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Artificial Intelligence and eHealth for Inflammatory Bowel Diseases

The quest to enhance patient experiences, outcomes and costs

Aria Zand

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This thesis is dedicated to my mother

دو کس سیری ندارند طالب دنیا و طالب علم

"Two there are who are never satisfied - the lover of the world and the lover of knowledge."

Rumi

1207 – 1273

TABLE OF CONTENTS

CHAPTER 1

General Introduction and outline of the thesis

Inflammatory Bowel Diseases (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC) are chronic immunological digestive diseases with a progressive character and accompanied with considerable healthcare costs[1,2]. IBD is generally characterized by frequent abdominal pain and diarrhea with the disease state alternating between remission and exacerbation[3]. IBD affects nearly 3 million Americans, who frequently require medical therapy, surgeries, and hospitalizations[4]. The impact of IBD is not limited to the hospital, but extends to other aspects of life. While medical therapies, including biologicals, are effective at improving patients' health outcomes and quality of life, many patients experience limitations in their daily lives. Studies have shown that a third of IBD patients felt their intimate relationships were negatively affected, a quarter of IBD patients felt it is problematic to maintain friends and two-third was worried about the availability of toilets when planning to attend an event[5]. In the workplace, IBD patients reported fatigue, irritability, and demotivation. Additionally, there is additional strain and burden when the impact of IBD extends onto their loved ones that act as their respective caregivers, an issue that is insufficiently studied and reported on in the literature.

Furthermore, the impact of IBD is associated with significant healthcare costs, which can be categorized in two distinct components, direct costs and indirect costs. Direct costs represent the costs related with medical resource utilization, such as inpatient, outpatient, and pharmaceutical services. Indirect costs can be defined as the expenditures incurred from the termination or reduction of work productivity as a result of the morbidity and mortality associated with a given (chronic) disease[6,7]. The estimated annual disease-attributable cost of IBD in the U.S. is estimated to be $6.3 billion[2], which it estimated to be a 3-fold higher direct cost of care compared with non-IBD controls[8], however most studies do not take indirect health costs in account and thus the impact of indirect costs in IBD warrants further research.

The disease course of IBD is progressive; each relapse increases the risk of permanent gastrointestinal damage and complications, which cause morbidity, disability and high costs[8]. In order to prevent disease progression and their associated negative outcomes, prevention and early identification of relapses is crucial[9–11]. However, the disease course of IBD alternates between active disease and remission and thus makes reliable risk factors for adverse outcomes challenging to detect[11]. Discovering novel methods that can identify reliable risk factors for adverse outcomes such as relapses outside of the traditional hospital setting would help to better inform treatment of these volatile disease states and prevent negative outcomes and reduce the substantial costs associated with IBD[12].

Innovation through the Triple Aim

U.S. payment models are undergoing a shift from fee for service models to capitated and performance based models. This will drastically change how we practice medicine and will require a robust conceptual framework to measure and improve quality.

These frameworks are warranted because while it is evident that innovative therapeutics have a positive effect on health outcomes, there is still a significant psychosocial and economic impact of IBD that is unaddressed. Early recognition of risks factors to avoid adverse outcomes of the disease and robust improvement of the patient experience outside the hospital setting are paramount. The patient experience includes the range of interactions that patients have with the health care system and includes several components of health care delivery that patients value highly such as easy access to information and clear communication with their care team[13].

To facilitate quality improvements in care delivery through innovative solutions there needs to be a clear and robust framework and implementation of change for all different stakeholders is imperative in order to achieve success. Different solutions have been proposed such as innovation in care monitoring or implementation of eHealth. The impact of these solutions for healthcare providers, patients, caregivers and healthcare costs in IBD needs investigation.

Conceptually, different frameworks have been proposed such as the Triple Aim which consists of three objectives; improvement of the patient experience, improvement of health outcomes, and reduction of costs[14]. The Triple Aim has been developed by the Institute for Health care Improvement (IHI) to assist health care organizations to optimize their performance by using these three metrics. The Triple Aim is particularly applicable to long-term management of chronic illnesses, since increasing healthcare expenditures have been partially attributed to suboptimal management of chronic illnesses including IBD[15]. The estimated annual disease-attributable cost of IBD is $6.3 billion[2]. There is an opportunity to reduce cost by increasing the efficiency and quality of outpatient care and prevention of adverse outcomes[16].

It is imperative to understand how these proposed frameworks like the Triple Aim affect traditional IBD care management. Conventionally, the management of IBD is centered around the treatment of symptoms alone, but managing active disease states (flare-ups) is insufficient to halt disease progression completely[17,18]. Shifting to a more ‘proactive’ rather than 'reactive' approach is pivotal[19]. Engaging and empowering patients to become active participants and stakeholders in their care management using novel approaches such as participatory and value-based care delivery models incorporating health technology and mobile applications may facilitate a more 'proactive' approach. Furthermore, these models may also be likely to be more successful in enhancing the patient experience and thus improve several key drivers of active disease, such as medication nonadherence and negative lifestyle factors[20,21].

eHealth & Artificial Intelligence in Care Delivery

The literature shows there is a tremendous variability in the care delivery in IBD. It is important to note that an inverse relationship exists between variation in care and quality of care delivered to an individual[22]. By adhering to the Triple Aim objectives there is a great potential to standardize the delivery of care through eHealth, which could improve the quality of care. This process can happen through the concept of care pathways, which would define all the required activities and costs for a healthcare provider and the patient with a certain diagnosis for a set period of time, thereby standardizing the care delivered. For a care pathway to be effectively executed, engagement and empowerment of the patient is pivotal, especially outside the hospital setting. Innovative eHealth solutions can be the key to accomplish this and can be incorporated in the quest to achieve the Triple Aim objectives.

eHealth and Artificial Intelligence are becoming increasingly more important. When looking at the advancement of technology in healthcare, we are at the forefront of disruptive innovation through digital health that is predicted to transform healthcare and redefine personalized medicine[23]. Firstly, we see a rapid increase in the use of internet and mobile phone use, with 81% of adults in North America owning a smartphone[24]. Mobile health — the application of sensors, mobile apps, social media, and location-tracking technology to obtain data pertinent to wellness and disease diagnosis, prevention, and management — makes it theoretically possible to monitor and intervene whenever and wherever acute and chronic medical conditions occur[25].

In the U.S. over 40% of adults have two or more chronic conditions and when looking at health expenditures, chronic conditions account for 71% of all health care costs[26,27], the potential and the opportunity for eHealth as a solution is alluring. As there is a rapid expansion in the multitude of ways data is collected with the introduction of electronic medical records, healthcare is presented with the challenge to leverage this opportunity to optimize the experience for providers and patients and to decrease costs. IBD is one of many chronic diseases that could benefit from eHealth, adding smartphone applications to the toolbox for care management has the potential improve disease understanding, enhance medication adherence, improve patient-physician communications, and for earlier interventions by medical professionals when problems arise[28].

Furthermore, the accessibility to Big Data and increased computational resources have paved the way for Artificial Intelligence (AI) to provide potential solutions for the management of prototypical complex diseases with advanced heterogeneity and alternating disease states, including IBD. AI algorithms may revolutionize practices for 3 major players in healthcare: clinicians, where it facilitates rapid diagnoses and decision making; health systems, where it may minimize inefficiencies and generate predictions for resource utilization; and patients, where it may enable them to self-monitor their health[29]. Despite many claims, the actually feasibility of AI solutions for IBD is still unclear and the role of eHealth in the care delivery process warrants further investigation.

Outline of this thesis

This thesis consists of three parts. In the first part we assessed the current economic and psychosocial impact of IBD by assessing its effect on indirect costs, productivity and caregiving. In the second part we assess if we can proactively identify IBD patients' needs using eHealth and Artificial Intelligence. Lastly, in the third part we analyze the impact of monitoring IBD patients using eHealth interventions in order to facilitate the delivery of high-value care.

PART I: The need for Innovation due to the Economic and Psychosocial Impact of IBD

Patients with a chronic conditions like IBD regularly have a decrease in their work productivity[30], which is described as either absenteeism or presenteeism. Absenteeim is time missed from work due to disease and presenteeism is decreased productivity at the workplace due to the disease. The impact of impaired productivity on healthcare expenditures is significant. It was reported that 76% of medical costs in chronic diseases are due to indirect medical costs, of which 83% (63% of total costs) is due to presenteeism[31]. Studies estimating indirect costs in the U.S. did not take presenteeism into account, therefore, in **Chapter 2** we assessed IBD work related problems in a prospective, high volume single-IBD center study and we aimed to quantify presenteeism; determine its associated costs and generate recommendations to reduce presenteeism and thus lower indirect costs related to IBD.

Furthermore, the high strain of IBD is not limited to patients but also impacts their caregivers. Caregiver burden is described as the emotional, physical, practical, and/or financial burden associated with taking care of a patient with a chronic condition. An informal caregiver, usually a family member or spouse, aids the care-recipient with their medication, post-operative wound dressing, and transport to the clinic[32]. **Chapter 3** investigated the burden of IBD on caregivers and their work productivity.

PART II: Identifying IBD Patients' Needs using eHealth and Artificial Intelligence

Electronic health (eHealth) interventions are one solution for more effective IBD care management beyond the clinical setting, both in terms of patient outcomes and cost reduction. Smartphone applications are widely available for consumers, and the large population of smartphone users make apps useful tools to manage chronic illnesses like IBD[33]. In fact, smartphone devices with mobile applications and short message reminders have been used effectively by patients with IBD of mild to moderate severity[34].

A major challenge in chronic disease management is medication non-adherence. In the US, about 117 million adults have at least one chronic disease[35] and 50% do not take their medications as prescribed[36]. For IBD, one study showed a non-adherence rate of 33%, of which 34% experienced at least one relapse after stopping treatment[37]. The resultant indirect and direct healthcare costs of non-adherence in chronic diseases are estimated to be between $100 billion and $300 billion annually in the US[38]. **Chapter 4** aimed to develop a brief screening tool to identify non-adherence levels and reasons for non-adherence in IBD for potential use in remote monitoring through eHealth applications.

The development of healthcare technologies driven by Artificial Intelligence (AI) is expected to see a growth of over $10 billion in just the next 5 years[39]. The opportunities to construct new strategies and technologies that can assist healthcare providers and patients in their care management are rapidly growing, as demonstrated by the vast amount of financing that is going into businesses that use AI for healthcare[40]. In fact, one novel role that AI may fill in IBD management is via medical chatbots, which strive to simulate natural conversations with a human user using natural language processing (NPL) methods [41]. Chatbots can improve healthcare delivery by increasing access to care beyond inpatient consultations and at patients' convenience and homes. Popular diagnostic chatbots have been used, but the role of chatbots in IBD is still being investigated[42]. **Chapter 5** aimed to elucidate the feasibility of chatbots in IBD care management by categorizing large datasets of electronic communications between patients and care providers using NLP.

With the explosive amount of Electronic Medical Records (EMRs), having doubled in size since 2005, studying patient data is easier now than in any previous era[40,43]. By taking full advantage of these Big Data repositories such as EMR data, insurance claims data, and other forms of patient information (e.g. wearables, microbiome/genetic testing, e-health applications, imaging), data driven treatment plans targeted at the disease- and individual level could be produced. In **Chapter 6** we assessed the feasibility and performance of various AI models in early prediction of adverse outcomes for IBD patients, including IBD-related surgeries, using Big Data, in this case consisting of large private insurance claims.

PART III: eHealth to Facilitate the Delivery of High-value Care in IBD

Despite innovations in therapeutics for inflammatory bowel disease (IBD)[44], up to 15% of ulcerative colitis (UC) patients will undergo surgery within 20 years of diagnosis and nearly 50% of Crohn's disease (CD) patients within 10 years of diagnosis[45,46]. Frequent monitoring is necessary for early discovery of relapse and complications given the complexity of IBD and risk of disease progression after surgery. In **Chapter 7** we developed a care pathway for IBD-related surgery, designed to tightly monitor patients at home after discharge using telemonitoring tools in order to improve the patient experience and to decrease postoperative readmissions and complications.

Furthermore, in **Chapter 8** we developed and evaluated UCLA eIBD, a mobile application with various components such as appointment reminders and medication trackers in addition to a healthcare provider portal. UCLA eIBD seeks to empower patients to self-manage their IBD by increasing their access to healthcare providers through the app and providing self-help educational modules. The application also monitors disease activity, quality of life, and work productivity using validated questionnaires. These eHealth tools allow healthcare providers to monitor patients and to take preemptive measures if required and to enhance patient outcomes by including direct connections to a healthcare team and extensive supportive module options.

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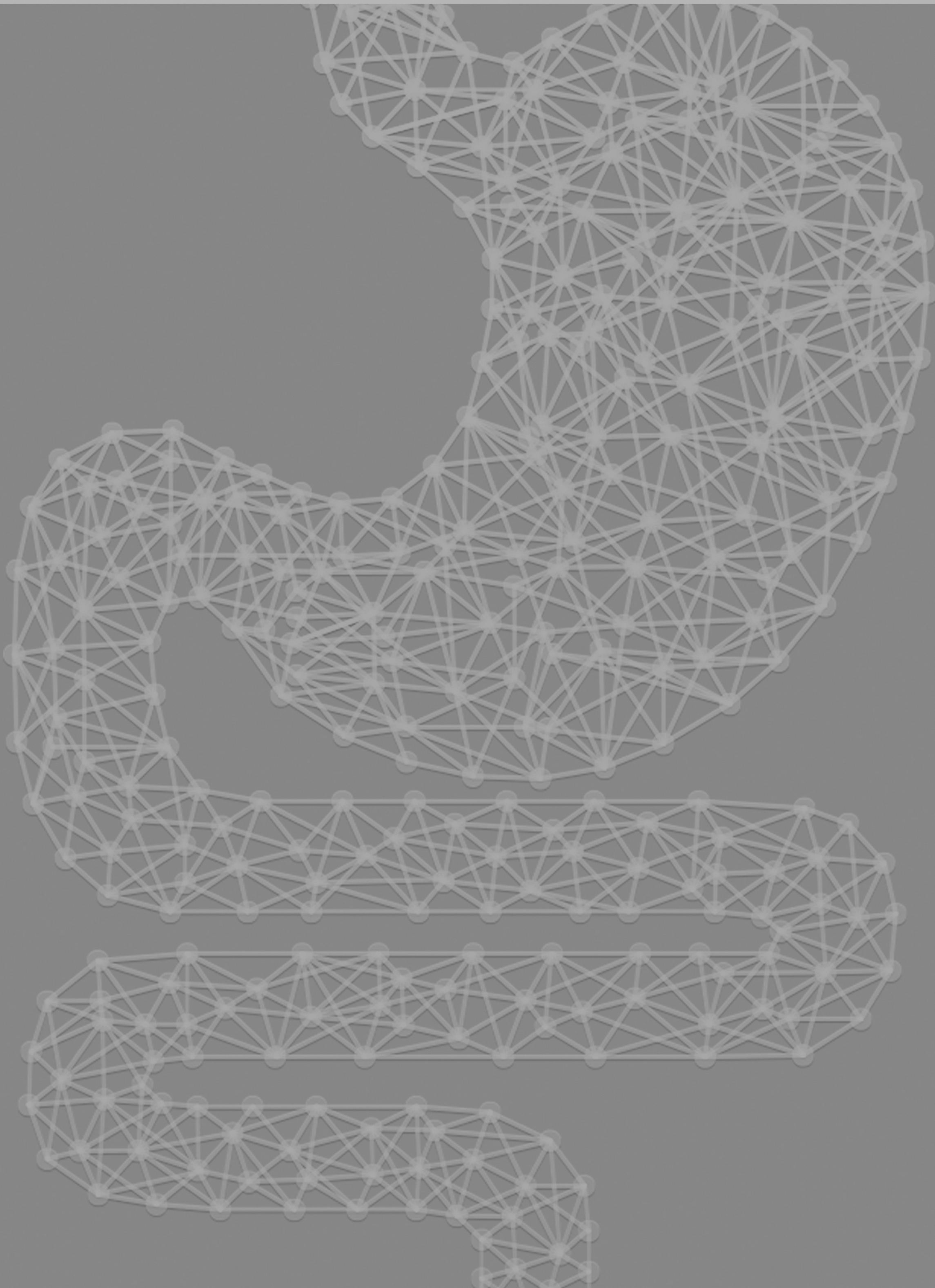
Part I: The Need for Innovation to Address the Economic and Psychosocial Impact of IBD



CHAPTER 2

Presenteeism in Inflammatory Bowel Diseases: a hidden problem with significant economic impact

Inflammatory Bowel Diseases. 2015 Jul;21(7):1623-30

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Abstract

Objectives

Indirect costs associated with impaired productivity at work (presenteeism) due to Inflammatory Bowel Disease (IBD) are a major contributor to health expenditures. Studies estimating indirect costs in the U.S. did not take presenteeism into account. We aimed to quantify work limitations, and presenteeism and its associated costs in an IBD population order to generate recommendations to reduce presenteeism and decrease indirect costs.

Methods

We performed a prospective study at a tertiary IBD center. During clinic visits work productivity, work related problems and adjustments, quality of life, and disease activity were assessed in IBD patients. Work productivity and impairment were assessed in a control population as well. Indirect costs associated with lost work hours (absenteeism) and presenteeism were estimated, as well as the effect of disease activity on those costs.

Results

Of the 440 included IBD patients 35.6% were unemployed. Significantly more presenteeism was detected in IBD patients (62.9%) compared to controls (27.3%) ($p=0.004$), with no significant differences in absenteeism. Patients in remission experienced significantly more presenteeism than controls (54.7% vs. 27.3%, respectively, $p<0.01$) and indirect costs were significantly higher for remissive patients versus controls ($17,766 per year vs. $9,179 per year, respectively, $p<0.03$). Only 34.3% had made adjustments to battle work related problems such as fatigue, irritability, and decreased motivation.

Conclusions

IBD patients in clinical remission still cope with significantly more presenteeism and work limitations than controls; this translates in higher indirect costs and decreased quality of life. The majority have not made any adjustments to battle these problems.

Introduction

A decrease in work productivity is commonly seen in patients suffering from chronic diseases[1]. This impairment is usually described in terms of presenteeism or absenteeism. Presenteeism is defined as the lost productivity that occurs when employees come to work but perform below par due to their illness. Absenteeism represents time missed from work due to their disease. Activity impairment is the effect of illness on regular everyday activities. The associated indirect costs are a major contributor to health expenditures. It was reported that 76% of medical costs in chronic diseases are due to indirect medical costs, of which 83% (63% of total costs) is due to presenteeism[2].

The inflammatory bowel diseases (IBD) are chronic, frequently progressive, conditions often with complications leading to disabilities[3]. The prevalence of Crohn's disease (CD) is 201 per 100,000 adults and 238 per 100,000 adults for ulcerative colitis (UC) in the U.S. population[4]. Impairment due to IBD has been shown to affect educational and employment prospects[5-8], triggering a socioeconomic burden on the economy and the patient[5,9]. Symptomatic IBD patients are less likely to have obtained a graduate or a professional degree than non-symptomatic patients[10]. IBD patients experience significant longer periods of unemployment[8] and have lower employment percentages[5-7]. Also, IBD associated problems can result in job loss, missed school days or reduced employment offers[9]. Even if IBD patients do go to work, their productivity is frequently impaired because of diminished motivation, irritability, avoidance of social activities and less participation during meetings[11]. Published estimates showed that 43% of employees with IBD need time off work due to the disease, averaging 7.2 days per employee with IBD per year[12]. This translates into a cost of \$138 million per year for the USA. The indirect cost of missed work time to IBD in 1998/1999 was more than \$3.6 billion U.S. dollars or \$5228 USD per person with IBD and symptoms[10]. Fortunately, more effective IBD therapies have resulted in improved health outcomes, which has been associated with improvements in employment status, hours worked and productivity[13-15].

So far, studies estimating the indirect costs for IBD in the U.S. did not take presenteeism into account[16-19]. Since presenteeism is the major contributor[2] to indirect medical costs, the actual costs are probably underestimated. Therefore, in addition to confirming IBD work related problems in a prospective, high volume single-IBD center study, we aimed to 1) quantify presenteeism; 2) determine its associated costs; and 3) generate recommendations to reduce presenteeism and thus lower indirect costs related to IBD.

Methods

Design and population

We performed a prospective study at a tertiary IBD care center in Los Angeles, California between March 2013 and February 2014. All included patients were above the age of 18 and participated in the Value-based Care Program[20] at the UCLA Center for Inflammatory Bowel Diseases. Consecutive patients were asked to participate in this study during clinic visits. In November 2013 a de-identified web-based questionnaire accessible through a 128-bit SSL encrypted link was sent out to patients who had not visited our clinic in the past year. Patients who could not be reached through email were approached by telephone. Included patients were approached by email to ask anyone they know (e.g., a family member or friend), above the age of 18 and without IBD, to serve as our control group. The study was approved by the UCLA IRB under protocol number 13-001507.

Questionnaires and data collection

The following questionnaires were administered: 1) the Work Productivity and Activity Impairment (WPAI)[21] questionnaire; 2) the short-IBD questionnaire (sIBDQ) for quality of life (QoL) assessment[22]; and 3) the disease activity scores 'Harvey-Bradshaw Index' for CD[23] and 'Partial Mayo Score' for UC[24]. Also, we developed a work impact questionnaire based on the IMPACT[11] study assessing work related problems. Finally, we included questions about 'job-lock' into the questionnaire (Supplementary figure 1). Job-lock is defined as the propensity of patients to stay in a job to retain insurance coverage. Data about race, ethnicity, initial symptoms, initial disease location, specific colon locations, fistula, extra intestinal manifestations, disease duration, surgeries, smoking and alcohol use were collected from the medical charts.

Controls filled out a general health version of the WPAI and a modified version of the work impact questionnaire, assessing the effect of general health problems on work productivity. To classify patients by type of employment we used the categorization of the United States Department of Labor Statistics[25].

Definitions

The WPAI calculates absenteeism, presenteeism and activity impairment independent of work status. Absenteeism is calculated based on the numbers of hours missed from work due to disease as a percentage of the total amount of hours worked in a week. Presenteeism and activity impairment are assessed on an 11 point Likert scale, where 0 was no effect of the disease and 10 was full impairment due to disease. Prevalence of absenteeism, presenteeism and activity impairment in our cohort were defined as any absenteeism, presenteeism or activity impairment; no threshold was imposed. Job-lock is defined as not being able to change employment because of employer provided health insurance and fear of loss of employee benefits. Remission of IBD was defined as a Harvey Bradshaw Index of ≤ 4 for CD and a Partial Mayo Score ≤ 2 for UC, with higher scores indicating active disease.

Outcomes

Absenteeism, presenteeism and work limitations were analyzed and differences between IBD patients and controls, UC and CD patients, and patients with active disease and inactive disease were assessed. Absenteeism costs were estimated using the "lost wages method"[26], which is defined as multiplying the estimated number of workdays missed by the estimated average daily compensation for full time employees and an average wage multiplier of 1.61[27]. Estimated daily earnings and benefits were defined as $31.93 per hour and based of the U.S. Department for Labor Statistics (DoL)[25]. To define a high and low salary group, we obtained the different hourly wages for the employment categories from the DoL, patients that made more than $32/hour were defined as the high salary group, whereas patients that made less than $32/hour were defined as the low salary group. Presenteeism costs were calculated assuming the hours of decreased productivity as partially non-worked hours and multiplying them by the estimated average daily compensation and the average wage multiplier.

Statistical Analysis

Descriptive statistics were provided for the results of the work impact questionnaire. Students' t-tests and ANOVA one way analysis for variance tests were performed for continuous data, and Fisher's exact tests and chi-square tests for categorical data. The data was analyzed using Microsoft Excel 2010 and SPSS 21.0.

Results

Patients

A total of 469 patients filled out the WPAI questionnaire. Twenty-nine patients were excluded, because 23 forms were filled out incorrectly and 6 patients did not have confirmed IBD, which left 440 IBD patients eligible for analysis. For a subset of 379 patients QoL and

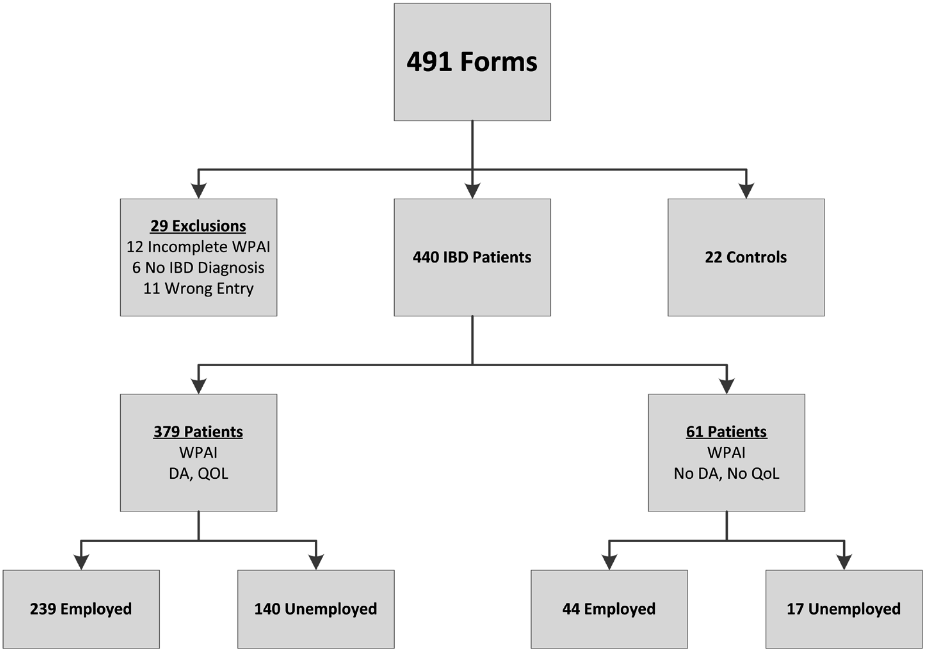

Figure 1. Study Flowchart

disease activity were assessed during the same clinic visit. In addition, a total of 213 patients filled out the work impact questionnaire. Disease activity and QoL scores were available for 152 of those. A total of 22 controls were included as a comparison (Figure 2.1).

Out of the 440 included IBD patients, 49.8% were male (Table 1). The median age was 37 years (range 18-83 years) and 73.9% had never smoked. The majority of the included patients (82%) were white, 7.3% were of Asian descent and 3.4% were black or African American. In total, 50.2% (221) were diagnosed with CD and 49.8% (219) with UC. No significant differences in gender, sex, smoking status, race, ethnicity and disease duration were observed between UC and CD patients. The median age at diagnosis for CD patients was slightly younger (24, range 8 - 68) then for UC patients (29, range 6 - 81) for UC patients (P=0.002). Rectal bleeding was the most common presenting symptom in UC (77.3%) and abdominal pain the most common in CD (69.7%). As expected, more CD patients (33.5%) have undergone abdominal surgery then UC patients (9.1%) (P<.0001). No significant differences in gender, age, intoxications, race and ethnicity were observed between the IBD and the control group (Table 2). 13,6% of the controls had a chronic disease.

2

Table 2.1. Demographics of IBD population

N=440	CD N= 221		UC N= 219		P Value
Male sex % (no.)	49.8%	(110)	49.8%	(109)	1.000
Median Age (range)	36	(19-79)	40	(18-83)	0.174
Smoking % (no.)					0.782
- Current	- 8.1%	(18)	- 6.4%	(14)	
- Past	- 18.1%	(40)	- 19.2%	(42)	
- Never	- 73.8%	(163)	- 73.9%	(162)	
- Unknown	- N/A		- 0.5%	(1)	
Drinking% (no.)					0.014
- Yes	- 48%	(106)	- 59.4%	(130)	
- No	- 51.6%	(114)	- 40.5%	(88)	
- Unknown	- 0.4%	(1)	- 0.9%	(2)	
Median age at diagnosis (range)	24 yrs (8-68 yrs)		29 yrs (6-81)		0.002
Median disease duration (range)	8 yrs (0-52)		6.5 yrs (0-52)		0.115
Race					0.083
- American Indian or Alaska Native	- 0.9%	(2)	- 0.5%	(1)	
- Asian	- 5.9%	(13)	- 8.6%	(19)	
- Black or African American	- 5.4%	(13)	- 1.4%	(2)	
- Native Hawaiian	- 0.5%	(1)	- 0.0%	(0)	
- White	- 81.9%	(181)	- 81.4%	(180)	
- Unknown	- 5.4%	(11)	- 7.7%	(17)	
N=440	CD N= 221		UC N= 219		P Value
Ethnicity					0.552
- Hispanic or Latino	- 4.98%	(11)	- 6.36%	(14)	
- Not Hispanic or Latino	- 89.14%	(198)	- 90.00%	(197)	
- Unknown	- 5.88%	(12)	- 3.64%	(8)	
Medication use					0.000
- Biological therapy	- 37.6%	(83)	- 18.3%	(40)	
- Immunomodulators	- 18.6%	(41)	- 9.1%	(20)	
- Steroids	- 8.1%	(18)	- 13.7%	(30)	
- Other	- 29.9%	(66)	- 48.4%	(106)	
- No medication	- 5%	(11)	- 6.4%	(14)	
- Unknown	- 0.9%	(2)	- 4.1%	(9)	
Initial symptoms (1 or more)					
- Abdominal pain	- 69.7%	(153)	- 51.4%	(113)	0.000
- Diarrhea	- 26.7%	(59)	- 31.4%	(69)	0.216
- Rectal bleeding	- 33.5%	(72)	- 77.3%	(171)	0.000
- Weight loss	- 30%	(64)	- 18.6%	(41)	0.014
- Unknown	- 3.4%	(16)	- 9.1%	(19)	
Initial disease extent (1 or more)					
- Upper GI tract	- 3.4%	(15)			
- Small bowel excluding terminal ileum	- 15.8% - 51.6%	(35) (114)			
- Terminal ileum	- 49.3%	(109)			
- Colon	- 14.9%	(33)			
- Unknown					

Table 2.1. Continued

N=440	CD N= 221	UC N= 219	P Value
Disease extent			
- Cecum-ascending		- 16.1% (59)	
- Transverse-descending		- 44.4% (163)	
- Rectum		- 30.8% (113)	
- Unknown		- 14.6% (32)	
Fistula			
- % Fistula	- 23.2% (51)	- 2.8% (6)	0.000
- Peri-anal	- 12.3% (27)	- 1.4% (3)	0.000
- Enterocutaneous	- 3.2% (7)	- 0.5% (1)	0.068
- Other	- 10.5% (23)	- 0.9% (2)	0.000
- Unknown	- 0.5% (1)	- 1.8% (4)	
Extra-intestinal manifestations (EIM)			
- % EIM	- 20.5% (45)	- 8.8% (19)	0.001
- Eye	- 5% (11)	- 1.9% (4)	0.112
- Skin	- 4.5% (10)	- 1.9% (4)	0.173
- Joint	- 16.4% (36)	- 5.1% (11)	0.000
- PSC	- 1.4% (3)	- 1.9% (4)	0.487
- Other	- 1.4% (4)	- 0.5% (1)	0.315
Surgeries			
- Abdominal surgeries	- 33.5% (74)	- 9.1% (20)	0.000

Employment

In total, 64.4% (283) of the total IBD cohort was employed and 35.6% (157) was not (Table 3). Supplementary Table 1 shows the industrial sectors in which patients were employed. Out of 62 unemployed patients that indicated a reason for being unemployed, 54.8% were retired or a student; 14.5% were on disability; 12.9% were homemakers (manager of the household); 4.8% could not work due to IBD; and 3.2% recently lost their job. All of our controls were employed. There was no significant difference in employment rate between UC and CD patients (63.3% and 65.3%, respectively (p=0.67)). In the employed group 54.5% were male, while in the unemployed group only 41.4% were male (p=0.009). Activity impairment was present in 65% of the employed group, while in the unemployed group this was 79% (p=0.002). Mean QoL was significantly higher in employed patients (QoL 50, SD 12) than in the unemployed patients (QoL 44, SD 15) (p<.001). No significant difference in disease activity was observed, with 24.3% active disease in the employed group versus 26.4% in the unemployed group (p=0.639).

Table 2.2. Demographics IBD patients versus controls

	IBD (n=440)		Controls N=(22)	P value
Male sex % (no.)	49.8%	(219)	54.5% (12)	0.662
Median Age (range)	37	(18-83)	37 (25-77)	0.439
Smoking % (no.)				0.908
- Current	- 7.3%	(32)	- 4.5% (1)	
- Past	- 18.6%	(82)	- 18.2% (4)	
- Never	- 73.9%	(325)	- 72.7% (16)	
- Unknown	- 0.2%	(1)	- 4.5% (1)	
Drinking% (no.)				0.085
- Yes	- 53.6%	(236)	- 72.7% (16)	
- No	- 45.7%	(201)	- 27.3% (6)	
- Unknown	- 0.7	(3)		
Race				0.379
- American Indian or Alaska Native	- 0.7%	(3)	- 4.5% (1)	
- Asian	- 7.3%	(32)	- 9.1% (2)	
- Black or African American	- 3.4%	(15)	- (0)	
- Native Hawaiian	- 0.2%	(1)	- (0)	
- White	- 82.0%	(361)	- 86.4% (19)	
- Unknown	- 6.4%	(28)	- N/A	
Ethnicity				0.785
- Hispanic or Latino	- 5.7%	(25)	- 4.5% (1)	
- Not Hispanic or Latino	- 89.8%	(395)	- 95.5% (21)	
- Unknown	- 4.5%	(20)	- N/A	

Work Productivity

Presenteeism and absenteeism were calculated in the employed patients (140 CD, 143 CD) and in 22 employed controls (Figure 2). No significant differences in absenteeism were observed between controls, UC and CD patients (13.6%, 22.4% and 20%, respectively). Significantly more presenteeism was detected in CD (61.4%) and UC patients (64.3%) compared to controls (27.3%) (p=0.004). Activity impairment was calculated as well and similar patterns were observed with 63.6% and 66.4% activity impairment in CD and UC, respectively, and 31.8% for controls (p=0.007). The strongest impairment was observed in patients with active disease. Of these, 46.6% experienced absenteeism, 94.8% presenteeism, and 98.9% activity impairment, compared to 14.4%, 54.7% and 62.7%, respectively, of patients in remission (p<.001). Absenteeism was similar between remissive patients and controls (14.4% and 13.6% respectively, p=1.000), while controls had significantly less presenteeism than remissive patients (27.3% and 54.7% respectively, p=0.022).

Table 2.3. Characteristics of employed versus unemployed IBD patients

Total (n=440)	Employed (n=283)	Unemployed (n=157)	P value
Median age (range)	36 (20-82)	41 (18-83)	0.094
Male gender %(n)	54.4% (154)	41.4% (65)	0.009
Disease type %(n)	49.5% CD(140) 50.5% UC (143)	51.6% CD (81) 48.4% UC (76)	0.670
Activity impairment %(n)	65.0% (184)	79% (124)	0.002
Active disease % (n) (n=379)	24.3% (58)	26.4% (37)	0.639
Mean QoL (SD) (n=379)	50 (SD 12)	44 (SD 15)	0.000

CD= Crohn's disease, UC= ulcerative colitis, QoL= Quality of life

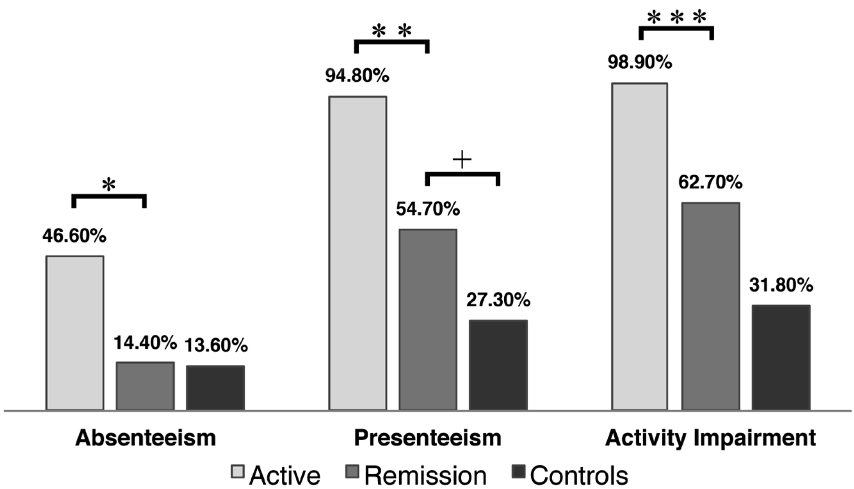

Figure 2. Prevalence of absenteeism, presenteeism, and activity impairment in controls and patients with IBD with active and inactive disease. *P < 0.01, **P < 0.01, ***P < 0.01, +P = 0.02.

Work Impact

Table 4 shows the limitations that IBD patients experienced at work. Most commonly reported limitations were fatigue (41.8% of patients), irritability (12.2%) and a decreased motivation (11.7%). The most frequent reasons to miss work were doctor appointments (39%), abdominal pain or cramping (24.4%) and hospital/emergency department visits (22.1%). Remarkably, only 34.3% were able to make work adjustments (e.g., telecommuting or flexible hours) to avoid taking time off due to their IBD. Stress or pressure when taking sick time off from work due to IBD was experienced by 37.1% of patients, 4.3% felt superiors and/or colleagues complained or made unfair remarks about their performance at work in

relation to their IBD, and 5.3% felt they were discriminated in the workplace as a direct consequence of their IBD. Furthermore, 26.2% felt that IBD had negatively affected their career path, opportunities for advancement, income and/or earning potential. Also, 11.2% lost a job or had to quit a job because of IBD, job-lock was observed in 14% of patients, and 3.3% reported to have been on disability at some point in the past year.
Unsurprisingly, significant differences were observed between patients with active disease versus inactive disease. Active patients experienced more fear of frequent stools or bowel movements interfering with work activities ($p=0.01$), felt more fatigued ($p<0.01$), made more adjustments to avoid taking sick days off from work due their IBD ($p=0.028$), and experienced more worry and fear of potential embarrassment at the workplace ($p<0.01$). We observed that patients who reported absenteeism or presenteeism felt more frequently stressed about taking time off work due to their disease, (78% and 49.6%, respectively, $p<0.01$) than those without absenteeism or presenteeism (27.2% and 15.6%, respectively, $p<0.01$)

Interestingly, patients who experienced absenteeism and presenteeism made work adjustments significantly more often (54% and 40%, respectively, $p<0.01$) than those without absenteeism or presenteeism (29% and 24%, respectively, $p=0.02$)

Indirect Costs

We estimated that total indirect costs for active patients on average were $1133/week, assuming an average hourly compensation of $31.93, a 40 hour work week, and a wage multiplier of 1.61. This equals 55.1% of the total weekly compensation. This was significantly more than patients in remission, whose total indirect cost was estimated to be 18% of the total weekly compensation or $370.13/week for a full time employee ($P<0.01$).

Presenteeism accounted for the majority of costs, with 33.8% of total weekly compensation ($695.03/week) for active patients and 13.5% of total weekly compensation ($277.60/week) for remissive patients. Absenteeism accounted for 21.3% of total weekly compensation ($437.99/week) in active patients and 4.5% of total weekly compensation for patients in remission.

Indirect costs encountered for patients in remission were still significantly higher when compared to controls ($p=0.029$). For controls average weekly indirect costs were estimated at 9.3% of total weekly compensation or $191.23/week (for a full time employee). Average indirect cost associated with absenteeism were on average 4.8% of total weekly compensation or $98.70 per week and costs associated with presenteeism were estimated at 4.6% of total weekly compensation or $94.59 per patient per week (Figure 3). Furthermore, patients in remission who made more than $32/hour experienced absenteeism more frequently than those who made less than $32/hour (24.5% and 6.9% absenteeism, respectively, p=0,01). Presenteeism was similar in both salary groups (56.6% and 55.2%, respectively). Average total indirect costs were estimated at $789.58 in the high salary group and $114.47 in the lower salary group (P=0.03).

Table 4. An overview of limitations IBD patients experience at work divided by disease activity.

	Remissive patients (111)	Active Patients (41)	p value
Which of the following adjustments have you made in your work to avoid taking sick days off from work due to your IBD?			
1) Working from home	12.6% (14)	12.2% (5)	1.000
2) Working part-time	4.5% (5)	12.2% (5)	0.134
3) Working flexible hours	13.5% (15)	24.4% (10)	0.139
4) I have not made any such adjustments	55.9% (62)	34.1% (14)	0.028
5) I do not have the possibility to make such an adjustment	16.2% (18)	19.5% (8)	0.633
6) Other	7.2% (8)	4.9% (2)	1.000
If you have missed work due to your IBD, what was the reason? Check all that apply	**Remissive patients (111)**	**Active Patients (41)**	**p value**
1) Hospital/emergency department visit	19.8% (22)	14.6% (6)	0.638
2) Doctor appointment	36% (40)	25.9% (14)	0.829
3) Incontinence or fear of incontinence	4.5% (5)	12.2% (5)	0.134
4) Abdominal pain or cramping	17.1% (19)	31.7% (13)	0.072
5) Fear of frequent stools or bowel movements interfering with work activities	13.5% (15)	31.7% (13)	0.017
If you have missed work due to your IBD, what was the reason? Check all that apply	**Remissive patients (111)**	**Active Patients (41)**	**p value**
6) Fear of frequent stools or bowel movements bringing attention to my condition from colleagues	4.5% (5)	12.2 (5)	0.134
7) Fatigue, and/or not enough energy to get through the day	15.3% (17)	36.6% (15)	0.004
8) Worry about gas pressure, discomfort	6.3% (7)	9.8% (4)	0.489
9) Worry/fear of potential for embarrassment	3.6% (4)	19.5% (8)	0.003
10) Rectal/anal pain or burning	2.7% (3)	9.8% (4)	0.212
11) Volume of blood in bleeding episode	3.6% (4)	4.9%(2)	0.661
12) I have never been absent from work due to IBD	22.5% (25)	7.3% (3)	0.035

Table 4. Continued

How does IBD affect your performance at work	Remissive patients (111)	Active Patients (41)	p value
1) I am quiet or quieter during meetings	5.4% (6)	12.2% (5)	0.168
2) I cancel my attendance at meetings at the last minute	5.4% (6)	7.3% (3)	0.703
3) I do not participate in work social activities	5.4% (6)	19.5% (8)	0.022
4) I am irritable at work	11.7% (13)	12.2% (5)	1.000
5) I am less motivated in my work	13.5% (15)	14.6% (6)	1.000
6) My IBD does not affect my behavior at work	27.9% (31)	4.9% (2)	0.002
How does IBD affect your performance at work	**Remissive patients (111)**	**Active Patients (41)**	**p value**
7) I am fatigued	37.8% (42)	65.9% (27)	0.002
8) Not applicable/other	26.1% (29)	12.2% (5)	0.081

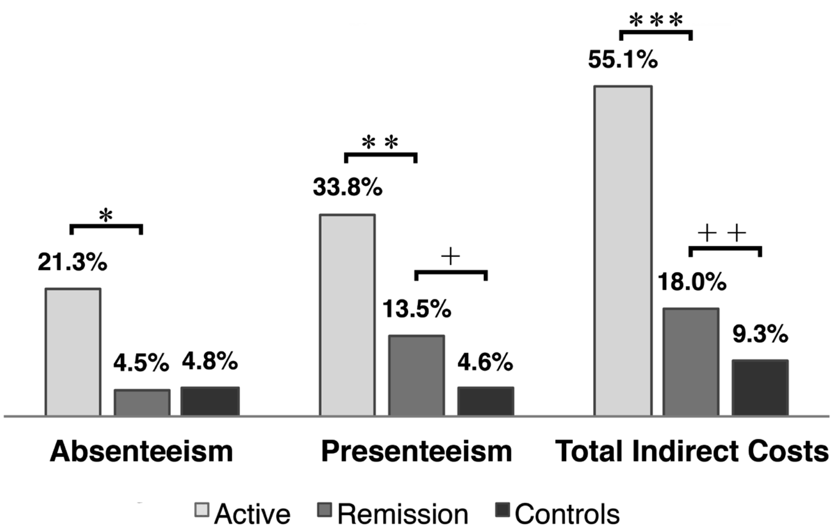

Figure 3. Indirect costs as a percentage of maximum weekly compensation for employees. *P < 0.01, **P < 0.01, ***P < 0.01, +P = 0.02, ++P < 0.03.

Discussion

"Without question, the single biggest force threatening U.S. workforce productivity, as well as health care affordability and quality of life, is the impact of chronic conditions"[28]. Indeed, the indirect costs of care are estimated to be approximately 76% of total cost of care[2]. This discussion has become especially relevant now that our daily clinical practice is faced with the transition from the fee-for-services model to the value-payment model in order to bend the cost curve. Tackling both direct and indirect costs will increasingly be placed on the agenda of the provider, especially in the management of costly chronic disease like IBD.

In this study we found that employed IBD patients, even when in complete clinical remission, still experienced decreased productivity significantly more frequently than healthy controls: 54.7% vs. 27.3%, respectively (P=0.02). This translates into a sizable economic impact as reflected by the indirect costs for patients even though they are in clinical remission (18% IBD vs. 9.3% controls of total compensation per week (P=0.03)). Disturbingly, we found that patients continue to cope with limitations at work that cause a lower QoL and an increase in stress, absenteeism, and presenteeism. The majority, 65.7%, has not made any adjustments in order to combat these problems, most likely due to their inability to deal with complaints like fatigue or with aligning their doctors' appointments with their job demands.

Interestingly, we did not observe a significant difference in absenteeism between IBD patients and controls, respectively 21.2% (CD 20%, UC 22,4%) compared to 13.6% (P=0.399). This could be attributed to improved treatments, like biologic therapy, inducing effective clinical remission and allowing patients to resume their work[13-15,29]. Other studies found comparable absenteeism percentages ranging from 18-36% for CD and 13-25% for UC[1]. Although the control population was small, differences for absenteeism, presenteeism, activity impairment and indirect costs were significant.

A limitation of this study is that controls were identified through our IBD patients, which could potentially lead to bias. However, it has been shown that caregivers of patient with chronic diseases usually tend to have reduced productivity compared to controls[9], which would suggest that this would only underestimate the measured effect. Furthermore, the included patients were selected in a tertiary care center, with potentially more patients with difficult to treat disease. To limit the effect of this we aimed to focus on the productivity of patients in clinical remission.

From a health economical perspective it has been shown that presenteeism makes up for the majority of indirect costs[2]. This is the first report on indirect costs including presenteeism of IBD patients in the United States. Our cost model shows that indirect costs are significantly lower when IBD patients enter a remissive state, dropping from $1333/week when clinically active to $370/week when in remission. A recent study from Hungary showed presenteeism costs of €2508/patient/year which translates to $3191/patient/year[30], that equals $66/patient/week. This number is lower than our estimated $354/patient/week. The difference can be explained by the average hourly wage which is lower in Hungary ($7) and the fact that we incorporated the average wage multiplier to correct for the variation in presenteeism cost among different kind of employment levels.

What can we as care givers, do to decrease presenteeism in IBD patients in remission? First of all it is important to note that patients themselves do not appear to make the necessary adjustments: only 34.3% were able to do so, which confirms results from a recent study that showed that only 40% of patients had made any adjustment[11]. Secondly, these patients continue to struggle with three types of problems: 1) persistent symptoms (e.g. fatigue, irritability, cramping); 2) lack of work motivation; and 3) missed work days due to medical appointments. Thirdly, we observed additional macro-economic issues: 1) career stagnation, 26.2% felt that their disease had negatively affected their career; and 2) job-lock, which was observed in 14% of patients. It has been reported that chronic illness reduces job mobility by about 40% those that rely on their employer coverage[31]. For IBD this has not been studied previously.

Our recommendations therefore are divided into care provider recommendations and employer recommendations. Care providers (e.g. physicians, nurses, social workers, dieticians) will need to pro-actively discuss and propose employment-related adjustments tailored to the individual. They need to encompass mental support, nutritional support, wellness (e.g. fitness, yoga, meditation) and elimination of unnecessary tests, procedures and medical appointments. Employer recommendations include job-coaching, an in depth discussion about career and work place related support measures. Surveys have shown that employees with chronic conditions are more likely to be highly satisfied with their jobs if they had high self-efficacy in managing their disease, perceive workplace support, and had less work limitations[32]. This would allow employers to make effective adjustments leading to a decrease of presenteeism.

In conclusion, this study shows that employed IBD patients in clinical remission still have significant loss of work productivity that goes unnoticed in the majority of cases. The associated high indirect costs constitute a significant economic burden on health expenditures. A way to decrease indirect costs includes both care provider and employer interventions, ideally converging into an integrated approach. The development and testing of practice guidelines and productivity enhancement tools will most likely have a meaningful and immediate impact.

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Supplementary

Supplementary Figure 1

Work Impact Questionnaire

1. What industry do you work in?

- ☐ Real estate, renting, leasing
- ☐ State and Local Government
- ☐ Finance and insurance
- ☐ Health/social care
- ☐ Manufacturing
- ☐ Retail trade
- ☐ Wholesale trade
- ☐ Federal Government
- ☐ Information
- ☐ Arts, entertainment
- ☐ Construction
- ☐ Waste services
- ☐ Other services
- ☐ Utilities
- ☐ Mining
- ☐ Corporate management
- ☐ Education services
- ☐ Agriculture
- ☐ Other, please specify: ....

....

2. Who is currently providing you with health insurance?

- ☐ Employer -> proceed to next question
- ☐ Other, please specify and proceed to question 5

....

3. Would you like to change your job?

- ☐ Yes -> proceed to next question
- ☐ No -> proceed to question 5

4. Is the risk of losing employer-provided health insurance your reason for not changing jobs?

- ☐ Yes
- ☐ No, please specify: ....

....

5. Have you been on disability in the past year? If yes please specify for how long

- ☐ Yes, for .... months -> proceed to next question
- ☐ No -> proceed to question 7

6. What was the reason you were on disability?

- ☐ Fatigue
- ☐ Hospitalization/Surgery

☐ Other, please specify: ....
....

7. Do you experience stress or pressure when taking sick time off from work due to your IBD?

☐ Yes

☐ No

☐ Not applicable/don't know

8. Which of the following adjustments have you made in your work to avoid taking sick days off from work due to your IBD?

☐ Working from home

☐ Working part-time

☐ Working flexible hours

☐ I have not made any such adjustments

☐ I do not have the possibility to make such an adjustment

☐ Other: ....
....

9. If you have missed work due to your IBD, what was the reason? Check all that apply.

☐ Hospital/emergency department visit

☐ Doctor appointment

☐ Incontinence or fear of incontinence

☐ Abdominal pain or cramping

☐ Fear of frequent stools or bowel movements interfering with work activities

☐ Fear of frequent stools or bowel movements bringing attention to my condition from colleagues

☐ Fatigue, and/or not enough energy to get through the day

☐ Worry about gas pressure, discomfort

☐ Worry/fear of potential for embarrassment

☐ Rectal/anal pain or burning

☐ Volume of blood in bleeding episode

☐ I have never been absent from work due to IBD

☐ Not applicable/other: ....
....

10. Have any of your superiors and/or colleagues complained or made unfair remarks about your performance at work in relation to your IBD?

☐ Yes ☐ No

11. Do you think you have been discriminated in the workplace as a direct consequence of your IBD?

☐ Yes ☐ No

12. How does IBD affect your performance at work

☐ I am quiet or quieter during meetings

☐ I cancel my attendance at meetings at the last minute

☐ I do not participate in work social activities

☐ I am irritable at work

☐ I am less motivated in my work

☐ My IBD does not affect my behavior at work

☐ I am fatigued

☐ Not applicable/other

How much do you agree with the following statements?

13. I believe that IBD has negatively affected my career path, opportunities for advancement, income and/or earning potential

☐ Strongly agree ☐ Disagree
☐ Agree ☐ Strongly disagree
☐ Neither agree nor disagree

14. Because of my IBD, I have lost a job or had to quit /leave a job

☐ Strongly agree ☐ Disagree
☐ Agree ☐ Strongly disagree
☐ Neither agree nor disagree

These questions were based on surveys and adapted for this study from the *European Federation of Crohn's and Ulcerative Colitis Associations* and *The National Association for Colitis and Crohn's Disease*.

Supplementary Table 1. Comparing the characteristics of responders to the non-responders.

N=560	Responders N=440		Non-responders N= 140		P Value
% Crohn's disease % Ulcerative colitis	50.2% (221) 49.8% (219)		51.4% (72) 48.6% (68)		0.804
Male sex % (no.	49.8% (219)		57.1% (80)		0.129
Median Age (range)	37 (18-83)		38 (19-83)		0.454
Median age at diagnosis (range)	26 yrs (6-81 yrs)		26 yrs (0-80)		0.166
Median disease duration (range)	7 yrs (0-52 yrs)		8 yrs (1-53 yrs)		0.447
Race					0.656
- American Indian or Alaska Native	- 0.7%	(3)	- N/A	(0)	
- Asian	- 7.3%	(32)	- 3.6%	(5)	
- Black or African American	- 3.4%	(15)	- 2.1%	(3)	
- Native Hawaiian	- 0.2%	(1)	- N/A	(0)	
- White	- 82.0%	(361)	- 69.3%	(97)	
- Unknown	- 6.4%	(28)	- 25%	(35)	
Ethnicity					0.369
- Hispanic or Latino	- 5.7%	(25)	- 6.4%	(9)	
- Not Hispanic or Latino	- 89.8%	(395)	- 70.7%	(99)	
- Unknown	- 4.5%	(20)	- 22.9%	(32)	
Initial symptoms (1 or more)					
- Abdominal pain	- 65.7%	(266)	- 57%	(69)	0.082
- Diarrhea	- 31.6%	(128)	- 66.1%	(80)	0.000
- Rectal bleeding	- 60%	(243)	- 58.7%	(71)	0.000
- Weight loss	- 25.9%	(105)	- 19.8%	(24)	0.172
- Unknown	- 8%	(35)	- 13.6%	(19)	
N=560	**Responders N=440**		**Non-responders N= 140**		**P Value**
Initial disease extent (1 or more)					
- Upper GI tract	- 4.1%	(15)	- N/A	(0)	0.039
- Small bowel excluding terminal ileum	- 9.5%	(35)	- 7.8%	(8)	0.610
- Terminal ileum					
- Colon	- 31.2%	(115)	- 34.3%	(35)	0.546
- Unknown	- 78.6%	(290)	- 78.4%	(80)	0.972
	- 16.1%	(71)	- 27.1%	(38)	
Disease extent (1 or more)					
- Cecum	- 22%	(85)	- 17.1%	(20)	0.256
- Ascending	- 9.3%	(36)	- 13.7%	(16)	0.173
- Transverse	- 21.2%	(82)	- 15.4%	(18)	0.168
- Descending-sigmoid	- 41.3%	(160)	- 36.8%	(43)	0.375
- Rectum	- 39.3%	(152)	- 31.6%	(37)	0.134
- Unknown	- 12%	(53)	- 16.4%	(23)	
Fistula					
- % Fistula	- 13.1%	(57)	- 11.4%	(16)	0.605
- Peri-anal	- 6.9%	(30)	- 5.7%	(8)	0.624
- Enterocutaneous	- 1.8%	(8)	- 0.7%	(1)	0.058
- Other	- 5.7%	(25)	- 5.7%	(8)	0.988
Surgeries					
- Abdominal surgeries	- 24.6%	(97)	- 34.3%	(48)	0.027

Supplementary Table 2. Percentages of presenteeism in the patient population, with and without a treshold.

% of presenteeism	All employed patients (n=283)	Employed patients in Remission (n=181)	Controls (n=22)	P value Employed vs. Controls
No treshold	62,9%	54,7%	27,3%	
20% treshold	43,5%	30,9%	18,2%	0.03

Supplementary Table 3. Patients split up by employment categories

Industry	N	%
Arts, entertainment	38	17.8%
Health/social care	33	15.5%
Education services	24	11.3%
Other services	23	10.8%
Corporate management	18	8.5%
Finance and insurance	15	7.0%
Retail trade	15	7.0%
Real estate, renting, leasing	10	4.7%
Information	9	4.2%
State and local government	7	3.3%
Construction	5	2.3%
Federal government	4	1.9%
Other	4	1.9%
Manufacturing	3	1.4%
Utilities	2	0.9%
Wholesale trade	2	0.9%
Agriculture	1	0.5%
Total	213	100%

CHAPTER 3

The Effects of Inflammatory Bowel Disease on Caregivers: Significant Burden and loss of Productivity

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Abstract

Background

Caregiver burden is the emotional, physical, practical, and/or financial burden associated with taking care of a patient with a chronic condition. Limited literature on caregiver burden in Inflammatory Bowel Diseases (IBD) has accounted for some predictors, but its effect on work productivity (absenteeism and presenteeism) is unknown.

Methods

In a prospective study, patients and their respective caregivers were surveyed from November 2015 until July 2017. Data on demographics, work productivity, quality of life, disease activity, caregiver burden and productivity were collected. The burden on caregivers was assessed and associations between caregiver productivity and caregiver burden were analyzed. Additionally, predictors for caregiver burden were identified.

Results

One hundred two IBD patients and their respective caregiver were included. In total, 39% of IBD caregivers experienced burden. Caregivers with burden experienced significantly more absenteeism and presenteeism (65 and 85% respectively). Furthermore, 51% of caregivers felt that they should be doing more for their care recipient and felt they could do a better job at caregiving. Predictors of burden included race/ethnicity, history of fistulas, diagnosis of ulcerative colitis, higher caregiver education, and hours spent caregiving.

Conclusion

Caregivers with burden had significantly more productivity decrease compared to those without burden. Additionally, the majority of caregivers feel they should be providing more and better care for their recipients. The development of strategies to address caregiver's distress and perceived burden when caring for IBD patients is warranted.

Background

Inflammatory Bowel Diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), are chronic immunological digestive diseases generally characterized by frequent abdominal pain and diarrhea with the disease state alternating between remission and exacerbation[1]. IBD affects nearly 3 million Americans who frequently require medical therapy, surgeries, and hospitalizations[2]. A study performed by Lönnfors et al.[3] among 4670 IBD patients from 25 countries found that 22% of IBD patients experienced periodic flare-ups. During a flare-up, 38% spent days in the hospital, 62% experienced gastrointestinal bleeding, and 87% experienced abdominal pain at least once a week. Furthermore, their study showed that a third of IBD patients felt their intimate relationships were compromised, a quarter of IBD patients felt it is difficult to maintain friends, 67% was concerned about the availability of toilets when planning to attend an event, and 40% woke up frequently due pain associated with their IBD. In the workplace, IBD patients reported fatigue, irritability, and demotivation. Additionally, IBD patients had difficulty coping with IBD-related limitations in the workplace resulting in increased stress-levels, lower quality of life (QoL) and a higher likelihood of absenteeism (time missed from work due to disease) and presenteeism (being present at work, but less productive due to disease), see Figure 1[4].

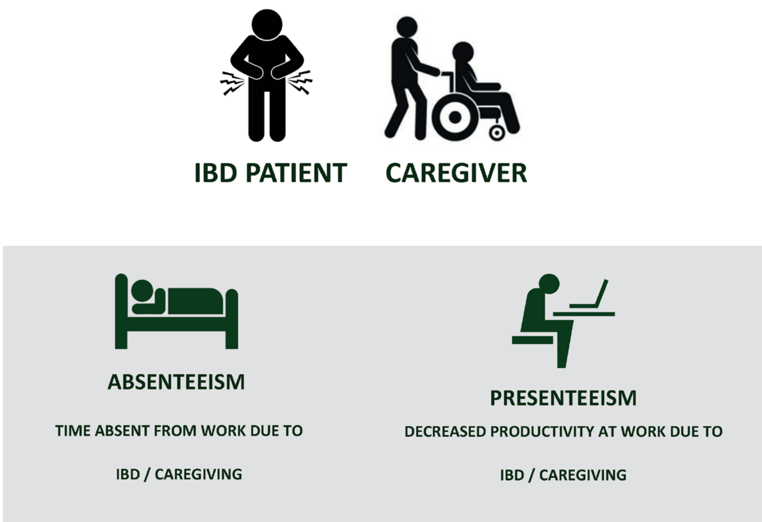

Figure 1. Absenteeism and presenteeism in IBD patients and their respective caregivers

3

The high strain of IBD is not limited to patients but also impacts their caregivers. Caregiver burden is described as the emotional, physical, practical, and/or financial burden associated with taking care of a patient with a chronic condition. An informal caregiver, usually a family member or spouse, aids the care-recipient with their medication, post-operative wound dressing, and transport to the clinic. Especially when the state of the disease fluctuates between remission and exacerbation, the caregiver has to respond to the unpredictable demands of the disease. Several studies have brought caregiver burden in IBD to light. Gray et al. found that pediatric IBD patients' disease activity increased parental stress[5]. Akobeng et al. showed that the source of parental anxiety and stress is largely due to concerns about the effects that IBD might have on their child's future[6]. A study by Parekh et al. in adult IBD patients found that caregiver burden is frequent in this population as well, affecting 44% of caregivers. Factors such as the presence of another dependent in the home (aside of the patient), the disease severity, and a caregiver's history of psychiatric illness were found to be predictors for caregiver burden and low QoL[7].

A more recent review by Shukla et al. reiterates the current scarcity of literature on caregiver burden in IBD and the lack of interventions that address caregiver burden[8]. Although the literature on IBD caregiver burden is limited, studies that assess the QoL of caregivers and the effects of caregiving for patients with other chronic conditions exist. Baanders and Heijmans reported that 53% of partners of those diagnosed with a chronic condition found that the chronic condition of their loved one put a strain on their personal life, while other partners reported personal burden, changes in their social relations, and financial nuisances[9]. Caregivers were reported to develop mental distress (e.g. depression, anxiety), found to use significantly more healthcare resources (i.e. physician and emergency visits), and in the case of elderly spouses, 63% higher mortality than non-caregivers[10,11]. Hours spent caregiving correlated with a decrease in work productivity and physical activity[12].

An caregiver's burden can easily go unnoticed. In order to develop effective interventions to relieve caregiver burden, it is imperative to obtain an in-depth understanding of the physical, mental, and social consequences of caregiving. More information is needed about the causes and consequences of caregiver burden in IBD, including the effects on work productivity. The aim of this study was to investigate the burden of IBD on caregivers, their work productivity (in terms of absenteeism and presenteeism), and to identify patient characteristics associated with caregivers' outcomes.

Methods

Objectives

The primary study objective was to investigate the impact of IBD on informal caregivers and to identify predictors for caregiver burden. The secondary objective was to assess the association between caregiver burden and QoL, activity impairment and work productivity in IBD patients and caregivers.

Design and population

For this cross-sectional study, IBD patients had to be at least 18 years old and to be diagnosed with UC or CD confirmed by endoscopy or radiology evaluation. Caregivers were informal, had to be at least 18 years old and had to assist an IBD patient with managing and/or coping with their disease, for instance by assisting them with post-operative wound dressing, helping with medications, and/or accompanying patients to the clinic. All participating IBD patients and caregivers consented to participate.

All patients enrolled in the UCLA Center for Inflammatory Bowel Diseases were approached via email to participate in a survey from November 2015 until September 2016. Additionally, patients and caregivers were asked to participate in person to participate between September 2016 and November 2017 during outpatient clinic visits. Through email, patients were sent an IBD patient survey and were asked to forward the caregiver survey to their respective caregiver. In clinic, IBD patients and caregivers filled out the survey on a tablet. If they were unable to finish, they were provided with a link to finish the survey at home. REDCap (Research Electronic Data Capture) was used to host a de-identified web-based questionnaire accessible through a 128-bit SSL encrypted link[13]. Both patient and caregiver were given a unique matching subject ID to confirm that both IBD patient and caregiver completed their respective surveys and to match the survey results to each other.

Questionnaires & Definitions

Two types of surveys were administered, one for the IBD patient and one for the caregiver. The questionnaires used for the IBD patient included: 1) basic demographics, 2) the Work Productivity and Activity Impairment Questionnaire for IBD (WPAI-IBD), which measures absenteeism (the time absent from work due to IBD) and presenteeism (decreased productivity at work due to IBD)[14], 3) the short-IBD Questionnaire (sIBDQ) to measure QoL [15]; the sIBDQ score ranges from 10 (worst QoL) to 70 (best QoL), and 4) the mobile Health Index UC (mHI-UC) or CD (mHI-CD)[16], a validated questionnaire to assess disease activity remotely.

The questionnaires used for the caregiver included: 1) basic demographics, 2) the Work Productivity and Activity Impairment Questionnaire for caregivers (WPAI-CG), which measures absenteeism (the time absent from work due to caregiving) and presenteeism (decreased productivity at work due to caregiving)[14], and 3) the Zarit Burden Interview Score (ZBI), a set of 22 questions that determine a caregiver's burden, and which categorizes caregiver burden in 4 levels: 1. Little or no burden, 2. Mild to moderate burden, 3. Moderate to severe burden, 4. Severe burden[17].

Statistical analysis

Descriptive statistics were provided for the result of the questionnaires. The two-sided Fisher's exact test was used to test for associations between categorical variables, the Student's t-test was used to compare means between groups. Patients with two caregivers were analyzed twice as separate patients.

A simple logistic regression model was used to examine which IBD patient and caregiver features predict caregiver burden. Caregiver burden was defined as any caregiver burden as indicated by ZBI levels 2–4 (mild – severe burden). Caregiver's demographics (i.e. age, gender, relationship to patient, education level, annual income, duration of caregiving, etc.) and IBD patient's characteristics (i.e. demographics, IBD type, QoL, productivity, etc.) were included in the model as independent variables.

All variables with p-value $\leq .35$ in the simple logistic regression analysis were subsequently included in a multiple logistic regression model to assess their independent contribution to caregiver burden. A backward selection model was run in which non-significant variables ($p > .05$) are removed in a step-wise fashion until only significant predicators of caregiver burden ($p < .05$) remained.

Statistical analyses were performed using statistical package program R 3.4.0[18].

Ethical considerations

The study was approved by the University of California Los Angeles Institutional Review Board (UCLA IRB) protocol number 15–001304. All subjects gave their informed consent before entering the study.

Results

In November 2015, 1233 patients of the UCLA Center of Inflammatory Bowel Diseases and their respective caregiver(s) were invited to participate in the online survey, an additional reminder was sent in December 2015. In total 109 IBD patients and 38 matching caregivers responded. In order to increase the study population, from July 2016 to November 2017 we included additional patients and caregivers in the clinic of our tertiary IBD center. This led to a total cohort 194 IBD patients and 108 caregivers. We excluded 92 IBD patients because we did not have a matching caregiver and 6 caregivers were excluded because of erroneous entry (e.g. did not finish survey or incorrect entry of data); 2 patients indicated having two caregivers. This resulted in a final cohort of 102 IBD patients and 102 matching caregivers (Figure 2).

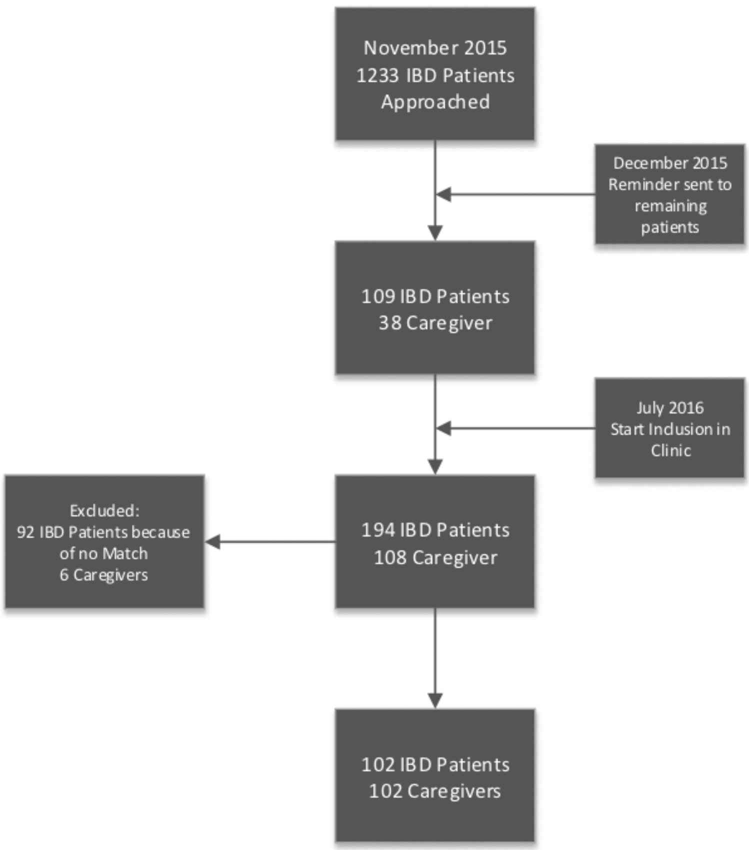

Figure 2. Flowchart of study inclusion

The 102 IBD patients who were successfully matched to a caregiver were more frequently female ($p < 0.01$), were older ($P = 0.02$), had fewer non-Hispanic whites ($p = 0.02$), fewer surgeries ($p = 0.01$), less active disease ($p < 0.01$), lower employment rates ($p < 0.01$) and less activity impairment ($p = 0.01$) than the 92 IBD patients that were not successfully matched to a caregiver (Supplementary Table 1)

Patient population

Table 1 summarizes the characteristics of the enrolled patients and their caregivers. Fifty-two percent were diagnosed with CD (n = 53) and 48% with UC (n = 49); 49% of patients had active disease as defined by the mHI-CD or mHI-UC at the time of the survey. There was no significant difference in the prevalence of disease activity between UC and CD patients (p = 0.07). The mean age was 39 years (SD 16), 70% were female (n = 71), and 60% (n = 60) were of white non-Hispanic origin. In total, 16% (n = 16) of CD patients and 6% (n = 6) of UC patients were taking biologics; 11% (n = 28) of CD patients and 15% (n = 15) of UC patients were on a combination of two or more medications; 18% (n = 18) of CD patients and 7% (n = 7) of UC patients indicated not to use any IBD-related medication.

In total 50% of IBD patients were employed, of whom 39% ($n = 20$) experienced absenteeism within the last week, with a mean of 10% of work hours missed (SD 20%); 66% experienced presenteeism with a mean decrease of 27% in productivity at work (SD 31%). The mean QoL, measured by the sIBDQ, was 45 (SD 13; Table 1).

Caregiver population

The mean age of the caregivers was 48 years, 48% were female ($n = 49$), and 59% ($n = 60$) were of white non-Hispanic origin. In total, 56% of caregivers were a spouse or partner, 24% were a parent or another family member, 14% were a child of the patient and 7% were in another category. Furthermore, we found that 75% ($n = 76$) of caregivers lived with the IBD patient, whereas 25% ($n = 26$) did not. The caregivers spent an average of 12 h (SD 25) per week on caregiving and had been caregiving for an average of 8.1 years (SD 8.5). In total 13.7% of caregivers indicated that they suffered from a chronic disease themselves (Table 1). The majority 77% ($n = 79$) had finished college or post college and 47% had an income of $100,000 or more. The employment rate in the caregiver population was 72% ($n = 73$), of whom 38% ($n = 28$) experienced absenteeism within the last week, with a mean of 9% of work hours missed (SD 17%); 57% experienced presenteeism with a mean decrease of 22% in productivity at work (SD 30%).

Caregiver burden

Using the ZBI, we found that 39% ($n = 40$) of caregivers experienced caregiver burden (either mild, moderate or severe). IBD caregivers were impacted by caregiving because they felt stressed between caring for the care recipient and trying to meet other responsibilities for family or work (41%), they experienced fear for the future of the care recipient (73%) or felt that their caregiver was dependent on them (55%). Additionally, 51% of caregivers felt that they should be doing more for their care recipient and felt they could do a better job at caregiving (Table 2). Importantly, 32% felt uncertain about what to do with their care recipient (question 19).

Predictors of caregiver burden

We explored if caregiver burden had an association with absenteeism, presenteeism and activity impairment in the IBD and caregiver population. We also looked at the association between caregiver burden and the IBD patients' and caregiver characteristics. We found that patients with lower QoL ($p = .04$), more absenteeism ($p = .03$), more presenteeism ($p < .01$) or more activity impairment ($p < .01$) were more likely to have a caregiver who experiences burden. The age of the patient and the caregiver relationship were not associated with caregiver burden. More importantly, caregivers who experienced burden had significantly more absenteeism ($p = .04$), presenteeism ($p < .01$) and activity impairment ($p < .01$) themselves than caregivers who did not experience caregiver burden (Table 3).

In the simple logistic regression models, 15 variables had a p-value of <.35 (Table 3). These variables were entered in a multiple regression model, which revealed that white non-Hispanic race ($p = .02$), the IBD patient having a history of a fistula ($p = .01$), a UC diagnosis (versus CD; $p < .01$), active disease ($p < .01$) and time spent on caregiving ($p < .01$) were independent predictors for caregiver burden (Table 4).

Table 1. The characteristics of IBD patients and Caregivers.

Variable	CD (n=53)	UC (n=49)	Caregivers (n=102)
Age, mean (SD)	37.7 (17.1)	40.9 (15)	48 (15.5)
Gender % (n)	69.8% Female (37)	69.4% Female (34)	48% Female (49)
Race % (n)			
White Non-Hispanic	67.9% (36)	71.4% (35)	58.8% (60)
White Hispanic			13.7% (14)
Other	11.3% (6)	12.2% (6)	11.8% (12)
Black/African American	5.6% (3)	8.2% (4)	3.9% (4)
Asian	5.6% (3)	0% (0)	11.7% (12)
American Indian/Alaska	7.5% (4)	8.2% (4)	0% (0)
Native	1.9% (1)	0% (0)	
Abdominal Surgery % (n)	52.8% Yes (28)	12.2% Yes (6)	N/A
Fistula % (n)	41.5% Yes (22)	16.3% Yes (8)	N/A
Medication Use % (n)			N/A
Biologics	16% (16)	6% (6)	
5ASA	2% (2)	11% (11)	
Immunomodulators	5% (5)	1% (1)	
Steroids	2% (2)	4% (4)	
Others (Antibiotic,	0% (0)	2% (2)	
Antispasmodic,	11% (11)	15% (15)	
Anti-diarrheal)	18% (18)	7% (7)	
Combo			
No IBD Related Medication			
Disease State (mHI) % (n)	58.5% Active Disease (31)	38.8% Active Disease (19)	N/A
Disease Location	26.4% (14) Small Bowel 17.0% (9) Large Bowel 37.7% (20) Both 18.9% (10) Unknown	2.0% (1) Proctitis 69.4% (34) Pancolitis 12.2% (6) Left-sided 16.3% (8) Unknown	
Disease Duration in years, mean (SD)	14.2 (9.8)	16.8 (18.6)	N/A
Quality of Life, mean (SD)	44.4 (12.2)	47.3 (13.1)	N/A
Employed % (n)	43.4% Yes (23)	59.2% Yes (29)	71.6% Yes (73)
Of those employed: **Absenteeism (Yes/No) last week % (n)** **If yes, mean absenteeism hours %**	Due to IBD 52.2% Yes (12) 15%	Due to IBD 27.6% Yes (8) 7.1%	Due to IBD caregiving 38.4% Yes (28) 9.1%
Of those employed: **Presenteeism (Likert) % (n)** **Mean Presenteeism %**	Due to IBD 78.3% Yes (18) 30.6%	Due to IBD 58.6% Yes (17) 27.3%	Due to IBD caregiving 57.5% Yes (42) 21.5%
For the entire group: **Activity Impairment (Likert) % (n)** **Mean Activity Impairment %**	Due to IBD 84.9% Yes (45) 38.9%	Due to IBD 71.4% Yes (35) 36.3%	Due to IBD caregiving 52% Yes (53) 18.7%

Table 1. Continued

Variable	CD (n=53)	UC (n=49)	Caregivers (n=102)
Relationship to Patient % (n)	N/A	N/A	55.9% Spouse or Partner (57) 23.5% Parent/Family member (24) 13.7% Child (14) 6.9% Other (7)
Environment % (n)	N/A	N/A	74.5% Living with Patient (76) 25.5% Living separately of Patient (26)
Education Level % (n)	N/A	N/A	77.5% College or Post-College Degree (79) 22.5% College-degree or less (23)
Annual Income level % (n)	N/A	N/A	47.1% $100,000 or more (48) 52.9% Less than $100,000 (54)
Mean Time Spent Caregiving (hours/week SD)	N/A	N/A	12.2 hours (25.4 hours)
Mean Duration of Caregiving (SD)	N/A	N/A	8.1 years (8.5)
Chronic Disease % (n)	N/A	N/A	13.7% Yes (14)

3

Table 2. Burden on Caregivers as measured by the ZBI.

Zarit Burden Interview Results Among Caregivers						
Question	Never	Rarely	Sometimes	Quite Frequently	Frequently	Nearly Always
1. Do you feel that your care recipient asks for more help than he/she needs?	65%	24%	10%	2%	0%	0%
2. Do you feel that because of the time you spend with your care recipient that you don't have enough time for yourself?	51%	17%	26%	3%	0%	3%
3. Do you feel stressed between caring for your care recipient and trying to meet other responsibilities for your family or work?	30%	28%	30%	6%	0%	5%
4. Do you feel embarrassed over your care recipient behavior?	73%	16%	12%	0%	0%	0%
5. Do you feel angry when you are around your care recipient?	68%	23%	9%	0%	0%	1%
6. Do you feel that your care recipient currently affects your relationships with other family members or friends in a negative way?	62%	22%	14%	2%	0%	1%
7. Are you afraid what the future holds for your care recipient?	14%	14%	40%	22%	1%	10%
8. Do you feel your care recipient is dependent on you?	15%	30%	37%	13%	1%	4%
9. Do you feel strained when you are around your care recipient?	51%	25%	23%	1%	0%	1%
10. Do you feel your health has suffered because of your involvement with your care recipient?	67%	16%	14%	4%	0%	0%
11. Do you feel that you don't have as much privacy as you would like because of your care recipient?	73%	16%	7%	3%	0%	2%
12. Do you feel that your social life has suffered because you are caring for your care recipient?	50%	24%	22%	3%	0%	2%
13. Do you feel uncomfortable about having friends over because of your care recipient?	81%	9%	9%	0%	0%	1%
14. Do you feel that your care recipient seems to expect you to take care of him/her as if you were the only one he/she could depend on?	54%	20%	16%	6%	0%	5%
15. Do you feel that you don't have enough money to take care of your care recipient in addition to the rest of your expenses?	51%	17%	24%	5%	1%	3%
16. Do you feel that you will be unable to take care of your care recipient much longer?	80%	12%	6%	2%	0%	0%
17. Do you feel you have lost control of your life since your care recipient's illness?	71%	11%	16%	3%	0%	0%

Table 2. Continued

Zarit Burden Interview Results Among Caregivers						
Question	Never	Rarely	Sometimes	Quite Frequently	Frequently	Nearly Always
18. Do you wish you could leave the care of your care recipient to someone else?	75%	14%	9%	1%	0%	1%
19. Do you feel uncertain about what to do about your care recipient?	37%	30%	25%	6%	0%	1%
20. Do you feel you should be doing more for your care recipient?	25%	25%	35%	13%	0%	3%
21. Do you feel you could do a better job in caring for your care recipient?	22%	27%	38%	11%	0%	2%
22. Overall, how burdened do you feel in caring for your care recipient?	46%	35%	11%	7%	0%	1%

Table 3. Comparison of IBD population with and without caregiver burden. Univariate logistic regression models for differences * = P<.35, #=not considered, bold = P < .05

IBD Population (n=102)	Caregiver Burden 39% (40)	No Caregiver Burden 61% (62)	p-value
Burden Type	82.5% (33) Mild to Moderate 15% (6) Moderate to Severe 2.5% (1) Severe		N/A
IBD patient characteristics			
Age mean (SD)	41.3 (16.8)	37.9 (15.6)	*P = 0.30
Gender % (n)	62.5% Female (25)	74.2% Female (46)	*P = 0.21
Race % (n)	75% White Non-Hispanic (30) 25% Other (10)	66.1% White Non-Hispanic (41) 33.9% Other (21)	*P = 0.34
Abdominal Surgery % (n)	30% (12)	35.5% (22)	P = 0.57
Fistula % (n)	35% (14)	25.8% (16)	*P = 0.32
Disease type % (n)	55% UC (22)	43.5% UC (27)	*P = 0.26
Disease State (mHI) % (n)	65% Active (26)	38.7% Active (24)	***P = 0.01**
IBD Quality of Life, mean (SD)	39.85 (12.29)	46.12 (11.68)	***P < 0.01**
Employed % (n)	50% Yes (20)	52% Yes (32)	#P = 0.24
IBD Absenteeism % (n) Mean Absenteeism % (SD)	65% Yes (13) 19% (11.9)	21.9% Yes (7) 5% (12.4)	***P < 0.01** **#P = 0.03**
IBD Presenteeism % (n) Mean Presenteeism % (SD)	85% Yes (17) 45.2% (35.6%)	56.3% Yes (18) 14.5% (19.5)	*P = 0.05 # P < 0.01
Activity Impairment % (n) Mean Activity Impairment % (SD)	87.5% Yes (35) 52.3% (31.1)	72.6% Yes (45) 28.2% (27.9)	*P = 0.08 **# P < 0.01**
Caregiver characteristics			
Caregiver age mean (SD)	47.3(14.2)	48.5(16.3)	P = 0.71
Caregiver gender % (n)	50% Female (20)	46.8% Female (29)	P = 0.75
Living together % (n)	22.5% No (9)	27.4% No (17)	P = 0.58

Caregiver relationship % (n)	52.5% Spouse/Partner (21)	58.1% Spouse/Partner (36)	P = 0.58
Caregiver education % (n)	82.5% College or Post-College (33)	74.2% College or Post-College (46)	*P= 0.33
Caregiver income % (n)	52.5% Under $100K (21)	53.2% Under $100K (33)	P = 0.94
Caregiver race % (n)	55% White Non-Hispanic (22)	61.3% White Non-Hispanic (38)	P = 0.53
Caregiver time spent hrs/week mean (SD)	20.0 (33.6)	7.4 (17.0)	*P < 0.01
Caregiver duration yrs mean (SD)	8.6 (10.3)	7.9 (7.3)	P = 0.85
Caregiver chronic disease % (n)	82.5% No (33)	88.7% No (55)	P = 0.38
Caregiver absenteeism %(n) Caregiver absenteeism mean (SD)	58.1% Yes (18) 14.1% (19.7)	23.8% Yes (10) 5.4% (13.8)	*P < 0.01 # P = 0.04
Caregiver presenteeism %(n) Caregiver presenteeism, **mean (SD)**	83.9% Yes (26) 38.1% (33.9)	37.2% Yes (16) 9.5% (20.3)	*P < 0.01 # P < 0.01
Caregiver activity impairment %(n) Caregiver activity impairment **mean (SD)**	80% Yes (32) 36.5% (30.3%)	33.9% Yes (21) 7.3% (14.3%)	*P = 0.01 # P < 0.01

3

Table 4. Multivariate stepwise regression results for caregiver burden.

Variable	Estimate	Standard Error	p-value
Race - White Non-Hispanic	1.4147	0.6037	0.02
History of Fistula - Yes	1.5534	0.6199	0.01
IBD subtype UC	1.7265	0.5946	<0.01
Active Disease - Yes	1.6349	0.554	<0.01
Caregiver Education - College or post-college	1.2586	0.6345	0.04
Time spent on Caregiving (hours)	0.5286	0.1452	<0.01

Discussion

This study reveals three important new insights for IBD patients and their caregivers: First, caregiving for IBD patient's causes significant productivity decreases that have not been reported before, with absenteeism rates as high as 38% and presenteeism as high as 58% in caregivers who experience burden. Second, we report on new predictors for caregiver burden, including a UC diagnosis (versus CD) and a history of fistulas. Finally, despite the burden, caregivers feel they should be doing more for their care recipient and feel they could do a better job at caregiving, warranting the need for more caregiver solutions.

Prior literature has shown that IBD caregivers retire early, change from full-time to part-time positions, or face work termination due to caregiving responsibilities[19]. However, an evaluation of presenteeism and absenteeism in IBD caregivers has not been performed. Our study showed that caregivers with burden have significantly more absenteeism (58%) and presenteeism (84%) than caregivers without burden (24% absenteeism and 37% presenteeism). These reductions in work productivity might be explained by the number of hours required to care for an IBD patient, which is consistent with our findings that caregivers who spend more time with their care recipient are more likely to experience burden. Our group has previously shown the dramatic economic impact of decreased productivity in the working IBD population[4]; our findings suggest there also may be hidden costs associated with IBD caregiving.

It is known that intensive caregiving can affect caregivers mentally, physically, and economically[4,12,19]. While there are many publications about caregivers for other chronic diseases, the literature on IBD caregiving is scarce[5-7,20]. A study on IBD caregivers of adult

IBD patients by Parekh et al. showed comparable findings to ours. Similar to Parekh's study, we found that active and more severe IBD disease are predictors for high caregiver burden. In contrast, their results suggest gender (female), age (younger), annual income level (less than $30,000), and a personal history of psychiatric illness also play a role in caregiver burden whereas our findings do not identify these factors as predictors. On the other hand, we found that caregivers who cared for a UC patient were more likely to experience caregiver burden than those who cared for a CD patient. It is possible that these differences are related to differences in the educational levels of the studies' participants; in Parekh's study a minority of patients had an education at the college level or above (30%)[9], compared to 78% in our population.

There are several limitations of our study. Due to an incomplete response rate our study may suffer from selection bias. The reasons for our low response rates are not clearly understood. We speculate that questionnaire fatigue played a role in both IBD patients and caregivers. Additionally, some IBD patients in clinic expressed they did not have a caregiver, or anyone aiding them that met our description. Furthermore, our results showed that the non-responder group (IBD patients that could not be matched to a caregiver) had worse disease outcomes, more employment and more activity impairment, this might have led to understated caregiver burden results. Furthermore, our study was a cross-sectional assessment and not a longitudinal one, because we assessed our outcomes at one point in time the effects of surgeries, hospitalizations, depression and anxiety on caregiver burden might be understated. Moreover, most of our participants were white non-Hispanic and were college-educated, which might affect the generalizability of our results to other populations. Lastly, due to the small sample size of this study, we were limited in exploring differences in outcomes based on stratification of our population on disease activity and medical therapy.

In summary, this study offers multiple new insights about caregiver burden to the existing IBD literature. First, caregiver absenteeism, presenteeism, and activity impairment are prevalent in IBD caregivers and these impairments are exacerbated when the IBD patient's disease is active. Our study suggests that disease activity in IBD patients and productivity in their caregivers are intertwined. Caregivers of IBD patients with active disease experience more burden, and caregivers with burden experience significantly more absenteeism, presenteeism, and activity impairment than caregivers without burden. These findings suggest that caregiver burden could have a substantial impact on the overall indirect cost associated with IBD. Second, we identified predictors for caregiver burden that had not previously been identified, including a UC diagnosis (versus CD) and a history of fistulas. Lastly, we found that caregivers feel that they should be doing more for their care recipient and feel they could do a better job at caregiving.

Shulz and Quittner have pointed out that a care recipient's poor QoL can negatively affect the caregiver's QoL as well[21]. In order to combat this, Shukla et al. recommends physicians to be proactive in screening caregivers and offer professional mental support (i.e. psychologists), educational materials, and problem-focused advice[8]. This need is confirmed by our results which show that IBD caregivers felt stressed between caring for the care recipient and trying to meet other responsibilities for family or work (41%) and they experienced fear for the future of the care recipient (73%).

Examples of interventions found in the literature that can positively empower patients and their caregivers are web-based and in-person support groups, being around those who are alike seems to help patients and caregivers[22,23]. Furthermore, behavioral interventions using web-based and mobile apps, have the power to provide accessibility to patients for better maintenance of their IBD, as well as motivation to engage in positive behavior[24], this could potentially apply to their caregivers as well.

Conclusions

By giving IBD patients the necessary tools to become an active stakeholder and providing caregivers with the necessary education and social support, a cooperative role in disease management may be able to reduce caregiver burden and increase caregiver empowerment. These efforts might relieve the detrimental effects on caregiver work productivity and could combat the uncertainty caregivers currently experience with regards to their care recipient. More intervention studies implementing solutions in caregivers for IBD patients could give the much-needed answers to a frequently overseen problem in IBD caregivers.

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Supplementary

Supplementary Table 1. Patient feature t-test (continuous) and chi-squared(binary) comparisons between patients with and without caregiver information

Variable	92 IBD Non-Responder group (No matching caregiver) Mean/Prop	102 IBD Responder group (matching caregiver) Mean/Prop.	p-value
Patient Age	36.372	41.209	P=0.02
Patient Gender Female	0.435	0.696	P<0.01
Patient Race Other	0.337	0.176	P=0.02
Surgery	0.739	0.539	P<0.01
Fistula	0.783	0.667	P=0.10
Activity Impairment	0.869	0.539	P<0.01
Active Disease	0.543	0.216	P<0.01
Employed	0.815	0.510	P<0.01

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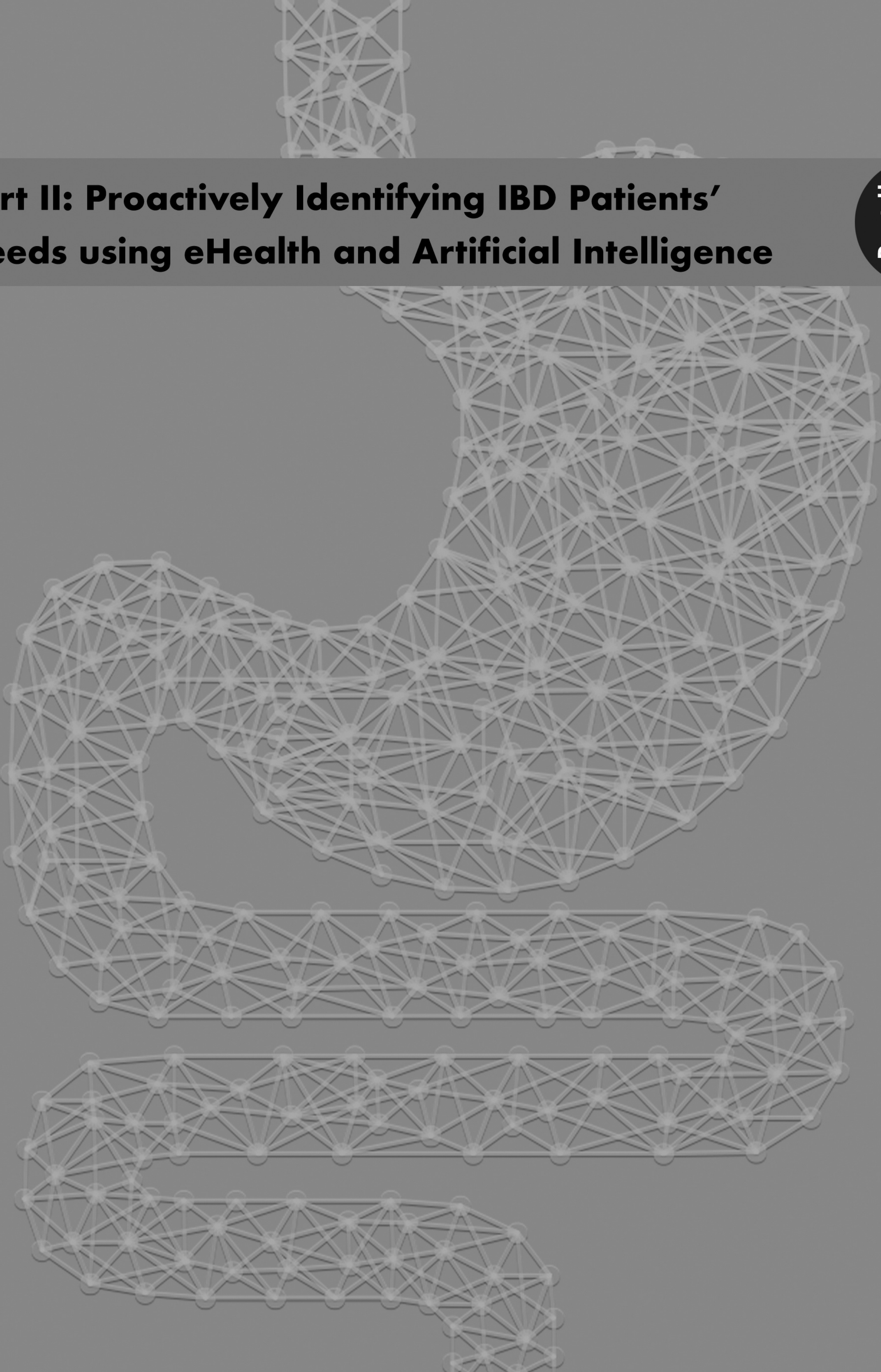
Part II: Proactively Identifying IBD Patients' Needs using eHealth and Artificial Intelligence



CHAPTER 4

The Development of a Screening Tool to Identify and Classify Non-adherence in Inflammatory Bowel Disease

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Abstract

Background

Medication non-adherence is a challenge in chronic disease management. Tools that can both determine adherence levels and analyze patient-specific reasons for non-adherence are lacking.

Methods

Our tool was developed using 23 patient-reported items and its predictive performance was compared to the most widely used instrument in the literature.

Results

133 IBD patients were included, 44 (33%) were nonadherent and 89 (67%) were adherent. Our screening question, with 87% sensitivity and 64% specificity was followed by a 9-item survey for patients qualified as nonadherent.

Conclusions

Quantifying reasons for non-adherence can lead to more effective and personalized interventions for nonadherent patients.

Introduction

Medication non-adherence remains a major challenge in chronic disease management. In the US, about 117 million adults have at least one chronic disease[1] and 50% do not take their medications as prescribed[2]. For inflammatory bowel diseases (IBD), one study showed a non-adherence rate of 33%, of which 34% experienced at least one relapse after stopping treatment[3]. Although the rate of non-adherence in IBD varies in many studies[4], the vast majority of literature reports non-adherence in the range of 30-45%[5].

Medication non-adherence is also associated with increased costs of healthcare utilization and negative health outcomes. It is estimated that non-adherence causes between one-third and two-thirds of all medication-related hospitalizations[6] and at least 10% of all hospitalizations in the US[7]. The resultant indirect and direct healthcare costs of non-adherence in chronic diseases are estimated to be between $100 billion and $300 billion annually in the US,[8] contributing between 10% and 30% of the overall estimated wasteful healthcare spending per year ($910 billion)[9]. Medication non-adherence has further been shown to be significantly correlated with increased disability in IBD patients[10].

Various solutions addressing non-adherence have been identified. Electronic-health (eHealth) technologies including web-based interventions for IBD management and mobile applications can improve short-term adherence[11]. Similarly, programs such as the TELE-IBD trial has suggested the promising potential and feasibility of telemedicine for improving health outcomes and disease monitoring[12,13]. Patients receiving daily short message service reminders to take medications have shown a significantly reduced rate of missed doses compared to those with no message reminders[14]. Motivational interviewing interventions have also been shown to improve adherence in chronic disease patients within a 6-month follow-up period[15].

To successfully improve adherence, however, the reasons behind a patient's non-adherence must first be identified so the most effective solution can be applied. The literature describes two main categories of reasons for non-adherence: intentional/intrinsic and unintentional/extrinsic factors, differentiated by their underlying cognitive processes[16–19]. Intrinsic non-adherence can arise due to a fear of side effects[20], lack of patient involvement in the treatment decision-making process[21], and a lack of understanding medication[22]. The extrinsic category can be divided into subcategories including poor health literacy[23], forgetfulness[24], inadequate funds[6], and disruptions in daily routine[25], In IBD the most

4

frequent intrinsic reason for non-adherence occurs when patients stop treatment after their symptoms resolve (42.7%), which indicates a lack of understanding of treatment regimens[3]. Meanwhile, the most frequent extrinsic reason for non-adherence in IBD is forgetfulness (5.2%)[3]. These non-adherence factors are especially crucial to address in IBD due to the complicated nature and lifelong management of the disease. IBD patients have noted complex treatment regimens, dose amount, and dose frequency as factors affecting their adherence[26]. The form of medication administration (oral or infusion) may also be burdensome to IBD patients and affect adherence levels[27]. With many factors to consider, monitoring of adherence is critical.

Several self-report assessment tools are used to measure adherence (i.e., 8-Item Morisky Medication Adherence Scale (MMAS-8)[28–31], Self-Efficacy for Appropriate Medication Use Scale (SEAMS)[25], the Medication Adherence Rating Scale (MARS[32]). However, these scales do not assess the intrinsic and extrinsic reasons behind non-adherence, such as patient access to resources or problems in the patient-physician relationship. In addition, many of these questionnaires are lengthy, which limits their use in clinical settings due to respondent fatigue[33]. Therefore, we aimed to develop a brief screening tool to identify non-adherence levels and reasons for non-adherence in IBD.

Materials and Methods

Study Design & Questionnaire Development

We performed a cross-sectional study to develop a screening tool that accurately screens for medication adherence in IBD patients and assesses the reasons for non-adherence to help guide medical providers in their management. Our tool was developed using patient self-reported measures and its predictive performance was compared to the widely used MMAS-8[28–30,34].

Eligible IBD patients filled out questionnaires assessing factors of non-adherence commonly identified in literature on medication adherence in IBD (Table, Supplementary Data Content 1)[3,5]. We compiled 25 questions drawn from previously validated adherence questionnaires (SEAMS[25], MARS[32]) and based on literature review of common non-adherence factors, including recommended questions from the World Health Organization[6] and questions assessing patient-physician interactions[35,36].

In total, 2 open-ended questions related to the types of medication used and 23 closed-ended questions related to adherence (Table, Supplementary Data Content 1) were included. The questions were categorized as either 1) intrinsic: measuring lack of understanding of disease/medication, lack of involvement in the treatment decision-making process, and fear of side effects; 2) extrinsic: measuring dose frequency, inadequate health literacy, forgetfulness, poor patient-physician communication, lack of funds, disruption in daily routine; or 3) general questions: neither intrinsic nor extrinsic factors.

In addition, we asked each patient the 8 questions included in the MMAS-8 (Table 1), a copyrighted tool for which a license was obtained and which served as our gold standard comparison. A total of 33 questions were therefore administered to participants. The online Morisky Widget[28–31] was used to score our results of the MMAS-8 as either adherent (score ≥6) or nonadherent (score <6).

Population & Data Collection

IBD patients 18 years and older were recruited via email or during clinic visits to the University of California, Los Angeles (UCLA) Center for IBD between June 2017 and November 2017. Patients with an underlying diagnosis of bipolar affective disorder, schizophrenia, substance abuse/dependence, pregnancy, terminal illness, and psychosis according to chart review were excluded. Chart review was performed to confirm the patients' IBD diagnosis and to collect patient characteristics such as race, ethnicity, marital status, smoking history, insurance type, comorbidities and to collect a list of current medications. For medications, we excluded medications that patients only used as needed or that were available over the counter (even if prescribed).

Software

Study data were collected on encrypted iPads using the Research and Electronic Data Capture (REDCap) tools hosted at UCLA[37]. Excel 2010 and RStudio V3.4.3 were used for statistical analysis.

Statistical Objectives and Analysis

Our primary goal was to find a subset of the 23 adherence questions that most accurately predict medication adherence in IBD patients. Our secondary goal was to develop a supplementary questionnaire that determines why nonadherent patients do not take their medication based on the 10 extrinsic or intrinsic reasons described in the literature. Furthermore, we conducted a post-hoc analysis to determine if patient characteristics were associated with non-adherence using the MMAS-8 outcomes. We tested if adherence is associated with patients' age, gender, race, Hispanic ethnicity, marital status, smoking status, insurance type, IBD subtype, number of medical conditions requiring a prescription medication, the number of prescription medications, and whether the patient was prescribed a self-injection (such as Adalimumab) or infusion medication (Infliximab). Table 1 shows the complete list of patient characteristics assessed.

Normal distribution of data was tested using a Normal-QQ-Plot. Fisher's exact test (two-sided) or the $\chi 2$ tests were used to explore differences of categorical data in adherent and nonadherent groups and the T-test was used to explore associations of parametric numerical data. A p-value <0.05 was considered statistically significant.

Model Building

Initially a simple logistic regression of each question was performed to understand their individual performance in predicting adherence as defined by the MMAS-8. Questions with a p-value <0.3 were selected for inclusion in a multiple logistic regression model with stepwise selection. The stepwise regression model adds questions if its benefit to the model does not overcome the penalty of having an extra question as defined by the Akaike information criterion[38]. Questions with low occurrence to one or more of the possible responses were omitted (<10 patients selecting one of the responses) due to the low predictive power and the potential to cloud the effects of the other questions in the model. We fit the multiple logistic model with the selected questions and obtained the coefficients. From the model coefficients we developed scores by dividing each by the smallest coefficient and rounding to obtain integer-value scores. The performance of the score was measured by the specificity, and sensitivity. The cutoff for every question was obtained from the model coefficients.

To get a complete overview of potential reasons for non-adherence in patients shown to be nonadherent, questions were added for all intrinsic and extrinsic categories that were not included in the questions selected by the stepwise regression model. These questions only need to be completed by those patients shown to be nonadherent in the prediction model. From each category the question with the highest predictive power based on the simple logistic regression model was included.

Ethical Considerations

All patients gave consent to participate in this study. This study was approved by the institutional review board at UCLA, under protocol number IRB#17-000602.

Table 1. Morisky Medication Adherence Scale-8 (MMAS-8) Items
The following 8 items were used as the gold standard comparison.

	Question
1	Do you sometimes forget to take your pills? - Yes - No
2	Over the past 2 weeks, were there any days when you did not take your medicine? - Yes - No
3	Have you ever cut back or stopped taking your medication without telling your doctor because you felt worse when you took it? - Yes - No
4	When you travel or leave home, do you sometimes forget to bring along your medications? - Yes - No
5	Did you take your medications yesterday? - Yes - No
6	When you feel like your symptoms are under control, do you sometimes stop taking your medicine? - Yes - No
7	Taking medication everyday is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan? - Yes - No
8	How often do you have difficulty remembering to take all your medications? - All the time - Usually - Sometimes - Once in a while - Never/rarely

Ref: Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive Validity of a Medication Adherence in an Outpatient Setting. **J Clin Hypertens**. 2008;10(5):348-354.

Results

Patient Characteristics

We included 133 (63 UC and 67 CD, 3 indeterminate colitis) patients in this study (Figure 1). Our study population was primarily Caucasian, non-Hispanic, non-smoking and privately insured (Table 2). Fewer than 10% of patients had other significant comorbidities. Nearly 40% of patients were taking an IBD medication delivered by infusion, and about half as many were taking an IBD medication requiring self-injection. On average, patients were taking 2-3 prescription medications at the time of our survey according to chart review.

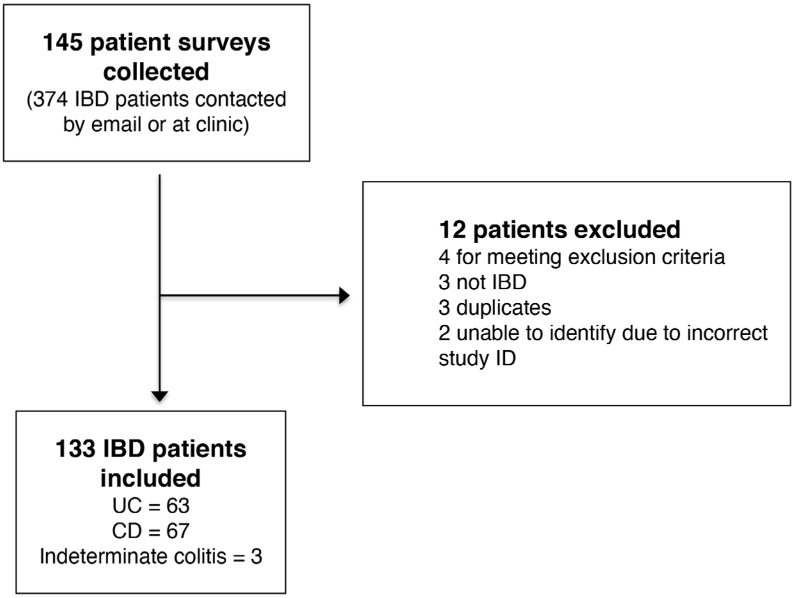

Figure 1. Patient flowchart for inclusion/exclusion.
Out of 145 total respondents, 133 met inclusion criteria and were included in the analysis.

Adherence Levels

Of the 133 patients, 44 (33%) were nonadherent (MMAS-8 score <6) and 89 (67%) were adherent (MMAS-8 score ≥6). There was no significant difference in patient demographics between these two groups (Table 2). Frequent reasons for non-adherence were: not being as careful about taking medications (29%; Question 1) and missing taking medication (41.4%; Question 13) (Table 3). In relation to patient-physician communication, a majority of patients indicated that their physician offers them choices in medical care (84%; Question 3), discusses the pros and cons of these choices with them (89%; Question 4), and considers their preferences when making treatment decisions (90%; Question 6) (Table 3).

Analysis, Interpretation and Final Questionnaire

Figure 2 outlines our questionnaire development. Out of 23 questions (excluding the 2 open-ended items), 10 provided little to no predictive power due to the low occurrence to

Table 2. Patient demographics of adherent vs nonadherent population (n=133).

Variable	89 (67%) Adherent	44 (33%) Nonadherent	p-value
Female gender	41 (46%)	21 (48%)	1.0
Age (mean)	42.4	40.1	0.41
Disease Type	CD 42 (47%) UC 45 (51%) Indeterminate colitis 2 (2%)	CD 25 (57%) UC 18 (41%) Indeterminate colitis 1 (2%)	0.57
Race			0.75
Caucasian	66 (74%)	30 (68%)	
Asian	2 (2%)	2 (5%)	
Black	2 (2%)	2 (5%)	
Other or not declared	19 (21%)	10 (23%)	
Hispanic Ethnicity	4 (4%)	1 (2%)	0.88
Education			
Less than high school	0 (0%)	0 (0%)	
Some high school	2 (2%)	0 (0%)	
High school graduate	6 (7%)	4 (9%)	
Some College	14 (16%)	11 (25%)	
College Graduate	33 (37%)	20 (45%)	
Post-College Degree	33 (37%)	9 (21%)	
Other	1	0 (0%)	
Married	39 (44%)	19 (43%)	1.0
Current Smoker	5 (6%)	2 (5%)	1.0
Insurance			0.36
Private HMO, PPO	68 (76%)	29 (66%)	
Medicaid	5 (6%)	5 (11%)	
Medicare	11 (12%)	4 (9%)	
Self	2 (2%)	2 (5%)	
Other or unknown	3 (3%)	4 (9%)	
Comorbidities			0.57
Diabetes mellitus	3 (3%)	2 (5%)	
Chronic Kidney Disease	2 (2%)	0 (0%)	
COPD or asthma	4 (4%)	3 (7%)	
Organ transplant	1 (1%)	1 (1%)	
Congestive Heart Failure	0 (0%)	0 (0%)	
HIV/AIDS	0 (0%)	1 (1%)	
Receiving Medication by Infusion (i.e., Infliximab, Vedolizumab)	34 (38%)	15 (34%)	0.79
Receiving Medication by Self-Injection (i.e., Adalimumab, Ustekinumab)	20 (22%)	7 (16%)	0.51

one or more of the possible answers and were thus omitted. Out of the remaining 13 questions our univariate model found questions 1, 3, 4, 5, 7, 15, 17, and 18 to have a p-value <0.3 (Table 3). After running our multiple logistic regression model with stepwise selection, question 1 and 17 remained significant (p-value <.05). The associated sensitivity and

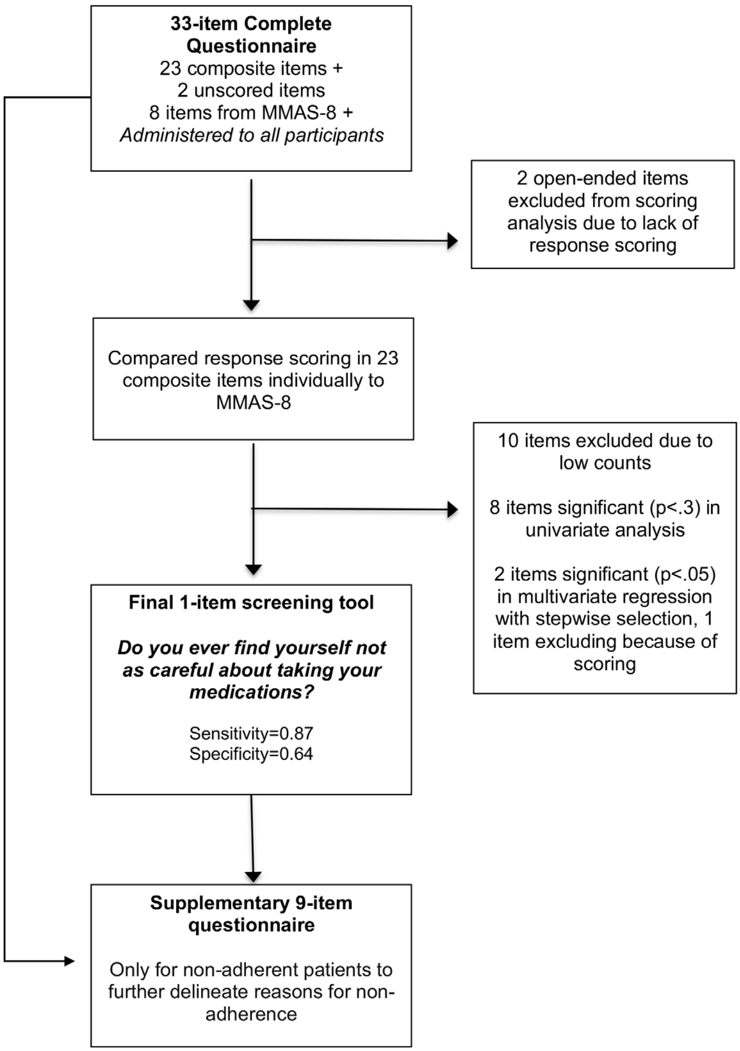

Figure 2. Flowchart of questionnaire development.
The initial 33-item questionnaire assessed extrinsic and intrinsic factors of nonadherence. Simple logistic regression analysis and multiple logistic regression with stepwise selection ultimately yielded a 1-item screening tool complemented by a 9-item scale

specificity of this model were 87% and 64%, respectively. However, the optimal cut off to classify a patient as adherent was 1.5 points, while the scoring assigned 2 points for question 1 alone and 1 point for question 17. In practical terms this meant that question 1 was all decisive on whether patient is adherent or not and question 17 effectively had no impact on the outcome. Looking at the questions separately, question 1 alone had a better sensitivity and specificity ratio to predict adherence (87% sensitivity; 64% specificity) than question 17 alone (90% sensitivity; 23% specificity). Therefore, we opted to use question 1 alone as a screening question to assess adherence.

Thus, our final screening survey included only question 1 ("*Do you ever find yourself not as careful about taking your medications?*").

Reasons for Non-adherence

Question 1 represents 1 category: general adherence. We assembled an additional 9-item survey to be administered to patients determined as "nonadherent" based on this question. The questions with the highest predictive power within each of the 9 remaining categories of non-adherence reasons (side effects, poor patient-physician communication, frequency of medication regimen, lack of understanding of disease/medication, forgetfulness, lack of involvement in the treatment decision-making process, inadequate health literacy, lack of funds and disruptions in daily routine) were included in the additional survey (Table 4).

Table 3. Outcomes of Patients (n=133)

	Question	Total n (%)	Ln (OR) (95% CI) for underlined answers	p-value
1	Do you ever find yourself not as careful about taking your medications?		2.49 (1.64-3.34)	* & ** p<.01
*	- Yes	39 (29.3%)		
**	- No	94 (70.7%)		
2	Do you understand how to take your medications?		0	N/A
++	- Yes	132 (99.2%)		
	- No	1 (0.8%)		
3	Does your physician offer choices in medical care?		0.74 (-0.17-1.64)	
*	- Yes	112 (84.2%)		p=.11
	- No	21 (15.8%)		
4 *	Does your physician discuss pros and cons of each choice with you?		0.94 (-0.09-1.96)	
	- Yes	118 (88.7%)		p=.07
	- No	15 (11.3%)		
5	Does your physician get you to state which choice or option you prefer?			
*	- Yes	113 (85%)	0.74 (-0.17-1.64)	p=.11
	- No	20 (15%)		
6	Does your physician take your preferences into account when making treatment decisions?			
	- Yes	120 (90.2%)	0.6 (-0.55-1.75)	p=.30
	- No	13 (9.8%)		
7 *	How confident are you that you can take your medicines correctly when they cause some side effects?			p=.25
	- Not confident	15 (11.3%)		
	- Somewhat confident	28 (21.1%)		
	- Very confident	90 (67.7%)	0.1 (0.97-1.43)	
8	Have you noticed any adverse effects from your medications?			
	- Yes	51 (38.3%)	0.18 (-0.54-0.9)	p=.62
	- No	82 (61.7%)		
9 ++	How confident are you that you can take your medicines correctly when you take medicines more than once a day?			
	- Not confident	10 (7.5%)		
	- Somewhat confident	28 (21.1%)	0.47 (1.48-1.92)	N/A
	- Very confident	95 (71.4%)		

Table 3. Continued

	Question	Total n (%)	Ln (OR) (95% CI) for underlined answers	p-value
10	How confident are you that you can take your medicines correctly when you are not sure how to take the medicine?			
	- Not confident	18 (13.5%)		
	- Somewhat confident	52 (39.1%)	-0.36 (0.46-1.01)	p=.34
	- Very confident	63 (47.4%)		
11	How confident are you that you can take your medicines correctly when you get a refill of your old medicines and some of the pills look different than usual?			
	- Not confident	13 (9.8%)		
	- Somewhat confident	33 (24.8%)	-0.21 (0.54-1.02)	p=0.8
	- Very confident	87 (65.4%)		
12	How confident are you filling out medical forms by yourself?			
++	- Not confident	3 (2.3%)		
	- Somewhat confident	24 (18%)	-0.8 (-0.36-0.1)	N/A
	- Very confident	106 (79.7%)		
13	I know it must be difficult to take all your medications regularly. How often do you miss taking them?			
++	- All the time	0 (0%)		
	- Usually	0 (0%)		
	- Sometimes	11 (8.3%)	0.97 (3.49-3.93)	N/A
	- Once in a while	44 (33.1%)		
	- Never/rarely	78 (58.6%)		
14	How often do you not take medication X? (address each medication individually)			
++	- All the time	21 (15.8%)		
	- Usually	1 (0.8%)		
	- Sometimes	10 (7.5%)	0.33 (2.2-2.68)	N/A
	- Once in a while	32 (24.1%)		
	- Never/rarely	69 (51.9%)		
15 *	Does your physician tell you everything?		0.54 (-0.46-1.55)	p=.28
	- Yes	116 (87.2%)		
	- No	17 (12.8%)		
16	Does your physician let you know test results when promised?			N/A
++	- Yes	128 (96.2%)	0.3 (-1.53-2.12)	
	- No	5 (3.8%)		

Table 3. Continued

	Question	Total n (%)	Ln (OR) (95% CI) for underlined answers	p-value
17	Does your physician explain treatment alternatives?			
*	- Yes	114 (85.7%)	1.06 (0.1-2.02)	* & ** p=.03
**	- No	19 (14.3%)		
18	Does your physician explain side effects of medications?			
*	- Yes	111 (83.5%)	0.76 (-0.12-1.64)	p=.09
	- No	22 (16.5%)		
19	Does your physician tell you what to expect from your disease or treatment?			
++	- Yes	125 (94%)	2.09 (0.47-3.7)	N/A
	- No	8 (6.2%)		
20	Do you ever delay a refill or skip a dose of your medication for financial reasons?			
	- Yes	16 (12%)	0 (-1.05-1.05)	N/A
	- No	117 (88%)		
21	Do you plan on rationing or sharing your medication for financial reasons?			
++	- Yes	6 (4.5%)	0.73 (-0.91-2.37)	N/A
	- No	127 (95.5%)		
22	How confident are you that you can take your medicines correctly when you are away from home?			
++	- Not confident	5 (3.8%)	1.14 (2.18-2.6)	N/A
	- Somewhat confident	23 (17.3%)		
	- Very confident	105 (78.9%)		
23	How confident are you that you can take your medicines correctly when your normal routine gets messed up?			
++	- Not confident	5 (3.8%)	0.6 (2.07-2.52)	N/A
	- Somewhat confident	41 (30.8%)		
	- Very confident	87 (65.4%)		

Table 4. Additional Targeted Questions for Nonadherent Patients
These questions are intended to assist providers in identifying specific, individualized reasons for nonadherence.

Question	Response Score	Type	Specific Factor
2. Do you understand how to take your medications?[2]	Yes No	General	Lack of understanding of disease/medication
3. Does your physician offer choices in medical care?[2]	Yes No	Intrinsic	Lack of involvement in the treatment decision-making process
7. How confident are you that you can take your medicines correctly when they cause some side effects?[1]	Very Confident: Somewhat Confident Not Confident	Intrinsic	Side Effects
9. How confident are you that you can take the medication correctly when you need to take it more than once a day?[1]	Not confident Somewhat confident Very confident	Extrinsic	Frequency of medication regimen
13. I know it must be difficult to take all your medications regularly. How often do you miss taking them?[3]	Yes No	Extrinsic	Forgetfulness
17. Does your physician explain treatment alternatives?[2]	Yes No	Extrinsic	Poor Patient-Physician Communication
20. Do you ever delay a refill or skip a dose of your medication for financial reasons?[3]	Yes No	Extrinsic	Lack of funds
22. How confident are you that you can take your medicines correctly when you are away from home?[1]	Not confident Somewhat confident Very confident	Extrinsic	Disruptions in daily routine
* How confident are you that you understand how to take all your medications correctly?[1,4]	Not confident Somewhat confident Very confident	Extrinsic	Inadequate health literacy

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4

Discussion

To address the significant impact of non-adherence in IBD, we assessed what questions can most accurately assess medication adherence and developed a 1-item screening tool based on a patient-reported outcome measurement (PRO) that is easy to administer. Our final predictive question identifies non-adherence with a sensitivity of 87% and a specificity of 64% and our supplementary survey assesses the leading extrinsic and intrinsic factors in the nonadherent population. The 1-item screening tool together with the 9-item survey can be used for managing adherence in IBD patients. Where a lot of studies have addressed non-adherence, few have adequately specified the reasons for non-adherence in IBD necessary for proper management.

Our study found that non-adherence was present in 33% of IBD patients, which is consistent with prior findings indicating non-adherence ranging from 30-45%[5]. However, while prior studies suggested a lack of understanding and poor patient-physician relationships, we were not able to confirm this. In our sample, most patients reported they had a good understanding of their disease or medication. This suggests that a lack of understanding was not a large contributor to non-adherence in our sample population, despite it being the most frequent intrinsic contributor to non-adherence in IBD overall[3]. This discrepancy could be explained by the fact that our sample is primarily white and highly educated (Table 2), or the strength of the patient-physician relationship in our study. In fact, patients who reported being involved in the decision-making process and who reported good patient-physician communication had higher odds of being adherent. This is consistent with previous work in which it was shown that when a physician is a strong communicator, the odds of a patient being adherent is 2.16 times better[24]. Physician communication is crucial to adherence because it enables more effective transmission of important clinical information, allows for discussion of barriers to adherence, and encourages patient involvement in the decision-making process[24].

Importantly, the accuracy of the 1-item screening tool we found is comparable to currently existing scales. A study validating the MMAS-8 in an outpatient setting of primarily low-income hypertensive patients estimated a sensitivity of 93% and specificity of 53%[34]. The MMAS-4 was shown to have a sensitivity and specificity of 81% and 44%, respectively[39]. A review of medication adherence measures discussed the pros and cons of several scales[40]. For example, the 10-item MARS examines behavior and attitude towards medication-taking, but is limited to use in patients with psychiatric illness[40]. The 13-item SEAMS demonstrates good reliability in both low and high literacy populations and is useful for chronic disease management, but difficult to administer due to its length[40].

A limitation of this study is the potential for recall bias. When completing the survey, patients were expected to recall when they had last taken their medications and if certain measures of non-adherence (i.e., forgetting to take pills, whether or not their physician had given them treatment alternatives) had occurred. In addition, as patients were recruited from a tertiary IBD referral center, our sample is likely homogenous, potentially limiting the generalizability of our study to other IBD patient populations. Lastly, our model was not validated in an independent sample, so the results presented are from the development of the screening tool.

Although the 1-item screening tool has not yet been tested in an independent sample, we found a relatively high sensitivity and specificity for our final 1-item model of 87% and 64%, respectively. With only 1 question, our tool is short and simple to administer, making it useful for clinical and remote monitoring. This is particularly important as studies have repeatedly shown the negative associations between response rates and questionnaire length[41,42]. The benefits of a 1-item screening tool[43] to screen for non-adherence can help minimize respondent fatigue and open the conversation for providers to follow-up with patients on specific reasons for non-adherence, distinguishing it from previous adherence tools. Use of the 1-item screening tool complemented with the 9-item survey allows practitioners the opportunity to further inquire about all the major categories of factors causing non-adherence and trigger potential solutions—all of which are important for creating patient-tailored interventions[19].

Our study was designed to provide an optimal screening method that monitors non-adherence both inside and outside the clinical setting. Integration of our tool into mobile technologies, for example, could have promising implications for IBD monitoring and management, as users may take the survey on the accessible platform of their mobile phone at a convenient time and show their results to providers to inform future interventions.

Conclusion

We developed a novel screening tool for management of medication non-adherence in IBD. To our knowledge, our adherence tool is the first that enables healthcare providers to screen for non-adherence in IBD and further identify the specific reasons for non-adherence so they may offer more tailored solutions. The use of this survey could allow for continuous monitoring of medication adherence. With IBD being a prototypic chronic disease, this tool can potentially be adapted for monitoring adherence in other chronic disease populations. Future studies should validate it in an independent and more heterogenous population and assess the effect of remote monitoring of adherence on medication adherence levels, patient satisfaction, and health care costs.

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Supplementary Table

Supplementary Data Content 1. Adherence Data Model Complete Questionnaire (25 questions)

Type of Nonadherence	Factors	Questions
General Adherence Questions		0. When was the last time you took medication X? Include the most recent dates for each medication that you have taken. (Answer format: medication name, date taken)
		0. Of all the medications prescribed to you, which ones are you taking? List all.
		1. Do you ever find yourself not as careful about taking your medications?
I. Intrinsic (Intentional)	I.1: Lack of Understanding of Disease/Medication	2. Do you understand how to take your medications?
	I.2: Lack of Involvement in the Treatment Decision–making Process	3. Does your physician offer choices in medical care?
		4. Does your physician discuss pros and cons of each choice with you?
		5. Does your physician get you to state which choice or option you prefer?
		6. Does your physician take your preferences into account when making treatment decisions?
	I.3: Side Effects	7. How confident are you that you can take your medicines correctly when they cause some side effects?
		8. Have you noticed any adverse effects from your medications?
II. Extrinsic (Unintentional)	II.1: Frequency	9. How confident are you that you can take your medicines correctly when you take medicines more than once a day?
	II.2: Inadequate Health Literacy	10. How confident are you that you can take your medicines correctly when you are not sure how to take the medicine?
		11. How confident are you that you can take your medicines correctly when you get a refill of your old medicines and some of the pills look different than usual?
		12. How confident are you filling out medical forms by yourself?
	11.3 Forgetfulness	13. I know it must be difficult to take all your medications regularly. How often do you miss taking them?
		14. How often do you not take Medication X?
	II.4: Poor Patient-physician Communication	15. Does your physician tell you everything?

Scoring (1 = good, 0 = bad)	Source
N/A	Medication Adherence: WHO Cares? Mayo Clinic Proceedings.[1]
N/A	Medication Adherence: WHO Cares? Mayo Clinic Proceedings.
yes = 0, no = 1	Medication Adherence Clinical Reference - American College of Preventive Medicine (Web. 20 July 2016.)[2]
yes = 1, no = 0	The Relative Importance of Physician Communication, Participatory Decision Making, and Patient Understanding in Diabetes Self-Management[3]
yes = 1, no = 0	The Relative Importance of Physician Communication, Participatory Decision Making, and Patient Understanding in Diabetes Self-Management
yes = 1, no = 0	The Relative Importance of Physician Communication, Participatory Decision Making, and Patient Understanding in Diabetes Self-Management
yes = 1, no = 0	The Relative Importance of Physician Communication, Participatory Decision Making, and Patient Understanding in Diabetes Self-Management
yes = 1, no = 0	The Relative Importance of Physician Communication, Participatory Decision Making, and Patient Understanding in Diabetes Self-Management
A: not confident/somewhat confident/ very confident	Development and Psychometric Evaluation of the Self-Efficacy for Appropriate Medication Use Scale (SEAMS) in Low-Literacy Patients With Chronic Disease[4]
yes = 0, no = 1	Medication Adherence: WHO Cares? Mayo Clinic Proceedings.
not confident = 0, somewhat confident = 0.5, very confident = 1	Development and Psychometric Evaluation of the Self-Efficacy for Appropriate Medication Use Scale (SEAMS) in Low-Literacy Patients With Chronic Disease
not confident = 0, somewhat confident = 0.5, very confident = 1	Development and Psychometric Evaluation of the Self-Efficacy for Appropriate Medication Use Scale (SEAMS) in Low-Literacy Patients With Chronic Disease
not confident = 0, somewhat confident = 0.5, very confident = 1	Development and Psychometric Evaluation of the Self-Efficacy for Appropriate Medication Use Scale (SEAMS) in Low-Literacy Patients With Chronic Disease
not confident = 0, somewhat confident = 0.5, very confident = 1	BRIEF REPORT: Screening Items to Identify Patients with Limited Health Literacy Skills[5]
all the time = 0, usually = 0.25, sometimes = 0.5, once in a while = 0.75, never/rarely = 1	Medication Adherence: WHO Cares? Mayo Clinic Proceedings.
all the time = 0, usually = 0.25, sometimes = 0.5, once in a while = 0.75, never/rarely = 1	Medication Adherence: WHO Cares? Mayo Clinic Proceedings.
yes = 1, no = 0	The Relative Importance of Physician Communication, Participatory Decision Making, and Patient Understanding in Diabetes Self-Management

Supplementary Data Content 1. Continued

Type of Nonadherence	Factors	Questions
		16. Does your physician let you know test results when promised?
		17. Does your physician explain treatment alternatives?
		18. Does your physician explain side effects of medications?
		19. Does your physician tell you what to expect from your disease or treatment?
	II.5: Lack of Funds	20. Do you ever delay a refill or skip a dose of your medication for financial reasons?
		21. Do you plan on rationing or sharing your medication for financial reasons?
	II.6: Disruptions in Daily Routine	22. How confident are you that you can take your medicines correctly when you are away from home?
		23. How confident are you that you can take your medicines correctly when your normal routine gets messed up?

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Scoring (1 = good, 0 = bad)	Source
yes = 1, no = 0	The Relative Importance of Physician Communication, Participatory Decision Making, and Patient Understanding in Diabetes Self-Management
yes = 1, no = 0	The Relative Importance of Physician Communication, Participatory Decision Making, and Patient Understanding in Diabetes Self-Management
yes = 1, no = 0	The Relative Importance of Physician Communication, Participatory Decision Making, and Patient Understanding in Diabetes Self-Management
yes = 1, no = 0	The Relative Importance of Physician Communication, Participatory Decision Making, and Patient Understanding in Diabetes Self-Management
yes = 0, no = 1	Medication Adherence: WHO Cares? Mayo Clinic Proceedings.
yes = 0, no = 1	Medication Adherence: WHO Cares? Mayo Clinic Proceedings
not confident = 0, somewhat confident = 0.5, very confident = 1	Development and Psychometric Evaluation of the Self-Efficacy for Appropriate Medication Use Scale (SEAMS) in Low-Literacy Patients With Chronic Disease
not confident = 0, somewhat confident = 0.5, very confident = 1	Development and Psychometric Evaluation of the Self-Efficacy for Appropriate Medication Use Scale (SEAMS) in Low-Literacy Patients With Chronic Disease

4

CHAPTER 5

An Exploration Into the Use of a Chatbot for Patients With Inflammatory Bowel Diseases: Retrospective Cohort Study

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Abstract

Background
The emergence of chatbots in health care is fast approaching. Data on the feasibility of chatbots for chronic disease management are scarce.

Objective
This study aimed to explore the feasibility of utilizing natural language processing (NLP) for the categorization of electronic dialog data of patients with inflammatory bowel diseases (IBD) for use in the development of a chatbot.

Methods
Electronic dialog data collected between 2013 and 2018 from a care management platform (*UCLA eIBD*) at a tertiary referral center for IBD at the University of California, Los Angeles, were used. Part of the data was manually reviewed, and an algorithm for categorization was created. The algorithm categorized all relevant dialogs into a set number of categories using NLP. In addition, 3 independent physicians evaluated the appropriateness of the categorization.

Results
A total of 16,453 lines of dialog were collected and analyzed. We categorized 8324 messages from 424 patients into seven categories. As there was an overlap in these categories, their frequencies were measured independently as symptoms (2033/6193, 32.83%), medications (2397/6193, 38.70%), appointments (1518/6193, 24.51%), laboratory investigations (2106/6193, 34.01%), finance or insurance (447/6193, 7.22%), communications (2161/6193, 34.89%), procedures (617/6193, 9.96%), and miscellaneous (624/6193, 10.08%). Furthermore, in 95.0% (285/300) of cases, there were minor or no differences in categorization between the algorithm and the three independent physicians.

Conclusions
With increased adaptation of electronic health technologies, chatbots could have great potential in interacting with patients, collecting data, and increasing efficiency. Our categorization showcases the feasibility of using NLP in large amounts of electronic dialog for the development of a chatbot algorithm. Chatbots could allow for the monitoring of patients beyond consultations and potentially empower and educate patients and improve clinical outcomes.

Background

Recent technological advances have allowed for artificial intelligence (AI) to successfully integrate itself into many aspects of daily life. Besides implementation in voice bots such as Amazon's Alexa and Apple's Siri, AI is also utilized to predict financial stock market changes and answer student questions in educational settings[1]. In health care, AI is expected to disrupt the role of physicians as well; however, experts predict that AI will support the intelligence and knowledge base of physicians rather than replace them entirely[2]. For instance, AI can utilize deep-learning algorithms, which function like the neural networks of the brain and distinguish patterns, to recognize certain types of brain tumors, vascular conditions, or pneumonia on imaging scans and prioritize these cases in the workflow of a radiologist[2,3]. In addition, AI can be used to quickly review patient scans and rule out certain diagnoses, thereby increasing the efficiency and accuracy of a radiologist[2].

Another significant way AI can augment health care delivery is through medical chatbots. A chatbot, or chatterbot, attempts to simulate a natural conversation with a human user[4]. Medical chatbots are already being implemented into regular practice: the Insomnobot-3000 helps insomniacs get through the night, and the Endurance bot acts as a companion for dementia patients[5]. In addition, there are significant efforts toward the development of diagnostic chatbots. Some popular ones include Your.MD, Buoy Health, Sensely, Infermedica, and Florence (Table 1)[6].

Although there are limited data on these general medical chatbots in clinical practice, some independent bodies have provided preliminary and positive results in tests with more specific medical chatbots[7,8].

Most chatbots utilize natural language processing (NLP), which can be simply defined as the use of computers for analyzing human language[9]. One application of NLP relies on human identification of key elements within an event or situation that might constitute a useful summary of a given document or dataset[10]. Recently, there have been growing trends toward the use of electronic health records (EHRs). Multiple studies have attempted to use NLP to extract useful information from EHRs. In one study, researchers used NLP to identify patients with ulcerative colitis and Crohn disease from EHR data collected from Massachusetts General Hospital and Brigham and Women's Hospital[11]. The study developed an algorithm that partly relied on recognizing keywords associated with ulcerative colitis or Crohn disease to analyze the narrative texts and was verified via comparison to a

Table 1. Overview of current medical chatbots

Name	Disease area	Objective	What does it do
Your.MD (UK[a])	General	Provide reliable information for common symptoms, recommends relevant resources	Safely advises patients based on symptoms described in an app-based messaging system
Endurance (Russia)	Dementia	Act as a companion for patients with short-term memory loss and help to identify signs of worsening patient condition	It works via voice recognition to ask questions and react to answers. It can speak on a variety of topics and pull interesting news from Google
Insomnobot-3000 (US[b])	Insomnia	Acts as a companion for insomniacs when they are awake at night.	Has conversations with patients via text
Pharmabot (Philippines)	Pediatrics	Designed to help pediatric patients get appropriate generic medicine for certain ailments	The system works in a software application that sets particular guidelines for interaction with the chatbot
Text-based healthcare chatbots on Mobile Coach (Switzerland)	Childhood obesity	Provide a peer character for obese teenagers and keep them engaged. In addition, sought to show the benefit of text-based chatbot interventions in health care	Works in a text channel within an app interface. Also, has predefined answer options for more efficient chat interactions
Molly by Sensely (US)	General	Diagnose patients with common ailments appropriately based on symptoms	Advises patients based on symptoms described in an app-based messaging system
Buoy Health (US)	General	Diagnose patients accurately based on symptoms. Harvard team developed the algorithm for this bot using 18,000 medical papers for data	Program asks a series of questions—for which there are predefined choices to choose from—to appropriately advise patient. Found on a Web-based software
Symptomate by Infermedica (Poland)	General	Attempt to increase health care provider efficiency, reduce costs, and improve patient flow by acting as a general symptom checker	Online software that collects and analyzes symptom data via predefined questions with answers to provide appropriate response
Florence (Germany)	General	Acts as a **personal nurse** that can remind patients to take prescriptions and keep track of user's health (weight, mood, etc)	Advises patients based on symptoms described in an app via Facebook messenger
Ada (international)	General	Help patients actively manage health based on common symptoms	Ada poses simple and relevant questions to patients and then compares their symptoms with thousands of similar cases to help provide possible explanations
Holly by Nimblr (US)	N/A[c]	Helps patients schedule and reschedule appointments to help prevent no shows or cancellations and improve patient experience	Interacts with patients via text and Amazon's Alexa to update electronic health records
Woebot (US)	Psychiatry	Make mental health care more accessible to people around the world	Uses methods from cognitive behavioral therapy to help patients think through situations. It also includes intelligent mood tracking

[a] UK: United Kingdom. [b] US: United States. [c] N/A: not applicable.

physician's review and classification of the same narrative texts[11]. Ultimately, the study determined that NLP of patient narrative texts provided a more accurate means of identifying patients who had ulcerative colitis and Crohn disease than previous models that had relied on reviewing billing codes[11].

In another study by the University of Alabama, researchers developed an algorithm that analyzed the EHRs of patients collected over 3 years and organized the EHRs into pathology clusters based on key terms[12]. This team also concluded that electronic text mining of health records, or NLP, is an effective method for analyzing large health care datasets[12]. More recent studies have even attempted to use NLP models to study the semantics and sentence flows found in clinical narrative data[13,14]. The literature shows that it is common to perform exploratory analysis on natural language data to understand the topics and vocabulary of a specific domain in health care[9-14]. This exploration is often done by grouping keywords and categorizing topics or using open-source technology such as clinical Text Analysis and Knowledge Extraction[13]. A deep initial understanding facilitates the creation and comparison of more complex, health care-focused NLP models. However, it is worth noting that certain aspects of patient consultations in clinical settings, such as electronic record style, patient behavior, and physician experience, can vary from clinic to clinic[9,14]. This variability found within patient data puts limits on what NLP can do without a large and diverse sample.

In addition, despite the extensive literature on the topic, there seems to be a lack of research into the use of NLP to analyze raw consultation dialog data of patients with specific chronic conditions such as inflammatory bowel diseases (IBD). The organization of the patient with IBD to health care provider (HCP) dialog is likely to be distinct from a general patient population due to the complex nature of the disease. Understanding how these dialogs can be organized is an important first step in assessing the feasibility of a chatbot for this population.

Chatbots that utilize NLP can help to improve the way health care is delivered in multiple ways. For one, they improve accessibility to health care for patients outside of clinics and hospitals. From kids to the elderly, patients often need care outside of inpatient consultations; lack of such support is associated with inefficiency, high health care costs, and burdened HCPs[15]. With a chatbot, these patients would have immediate and autonomous support at home.

Objectives

The primary objective of this study was to accurately categorize large datasets of electronic messages between patients with IBD and HCPs using natural language processing (NLP) to assess the feasibility of developing a medical chatbot for patients with IBD.

Methods

Design and Population

In this study, we aimed to assess the feasibility of utilizing NLP on historical electronic messaging data of patients with IBD for use in the development of a medical chatbot. As IBD is a chronic illness characterized by severe and recurring abdominal pain and diarrhea, patients require frequent contact with their physicians and care team to monitor these alternating disease states and potential relapses[16]. There is great potential here for a chatbot as patients need frequent monitoring beyond regular consultations, which is often troublesome due to the complex nature of the disease and a busy care team.

Patients enrolled in the University of California, Los Angeles (UCLA) Center for IBD electronic care management platform (UCLA eIBD) were retrospectively assessed. The UCLA eIBD platform is a care management software as a service with a Web-based platform for providers that includes treatment decision support, business intelligence, messaging functionality, and performance improvement tools. On the patient's side, there is a mobile app that includes care management insight, educational modules, surveys, and messaging (Figure 1)[16]. Retrospective dialog data between patients and their care team from 2013 until 2018 was extracted and the feasibility of applying NLP categorization algorithms was assessed.

All patients gave informed consent to participate. This study was approved by the Institutional Review Board (IRB) at UCLA with IRB protocol number 17-001208.

Data Collection and Anonymization

The dialogs were extracted from the UCLA eIBD database. The data consisted of the following: (1) a unique identifier, (2) first name, (3) last name, (4) date and time of message, (5) direction of message (HCP to patient or vice versa), (6) message content, (7) potential attachments, (8) HCP classification (urgent and nonurgent), (9) HCP action (responded yes or no), and (10) HCP response message content (Multimedia Appendix 1). The data

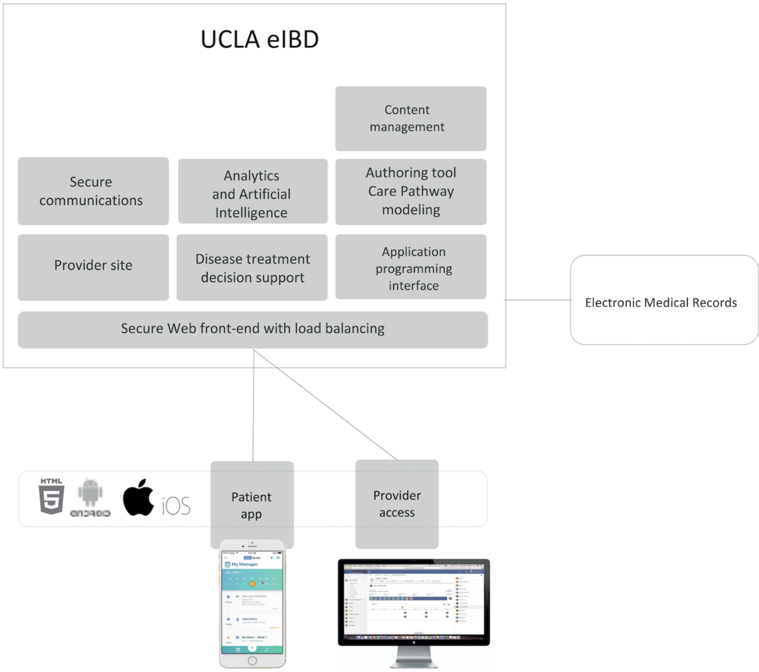

Figure 1. Overview of UCLA eIBD platform. AI: artificial intelligence; API: application programming interface.

were anonymized by removing the first and last names; for identification, we made use of the unique identifier in our analysis.

Categorization Method: Use of Natural Language Processing

Once the patient to HCP dialogs were stored in a Microsoft Excel sheet, the first 400 lines within the sheet were manually analyzed to identify relevant categories for use in our NLP algorithm. To clarify that the first 400 lines were representative, an additional 400 lines were randomly generated and manually reviewed as well (by AS and ZS). The analysis consisted of reading over each line to find an intent; if a particular intent was seen to occur frequently in these first lines, it was noted as a relevant category. The rationale behind using only categories observed in the sample was to make sure that the categories coded for were relevant to what the patient sample was discussing with their HCPs. Furthermore, 2 IBD gastroenterologists reviewed the categories found from the sample and reaffirmed that each category was representative of the IBD patient conversations they had encountered through electronic channels such as email. The same first 400 lines were then used to identify which keywords could assign a given dialog to a certain category (Multimedia Appendix 2). If a term appeared roughly 10 or more times in a given category, it was noted as a potential keyword; 2 physicians then reviewed and approved our list terms. Using these keywords, we employed a simplified, rule-based bag-of-words model to assign each line of dialog to the appropriate categories (Figure 2). The bag-of-words model essentially allows one to

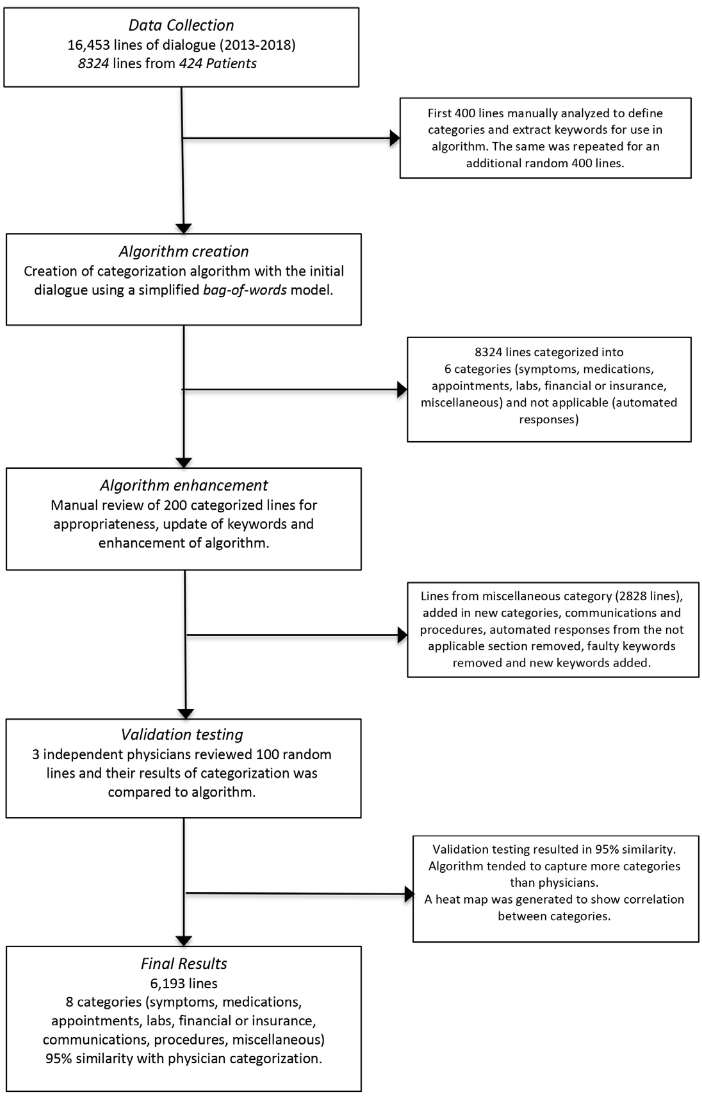

Figure 2. Flowchart of inclusion and categorization. N/A: not applicable.

extract particular features of a text, that is, keywords, and score them with relevant numbers for modeling, or in our case, categorization[17]. To be certain, each line was converted into a standard bag-of-words with a score for each word in the form of a count of the number of times it appears within the line. With stop words removed, we extract the score of each keyword from all lines and assign to each line all categories for which any one keyword has a positive score.

Enhancement and Correlation Assessment

On the basis of the preliminary results, the keywords of our initial categorization algorithm were refined, and new categories were created if necessary. If the categorization was not logical, we analyzed which keywords in the model miscategorized the dialog and made the necessary improvements. In addition, any uncategorized lines of dialogs were assigned a category, and their keywords were identified. The categorization algorithm was updated with the new, physician-approved keywords extracted from the uncategorized lines of dialog and the improvements of the existing categorization.

Once the code was refined to capture all the lines of dialog, a heat map was generated to showcase the overlap in categories, which refers to one line of dialog from a patient falling into two categories. It is worth noting that more than two categories could overlap, but there was no way to represent the higher levels of overlap in a relevant and concise diagram such as a heat map. The goal was to paint a picture of what types of questions or concerns popped up together, which is instrumental in the actual development of a chatbot and creation of multicategory scenarios.

Validation of Accuracy

The accuracy of our categorization algorithm was tested by having 3 independent physicians from the UCLA Division of Digestive Diseases (AZ, CR, and DH) evaluate the appropriateness of the categorization. Each physician was assigned to categorize 100 randomly collected lines of dialog using the defined corresponding category number. In addition, the physicians categorized each line in the same style as the algorithm: numerical order with no spaces.

Once each of the doctors had finished categorizing the lines, the results were compared with the algorithm's categorization. We showcased the extent to which the algorithm and the doctors agreed or disagreed. To do this, the number of underclassifications and overclassifications the categorization algorithm made relative to the doctors' categories was

calculated. For instance, if the algorithm missed a category that the doctor had, it would be counted as an underclassification of 1; if the category code had an extra category compared with the doctor, it would be counted as an overclassification of 1. We then created a bar chart plot based on this data. In addition, to understand the practicality of treating the doctors' assessments as ground truth, we computed the level of agreement between the three raters using Krippendorf alpha. This is a standard estimate of inter-rater reliability across ratings on a nominal scale.
To calculate a metric for the accuracy of the algorithm itself, we opted to use a nonstandard method of computing the success of the classification algorithm in an attempt to incorporate expert knowledge about the severity of misclassifications. As standard reliability measures such as Krippendorf alpha treat all disagreements between the raters and the algorithm with equal weight, we would not get a realistic view of the algorithm's strength across the spectrum of categories by following this approach. This was also done in an attempt to avoid aggregating our multiclass labels from the raters as doing so would put us at risk of destroying the variability in the ratings and inflating performance.

Software
Excel 2010 and R studio programming tool (R 3.4.0) were used for our analysis and algorithm creation (Multimedia Appendix 3).

Results

Data and Population Characteristics
Our sample consisted of 424 patients, 3 physicians, 3 nurses, and 2 administrative assistants with 16,453 lines of electronic dialog. Of the dialogs, 8324 lines were sent by 424 patients to their HCP (patient to HCP). Our analyzed patient cohort is 51.9% (220/424) female, 50.7% (215/424) have Crohn disease, and 46.9% (199/424) have ulcerative colitis with a mean disease duration of 13.4 (SD 10.4) years. The majority of the population is of the white (284/424, 67.0%) race and not of Hispanic or Latino ethnicity (386/424, 91.0%). Furthermore, most of the patients are employed (283/424, 66.7%) and have been enrolled in the care program for a mean of 4.6 (SD 1.3) years (Table 2).

Algorithm Development and Initial Results
In our manual run-through of the first 400 out of the 8324 lines of dialog, we categorized them in six newly created and distinct categories: (1) medications, (2) symptoms, (3) appointments, (4) laboratory investigations, (5) finance/insurance, and (6) miscellaneous

Table 2. Characteristics of the inclusion cohort (N=424)

Variable	Values
Age (years), mean (SD)	42 (14)
Gender, n (%)	
Female	220 (51.9)
Male	204 (48.1)
Disease type, n (%)	
Crohn's disease	215 (50.7)
Ulcerative colitis	199 (46.9)
Indeterminate colitis	10 (2.4)
Disease duration (years), mean (SD)	13.4 (10.4)
Race, n (%)	
White	284 (67.0)
Unknown	97 (22.9)
Asian	26 (6.1)
Black or African American	12 (2.8)
American Indian or Alaska Native	4 (0.9)
Native Hawaiian	1 (0.2)
Ethnicity, n (%)	
Not Hispanic or Latino	386 (91.0)
Hispanic or Latino	29 (6.8)
Unknown	9 (2.1)
Employment, n (%)	
Employed	283 (66.7)
Unemployed or unknown	141 (33.2)
Duration in program (years), mean (SD)	4.6 (1.3)

(lines that did not fall into any of the other categories). When the additional randomly generated 400 lines were reviewed for clarification, the same five relevant categories were found. At this point, we also kept a not applicable (N/A) section for automated responses produced by the mobile app itself that were in the dataset. For instance, "Patient has indicated there are no changes to medications."

We identified what keywords were relevant to each of the categories (Multimedia Appendix 2). A categorization algorithm (bags-of-words model) was created based on the keywords extracted from the dialogs in the categories and applied to categorize the remaining lines of dialog.

Out of the 8324 lines of dialogs, the algorithm initially returned symptoms (1781/8324, 21.40% lines), medications (2114/8324, 25.40% lines), appointments (1781/8324, 21.40% lines), laboratory investigations (1648/8324, 19.80% lines), finance or insurance (358/8324, 4.30% lines), miscellaneous (2830/8324, 34.00% lines), and N/A (666/8324, 8.00% lines).

Enhancement of Natural Language Processing Categorization Algorithm

The miscellaneous section (2828/8317, 34.00% lines) was manually reviewed for 200 lines. The miscellaneous section was essentially randomly generated in that it was not organized by any dialog identifier, such as medical record number or patient name; it was simply the arbitrarily leftover dialogs from our initial run of the algorithm. As the dialogs here were short and not dominated by any one patient, we found it appropriate to review the first 200 lines as an accurate representation of the larger section. On review, two additional categories were identified within it: communications and procedures. In addition, the miscellaneous category was analyzed for keywords that would improve the scope of our initial categories. For instance, there were some medications we missed in our first test, such as Tylenol, that we were able to find upon review of the miscellaneous section and add as a keyword for medications. Furthermore, we removed keywords from the algorithm that were too general and inflated certain categories, such as the keyword take for the medications category. Finally, the categorization algorithm was enhanced to remove dialog that only contained generic greetings, such as Thank you or Hello, and the automated responses from the N/A section from the dataset so that they did not affect the final counts. After this enhancement, 2131 lines were excluded and 6193 lines of dialog were left for categorization.

Final Natural Language Processing Categorization Results

These refinements ultimately led to the algorithm yielding 32.83% (2033/6193) of the dialog relating to symptoms, 38.70% (2397/6193) to medications, 24.51% (1518/6193) to appointments, 34.01% (2106/6193) to laboratory investigations, 7.22% (447/6193) to finance or insurance, 34.89% (2161/6193) to communications, 9.96% (617/6193) to procedures, and 10.08% (624/6193) being miscellaneous (Table 3). The frequency of this overlap was measured for each possible pair combination of the categories and is displayed in a heat map (Figure 3). For instance, medications and symptoms appeared more together than they did on their own, as did communications and symptoms. Similarly, procedures and finance were very rarely brought up on their own (Figure 3).

Table 3. Final categorization results (N=6193)

Category	Percentage of total sample[a], %
Symptoms	2033 (32.83)
Medications	2397 (38.70)
Appointments	1518 (24.51)
Laboratory investigations	2106 (34.01)
Finance or insurance	447 (7.22)
Communications	2161 (34.89)
Procedures	617 (9.96)
Miscellaneous	624 (10.08)

[a]These percentages represent how frequently these categories occur in the sample of dialogs. As the categories mostly overlap in the dialogs, the percentages do not add up to 100%.

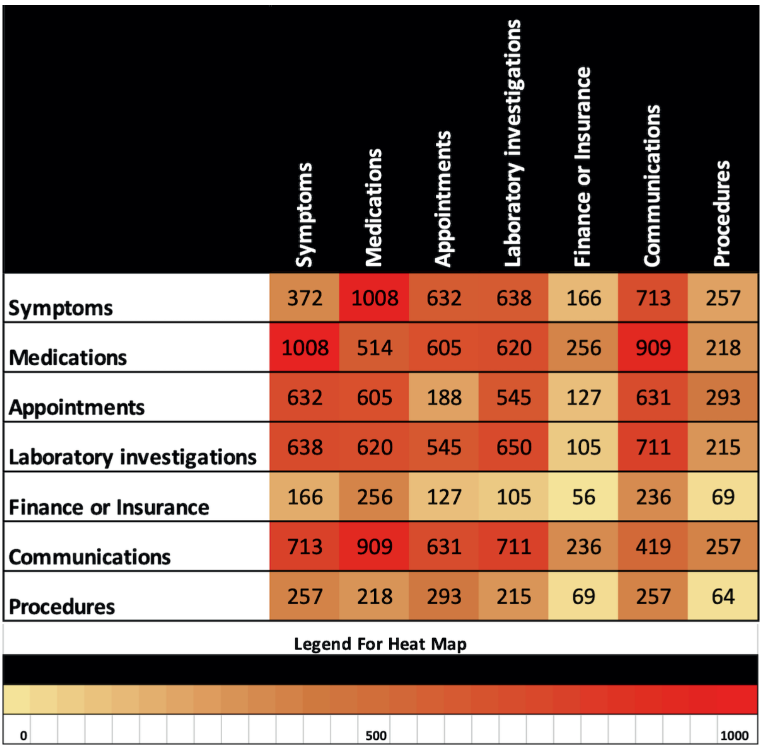

Figure 3. Heat map of category overlaps in dialog. This map shows the frequency of category overlap in pairs and how often the categories occurred by themselves out of the 6193 dialogs. Note: across the diagonal, the map is a mirror of itself.

Validation of Natural Language Processing Accuracy

Three independent raters (AZ, DH, and CR) categorized 100 random lines of dialog, and their categorization was compared with our algorithms. The raters categorized in the exact style of the algorithm, so if the categories were symptoms, appointments, and medications, they would write 123. Applying Krippendorf alpha to these assessment ratings, we get an estimate of .61, indicating that there was moderate-to-high agreement between the doctors. In our underclassification and overclassification representation of the chatbot's accuracy, we found that most of the errors were pooled at one difference, suggesting that the code and the doctors had a high level of agreement on most of the dialogs. Furthermore, the graph we constructed shows that the category code tended to over classify rather than under classify the subjects of the dialogs (Table 4). As one can see from the table, there is a significant drop in the instances of two or more underclassifications, with four to five missed categories having a frequency of 0 (Table 4). When we accounted for the 1 to 2 overclassifcation differences and the one category underclassification differences as minor, we found that 285 of the 300 tests had the program and physicians reasonably agreeing on categories. This meant that our code showed minor to no differences in 95% (285/300) of cases.

Table 4. Accuracy Test Results

Number of categories added or missed by the algorithm in a given line	Instances in Sample for Overclassification	Instances in Sample for Underclassification
1	71	47
2	29	5
3	5	1
4	3	0
5	1	0

Discussion

Principal Findings

We were successful in categorizing large amounts of electronic messages between patients and providers into a reasonable number of categories (<10). Roughly 90.00% (5574/6193) of dialogs that came from patients fell into only seven categories, which shows potential for developing a chatbot with an NLP algorithm that can handle most IBD patient's questions and concerns. In addition, our heat map gave us insight into how these categories correlate with each other in the dialogs. In terms of chatbot development, this map allows a developer to be aware of what categories or topics tend to appear together in patient with IBD to HCP dialogs. This insight would allow the developer to better prepare the chatbot's NLP algorithm to identify topic transitions in a patient conversation and respond appropriately. In addition, our accuracy test supported the reliability of this result. Most of the differences recorded in our test (100/162, 61.0%) were simply due to code over classifying with one or two categories, but it rarely missed the primary intent (Table 4). Even when it did miss a category relative to the physician, the program was not necessarily incorrect upon review. For instance, one of the dialogs in the accuracy sample had a patient describing their symptoms or medications and subtly mentioning their laboratory investigations as their previous averages. Although the doctors recognized this and appropriately categorized the line as symptoms, medications, and laboratory investigations, the algorithm categorized it as symptoms and medications only, as averages was not a keyword we had programmed for laboratory investigations. Despite this, the program correctly identified the primary intent of the dialog, which is why we considered these types of differences minor in measuring the accuracy of our program.

Limitations

One limitation of this study is that our patient sample is fairly homogenous, consisting of mostly young (mean age 42 years) and white patients, which limits the generalizability of our results to other populations. In addition, most of the patients in the study are employed, which could have potentially changed the types of questions or concerns they expressed and the overall category distribution relative to other patient populations. It is also worth noting that we used the expert opinions of 2 IBD gastroenterologists to support the validity of the categories chosen and the selected keywords. This may affect the reproducibility of our results.

Comparisons With Prior Work

The next step from collecting data to developing a chatbot is to use machine learning methods to model the relationship between questions and responses[18]. Many chatbot knowledge bases (the database from which a chatbot draws its responses from) are hand constructed, which is time consuming and reduces the algorithm's versatility[19]. For instance, Artificial Linguistic Internet Computer Entity and ELIZA, two classic chatbots, utilize hand-constructed databases to generate a response that matches a given human input[20]. As an alternative, some developers have attempted to extract high-quality dialog data from online discussion forums to efficiently create a knowledge base for specific domain chatbots[19]. The purpose of collecting these dialog datasets is to give the chatbot a training ground to learn how to accurately respond to a specific domain of human input responses with minimal human fine tuning, or simply put: machine learning[18,21]. This machine learning approach also allows for the chatbot to continue learning through its interactions and improve its accuracy. Microsoft's Xiaoice chatbot has successfully applied this model and has already amassed a following of about 660 million online users[22]. When assessing the appropriateness of our data for actual chatbot development, our code could be distributed and tested in other centers with the same historical data without requiring much customization and would eliminate the need for hand-constructed databases.

Conclusions

Looking at the global trends of technology in health care, usage of smartphones and electronic health apps is on the rise[2,4,6]. Patient-provider communication through electronic messaging apps is becoming the standard. In our population, 25.0% (1518/6193) of messages were related to appointments. A chatbot could effectively automate requests regarding booking and cancellations or even play an instrumental part of triage, following the same guidelines as nurses, saving the provider team valuable time that could be redistributed to better patient care. The benefit is that a chatbot is available at all times, can handle tremendous amounts of conversation, and has no wait times.

Through the UCLA eIBD platform, we have already created a high-quality knowledge base of human dialogs that can be used to train an IBD chatbot using NLP. We showcased that it is feasible to categorize large amounts of electronic messaging data in one of the most complex chronic conditions into a reasonable number of categories. Given the feasibility of this categorization and the potential benefits of a chatbot, the next step would be to develop a chatbot and test it in a patient population with IBD. Further studies are required to showcase the effect on patients, providers, and costs and potential extrapolation to other chronic conditions.

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Supplementary

Supplementary Table 1. Dialogue data content

Unique Identifier	Report Messages Received/Sent by
Report Messages Content	Report Messages Nurse Note Content
First name	
Last name	
Report Messages Patient Alert	
Report Messages Date & Time	
Report Messages Nurse Alert	

Supplementary Table 2. Keywords for Categories

Category of Dialogue	Description	Keywords
Symptoms	Patient describing characteristics of ailment/problem they are having.	"I'm noticing", "be concerned", "diagnose", "I have been" ,"breaking", "ability", "I have a", "figure out", "pale", "I haven't had", "nausea", "weight", "anemia", "restroom", "bathroom", "stomach pain", "weaken", "sore", "serious pain", "infection", "bloated", "kidney", "itch", "tendon", "sensation", "bowel movement", "sick", "BM", "discomfort", "hurts", "my disease", "pooping", "GI track", "strokes", "spots", "sleep", "ache", "recovering", "BLEEDING", "reaction", "Crohn", "effect", "affect", "symptom", "feel", "problem", "fever", "cramp", "I was experiencing", "I've been", "I've had", "rash", "inflammation", "bleeding", "depression", "anxiety", "stool", "Stool", "depressed", "having pain", "abdominal pain", "medicine"
Medications	Any mention of or changes to a patients medications.	"meds", "prescription", "drug", "treatment", "infusion", "injection", "Vaccine", "taking", "prescribe", "prescription", "refill", "take the", "tabs", "daily", "tablet", "pill", "vaccinate", "miralax", "Miralax", "laxative", "Antibiotic", "antibiotic", "steroids", "supplement", "My medication", "my medication", "vaccine", "shot", "flu shot", "oral", "Flu shot", "the medication", "Walgreens", "walgreens", "CVS", "cvs", "pharmacy", "Pharmacy", "over the counter", "mg", "miligrams", "dose", "dosage", "pro biotic", "probiotic", "Probiotic", "Entyvio", "entyvio", "6MP", "6mp".... (Additionally, listed out about 50 different medications used by the UCLA IBD Center as keywords.)
Appointments	Patients trying to schedule appointments with provider.	"scheduling", "apt"," appointment", "see me", "see her", "see him", "see Dr", "see the", "seeing", "appt", "I can make", "schedule", "come in", "be there", "head over", "followup", "visit", "SEE OR", "meet"

Supplementary Table 2. Continued

Category of Dialogue	Description	Keywords
Labs	Any question or concerns (troubleshooting, results, etc.) the patient may have.	"lab", "Lab", "results", "blood test", "CBC", "blood panel", "draw", "result", "blood work", "Quest", "quest diagnostic", "sample", "drew blood", "tests", "CRP", "test for", "bloods", "more blood", "this test", "my blood", "Vitamin D", "vitamin D", "Vitamin d", "iron", "glucose"
Finance/Insurance	Patient discussing any questions or concerns related to monetary issues.	"insurance", "cost", "careplan", "expensive", "money", "health plan", "$", "paystub", "Blue Shield", "financial", "funds", "PPO", "HMO", "Tricare", "tricare", "medical bills", "pricing", "Remistart", "remistart", "Co-Pay", "co-pay", "Healthcare"
Communications	The patient trying to get ahold of providers or leaving their contact information.	"E-mail", "email", @gmail.com, "altour.com", "@mednet.ucla.edu", "phone", "number", "my cell", "fax", "message", "Email", "error", "call", "get a hold of", "contact", "speak", "mail", "Zip code", "located", "location", "address"
Procedures	Patient discussing any questions or concerns related to procedures.	"colonoscopy", "procedure", "scopy", "MRI", "PT scan", "Petscan", "CT", "CAT", "x-ray", "X-ray", "surgery", "biopsy", "biop", "TB test", "tuberculosis"

Supplementary Table 3. Algorithm Code

```
setwd(“I:/IBDcenter/`STUDIES/Chat-Bot”)
Chat = read.csv(“Chat.csv”,header=TRUE, stringsAsFactors = FALSE)
Messages = Chat[,c(5,6,7)]
Messages[,2] = 0
MessagesHP = subset(Messages, grepl(levels(factor(Messages[,1]))[1], Messages[,1]))
MessagesPH = subset(Messages, grepl(levels(factor(Messages[,1]))[2], Messages[,1]))

#######Categorization CODE####################################################################################
######################################
one = c(“I’m noticing”,”be concerned”,”diagnose”,”I have been”,”breaking”,”ability”,”I have a”,”figure out”,”pale”,”I haven’t had”,”nausea”,”weight”,”
anemia”,”restroom”,”bathroom”,”stomach pain”,”weaken”,”sore”,”serious pain”,”infection”,”bloated”,”kidney”,”itch”,”tendon”,”sensation”,”bowel
movement”,”sick”,”BM”,”discomfort”,”hurts”,”my disease”,”pooping”,”GI track”,”strokes”,”spots”,”sleep”,”ache”,”recovering”,”BLEEDING”,”reaction”,
”Crohn”,”effect”,”affect”, “symptom”,”feel”,”problem”,”fever”,”cramp”,”I was experiencing”,”I’ve been”,”I’ve had”,”rash”,”inflammation”,”bleeding”,”
depression”,”anxiety”,”stool”,”Stool”,”depressed”,”having pain”,”abdominal pain”,”medicine”)
two = c(“meds”,”prescription”,”drug”,”treatment”,”infusion”,”injection”,”Vaccine”,”taking”,”prescribe”,”prescription”,”refill”,”take the”,”tabs”,”daily”,
”tablet”,”pill”,”vaccinate”,”miralax”,”Miralax”,”laxative”,”Antibiotic”,”antibiotic”,”steroids”,”supplement”,”My medication”,”my medication”,”vacci-
ne”,”shot”,”flu shot”,”oral”,”Flu shot”,”the medication”,”Walgreens”,”walgreens”,”CVS”,”cvs”,”pharmacy”,”Pharmacy”,”over the counter”,”mg”,”
miligrams”,”dose”,”dosage”,”pro biotic”,”probiotic”,”Probiotic”,”Probiotic”,”tylenol”,”Entyvio”,”entyvio”,”6MP”,”6mp”,”Asprin”,”asprin”,”Apriso”,”
Allopurinol”,”Asacol”,”Azulfidine”,”azathioprine”,”Budesondie”,”Entocort”,”Canasa”,”antidepressants”,”Cimzia”,”Cipro”,”Creon”,”Colazal”,”
Cortenema”,”Cortifoam”,”Dipentum”,”Entocort”,”Flagyl”,”humira”,”Humira”,”Imuran”,”immodium”,”Immodium”,”Lialda”,”methylpredniso-
lon”,”Natalizumab”,”NyQuil”,”Ibuprofen”,”Pentasa”,”Prilosec”,”Prevacid”,”Aciphex”,”Protonix”,”Methotrexate”,”Nexium”,”Dexilant”,”Prednsione”,”
Phenergan”,”Purinethol”,”Remicade”,”Rowasa”,”Simponi”,”Solu-Medrol”,”Prozac”,”Stelara”,”Tylenol”,”Useris”,”vicodin”,”Vicodin”,”Zosyn”)
three = c(“scheduling”,”apt”,”appointment”,”see me”,”see her”,”see him”,”see Dr”,”see the”,”seeing”,”appt”,”I can make”,”schedule”,”come in”,”
be there”,”head over”,”followup”,”visit”,”SEE OR”,”meet”)
four = c(“lab”,”Lab”,”results”,”blood test”,”CBC”,”blood panel”,”draw”,”result”,”blood work”,”Quest”,”quest diagnostic”,”sample”,”drew blood”,”tests”,
”CRP”,”test for”,”bloods”,”more blood”,”this test”,”my blood”,”Vitamin D”,”vitamin D”,”Vitamin d”,”iron”,”glucose”)
five = c(“insurance”,”cost”,”careplan”,”expensive”,”money”,”health plan”,”\\$”,”hemoglobin”,”paystub”,”Blue Shield”,”financial”,”funds”,”PPO”,”
HMO”,”Tricare”,”tricare”,”medical bills”,”pricing”,”Remistart”,”remistart”,”Co-Pay”,”co-pay”,”Healthcare”)
six = c(“E-mail”,”email”,”@gmail.com”,”altour.com”,”@mednet.ucla.edu”,”phone”,”number”,”my cell”,”fax”,”message”,”Email”,”error”,”call”,”get a hold
of”,”contact”,”speak”,”mail”,”Zip code”,”located”,”location”,”address”)
seven = c(“colonoscopy”,”procedure”,”scopy”,”MRI”,”PT scan”,”Petscan”,”CT”,”CAT”,”x-ray”,”X-ray”,”surgery”,”biopsy”,”biop”,”TB test”,”tuberculo-
sis”)
eight = c(“Patient has indicated there are changes to”,”Patient has indicated there are no changes”,”See attachment...”)
nine = c(“Thank”,”thank”,”Hi”,”hi”,”Hey”,”hey”,”Hello”,”hello”,”Ok”,”ok”,”Yes”,”yes”,”thx”,”Testing”,”testing”,”Merry Christmas”,”Good Morning”,
”Good morning”,”Good afternoon”,”Good Afternoon”,”good afternoon”,”Happy New Year”,”Happy Thanksgiving”, “Nice”,”Happy”)

cats = list(one,two,three,four,five,six,seven,eight,nine)
for(g in 1:length(cats)){
 res = rep(0, nrow(MessagesPH))
 for(i in 1:length(cats[[g]])){
  res = res+as.numeric(grepl(cats[[g]][i], MessagesPH[,3]))
 }
 MessagesPH[which(res>0),2] = g + 10*MessagesPH[which(res>0),2]
}
for(j in 1:nrow(MessagesPH)){
 if(MessagesPH[j,2] == 9){
  if(grepl(“\\?”, MessagesPH[j,3])){
   MessagesPH[j,2]=0
  }
  else{
   if(length(strsplit(MessagesPH[j,3],” “)[[1]])>15){
    MessagesPH[j,2]=0
   }
  }
 }
}
for(y in 1:nrow(MessagesPH)){
 if(grepl(“New medication was added on”, MessagesPH[y,3])){
  MessagesPH[y,2]=8
 }
}


for(n in 1:nrow(MessagesPH)){
```

```
  if(grepl("<p>", MessagesPH[n,3])){
    MessagesPH[n,2]=8
  }
}
#Phone number searcher
for(w in 1:nrow(MessagesPH)){
  if(MessagesPH[w,2]==0){
    Test= MessagesPH[w,3]
    Test= as.numeric(strsplit(Test,"")[[1]])
    count = 0
    NAcount = 0
    for(z in 1:length(Test)){
      if(!is.na(Test[z])){
        count = count + 1
        NAcount = 0
        if(count==10){
          MessagesPH[w,2]= 6
          break
        }
      }
      else{
        if(NAcount==2 && count > 0){
          count = 0
          NAcount = 0
        }
        if(NAcount<2 && count > 0){
          NAcount = NAcount + 1
        }
      }
    }
  }
}
########################################

########THE CLEANER: Get rid of 9's and 8's########
remove = NULL
for(w in 1:nrow(MessagesPH)){
  if((MessagesPH[w,2]-9)%%10==0){
    if(((MessagesPH[w,2]-9)/10)==0){
      remove = c(remove,w)
    }
   MessagesPH[w,2] = (MessagesPH[w,2]-9)/10
  }
  if((MessagesPH[w,2]-8)%%10==0){
    if(((MessagesPH[w,2]-8)/10)==0){
    remove = c(remove,w)
    }
  }
}
MessagesPH = MessagesPH[-unique(remove),]

#############Use wisely#################
write.csv(MessagesPH, "Categories2.csv")
##########################################

#######Category Frequency Printer###########
x = table(MessagesPH[,2])
for(h in 0:7){
  print(h)
  print(100*sum(x[which(grepl(as.character(h), rownames(x)))])/6193)

}
##############################################
```

```
#####################HEATMAP########################
#1.create blank matrix
Heat = matrix(0,nrow = 7, ncol = 7)
#2. THE LOOP
tab = table(MessagesPH[,2])
names = row.names(tab)
for(x in 1:nrow(Heat)){
 for(y in 1:ncol(Heat)){
  for(z in 1:length(names)){
   if((x %in% as.numeric(strsplit(names[z],"")[[1]])) && (y %in% as.numeric(strsplit(names[z],"")[[1]]))){
    Heat[x,y] = Heat[x,y] + tab[z]
   }
  }
 }
}

diag(Heat) = tab[2:8]
color = heat.colors(256)
color = color[256:1]
#heatmap(Heat, main ="Overlap of Categories in Pairs", Rowv=NA, Colv=NA, labRow = c("Medications","Symptoms","Appoint-
ments","Labs","Finance/Insurance","Communications","Procedures"),labCol = c("Medications","Symptoms","Appointments","Labs","Finance/
Insurance","Communications","Procedures"), col = color, scale= "none", margins=c(5,10),symm=TRUE,revC=TRUE)
heatmap.2(Heat, main ="Overlap of Categories in Pairs", Rowv=NA, Colv=NA, labRow = c("Medications","Symptoms","Appoint-
ments","Labs","Finance/Insurance","Communications","Procedures"),labCol = c("Medications","Symptoms","Appointments","Labs","Finance/
Insurance","Communications","Procedures"), col = color, margins=c(5,10),symm=TRUE,revC=TRUE)
####Sample Test For Accuracy Creator###################
set.seed(100)
rownumber = sort(sample(1:nrow(MessagesPH),size=100, replace=FALSE))

subset = MessagesPH[rownumber,3]
subset = cbind(exam,subset)

write.csv(subset, "Catergoriestest.csv", row.names=FALSE)

subsetfull = table(MessagesPH[rownumber,2])

for(h in 0:7){
 print(h)
 print(100*sum(subsetfull[which(grepl(as.character(h), rownames(subsetfull)))])/100)

}
#######################################################

###############Accuracy Checker########################
Testresults = read.csv("Mastertest.csv",header = TRUE)

Computer = matrix(0,nrow = 100, ncol = 9)
Dan = matrix(0,nrow = 100, ncol = 9)
Aria = matrix(0,nrow = 100, ncol = 9)
Courtney = matrix(0,nrow = 100, ncol = 9)

populate = function(frame,data){

 for(u in 1:nrow(frame)){
  for(g in 9:1){
   if((data[u]-g)%%10 == 0){
    frame[u,g] = 1
    data[u] = (data[u]-g)/10
   }

  }

 }
 return(frame)
}
```

```
Computer = populate(Computer, Testresults[,2])
Dan = populate(Dan, Testresults[,3])
Aria = populate(Aria, Testresults[,4])
Courtney = populate(Courtney, Testresults[,5])

scores = rep(0,300)
underscore = rep(0,300)
overscore = rep(0,300)

for(v in 1:nrow(Computer)){
scores[v] = sum(Computer[v,] != Dan[v,])
scores[v+100] = sum(Computer[v,] != Aria[v,])
scores[v+200] = sum(Computer[v,] != Courtney[v,])
}

for(o in 1:nrow(Computer)){
 for(x in 1:9){
  if(Computer[o,x]-Dan[o,x]<0){
   underscore[o] =  underscore[o]-1
  }
  if(Computer[o,x]-Aria[o,x]<0){
   underscore[o+100] =  underscore[o+100]-1
  }
  if(Computer[o,x]-Courtney[o,x]<0){
   underscore[o+200] =  underscore[o+200]-1
  }
 }
}

for(o in 1:nrow(Computer)){
  for(x in 1:9){
   if(Computer[o,x]-Dan[o,x]>0){
   overscore[o] = overscore[o]+1
   }
   if(Computer[o,x]-Aria[o,x]>0){
   overscore[o+100] =  overscore[o+100]+1
   }
   if(Computer[o,x]-Courtney[o,x]>0){
   overscore[o+200] =  overscore[o+200]+1
   }
  }
}
hist(scores,
     main="Histogram for Raw Differences between Program and Doctor Categorization",
     xlab ="Differences", border="blue", col="green", ylim=c(0,250))
hist(underscore,
     main="Histogram for Underestimations of Categories by Program relative to Doctor",
     xlab ="Number of Missed Categories", border="orange", col="red", ylim=c(0,250))
hist(overscore,
     main="Histogram for Overestimations of Categories by Program relative to Doctor",
     xlab ="Number of Missed Categories", border="brown", col="blue", ylim=c(0,250))
```

CHAPTER 6

Artificial Intelligence for Inflammatory Bowel Diseases (IBD); Developing and Validating Machine Learning Models in Big Data to Predict Negative Outcomes

Submitted

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Abstract

Background and Aims

The accessibility to Big Data and increased computational resources have paved the way for Artificial Intelligence (AI) to potentially predict adverse health events in complex diseases such as Inflammatory Bowel Diseases (IBD) characterized by considerable heterogeneity and alternating disease states.

Methods

We assessed the feasibility and performance of various statistical and AI models in early prediction of adverse outcomes (hospitalizations, surgeries, long-term steroid and biologics use) for IBD patients using The OptumLabs® Data Warehouse (OLDW), a longitudinal, real-world data asset with de-identified administrative claims and electronic health record (EHR) data, and 108 potentially predictive variables. We built a training model cohort and validated our result in another cohort. We used LASSO and Ridge regressions, Support Vector Machines, Random Forests and Neural Networks and assessed their respective performances and analyzed the strongest predictors to the respective models.

Results

72,178 and 69,165 patients were included in the training and validation set, respectively. In total, 4.1% of patients in the validation set were hospitalized, 2.9% needed IBD-related surgeries, 17% used long term steroids and 13% of patients were initiated with biological therapy. Of the AI models we tested, the Random Forest resulted in the highest accuracy (AUCs 0.71-0.92). The artificial neural network performed well in some but not all of the models (AUCs 0.61-0.90).

Conclusions

This study demonstrates that it is feasible to successfully run complex and novel AI models on large longitudinal data sets of IBD patients (Big Data). These models can be applied for risk stratification and implementation of preemptive measures to avoid adverse outcomes in a clinical setting.

Introduction

The burden of Inflammatory Bowel Disease (IBD) on patients as well as society is large. IBD is a progressive disease with a destructive character and is associated with substantial healthcare costs[1,2]. Prevention of flares is key to preventing disease progression[3–5]. However, the disease course is unpredictable and reliable risk factors for flares are difficult to identify[5]. Finding an approach that identifies patients at risk for disease progression would help to better fine-tune treatment strategies in order to prevent adverse outcomes such as hospitalizations, long term steroid use, the initiation of expensive biologics and surgeries. This could help reduce the substantial costs associated with IBD care and improve long-term outcomes[6].

The development of healthcare technologies driven by Artificial Intelligence (AI) is expected to see a growth of over $10 billion in just the next 5 years[7]. With the explosive amount of Electronic Medical Records (EMRs), having doubled in size since 2005, studying patient data is easier now than in any previous era[8]. By taking full advantage of EMR data and, other forms of patient information (e.g. wearables, microbiome/genetic testing, e-health applications, imaging), data driven treatment plans targeted at the disease and individual level could be introduced. The opportunities to construct new strategies and technologies that turn this data into actionable provider recommendations is expected to rapidly grow, as showcased by the immense amount of funding that is going into companies that use AI for healthcare[9].

Recently, there have been multiple studies that were able to accurately and inexpensively use a subset of AI known as Machine Learning (ML) to predict a variety of outcomes and create distinct classifications for IBD patients (Figure 1)[10–18]. Han et al created a gene-based ML classification model to better differentiate between patients with Crohn's disease (CD) and ulcerative colitis (UC)[16]. Also using a large sample of genetic data, Wei et al were able to successfully create a genotype-based risk prediction model for IBD[14]. Beyond gene-based data, researchers have used AI models with insurance claims data to accurately predict IBD related hospitalization or steroid use within a six-month period[10]. This ML approach outperformed more costly biomarker methods of predicting negative outcomes, such as testing for fecal calprotectin. These kind of ML approaches to healthcare have not been limited to IBD[19–23].

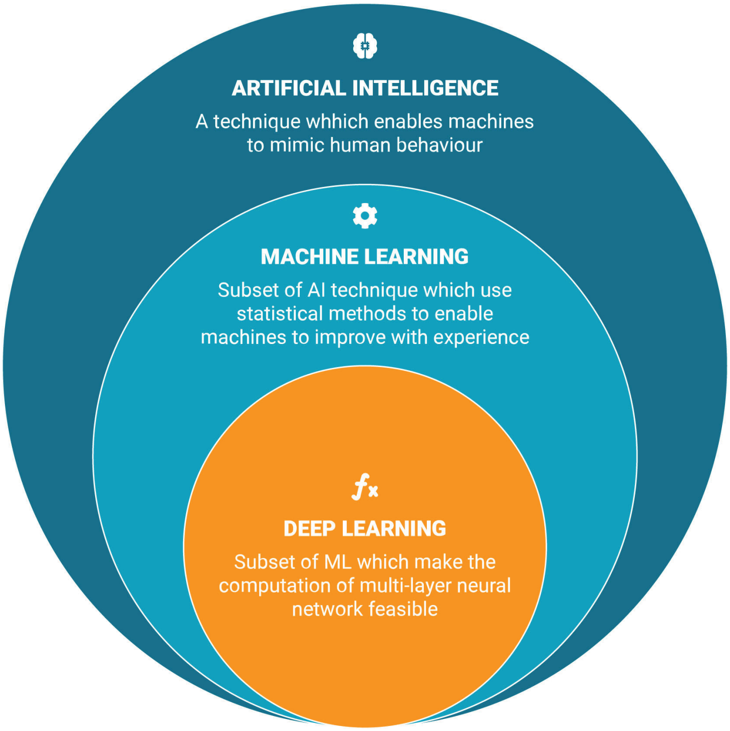

Figure 1. AI is the broad umbrella term of techniques which enables machines to mimic human behavior, when talking about predictive models we usually refer to machine learning which is a subset of AI that uses statistical methods to improve the accuracy of their outcome with experience. Deep Learning is a subset that makes the computation of multi-layer neural networks feasible and thus improving the accuracy even further.

However, studies using the most straightforward data resource, which are administrative databases due to the standardized format and accessibility, to build data driven predictive models for IBD patients were limited in their generalizability. The data came from public health insurance records, while the majority (67.2%) of United States citizens use private insurance, and their samples have limited geographic spread[13,24]. Additionally, these studies have not attempted to predict other costly negative outcomes such as IBD-related surgeries[10,13]. To our knowledge, no other study has attempted to apply this ML approach to a larger set of private insurance claims data or use novel deep learning methods such as neural networks. Our goal is to assess the feasibility and performance of various ML models in early prediction of adverse outcomes for IBD patients, including IBD-related surgeries, using a large private insurance claims dataset.

Methods

Study Objectives

The main objective of this study was to assess if variables extracted from insurance claims can predict negative health outcomes in IBD. To achieve this, we assessed the performance of different Machine Learning and Deep Learning models to and compared the performances of the aforementioned models using different performance outcomes.

Data Collection

Deidentified medical, pharmacy and facility claims, were extracted from The OptumLabs® Data Warehouse (OLDW), which includes claims from commercially insured individuals and Medicare Advantage beneficiaries (≥65 years old) who are representative of the U.S. population with regards to geographical spread, age and race [25]. Patient-identifying data is removed from the OLDW by OptumLabs before access is granted to investigators. Therefore, this study is not considered human subjects research and is exempt from Institutional Review Board (IRB) regulation.

We created two datasets: a training cohort and a validation cohort. The training cohort contained all patients that were continuously enrolled in their insurance plan between January 1, 2015 and December 31, 2016. The validation cohort includes patients who were continuously enrolled between January 1, 2016 and December 31, 2017. In each cohort, we aimed to predict outcomes in the second year (follow-up) using claims data available in the first year (baseline).

Population

IBD patients were identified using a combination of inpatient and outpatient claims. Patients were included if they had at least two medical claim with diagnosis codes for IBD (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9] 555.x or 556.x) **OR** one IBD-related medical claim and one pharmacy claim for IBD-related medication (Supplementary Table 4) in the first year of data.

To ensure enrollees had a specified period of continuous enrollment and the inability to identify an outcome was not due to missing claims data (e.g. enrollee claim was administered by another payor) a continuous enrollment code provided by OLDW was used to make sure the cohorts were continuously enrolled with the respective payor.

Predictive Variables

We constructed 108 variables related to IBD-related care using the claims in the first year of each dataset. These variables were defined based on definitions previously described by

6

van Deen et al [13]. The variables include the number of IBD-related claims, hospitalizations, emergency department (ED) visits, office visits, procedures, lab and imaging tests, medication use, relapse rate, and comorbidities (for a complete list, see Supplementary Table 1) [13].

Model Development

In our models we aimed to predict IBD-related hospitalizations, initiation of biologics, long-term steroid use, and IBD-related surgery in the second year of the data (follow-up) using the 108 utilization-events that occurred in the prior year (baseline). There is consensus in the literature that these are negative outcomes for IBD that should be avoided[5,6]. *IBD-related hospitalizations* were defined as the presence of any claim for an IBD-related inpatient hospital stay[13]. *Initiation of biologics* was defined as a pharmacy or medical claim for adalimumab, certolizumab pegol, infliximab or natalizumab in the second year, with no claim for that medicine in the first year. *Long-term steroid use* was defined as the use of hydrocortisone, prednisolone, dexamethasone, prednisone and/or methylprednisolone during a consecutive period longer than 90 days based on pharmacy and medical claims. *IBD-related surgery* was defined as any claim with a Current Procedural Terminology (CPT) code specific to an IBD related surgery (See supplementary Table 2 for a full overview).

Logistic and Machine Learning Models

After these datasets were constructed for both cohorts of patients, we trained several logistic regression and machine learning models: a Ridge regression, a LASSO regression, a Support Vector Machine, a Random Forest model, and a Neural Network (See Table 1). Each of these models was trained to predict the probability of a patient incurring a specific negative health outcome in the next year, using the 108 variables from the previous year. We trained five models on the training set of patients and tested them on the validation set.

Ridge regression and LASSO are regression techniques that place a penalty on the model coefficients to ensure that we do not overfit to the training data. Support Vector Machines attempt to separate the patients in the training set who did experience the negative health outcome from those who did not with the largest margin possible. After experimenting with various kernels, we decided on the Gaussian radial basis function. A Random Forest model generates a collection of decision trees, in which each decision tree attempts to find a cut point for each predictor that best separates patients who experienced the negative outcome from those that did not. The cut that achieves the best separation is added to the tree and this process is repeated for each of the two resulting slices of the data, and so on until some minimum number of patients are left in each slice. To capture the nuances in

Table 1. Introduction and Description of Different Models

Model	Explanation	Method	Advantages	Disadvantages
Ridge Logistic	This method creates a model that is not perfectly fit, or overfit, to the data in a given training set. In doing so, it reduces variance and makes the model a better predictor of data points outside of the training set.	Regression	Can reduce overfitting Shrinks effects towards 0 Fast/easy to implement	Simplistic representation may be far from reality Assumptions may be difficult to justify with many predictors
LASSO Logistic	This method attempts to do the same thing as Ridge Regression but uses slightly different mathematical formulas that make it better in certain situations.	Regression	Can reduce overfitting Performs variable selection Fast/easy to implement	Simplistic representation may be far from reality Variable selection is not robust to multicollinearity
Support Vector Machine	Attempts to find the largest separation between two groups. Sometimes the space of observations has to be transformed to find a clear separation.	Machine Learning	Works well with many predictors Makes prediction easy by clearly segmenting population	Lack of a clear separation can lead to poor performance Requires long training times for big data
Random Forest	Random forest is a collection of decision trees trained on different subsets of the data. Each decision tree decides the best places to cut so that observations from the same class fall on the same side of the cut.	Machine Learning	Performs variable selection Good performance for linear and non-linear relationships Fast/easy to implement	Difficult to interpret Prone to overfitting
Neural Network	Neural networks consists of layers of nested linear models (neurons) with a non-linear transformation (activation) after each layer. The output is often the probability that a given observation is a success.	Deep Learning	Captures complex non-linear relationships Fully utilizes big data	Difficult to implement Requires many small decisions that can greatly affect performance

the data, each tree is trained and evaluated on random subsets of the data drawn with replacement. To avoid having too many correlated trees that choose the same best predictors, at each split in the tree only a fraction of the predictors is considered.

Lastly, Neural Networks can identify complex non-linear patterns in the data. These models consist of several imbedded linear functions, known as hidden layers, wrapped in non-linear "activation" functions. These non-linearities in the model work to capture the complicated relationships between the predictors and the probability that a patient will experience the negative outcome. The choice of activation function at each layer plays a big role in determining how well this relationship will be captured by the resulting model. After experimenting with several options, we found that a mix of standard and parametric Rectified Linear Units (ReLUs) performs the best. The last hidden layer is followed by a sigmoid activation function, which outputs a normalized score that we can interpret as the probability that the patient will experience the outcome.

Model Selection Rationale

We trained a battery of machine learning models to discriminate between patients who experienced negative outcomes and those that did not while emphasizing the clinical insights and practical significance that could be understood from the result. To choose the set of base models, on which we would improve with regularization and hyperparameter tuning, we considered the current gap between an algorithm's complexity/performance and its explainability. We chose several simple linear models with different regularization penalties as they are easy to interpret and align with existing clinical knowledge but often miss complex associations between the variables. We also explored a variety of neural network architectures and tuning procedures to understand the extent to which non-linear relationships in the data could be exploited to improve performance. These models are infamously difficult to understand, as theoretical notions such as statistical significance are difficult to define. With these two extremes covered the SVM and random forest models we considered attempt to strike a balance between performance and interpretability by blending simple structures with complex training procedures. By choosing models that cover this spectrum we can find complicated relationships that lead to solid predictions and warrant prospective validation as well as simpler associations that are easy to validate through expert knowledge.

Performance of the Models

For each model we obtain a prediction for each patient in the validation set. A series of cutoffs were then considered and predictions above the cutoff were labeled as predicted true cases. With these labels the true positive (sensitivity) and true negative (specificity) rates of the model were calculated based on which receiver operating curves (ROC) were constructed. The area under the ROC curve (AUC) for a specific model quantifies the overall certainty with which the model can predict outcomes at different cut-offs. The single cutoff with the highest geometric average of sensitivity and specificity was selected for each model and specificity and sensitivity values were reported.

Additionally, we calculated the Brier Score which measures the correctness of a model's predictions by summing the differences between the predicted probability of an observation belonging to a class and its actual class label. A low Brier score indicates that the model on average confidently places observations into the correct class. While the AUC quantifies the accuracy of the model, the Brier score quantifies the certainty of the model. For example, if a model assigns a score of 0.51 to every at-risk patient and 0.49 to all other patients, then a cutoff of 0.5 will correctly classify every patient in the validation set and produce a good AUC, but it does not give us a sense of how certain we are about the predictions. The Brier score solves this by measuring the difference between the scores the model predicts (e.g. 0.51) and the true labels (e.g. 1). If all scores are closer to the true label than the Brier score will be close to 0. In this way the Brier score can be used to select the best model from a set with high AUC when the goal is to give not only accurate, but also strong predictions. This is relevant when extrapolating these results to potential meaningful use in a clinical setting.

Feature Importance (except SVM)

The relative importance of the predictive variables in the different models were calculated. For the LASSO and Ridge regression we looked at the magnitude of coefficients and their respective p-values and present the odds ratio. For the Random Forest we measured the importance of each variable by quantifying the change in accuracy of the final predictions after the variable is added to a tree. Larger values indicate the variable is more important. Since the Support Vector Machines did not result in accurate predictions, we did not investigate the relative importance of the predictors. For the neural network we randomly shuffled the observations of a particular variable in the validation set and measured the change in the model's AUC. Variables that create the largest negative change in AUC are defined as the most important.

TRIPOD Statement

Our methodology and research objectives were subject to the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) statement which includes a 22-item checklist, which aims to improve the reporting of studies developing, validating, or updating a prediction model, whether for diagnostic or prognostic purposes[26]. See supplementary table 5 for a full overview.

Tools and Software

Statistical analyses were performed using statistical package program R 3.4.0 and Python.

Results

Population

We included 72,178 patients in our training set and 69,165 patients in our validation set. For both sets the claims from the baseline year (first) were used to generate the 108 predictive features, the follow-up year (second) was used to create our four main outcomes.

Demographics

The mean age of the populations was around 48 years (SD 16.8) for both cohorts and gender was distributed fairly evenly with approximately 52% being female. Both cohorts were predominantly non-Hispanic whites (66% in the training cohort, and 64% in the validation cohort). Looking at medications, biologics use was around 13% for both cohorts in the baseline year, and steroid use was around 27% for both cohorts. We found that 3% of patients in both cohorts had an IBD-related surgery in the baseline year and 6% had an IBD-related hospitalization (Table 2). For a complete overview of the extracted variables during the baseline years of both cohorts, including the average number of hospitalizations, emergency department (ED) visits, insurance coverage, office visits, procedures, lab and imaging tests, and medication use, see Supplementary Table 1.

In the training cohort, 3392 (4.7%) patients had an IBD-related hospitalization, 2454 (3.4%) had IBD-related surgery, 11332 (15.7%) used long term-steroids, and 8661 (12.0%) patients started biological therapy during the one year of follow-up (Table 2).

In the validation cohort, 2863 (4.1%) patients had an IBD-related hospitalization, 2006 (2.9%) had an IBD-related surgery, 11758 (17.0%) used long term steroids, and 9199 (13.3%) of patients started biological therapy during the one year of follow-up (Table 2).

Performance the Validation Model

For the prediction of *IBD-related hospitalizations*, the Random Forest model performed most optimally with an AUC of 0.73 (66% sensitivity, 67% specificity) and a Brier score of 0.21 (See Table 3 and Figure 2). For the prediction of *Initiation of biologics*, the LASSO regression performed best with an AUC of 0.94 (83% sensitivity, 96% specificity) and a Brier Score of 0.05, followed by the Random Forest with an AUC 0.92 (82% Sensitivity, 92% Specificity) and Brier Score of 0.10. Similarly, the Random Forest performed best for

Table 2. Baseline Demographics and Variables of Training and Validation Cohorts in the baseline year

Variable	Training Set Baseline (2015) N= 72,178		Validation Set Baseline (2016) N= 69,165	
Age, mean (SD)	48.5 years (16.8)		47.9 years (16.5)	
Female Gender, n (%)	38254	(53%)	35966	(52%)
Race, n (%)				
White	47710	(66.1%)	44473	(64.3%)
Unknown	12776	(17.7%)	12381	(17.9%)
Black	5052	(7%)	5672	(8.2%)
Hispanic	4692	(6.5%)	4219	(6.1%)
Asian	1949	(2.7%)	2490	(3.6%)
Hospitalizations and ER visits in baseline year, n (%)				
Any ER Visit (#103)	10827	(15%)	11066	(16%)
Any Hospitalization (#97)	4331	(6%)	4150	(6%)
Any IBD-related Hospitalization (#100)	3609	(5%)	3458	(5%)
Any IBD-related ER Visit (#105)	2887	(4%)	2767	(4%)
Any IBD-related surgery (#64)	2165	(3%)	2075	(3%)
Medication use during baseline year, n (%)				
Any IBD Medication use (#1)	28149	(39%)	15908	(23%)
Any Aminosalicylate use (#2&6)	12270	(17%)	11758	(17%)
Any Antibiotic use (#8)	7218	(10%)	6917	(10%)
Any Corticosteroid use (#11,14,17)	18766	(26%)	18675	(27%)
Any Immunomodulator use (#21, 24, 27)	5774	(8%)	5533	(8%)
Any Biologics use (#42)	8661	(12%)	8991	(13%)
Adverse outcomes follow-up year	**Follow-up year (2016)**		**Follow-up year (2017)**	
IBD-related hospitalizations	3392	(4.70%)	2863	(4.14%)
Initiation of biologics	8661	(12%)	9199	(13.3%)
Long-term steroid Use	11332	(15.7%)	11758	(17%)
IBD-related surgery	2454	(3.4%)	2006	(2.9%)

Refers to the corresponding feature in Supplementary Table 1.

the prediction of *Long-term steroid use* with an AUC of 0.81 (48% Sensitivity, 86% Specificity) and Brier score of 0.15. For the prediction of *IBD-related surgery*, the LASSO Regression and Random Forest had the highest AUC, 0.71 and Brier scores of 0.22 and 0.21, respectively.

Overall, the Random Forest resulted in high AUCs for all outcomes, as did the LASSO regression. The Neural Network performed well for some outcomes, but not others. The Support Vector Machine and Ridge regressions, on the other hand, consistently had lower performance than other models. Of the four outcomes included, the models were able to predict the initiation of biologics with the highest accuracy, while IBD-related surgery was the most challenging to predict.

Feature Importance

The relative importance of the predictive variables (Supplementary Table 1) in the different models were calculated except the SVM because of its poor performance. To predict *IBD-related hospitalizations*, long-term steroid use and IBD-related surgeries were strong predictors in both the LASSO and Ridge Regressions. Interestingly, the intensity of healthcare utilization as measured by the number of claims or office visits were the strongest predictors in the Random Forest model, which resulted in similar accuracy compared to the regression models. In the Neural Network on the other hand medication use variables were the most important predictors, but with much lower accuracy, indicating that this model was unable to identify the strongest relationship with IBD-related hospitalizations (Table 3).

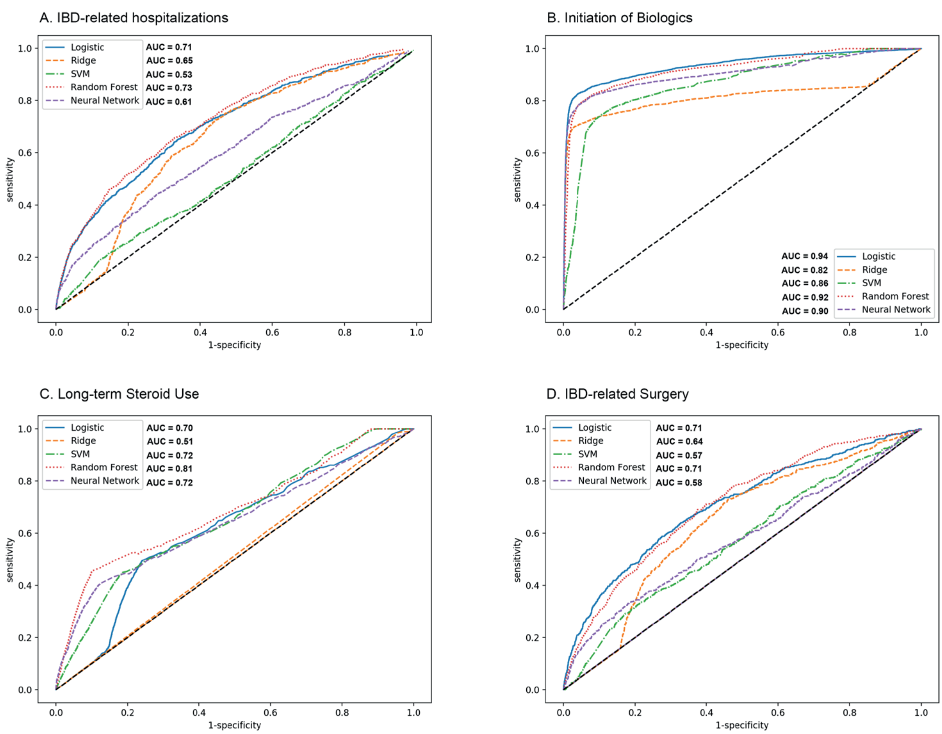

Figure 2. Overview of the performance of the different models for the 4 main outcomes

Table 3. Performance of the different models for the 4 main outcomes

	Sensitivity	Specificity	AUC	Brier Score
IBD-related Hospitalizations				
Ridge Logistic	72%	56%	0.65	0.95
LASSO Logistic	65%	66%	0.71	0.17
Support Vector Machine	54%	48%	0.53	0.04
Random Forest	66%	67%	0.73	0.21
Neural Network	57%	58%	0.61	0.04
Initiation of Biologics				
Ridge Logistic	70%	97%	0.82	0.07
LASSO Logistic	83%	96%	0.94	0.05
Support Vector Machine	75%	89%	0.86	0.10
Random Forest	82%	92%	0.92	0.10
Neural Network	81%	93%	0.90	0.05
Long-term Steroid Use				
Ridge Logistic	99%	4%	0.51	0.83
LASSO Logistic	52%	74%	0.70	0.83
Support Vector Machine	50%	74%	0.72	0.13
Random Forest	48%	86%	0.81	0.15
Neural Network	50%	74%	0.72	0.16
IBD-related surgery				
Ridge Logistic	72%	55%	0.64	0.97
LASSO Logistic	64%	67%	0.71	0.22
Support Vector Machine	54%	55%	0.57	0.03
Random Forest	69%	63%	0.71	0.21
Neural Network	50%	63%	0.58	0.03

Regarding *initiation of biologics*, across all models the use of previous steroids was strongly predictive of a patient being initiated on biologics. The LASSO and Ridge Regressions also found previous CRP lab test and IBD surgeries as strong predictors as well. The random forest, which had the highest accuracy overall, found more heterogenous predictors including ED visits, number of upper endoscopies and X-ray whereas the neural network mostly found previous use of steroids as the strongest predictor.

Table 4. Feature Importance of the Different Models
The performance of the Support Vector Machine was excluded because of it's overall poor performance.

IBD-related Hospitalizations

	Ridge Logistic (AUC = 0.65; Brier score = 0.95)	OR	**LASSO Logistic** (AUC = 0.71; Brier score = 0.17)	OR	**Random Forest** (AUC = 0.73; Brier score = 0.21)	**Neural Network** (AUC = 0.61; Brier score = 0.04)
1	#65 Number of acute IBD surgeries	8.72	#20 Episodes of long-term steroids	1.96	#44 Number of IBD claims	#102 Number of ED visits
2	#64 Any IBD surgeries	2.74	#88 Number of Clostridium difficile stool tests	1.57	#49 Number of office visits	#36 Any certolizumab used this year
3	#88 Number of Clostridium difficile stool tests	2.24	#65 Number of acute IBD surgeries	1.52	#47 Number of UC claims	#35 Episodes of infliximab
4	#20 Episodes of long-term steroids	1.72	#43 Number of episodes of biologics	1.52	#94 Total number of claims	#5 Any oral aminosalicylates used this year
5	#54 Any IBD-related GI visits	1.61	#84 Any MR scans this year	1.51	#96 Number of hospitalizations	#30 Any adalimumab used this year

Initiation of Biologics

	Ridge Logistic (AUC = 0.82; Brier score = 0.07)	OR	**LASSO Logistic** (AUC = 0.94; Brier score = 0.05)	OR	**Random Forest** (AUC = 0.92; Brier score = 0.10)	**Neural Network** (AUC = 0.90; Brier score = 0.05)
1	#42 Any Biologics this year	4.65	#42 Any Biologics this year	8.72	#8 Any antibiotics used this year	#16 Episodes of rectal steroids
2	#13 Episodes of budesonide	2.71	#13 Episodes of budesonide	2.74	#103 Any ED visits this year	#17 Any systemic steroids used
3	#90 Any TB tested this year	2.31	#90 Any TB tested this year	2.24	#10 Episodes of antibiotics	#19 Episodes of systemic steroids
4	#64 Any IBD surgeries	2.29	#23 Episodes of thiopurines	1.72	#80 Any X-rays this year	#20 Episodes of long-term steroids
5	#23 Episodes of thiopurines	2.14	#67 Number of c-reactive protein tests	1.61	#59 Number of upper endoscopies	#21 Any thiopurines used this year

Long-term Steroid Use

	Ridge Logistic (AUC = 0.51; Brier score = 0.83)	OR	LASSO Logistic (AUC = 0.70; Brier score = 0.83)	OR	Random Forest (AUC = 0.81; Brier score = 0.15)	Neural Network (AUC = 0.72; Brier score = 0.16)
1	#20 Episodes of long-term steroids	2.47	#20 Episodes of long-term steroids	2.52	#91 Any influenza vaccine this year	#2 Any rectal aminosalicylates used this year
2	#23 Episodes of thiopurines	2.01	#1 Any IBD medication use	1.61	#103 Any ED visits this year	#7 Episodes of oral aminosalicylates
3	#38 Episodes of certolizumab	1.89	#8 Any antibiotics used this year	1.49	#81 Number of CT scans	#8 Any antibiotics used this year
4	#32 Episodes of adalimumab	1.80	#32 Episodes of adalimumab	1.42	#90 Any TB tested this year	#3 Number of days rectal aminosalicylates used
5	#1 Any IBD medication use	1.58	#78 Any hepatitis B vaccination this year	1.32	#69 Number of sedimentation rate tests	#4 Episodes of rectal aminosalicylates

IBD-related surgery

	Ridge Logistic (AUC = 0.64; Brier score = 0.97)	OR	LASSO Logistic (AUC = 0.71; Brier score = 0.22)	OR	Random Forest (AUC = 0.71; Brier score = 0.21)	Neural Network (AUC = 0.58; Brier score = 0.03)
1	#11 Any budesonide this year	4.85	#108 Any severe disease this year	1.96	#33 Any infliximab used this year	#3 Number of days rectal aminosalicylates used
2	#65 Number of acute IBD surgeries	3.32	#11 Any budesonide this year	1.78	#44 Number of IBD claims	#2 Any rectal aminosalicylates used this year
3	#54 Any IBD-related GI visits	3.18	#65 Number of acute IBD surgeries	1.76	#81 Number of CT scans	#5 Any oral aminosalicylates used this year
4	#84 Any MR scans this year	2.48	#84 Any MR scans this year	1.68	#82 Any CT scans this year	#17 Any systemic steroids used
5	#20 Episodes of long-term steroids	2.48	#20 Episodes of long-term steroids	1.68	#51 Number of IBD office visits	#16 Episodes of rectal steroids

6

Concerning *long-term steroid use*, the regression models again found previous episodes of IBD medication use to be the strongest predictors. The random forest had the highest accuracy and found medical procedures such as imaging and lab tests and ED visits amongst one of the most predictive features. Similar to initiation of biologics, the neural network found episodes and use of IBD medication, in this particular instance aminosalicylates as the strongest predictor.
Lastly, for our fourth outcome *IBD-related surgery* we found comparable patterns within the regression models showing similar results with episodes of long-term steroids, imaging studies, gastroenterology related visits and severe disease being the greatest predictors. The random forest, which was again one of the best performing models, found infliximab use as the strongest predictor, followed by the total of numbers of IBD-related claims, indicating overall utilization was a strong predictor of IBD-related surgery. Interestingly, the neural net again found use of aminosalicylates as the most predictive feature.

Applying Outcomes in the Daily Clinical Practice

There are several ways that these models can be impactful in daily clinical practice. First, the odds ratios provided by the linear models (ridge logistic and LASSO logistic) can be used to evaluate the risk of patients. For example, we found that risk of hospitalization is strongly linked to previous acute IBD surgeries. Specifically, all else being equal an acute IBD surgery increases the odds of a patient being hospitalized by a factor of more than 8.
Second, the complex models that pick up on detailed interactions between the features can be used to make precise risk assessments based on an individual patient's data. As demonstrated by the accuracy of these models, these risk assessments can be used to flag patients that are likely to have a negative outcome with enough notice that providers have time to react and course correct. For example, if we consider a patient with a set of features similar to that of the average patient in the training dataset we can use our models to find that the probability of this patient being hospitalized within the next year is approximately 0.41. This value can give us a sense of the risk assumed by the average IBD patient. Patients whose risk far exceeds this value can be treated as high risk monitored more frequently for predictive markers like CRP of fecal calprotectin.
Lastly, alongside general conclusions about the patient population and risk assessments, these models can be used to evaluate and rank clinical recommendations at the patient level. In this way the models can be used in conjunction with clinical knowledge to motivate actionable, tailored recommendations that are aimed at de-escalating the patient to a lower risk category. Returning to our example of the average patient, we can consider changes to their features that reduce the risk of hospitalization. By examining each feature individually,

the model finds that similar patients to this one benefit from a Clostridium difficile stool test. Specifically, our patient is forecasted to see a reduction in their probability of being hospitalized from 0.41 to approximately 0.29 as a result of this intervention. Between these three applications of our results to clinical practice it is clear that the models we have found provide the foundation for a novel, targeted approach to data-driven IBD care.

Discussion

This study demonstrated that it was feasible to successfully run complex machine learning models on large (Big Data) and representative longitudinal claims data sets of IBD patients. We analyzed traditional models including LASSO and Ridge regressions, machine learning methods such as Support Vector Machines and Random Forests but also included more novel methods like Neural Networks, and successfully compared their relative performance. Overall, the Random Forest performed best across all outcomes, which might indicate that the relationships between the claim's features are best captured by a Random Forest model and that this model framework might work best for claims predictions in general.

Regarding feature importance, it is worth noting that the models returned different features for the different outcomes. The regression models overall had comparable findings, with the most predictive features of negative outcomes being largely related to medication use. The random forest had the highest accuracy overall but had more heterogenous findings, being less limited to medication use as the most predictive feature but also including procedures such as imaging and lab tests as strong predictors. Lastly, the neural net had the most consistent findings across all outcomes, which were mostly medication use related. The difference in findings across the models would argue for the need to explore various models depending on the available data and the choice of outcomes. Based on the research objectives and available data, the models can expose different outcomes and relationships, and this can have an impact on the interpretation and clinical implementation. Furthermore, more novel methods such as neural networks should be further investigated and explored in order to increase accuracy and to examine if they can potentially expose correlations and non-linear relationships that might not be found in more conventional methods.

Several others have used claims data to predict IBD-related utilization events in specific IBD sub-populations. For instance, Waljee et al. applied their model to a set of Veteran's Heath Administration data, which limited their sample to a 93% male and old (mean age

59 years) population[10]; furthermore, public insurance is only used by a minority of United States population[24]. Other prior works that have used ML approaches on private insurance data have been limited by the geographic spread of their sample[13] To our knowledge, this is the first study utilize this ML based prediction approach on a nationally representative IBD population. Additionally, different outcomes were used in some of these studies. Waljee et al. used a composite measure capturing both hospitalization and corticosteroid use, where we have split up these outcomes and checked for long-term steroid use. Their composite measure had an AUC of 0.85 and Brier score of 0.20. We found similar results in our Random Forest model with a AUC of 0.73 and Brier score of 0.21 for hospitalizations and 0.81 AUC and 0.15 Brier Score for long-term steroid use. Furthermore, to our knowledge, our study is the first to predict IBD-related surgery using claims data. Additionally, to our knowledge, the use of novel deep learning methods such as Neural Networks has not been described previously in the IBD literature. These new methods should be further explored and reported on as they have the potential to unlock new opportunities for personalized management in IBD and also because of the fact that these models are now feasible to run because of the increased availability of Big Data and increased computational resources.

There are some limitations worth noting to this study. While a data driven approach to healthcare has great potential to improve patient outcomes, there are some limitations to ML that are worth noting. For one, ML algorithms can only describe correlations between variables or features of interest, not necessarily causation[27]. Furthermore, assumptions are generally made about data sets when applying a given ML algorithm to it, which can narrow the scope of the model in real world situations[27]. In our case, we pre-defined 108 variables to include in our model. Additionally, some outcomes may have a more complicated (i.e. non-linear) relationship with the predictors, and the models we chose may not capture those relationships. Also, we did not include data from the EMR in our prediction model, inclusion of clinical variables could improve the predictive accuracy. However, administrative databases are more readily accessible due to the standardized format and are therefore remain a more straightforward source of data for these initiatives.

Looking ahead, the practical reality of AI is an enigma to many practitioners (See Figure 1 and Table 1). With boundless publications discussing the new wealth of electronic databases and promises of "Big Data", most never go into details about what exactly these new technologies are doing to, for example, "outperform cardiologists reading EKGs"[9]. Unlike the days of small data sets collected through calculated experiment and observation, this data cannot be studied with the standard methods of statistical analysis[9]. The computations that are generally feasible in experimental settings require vast computational resources when the data is on the order of millions of observations. Therefore, smarter algorithms were created to perform statistical analysis on large data sets. Many would refer to this jump as the development of Machine Learning (ML), but formally it is closer to the sub-field of Computational Statistics. The real jump to ML utilizes the vast amounts of data in a sophisticated way that emphasizes accurate predictions of outcomes over significance and interpretability[9]. With this mindset change, outcomes can be evaluated by experts and the entire process can be incorporated into decision support in daily clinical practice. Now, without much effort from the user, algorithms can make predictions given new data and automatically make a recommendation or perform some action, appearing to have Artificial Intelligence (AI)[9]. With the increase of computational power and abundance of longitudinal patient data, applying machine learning and its subset of Deep Learning in Big Data sets has become feasible. In this study we provide the first steps in this direction. Kim et al. (2019) has already showcased transferability of these models to different institutions, alleviating a major concern[19]. The next step would be to integrate these models in a prospective setting to study their performance on reliability, patient outcomes and costs.

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Supplementary Table 1. 110 predictive features
Summary of the overall prevalence of the 110 potentially predictive factors included in our models. These features were compiled by experts in the IBD field (WD and DH) and pulled from the 110 features earlier published by WD and DH (Vaughn et al. 2018). Shading of pink represents binary variables, yellow represents variables related to days, and cyan represents variables related to courses of medication. Values reflect the MEAN, which included claims submitted to United HealthCare between 2015 and 2017. Two of the features could not be constructed and were excluded from the analysis (#55 and #93)

#	explanation	Training 2015 mean	Validation 2016 mean	Comparison Vaughn et al.
1	Any IBD related medications use (all the medications in variables #2 - #41)	0.39	0.23	0.88
2	Any rectal aminosalicylates used in this year	0.03	0.03	0.14
3	Number of days rectal aminosalicylates used	99.51	100.39	15
4	Number of times an episode of rectal aminosalicylates started	0.03	0.04	0.17
5	Any oral aminosalicylates used in this year	0.14	0.14	0.53
6	Number of days oral aminosalicylates used	27.78	28.73	124
7	Number of times an episode of oral aminosalicylates started	0.15	0.15	0.47
8	Any antibiotics used in this year	0.1	0.1	0.24
9	Number of days antibiotics used	2.03	1.9	6.6
10	Number of times an episode of antibiotics started	0.1	0.1	0.32
11	Any budesonide (local release steroid) used in this year	0.04	0.04	0.06
12	Number of days budesonide (local release steroid) used	3.43	3.62	7.7
13	Number of times an episode of budesonide (local release steroid) started	0.04	0.04	0.07
14	Any rectal steroids used in this year	0.09	0.09	0.08
15	Number of days rectal steroids used	2.11	2.1	3.9
16	Number of times an episode of rectal steroids started	0.09	0.09	0.10
17	Any systemic steroids used in this year	0.13	0.14	0.28
18	Number of days systemic steroids used	4.87	4.98	19
19	Number of times an episode of systemic steroids started	0.13	0.14	0.39
20	Number of times an episode of long term (>3 consecutive months) steroids started	0.15	0.17	0.06
21	Any thiopurines used in this year	0.06	0.06	0.19
22	Number of days thiopurines used	12.1	12.5	48
23	Number of times an episode of thiopurines started	0.06	0.06	0.13
24	Any methotrexate used in this year	0.01	0.01	0.03
25	Number of days methotrexate used	1.63	1.95	6.0
26	Number of times an episode of methotrexate started	0.01	0.01	0.03
27	Any cyclosporine or tacrolimus used in this year	0.01	0.01	0.01
28	Number of days on cyclosporine or tacrolimus	1.02	0.99	1.4

Supplementary Table 1. Continued

#	explanation	Training 2015 mean	Validation 2016 mean	Comparison Vaughn et al.
29	Number of times an episode of cyclosporine or tacrolimus was started	0.01	0.01	0.00
30	Any adalimumab used in this year	0.03	0.04	0.06
31	Number of days adalimumab used	6.22	8.1	15
32	Number of times an episode of adalimumab started	0.03	0.04	0.04
33	Any infliximab used in this year	0.08	0.09	0.11
34	Number of days infliximab used	20.47	22.13	28
35	Number of times an episode of infliximab started	0.08	0.09	0.08
36	Any certolizumab used in this year	0.01	0.01	0.01
37	Number of days certolizumab used	1.82	1.43	2.9
38	Number of times an episode of certolizumab started	0.01	0.01	0.01
39	Any natalizumab used in this year	0	0	0.00
40	Number of days natalizumab used	0.1	0.11	0.40
41	Number of times an episode of natalizumab started	0	0	0.00
42	Any biologics (variables #30-#41) used in this year	0.12	0.13	0.18
43	Number of times an episode of biologics (variables #30-#41) started	0.12	0.13	0.13
44	Number of IBD claims	20.45	23.21	5.9
45	Number of Crohn's disease claims	12.58	14	3.3
46	Any Crohn's disease claims this year	0.41	**0.42**	0.51
47	Number of ulcerative colitis claims	8.04	9.41	2.7
48	Any ulcerative colitis claims this year	0.47	**0.51**	0.63
49	Number of office visits	8.47	8.39	8.1
50	Any office visits this year	0.96	0.96	0.98
51	Number of IBD related office visits	1.73	1.87	2.3
52	Any IBD related office visits this year	0.62	0.65	0.80
53	Number of IBD related office visits with a gastroenterologist	0	0	1.2
54	Any IBD related office visits with a gastroenterologist this year	0	0	0.53
55	Number of IBD related office visits with a UCLA gastroenterologist	N/A	N/A	0.02
56	Any IBD related office visits with a non-UCLA gastroenterologist this year	0.02	0.01	0.51
57	Number of colonoscopies	0.39	0.41	0.49
58	Any colonoscopies this year	0.32	0.34	0.44
59	Number of upper endoscopies	0.11	0.11	0.14
60	Any upper endoscopies this year	0.11	0.11	0.13
61	Number of endoscopies of the small intestine	0	0	0.03

6

Supplementary Table 1. Continued

#	explanation	Training 2015 mean	Validation 2016 mean	Comparison Vaughn et al.
62	Any endoscopies of the small intestine this year	0	0	0.02
63	Number of IBD related surgeries	0.05	0.06	0.06
64	Any IBD related surgeries this year	0.03	0.03	0.04
65	Number of acute IBD related surgeries (this is a subset of IBD related surgeries)	0.05	0.05	0.06
66	Any acute IBD related surgeries (this is a subset of IBD related surgeries) this year	0.03	0.03	0.04
67	Number of C-reactive protein tests	0.27	0.29	0.68
68	Any C-reactive protein tests this year	0.27	0.29	0.32
69	Number of sedimentation rate tests	0.27	0.28	0.89
70	Any sedimentation rate tests this year	0.25	0.26	0.39
71	Number of stool calprotectin tests	0.04	0.05	0.03
72	Any stool calprotectin tests this year	0.04	0.05	0.02
73	Number of complete blood counts	1.02	1.04	2.7
74	Any complete blood counts this year	0.76	0.77	0.82
75	Number of liver enzyme tests	1.01	1.04	2.3
76	Any liver enzyme tests this year	0.73	0.75	0.79
77	Number of Hepatitis B tests	0.23	0.26	0.12
78	Any hepatitis B vaccination this year	0.1	0.11	0.10
79	Number of X-rays	0.15	0.14	0.24
80	Any X-rays this year	0.11	0.1	0.13
81	Number of CT scans	0.23	0.23	0.29
82	Any CT scans this year	0.20	0.19	0.19
83	Number of MR scans	0.08	0.08	0.06
84	Any MR scans this year	0.05	0.06	0.05
85	Number of ultrasounds	0.08	0.08	0.10
86	Any ultrasounds this year	0.07	0.07	0.08
87	Any bone loss assessment this year	0.06	0.06	0.07
88	Number of Clostridium difficile stool tests	0.1	0.09	0.16
89	Any Clostridium difficile stool tests this year	0.09	0.09	0.12
90	Any TB tested this year	0.09	0.11	0.08
91	Any influenza vaccine this year	0.16	0.13	0.17
92	Any pneumococcal vaccine this year	0.06	0.06	0.02
93	Charlson comorbidity score (higher score implies comorbidities)	N/A	N/A	0.51

Supplementary Table 1. Continued

#	explanation	Training 2015 mean	Validation 2016 mean	Comparison Vaughn et al.
94	Total number of claims	27.45	27.82	73
95	Total number of days prescriptions were covered by plan	113.59	119.61	364
96	Number of hospitalizations	0.13	0.11	0.28
97	Any hospitalizations this year	0.06	0.06	0.17
98	Total number of days hospitalized	0.85	0.74	1.8
99	Number of IBD related hospitalizations	0.16	0.16	0.10
100	Any IBD related hospitalizations this year	0.05	0.05	0.08
101	Total number of days hospitalized related to IBD	0.52	0.53	0.76
102	Number of ED visits	0.72	0.73	0.58
103	Any ED visits this year	0.15	0.16	0.26
104	Number of IBD related ED visits	0.06	0.07	0.24
105	Any IBD related ED visits this year	0.04	0.04	0.13
106	Age	50.13	48.68	42
107	Any moderate disease this year (based on a combination of number of relapses and long term steroid use)	0.01	0	0.21
108	Any severe disease this year (based on a combination of number of relapses and long term steroid use)	0.13	0.19	0.15
109	Relapse rate (based on how use of systemic steroids, use of biologics, and acute IBD related surgeries)	0.06	0.06	0.58
110	The number of years someone has been a continuous member of United HealthCare or Anthem	1.96	2.56	1.6

Supplementary Table 2. Development of Main Outcomes

Hospitalization	For each patient take all claims with place of service code = 21 (inpatient hospital). Next check the 9 diagnosis codes for each hospital claim for any of the following IBD-related ICD 9/10 codes: 5551, 5552, 5559, 5561, 5562,5563,5564, 5565,5566, 5568, 5569, K500, K501, K508, K509, K510, K512, K513, K514, K515, K518, K519. If any of these codes are present in any of the hospitalization claims, then the patient is considered to have had an IBD-related hospitalization that year.
Biologics	For each patient search for facility and pharmacy claims with any of the following drug names or CPT codes: ADALIMUMAB, CERTOLIZUMAB PEGOL, INFLIXIMAB, NATALIZUMAB, J0135, J1745, J2323, Q4079, J0718, C9249. If any claims are found, then the patient is considered to have initiated Biologics that year.
Surgery	For each patient search the medical and facility claims for any claims with the following CPT codes: 44005-44346, 44602-44701, 45000-45190, 45395-45999, 46020-46060, 46270-46288, 49000-49084. If any claims are found, then the patient is considered to have had an IBD-related surgery that year.
Long-term Steroids	For each patient search for claims where any of the following steroids were given: HYDROCORTISONE, PREDNISOLONE, DEXAMETHASONE, PREDNISONE, METHYLPREDNISOLONE. Using the variable COUNT_DAYS_SUPPLY calculate the length of time of each episode of steroids. If any episode lasts longer than 3 months (90 days), then the patient is considered to have had an episode of long-term steroids for that year.

Supplementary Table 3. Technical Appendix Models

Model	Technical Detail
Ridge regression and LASSO	The first two models fit include Ridge regression and LASSO. These are regression techniques that place a penalty on the model coefficients to ensure that we do not overfit to the training data. In this way these methods jointly perform variable selection and model training. The primary difference between these two models is in the choice of penalty. Ridge regression penalizes the sum of squares of the least squares estimates and as the user-selected size of the penalty increases all estimates become increasingly smaller but never reach 0. This can be problematic for researchers who are interested in the substantive interpretation of all coefficients in the model. LASSO corrects this problem by instead penalizing the sum of absolute values of the estimates. This change leads some of the estimates to become 0 as the size of the penalty increases. The resulting model then consists only of the estimates that are significantly large.
Support Vector Machine	We also trained several Support Vector Machines with varying kernels. These models attempt to separate the patients in the training set who did experience the negative health outcome from those who did not with the largest margin possible. Since many high-dimensional data are not separable with linear support vectors, transformations through the use of kernels are employed to achieve non-linear regions. We try several such kernels, but the one which obtains the highest testing accuracy, which also happens to be one of the most often used kernels, is the Gaussian radial basis function.
Random Forest	To isolate important variables, we also fit Random Forest models. These are ensemble classifiers made up of collections of decision trees. Each decision tree makes linear cuts through the variable space to achieve the best division between the two classes. To capture the nuances in the data each tree is trained and evaluated on random subsets of the data drawn with replacement. To avoid having too many correlated trees that choose the same best predictors, at each split in the tree only a fraction of the predictors is considered.
Neural Networks	To understand the complex non-linear patterns in the data, we train several Neural Networks. These models consist of several imbedded linear functions, known as hidden layers, wrapped in non-linear "activation" functions. The choice of activation function at each layer determines the functional form of the model. After experimenting with several options we use a mix of standard and parametric Rectified Linear Units (ReLUs). The output layer is followed by a sigmoid activation function, so that we may interpret the output as the probability that the patient will experience the outcome. To train the model we use stochastic gradient descent to minimize a binary cross entropy loss.

Supplementary Table 4. Medications

Drug group	Drug type	Included drugs	CPT
Aminosalicylates	ASA - oral ASA - rectal	mesalamine, sulfasalazine, balsalazide, olsalazine	
Antibiotics		metronidazole, ciprofloxacin	
Corticosteroids	budesonide systemic rectal	budesonide prednisone, methylprednisolone, hydrocortisone, prednisolone, dexamethasone	
Immunomodulators	thiopurines methotrexate cyclosporine tacrolimus	azathioprine, mercaptopurine, methotrexate cyclosporine tacrolimus	
Biologics	adalimumab certolizumab infliximab natalizumab	adalimumab certolizumab pegol infliximab natalizumab	J0135 J0718, C9294 J1745 J2323, Q4079

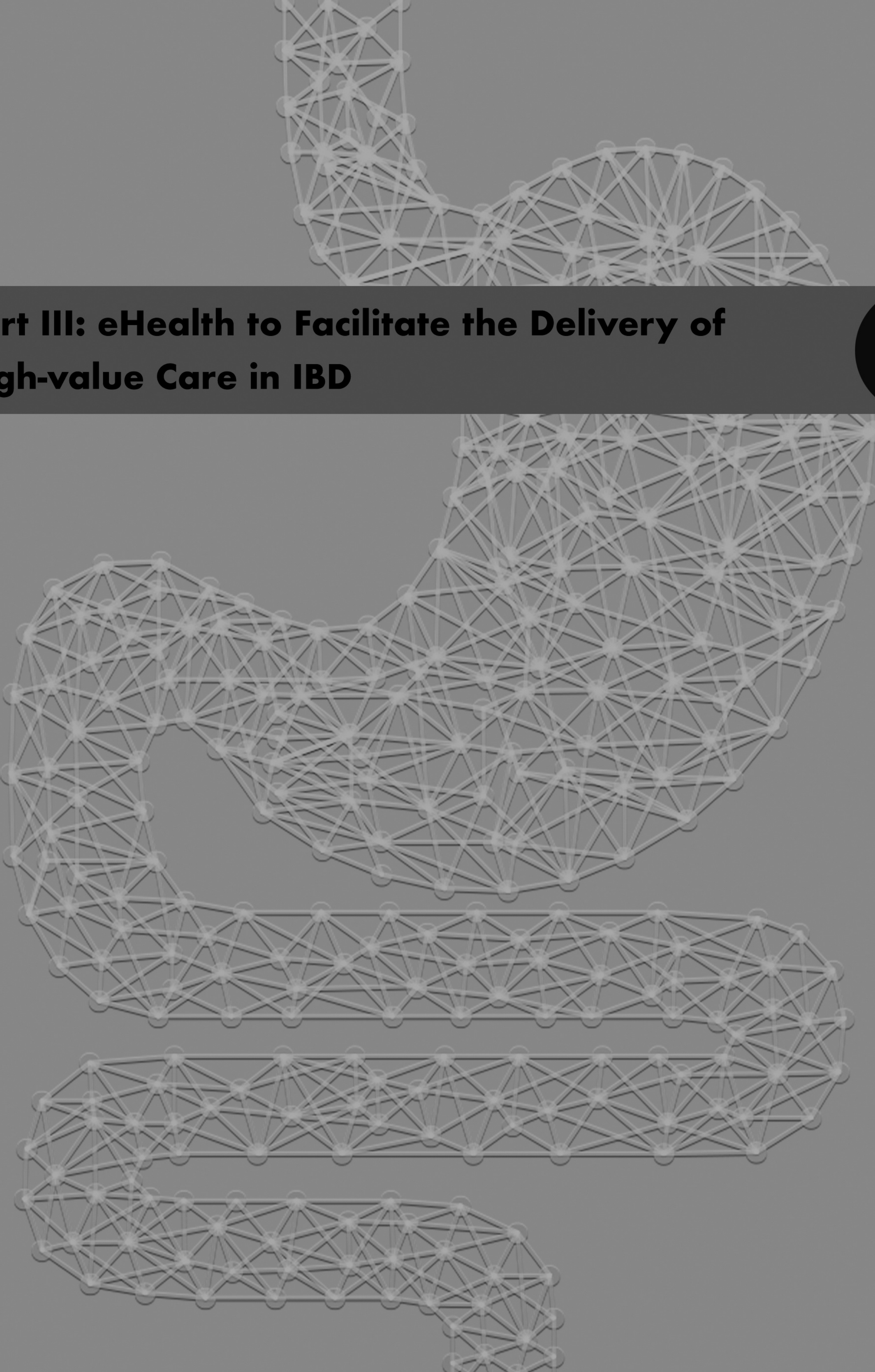
Supplementary Table 5. TRIPOD Checklist: Prediction Model Development

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4,5
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	4,5
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	6
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6
	5b	Describe eligibility criteria for participants.	6
	5c	Give details of treatments received, if relevant.	6
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	7
	6b	Report any actions to blind assessment of the outcome to be predicted.	7
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	7
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	7
Sample size	8	Explain how the study size was arrived at.	6,7
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	6,7
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	6
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	7,8
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	9
Risk groups	11	Provide details on how risk groups were created, if done.	7

Supplementary Table 5. Continued

Section/Topic	Item	Checklist Item	Page
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	11
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	11
Model development	14a	Specify the number of participants and outcome events in each analysis.	11
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	11
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	11,12
	15b	Explain how to the use the prediction model.	13
Model performance	16	Report performance measures (with CIs) for the prediction model.	11,12
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	16
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	15
Implications	20	Discuss the potential clinical use of the model and implications for future research.	17
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	18
Funding	22	Give the source of funding and the role of the funders for the present study.	1

Part III: eHealth to Facilitate the Delivery of High-value Care in IBD



CHAPTER 7

Patient Experiences and Outcomes of a Telehealth Clinical Care Pathway for Postoperative Inflammatory Bowel Disease Patients

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Abstract

Background
Despite advancements in treatment for inflammatory bowel disease (IBD), surgery remains inevitable for patients and IBD management is costly.

Introduction
Frequent postoperative monitoring is needed for early detection of both short-term complications and long-term disease recurrence. We developed a care pathway for postoperative home monitoring of IBD patients using telehealth applications.

Materials and Methods
We performed a retrospective cohort study with a matched control group to assess the efficacy of the Tight Control Surgery Scenario (TCSS), a four-week postoperative care pathway. IBD patients aged 18 or older who underwent an IBD-related intestinal operation between October 2013 and December 2015 were eligible. Enrolled participants submitted post-surgical questionnaires and wound photos via email. We measured patient satisfaction with the care pathway and assessed its impact on 30-day postoperative hospital readmission rates, emergency department (ED) visits, and GI-related office visits.

Results
64 cases were enrolled in TCSS and matched to 64 historic controls. Patients who completed the additional evaluation survey expressed overall satisfaction. Readmissions, 30-day ED rates, and GI visits were numerically higher in cases compared to controls, but this difference was not statistically significant.

Discussion: TCSS demonstrates the feasibility of implementing a telehealth care coordination platform for post-surgery IBD management. Patients with more complications may have sent in more photos due to greater concern for maintaining their health.

Conclusions
The implementation of TCSS for easy home monitoring is feasible. While we did not see reductions in ED visits, GI follow-up visits, or readmissions, patient satisfaction was high thus demonstrating its feasibility for telehealth applications.

Introduction

Despite advancements in medical pharmaceuticals for inflammatory bowel disease (IBD)[1], up to 15% of ulcerative colitis (UC) patients will undergo surgery within 20 years of diagnosis and nearly 50% of Crohn's disease (CD) patients within 10 years of diagnosis[2,3]. Unfortunately, surgery is not always curative but rather ameliorates symptoms. Up to 30% of CD patients will require additional bowel resections within 10 years[1]. Recurrence of CD post-surgical resection has also been shown to be at a rate of 55% 5 years post-surgery and 76% 7 years post-surgery[4], demonstrating the high prevalence of disease recurrence. Additionally, postoperative morbidity remains high following intestinal surgery in CD with 30-day infectious complications and intra-abdominal sepsis as high as 30%[5],

IBD management is also costly due to excess utilization of healthcare services. Kappelman et al. found that the mean number of excess ED visits per 100 CD patients, compared to their non-IBD controls matched by gender, age, and geographic region, is 20.1; the mean number of excess ED visits per 100 UC patients was 10.3 when compared to controls[6]. In addition, it has been shown that the frequency of IBD-related ED visits has increased by approximately 51% over the last decade[7] and the cumulative nationwide cost of IBD-related ED visits has increased by over 200% in the past decade[7]. The most costly cases included IBD patients who had a surgical stay[8].

Readmission after colorectal surgery is common, with rates ranging from 6-25% often due to bowel obstruction, surgical site infection, or abscesses[9]. Bliss et al. found that 14.7% of IBD patients were readmitted within 30 days after a colectomy[10]. Hospital readmissions after surgery are a significant driving factor of financial costs. One study found that 13% of patients readmitted after receiving a hospital resection required resources from the intensive care unit and 6% required a reoperation. The combined median direct cost was over twice as high for readmitted patients than for non-readmitted ones[11]. High costs associated with managing IBD after surgery underscore the need for more effective postoperative care management.

Given the complexity of IBD and risk of disease progression after surgery, frequent monitoring is needed for early detection of recurrence and complications. Telemonitoring has been shown to be effective in managing chronic diseases including COPD[12], cardiovascular disease[13,14], and IBD[15]. In IBD, a study on home telemonitoring in teenagers found that telemonitoring can decrease outpatient visits and costs of care compared to conventional follow-up[16]. In addition, the UC HAT home telemanagement system showed gains in quality of life for patients using UC HAT compared to those receiving the best available care[17]. However, no significant improvements were found in medication adherence or disease activity, suggesting the need for further research in the effectiveness of telemedicine for IBD[18]. While there have been some conflicting findings, electronic health (eHealth) interventions for IBD have overall been shown to improve quality of life, disease activity, and reduce healthcare costs[19]. To our knowledge, there has not yet been a published study conducted on telemanagement specifically for postoperative IBD care.

To address the high costs and complications of post-surgery maintenance, the University of California, Los Angeles (UCLA) Center for IBD developed a care pathway for IBD-related surgery, designed to tightly monitor patients at home after discharge using telemonitoring tools in order to improve the experience. According to the 2011 Annual excHangE on the ADvances in Inflammatory Bowel Disease (IBD Ahead) educational program, robust monitoring should involve different clinical measurements[18]. Our pathway included postoperative symptom assessments, including endoscopic evaluations and self-reported patient outcomes. We hypothesized that frequent and proactive monitoring of IBD patients would improve the patient experience and could reduce postoperative complications and IBD-related hospital readmissions, thus improving postoperative management.

Materials and Methods

Design & Outcomes

After institutional review board approval (IRB#16-000263), we performed a retrospective cohort study with a matched control group to assess the effects of an electronic postoperative care pathway on patient experience and resource utilization. Enrolled patients followed a 4-week reporting schedule that culminated in a follow-up visit with a gastroenterologist (GI). Participants filled out daily to weekly online questionnaires about symptoms and wound-healing and uploaded wound photos. Participants also had direct e-mail access to a specialized surgical IBD nurse for questions.

We assessed the impact of the pathway during 30-day post-discharge on 1) hospital readmission rates, 2) ED visits, and 3) GI office visits. Secondarily, the number of wound photos submitted per case was measured to estimate TCSS adherence.

Population

Patients aged 18 or older, who had an IBD diagnosis confirmed by endoscopy or radiological evaluation and underwent IBD-related intestinal surgery performed by a single IBD surgeon, were eligible for study inclusion.

Between October 2013 and December 2015, a research nurse identified cases from a surgical list and explained the TCSS study to patients by phone. Participants were then consented by the research nurse at their pre-operative clinical visit. Patients that underwent surgery between that same timeframe and were not assigned to the scenario were selected as controls (**Figure 1**). We used a custom matching algorithm to make accurate, representative case-control matches based on age, gender, disease type and type of surgery.

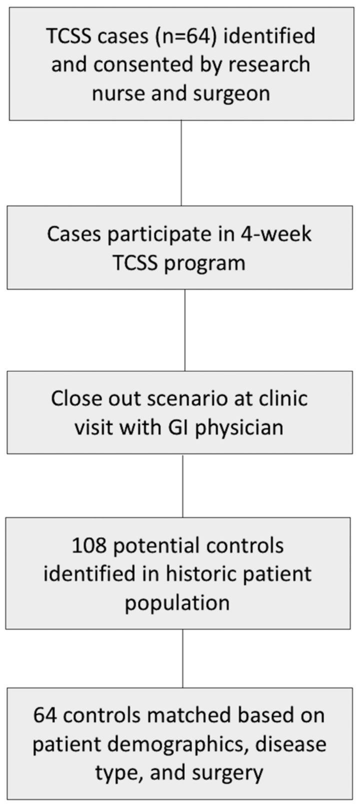

Figure 1. Flowchart of study design

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The Care Pathway: Tight Control Surgery Scenario (TCSS)

TCSS is a four-week program monitoring the recovery of IBD patients after surgery. All enrolled patients filled out a post-surgery questionnaire via email for 4 weeks after discharge (Figure 2). In Week 1 they filled out the questionnaire and uploaded a picture of their abdominal surgery wound(s) every day. In Week 2 they did so on days 2, 4, and 7. In Weeks 3 and 4, patients filled out the questionnaire and uploaded a picture on day 7. A total of 12 questionnaires were collected over the course of 4 weeks. Pain was measured with a 0-10 Likert scale; wound healing was assessed through submission of wound photos; and bowel function was evaluated using ostomy output and stool frequency.

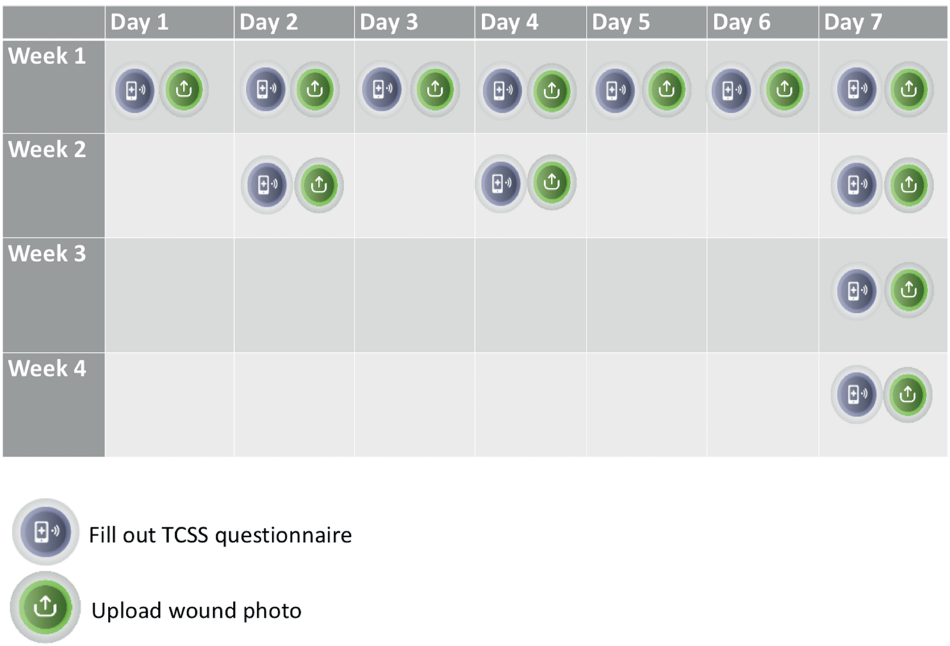

Figure 2. Calendar of four week TCSS program

All questionnaires and wound photo uploads were completed by patients and sent by email to a dedicated research nurse who also checked information and pictures daily to help monitor patients. After the four weeks, patients had a clinic visit with their gastroenterologist, who closed this surgical scenario and decided with the patient the next steps for care.

Questionnaires & Definitions

Post-Surgery TCSS Questionnaire and picture uploads

Questions in the TCSS questionnaire (Table 1) were developed to identify abnormalities and to assess pain, weight, temperature, diet, and wound information. When patients responded with certain "red-flag" answers, the surgical nurse would discuss the patient with the surgeon for appropriate actions. These red flags included certain answers that would be detected by nurses, including: fever over 100 degrees Fahrenheit; pain increase (VAS) equal to or more than 2 points in 24 hours; ileostomy output lower that 500 mL or more than 1000 ml; and bowel movements of 0 in patients without an ostomy. An optional TCSS evaluation survey was administered to all cases one week after the end of the TCSS via email. It contained questions gathering patient feedback on their experience in the TCSS.

Data collection & Statistical Analysis

Data on the three measured outcomes (GI follow-up visits, ED visits, and hospital readmission) was collected from electronic medical records (EMR) and clinic visit summaries for both cases and matched controls. Data on ostomy output, wounds, and physiological conditions (temperature, diet, etc.) were collected from patient-reported outcomes (PROs) via the TCSS for the cases only.

TCSS participants and the matched controls were compared to assess the effect of the TCSS on GI-follow-up visits, ED visits and hospital readmissions. We matched each of the 64 TCSS cases to a control patient based on patient characteristics (age, gender, disease type, type of surgery).

Cases were matched to controls by calculating the matching distance between every case and every potential control based on age, gender disease type and type of surgery. The closer the match between case and control in features (age, gender, etc.), the smaller the distance and the more appropriate the match. The algorithm matches every case to the closest control, but if a later case is found to be a closer match to a control that has already been assigned, it is subsequently assigned to the later case. This leaves some unmatched cases at the end of the first iteration. The algorithm goes through those that are still unmatched until all 64 matches are made.

For statistical purposes, we considered the matched case and control to be the same subject with two different set of outcomes, one in which they use the telemonitoring (TCSS) and

Table 1. TCSS Surgery Questionnaire Form

Question	Response
1. Pain: Rate your abdominal pain on a scale from 0 to 10, where 0 is no pain and 10 is the worst pain.	Visual analog scale
2. Weight: Weigh yourself on the indicated days. Preferably do this after getting up in the morning after going to the bathroom wearing nothing but your underwear.	Short answer in lbs or kg
3. Temperature: Measure your body temperature. (Preferably in the morning.)	Short answer in degrees F or C
4. Diet: Let us know what you eat and drink! • How many cups did you drink today (water, tea, coffee, etc) (#) ? • What did you eat today? a. Fluids (soup etc.) b. Soft foods (oatmeal, yoghurt, etc.) c. Solid food (meat, pasta, rice, potatoes, vegetables, etc.)	 Short answer Yes or no
5. Do you have an ostomy:	Yes, an ileostomy [Question 6A] Yes, a colostomy [Question 6B] No [Question 6C]
6. A) how much did your ileostomy produce this day (mL)? B) how many times did you empty your ostomy bag this day? (#) C) How many stools did you have the past 24 hours? (#)	Short answer
Now some questions regarding your wound: 7. Is your wound open or closed? 7A. does your wound drain?	open [Question 7A] closed [Question 8] yes [open drop down menu: What does the wound drain? Blood, pus, other] no [Question 8]
8. Do you have any other problems (e.g. nausea/painful urination/headaches)?	Short answer
9. Pain medication: Did you use Tylenol or Narcotics? How many pills did you take?	Yes or no Short answer indicating pill type and corresponding number of pills
10. Upload wound photo: When taking the photo of the surgical wound, make sure there is enough light to get a picture of good quality. Also make sure the entire wound is covered in the picture and it is in focus. When to upload: - week 1: every day - week 2: at day 7 - After that you don't have to send pictures anymore, but whenever you feel something is wrong or you want us to look at the wound, please send a picture.	Attach photo in email to research nurse

one in which they did not. We used a McNemar test to compare proportions between cases and controls. We used a two-proportion z-test to compare outcomes between low (0-3 photos) and high (≥4) number of wound photos.

Results

Sample Characteristics

In total, 64 cases were enrolled in the TCSS pathway. Out of 108 historic controls identified in the patient population that did not choose to participate in the TCSS, we matched 64 with our cases based on age, diagnosis, and surgery characteristics (Table 2). Our case and control samples were both predominantly Caucasian (76.5% and 71.9%, respectively), and had never smoked (70.3% and 68.8%, respectively). Median age of cases was 35 years and 48% were male. Median age of controls was 33.5 and 60.9% were male. A greater number of cases than controls used biological therapies, antibiotics, and 5ASA. In the cases, 50% (n=32) of the surgeries were for CD, 44% (n=28) were for UC, and 6.3% (n=4) were for indeterminate colitis. Case surgeries included bowel resection, colectomy, ileostomy, and stomas. The 64 matched historic controls had a median age of 33.5 and 61% were male. Of the controls, 50% of surgeries were for CD (n=32) and 50% were for UC (n=32).

Mean number of wound photos sent was 3.8 (median of 3 wound photos). Average daily stool frequency was 6 in patients without ileostomy; patients with an ileostomy had an average ileostomy output of 930 mL; an initial pain score of greater than or equal to 5 was reported in 34% of patients, and an average 2-point decrease was observed during the program.

Patient Experience

16 patients (25%) enrolled in the TCSS pathway opted to complete the post-surgical care survey (**Table 3**). Patients expressed overall satisfaction with the program, with 81% describing their experience as “excellent” and 94% describing the amount of TCSS questions as reasonable. Patients reported that without participation in the TCSS pathway, they would most likely have used a phone call to the doctor’s office as a resource for care (94%). Additionally, 56% of patients felt their recovery would have had a different result without participation in the TCSS program.

Table 2. Patient Demographics

Variable	Subvariable	Cases (n=64)	Controls (n=64)
Mean age		37.9	38.3
Median age		34.5	33.5
Male gender		31 (48.4%)	39 (60.9%)
Diagnosis			
	UC	28 (43.8%)	29 (45.3%)
	CD	32 (50.0%)	34 (53.1%)
	Indeterminate colitis	4 (6.3%)	1 (1.6%)
Race			
	Caucasian	49 (76.5%)	46 (71.9%)
	Black	5 (7.8%)	7 (10.9%)
	Asian	5 (7.8%)	1 (1.6%)
	Other or not declared	5 (7.8%)	10 (15.6%)
Ethnicity			
	Non-Hispanic	55 (85.9%)	53 (81.5%)
	Hispanic, Mexican/ Mexican American, Chicano/a	9 (14.1%)	11 (17.2%)
Marital status			
	Married	31 (48.4%)	28 (43.8%)
	Single	30 (46.9%)	32 (50%)
	Divorced	3 (4.7%)	3 (4.7%)
	Significant other	0	1 (1.5%)
Smoking status			
	Current smoker	1 (1.5%)	2 (3.1%)
	Past smoker	18 (28.1%)	18 (28.1%)
	Never smoker	45 (70.3%)	44 (68.8%)
Insurance			
	Medicare	9 (14.1%)	12 (18.8%)
	Medicaid or Medi-Cal	0	2 (3.1%)
	Other or unknown	55 (85.9%)	50 (78.1%)
Comorbidities			
	Diabetes mellitus	4 (6.3%)	9 (14.1%)
	Chronic kidney disease	0 (0%)	1 (1.6%)
	COPD or asthma	4 (6.3%)	4 (6.3%)
	Cancer	6 (9.4%)	6 (9.4%)
	Organ transplant	1 (1.6%)	1 (1.6%)
	Congestive heart failure	1 (1.5%)	0
	HIV/AIDS	0	0
	Hypertension	4 (6.3%)	6 (9.4%)
	Hypothyroid	1 (1.6%)	3 (4.7%)

	Mental illness (depression, anxiety, etc.)	18 (28%)	29 (45.3%)
Medications			
	5ASA Corticosteroids	5 (7.8%) 2 (3.1%)	4 (6.3%) 4 (6.3%)
	Immunomodulators	9 (14.1%)	10 (15.6%)
	Antibiotics	13 (20.3%)	6 (9.4%)
	Biological therapies	29 (45.3%)	24 (37.5%)
Surgery Type			
	Abdominal	64 (100%)	64 (100%)
	Small bowl resection	1 (1.6%)	7 (10.9%)
	Ileocaecal or ileocolonic resection	22 (34.4%)	14 (21.9%)
	Stoma takedown	20 (31.3%)	20 (31.3%)
	Colectomy or proctectomy	22 (34.4%)	24 (37.5%)
	Non rescue stoma	19 (29.7%)	17 (26.6%)
	Rescue ileostomy	3 (4.7%)	6 (9.4%)
	Small repairs	20 (31.3%)	30 (46.9%)
	Resection	40 (62.5%)	40 (62.5%)
	Stoma	22 (34.4%)	23 (35.9%)

In the post-surgical care survey, patients were also able to provide optional comments on their experience in the TCSS program. Two (13%) patients indicated that they would not change the program when asked what they suggest could be improved. Three (19%) expressed feeling comforted that they were receiving personalized follow-up care. Five (31%) patients expressed positive satisfaction with the ease of accessibility to the care team. One patient stated, “I loved knowing that someone was always checking up on me and my recovery through the emails. It was nice knowing that I could ask any questions I had at any time. I probably would have felt a little lost, on my own, and stressed out without the program.” Another patient expressed, “I just knew I had expert help just a click away to someone who knew me.”

Other patients gave feedback on ways to improve the program. One participant suggested having a more personal follow-up process in addition to emails, such as having a care coordinator check in with phone calls. A notable comment from another participant was that they would have liked to receive feedback from staff about the wound photos patients sent in.

Table 3. Patient Experience. Questions of the post-surgical care survey with proportion of respondents (n=16) who answered. Question #5 was open-ended, allowing participants to list suggestions for change. Many opted to highlight positive aspects of the program for this question.

Question	Response Percentages n (%)
1. How was your experience participating in the post-surgery questionnaire and follow up program?	Excellent: 13 (81.3) Good: 2 (12.5) Had no effect on recovery: 1 (6.3)
2. Would you say the questions you answered were	Reasonable: 15 (93.8) Too time consuming: 1 (6.3)
3. What other resources would you have used had you not participated in this post-surgery program? *Participants were able to choose multiple options.	Phone call to doctor's office: 15 (93.8) Clinic visits: 6 (37.5) ER visits: 4 (25.0) Visiting nurse: 4 (25.0)
4. Do you think your recovery may have turned out differently had you not participated in the post-surgery program?	Yes: 9 (56.3) No: 7 (43.8)
5. What areas of the post-surgery program would you improve?	More feedback and interaction with staff/providers: 2 (12.5) No suggested changes: 2 (12.5) No response: 2 (12.5) **Positive highlights** Ease of access to care team: 5 (31.3) Feeling that staff cared post-surgery: 3 (18.8)

Clinical Outcomes (ED Visits, Readmissions, 30-Day GI Follow-up visit)

Readmissions, 30-day ED rates, and GI visits were numerically higher in cases compared to controls, but this difference was not statistically significant (**Table 4**). ED rates were 20% in the control group and 25% in cases (p=0.677); readmission rates were 22% in the control group and 22% in cases (p=1.00); finally, GI follow-up rates were 47% in controls and 58% in cases (p=0.265).

Patients who sent in 4 or more wound photos (more adherent to the care pathway) were more likely to have a 30-day GI follow-up visit (not significant; **Figure 3**). There was no difference in the number of ED visits or readmission rates between patients who submitted greater than 4 wound photos and those who submitted fewer.

Table 4. Summary of Results

		Cases	Controls	P-Value
N, IBD surgery		64	64	
ED visits n (%)		16 (25.0%)	13 (20.3%)	0.677
Readmissions n (%)		14 (21.9%)	14 (21.9%)	1.000
30-day GI follow-up visit n (%)		37 (57.8%)	30 (46.9%)	0.265
TCSS results				
	Stool frequency **mean (SD)**	5.8 (3.7)		
	Stoma output in mL **mean (SD)**	930 (499)		
TCSS adherence n (%)				
	Wound photos **n (%)**			
	≥1 photo	61 (95.3%)		
	≥4 photos	29 (45.3%)		
	Avg # photos	3.8		

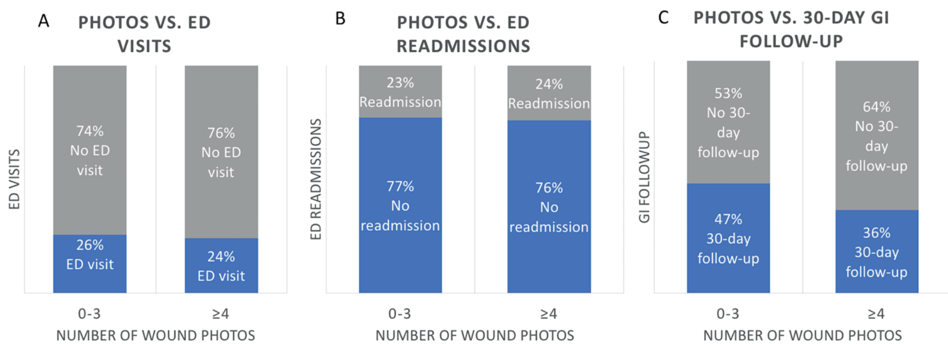

Figure 3. (A) Adherence to TCSS (measured by number of photos sent in) versus 30-day ED visits. Those with four or more wound photos sent in were less likely to visit the ED; p-value = 0.88. **(B)** Adherence to TCSS (measured by number of photos sent in) versus 30-day readmissions. No statistically significant difference, p-value = 0.90. **(C)** Adherence to TCSS (measured by number of photos sent in) versus 30-day GI follow-up. Those who sent in four or more wound photos were more likely to have a 30-day GI follow-up; p-value = 0.36. ED, emergency department; GI, gastroenterologist.

Discussion

We developed and investigated the feasibility and efficacy of a telehealth pathway in reducing 30-day readmission rates, ED rates, and GI follow-up visits. Our TCSS pathway demonstrates the feasibility of implementing a telehealth care coordination platform for post-surgery IBD management. By having patients fill out frequent questionnaires after hospital discharge, we were able to monitor patient-reported outcomes and identify complications. For instance, if a patient reported that their abdominal pain increased, the patient was called for triage by a surgical nurse who consulted with the IBD surgeon. If it was deemed necessary by the care team, the patient would be called in for a clinic visit or change of medication. The acceptability of the pathway was high, with 81% (13/16) rating their experience as "excellent".

As indicated by our post-surgical care survey results, patients felt that they were cared for and comforted during their participation. They particularly appeared to be reassured by the ease with which they could access their care providers, suggesting the importance of increased accessibility to care teams in electronic health applications. A majority of those who responded chose to answer the open-ended question about suggested improvements with either positive feedback or no suggested changes. Those who did suggest changes seemed to call for more involvement and communication from the care team, furthering highlighting the importance of accessibility to the care team. Despite the relatively small sample size of respondents to this survey, overall patient satisfaction showcases the potential of this telehealth intervention to enhance the patient experience.

Our adherence rates also indicate that patients were active participants in the pathway. This in line with a previous study conducted by Con et al. that found that a majority of IBD patients have internet access and feel confident entering information into a computer or phone[20]. Despite the relatively small sample size (n=86), their study demonstrates the willingness of patients to participate in telehealth solutions for disease management. In addition, previous studies assessing care coordination through use of mobile technologies has shown efficacy in cancer[21], HIV[22], and diabetes[23]. Such complex chronic diseases including IBD should strive to involve more patient engagement in their care.

One of the aims of the TCSS was to increase the likelihood that patients would attend a follow-up visit with a gastroenterologist to restart or optimize medical management postoperatively. Indeed, we found that numerically more TCSS patients had a postoperative

GI visit. We also found that patients who sent in 4 or more wound photos were more likely to have a GI follow-up visit. We hypothesize that patients with more complications may have sent in more photos due to greater concern for maintaining their health and seeing their GI physician more frequently. Alternatively, GI patients who sent in more photos seemed to demonstrate higher adherence to our program.

This study has some limitations. Despite our best efforts to match patients to similar controls, a selection bias might have occurred; it is possible that patients who opted in to the TCSS were at higher risk for complications compared to their matched controls. This is supported by the observation that patients included in the TCSS had a higher rate of biologic use then the control group (**Table 2**), potentially reflecting more severe disease. Our study might also suffer from measurement bias; it is possible that we observed more ED visits, hospitalizations, and complications in our TCSS group because TCSS patients were more likely to return to our hospital as we followed-up with them more closely, while controls might have been more likely to go to an outside hospital. This is consistent with findings in other telemonitoring programs such as Constant Care, in which higher relapse rates were found in the intervention group, likely due to a higher detection rate[24]. As our sample population was predominantly Caucasian and were treated by a single surgeon, our findings may not be representative of the general IBD population based on geographical or racial identities. The relatively small sample size could have affected the significance of our results and limits the generalizability of our findings. Similarly, our small sample size of 16 respondents to the post-surgical care survey limits how representative our findings are.

Still, the use of telemedicine interventions in a postoperative setting have shown potential for enhancing clinical outcomes. Williams et al. found that complication rates for certain elective low-risk procedures were not statistically different from traditional clinical follow-ups[25]. Clinical outcomes from telemedicine use are therefore comparable to that of traditional clinic follow-ups. Additionally, Gunter et al. conducted a systematic review of 21 articles on the use of telemedicine in post-discharge surgical care. Similar to our study, they found high patient satisfaction rates and significant patient-reported savings of time, travel, and distance; one study reported savings in the health system due to an increased availability of clinic slots for new patients[26]. No studies have reported statistically higher complication rates in telemedicine interventions for post-surgical care compared to traditional follow-up visits[25,26].

Though we did not find statistical significance in the three main outcomes assessed (30-day ED visits, readmission, and GI follow-up visits), future studies should evaluate other healthcare utilization outcomes in addition to these, such as visits to walk-in clinics for pain or consultations with non-traditional providers. In addition, previous studies have demonstrated the financial burden of resource utilization and care management for IBD patients, particularly those undergoing surgery[11,27]. While our study did not assess reduced costs associated with increased self-management through use of telemedicine, future studies should also include cost analyses to determine the optimally cost-effective method for post-surgery maintenance.

To our knowledge, this is the first study assessing a telehealth intervention involving both patient and provider aspects for post-surgery IBD management. This module aimed to make patients feel safe, prevent complications from happening, and intervene earlier in case of disease complications. TCSS is one pathway that has the potential to allow for monitoring and detection of post-surgery complications. It was well-received by enrolled patients, supporting the use and acceptability of a telehealth intervention for patient care.

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CHAPTER 8

Patient Experience and Satisfaction with an e-Health Care Management Application for Inflammatory Bowel Diseases

Submitted

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Abstract

Rising healthcare expenditures have been partially attributed to suboptimal management of chronic illnesses including Inflammatory Bowel Diseases (IBD). Recognizing the need to increase efficiency of outpatient care and prevent hospitalizations, we developed a mobile app for IBD disease monitoring, UCLA eIBD, that includes disease activity monitoring and educational modules. We provide preliminary evaluation of patient satisfaction and experience with this mobile app. We surveyed IBD patients treated at the UCLA Center for Inflammatory Bowel Diseases. The Patient Experience Survey assessed patients' overall satisfaction with the app, perception of health outcomes after app participation, and open-ended feedback on educational modules and ways to improve the platform. 50 patients were included in this study. Responses indicated that users were greatly satisfied with the ease of patient-provider communication within the app and appointment scheduling features (68%). A majority of respondents (54%) also reported that program participation resulted in improved perception of disease control and quality of life. Lastly, a majority of participants (79%) would recommend this app to others. Mobile tools such as UCLA eIBD have promising implications in improving healthcare delivery and integrating into patients' daily lives. The findings of this patient satisfaction study of UCLA eIBD suggest the feasibility of using this tool by patients and providers. We further showed that UCLA eIBD and its holistic approach has led to improved patient experience and satisfaction, which can provide useful recommendations for future e-Health solutions.

Introduction

Value-based healthcare (VBHC) can be described as the systematic pursuit of the triple aim in healthcare: to improve the individual's experience, improve health outcomes, and reduce costs[1]. The concept of VBHC is particularly ready for application to long-term management of chronic illnesses, since rising healthcare expenditures have been partially attributed to suboptimal management of chronic illnesses including inflammatory bowel disease (IBD)[2]. The estimated annual disease-attributable cost of IBD is $6.3 billion[3]. Hospitalization represented over a third of costs and outpatient services one third. Reducing hospitalization and readmission therefore continues to be a challenge in chronic disease management. There is clearly an opportunity to reduce cost by increasing the efficiency of outpatient care and preventing hospitalizations.

Electronic health (e-Health) interventions are one solution for more effective IBD care management beyond the clinical setting, both in terms of patient outcomes and cost reduction. Smartphone applications are widely available for consumers, and the large population of smartphone users make apps useful tools to manage chronic illnesses like IBD[4]. In fact, smartphone devices with mobile applications and short message reminders have been used effectively by patients with IBD of mild to moderate severity[5].

Furthermore, mobile health technologies have been shown to improve patient outcomes and quality of life[6]. Patient satisfaction in mobile technologies has been found for many chronic diseases, including asthma[7], HIV[8], diabetes[9], atrial fibrillation[10], and IBD[11]. IBD patients generally have positive views on mobile apps, but there are desired improvements. A study from Con et al. surveying 86 IBD patients found that 98.8% of participants were willing to use communication technologies for IBD management, with mobile apps being one of the top two preferred forms[11]. These previous IBD mobile technologies were often created to assess a major single aspect such as quality of life[5], education curriculum[12], or diets[13]. Additional features that patients seek in their chronic disease management apps include easy user interface[14], tracking of disease symptoms[11], and easy access to medical data and services[11].

A systematic assessment of 26 IBD mobile applications found that apps offered a variety of features including diary functionalities, pain tracking, bowel movement tracking, and reminders, with app content playing a major role in driving patient behavior change[4]. The MyIBD Coach telemedicine tool, which monitors adherence, disease activity, quality of life, and mental health among other measures through validated questionnaires, was shown to be successful with high rates of patient satisfaction and compliance[15]. It involves collaboration among healthcare providers but does not sync with electronic medical records and lacks educational app features on alternative medicine, behavioral health and physical activity.

To enhance VBHC in IBD, we developed UCLA eIBD to integrate various successful features of previous apps (i.e., appointment reminders, medication trackers) in addition to a healthcare provider portal. UCLA eIBD seeks to provide patients more agency in managing their IBD by increasing their access to healthcare professionals and providing self-help educational modules. Access to care providers through a messaging app provides patients with fast feedback on their conditions and streamlines patient care[16]. The application also contains disease activity, quality of life, and work productivity surveys that facilitate interactions between patients and providers. These tools allow healthcare providers to monitor patients' disease activity and give direct feedback. This comprehensive app therefore seeks to enhance patient outcomes by including direct connections to a healthcare team and extensive module options.

We previously conducted a pilot study of UCLA eIBD, which found significantly fewer endoscopies and decreases in healthcare utilization, long-term steroid use and IBD-related costs[17]. While it is important to evaluate the efficacy and outcomes of IBD self-management platforms, however, it is just as crucial to understand patients' satisfaction with these platforms to inform their feasibility. Gathering user feedback is necessary to develop the next generation of apps, improve product design, and reduce disconnect between app developers and consumers[18-20]. The present study therefore aims to provide an evaluation of perceived patient satisfaction and experience with the UCLA eIBD mobile app.

Methods

Objectives

The primary objective was to measure patient satisfaction and experience with the UCLA eIBD mobile application for care management. The secondary objective was to capture patient feedback on how to improve the mobile application.

Design and Population

We surveyed IBD patients treated at the UCLA Center for Inflammatory Bowel Diseases from October 2017 to October 2018. Included patients were 18 years old; diagnosed with

Crohn's disease (CD) or ulcerative colitis (UC) either by endoscopy, imaging or pathology; and had objectively logged into the app in the past year (assessed on platform). Patients with intestinal cancer, active chemotherapy, or a known intestinal infection were excluded. All eligible patients who had logged into the app in the past year were emailed and asked to complete a patient experience survey. Those who did not complete the survey in response to the initial email were followed up and interviewed via phone.

Description of UCLA eIBD

UCLA eIBD is a mobile app that administers a clinic-centered, care management program to its users (Figure 1). It was designed to be a comprehensive tool for patients' long-term disease management in the IBD outpatient setting. The features of this app include disease activity monitoring, messaging, educational modules, lifestyle modules, and electronic cognitive behavioral therapy (eCBT). The platform is also integrated with UCLA Health's electronic medical record, allowing patients to view their testing and lab results within the app.

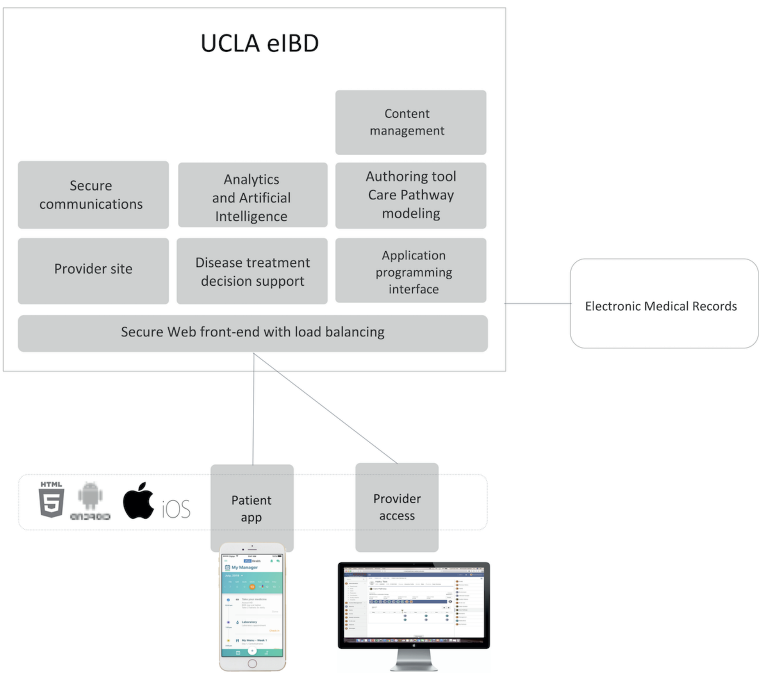

Figure 1. UCLA eIBD mobile app is an integrative care management platform for patients and providers.

For disease activity monitoring, a tool that was previously validated for use in mobile apps was integrated to assess patients' disease activity, quality of life and work productivity[21]. If the surveys indicated poor disease control or a significant change from prior surveys, a message was automatically generated through the app to clinic staff. Enrolled patients could also elect to take these surveys on their own time if they felt they were experiencing a sudden change in their health.

Lastly, the app provided education through several optional interactive modules designed to promote healthy lifestyle habits, including: nutrition (My Menu), exercise (My Yoga, My Fitness), relaxation (My Acupressure, My Meditation), and mental health (My Coach). My Menu teaches patients about specific foods to eat and avoid and includes recipes (Breakfast, Snack, Lunch and Dinner) designed for IBD patients. My Yoga provides a 6-week program promoting relaxation and flexibility for users. My Acupressure teaches patients about different pressure points focusing on elevating IBD pain via instructional videos and pictures. My Meditation is a self-guided mindfulness therapy that aims to reduce stress-related health issues. My Coach is a personalized mental life coach (6-week mental support program) aimed at improving mental wellbeing and stress management through a cognitive behavioral therapy method.

Data Collection & Outcomes

Patient demographic data was acquired via chart review. Data from the Patient Experience Survey was collected via REDCap[22]. The Patient Experience Survey (Table 1) consisted of 24 items aimed at assessing patients' overall satisfaction with the app and their perception of health outcomes after participation in the program. Responses were provided either via Likert scale or open text. Questionnaire items addressing the app's features and interface requested feedback on the ease of app use, ability to communicate with staff, and informativeness of modules. Questionnaire items pertaining to the patient's outcomes asked patients how effective they felt the app was at improving disease control, work productivity and quality of life.

Ethical Considerations

All patients gave informed consent to participate. This study was approved by the Institutional Review Board at UCLA with IRB protocol number 17-001208.

Statistical Analyses

Descriptive statistics were provided for the result of the questionnaires.

Table 1. Patient Experience Survey

#	Question	N=50
1	**How easy was it to communicate with program staff overall?**	26 (52%) Very Easy 8 (16%) Somewhat Easy 13 (26%) Neutral 3 (6%) Somewhat Difficult
2	How easy was it to schedule appointments?	26 (52%) Very Easy 8 (16%) Somewhat Easy 13 (26%) Neutral 3 (6%) Somewhat Difficult
3	How satisfied were you with program staff's response rate to messages and questions?	22 (44%) Very Satisfied 18 (36%) Satisfied 3 (6%) Somewhat Dissatisfied 7 (14%) Neutral
4	How did participating in the program affect your disease control?	15 (30%) Significant Improvement 12 (24%) Some Improvement 21 (42%) No Change 2 (4%) Somewhat Worse
5	How participating in the program affect your quality of life?	13 (26%) Significant Improvement 15 (30%) Some Improvement 20 (40%) No Change 2 (4%) Somewhat Worse
6	How did participating in the program affect your work productivity?	11 (22%) Significant Improvement 14 (28%) Some Improvement 24 (48%) No Change 1 (2%) Somewhat Worse
7	Did you participate in the cognitive behavioral therapy modules?	6 (12%) Yes 44 (88%) No
8	How did participating in the program affect your mental health?	8 (16%) Significant Improvement 6 (12%) Some Improvement 25 (50%) No Change 1 (2%) Somewhat Worse 10 (20%) Unknown
9	Were your clinic visits scheduled too often, just right or not often enough?	44 (88%) Just Right 6 (2%) Not Often Enough
10	Did you feel you were having lab tests done too often, just right or not often enough?	44 (88%) Just Right 1 (2%) Not Often Enough 5 (10%) Too Often
11	Did you feel you had to fill out surveys too often, just right or not often enough?	39 (78%) Just Right 4 (8%) Not Often Enough 7 (14%) Too Often
12	How accurately do you feel the survey results reflected your opinion of your disease activity and well-being?	17 (34%) Very Accurately 20 (40%) Somewhat Accurately 11 (22%) Neutral 2 (4%) Somewhat Inaccurate
13	How easy was it to navigate the mobile application?	18 (36%) Very Easy 19 (38%) Somewhat Easy 6 (12%) Neutral 4 (8%) Somewhat Difficult 3 (6%) Very Difficult

Table 1. Continued

#	Question	N=50
14	Did you find the graphics and overall 'look' of the application appealing?	40 (81.63%) Yes 9 (18.37%) No
15	Overall, how informative was the application, particularly My Academy?	12 (24%) Very Informative 11 (22%) Somewhat Informative 24 (48%) Neutral 3 (6%) Not Informative
16	Which of the following modules did you complete? (choice=My Fitness)	17/50 (34%)
17	Which of the following modules did you complete? (choice=My Meditation)	13/50 (26%)
18	Which of the following modules did you complete? (choice=My Menu)	17/50 (34%)
19	Which of the following modules did you complete? (choice=My Yoga)	10/50 (20%)
20	Which of the following modules did you complete? (choice=My Accupressure)	5/50 (10%)
21	Is there a topic you would like to see added to My Academy or My Wellness? If so, what topic?	Displayed in Supplementary Table 1.
22	Did you need to access technical support at any time during this study?	7 (14%) Yes 43 (86%) No
23	If so, how many times did you need to access technical support?*	4 (1 Time) 5 (2-5 Times)
24	How reliably were you able to reach technical support?*	3 (27%) Somewhat Reliable 7 (64%) Neutral 1 (9%) Very Unreliable

*Optional question

Results

Patient Demographics

In total, 151 patients had been active on the mobile application in the past year, of which 50 patients were included in this study (Table 2). Regarding the type of IBD, 44% were diagnosed with CD (n=22) and 56% with UC (n=28). Our inclusion cohort had a mean age of 43 years (SD 14 years) and an average BMI of 25.3 (SD 6.6). Of the patients, 44% was female and the majority were White (42%) and of Non-Hispanic ethnicity (90%). Most patients were non-smokers (78%) and 28% of the patients reported alcohol use. The patients stated use of the following medications: Anti-TNF (34%), ASA (16%), Combo-therapy (32%), IMM (10%) and Steroids (6%). Previous abdominal surgeries were reported in 36% of participants.

Table 2. Patient demographics

Variable	All (n=50)
Gender	22 (44%) Female
Disease Type	22 (44%) Crohn's disease 28 (56) Ulcerative colitis
Race	21 (42%) White 4 (8%) Black 3 (6%) Asian 1 (2%) Armenian 21 (42%) Unknown
Ethnicity	4 (8%) Hispanic 45 (90%) Non- Hispanic 1 (2%) Unknown
Current smoker	3 (6%) Current smoker 8 (16%) Former smoker 39 (78%) Never smoker
Age (mean SD)	42.58 SD 13.6
Alcohol use	14 (28%) Yes 36 (42%) No
BMI (mean SD)	25.3 SD 6.6
Disease duration (mean SD)	14.6 SD 11.2
Disease Activity	29 (58%) Clinical remission 11 (22%) Mild disease activity 6 (12%) Moderate disease activity 3 (6%) Severe disease activity 1 (2%) Unknown
Medications - Anti-TNF - ASA - Combo of any - IMM - Steroids - No Meds	17 (34%) Anti-TNF 8 (16%) ASA 16 (32%) Combo 5 (10%) IMM 3 (6%) Steroids 1 (2%) No Meds
Abdominal Surgeries (%)	18 (36%)

Patient Satisfaction

50 participants completed the Patient Experience Survey to provide feedback on the mobile app (Table 1). Responses to Likert scale questions indicated that patients were overall satisfied with the patient-provider communication interface of the app. When asked how easy it was to communicate with program staff overall, 52% of participants responded with "Very Easy" and 16% responded with "Somewhat easy". A majority of participants also found it easy to schedule appointments through the app, with 52% and 16% responding with "Very Easy" and "Somewhat Easy", respectively. In addition, a large majority (88%) of

participants reported that the frequency of completing lab tests, surveys, and scheduling clinic visits was "just right" (Table 1). Regarding the ease of app use, 74% of participants expressed the app was either "Very easy" or "Somewhat easy" to navigate.

Additionally, a majority of participants reported an improved perception of disease control and QoL. 54% of participants indicated significant or some improvement in their disease control. When asked how program participation affected QoL, 26% expressed significant improvement and 30% expressed some improvement. Regarding work productivity, 44% expressed significant or some improvement.

When participants were asked whether they would recommend this app to their friends, family, or other patients on a ten-point scale, with 10 being most likely, the median score was 8 and 79% indicated a score of greater than 5. When asked about how informative the app was, 46% of patients felt that application was "somewhat" or "very" informative.

Patient Usage of Educational Modules

A majority of patients completed modules as part of their participation in the program. The most-used modules were "My Fitness" and "My Menu" (Table 1). Among the patients that participated in the CBT modules (12%), 28% indicated significant or some improvement in their mental health.

When asked about what they liked and disliked about the modules, patients identified positive aspects to be the modules' informative content, ease of use, and support of overall well-being (Table 3). For example, one patient said, "They're easy and I feel great afterwards." Another patient expressed liking the modules because they "encourage me to take care of my whole self instead of the focus just being on taking my meds".
The most common reason for not liking the modules was being unsure of the purpose or need for them (8%), particularly for modules where patients already had their own interventions in place. For example, one patient said they "didn't feel [the modules] applied to me" while another expressed that they "thought [the module] was good but [I have my] own routine for working out [with regards to My Fitness]."

Patient Feedback

In the Patient Experience Survey, patients could provide optional suggestions about additional topics and functionalities they would like the app to cover, which were not presently included (Table 4). One participant for instance suggested adding a subsection

Table 3. Patient Optional Feedback on Modules (n=50).
Patients provided open-ended feedback about the educational modules. Their responses were grouped into categories based on common themes identified across responses.

What patients liked about modules	Count	Examples of patient feedback
Informative content	7	"Modules contained useful information." "My Meditation provided helpful tips."
Ease of use	3	"Very user friendly"
Ease of communication with provider	1	"Liked the VQ visual display. The app gave me comfort because it gave me access to the doctors especially when you have this disease."
Supports overall well-being	2	"I like that the modules encourage me to take care of my whole self instead of the focus just being on taking my meds."
Reminders to complete the modules	1	"I like to get reminded to complete the modules, they're easy and I feel great afterwards."
Yoga module was simple and effective	1	"I liked the yoga app because it was simple and effective.."
Total	15	
What patients disliked about modules	**Count**	**Examples of patient feedback**
Not informative	1	"Modules need to contain information that is more specialized."
Difficult to use	2	"Hard to navigate."
Unresponsiveness from staff	1	"Not responsive from staff."
Didn't know about modules	2	"I did not know about the modules."
Takes too long to complete	1	"Liked overall content and goal that IBD trying to aim for. Time issue for completing the module."
Problem with a specific module (My Yoga, My Acupuncture, etc.)	1	"Yoga portion could contain an audio aspect... stopping and reading about doing the yoga was counter-productive to my relaxation."
Unsure of purpose or need for them	4	"Didn't feel like they applied to me, personally."
Total	12	

about nutritional advice related to "Veganism" within the My Menu module. Other recommendations included adding a "symptoms tracker", allowing patients to indicate what symptoms or lack thereof that they were experiencing, and generating in-app reminders for blood draws or lab orders. Other patient-recommended categories to add were the ability to chart lab results, side effects of their consequent medications, and health topics specific to gender (Table 4).

Table 4. Patient Optional Feedback on UCLA eIBD
Patients provided open-text suggestions to improve the app in general. These suggestions were grouped into categories of comment types, including improvements in app content such as possible additional topics and features, as well as miscellaneous critiques.

Comment Types	Total Count	Examples of patient feedback (count)
Suggestions for new app articles and topics	8	Module on acupuncture (1) Module on veganism (1) Medication side effects (1) Female health topics (1) Blood draw instructions (1) Resources for recommended pathways (i.e., local places to get nutritional advice, do yoga, fitness) (1) FAQ for family and friends (1)
Suggestions for new app features and tools	3	Ability to chart lab results (1) Symptom tracker (2)
Suggestions for better app technical aspects	3	Touch ID for sign in (1) No automatic logoff (1) Different languages (1)
Miscellaneous improvement suggestions	4	Staff response rate faster at beginning of program (1) Poor wording of some in-app questionnaires (2) - i.e., "I don't like the wording of the questionnaires. i felt they lacked nuance. none asked if i felt overwhelmed, anxious, or preoccupied by disease things. just 'angry' or 'depressed' which i think are really different experiences." - i.e., "Sometimes I feel just saying on a scale from 1 to 10, how my disease affects my work or social life is too broad a question" Lacks in-depth, longer-term info about IBD (1) - i.e., "app is good for people new to ibd but doesnt offer as much for people who have had ibd for a while and want more in depth information."

Patients' feedback regarding general comments about the app are also shown in Table 4 ("Miscellaneous Improvement Suggestions"). One patient stated, "I think this is a great idea and will be very helpful to future patients. I really like being able to communicate with the office without always having to call." Most patients who provided comments also highlighted aspects that could be improved, such as the app interface (i.e., adding a touch ID option to login; prevent automatic logoff from the app). Other participants reported critical feedback on app content. For instance, one patient stated that the app "this is good for people new to IBD, but doesn't offer as much for people who have had IBD for a while and want more in depth information."

Discussion

Principal Findings

Our study collected feedback on patient experiences with the UCLA eIBD app after one year of use. Our results could provide guidance for further app development and provide critical feedback for other e-Health apps like it. The outcomes suggest that patients strongly favored the ease of patient-provider communication, with 78% being satisfied. Beneficial outcomes were also seen in patient-reported measures, with 54% reporting a perceived improvement in disease control and 56% reporting a perceived improvement in QoL, indicating that a majority of patients felt the platform positively impacted their health. Patients having access to home telemonitoring in the palm of their hand may give them a greater sense of autonomy of their chronic condition management.

Additionally, participants rated this app with median score of 8 on a ten-point scale (10 being most likely) to recommend this app to friends, family or other patients. This rating suggests that while patients would strongly recommend the app to others, there is still room for improvement. Their suggestions to improve the app were centered on specific content interests and the need for additional educational categories (i.e. female health topics) rather than technical problems or lack of need for an app. The fact that suggestions were less focused on the design features could be explained by the overall satisfaction rate of 74% of participants finding the app easy to navigate. “My Fitness” and “My Menu” were the two most-used optional wellness modules, with each receiving 34% completed status. Our findings suggest that a platform with interactive modules promoting healthy lifestyle habits along with increased access to communication with healthcare providers is well-received by IBD patients and may potentially result in enhanced satisfaction with outpatient care delivery.

Comparisons

Mobile tools such as UCLA eIBD have been shown to have promising implications in improving healthcare delivery and integrating into patients’ daily lives. Earlier comparison studies of UCLA eIBD have found impacts on cost and healthcare utilization and identified its unique features, such as automated messaging to care coordinators[17,23-25]. To complement previous outcome studies, this study aimed to understand patients’ satisfaction and feedback to help elucidate gaps in current e-Health technologies and inform future designs.

For instance, GI Buddy is a mobile app developed by the Crohn's Colitis Foundation which enables patients to self-monitor their disease and receive reminders about clinical appointments; however, users cannot directly interact with their providers[26]. Similarly, while current apps for IBD may be useful for patient monitoring and self-management, many lack professional medical involvement and adherence to clinical guidelines[4]. UCLA eIBD addressed this gap by allowing users to make appointments and message their providers via the platform, in which a majority of users found it "easy" or "very easy" to communicate with their providers. Another self-management tool, myIBD Coach, showed feasibility among patients and providers[15]. 79% of UCLA eIBD users would recommend this app to others (indicated by a score of greater than 5 on the recommendation score item), compared to the 93% found from myIBD Coach's feasibility study[15].

The findings of this patient satisfaction study demonstrate the feasibility of UCLA eIBD as a remote monitoring tool and some advantages it can provide for both patients and providers. In addition to patient-provider communication features, the platform's educational modules are more diverse than previous tools and provide patients with more alternatives to aid traditional medicine, such as acupuncture, cognitive behavioral therapy, and meditation. These optional modules may improve IBD patients' wellbeing and productivity beyond the scope of their disease. Tracking the various modules that patients use can also provide care teams with broader information to create more personalized treatments.

Limitations

Some study limitations should be noted. As selected patients were individuals who use smartphones, they may be more adept to the usage of apps. Participants were also actively recruited and agreed to participate in this study; thus a selection bias may have impacted study results due to participants being predisposed to wanting to improve their health via e-Health solutions. We further acknowledge the sample size was small and relatively homogenous; however, we feel it was adequate for the purpose of directing the future development of this UCLA app and other healthcare apps.

Additionally, the fact that we invited participants to evaluate the app's feasibility, rather than making it mandatory during app usage, may explain the response rate of 33%. The response rate should further be considered in the context of challenges associated with adopting e-Health technologies into the healthcare space. The obstacles to widespread, long-term integration of e-Health technologies (i.e., loss of interest, data entry burdens) are still being investigated[27,28]. Despite the growing population of individuals who use mobile health apps, many stop using them over time[29]. Our findings help provide insight to consumer perspectives on app usability and possible explanations to circumvent these challenges.

Future Outlook

In an era where the use of mobile technology has become irreplaceable in daily life, there is undoubted benefit of incorporating e-Health applications in the management of chronic conditions. Studies have shown proven effect of mobile applications but also that patients still desire improvements to existing solutions. We showed that UCLA eIBD and its holistic approach has led to greater patient experience and satisfaction, which can provide useful recommendations for healthcare providers and app developers. However, larger and controlled studies are recommended to assess its efficacy at a larger scale and its impact on costs.

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CHAPTER 9

Summary of Chapters, General Discussion, Future Perspectives

Summary of Chapters

Inflammatory Bowel Diseases (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC) are chronic immunological digestive diseases with a progressive character and associated with significant healthcare costs[1,2]. The symptoms of IBD are generally frequent abdominal pain and diarrhea and the disease state alternates between remission and exacerbation. In the United States, IBD affects nearly 3 million people who regularly require medical therapy, surgeries, and hospitalizations[3]. The impact is not limited to the hospital but also affects patients and their caregivers in their daily life and at the workplace. Due to the unpredictable course of the disease, developing innovative methods using technology that can identify patients at risk for adverse outcomes such as relapses outside of the traditional hospital setting would help to better manage this chronic condition, prevent negative outcomes and reduce the associated healthcare costs.

PART I: The Need for Innovation to Address the Economic and Psychosocial Impact of IBD

There is still a tremendous psychosocial and economic impact of IBD that has not been sufficiently addressed. The impact of chronic conditions remains a big force threatening the U.S. workforce productivity[4], not just deteriorating the patient experience and quality of life but also causing significant economic impact due to the associated indirect costs. **Chapter 2** looked at the impact of IBD on the productivity of patients and revealed that employed IBD patients experience significantly more presenteeism (decreased productivity at work) than healthy controls without IBD (54.7% vs. 27.3%, respectively; P=0.02), even when these patients are in complete clinical remission. We showed that indirect costs encountered for IBD patients in remission were still significantly higher when compared to healthy controls without IBD (p=0.02). Additionally, we demonstrated that patients continue to deal with decreased productivity at the workplace, where 66% of patients had not taken any necessary measures (like workplace adjustments) to tackle these issues, most likely due to the social stigma but also because of a lack of the appropriate tools and shortage of meaningful interventions.

Furthermore, in **Chapter 3** we discovered that the impact of IBD is not limited to only patients but extends to their caregivers as well. Caregiver burden is described as the emotional, physical, practical, and/or financial burden associated with taking care of a

patient with a chronic condition[5]. We found that caregivers with burden have significantly more absenteeism
(taking sick day; 58%) and presenteeism (84%) than caregivers without burden (24% absenteeism and 37% presenteeism). More importantly, caregivers expressed that they felt they should be doing more and better for their care recipients. This indicates that the development of strategies to address caregiver's distress and perceived burden when caring for IBD patients is warranted. Innovative solutions are required to battle these problems for patients with IBD and their caregivers, to improve outcomes and decrease costs.

PART II: Identifying IBD Patients' Needs using eHealth and Artificial Intelligence

The rising costs of healthcare with its associated negative experiences and adverse outcomes for patients has accelerated the quest for potential solutions. The Triple Aim is a framework of health care delivery improvement that consists of three objectives, 1) to improve outcomes, 2) to improve patient experience and 3) to decrease costs[6]. This framework has been proposed by the Institute for Health care Improvement (IHI) in order to assist health care organizations to optimize their performance by using these three metrics. This framework provides guidance on how to structurally implement change to improve the quality of the care delivered. It is applicable to chronic conditions like IBD, where rising healthcare expenditures are a major problem, patient experiences need improvement and outcomes are not fully optimized. Electronic health (eHealth) interventions are a potential solution for more effective care management beyond the clinical setting, both in terms of patient outcomes and cost reduction. Smartphones with mobile applications are extensively available and short message reminders have been already been used effectively by patients with IBD[7]. Furthermore, eHealth could be further enhanced with artificial intelligence (AI) to optimize care processes, identify patients in need of intervention, and improve the quality of care.

In **Chapter 4** we discovered that medication non-adherence was present in 33% of IBD patients, consistent with prior findings in the literature[8]. We then assessed what questions can most accurately assess medication adherence based on previously reported patient-reported outcome measurements, based on which we developed a single-item screening tool for medication non-adherence that can be used to monitor adherence remotely through eHealth applications. Our 1-item screening tool detects non-adherence with a sensitivity of 87% and a specificity of 64% and is accompanied by a 9-item survey to assess the leading extrinsic and intrinsic factors that contribute to nonadherence. The 1-item screening tool together with the 9-item survey can be used for detecting and managing adherence in IBD patients. While several tools are available to assess non-adherence, few specify the reasons for non-adherence in IBD, which is critical for appropriate management. The unsurmountable surge of AI in healthcare has offered a tremendous amount of opportunities to develop new strategies and technologies that can assist healthcare providers and patients in their care management in order to achieve the Triple Aim objectives.

In **Chapter 5** the feasibility of categorizing large datasets of electronic communications between patients and care providers using NLP for potential use in chatbots for IBD care management was demonstrated. We successfully categorized large amounts of electronic messaging data (>8000 lines) using a bag-of-words model into less than 10 categories. Furthermore, 90% of all dialogue fell into only seven categories: symptoms, medications, appointments, labs, finance or insurance, communications and miscellaneous. When comparing our algorithm to the assessment of three independent physicians, there were minor to no differences in 95% of cases. This demonstrates the potential to develop a chatbot with an NLP algorithm that can successfully categorize most questions and concerns of IBD patients.

With the increased use of Electronic Medical Records (EMRs), which has doubled in size since 2005, analyzing patient data is easier now than ever[9,10]. Furthermore, due to increased computational resources and availability of large data sets, a tremendous surge in development of healthcare technology driven by Artificial Intelligence has manifested. In **Chapter 6** we exhibited that it was feasible to successfully run complex AI models on large (Big Data), longitudinal claims data sets of IBD patients. We looked at four adverse outcomes for IBD (hospitalizations, surgeries, long-term steroid and biologics use) and assessed if 108 features regarding IBD-related care could be predictive of these adverse outcomes. We analyzed traditional regression models like LASSO and Ridge, machine learning methods such as Support Vector Machines and Random Forests but also involved more innovative methods like Neural Networks. We assessed the feasibility and performance of these models in early prediction of the aforementioned negative outcomes.

The Random Forest performed the best with the highest accuracy (AUCs between 0.71-0.92), this might indicate that the relationships between the claim's features are best captured by a Random Forest model and that this model framework might work best for claims predictions in general. We observed that different models identified different predictors for the each of the outcomes. The regression models and the neural network had comparable findings, in which the most predictive features were related to medication use. The random forest used more heterogenous types of predictors, not only identifying medication use as predictive features but also procedures such as lab tests and imaging. Therefore, we believe that that these findings can be applied to the daily clinical practice to identify at-risk patients. The complex models pick up on detailed interactions between the features and can be used to make precise risk assessments based on an individual patient's data. We have identified several strategies that could enhance the use of eHealth and AI in IBD clinical practice and assist in the transition to data-driven IBD care.

PART III: eHealth to Facilitate the Delivery of High-value Care in IBD

There is significant variation in how care is delivered to IBD patients, a factor known to be inversely associated with quality of care[11]. As engagement with patients outside the hospital setting is becoming more relevant, standardization of outpatient care using eHealth could be a potential solution to reduce variation, and improve the patient experience, health outcomes and decrease costs. This process can be facilitated through the concept of care pathways, which pre-define the clinical activities and costs associated with a specific diagnosis for a defined amount of time, thereby standardizing the care delivered. eHealth solutions could facilitate the implementation and monitoring of care pathways in order to improve the quality of care delivered for IBD patients.

Despite significant advancement in novel medical therapeutics for IBD, a large percentage of IBD patients and in particular Crohn's disease patients will undergo surgery[12]. These surgical interventions are associated with costly readmissions and complications . In **Chapter 7** we assessed the feasibility and efficacy of a surgical eHealth intervention on readmission rates, emergency department (ED) visits and outpatient gastroenterology follow-up visits. We demonstrated the feasibility of implementing a surgical care pathway using eHealth for post-surgery IBD management. After being discharged from the hospital after surgery, patients filled out frequent surveys in order to monitor patient reported measures and correct potential complications. For example, patients who reported an increase in abdominal pain were triaged by a surgical nurse who then consulted the IBD surgeon. If necessary, the patient would be called into clinic or there would be an adjustment of medical management. In our pilot, 81% of participating patients rated their experience as "excellent" and 94% described the amount of questions in the surveys as reasonable. Additionally, 54% of patients felt their recovery would have had a different result without participation in the program. We did not find a statistically significant difference on readmission rates, ED visits and outpatient clinic follow up, but demonstrated high acceptability and feasibility of this eHealth application for remote post-operative IBD management.

In **Chapter 8** we assessed the patient experience with the UCLA eIBD app after one year of use. UCLA eIBD is a mobile application that incorporates various components of care delivery such as appointment reminders and medication trackers for patients, a healthcare provider portal for the treating provider, and patient-provider chat functionality. UCLA eIBD seeks to empower patients to self-manage their IBD by increasing their access to healthcare providers through the app and providing self-help educational modules. The application also monitors disease activity, quality of life, and work productivity using validated questionnaires. As mobile applications are becoming more relevant in care management, our results provide guidance for further app improvement and provide critical feedback for other eHealth solutions.

In this study, we demonstrated 78% satisfaction with patient-provider communication through the app, a critical component of the patient experience. Furthermore, 54% of app users reported a perceived improvement in disease control and 56% reported a perceived improvement in quality of life (QoL), indicating that a majority of patients felt the platform positively impacted their health. When asked if they would recommend this app to friends, family or other patients, users rated this app with a median score of 8 on a ten-point scale (0 being the least likely to recommend and 10 being the most likely to recommend). Recommendations from patients on improving the app centered on specific content interests and the demand for additional educational subjects (i.e. female health topics) rather than technical problems or lack of need for an app. The result translates back to the overall satisfaction rate of 74% of participants finding the app easy to navigate. Educational fitness and nutrition modules were the two most-used optional wellness modules, with was each completed by 34% of users. Our findings suggest that a platform with interactive modules promoting healthy lifestyle habits along with increased access to communication with healthcare providers is well-received by IBD patients with self-reported improvement in disease outcomes and quality of life and may potentially result in enhanced satisfaction with outpatient care delivery.

General Conclusion and Future Perspectives.

Despite advances in medical therapy, IBD still has a significant economic and psychosocial impact. To improve quality of care, empowerment and self-management of patients outside the traditional clinical setting is imperative to improve the experience, decrease costs and improve outcomes.

In **Chapter 2** we demonstrated that employed IBD patients in clinical remission still have a substantial decrease in work productivity that mostly goes undetected. The associated high indirect costs constitute a significant economic burden on health expenditures. A method to lower indirect costs includes both care provider and employer interventions, ideally converging into an integrated approach[13]. The development and testing of productivity measuring enhancement tools could have a meaningful and immediate impact. Care providers (e.g. physicians, nurses, social workers, dieticians) should pro-actively discuss and propose employment-related adjustments tailored to the individual. Using eHealth applications, care providers can incorporate mental support, nutritional support, and wellness (e.g. fitness, yoga, meditation) in their care plan, thereby potentially improving patients' health and productivity at work. In addition, eHealth can facilitate the elimination of unnecessary tests, procedures and medical appointments through care pathways, which could reduce absenteeism. Surveys have demonstrated that employees with chronic conditions are more likely to be highly satisfied with their jobs if they had high self-efficacy in managing their disease, perceive workplace support, and had less work limitations[14]. This would also allow employers to make successful adjustments leading to a reductions in presenteeism and absenteeism and the associated indirect costs.

In **Chapter 3** we presented that caregiving for IBD patients causes significant work productivity decreases in caregivers. In addition, despite the burden, caregivers felt they should be doing more for their care recipient and felt they could do a better job at caregiving, warranting the need for more caregiver solutions. Behavioral interventions using web-based and mobile apps, have the ability to provide the power to patients for better management of their IBD, as well as motivation to engage in positive behavior[15], there is potential for caregivers in these solutions as well. Caregivers can be provided with necessary education on the disease of the care recipient and social support(contact with other caregivers) through eHealth applications in order to reduce caregiver burden and increase caregiver empowerment[16]. The development and implementation of such solutions for caregivers of IBD patients can be of tremendous value to a frequently overseen and challenging issue.

9

Electronic health (eHealth) technologies have the potential for promoting self-management and reducing the impact of the growing burden of IBD on health care resource utilization. Therefore in **Chapter 4** we developed an innovative screening tool for management of medication non-adherence in IBD. This allows care providers to screen for non-adherence in IBD and further identify the exact reasons for non-adherence so they may offer more personalized solutions. The use of this tool could allow for continuous and remote monitoring of medication adherence. Future studies should validate the effect of remote monitoring of adherence on medication adherence levels, patient satisfaction, and health care costs.

Furthermore, usage of smartphones and eHealth applications are on the rise, just like in daily life, electronic communication between patients and their providers is becoming the standard. In **Chapter 5** we demonstrated the feasibility of categorizing large sets of electronic messaging data in one of the most complex chronic conditions into a low (<10) number of categories. Our results showed that 25% of messages were related to appointments. This provides an opportunity for AI to play a role in care optimization. A chatbot could efficiently automate requests regarding appointments or even play an active role in triage, following the same guidelines of questioning as nurses, saving the provider team valuable time that could be reallocated to better patient care. The value of a chatbot is clear and has been demonstrated in other industries[17]; a chatbot is available at all times, can handle large amounts of communications simultaneously, and has no wait times. Now that feasibility has been showcased, further studies are necessary to assess the technical build and implementation as well as the effect on patients, providers, and costs.

Due to increased use of EMRs[9,10], availability of large patient data repositories and advancement of computational processing power, AI has now been presented as the next best thing for healthcare. The practical reality of AI is an enigma to many clinicians. However it is clear that big data cannot be optimally studied with the standard methods of statistical analysis[10]. In **Chapter 6** we exhibited that it was feasible to successfully run complex AI models on large data sets (Big Data) of IBD patients. Additionally, we demonstrated that these findings can have potential use in daily clinical practice by risk profiling patients. Transferability of these models to different institutions has been successful, alleviating a major concern[18]. The next step would be to integrate these models in a prospective setting to study their performance on reliability, patient outcomes and costs.

In an era where the use of mobile technology has become irreplaceable in daily life, disruptive innovation in healthcare is predicted to redefine personalized medicine. There is undoubted benefit of incorporating AI and eHealth applications in the management of chronic conditions. Studies have shown the effectiveness of mobile applications but also that patients still desire improvements to existing solutions[19,20]. In **Chapter 7** we demonstrated the feasibility of implementing a surgical care pathway using eHealth for post-surgery IBD management. It was well-received by patients, supporting the use and acceptability of a eHealth intervention for patient care. In Chapter 8 we showed that UCLA eIBD and its holistic approach has led to better patient experience and satisfaction, which can provide valuable recommendations for healthcare providers and app developers. However, bigger and controlled studies are recommended to assess its efficacy at a larger scale and its impact on costs.

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APPENDICES

Dutch Summary (Nederlandse Samenvatting)

Inflammatoire darmziekten (IBD) zoals de ziekte van Crohn (CD) en colitis ulcerosa (UC) zijn chronische immunologische gastro-intestinale aandoeningen met een progressief karakter, welke gepaard gaan met hoge zorgkosten[1,2]. IBD wordt over het algemeen gekenmerkt door frequente buikpijn en diarree, waarbij de ziektetoestand wisselt tussen remissie en ziekteopvlamming[3]. IBD treft bijna 3 miljoen Amerikanen, die vaak medicatie, operaties en ziekenhuisopnames behoeven[4]. De impact van IBD beperkt zich niet alleen tot vele ziekenhuisbezoeken, maar is ook terug te zien in het dagelijks leven van de patiënt. Ondanks dat medische therapieën zoals *biologicals* (biologische geneesmiddelen), de ziekte uitkomsten en kwaliteit van leven van patiënten verbeteren, ervaren veel patiënten namelijk beperkingen in hun dagelijks leven. Studies tonen aan dat een derde van de IBD-patiënten het gevoel heeft dat hun persoonlijke relaties negatief worden beïnvloed. Een kwart van de IBD-patiënten ervaart het onderhouden van vriendschappen als problematisch en maar liefst twee derde van de IBD-patiënten maakt zich zorgen over de beschikbaarheid van toiletten bij sociale evenementen[5]. Op de werkplek hebben IBD-patiënten last van vermoeidheid, prikkelbaarheid en demotivatie. Wanneer de gevolgen van IBD ertoe leiden dat dierbaren moeten optreden als mantelzorger, ervaren de mantelzorgers bovendien extra spanning en ongemak; een probleem dat onvoldoende is bestudeerd en waarover nauwelijks wordt gerapporteerd in de medische literatuur.

IBD gaat gepaard met hoge zorgkosten, die kunnen worden onderverdeeld in twee verschillende componenten: directe kosten en indirecte kosten. Directe kosten betreffen de kosten die verband houden met het zorgverbruik, zoals (poli)klinische bezoeken en medicatiegebruik. Indirecte kosten zijn geassocieerd met beëindiging of vermindering van de arbeidsproductiviteit als gevolg van de morbiditeit en mortaliteit die samenhangen met een bepaalde (chronische) ziekte[6,7]. De geschatte jaarlijkse ziekte-gerelateerde kosten van IBD in de VS worden geschat op 6.3 miljard dollar[2], wat naar schatting driemaal hogere directe zorgkosten zijn dan de directe zorgkosten van mensen zonder IBD[8]. De meeste onderzoeken houden geen rekening met indirecte gezondheidskosten, dus de impact van indirecte kosten bij IBD vereist verder onderzoek.

Het ziekteverloop van IBD is progressief; elke opvlamming van ziekteactiviteit verhoogt het risico op blijvende gastro-intestinale schade en complicaties, die morbiditeit, invaliditeit en hoge kosten veroorzaken[8]. Om ziekteprogressie en de daarmee samenhangende negatieve uitkomsten te voorkomen, is preventie en vroege identificatie van ziekteopvlamming van cruciaal belang[9–11]. Het ziekteverloop van IBD wisselt echter af tussen actieve ziekte en remissie, wat het moeilijk maakt om betrouwbare risicofactoren voor negatieve uitkomsten op te sporen[11]. Het ontdekken van nieuwe methoden die betrouwbare risicofactoren kunnen identificeren voor negatieve uitkomsten, zoals ziekteopvlamming buiten het ziekenhuis, kan helpen om de behandeling van IBD te verbeteren. Zo kunnen negatieve uitkomsten worden voorkomen en de daarmee gepaarde gaande hoge kosten van IBD worden verminderd[12].

Innovatie middels de 'Triple Aim'

Amerikaanse betaalmodellen in de zorg ondergaan een verschuiving van zogenaamde *fee for service*-modellen naar modellen met vergoedingen op basis van de geleverde zorgkwaliteit. Deze verschuiving zal de manier waarop zorg wordt verleend in de toekomst drastisch veranderen en vereist een robuust conceptueel raamwerk om zorgkwaliteit te meten en te verbeteren.

Een dergelijk raamwerk met duidelijke handvaten is essentieel omdat – hoewel het evident is dat innovatieve therapieën een positief effect hebben op ziekte-uitkomsten – er nog steeds een aanzienlijke psychosociale en economische impact van IBD is die niet wordt bestreden. Vroegtijdige herkenning van risicofactoren om nadelige gevolgen van de ziekte te voorkomen en een aanzienlijke verbetering van de patiëntervaring buiten de ziekenhuisomgeving, zijn in dat kader van groot belang. De patiëntervaring omvat het scala aan interacties die patiënten hebben met het gezondheidszorgsysteem. Ook omvat het verschillende componenten van de zorgverlening die patiënten zeer waarderen, zoals gemakkelijke toegang tot informatie en duidelijke communicatie met een zorgteam[13].
Een robuust raamwerk is bovendien nodig om kwaliteitsverbetering in de zorgverlening middels innovatieve oplossingen mogelijk te maken. Ditzelfde geldt voor het implementeren van de voor de verschillende betrokkenen noodzakelijke veranderingen in de gezondheidszorg.

Er zijn verschillende oplossingen aangedragen zoals innovatie in de wijze van monitoren van patiënten of implementatie van *electronic health* (eHealth). eHealth is het gebruik van informatie- en communicatietechnologieën, en vooral internet-technologie en de mobiele telefoon, om gezondheid en gezondheidszorg te ondersteunen of te verbeteren.
De impact van deze oplossingen op zowel de zorgverleners, patiënten en mantelzorgers evenals de met IBD gepaard gaande zorgkosten, moet nog worden onderzocht.

A

Een voorbeeld van een raamwerk is de Triple Aim die uit drie doelstellingen bestaat; verbetering van de patiëntervaring, verbetering van gezondheidsuitkomsten en verlaging van zorgkosten[14]. De Triple Aim is ontwikkeld door het *Institute for Health Care Improvement* (IHI) om zorgorganisaties te helpen hun prestaties te optimaliseren door zich te focussen op deze drie doelstellingen. De Triple Aim is met name van toepassing op chronische ziekten omdat de oorzaak van de stijgende zorgkosten gedeeltelijk zijn toegeschreven aan suboptimaal management van chronische ziekten, waaronder IBD[15]. Zo worden de jaarlijkse ziekte-gerelateerde kosten van IBD in de VS geschat op 6.3 miljard dollar[2]. Er is een mogelijkheid om deze kosten te verlagen door de efficiëntie en kwaliteit van de zorg te verhogen en hiermee negatieve zorguitkomsten te voorkomen[16].

Het is cruciaal om te begrijpen hoe deze voorgestelde raamwerken, zoals de Triple Aim, de traditionele behandeling van IBD beïnvloeden. Conventioneel is de behandeling van IBD voornamelijk gericht op de behandeling van symptomen, maar het controleren van actieve ziekteopvlamming (*flare-ups*) is onvoldoende om de progressie van de ziekte volledig te stoppen[17,18]. Een verschuiving naar een 'proactieve' in plaats van 'reactieve' benadering is cruciaal[19]. Om dit te bewerkstelligen is het van belang patiënten te betrekken bij hun behandeling en hen in staat stellen daaraan actief deel te nemen door gebruik van nieuwe benaderingen, zoals participatieve en op kwaliteit gedreven zorgmodellen. Middels de implementatie van gezondheidstechnologie en mobiele applicaties, kan een meer 'proactieve' benadering bereikt worden. Bovendien zullen deze innovatieve modellen waarschijnlijk ook succesvoller zijn in het verbeteren van de patiëntervaring en zo verschillende belangrijke oorzaken van ziekteopvlamming verbeteren, zoals het niet goed innemen van medicatie en ongezonde leefstijlfactoren[20,21].

eHealth & Artificiële Intelligentie in de zorgverlening

Uit de literatuur blijkt dat er een enorme variatie bestaat in de zorgverlening voor IBD-patiënten. Het is belangrijk op te merken dat er een negatieve relatie bestaat tussen de aan een individu verleende 'variatie in zorg' en 'kwaliteit van zorg': hoe meer variëteit in de geleverde zorg, hoe slechter de kwaliteit; hoe meer variëteit in de geleverde zorg, hoe slechter de kwaliteit[22]. Het nastreven van de Triple Aim doelstellingen vergroot het potentieel om de zorgverlening via eHealth te standaardiseren, wat de kwaliteit van de zorg en de patiëntervaring zou kunnen verbeteren. Dit proces kan plaatsvinden door middel van het concept van zorgpaden, waarbij alle vereiste activiteiten en kosten voor een zorgverlener en de patiënt met een bepaalde diagnose voor een bepaalde periode worden gedefinieerd. Hierdoor wordt de geleverde zorg gestandaardiseerd. Om een zorgpad effectief uit te voeren, is betrokkenheid en zelfbeschikking van de patiënt cruciaal, vooral buiten de ziekenhuisomgeving. Innovatieve eHealth oplossingen kunnen hierbij de sleutel tot succes zijn.

eHealth en Artificiële Intelligentie (AI) worden steeds belangrijker. Als we kijken naar de vooruitgang van technologie in de gezondheidszorg, staan wij aan de vooravond van ingrijpende innovatie door middel van digitale en technologische oplossingen. Naar alle waarschijnlijkheid zullen deze initiatieven de gezondheidszorg transformeren en de toepassing van gepersonaliseerde oplossingen mogelijk maken[23]. Ten eerste zien we een snelle toename in het gebruik van internet en mobiele telefoons, waarbij 81% van de volwassenen in Noord-Amerika een smartphone heeft[24]. *Mobile health* - de toepassing van sensoren, mobiele apps, sociale media en locatietrackingstechnologie voor het verkrijgen van gegevens die relevant zijn voor de diagnose, preventie en behandeling van welzijn en ziekten - maakt het theoretisch mogelijk om te monitoren en in te grijpen wanneer en waar acute en chronische medische aandoeningen zich voordoen[25].

In de VS heeft meer dan 40% van de volwassenen twee of meer chronische aandoeningen en als we kijken naar het kostenplaatje, zijn chronische aandoeningen verantwoordelijk voor 71% van alle kosten in de gezondheidszorg[26,27]. De potentie en kansen voor eHealth als oplossing zijn aantrekkelijk. Door de introductie van elektronische medische dossiers is er een significante toename in de hoeveelheid manieren waarop gegevens worden verzameld. De weg ligt open voor de gezondheidszorg om hiervan gebruik te maken bij het optimaliseren van de ervaring van zorgverleners en patiënten evenals het verlagen van de kosten. IBD is één van de vele chronische ziekten die baat kan hebben bij eHealth. Smartphonetoepassingen kunnen zorgverleners en patiënten helpen in de behandeling, bijvoorbeeld door het begrip van de ziekte te verbeteren, de therapietrouw verbeteren, de communicatie tussen patiënt en arts te verbeteren en door te zorgen voor eerdere interventies door zorgverleners wanneer patiënten symptomen hebben[28].

Bovendien hebben de toegankelijkheid van *Big Data* (grote datasets) en de toegenomen processorkracht de weg vrijgemaakt voor artificiële intelligentie om mogelijke ondersteuning te bieden in de behandeling van complexe ziekten met een complexe diversiteit en wisselende ziektetoestanden, zoals IBD. AI-algoritmen kunnen een revolutie teweegbrengen voor de drie grote spelers in de gezondheidszorg: clinici, waar het snelle diagnoses en besluitvorming ondersteuning mogelijk maakt; gezondheidsorganisaties zoals ziekenhuizen, waar het inefficiënties tot een minimum kan beperken en voorspellingen kan genereren voor het gebruik van hulpbronnen; en patiënten, waar het hen in staat kan stellen hun gezondheid zelf in de gaten te houden[29]. Ondanks de belofte is de praktische haalbaarheid van AI-oplossingen voor IBD nog steeds onduidelijk. De rol van eHealth in het zorgverleningsproces verdient dan ook nader onderzoek.

Overzicht van dit proefschrift

Dit proefschrift bestaat uit drie delen. In het eerste deel hebben we de huidige economische en psychosociale impact van IBD beoordeeld door het effect ervan op indirecte kosten, productiviteit en zorgverlening te bestuderen. In het tweede deel hebben we bekeken of de behoeften van IBD-patiënten proactief kan worden ondersteund met behulp van eHealth en AI. Ten slotte hebben we in het derde deel de impact geanalyseerd van het monitoren van IBD-patiënten met behulp van eHealth om de levering van hoogwaardige zorg te vergemakkelijken.

DEEL I: De behoefte aan innovatie vanwege de economische en psychosociale impact van IBD

Patiënten met een chronische aandoening zoals IBD hebben regelmatig een afname van hun arbeidsproductiviteit[30], die wordt omschreven als *absenteeism* of *presenteeism*. Absenteeism is afwezigheid op het werk door ziekte en presenteeism is een verminderde productiviteit op de werkplek als gevolg van de impact van een chronische aandoening. De impact van verminderde productiviteit op de uitgaven voor de gezondheidszorg zijn aanzienlijk. Naar verluidt is 76% van de medische kosten bij chronische ziekten te wijten aan indirecte medische kosten, waarvan 83% (63% van de totale kosten) aan presenteeism[31]. Studies die de indirecte kosten in de VS beschrijven, houden vaak geen rekening met presenteeism. In **Hoofdstuk 2** hebben we gekeken naar de impact van IBD op de productiviteit van patiënten en ontdekt dat werkende IBD-patiënten significant meer presenteeism (verminderde productiviteit op het werk) ervaren dan gezonde controles zonder IBD (respectievelijk 54,7% vs. 27,3%; P = 0,02), zelfs als deze IBD-patiënten geen actieve ziekte hebben. We toonden aan dat de indirecte kosten voor IBD-patiënten zonder actieve ziekte nog steeds significant hoger is in vergelijking met gezonde controles zonder IBD (p = 0,02). Ook hebben we aangetoond dat patiënten nog steeds te maken hebben met verminderde productiviteit op de werkplek. Daarbij geldt dat 66% van de patiënten geen aanpassingen heeft kunnen verrichten om deze problemen aan te pakken, hoogstwaarschijnlijk vanwege het sociale stigma maar ook vanwege een gebrek aan adequate oplossingen en een tekort aan zinvolle interventies.

Bovendien is de impact van IBD niet beperkt tot patiënten, maar heeft het ook invloed op hun mantelzorgers. De impact op de mantelzorger wordt omschreven als de emotionele, fysieke, praktische en/of financiële last die gepaard gaat met de zorg voor een patiënt met een chronische aandoening. Een mantelzorger, meestal een familielid of echtgenoot, helpt de patiënt onder andere met zijn of haar medicatie, postoperatieve zorg en transport naar het ziekenhuis[32]. In **Hoofdstuk 3** bevestigen we dan ook dat de impact van IBD niet beperkt is tot alleen de patiënten zelf, maar zich ook uitbreidt tot hun mantelzorgers. Zo zagen we dat bij mantelzorgers die emotionele, fysieke, praktische en/of financiële last ervaren van hun zorg voor hun IBD-patiënt, sprake is van 58% absenteeism (ziekteverzuim) en 84% presenteeism. Voor mantelzorgers van IBD-patiënten die deze last niet ervaren, zijn deze percentages lager maar nog steeds significant, te weten 24% absenteeism en 37% presenteeism. Belangrijker nog; mantelzorgers gaven aan dat ze vonden dat ze meer en beter zouden moeten zorgen voor hun naasten met IBD. Dit geeft aan dat de ontwikkeling van strategieën om de impact en de ervaren last van de mantelzorger te bestrijden, eveneens essentieel is bij de zorg voor IBD-patiënten.

DEEL II: De behoeften van IBD-patiënten identificeren met behulp van eHealth en artificiële intelligentie

eHealth interventies zijn één oplossing voor effectievere IBD-behandeling buiten de klinische setting, zowel wat betreft patiëntuitkomsten als kostenreductie. Smartphoneapplicaties zijn makkelijk verkrijgbaar voor patiënten, en de grote populatie van smartphonegebruikers maakt apps tot nuttige hulpmiddelen voor chronische ziekten zoals IBD[33]. Smartphones met apps en notificaties met korte herinneringsberichten zijn effectief gebruikt door IBD-patiënten met milde tot matige ziekteactiviteit[34]. Bovendien zou eHealth verder kunnen worden verbeterd met artificiële intelligentie om zorgprocessen te optimaliseren, patiënten met symptomen vroegtijdig te identificeren en de kwaliteit van de geleverde zorg te verbeteren.

Een grote uitdaging in de behandeling van chronische ziekten is het niet of incorrect innemen van medicatie (therapietrouw). In de VS hebben ongeveer 117 miljoen volwassenen ten minste één chronische ziekte [35] en 50% gebruikt zijn of haar medicatie niet zoals voorgeschreven[36]. Voor IBD toonde één studie therapieontrouw van 33%, waarvan 34% van de patiënten minstens één opvlamming van ziekteactiviteit ervaarde na stopzetting van de medicamenteuze behandeling[37]. De resulterende indirecte en directe zorgkosten van therapieontrouw bij chronische ziekten worden geschat op tussen de 100 miljard en 300 miljard dollar per jaar in de VS[38]. In **Hoofdstuk 4** hebben we een korte screeningstool ontwikkeld om therapieontrouw te identificeren en redenen voor therapieontrouw te achterhalen. Deze tool kan worden gebruikt voor monitoring op afstand via eHealth applicaties. We bevestigden dat therapieontrouw aanwezig was bij 33% van de IBD-patiënten, welk cijfer consistent is met eerdere bevindingen in de literatuur. Vervolgens hebben we beoordeeld welke vragen therapieontrouw het meest nauwkeurig kunnen inschatten op basis van eerder beschreven patiënt georiënteerde vragenlijsten. Op basis van deze analyses hebben we een screeningtool voor therapietrouw ontwikkeld die uit één vraag bestaat en die kan worden gebruikt om therapietrouw op afstand te monitoren via eHealth-toepassingen. Onze 1-item screening tool detecteert therapieontrouw met een sensitiviteit van 87% en een specificiteit van 64% en kan met een aanvullende 9-item vragenlijst bij daadwerkelijke therapieontrouwe patiënten de leidende extrinsieke en intrinsieke factoren te identificeren die bijdragen aan therapieontrouw. De screeningstool kan zo samen met de aanvullende 9-item bestaande vragenlijst worden gebruikt voor het detecteren en behandelen van therapieontrouw bij IBD-patiënten. Hoewel er verschillende tools beschikbaar zijn om therapieontrouw te beoordelen, specificeren slechts enkele de redenen voor IBD-therapieontrouw, wat cruciaal is voor preventie en behandeling.

De ontwikkeling van technologieën in de gezondheidszorg aangedreven door artificiële intelligentie zal naar verwachting in de komende 5 jaar een groei doormaken die gepaard gaat met meer dan 10 miljard dollar aan investeringen[39]. De mogelijkheden om nieuwe strategieën en technologieën te ontwikkelen die zorgverleners en patiënten kunnen helpen bij hun behandeling, groeien snel. Dit blijkt onder meer uit de enorme hoeveelheid financiering die naar bedrijven gaat die AI willen implementeren in de gezondheidszorg[40]. Een nieuwe rol die AI kan vervullen in het management van IBD is via medische chatbots, die ernaar streven natuurlijke gesprekken met een mens te simuleren door automatische verwerking en interpretatie van tekst middels *natural language processing* (NPL)[41]. Chatbots kunnen de zorgverlening verbeteren door de toegang tot de zorg te vergroten. De zorg omvat dan immers niet alleen fysiek contact met de zorgverlener tijdens poliklinische consultaties, maar voorziet patiënten thuis ook van de nodige gemakken. Er zijn populaire diagnostische chatbots ontwikkeld, maar de rol van chatbots bij IBD wordt nog onderzocht[42].

In **Hoofdstuk 5** hebben we de haalbaarheid aangetoond van het categoriseren van grote datasets van elektronische communicatie tussen IBD-patiënten en zorgverleners middels NLP. Dit efficiënt categoriseren van elektronische communicatie datasets zou mogelijk toegepast kunnen worden in de ontwikkeling van chatbots voor IBD-patiënten. We hebben met succes grote hoeveelheden elektronische dialogen (> 8000 regels) in minder dan 10 categorieën ingedeeld met behulp van een *bag-of-words* model. 90% van alle dialoog viel in slechts zeven categorieën: symptomen, medicatie, afspraken, labs, financiën of verzekeringen, communicatie en overig. Bij het vergelijken van ons NLP-algoritme met dezelfde beoordeling van de communicatie door drie onafhankelijke artsen, waren er in 95% van de gevallen weinig tot geen verschillen. Dit toont de mogelijkheid aan om een chatbot te ontwikkelen met een NLP-algoritme die met succes de meeste vragen en zorgen van IBD-patiënten kan categoriseren.

Met de explosieve toename van het aantal elektronische patiëntendossiers (EPD), dat sinds 2005 in aantal is verdubbeld, is het bestuderen van patiëntgegevens nu gemakkelijker dan ooit[40,43]. Door optimaal gebruik te maken van deze grote hoeveelheden data, zoals in het EPD, gegevens van de zorgverzekeraar en andere vormen van patiëntinformatie (bijv. wearables, microbioom/genetische tests, e-health apps en beeldvorming), kunnen data-gestuurde en op het individu gerichte behandelplannen gerealiseerd worden. In **Hoofdstuk 6** hebben we succesvol complexe AI-modellen toegepast op grote verzekering datasets (*Big Data*) van IBD-patiënten. We hebben naar vier negatieve uitkomsten voor IBD-patiënten gekeken; ziekenhuisopnames, operaties, langdurig gebruik van steroïden en start van biologicals. We beoordeelden of 108 kenmerken met betrekking tot IBD-gerelateerde zorg voorspellend zouden kunnen zijn voor deze vier negatieve uitkomsten. We analyseerden traditionele regressiemodellen zoals LASSO en Ridge, *machine learning* methoden zoals Support *Vector Machines* en *Random Forests*, maar ook meer innovatieve methoden zoals neurale netwerken. Ten slotte hebben we de haalbaarheid en prestaties van deze modellen beoordeeld bij de vroege voorspelling van de bovengenoemde negatieve uitkomsten.

De Random Forest presteerde het beste met de hoogste nauwkeurigheid (AUCs tussen 0,71-0,92). Dit zou erop kunnen wijzen dat de relaties tussen de kenmerken in de verzekeringsdataset het best worden vastgelegd door een Random Forest-model en dat dit modelraamwerk het beste werkt voor gezondheidsverzekeringsdata in het algemeen. We hebben vastgesteld dat verschillende modellen verschillende voorspellers identificeerden voor elk van de negatieve uitkomsten. De regressiemodellen en het neurale netwerk hadden vergelijkbare bevindingen, waarbij de meest voorspellende kenmerken gerelateerd waren aan medicatiegebruik. De Random Forest gebruikte meer verscheidenheid in zijn soorten voorspellers, die niet alleen medicatiegebruik identificeerden als voorspellende kenmerken, maar ook procedures zoals laboratoriumtests en beeldvorming. Deze bevindingen kunnen mogelijk worden toegepast in de dagelijkse klinische praktijk om risicopatiënten te identificeren. De complexe modellen pikken gedetailleerde interacties in de data op en kunnen worden gebruikt om nauwkeurige risicobeoordelingen te maken op basis van de gegevens van een individuele patiënt. We hebben verschillende strategieën geïdentificeerd en beoordeeld die het gebruik van eHealth en AI in de klinische praktijk van IBD kunnen worden toegepast en die kunnen bijdragen bij de overgang naar data gestuurde IBD-zorg.

DEEL III: eHealth om de levering van hoogwaardige zorg bij IBD te bewerkstelligen

Ondanks de innovatie en vooruitgang in medicamenteuze therapie voor IBD[44], ondergaat tot 15% van de patiënten met colitis ulcerosa binnen 20 jaar na diagnose een operatie. Voor patiënten met de ziekte van Crohn ondergaat bijna 50% van de patiënten binnen 10 jaar na diagnose een operatie[45,46]. Frequente monitoring is noodzakelijk voor vroege ontdekking van ziekteopvlamming en complicaties, gezien de complexiteit van IBD en het risico op ziekteprogressie na een operatie. In **Hoofdstuk 7** hebben we een zorgpad ontwikkeld voor postoperatieve IBD-patiënten, ontworpen om patiënten thuis na ontslag nauwlettend te volgen met behulp van telemonitoring om zo de patiëntervaring te verbeteren en postoperatieve heropnames en complicaties te verminderen. In **Hoofdstuk 7** hebben we eveneens de haalbaarheid en effectiviteit van deze eHealth interventie onderzocht op het aantal heropnames, bezoeken aan de spoedeisende hulp (SEH) en poliklinische consulten.

We hebben de uitvoerbaarheid aangetoond van het implementeren van een chirurgisch zorgpad met behulp van eHealth voor postoperatieve IBD-patiënten. Nadat ze na de operatie uit het ziekenhuis waren ontslagen, vulden patiënten regelmatig vragenlijsten in om zo eventuele complicaties vroegtijdig op te sporen. Patiënten die een toename van buikpijn meldden, werden bijvoorbeeld geëvalueerd door een chirurgische verpleegkundige die vervolgens de IBD-chirurg raadpleegde. Indien nodig wordt de patiënt verzocht naar het ziekenhuis te komen of vond er een aanpassing van de medische behandeling plaats. In onze pilot beoordeelde 81% van de deelnemende patiënten hun ervaring als 'uitstekend' en 94% beschreef het aantal vragen in de enquêtes als redelijk. Bovendien vond 54% van de patiënten dat hun herstel een ander resultaat zou hebben gehad zonder deelname aan het programma. We vonden geen statistisch significant verschil in het aantal heropnames, SEH-bezoeken en poliklinische follow-ups. Desalniettemin tonen de resultaten een hoge aanvaardbaarheid van patiënten evenals haalbaarheid van de eHealth applicatie aan waar het gaat om postoperatief IBD-management op afstand.

Verder hebben we in **Hoofdstuk 8** de patiëntervaring met de UCLA eIBD app beoordeeld na een jaar van gebruik. UCLA eIBD is een mobiele applicatie die verschillende componenten van zorgverlening omvat, zoals afspraakherinneringen en medicatie trackers voor patiënten, een beslisondersteuning portaal voor de behandelende zorgverlener en chatfunctionaliteit tussen patiënten en zorgverleners. UCLA eIBD probeert patiënten in staat te stellen hun IBD zelf beter te beheren door de toegang tot de behandeling via de app te vergroten en educatieve modules voor zelfhulp aan te bieden. UCLA eIBD checkt ook de ziekteactiviteit, kwaliteit van leven en arbeidsproductiviteit met behulp van gevalideerde vragenlijsten. Aangezien mobiele applicaties steeds relevanter worden in de zorgverlening, bieden onze resultaten van de patiënten ervaring handvaten voor verdere app-ontwikkeling en geven ze kritische feedback voor andere eHealth oplossingen.

Uit de UCLA eIBD app-studie bleek dat 78% van de gebruikers tevreden is over de communicatie tussen patiënt en zorgverlener via de app, een cruciaal onderdeel van de patiëntervaring. Bovendien meldde 54% van de app-gebruikers een waargenomen verbetering in ziekteactiviteit en 56% een waargenomen verbetering in de kwaliteit van leven (QoL), wat aangeeft dat een meerderheid van de patiënten vindt dat het platform een positieve invloed heeft op hun gezondheid. Op de vraag of ze deze app zouden aanbevelen aan vrienden, familie of andere patiënten, beoordeelden gebruikers deze app met een mediane score van 8 op een tienpuntsschaal (0 zou het minst waarschijnlijk aanbevelen en 10 het meest waarschijnlijk aanbevelen). Aanbevelingen van patiënten over het verbeteren van de app waren gericht op specifieke inhoudelijke interesses en de vraag naar aanvullende educatieve onderwerpen (bijvoorbeeld onderwerpen over gezondheid van vrouwen) in plaats van technische problemen of het überhaupt ontbreken van een app. Dit resultaat vertaalt zich terug naar het algemene tevredenheidspercentage van 74% van de deelnemers die de app gemakkelijk te navigeren vond. Educatieve fitness- en voedingsmodules waren de twee meest gebruikte modules, die elk door 34% van de gebruikers werden voltooid. Onze bevindingen suggereren dat een platform met interactieve modules ter bevordering van gezonde leefgewoonten en verbeterde toegang tot communicatie met zorgverleners, goed wordt ontvangen door IBD-patiënten met zelf gerapporteerde verbetering van de ziekteactiviteit en kwaliteit van leven, en mogelijk kan resulteren in een grotere tevredenheid bij de poliklinische zorgverlening.

Algemene conclusie en toekomstperspectieven

Ondanks de vooruitgang in medische therapie heeft IBD nog steeds een grote economische en psychosociale impact. Om de kwaliteit van de zorg te verbeteren, is zelfbeschikking en zelfmanagement van patiënten buiten de traditionele klinische setting om, noodzakelijk om de ervaring en uitkomsten te verbeteren en de kosten te verlagen.

In **Hoofdstuk 2** hebben we aangetoond dat werkende IBD-patiënten in klinische remissie nog steeds een substantiële afname in arbeidsproductiviteit hebben die meestal onopgemerkt blijft. De daarmee gepaard gaande hoge indirecte kosten vormen een aanzienlijke economische last voor de gezondheidsuitgaven. Een methode om indirecte kosten te verlagen omvat zowel interventies van zorgverleners als werkgevers, die idealiter samenkomen in een geïntegreerde aanpak[47]. De ontwikkeling en het testen van hulpmiddelen voor het verbeteren van productiviteitsmeting kunnen een zinvolle en onmiddellijke impact hebben. Zorgverleners (bijv. artsen, verpleegkundigen, maatschappelijk werkers endiëtisten) moeten proactief werk gerelateerde aanpassingen op het individu kunnen bespreken en voorstellen. Met behulp van eHealth-toepassingen kunnen zorgverleners mentale ondersteuning, voedingsondersteuning en welzijn (bijv. fitness, yoga en meditatie) opnemen in hun zorgplan, waardoor de gezondheid en productiviteit van patiënten op het werk mogelijk verbeteren. Daarnaast kan eHealth het elimineren van onnodige onderzoeken, procedures en medische afspraken via zorgpaden vereenvoudigen, waardoor het ziekteverzuim kan worden teruggedrongen. Uit enquêtes is gebleken dat werknemers met chronische aandoeningen meer geneigd zijn zeer tevreden te zijn met hun baan als ze een hoge mate van zelfredzaamheid hebben bij het omgaan met hun ziekte, steun ervaren op de werkplek en minder werkbeperkingen hebben[48]. Dit zou werkgevers ook in staat stellen om met succes bij te sturen, wat leidt tot een verbetering van arbeidsproductiviteit, vermindering van ziekteverzuim en de bijbehorende indirecte kosten.

In **Hoofdstuk 3** presenteerden we dat de zorg voor IBD-patiënten ook resulteert tot verlaagde arbeidsproductiviteit bij hun mantelzorgers. Bovendien vonden mantelzorgers, ondanks de last, dat ze meer en beter moesten doen voor hun IBD-patiënt, waaruit blijkt dat er een noodzaak is voor gepaste oplossingen. Gedragsinterventies via online platformen of mobiele apps, bieden voor patiënten een beter management van hun IBD aan, naast motivatie om positief leefstijl gedrag te vertonen[49]. Mantelzorgers zouden ook van dit soort oplossingen kunnen profiteren. Mantelzorgers kunnen via eHealth-toepassingen de nodige voorlichting over de ziekte van de patiënt en sociale ondersteuning (contact met andere mantelzorgers) krijgen om de belasting van de mantelzorger te verminderen en de zelfbeschikking te vergroten[50]. De ontwikkeling en implementatie van dergelijke oplossingen voor mantelzorgers van IBD-patiënten kan van grote waarde zijn voor een vaak over het hoofd gezien en uitdagend probleem.

eHealth heeft het potentieel om zelfmanagement van patiënten te vergroten en hierdoor een vermindering van de groeiende last van IBD op de zorguitgaven te bewerkstelligen. Daarom hebben we in **Hoofdstuk 4** een innovatief screeningsinstrument ontwikkeld voor het detecteren van therapieontrouw van medicatie bij IBD-patiënten. Hierdoor kunnen zorgverleners de exacte redenen voor therapieontrouw uitvragen, zodat ze meer gepersonaliseerde oplossingen kunnen bieden. Het gebruik van deze tool kan zorgen voor continue monitoring op afstand van therapieontrouw. Toekomstige studies zouden het effect van monitoring op afstand moeten valideren en moeten kijken naar het effect op patiënttevredenheid en de gezondheidszorgkosten. Het gebruik van smartphones en eHealth-toepassingen neemt toe. Net als in dagelijks leven, wordt elektronische communicatie tussen patiënten en hun zorgverleners de norm.

In **Hoofdstuk 5** hebben we de haalbaarheid aangetoond van het categoriseren van grote datasets van elektronische communicatie in één van de meest complexe chronische aandoeningen in een laag (<10) aantal categorieën. Onze resultaten toonden aan dat 25% van de berichten betrekking had op afspraken. Dit biedt de mogelijkheid voor AI om een rol te spelen in de zorgoptimalisatie. Een chatbot zou efficiënt specifieke zorgprocessen kunnen automatiseren. Gedacht kan worden aan verzoeken met betrekking tot afspraken of zelfs het initieel uitvragen van patiënten bij symptomen. De chatbot zou vervolgens zelfs ingezet kunnen worden om de antwoorden van patiënten aangaande de symptomen te categoriseren om daarna middels beslisbomen (ook gebruikt door verpleegkundigen) de ernst van de situatie in te schatten. Hierdoor kunnen zorgverleners efficiënter werken en de bespaarde administratieve last besteden aan betere patiëntenzorg. De waarde van een chatbot is duidelijk aangetoond in andere bedrijfstakken[51]; een chatbot is altijd beschikbaar, kan grote hoeveelheden communicatie gelijktijdig uitvoeren, en heeft geen wachttijden. Nu wij de haalbaarheid hebben aangetoond, zijn verdere studies nodig om ook de technische bouw en implementatie te beoordelen en mede als het effect op patiënten, zorgverleners en de kosten.

Vanwege de toename van het gebruik van EPDs[40,43], de beschikbaarheid van grote datasets van patiëntengegevens en vooruitgang van de processorkracht van computers, is AI gepresenteerd als een oplossing voor de grootste vraagstukken in de gezondheidszorg.

De praktische toepassing is echter voor de meeste clinici een raadsel. Het is duidelijk dat big data niet optimaal bestudeerd kunnen worden met de standaardmethoden van statistische analyse[40]. In **Hoofdstuk 6** hebben we laten zien dat het haalbaar is om met succes complexe AI-modellen uit te voeren op grote datasets (Big Data) van IBD-patiënten. Bovendien hebben we aangetoond dat deze bevindingen potentieel gebruikt kunnen worden in de dagelijkse klinische praktijk door risicoprofilering van patiënten. Tevens is de overdraagbaarheid van deze modellen en hun resultaten naar verschillende instellingen succesvol aangetoond, waardoor een grote barrière in de implementatie is weggenomen[52]. De volgende stap zou zijn om deze modellen te integreren in een prospectieve omgeving om de prestaties op betrouwbaarheid te bestuderen en tevens te kijken naar het effect op de uitkomsten en kosten voor de patiënt.

In een tijdperk waarin het gebruik van mobiele technologie in het dagelijks leven onvervangbaar is geworden, zal technologische innovatie in de gezondheidszorg naar verwachting gepersonaliseerde zorg herdefiniëren. Dat het implementeren van AI- en eHealth-toepassingen in de zorgverlening van chronische aandoeningen voordelen biedt, staat onmiskenbaar vast. Studies hebben de effectiviteit van mobiele applicaties aangetoond, maar tegelijkertijd bewezen dat patiënten nog steeds verlangen naar verbeteringen aan bestaande oplossingen[34,53]. In **Hoofdstuk 7** hebben we de haalbaarheid getoond van het implementeren van een chirurgisch zorgpad middels eHealth voor postoperatieve IBD-monitoring. Het middels eHealth aangeboden chirurgisch zorgpad werd goed ontvangen door patiënten, hetgeen bewijst dat het gebruik van eHealth-interventies voor patiëntenzorg door patiënten aanvaard evenals gebruikt zou worden. In **Hoofdstuk 8** hebben we laten zien dat UCLA eIBD en zijn holistische benadering hebben geleid tot betere patiëntervaringen en tevredenheid. De resultaten hiervan kunnen aangemerkt worden als waardevolle aanbeveling voor de gezondheidszorg en eHealth-ontwikkelaars. Om de effectiviteit op grotere schaal en de impact op de kosten te beoordelen, zijn meer en grotere studies noodzakelijk.

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List of Publications

This thesis

1. **Zand, A**, van Deen, WK, Inserra, EK, Hall, L, Kane, E, Centeno, A, Choi, JM, Ha, CY, Esrailian, E, D'Haens, GR, Hommes, DW. Presenteeism in Inflammatory Bowel Diseases: A Hidden Problem with Significant Economic Impact. *Inflamm Bowel Dis. 2015 Jul;21(7):1623-30*

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5. **Zand A**, Nguyen A, Stokes Z, van Deen WK, , Lightner A, Platt A, Jacobs R, Reardon S, Kane E, Sack J, Hommes DW. Patient Experiences and Outcomes of a Telehealth Clinical Care Pathway for Postoperative Inflammatory Bowel Disease Patients. *Telemed J E Health. 2020 Jul;26(7):889-897*

6. **Zand A**, Nguyen A, Reynolds C, Khandadash A, Esrailian E, Hommes DW. Patient Experience and Satisfaction with an e-Health Care Management Application for Inflammatory Bowel Diseases. *Submitted*

7. **Zand A**, Stokes Z, Sharma A, van Deen WK, Hommes DW. Artificial Intelligence for Inflammatory Bowel Diseases (IBD); Developing and Validating Machine Learning Models in Big Data to Predict Negative Outcomes. *Submitted*

Other

8. Van Deen WK, van der Meulen-de Jong AE, Parekh NK, Kane E, **Zand A**, DiNicola CA, Hall L, Inserra EK, Choi JM, Ha CY, Esrailian E, van Oijen MG, Hommes DW. Development and Validation of an Inflammatory Bowel Diseases Monitoring Index for Use With Mobile Health Technologies. *Clin Gastroenterol Hepatol. 2016 Dec;14(12):1742-1750.e7*

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