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.

References

1. Pariente B, Cosnes J, Danese S, et al. Development of the Crohn's disease digestive damage score, the Lémann score. *Inflammatory Bowel Diseases*. 2011;17(6):1415-1422. doi:10.1002/ibd.21506

2. Kappelman MD, Rifas-Shiman SL, Porter CQ, et al. Direct Health Care Costs of Crohn's Disease and Ulcerative Colitis in US Children and Adults. *Gastroenterology*. 2008;135(6):1907-1913. doi:10.1053/j.gastro.2008.09.012

3. Petryszyn PW, Witczak I. Costs in inflammatory bowel diseases. *Przeglad Gastroenterologiczny*. 2016;11(1):6-13. doi:10.5114/pg.2016.57883

4. Dahlhamer JM, Zammitti EP, Ward BW, Wheaton AG, Croft JB. Prevalence of inflammatory bowel disease among adults aged ≥18 years — United States, 2015. *Morbidity and Mortality Weekly Report*. 2016;65(42):1166-1169. doi:10.15585/mmwr.mm6542a3

5. Lönnfors S, Vermeire S, Greco M, Hommes D, Bell C, Avedano L. IBD and health-related quality of life - Discovering the true impact. *Journal of Crohn's and Colitis*. 2014;8(10):1281-1286. doi:10.1016/j.crohns.2014.03.005

6. Hodgson TA, Meiners MR. Cost-of-illness methodology: a guide to current practices and procedures. *The Milbank Memorial Fund quarterly Health and society*. 1982;60(3):429-462. doi:10.2307/3349801

7. Eisenberg JM. Clinical Economics: A Guide to the Economic Analysis of Clinical Practices. *JAMA: The Journal of the American Medical Association*. 1989;262(20):2879-2886. doi:10.1001/jama.1989.03430200123038

8. Park KT, Ehrlich OG, Allen JI, et al. The Cost of Inflammatory Bowel Disease: An Initiative from the Crohn's & Colitis Foundation. *Inflammatory Bowel Diseases*. 2020;26(1):1-10. doi:10.1093/ibd/izz104

9. D'Haens G, Baert F, van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *The Lancet*. 2008;371(9613):660-667. doi:10.1016/S0140-6736(08)60304-9

10. Olivera P, Danese S, Jay N, Natoli G, Peyrin-Biroulet L. Big data in IBD: a look into the future. *Nature Reviews Gastroenterology and Hepatology*. 2019;16(5):312-321. doi:10.1038/s41575-019-0102-5

11. Kang B, Choi SY, Kim HS, Kim K, Lee YM, Choe YH. Mucosal healing in paediatric patients with moderate-to-severe luminal Crohn's disease under combined immunosuppression: Escalation versus early treatment. *Journal of Crohn's and Colitis*. 2016;10(11):1279-1286. doi:10.1093/ecco-jcc/jjw086

12. van der Valk ME, Mangen MJJ, Severs M, et al. Evolution of costs of inflammatory bowel disease over two years of follow-up. *PLoS ONE*. 2016;11(4). doi:10.1371/journal.pone.0142481

13. Agency for Healthcare Research and Quality. What Is Patient Experience? | Agency for Health Research and Quality. *Agency for Health Research and Quality*. Published online 2017:n/a. Accessed August 5, 2020. https://www.ahrq.gov/cahps/about-cahps/patient-experience/index.html

14. Berwick DM, Nolan TW, Whittington J. The triple aim: Care, health, and cost. *Health Affairs*. 2008;27(3):759-769. doi:10.1377/hlthaff.27.3.759

15. Thorpe KE. The rise in health care spending and what to do about it: Disease prevention/health promotion approaches are key to slowing the rise in health care spending. *Health Affairs*. 2005;24(6):1436-1445. doi:10.1377/hlthaff.24.6.1436

16. Zand A, Nguyen A, Stokes Z, et al. Patient Experiences and Outcomes of a Telehealth Clinical Care Pathway for Postoperative Inflammatory Bowel Disease Patients. *Telemedicine journal and e-health : the official journal of the American Telemedicine Association*. 2020;26(7):889-897. doi:10.1089/tmj.2019.0102

17. Cosnes J, Gowerrousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology*. 2011;140(6):1785-1794.e4. doi:10.1053/j.gastro.2011.01.055

18. Sandor Kiss L, Laszlo Lakatos P. Natural History of Ulcerative Colitis: Current Knowledge. *Current Drug Targets*. 2011;12(10):1390-1395. doi:10.2174/138945011796818117

19. PricewaterhouseCoopers Australia. Improving Inflammatory Bowel Disease Care Across Australia. 2013;(March):1-53. Accessed June 23, 2020. https://www.crohnsandcolitis.com.au/research/studies-reports/

20. Ramsden VR, Mcfp RN, Shari H, et al. Participatory health research. *Canadian Family Physician*. 2013;59(9):1014-1015.

21. Parchman ML, Zeber JE, Palmer RF. Participatory decision making, patient activation, medication adherence, and intermediate clinical outcomes in type 2 diabetes: A starnet study. *Annals of Family Medicine*. 2010;8(5):410-417. doi:10.1370/afm.1161

22. Weaver KN, Kappelman MD, Sandler RS, et al. Variation in Care of Inflammatory Bowel Diseases Patients in Crohn's and Colitis Foundation of America Partners: Role of Gastroenterologist Practice Setting in Disease Outcomes and Quality Process Measures. *Inflammatory Bowel Diseases*. 2016;22(11):2672-2677. doi:10.1097/MIB.0000000000000933

23. Yin AL, Hachuel D, Pollak JP, Scherl EJ, Estrin D. Digital health apps in the clinical care of inflammatory bowel disease: Scoping review. *Journal of Medical Internet Research*. 2019;21(8). doi:10.2196/14630

24. Taylor K, Silver L. Smartphone Ownership Is Growing Rapidly Around the World, but Not Always Equally. *Pew Research Center*. 2019;(February):47. doi:February 5, 2019

25. Sim I. Mobile devices and health. *New England Journal of Medicine*. 2019;381(10):956-968. doi:10.1056/NEJMra1806949

26. Buttorff C, Ruder T, Bauman M. *Multiple Chronic Conditions in the United States*. RAND Corporation; 2017. doi:10.7249/tl221

27. Gerteis J, Izrael D, Deitz D, et al. Multiple Chronic Conditions Chartbook: 2010 Medical Expenditure Panel Survey Data. Published online 2014:7. Accessed June 23, 2020. https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/prevention-chronic-care/decision/mcc/mccchartbook.pdf

28. Kelso M, Feagins LA. Can smartphones help deliver smarter care for patients with inflammatory bowel disease? *Inflammatory Bowel Diseases*. 2018;24(7):1453-1458. doi:10.1093/ibd/izy162

29. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. *Nature Medicine*. 2019;25(1):44-56. doi:10.1038/s41591-018-0300-7

30. Büsch K, da Silva SA, Holton M, Rabacow FM, Khalili H, Ludvigsson JF. Sick leave and disability pension in inflammatory bowel disease: A systematic review. *Journal of Crohn's and Colitis*. 2014;8(11):1362-1377. doi:10.1016/j.crohns.2014.06.006

31. Hemp P. *Presenteeism: At Work-But Out of It*.; 2012. Accessed June 23, 2020. Harv Bus Rev. 2004;82(10):49-155.

32. Zand A, Zand A, Kim BJ, et al. The effects of inflammatory bowel disease on caregivers: Significant burden and loss of productivity. *BMC Health Services Research*. 2020;20(1):556. doi:10.1186/s12913-020-05425-w

33. Con D, de Cruz P. Mobile Phone Apps for Inflammatory Bowel Disease Self-Management: A Systematic Assessment of Content and Tools. *JMIR mHealth and uHealth*. 2016;4(1):e13. doi:10.2196/mhealth.4874

34. Stunkel L, Karia K, Okoji O, et al. Impact on Quality of Life of a Smart Device Mobile Application in Patients with Inflammatory Bowel Disease. *American Journal of Gastroenterology*. 2012;107:S635-S636. doi:10.14309/00000434-201210001-01575

35. Ward BW, Schiller JS, Goodman RA. Multiple chronic conditions among us adults: A 2012 update. *Preventing Chronic Disease*. 2014;11(4). doi:10.5888/pcd11.130389

36. Sabaté E. WHO | ADHERENCE TO LONG-TERM THERAPIES: EVIDENCE FOR ACTION. 2015. Published 2015. Accessed June 23, 2020. http://www.who.int/chp/knowledge/publications/adherence_report/en/

37. Ghadir MR, Bagheri M, Vahedi H, et al. Nonadherence to Medication in Inflammatory Bowel Disease: Rate and Reasons. *Middle East Journal of Digestive Diseases*. 2016;8(2):116-121. doi:10.15171/mejdd.2016.16

38. Benjamin RM. Surgeon General's Perspectives: Medication adherence: Helping patients take their medicines as directed. *Public Health Reports*. 2012;127(1):2-3. doi:10.1177/003335491212700102

39. Statista. Global AI software market size 2018-2025 | Statista. Tractica. Published 2019. Accessed July 19, 2020. https://www.statista.com/statistics/607716/worldwide-artificial-intelligence-market-revenues/

40. Derrington D. *Artificial Intelligence for Health and Health Care*.; 2017. Accessed June 23, 2020. https://pdfs.semanticscholar.org/4f32/7be94508a5c1f2a6f09917d7dcf57698af24.pdf

41. Iroju OG, Olaleke JO. A Systematic Review of Natural Language Processing in Healthcare. *International Journal of Information Technology and Computer Science*. 2015;7(8):44-50. doi:10.5815/ijitcs.2015.08.07

42. Zand A, Sharma A, Stokes Z, et al. An Exploration into the Use of a Chatbot for Patients with Inflammatory Bowel Diseases: Retrospective Cohort Study. *Journal of Medical Internet Research*. 2020;22(5):e15589. doi:10.2196/15589

43. E YNJE and H. Office-based Physician Electronic Health Record Adoption. *December*. Published online 2016. Accessed July 19, 2020. https://dashboard.healthit.gov/quickstats/pages/physician-ehr-adoption-trends.php

44. Kozuch PL, Hanauer SB. Treatment of inflammatory bowel disease: A review of medical therapy. *World Journal of Gastroenterology*. 2008;14(3):354-377. doi:10.3748/wjg.14.354

45. Targownik LE, Singh H, Nugent Z, Bernstein CN. The Epidemiology of Colectomy in Ulcerative Colitis: Results From a Population-Based Cohort. *American Journal of Gastroenterology*. 2012;107(8):1228-1235. doi:10.1038/ajg.2012.127

46. Peyrin-Biroulet L, Loftus E v., Colombel JF, Sandborn WJ. The natural history of adult crohn's disease in population-based cohorts. *American Journal of Gastroenterology*. 2010;105(2):289-297. doi:10.1038/ajg.2009.579