in Germany - results of a multicentre and longitudinal study. Eur J Cancer 2015;51(5):653–67.

134. Chen SC, Pennie ML, Kolm P, et al. Diagnosing and managing cutaneous pigmented lesions: primary care physicians versus dermatologists. J Gen Intern Med 2006;21(7):678–82.

135. Pennie ML, Soon SL, Risser JB, Veledar E, Culler SD, Chen SC. Melanoma outcomes for

Medicare patients: association of stage and survival with detection by a dermatologist vs a nondermatologist. Arch Dermatol 2007;143(4):488–94.

136. Overview of the Medicare Physician Fee Schedule. [cited 2017 May 7];Available from: https://www.cms.gov/apps/physician-fee-schedule/overview.aspx

137. Yabroff KR, Lamont EB, Mariotto A, et al. Cost of care for elderly cancer patients in the United States. J Natl Cancer Inst 2008;100(9):630–41.

138. 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(12):1138–45.

139. King SM, Bonaccorsi P, Bendeck S, et al. Melanoma quality of life: pilot study using utility measurements. Arch Dermatol 2011;147(3):353–4.

140. Shahwan KT, Kimball AB. Should we leave the skin biopsies to the dermatologists? JAMA dermatology 2016;152(4):371–2.

141. Gold MR, Franks P, McCoy KI, Fryback DG. Toward consistency in cost-utility analyses: using national measures to create condition-specific values. Med Care 1998;36(6):778–92.

142. Briggs AH, Weinstein MC, Fenwick EA, et al. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--6. Value Health 2012;15(6):835–42.

143. Regueiro MD, McAnallen SE, Greer JB, Perkins SE, Ramalingam S, Szigethy E. The Inflammatory Bowel Disease Specialty Medical Home: A New Model of Patient-centered Care. Inflamm Bowel Dis 2016;22(8):1971–80.

144. Uscher-Pines L, Malsberger R, Burgette L, Mulcahy A, Mehrotra A. Effect of teledermatology on access to dermatology care among medicaid enrollees. JAMA

dermatology 2016;152(8):905–12.

145. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med 2011;364(5):422–31.

146. Stranges PM, Hutton DW, Collins CD. Cost-effectiveness analysis evaluating fidaxomicin versus oral vancomycin for the treatment of Clostridium difficile infection in the United States. Value Health 2013;16(2):297–304.