Dietary Therapy for Pediatric Inflammatory Bowel Disease:

An Epidemiologic and Economic Analysis

Naomi Rose Maas Schwartz

A dissertation submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

University of Washington

2021

Reading Committee:

Beth Devine, Chair

Amanda Phipps

Josh Roth

David Suskind

Program Authorized to Offer Degree:

School of Pharmacy

University of Washington

Abstract

Dietary Therapy for Pediatric Inflammatory Bowel Disease:

An Epidemiologic and Economic Analysis

Naomi Rose Maas Schwartz

Chair of the Supervisory Committee:

Dr. Beth Devine

The objective of this study was to assess the potential health outcomes and economic impact of the Specific Carbohydrate Diet (SCD) as a therapeutic option for pediatric patients with inflammatory bowel disease (IBD).

In Aim 1, we evaluated the comparative effectiveness of the SCD as an adjunct to pharmacotherapy by using registry data to create an external control arm for an N-of-1 trial. In the full population, there was no statistically significant difference in the change in disease activity from baseline to eight weeks comparing the SCD plus pharmacotherapy to pharmacotherapy alone. In subgroup analyses limited to patients with active disease at baseline, the difference in differences in disease activity was statistically significant, but did not reach clinical significance.

In Aim 2, we developed a hybrid decision tree Markov model to assess the value-based price (VBP) of the SCD for induction of remission in pediatric patients with active Crohn's disease (CD). At an effectiveness of only 50%, we found that the VBP of the SCD at a willingness-to-pay threshold of $50,000 per quality-adjusted life year was close to $20,000, which far exceeds the likely cost of the diet.

In Aim 3, we conducted a qualitative study of parents of patients with IBD treated at Seattle Children's Hospital to assess perceived barriers to initiating and/or maintaining the SCD. We found that parents of children diagnosed with IBD primarily chose to try the SCD due to concerns about medication safety. Additionally, we identified that cost, time commitment, and psychosocial impact are three major barriers to utilizing the SCD.

This work provides a foundation for further research into the population health and economic impacts of dietary therapy for IBD. Future studies are needed to assess both the direct and indirect costs of the SCD, as well as the effectiveness of the SCD as a stand-alone therapy and as an adjunct to pharmacotherapy. These data would enable more robust evaluation of the SCD as a therapeutic option, therefore providing essential information for clinicians, patients, payers, and policy-makers.

Contents

Introduction

In North America, more than 1.3% of the general population has inflammatory bowel disease (IBD), amounting to over 3.1 million Americans.[1] From 1990 through the 2000s, the burden of pediatric IBD has increased globally.[2] Pediatric IBD is particularly aggressive, leading to growth failure, high rates of surgery, and increased risk of certain cancers;[3,4] it also confers a substantial economic burden on families and healthcare systems.[5,6] Medications are the leading driver of direct costs among patients with IBD (approximately 35%),[7-9] greatly outpacing costs of hospitalization and surgery. Factors most strongly associated with IBD costs are uncontrolled disease, corticosteroid treatment in the previous year, and comorbidity burden.[9] Specifically, compared to children without IBD, those with IBD have higher rates of primary sclerosing cholangitis, arthritis, atopic dermatitis, thyroid disease, autoimmune hepatitis, nephrolithiasis, and pancreatitis (results vary in magnitude and type of point estimate, but consistently show elevated risk among children with IBD).[10-12]

Treatment for IBD aims to suppress the immune system's ability to instigate an inflammatory reaction. The choice of agent is determined by disease severity, IBD-related complications, prior medication failures, and the need for surgery.[8] Typically, treatment for IBD follows a step-up approach, beginning with therapies such as corticosteroids and immunomodulators (e.g. methotrexate, 6-mercaptopurine, azathioprine).[9] If these agents fail to induce remission, biologic therapies are used, according to clinical guidelines.[10] Tumor necrosis factor (TNF) antagonists, such as infliximab and adalimumab, are considered first-line biologics. However, up to 30% of patients do not respond to anti-TNF drugs, and almost 50% of those who do respond lose clinical benefits within the first year.[11,12] Additionally, treatment with anti-TNF agents is associated with multiple safety concerns, such as opportunistic infections, malignancies, and adverse drug reactions.[13]

Given the high cost of pharmacotherapy, and the risk of adverse effects, considerable attention has been given to the potential role of dietary therapy for IBD. While there is evidence

that specific types of nutritional therapy (exclusive enteral nutrition) are as effective as steroids for inducing remission in pediatric patients with IBD,[14,15] studies of the efficacy of diet in treating and controlling IBD symptoms are limited.[16] One such therapy, the Specific Carbohydrate Diet (SCD) has been shown to result in symptom relief, improvement in inflammatory biomarkers, and mucosal healing in observational, uncontrolled studies.[17-20]

The SCD is a restrictive dietary program created by Dr. Sydney Haas in the 1920s, and popularized by Elaine Gottschall with the publication of her book *Breaking the Vicious Cycle: Intestinal Health Through* Diet.[21] The SCD is based on the association of gut microbiome dysbiosis and IBD.[21] The objective of the diet is to eliminate factors that contribute to dysbiosis, thereby allowing for restoration of the disrupted gut microbiome. Allowed foods include meat/fish/poultry, eggs, some legumes, fully fermented yogurt, non-starchy vegetables, ripe fruit, nuts/seeds, honey, and nut flours. Restricted foods include all grains, milk products (aside from 24-hour fermented SCD yogurt and cheeses aged greater than 30 days), starchy vegetables, processed foods with food additives, and sweeteners other than honey. The modified SCD (mSCD) is a more liberal version of the SCD in which allowed foods are expanded to include organic rice, oats, sweet potatoes, Grade A maple syrup, and 100% unsweetened cocoa powder (not Dutch processed) or 100% cacao powder, nibs, and butter (no sugar added).[22]

Despite promising observational findings, evidence from controlled, large-scale trials is lacking. The Personalized Research on Diet in Ulcerative Colitis and Crohn's Disease (PRODUCE) study is a recently completed series of N-of-1 trials (similar to a crossover randomized controlled trial, but with a single patient as the unit of analysis) evaluating the effectiveness of the SCD versus a modified SCD in reducing symptoms and inflammatory burden among patients aged 7-18 years of age with mild to moderate IBD.[23] The PRODUCE study is a groundbreaking step forward for dietary therapy research in IBD. The results will provide direct benefit to patients and inform clinicians' treatment choices. However, because PRODUCE lacks a control arm, the effectiveness of the SCD compared to standard

pharmacotherapy will remain unanswered unless additional studies are conducted. This study seeks to fill that gap in knowledge, and to assess the potential health outcomes and economic impact of using the SCD versus pharmacotherapy alone.

Specific Aims

The objective of Aim 1 is to compare the effectiveness of the SCD plus pharmacotherapy vs. pharmacotherapy alone for inducing remission in an observational study, as measured by the Short Pediatric Crohn's Disease Activity Index (sPCDAI), in pediatric patients with active mild to moderate Crohn's disease (CD). The methods included a propensity score matched differences-in-differences model using data from the PRODUCE trial and the ImproveCareNow (ICN) registry. My hypothesis is that compared to standard pharmacotherapy, the SCD will result in greater improvement in sPCDAI after 8 weeks.

The objective of Aim 2 is to assess the potential cost-effectiveness of the SCD for induction of remission, as defined by the sPCDAI, in pediatric patients with active mild to moderate IBD. A hybrid decision-tree Markov model was developed in Microsoft® Excel to compare the projected costs and outcomes from the SCD arm to the pharmacotherapy arm. My hypothesis is that the SCD will be a cost-effective therapeutic option for induction of remission in pediatric IBD patients.

The objective of Aim 3 is to conduct a qualitative study of parents of patients with IBD treated at Seattle Children's Hospital to assess perceived barriers to initiating and/or maintaining the SCD. Methods included primary data collection via one-on-one video interviews with parents of children with IBD receiving care at Seattle Children's Hospital and qualitative analysis of interview content. This is an exploratory study designed to generate hypotheses for future studies.

Collectively, these specific aims will serve as a foundation for future research into the population health and economic impacts of dietary therapy for IBD. The results of this study will

inform clinical decision-making, and if the SCD is found to be effective and cost-effective, potentially shift the paradigm for management of pediatric IBD toward a future in which dietary therapy is a pillar of treatment that is accessible to all patients.

References

1. Dahlhamer J, Zammitti E, Ward B, Wheaton A, Croft J. Prevalence of Inflammatory Bowel Disease Among Adults Aged ≥18 Years - United States, 2015. *Morb Mortal Wkly Rep.* 2016;65:1166-1169.
2. Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. *Inflammatory bowel diseases.* 2011;17(1):423-439.
3. Heuschkel R, Salvestrini C, Beattie RM, Hildebrand H, Walters T, Griffiths A. Guidelines for the management of growth failure in childhood inflammatory bowel disease. *Inflammatory bowel diseases.* 2008;14(6):839-849.
4. Nasiri S, Kuenzig ME, Benchimol EI. Long-term outcomes of pediatric inflammatory bowel disease. *Seminars in Pediatric Surgery.* 2017;26(6):398-404.
5. Heaton PC, Tundia NL, Schmidt N, Wigle PR, Kelton CM. National burden of pediatric hospitalizations for inflammatory bowel disease: results from the 2006 Kids' Inpatient Database. *Journal of pediatric gastroenterology and nutrition.* 2012;54(4):477-485.
6. Sin AT, Damman JL, Ziring DA, et al. Out-of-pocket Cost Burden in Pediatric Inflammatory Bowel Disease: A Cross-sectional Cohort Analysis. *Inflammatory bowel diseases.* 2015;21(6):1368-1377.
7. van der Valk ME, Mangen MJ, Leenders M, et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFalpha therapy: results from the COIN study. *Gut.* 2014;63(1):72-79.
8. Floyd DN, Langham S, Severac HC, Levesque BG. The economic and quality-of-life burden of Crohn's disease in Europe and the United States, 2000 to 2013: a systematic review. *Dig Dis Sci.* 2015;60(2):299-312.
9. El-Matary W, Kuenzig ME, Singh H, et al. Disease-Associated Costs in Children With Inflammatory Bowel Disease: A Systematic Review. *Inflammatory bowel diseases.* 2020;26(2):206-215.
10. Ghersin I, Khateeb N, Katz LH, Daher S, Shamir R, Assa A. Comorbidities in adolescents with inflammatory bowel disease: findings from a population-based cohort study. *Pediatric Research.* 2020;87(7):1256-1262.
11. Ludvigsson JF, Büsch K, Olén O, et al. Prevalence of paediatric inflammatory bowel disease in Sweden: a nationwide population-based register study. *BMC Gastroenterol.* 2017;17(1):23-23.
12. Karve S, Candrilli S, Kappelman MD, Tolleson-Rinehart S, Tennis P, Andrews E. Healthcare utilization and comorbidity burden among children and young adults in the United States with systemic lupus erythematosus or inflammatory bowel disease. *The Journal of pediatrics.* 2012;161(4):662-670.e662.
13. Stallmach A, Hagel S, Bruns T. Adverse effects of biologics used for treating IBD. *Best practice & research Clinical gastroenterology.* 2010;24(2):167-182.
14. Dziechciarz P, Horvath A, Shamir R, Szajewska H. Meta-analysis: enteral nutrition in active Crohn’s disease in children. *Alimentary Pharmacology & Therapeutics.* 2007;26(6):795-806.
15. Limketkai BN, Iheozor-Ejiofor Z, Gjuladin-Hellon T, et al. Dietary interventions for induction and maintenance of remission in inflammatory bowel disease. *Cochrane Database Syst Rev.* 2019;2(2):CD012839-CD012839.
16. Green N, Miller T, Suskind D, Lee D. A Review of Dietary Therapy for IBD and a Vision for the Future. *Nutrients.* 2019;11(5):947.
17. Suskind DL, Wahbeh G, Gregory N, Vendettuoli H, Christie D. Nutritional therapy in pediatric Crohn disease: the specific carbohydrate diet. *Journal of pediatric gastroenterology and nutrition.* 2014;58(1):87-91.

18. Suskind DL, Cohen SA, Brittnacher MJ, et al. Clinical and Fecal Microbial Changes With Diet Therapy in Active Inflammatory Bowel Disease. *Journal of clinical gastroenterology.* 2018;52(2):155-163.
19. Cohen SA, Gold BD, Oliva S, et al. Clinical and mucosal improvement with specific carbohydrate diet in pediatric Crohn disease. *Journal of pediatric gastroenterology and nutrition.* 2014;59(4):516-521.
20. Cohen SA, Stallworth AN, Koch BM, Mason DH, Blumenthal J, Gold BD. Sa1992 Mucosal Healing With the Specific Carbohydrate Diet in Pediatric Crohn's Disease: Preliminary Results of a Prospective Pilot Study. *Gastroenterology.* 2012;142(5):S-376.
21. Gottschall E, Gottschall EG. *Breaking the vicious cycle: intestinal health through diet.* Kirkton, Ont.: Kirkton Press; 1994.
22. Personalized Research on Diet in Ulcerative Colitis and Crohn's Disease (PRODUCE). ClinicalTrials.gov Identifier NCT03301311. Accessed March 17, 2020.
23. Kaplan HC, Opipari-Arrigan L, Schmid CH, et al. Evaluating the Comparative Effectiveness of Two Diets in Pediatric Inflammatory Bowel Disease: A Study Protocol for a Series of N-of-1 Trials. *Healthcare (Basel).* 2019;7(4):129.

Chapter 1

Introduction

Much of the literature surrounding diet and health status is observational in nature, raising concerns about the validity of findings given the potential for confounding due to lifestyle and environmental factors.[1] However, randomized controlled trials (RCTs) of dietary interventions are challenging to conduct because they require a high level of participant commitment and involvement. Conventional RCT methods are prone to selective dropout and questions about generalizability to the real world where people choose their therapies.[2] Additionally, while randomized double blind placebo-controlled studies, often hailed as the "gold standard," are common in drug trials, there are substantial obstacles to using placebos in dietary research.[3] Specifically, it is extremely difficult to develop a placebo that is similar enough to the intervention to maintain blinding but different enough that it does not impact the outcome of interest. Because of this, many dietary studies utilize an "active comparator group." While these trials can assess comparative effectiveness of diets, the lack of a control arm limits the inference about the effectiveness of either intervention compared to a normal diet. This is potentially problematic, especially in a disease space such as inflammatory bowel disease (IBD), where dietary therapy is not standard of care. An example of this is the Personalized Research on Diet in Ulcerative Colitis and Crohn's Disease (PRODUCE) study, a recently completed series of N-of-1 trials evaluating the effectiveness of the Specific Carbohydrate Diet (SCD) versus a modified SCD in reducing symptoms and inflammatory burden among patients aged 7-18 years of age with mild to moderate IBD.[4] Because PRODUCE lacks a control arm, the effectiveness of the SCD compared to standard pharmacotherapy will remain unanswered unless additional studies are conducted.

Thus, the objective of this aim is to compare the effectiveness of the SCD plus pharmacotherapy vs. pharmacotherapy alone for inducing remission in pediatric patients with

active mild to moderate IBD, using an external control arm derived from a registry of pediatric patients with IBD.

Methods

Setting and Data Sources

This aim used data from the PRODUCE trial and the ImproveCareNow (ICN) registry. The PRODUCE study is a recently completed series of N-of-1 trials evaluating the effectiveness of the SCD versus a modified SCD in reducing symptoms and inflammatory burden among patients aged 7-18 years of age with mild to moderate IBD.[4] The PRODUCE study is part of ICN, a network established under the sponsorship of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, and the American Board of Pediatrics.[5] The ICN registry contains data for more than 330,000 outpatient visits for over 45,000 pediatric IBD patients ≤21 years of age who have consented for research. Due to the small number of participants with ulcerative colitis in the PRODUCE trial (N=14), we restricted the analysis to patients with Crohn's Disease (CD).

Patients with CD who had initiated a new immunotherapy or biologic therapy were identified in the ICN registry. The date of therapy initiation was defined as the index date. Of those patients, those with a follow-up visit 6-10 weeks after index and non-missing short Pediatric Crohn's Disease Activity Index (sPCDAI) were eligible for inclusion in the external control arm (N=359). Participants in the PRODUCE trial with CD and non-missing sPCDAI at baseline and follow-up after completion of the first eight week trial period were included in the treatment arm (N=31). Because results from the PRODUCE trial analyses suggested no statistically significant difference in effect between the SCD and the modified SCD (mSCD), these patients were pooled into a single group, regardless of which dietary intervention they completed.

Outcome

The outcome of interest was the sPCDAI.[6] The sPCDAI was developed as a more feasible alternative to the PCDAI, which requires determination of height velocity, analysis of laboratory tests, and components of a physical exam that are not always completed during patient visits.[7] Components of the sPCDAI include abdominal pain (20 points), well-being (20 points), weight (20 points), stool (10 points), abdominal exam (10 points), and extraintestinal manifestations (10 points). Scores range from 0-90 points, with higher scores indicating more severe disease. Inactive disease is defined as scores <15, mild disease is defined as scores 15≥ and <30, and moderate-severe disease is defined as scores ≥30. The sPCDAI has been validated in a large, multicenter study.[6] A clinically meaningful difference is defined as a change of ≥12.5.[8]

Missing data

There are a variety of approaches for handling missing data, depending on the assumptions about the causes of the missing data.[9] If the data are missing completely at random (MCAR), simply excluding the patients who dropped out would not bias the effect estimate.[10] If data are assumed to be missing in a predictable manner according to observed variables, the data is considered missing at random (MAR).[10] The third type of missing data occurs when the probability of missing data depends on unobserved variables.[10] This is called missing not at random (MNAR). In clinical epidemiological research, MAR is the most common type of missing data,[11] but there is no empirical way to be sure that data are MAR and not MNAR. When study attrition is not random, there is the potential for bias in the effect estimates.

Single imputation was used when >10% of participants were missing data.[12] Variables with >50% missingness were not included in the analysis.[13] Imputation was performed using the random “hot deck” method.[14,15] This entails replacing each missing value with an observed response from a random patient and is commonly used by government statistics agencies and

other survey organizations.[16] Additionally, in simulation studies, the hot deck technique performed the same with both MCAR and the MAR data.[17]

Propensity Scores

Propensity scores can be thought of as "balancing" scores such that conditioning on the propensity scores should balance the distribution of baseline covariates between treated and untreated individuals.[18] When building an external control arm for a single-arm trial, there is an added element of complexity because the goal is not only to match on the probability of receiving the experimental treatment, but also to match on the probability of being included in the trial.[19] With respect to the PRODUCE study, this is especially important, because the SCD is a strict diet and there are likely to be systematic differences across individuals who agreed to participate in the study and those who did not.

There is a robust body of literature on propensity scores, and several studies have shown that propensity scores with more covariates (e.g., high dimensional propensity scores) control confounding better than propensity scores estimated with fewer covariates.[20-24] It is generally recommended to include as many covariates as possible in the propensity score regression model; however, some experts emphasize that variables with weak effects in the propensity score model should only be kept in the model if they also predict the outcome of interest.[25] Additionally, variables that are strongly correlated with the exposure but not the outcome should not be included because they increase standard errors and bias.[26,27]

While there is no literature describing characteristics of parents that are predictive of enrolling one's child in a clinical trial for IBD, studies in other disease spaces indicate that race,[28] socioeconomic status,[29] and age of the child[30,31] are all factors that affect the likelihood of a parent consenting a child for a trial. Additionally, evidence suggests that sex is an important predictor of treatment decisions in IBD.[32-34] Unfortunately, due to data limitations, covariates included in the propensity score were restricted to age, race, sex, insurance type, BMI, and

current pharmacotherapy regimen. Propensity scores were calculated using these predictors by fitting a logistic regression model to obtain predicted probabilities of being in the treatment group for each individual.

Matching

The two primary types of individual matching include direct matching, in which individual study participants are matched on potential confounder(s) across comparison groups, and propensity score matching. For this study, matching was done via propensity scores, due to several advantages over exact matching. First, exact matching results in throwing out controls which are similar, but not exactly the same as the treated patients. While exact matching results in controls that are "exchangeable" with the treated population, it also throws away most of the sample. Additionally, propensity score matching has a conceptual advantage in that it gives a "region of support" in the population (both treated and untreated) where there is realistic probability of being treated. This allows for increased transparency in the balance. In this specific case, we are matching not only on receipt of treatment, but also likelihood of being in the PRODUCE trial. Thus, we want to exclude patients from the control population who would never have been in the trial. Looking at the distribution of propensity scores in the population allows us to identify the size of the population of patients who are very unlikely to be treated in the PRODUCE trial. Four patients from the ICN registry were propensity score matched to each patient from PRODUCE using a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score.[35]

Covariate Balancing Propensity Scores

In 2014, Kosuke Imai and Marc Ratkovic proposed a new method called the "covariate balancing propensity score" (CBPS).[36] In contrast to traditional propensity score methods, which can result in substantial bias of the treatment effect if the model is mis-specified,[37,38] CBPS uses

the generalized method of moments framework, iteratively finding estimates for β that optimize the likelihood function and balance the condition simultaneously.[36] Essentially, this means that CBPS gives more weight to covariates that are more predictive of treatment assignment. In simulation studies, the CBPS has been shown to be more robust in terms of balancing covariates and reducing bias compared with mis-specified logistic propensity score models.[39] Therefore, for this study, I computed CBPS in addition to traditional logistic propensity scores. Calculation of CBPS was done using the CBPS package for R.[40]

Inverse Probability of Treatment Weighting

As an alternative to matching, propensity scores can be used to create weights. Specifically, for the inverse probability of treatment weighting (IPTW) method, weights are assigned based on the inverse probability of receiving treatment.[41] When the outcome of interest is the average treatment effect on the treated (ATT), for a given observation *j,* the weight is calculated as follows:

$$w_j = \begin{cases} 1, for\ observations\ in\ the\ treated\ group \\ \dfrac{p_j}{1-p_j}, for\ observations\ in\ the\ control\ group \end{cases}$$

Where p_j is the propensity score for observation *j*. This method therefore upweights individuals in the control group who are very likely to be in the treatment group.

Differences in Differences

The ATT was estimated using the difference-in-differences (DiD) approach. DiD methods assume that the average outcomes for the experimental and control groups would have followed parallel trends over time in the absence of treatment.[42] However, this assumption is implausible in this setting, because it is likely that there are systematic differences between individuals who enrolled in PRODUCE and those who did not. If it is indeed the case that

assignment to the experimental arm and the outcome are both influenced by a common factor, that factor could potentially lead to bias in the estimated ATT.[43] Propensity score methods aim to eliminate as much observed heterogeneity as possible by ensuring that the observed characteristics of the experimental group and control group are comparable. Because the matched/weighted control group provides a counterfactual for the intervention group had there been no intervention, the difference-in-differences part of the model removes unobserved heterogeneity that was fixed over time or that followed parallel time trends between groups, thus providing a robust estimator, and has been shown to provide a less biased estimate of ATT than an unmatched approach when the parallel trends assumption does not hold.[43-46]

The DiD model was parameterized as follows:

$$Y_{ijt} = B_0 + B_1 treatment_j + B_2 post_t + \delta(treatment_j * post_t) + \varepsilon_{ijt}$$

where *i* indexes each individual, *j* indexes matched groups, *t* indexes time, treatment is an indicator for the exposure, post is an indicator for timing of the measurement assessment (pre- or post-treatment), and ε is the random error term.

The ATT is given by the following equation:

$$\hat{\delta} = \left(\bar{Y}_{treatment,post} - \bar{Y}_{treatment,pre}\right) - \left(\bar{Y}_{control,post} - \bar{Y}_{control,pre}\right)$$

All analyses were conducted using R version 4.05.[47]

Results

After applying the inclusion and exclusion criteria, 359 patients from the ICN Registry were eligible for the control arm (Figure 1). Though the PRODUCE study enrolled 54 participants, only 31 of the patients with CD had baseline and follow-up visits and non-missing sPCDAI. Baseline characteristics are reported stratified by disease status at index in Table 1. A subgroup analysis was conducted among patients with active disease (i.e., not in remission) at index.

Comparison of Propensity Score Methods

As expected, propensity-score matching resulted in a substantially decreased sample size in both the main analysis and the subgroup analysis (Table 2). A comparison of standardized mean differences demonstrated that the IPTW CBPS method produced the most balance in the covariates in both the full patient population and the subgroup analysis (Figures 2 and 3).

Average Treatment Effect on the Treated

In the full cohort, none of the propensity score methods demonstrated a statistically or clinically significant difference in sPCDAI from baseline to eight weeks (Table 2). The estimated ATT was numerically similar across all approaches, though closest to the null using CBPS. In the active disease subgroup, the ATT was statistically significant, but not clinically meaningfully different, using propensity score matching and logistic IPTW (Table 3). The ATT was not statistically significant using CBPS IPTW. Given that CBPS IPTW resulted in the most balance, as shown in Figures 2 and 3, it is likely that this approach is the least biased and therefore most reflective of the true ATT.

Discussion

To-date, there are no published studies directly comparing the SCD to pharmacotherapy. However, previous studies have shown that exclusive enteral nutrition (EEN) is as effective as corticosteroids for inducing remission in pediatric patients with CD[48] and concomitant EEN with infliximab is superior to infliximab alone.[49] In combination with evidence from uncontrolled studies of the SCD, these findings highlight the potential for dietary therapy in CD. Therefore, the objective of this study was to compare the effectiveness of the SCD in combination with pharmacotherapy to pharmacotherapy alone.

We found no statistically nor clinically significant difference in change in sPCDAI from baseline to eight weeks comparing the SCD with pharmacotherapy to pharmacotherapy alone in

patients with mild to moderate Crohn's disease. These findings were consistent, regardless of propensity score methodology. Though the sample size was small, the SCD resulted in a statistically significant, but not clinically significant, improvement in sPCDAI compared to pharmacotherapy alone among patients with active disease (i.e., sPCDAI ≥15) at baseline. Given that a smaller proportion of patients in the control arm had active disease at baseline compared to the PRODUCE study arm (51% vs 68%), it is likely that the results of the full analysis did not capture the true effect of the SCD.

The strength of this study is the use of multiple different robust propensity score methodologies that have been shown to reduce bias. Despite this, there are limitations to this analysis that need to be considered. First, the sample size for the SCD arm (from the PRODUCE study) was small, thus limiting the power of the analysis. Additionally, we cannot rule out the possibility of selection bias by requiring patients to have follow-up visits at six to eight weeks post treatment initiation. Finally, as is commonly the case with registry data, there was substantial missingness among some of the variables that would have otherwise contributed to the propensity score calculation (e.g., parental education, race/ethnicity); other potential confounders were not available at all (e.g., current dietary habits or allergies, family income, geographic location). The inability to include those factors in the analysis may have resulted in residual confounding.

While there have been substantial recent advances in the understanding of the pathogenesis of CD, there are still gaps in understanding. Previous longitudinal and cross-sectional studies have shown that IBD is associated with changes in the composition of the gut microbiota,[50,51] and it is thought that dietary therapies have an effect on disease activity via manipulation of the intestinal microbiome.[52] Multiple prospective studies of pediatric patients with active Crohn's disease have found that treatment with the SCD results in improved clinical disease activity associated with significant changes in the microbial composition of the intestine.[53-55] However, the mechanism by which the SCD induces these changes is still

unknown, and further research should investigate the biological basis of the SCD as a treatment option.

The results of this analysis indicate there may be some benefit to treatment with the SCD, and future large-scale studies are warranted. As the economic and humanistic burden of pediatric CD continue to grow, it is imperative to better understand the potential of the SCD as a therapeutic option.

Tables

Table 1. Baseline characteristics of pediatric patients with Crohn's disease included in the difference in differences analysis

	PRODUCE (N=31)			Control (N=359)		
	Remission (n=10)	Mild (n=10)	Moderate-Severe (n=11)	Remission (n=175)	Mild (n=95)	Moderate-Severe (n=89)
Age at index	12 (6-16)	11 (6-16)	12 (8-17)	14 (5-23)	14 (4-23)	14 (6-21)
Sex (% Male)	90%	70%	36%	62%	54%	52%
BMI, mean (range)	18.8 (16.1, 23.2)	19.1 (15.2, 29.3)	19.0 (13.8-27.2)	20.1 (13.5-50.2)	19.4 (11.1-37.2)	19.7 (13.4-36.4)
Insurance type (%)						
Medicaid	10%	30%	9%	26%	26%	25%
Commercial	90%	70%	82%	70%	66%	71%
Commercial and Medicaid	0%	0%	9%	3%	3%	0%
None	0%	0%	0	<1%	2%	2%
Unknown	0%	0%	0	1%	2%	2%

Table 2. Sample sizes after propensity score matching an external control arm of pediatric patients with Crohn's disease in the ImproveCareNow registry to participants in the PRODUCE trial

	PRODUCE sample size, full cohort	Control sample size, full cohort	PRODUCE sample size, active disease subgroup	Control sample size, active disease subgroup
All	31	359	21	184
Matched	28	92	19	56
Unmatched	3	267	2	128

Table 3. Average treatment effect on the treated (difference in differences in sPCDAI score) from baseline to eight weeks by propensity score method among pediatric patients with Crohn's disease, full cohort

Method	ATT	95% CI	p-value
Naïve	4.65 points	-1.43, 10.73	0.13
PS matching	3.65 points	-4.02, 11.31	0.35
Logistic IPTW	3.42 points	-2.30, 9.15	0.24
CBPS IPTW	2.12 points	-4.85, 9.10	0.55

Table 4. Average treatment effect on the treated (difference in differences in sPCDAI score) from baseline to eight weeks by propensity score method among pediatric patients with Crohn's disease, active disease subgroup

Method	ATT	95% CI	p-value
Naïve	10.01 points	2.38, 17.64	0.010
PS matching	10.35 points	1.42, 19.29	0.023
Logistic IPTW	10.40 points	3.31, 17.49	0.004
CBPS IPTW	7.90 points	-1.09, 16.88	0.085

References

1. Ioannidis JP. Implausible results in human nutrition research. *BMJ (Clinical research ed).* 2013;347:f6698.
2. Hébert JR, Frongillo EA, Adams SA, et al. Perspective: Randomized Controlled Trials Are Not a Panacea for Diet-Related Research. *Adv Nutr.* 2016;7(3):423-432.
3. Staudacher HM, Irving PM, Lomer MCE, Whelan K. The challenges of control groups, placebos and blinding in clinical trials of dietary interventions. *Proceedings of the Nutrition Society.* 2017;76(3):203-212.
4. Kaplan HC, Opipari-Arrigan L, Schmid CH, et al. Evaluating the Comparative Effectiveness of Two Diets in Pediatric Inflammatory Bowel Disease: A Study Protocol for a Series of N-of-1 Trials. *Healthcare (Basel).* 2019;7(4):129.
5. Crandall W, Kappelman MD, Colletti RB, et al. ImproveCareNow: The development of a pediatric inflammatory bowel disease improvement network. *Inflammatory bowel diseases.* 2011;17(1):450-457.
6. Kappelman MD, Crandall WV, Colletti RB, et al. Short pediatric Crohn's disease activity index for quality improvement and observational research. *Inflammatory bowel diseases.* 2011;17(1):112-117.
7. Turner D, Hyams J, Markowitz J, et al. Appraisal of the pediatric ulcerative colitis activity index (PUCAI). *Inflammatory bowel diseases.* 2009;15(8):1218-1223.
8. Kundhal PS, Critch JN, Zachos M, Otley AR, Stephens D, Griffiths AM. Pediatric Crohn Disease Activity Index: responsive to short-term change. *Journal of pediatric gastroenterology and nutrition.* 2003;36(1):83-89.
9. Cheng TC, Trivedi PK. Attrition Bias in Panel Data: A Sheep in Wolf's Clothing? A Case Study Based on the Mabel Survey. *Health Economics.* 2015;24(9):1101-1117.
10. Kang H. The prevention and handling of the missing data. *Korean J Anesthesiol.* 2013;64(5):402-406.
11. Pedersen AB, Mikkelsen EM, Cronin-Fenton D, et al. Missing data and multiple imputation in clinical epidemiological research. *Clin Epidemiol.* 2017;9:157-166.
12. Madley-Dowd P, Hughes R, Tilling K, Heron J. The proportion of missing data should not be used to guide decisions on multiple imputation. *Journal of Clinical Epidemiology.* 2019;110:63-73.
13. Dong Y, Peng C-YJ. Principled missing data methods for researchers. *Springerplus.* 2013;2(1):222-222.
14. *VIM: Visualization and Imputation of Missing Values* [computer program]. Version 6.1.02021.
15. Kowarik A, Templ M. Imputation with the R Package VIM. *Journal of Statistical Software; Vol 1, Issue 7 (2016).* 2016.
16. Andridge RR, Little RJA. A Review of Hot Deck Imputation for Survey Non-response. *Int Stat Rev.* 2010;78(1):40-64.
17. Twisk J, de Vente W. Attrition in longitudinal studies: How to deal with missing data. *Journal of Clinical Epidemiology.* 2002;55(4):329-337.
18. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res.* 2011;46(3):399-424.
19. Thorlund K, Dron L, Park JJH, Mills EJ. Synthetic and External Controls in Clinical Trials - A Primer for Researchers. *Clin Epidemiol.* 2020;12:457-467.
20. Seeger JD, Kurth T, Walker AM. Use of propensity score technique to account for exposure-related covariates: an example and lesson. *Med Care.* 2007;45(10 Supl 2):S143-148.
21. Hirano K, Imbens GW. Estimation of causal effects using propensity score weighting: An application to data on right heart catheterization. *Health Services and Outcomes research methodology.* 2001;2(3-4):259-278.

22. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology.* 2009;20(4):512-522.
23. Austin PC, Wu CF, Lee DS, Tu JV. Comparing the high-dimensional propensity score for use with administrative data with propensity scores derived from high-quality clinical data. *Stat Methods Med Res.* 2019;29(2):568-588.
24. Guertin JR, Rahme E, Dormuth CR, LeLorier J. Head to head comparison of the propensity score and the high-dimensional propensity score matching methods. *BMC Medical Research Methodology.* 2016;16(1):22.
25. Judkins DR, Morganstein D, Zador P, Piesse A, Barrett B, Mukhopadhyay P. Variable selection and raking in propensity scoring. *Statistics in medicine.* 2007;26(5):1022-1033.
26. Robins JM, Mark SD, Newey WK. Estimating exposure effects by modelling the expectation of exposure conditional on confounders. *Biometrics.* 1992;48(2):479-495.
27. Van der Laan MJ, Laan M, Robins JM. *Unified methods for censored longitudinal data and causality.* Springer Science & Business Media; 2003.
28. Shaw MG, Morrell DS, Corbie-Smith GM, Goldsmith LA. Perceptions of pediatric clinical research among African American and Caucasian parents. *Journal of the National Medical Association.* 2009;101(9):900-907.
29. Hoberman A, Shaikh N, Bhatnagar S, et al. Factors that influence parental decisions to participate in clinical research: consenters vs nonconsenters. *JAMA pediatrics.* 2013;167(6):561-566.
30. Buscariollo DL, Davidson MA, Black M, Russell WE, Rothman RL, Moore DJ. Factors that influence parental attitudes toward enrollment in type 1 diabetes trials. *PLoS One.* 2012;7(8):e44341.
31. McCullough MB, Janicke D, Odar Stough C, et al. Barriers to recruitment in pediatric obesity trials: comparing opt-in and opt-out recruitment approaches. *Journal of pediatric psychology.* 2017;42(2):174-185.
32. Sulz MC, Burri E, Michetti P, Rogler G, Peyrin-Biroulet L, Seibold F. Treatment Algorithms for Crohn's Disease. *Digestion.* 2020;101(suppl 1)(1):43-57.
33. Baumgart DC. The diagnosis and treatment of Crohn's disease and ulcerative colitis. *Dtsch Arztebl Int.* 2009;106(8):123-133.
34. Fakhoury M, Negrulj R, Mooranian A, Al-Salami H. Inflammatory bowel disease: clinical aspects and treatments. *J Inflamm Res.* 2014;7:113-120.
35. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharmaceutical statistics.* 2011;10(2):150-161.
36. Imai K, Ratkovic M. Covariate balancing propensity score. *Journal of the Royal Statistical Society: Series B (Statistical Methodology).* 2014;76(1):243-263.
37. Kang JDY, Schafer JL. Demystifying Double Robustness: A Comparison of Alternative Strategies for Estimating a Population Mean from Incomplete Data. *Statistical Science.* 2007;22(4):523-539.
38. Smith JA, Todd PE. Does matching overcome LaLonde's critique of nonexperimental estimators? *Journal of Econometrics.* 2005;125(1):305-353.
39. Wyss R, Ellis AR, Brookhart MA, et al. The role of prediction modeling in propensity score estimation: an evaluation of logistic regression, bCART, and the covariate-balancing propensity score. *American journal of epidemiology.* 2014;180(6):645-655.
40. *CBPS: Covariate Balancing Propensity Score* [computer program]. Version 0.222021.
41. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Statistics in medicine.* 2015;34(28):3661-3679.

42. Abadie A. Semiparametric difference-in-differences estimators. *The Review of Economic Studies.* 2005;72(1):1-19.
43. O'Neill S, Kreif N, Grieve R, Sutton M, Sekhon JS. Estimating causal effects: considering three alternatives to difference-in-differences estimation. *Health services & outcomes research methodology.* 2016;16:1-21.
44. Daw JR, Hatfield LA. Matching and Regression to the Mean in Difference-in-Differences Analysis. *Health Services Research.* 2018;53(6):4138-4156.
45. Heckman JJ, Ichimura H, Todd PE. Matching as an Econometric Evaluation Estimator: Evidence from Evaluating a Job Training Programme. *The Review of Economic Studies.* 1997;64(4):605-654.
46. Blundell R, Costa Dias M. Evaluation Methods for Non-Experimental Data. *Fiscal Studies.* 2000;21(4):427-468.
47. *R: A language and environment for statistical computing* [computer program]. Version 4.05: R Foundation for Statistical Computing; 2020.
48. Yu Y, Chen KC, Chen J. Exclusive enteral nutrition versus corticosteroids for treatment of pediatric Crohn's disease: a meta-analysis. *World journal of pediatrics : WJP.* 2019;15(1):26-36.
49. Hirai F, Ishihara H, Yada S, et al. Effectiveness of concomitant enteral nutrition therapy and infliximab for maintenance treatment of Crohn's disease in adults. *Dig Dis Sci.* 2013;58(5):1329-1334.
50. Frank DN, St. Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *PNAS.*104(34):13680-13785.
51. Shaw KA, Bertha M, Hofmekler T, et al. Dysbiosis, inflammation, and response to treatment: a longitudinal study of pediatric subjects with newly diagnosed inflammatory bowel disease. *Genome Med.* 2016;8(1):75.
52. Lane ER, Zisman TL, Suskind DL. The microbiota in inflammatory bowel disease: current and therapeutic insights. *J Inflamm Res.* 2017;10:63-73.
53. Suskind DL, Cohen SA, Brittnacher MJ, et al. Clinical and Fecal Microbial Changes With Diet Therapy in Active Inflammatory Bowel Disease. *Journal of clinical gastroenterology.* 2018;52(2):155-163.
54. Suskind DL, Lee D, Kim Y-M, et al. The Specific Carbohydrate Diet and Diet Modification as Induction Therapy for Pediatric Crohn's Disease: A Randomized Diet Controlled Trial. *Nutrients.* 2020;12(12):3749.
55. Cohen SA, Gold BD, Oliva S, et al. Clinical and mucosal improvement with specific carbohydrate diet in pediatric Crohn disease. *Journal of pediatric gastroenterology and nutrition.* 2014;59(4):516-521.

Figures

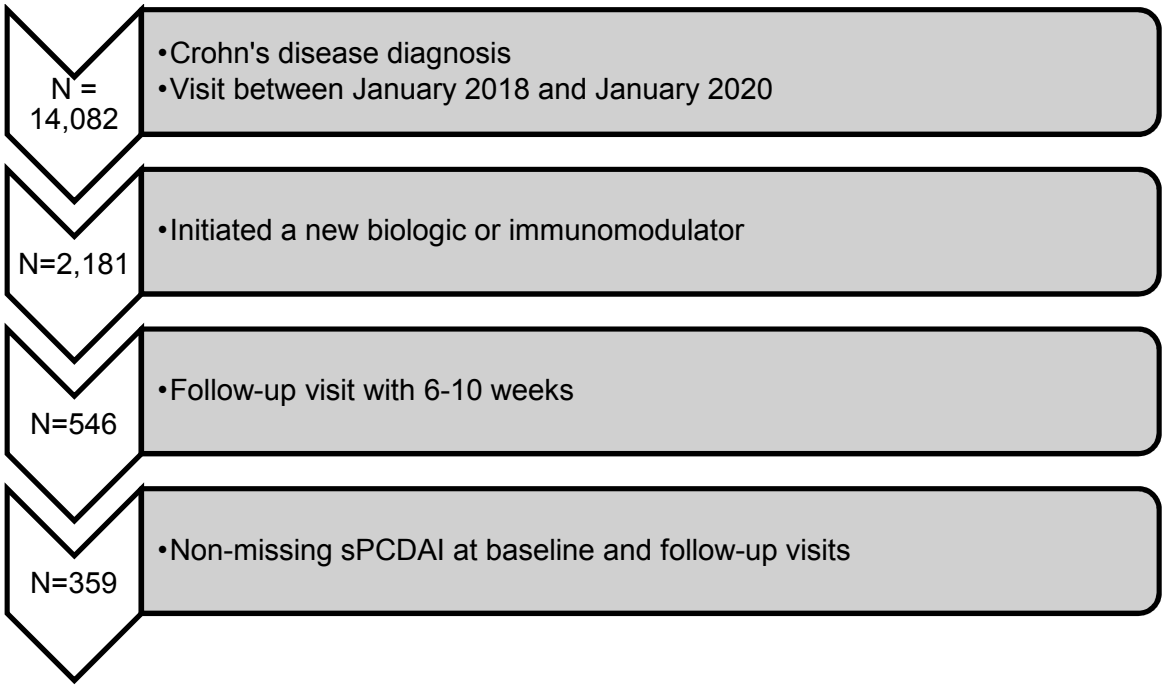

Figure 1. Selection of pediatric patients with Crohn’s disease from the ImproveCareNow registry into an external control arm

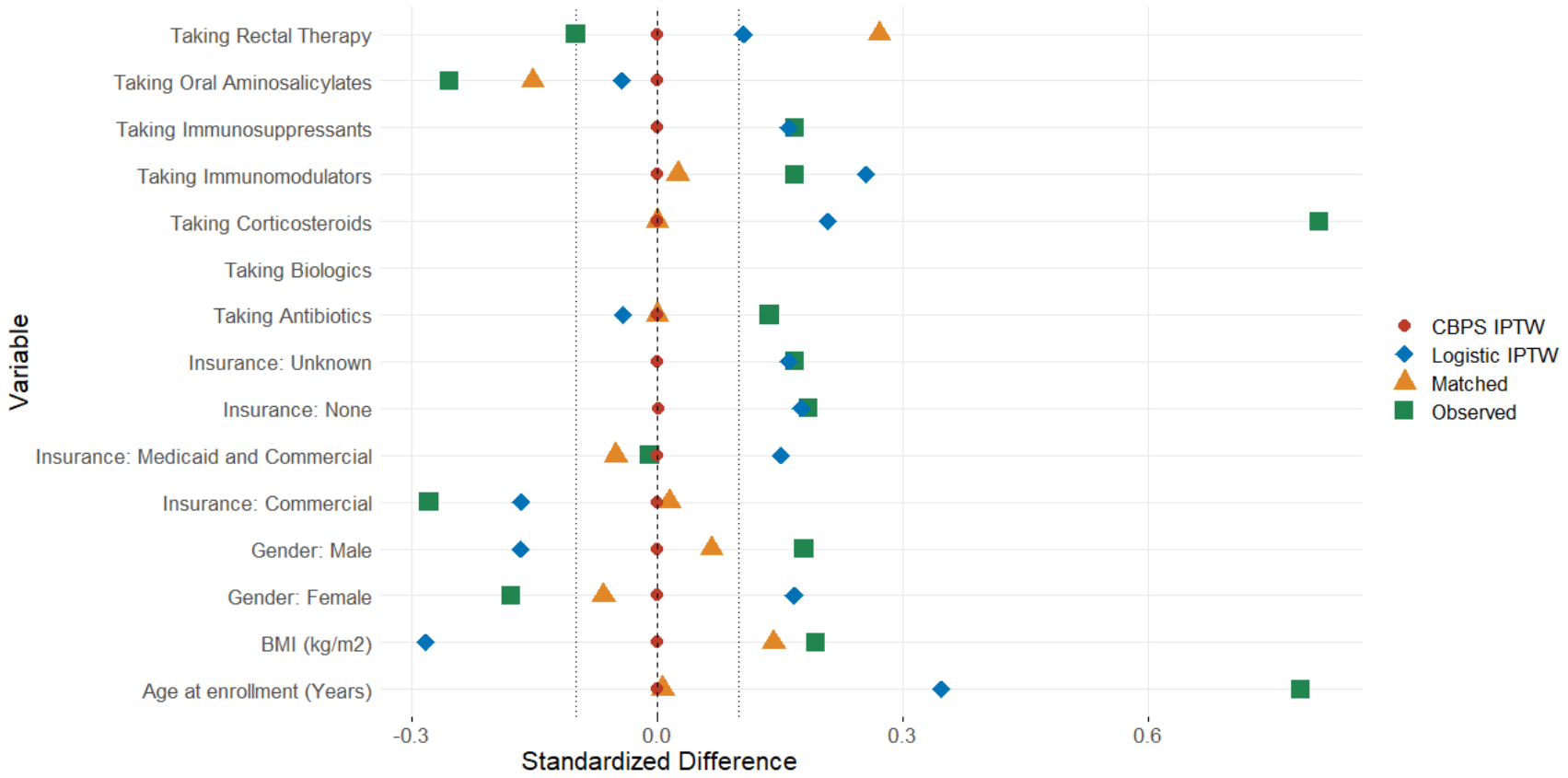

Figure 2. Standardized mean difference for all included covariates by propensity score method among pediatric patients with Crohn's disease, full cohort

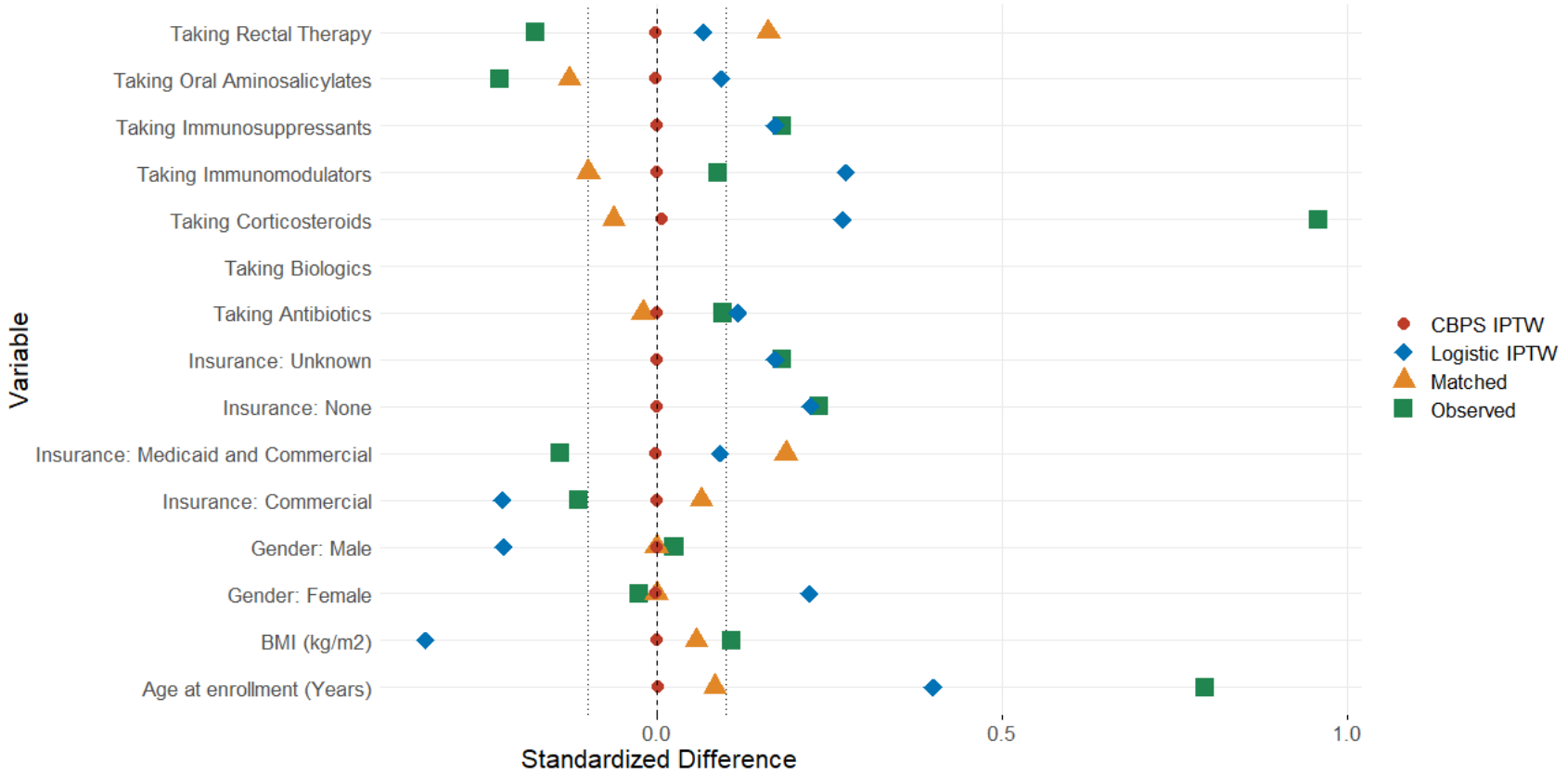

Figure 3. Standardized mean difference for all included covariates by propensity score method among pediatric patients with Crohn's disease with active disease at baseline

Chapter 2

Introduction

Crohn's disease (CD) is a chronic immune-mediated inflammatory disorder of the gastrointestinal tract.[1,2] In 2016, the prevalence of pediatric CD in the United States (US) was 45.9 cases per 100,000 individuals, and annual incidence rates are increasing.[3] Pediatric CD can result in adverse consequences, such as delayed puberty and growth failure.[4] Additionally, CD results in decreased quality of life and lost productivity and, consequently, substantial health care costs.[5] It is estimated that CD is associated with costs of $6.3 billion annually in the US alone.[6] Healthcare-related expenditures related to CD increased by about 50% between 2003 and 2013, driven primarily by the introduction of biologic drugs.[6] Prescription expenditures now constitute the largest cost category for CD.[7,8]

Treatment for CD aims to suppress the immune system's ability to instigate an inflammatory reaction. The choice of agent is determined by disease severity, CD-related complications, prior medication failures, and the need for surgery.[9] Typically, treatment for CD follows a step-up approach, beginning with first-line therapies such as corticosteroids and immunomodulators (e.g. methotrexate, 6-mercaptopurine, azathioprine). If these agents fail to induce remission, biologic therapies are used, according to clinical guidelines.[9] Tumor necrosis factor (TNF) antagonists, such as infliximab and adalimumab, are considered first-line biologics. However, up to 30% of patients do not respond to anti-TNF drugs, and almost 50% of those who do respond lose clinical benefits within the first year.[10,11]

The limited efficacy, high cost, and associated toxicities of these therapies have led to research into the potential role of dietary therapy for CD. In particular, the Specific Carbohydrate Diet (SCD) is an exclusion diet that has risen in popularity. The objective of the diet is to eliminate factors that contribute to dysbiosis, thereby allowing for restoration of the disrupted gut microbiome. Allowed foods include meat/fish/poultry, eggs, some legumes, fully fermented

yogurt, non-starchy vegetables, ripe fruit, nuts/seeds, honey, and nut flours. Restricted foods include all grains, milk products (aside from 24-hour fermented SCD yogurt and cheeses aged greater than 30 days), starchy vegetables, processed foods with food additives, and sweeteners other than honey. The modified SCD (mSCD) is a more liberal version of the SCD in which allowed foods are expanded to include organic rice, oats, sweet potatoes, Grade A maple syrup, and 100% unsweetened cocoa powder (not Dutch processed) or 100% cacao powder, nibs, and butter (no sugar added).[12]

To date, there are no published studies directly comparing the SCD to pharmacotherapy. However, the SCD has been shown to result in symptom relief, improvement in inflammatory biomarkers, and mucosal healing in observational, uncontrolled studies.[13-16] In addition to observational studies, evidence from two recently completed randomized trials supports the potential of the SCD as a therapeutic option for CD. The recently completed Personalized Research on Diet in Ulcerative Colitis and Crohn's Disease (PRODUCE) study was a series of N-of-1 trials[17] evaluating the effectiveness of the SCD versus a modified SCD (mSCD) in reducing symptoms and inflammatory burden among patients aged 7-18 years of age with mild to moderate IBD.[18] Patients on both the SCD and the mSCD had a high probability of improvement in gastrointestinal symptoms, pain, and inflammatory biomarkers on both the SCD and the mSCD compared to baseline diet.[19] In the Trial of Specific Carbohydrate and Mediterranean Diets to Induce Remission of Crohn's Disease (DINE-CD), a multi-center randomized trial comparing the SCD with the Mediterranean diet for induction of remission in adult patients with CD, participants saw improvements in inflammatory biomarkers on both diets.[20] These findings highlight the important role of diet in treatment of CD.

While no studies have evaluated the cost of the SCD compared to standard diets, many parents of children on the SCD report substantial increases in grocery expenditures (see Chapter 3). Research has shown that processed foods, such as those not permitted by the SCD, are less expensive than their unprocessed alternatives.[21] Regional variation in food prices and

availability may affect the feasibility of the diet for many patients, as well.[22-24] If health plans provided financial assistance for patients, the SCD would be more accessible as a treatment option. A model for this already exists in the United States, where patients with celiac disease can deduct the cost of gluten-free foods from their taxes and/or use Flexible Spending Account provisions to pay for the incremental cost of the foods, including shipping expenses.[25] Across the world, many countries either offer free gluten-free staples or subsidies to patients with celiac disease.[25,26] Such policies such would help diminish any economic barrier to the SCD for patients, thereby improving adherence and leading to improved health outcomes.

There is evidence that, among patients on anti-TNFs, the strongest predictor of cost is a history of switching from one anti-TNF to another.[27] Thus, there will be substantial cost savings for the payer if the SCD can improve rates of induction of remission among patients who combine the SCD with an anti-TNF, thereby reducing the proportion of patients who have to switch anti-TNFs. However, the cost-effectiveness of the SCD compared to pharmacotherapy is unknown. While the use of health economic modelling has historically been confined to late stages in drug development, after clinical trials, the utility of early-stage assessments is becoming increasingly evident. Preliminary economic evaluations aim to predict the economic value of a potential therapy asset, and serve to guide decision-making and priority setting.[28] Early-stage economic models provide insight into how a new treatment's efficacy, side-effects, and price impact outcomes and the product's cost-effectiveness. This approach entails calculating the "value-based price" (VBP) which is the maximum cost of a treatment, given an expected level of efficacy, which produces an incremental cost-effectiveness ratio equal to the willingness-to-pay (WTP) threshold.[29]

Given the lack of head-to-head trials comparing the SCD to standard of care pharmacotherapy (SOC), the objective of this study was to explore the VBP of the SCD across a range of effectiveness.

Methods

Decision Analytic Model

We evaluated value-based pricing across a range of different effectiveness levels of the SCD among pediatric patients with CD using a hybrid decision tree Markov model that was developed in Microsoft® Excel to compare the projected costs and outcomes of the induction therapy using the SCD with pharmacotherapy compared to pharmacotherapy alone (i.e., standard of care [SOC]) (Figure 1). The decision tree represents the eight-week induction period. At the end of eight weeks, patients who achieve remission enter the Markov model for maintenance therapy in the "Remission" health state. Over the course of treatment, patients may move to the "Active Disease" health state if they lose response to treatment. Patients who fail to respond to induction with SCD and pharmacotherapy or subsequently lose response, transition to the SOC arm. Patients who fail to respond to SOC, or who lose response to SOC (e.g. transition to the active disease state) may require surgery. Patients may transition from any health state to death at any point in the model.

The analysis was conducted from the healthcare sector perspective with a time horizon of five years. This time horizon has been deemed appropriate to capture all relevant outcomes in models of CD, as disease status tends to stabilize to a steady state within that time frame.[30] The majority of published cost-effectiveness models in IBD use time horizons of five years or shorter.[31,32] Costs and outcomes were discounted at 3% per year following the recommendation of the Second Panel on Cost-Effectiveness in Health and Medicine.[33]

Clinical Inputs

In the absence of published literature on the effectiveness of the SCD (defined as the percent of patients in remission after eight weeks of therapy), a conservative estimate was used in the base case, informed by studies comparing exclusive enteral nutrition (EEN) to corticosteroids.[34-36] The effectiveness of pharmacotherapy alone was derived from a prospective

cohort of pediatric patients with CD.[34] The cost of SCD was set to the VBP at a WTP threshold of $50,000 per quality-adjusted life-year (QALY) gained. This threshold was chosen to provide a conservative estimate of the VBP, but the cost-effectiveness of the SCD at WTP thresholds of $100,000 and $150,000 per QALY gained was also assessed. The probability of loss of response to treatment (transitioning from remission to active disease) was sourced from a 2019 study of 5,612 adult patients with CD in the Truven MarketScan database.[37] Probability of surgery was derived from a 2018 study of 1,442 children with CD in the Pediatric Inflammatory Bowel Disease Collaborative Research Group registry,[38] and the risk of severe surgical complications (i.e., intra-abdominal abscess) came from a multicenter cohort analysis of complications after surgical resection in pediatric Crohn's disease.[39]

Costs

Study costs included costs for each health state, surgery, and surgical complications. Because the model was intended to estimate incremental effects and not the absolute effects of each treatment strategy, it did not include costs equally incurred equally across both treatment arms. Health state costs, including surgery, were derived from a population-based cohort study and that calculated projected lifetime costs of Crohn's disease by disease severity state from a payer perspective.[40] The cost of severe surgical complications (abdominal abscess) was sourced from the Healthcare Cost and Utilization Project National Inpatient Sample.[41]

Health State Utilities

The impact of disease progression on patients' quality of life was measured using utility values specific to each health state to estimate QALYs. These values were sourced from a study that mapped two IBD-specific health-related quality of life measures to the EQ-5D using data from two multinational, randomized, placebo-controlled trials (ENACT-1 and ENACT-2).[42] ENACT-1 and ENACT-2 were trials to evaluate natalizumab as induction and maintenance

therapy in patients with active Crohn's disease.[43] In ENACT-1, 905 patients were randomly assigned to receive either 300mg of natalizumab or placebo at baseline, week four, and week eight. In ENACT-2, 339 patients who responded to natalizumab in ENACT-1 were randomly reassigned to receive either 300mg of natalizumab or placebo every four weeks through week 56. The health state utility for surgical complications was derived from a study that included 100 members of the general public who completed background questions, EQ-5D-3L, visual analogue scale rating task, and time trade-off (TTO) interviews.[44] In the absence of age-specific utility data, and because there is no evidence to suggest health state utilities differ by age among patients with CD, age-based utility effects were not used.

Sensitivity Analyses

To quantify the impact of parametric uncertainty on model results, both univariate and probabilistic sensitivity analyses were run. For the one-way sensitivity analysis, we varied each fixed parameter around the maximum and minimum of its uncertainty intervals (as derived from standard errors) and plotted the model results in a tornado diagram. In this way, it was possible to get an idea of which parameters drive model results, though this method ignores correlation between parameters. The probabilistic sensitivity analysis (PSA) allowed us to estimate how the uncertainty around each parameter contributes to overall uncertainty in model outcomes. The PSA drew input values from distributions defined by 95% confidence intervals and standard uncertainty ranges (probabilities=beta, counts & costs=normal, hazard ratios=log-normal) and results were used to develop a Cost Effectiveness Acceptability Curve that displays the likelihood of cost-effectiveness across a range of WTP thresholds commonly assessed in the United States ($0 to $300,000).

Results

Value-Based Price

At a WTP level of $50,000 per QALY, as the effectiveness the SCD increased, the value-based price decreased (Figure 2). The highest value-based price was $19,421 at 50% effectiveness and the lowest value-based price was $10,455 at an effectiveness of 99%.

Base Case

In the base case, the SCD and SOC resulted in 4.18 and 3.32 QALYs, respectively (Table 2). Both strategies resulted in 5 LYs. The corresponding 5-year expected costs were $51,872 and $8,631.

Sensitivity Analyses

In one-way sensitivity analyses, the three most influential parameters in the model were the probability of remission at eight weeks on the SCD, the probability of remission at eight weeks with SOC, and the monthly cost of active disease (Figure 3).

At the value-based price for $50,000 per QALY and with a 50% effectiveness, the SCD had 50.7% chance of being cost-effective compared to SOC at a WTP threshold of $50,000 per QALY (Figure 4). The SCD had a 100% probability of being cost effective at thresholds of both $100,000 and $150,000 per QALY.

Discussion

The introduction of biologic drugs has contributed to a substantial increase in CD-related health care expenditures over the past decade.[6] Evidence suggests that prescription expenditures constitute the highest cost category for CD patients.[7,8] This highlights the need for new treatments that offer comparable therapeutic benefit while decreasing health care costs. Even at an effectiveness of only 50%, the VBP of the SCD in analysis was close to $20,000, which far exceeds the likely cost of the diet. According to the United States Department of Agriculture, the average monthly cost of a “liberal” grocery plan for a family of four with children

9-11 years old in May 2021 was $1,370.[45] The SCD would need to increase grocery expenditures by a factor of 15 in order to exceed this VBP. This suggests that the SCD has the potential to be a highly cost-effective treatment option.

Our results indicate that the VBP of the SCD decreases as its efficacy increases. This is driven primarily by the fact that the cost of the active disease state is much lower than the modeled cost of the SCD. Because patients were assumed to transition to SOC if they did not achieve remission by eight weeks, a lower efficacy corresponds to fewer patients persisting on the SCD and more patients remaining in the active disease state. Thus, total costs are lower than if efficacy is high and patients persist on the SCD. Though somewhat counterintuitive, this result does reflect real-world findings that indicate prescription expenditures constitute the highest cost category for CD patients.[7,8] However, even at lower effectiveness levels, the VBP of the SCD at a WTP threshold of $50,000 per QALY was much higher than we would expect the diet to cost.

Parents of patients on the SCD have expressed desire for formal recognition of the SCD as a legitimate treatment option for IBD (see Chapter 3). As more data about the SCD become available, it will be important to reassess the cost-effectiveness of the diet from the patient perspective. While incremental cost-effectiveness ratios are useful for population-level decision-making, they do not take into account differences across individuals that could affect the value of an intervention. CD is a clinically complex disease with heterogeneous pathogenesis and variable response to treatment[46] and the SCD is a strict diet that may not be appealing or accessible to all patients, regardless of effectiveness. Individuals may weigh certain costs and outcomes differently, thus the limitations of the SCD may outweigh the benefits of fewer trips to the hospital for infusions, while another patient may find the trade-off to be “worth it.” There are also differences in risk aversion across individuals. One individual may be willing to accept the risk of treatment-related adverse events with pharmacotherapy, while another may want to minimize those risks as much as possible. Regional variation in food prices and availability

could also impact the feasibility of the SCD as an option for many patients.[22-24] Especially as the costs of prescription drugs escalate,[47] and a broader array of treatment options become available,[48] the value of providing patients with tools to aid in decision-making cannot be overlooked.

An important consideration when interpreting the results of this model is that there is considerable heterogeneity when it comes to financial burden of CD.[5,49,50] Disease severity and age have both been shown to be significantly associated with total five-year expenditure for CD.[5] Additionally, two reviews of claims data demonstrated that the top 2% and 25% of CD patients accounted for 34.3% and 80% of costs, respectively.[49,51] The cost of the active disease state in this model was sourced from the literature, but it does not capture this real-world heterogeneity. It is possible, then, that the results of this model do not apply to the sickest patients with the most severe disease. As clinical evidence becomes available, it will be worth revisiting the cost-effectiveness among patient populations with varying disease severity.

This model has several limitations. CD is a complex disease state, and this model made some simplifying assumptions which may not reflect the true course of treatment for all patients. Depending on clinician opinion, patient preferences, and disease severity, the induction period may vary in duration for different patients. Additionally, some patients may be more hesitant to undergo surgery than others. We attempted to address the potential effect of this uncertainty by conducting sensitivity analyses. As more longitudinal data become available on the clinical course of pediatric CD, the impact of heterogeneity in clinical practice will need to be reassessed.

To our knowledge, this is the first study to estimate the potential cost-effectiveness of the SCD for treatment of pediatric CD. We found that the SCD has a high probability of being cost-effective at traditional WTP thresholds. This model provides insight to direct future research into the SCD for pediatric CD, given the high cost of pharmacotherapy in this disease space. Future research is needed to assess both the direct and indirect costs of the SCD, as well as the

effectiveness of the SCD as a stand-alone therapy and as an adjunct to pharmacotherapy. These data would enable evaluation of the cost-effectiveness of the SCD from a societal perspective and would provide essential information for clinicians, patients, payers, and policy-makers.

Tables

Table 1. Inputs for Markov model

Parameter	Base Case Value	Low Value	High Value	Source
Clinical Parameters				
Probability of remission during induction period SCD SOC	50.0% 47.0%	40.0% 36.5%	60.0% 57.5%	Assumption [34]
Probability of surgery for Crohn's disease 0-3 months 3-12 months 12-36 months 36-60 months	5.54% 0.52% 1.63% 0.78%	4.43% 0.41% 1.31% 0.63%	6.64% 0.62% 1.96% 0.94%	[38]
Probability of loss of response Year 0 Year 1 Year 2 Year 3 Year 4	1.66% 0.86% 0.52% 0.63% 0.55%	1.50% 0.78% 0.47% 0.57% 0.49%	1.83% 0.95% 0.57% 0.70% 0.60%	[37]
Probability of severe surgery complications	28%	22.4%	33.6%	[39]
Health State Utilities				
Remission	0.830	0.827	0.833	[42]
Active disease	0.420	0.417	0.423	[42]
Surgery	0.730	0.796	0.941	[42]
Surgery complications	0.560	0.490	0.620	[44]
Population Characteristics				
Mean age (years)	12.5	11.25	13.75	[19]
Costs				
Monthly cost of active disease	$1,969	$1,575	$2,362	[40]
Monthly cost of remission on standard of care therapy	$1,296	$1,041	$1,551	[40]
Cost of surgery (one time cost)	$16,441	$12,056	$20,826	[40]
Cost of surgical complications (one time cost)	$17,046	$16,240	$17,851	[41]
Other Model Inputs				
Discount rate	3%	0%	5%	[52]

Table 2. Base case results comparing cost effectiveness of the Specific Carbohydrate Diet to standard of care among pediatric patients with Crohn's disease

	Total Cost	LYs	QALYs	Cost per LY	Cost per QALY
Specific Carbohydrate Diet	$51,872	5.0	4.18	$10,209	$12,404
Standard of care	$8,631	5.0	3.32	$1,699	$2,602
Incremental	$43,241	0	0.88		

Figures

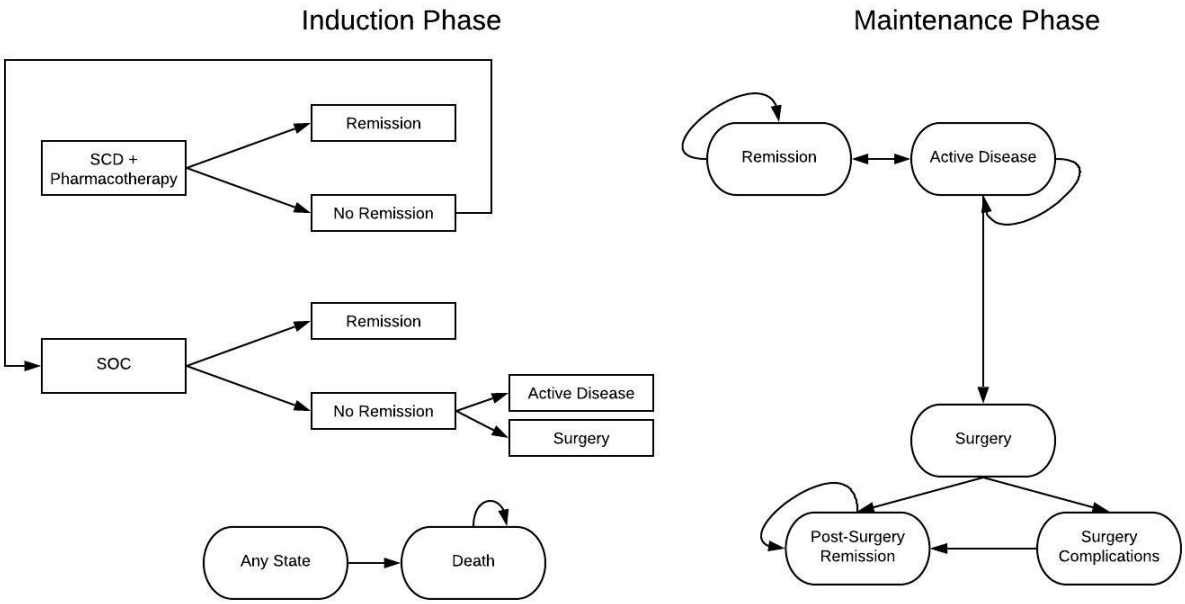

Figure 1. Hybrid decision tree and Markov model structure

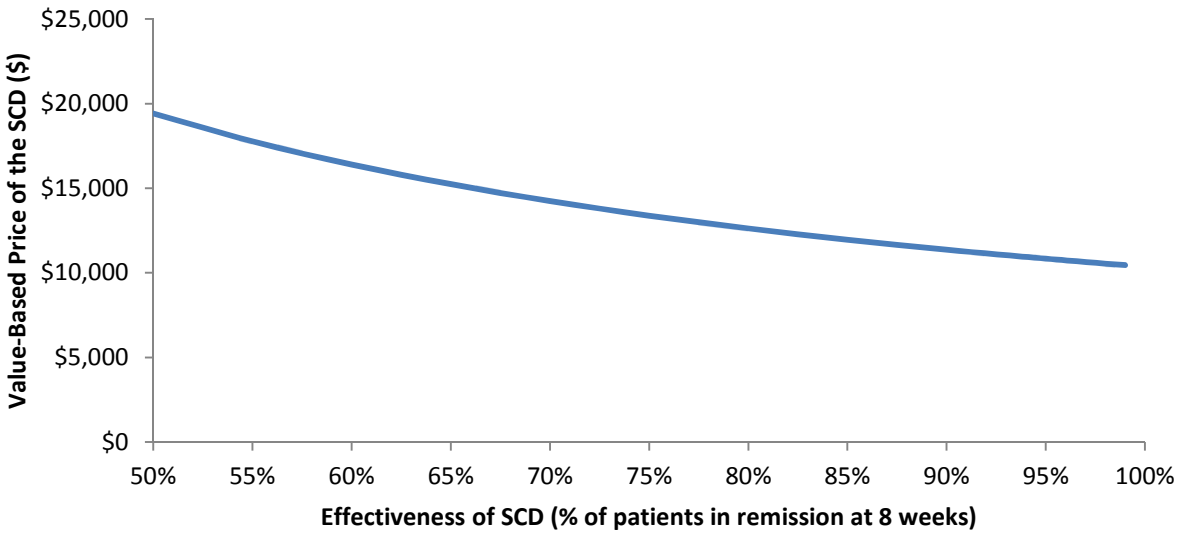

Figure 2. Value-based price of the SCD over a range of effectiveness at a willingness-to-pay threshold of $50,000 per QALY

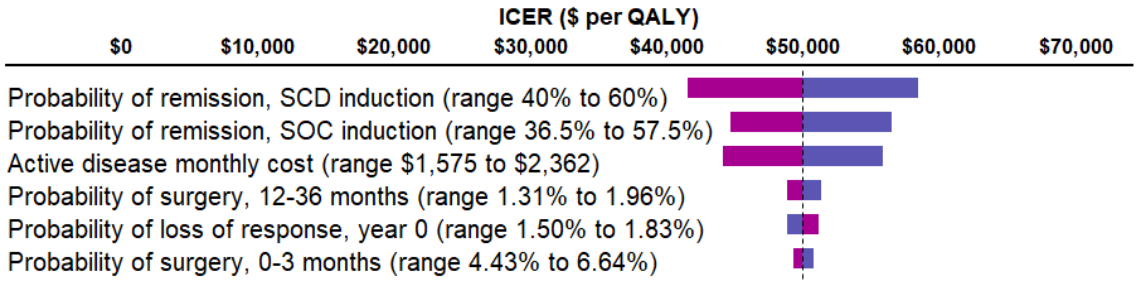

Figure 3. Tornado diagram of the six most influential inputs in the base case comparing the cost effectiveness of the Specific Carbohydrate Diet to standard of care among pediatric patients with Crohn's disease

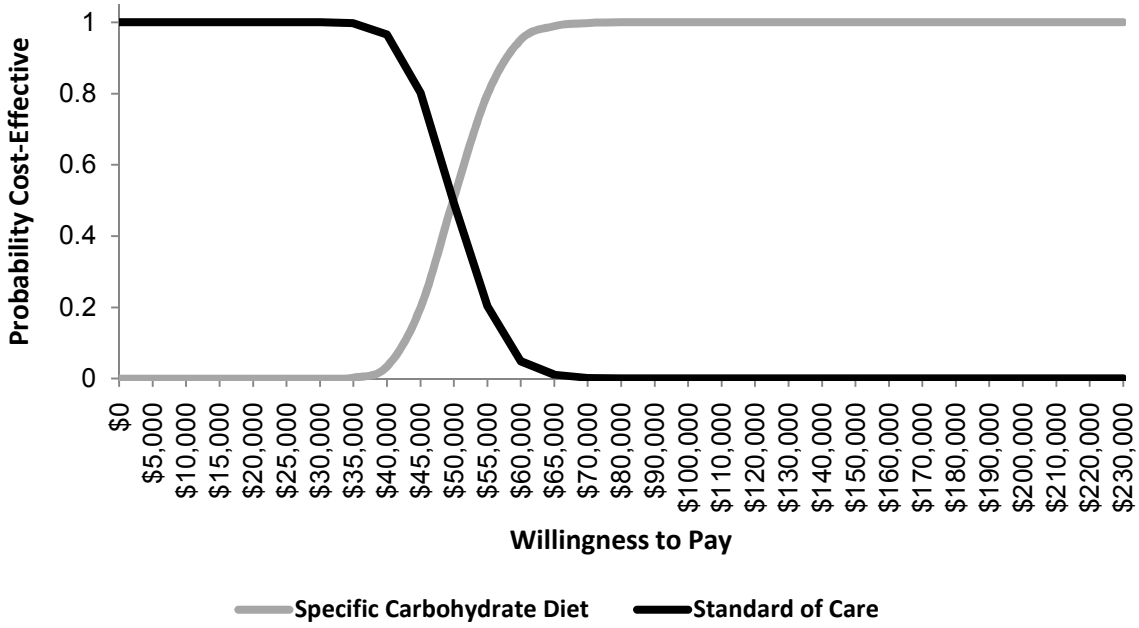

Figure 4. Cost-effectiveness acceptability curve comparing the Specific Carbohydrate Diet to standard of care among pediatric patients with Crohn's disease

References

1. Freeman HJ. Natural history and long-term clinical course of Crohn's disease. *World J Gastroenterol.* 2014;20(1):31-36.
2. Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet (London, England).* 2012;380(9853):1590-1605.
3. Ye Y, Manne S, Treem WR, Bennett D. Prevalence of Inflammatory Bowel Disease in Pediatric and Adult Populations: Recent Estimates From Large National Databases in the United States, 2007–2016. *Inflammatory bowel diseases.* 2019;26(4):619-625.
4. Heuschkel R, Salvestrini C, Beattie RM, Hildebrand H, Walters T, Griffiths A. Guidelines for the management of growth failure in childhood inflammatory bowel disease. *Inflammatory bowel diseases.* 2008;14(6):839-849.
5. Rao BB, Click BH, Koutroubakis IE, et al. The Cost of Crohn's Disease: Varied Health Care Expenditure Patterns Across Distinct Disease Trajectories. *Inflammatory bowel diseases.* 2017;23(1):107-115.
6. Bounthavong M, Li M, Watanabe JH. An evaluation of health care expenditures in Crohn's disease using the United States Medical Expenditure Panel Survey from 2003 to 2013. *Research in Social and Administrative Pharmacy.* 2017;13(3):530-538.
7. van der Valk ME, Mangen MJ, Leenders M, et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFalpha therapy: results from the COIN study. *Gut.* 2014;63(1):72-79.
8. Floyd DN, Langham S, Severac HC, Levesque BG. The economic and quality-of-life burden of Crohn's disease in Europe and the United States, 2000 to 2013: a systematic review. *Dig Dis Sci.* 2015;60(2):299-312.
9. van Rheenen PF, Aloi M, Assa A, et al. The Medical Management of Paediatric Crohn's Disease: an ECCO-ESPGHAN Guideline Update. *Journal of Crohn's and Colitis.* 2020;15(2):171-194.
10. Yarur AJ, Rubin DT. Therapeutic Drug Monitoring of Anti-tumor Necrosis Factor Agents in Patients with Inflammatory Bowel Diseases. *Inflammatory bowel diseases.* 2015;21(7):1709-1718.
11. Adegbola SO, Sahnan K, Warusavitarne J, Hart A, Tozer P. Anti-TNF Therapy in Crohn's Disease. *Int J Mol Sci.* 2018;19(8):2244.
12. Personalized Research on Diet in Ulcerative Colitis and Crohn's Disease (PRODUCE). ClinicalTrials.gov Identifier NCT03301311. Accessed March 17, 2020.
13. Suskind DL, Wahbeh G, Gregory N, Vendettuoli H, Christie D. Nutritional therapy in pediatric Crohn disease: the specific carbohydrate diet. *Journal of pediatric gastroenterology and nutrition.* 2014;58(1):87-91.
14. Suskind DL, Cohen SA, Brittnacher MJ, et al. Clinical and Fecal Microbial Changes With Diet Therapy in Active Inflammatory Bowel Disease. *Journal of clinical gastroenterology.* 2018;52(2):155-163.
15. Cohen SA, Gold BD, Oliva S, et al. Clinical and mucosal improvement with specific carbohydrate diet in pediatric Crohn disease. *Journal of pediatric gastroenterology and nutrition.* 2014;59(4):516-521.
16. Cohen SA, Stallworth AN, Koch BM, Mason DH, Blumenthal J, Gold BD. Sa1992 Mucosal Healing With the Specific Carbohydrate Diet in Pediatric Crohn's Disease: Preliminary Results of a Prospective Pilot Study. *Gastroenterology.* 2012;142(5):S-376.
17. Guyatt G, Sackett D, Taylor DW, Chong J, Roberts R, Pugsley S. Determining optimal therapy--randomized trials in individual patients. *The New England journal of medicine.* 1986;314(14):889-892.
18. Kaplan HC, Opipari-Arrigan L, Schmid CH, et al. Evaluating the Comparative Effectiveness of Two Diets in Pediatric Inflammatory Bowel Disease: A Study Protocol for a Series of N-of-1 Trials. *Healthcare (Basel).* 2019;7(4):129.

19. Kaplan HC, Opipari-Arrigan L, Yang J, et al. Personalized Research on Diet in Ulverative Colitis and Crohn's Disease (PRODUCE): a Series of N-of-1 Trials Comparing the Effectiveness of Two Diets. *JPGN.* 2020;71(Supplement 1):S68-69.
20. Lewis JD, Sandler R, Brotherton C, et al. A Randomized Trial Comparing the Specific Carbohydrate Diet to a Mediterranean Diet in Adults with Crohn's Disease. *Gastroenterology.* 2021.
21. Gupta S, Hawk T, Aggarwal A, Drewnowski A. Characterizing Ultra-Processed Foods by Energy Density, Nutrient Density, and Cost. *Front Nutr.* 2019;6:70-70.
22. Sturm R, Datar A. Regional price differences and food consumption frequency among elementary school children. *Public Health.* 2011;125(3):136-141.
23. Hardin-Fanning F, Wiggins AT. Food Costs Are Higher in Counties With Poor Health Rankings. *J Cardiovasc Nurs.* 2017;32(2):93-98.
24. Kern DM, Auchincloss AH, Stehr MF, et al. Neighborhood Prices of Healthier and Unhealthier Foods and Associations with Diet Quality: Evidence from the Multi-Ethnic Study of Atherosclerosis. *Int J Environ Res Public Health.* 2017;14(11):1394.
25. Pinto-Sanchez MI, Verdu EF, Gordillo MC, et al. Tax-deductible provisions for gluten-free diet in Canada compared with systems for gluten-free diet coverage available in various countries. *Canadian journal of gastroenterology & hepatology.* 2015;29(2):104-110.
26. See JA, Kaukinen K, Makharia GK, Gibson PR, Murray JA. Practical insights into gluten-free diets. *Nature reviews Gastroenterology & hepatology.* 2015;12(10):580-591.
27. Lawton J, Achit H, Pouillon L, et al. Cost-of-illness of inflammatory bowel disease patients treated with anti-tumour necrosis factor: A French large single-centre experience. *United European Gastroenterol J.* 2019;7(7):908-913.
28. Clemens K, Garrison LP, Jr., Jones A, Macdonald F. Strategic use of pharmacoeconomic research in early drug development and global pricing. *PharmacoEconomics.* 1993;4(5):315-322.
29. Mladsi D, Earnshaw S, Akashi-Ronquest N, Keith MS. PMC19 THE THRESHOLD PRICING MODEL: NOT JUST ANOTHER COSTEFFECTIVENESS MODEL. *Value in Health.* 2010;13(7):A332.
30. Young C, Campbell K. Biologics versus Immunomodulators or Antibiotics for the Management of Fistulizing Crohn’s Disease: A Review of Comparative Clinical Effectiveness and Cost-Effectiveness. In: Canadian Agency for Drugs and Technologies in Health, Ottawa (ON); 2019.
31. Jean L, Audrey M, Beauchemin C, Consortium oboti. Economic Evaluations of Treatments for Inflammatory Bowel Diseases: A Literature Review. *Canadian Journal of Gastroenterology and Hepatology.* 2018;2018:7439730.
32. Pillai N, Dusheiko M, Burnand B, Pittet V. A systematic review of cost-effectiveness studies comparing conventional, biological and surgical interventions for inflammatory bowel disease. *PLoS One.* 2017;12(10):e0185500-e0185500.
33. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *JAMA.* 2016;316(10):1093-1103.
34. Cohen-Dolev N, Sladek M, Hussey S, et al. Differences in Outcomes Over Time With Exclusive Enteral Nutrition Compared With Steroids in Children With Mild to Moderate Crohn’s Disease: Results From the GROWTH CD Study. *Journal of Crohn's and Colitis.* 2017;12(3):306-312.
35. Levine A, Turner D, Pfeffer Gik T, et al. Comparison of outcomes parameters for induction of remission in new onset pediatric Crohn's disease: evaluation of the porto IBD group "growth relapse and outcomes with therapy" (GROWTH CD) study. *Inflammatory bowel diseases.* 2014;20(2):278-285.

36. Yu Y, Chen KC, Chen J. Exclusive enteral nutrition versus corticosteroids for treatment of pediatric Crohn's disease: a meta-analysis. *World journal of pediatrics : WJP.* 2019;15(1):26-36.
37. Chen C, Hartzema AG, Xiao H, et al. Real-world Pattern of Biologic Use in Patients With Inflammatory Bowel Disease: Treatment Persistence, Switching, and Importance of Concurrent Immunosuppressive Therapy. *Inflammatory bowel diseases.* 2019;25(8):1417-1427.
38. Kerur B, Machan JT, Shapiro JM, et al. Biologics Delay Progression of Crohn's Disease, but Not Early Surgery, in Children. *Clinical Gastroenterology and Hepatology.* 2018;16(9):1467-1473.
39. Diederen K, de Ridder L, van Rheenen P, et al. Complications and Disease Recurrence After Primary Ileocecal Resection in Pediatric Crohn's Disease: A Multicenter Cohort Analysis. *Inflammatory bowel diseases.* 2017;23(2):272-282.
40. Silverstein MD, Loftus EVJ, Sandborn‖ WJ, et al. Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort. *Gastroenterology.* 1999;117(1):49-57.
41. HCUPnet. http://hcupnet.ahrq.gov/. Accessed January 30, 2021.
42. Buxton MJ, Lacey LA, Feagan BG, Niecko T, Miller DW, Townsend RJ. Mapping from disease-specific measures to utility: an analysis of the relationships between the Inflammatory Bowel Disease Questionnaire and Crohn's Disease Activity Index in Crohn's disease and measures of utility. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2007;10(3):214-220.
43. Sandborn WJ, Colombel JF, Enns R, et al. Natalizumab induction and maintenance therapy for Crohn's disease. *The New England journal of medicine.* 2005;353(18):1912-1925.
44. Worbes-Cerezo M, Nafees B, Lloyd A, Gallop K, Ladha I, Kerr C. Disutility Study for Adult Patients with Moderate to Severe Crohn's Disease. *J Health Econ Outcomes Res.* 2019;6(2):47-60.
45. *Official USDA Food Plans: Cost of Food at Home at Four Levels, U.S. Average, May 2021.* United States Department of Agriculture;2021.
46. Chowers Y. Taking Crohn's disease personally. *Rambam Maimonides Med J.* 2013;4(2):e0011-e0011.
47. Policy Recommendations for Public Health Plans to Stem the Escalating Costs of Prescription Drugs: A Position Paper From the American College of Physicians. *Annals of Internal Medicine.* 2019;171(11):825-827.
48. Hazel K, O'Connor A. Emerging treatments for inflammatory bowel disease. *Ther Adv Chronic Dis.* 2020;11:2040622319899297-2040622319899297.
49. Feagan BG, Vreeland MG, Larson LR, Bala MV. Annual cost of care for Crohn's disease: a payor perspective. *The American journal of gastroenterology.* 2000;95(8):1955-1960.
50. Yu AP, Cabanilla LA, Wu EQ, Mulani PM, Chao J. The costs of Crohn's disease in the United States and other Western countries: a systematic review. *Current medical research and opinion.* 2008;24(2):319-328.
51. Hay JW, Hay AR. Inflammatory bowel disease: costs-of-illness. *Journal of clinical gastroenterology.* 1992;14(4):309-317.
52. Gold M. Panel on Cost-Effectiveness in Health and Medicine. *Medical Care.* 1996;34(12).

Chapter 3

Introduction

In North America, more than 1.3% of the population has inflammatory bowel disease (IBD), amounting to over 3.1 million Americans.[1] A quarter of new diagnoses occur during childhood with incidence of pediatric IBD increasing globally over the last half century.[2] Pediatric IBD is particularly aggressive, leading to growth failure, high surgery rates to manage pharmacotherapy-resistant disease, and decreased quality of life.[3,4] In addition, IBD confers a substantial economic burden on families and healthcare systems.[5,6] In a recent study of pediatric IBD patients, mean five-year costs of care were $45,753 for Crohn's disease (CD) and $50,516 for ulcerative colitis (UC).[7] Medications are the leading driver of direct costs among IBD patients, accounting for ~35% of total costs,[8-10] greatly outpacing hospitalization and surgery costs.

Current therapies for IBD focus on medications that suppress the immune system's ability to instigate and perpetuate an inflammatory reaction in the gastrointestinal tract. Choice of therapy is determined by disease severity, IBD-related complications, prior medication failures, and need for surgery.[9] Treatment approaches for IBD may follow a step-up approach, beginning with therapies such as corticosteroids and immunomodulators (e.g. methotrexate, 6-mercaptopurine, azathioprine),[10] or begin with biologic therapies,[11] such as tumor necrosis factor (TNF) antagonists. Although these therapies are effective for many, not all patients respond. For example, with Infliximab, a commonly prescribed biologic, up to 30% of patients do not respond, and almost 50% of responders lose clinical benefits within one year.[12,13] Additionally, anti-TNF treatment is associated with multiple safety concerns, such as opportunistic infections, malignancies, and adverse drug reactions.[14]

Given the high cost of pharmacotherapy and risk of adverse effects, considerable attention has been given to dietary therapy as a potential alternative or a supplement to pharmacotherapy for IBD. The Specific Carbohydrate Diet (SCD) is a dietary program created

by Dr. Sidney Haas in the 1920s,[15] and popularized by Elaine Gottschall with her book, *Breaking the Vicious Cycle: Intestinal Health Through Diet*.[16] Dietary intervention is based upon the role of intestinal dysbiosis as a presumed primary immunologic trigger in IBD. With diet a major determinant of intestinal microbiome composition, diet change has been shown to effectively and reproducibly alter the microbiome.[16] The goal of the SCD is to eliminate factors contributing to dysbiosis, supporting an eubiotic microbiome.[17]

Multiple observational, uncontrolled studies show the SCD provides symptom relief, improves inflammatory burden, and improves mucosal healing in pediatric patients.[18-21] A survey of patients on the SCD found most patients perceive it to construe clinical benefit.[22] More recently, the PRODUCE study, a large multicenter prospective cohort study confirmed the anti-inflammatory effect of the SCD.[23] While not specific to the SCD, many physicians indicate a lack of comfort with providing nutritional counseling.[24-26] As evidence of the benefits of dietary interventions such as the SCD continues to grow, it is imperative for physicians and parents to understand factors affecting utilization. Thus, we conducted a qualitative study of parents of IBD patients treated at a single clinical institution to assess barriers to initiating and/or maintaining the SCD to inform strategies for improving access and adherence to the diet.

Methods

Recruitment

Participants were enrolled from the IBD Center at Seattle Children's Hospital, a clinic providing comprehensive multidisciplinary treatment for approximately 300 IBD patients annually. Recruitment was conducted via purposive sampling[27] to identify parents of patients who met pre-defined criteria. Parents were eligible if their child with IBD was either currently on the SCD, previously on the SCD, or opted not to initiate the SCD. Parents were contacted via phone and asked if they were interested in participating in the study. If they agreed, they were sent an online consent form and a HIPAA-compliant Zoom interview was scheduled. Interviews

were conducted until the point of saturation[28,29] – the point at which no new themes emerge from data collection. Evidence suggests saturation can occur within 10 interviews when the research scope is narrow.[29] All study procedures were approved by Institutional Review Boards at University of Washington (00006878) and Seattle Children's Hospital (00002774).

Interviews

Interviews were semi-structured. Core questions were developed in conjunction with IBD clinical experts. Interviews also explored considerations raised during the course of conversation. For parents of patients currently on the SCD (n=4 patients), questions addressed reasons for choosing to use the SCD, satisfaction, as well as shopping, eating, and food preparation routines before/during the SCD. Parents of patients with past SCD use (n=4 patients) were also asked about reasons for discontinuation. Parents of patients who did not initiate the SCD (n=2 patients) were asked about reasons for not pursuing it as a treatment option.

Qualitative Analysis

Interview transcripts were imported into Taguette[30] and coded using an inductive approach.[31] The lead coder (NRMS) performed a close reading of the text, developing categories that encapsulated prominent themes. NRMS then completed an iterative process of revising and refining categories to create a final codebook that was used by both coders (NRMS and SM) to independently code responses. After coding was complete, the coders compared their coding for consistency.

Results

Participant Demographics

We conducted a total of nine interviews with twelve parents of ten patients (two patients were siblings). All contacted parents chose to participate. Two patients never initiated the SCD, four were previously on the SCD, and four were currently on the SCD. Among patients currently on the SCD, three were using it as the only therapy while one was also using pharmacotherapy (Table 1).

Family Involvement

Among the nine families interviewed, one patient followed the SCD alone, two sets of parents followed the SCD with the patient, and another parent chose to follow the SCD with her daughter while other family members did not. The remaining families (n=4) had SCD-friendly dinners, but family members did not adhere to the SCD for other meals.

Decision Process

The primary rationale for SCD initiation was concern about the use of pharmacotherapy. Parents (n=8) expressed desire to try the SCD initially due to concerns about medication toxicity and/or long-term adverse drug effects. One parent also noted concerns about the child's future health insurance and affordability of medications, saying, "it seems more sustainable than long term drugs, I know a lot of the drugs are lifetime and not sure how well off [he] will be… financially, so affording those drugs, or getting health insurance when he turns 18 might be a struggle."

Two patients were non-initiators. One child had too many food allergies for it to be feasible. Allergies to ingredients like nuts, commonly used on the SCD, would have made it harder to follow and further restricted his diet, interfering with adequate nutrition. The other child never initiated the SCD because his disease was too severe. At diagnosis, the patient was significantly underweight. The priority was supplying him with adequate calories; restricting his diet may have interfered.

Four SCD-initiators later discontinued the diet. One patient took a trip abroad where he was unable to adhere to the diet and acquired a *C. difficile* infection that required him to initiate pharmacotherapy, at which point he chose not to continue the SCD. The other three discontinued due to lack of response.

Potential Barriers

Cost

Most (n=7) parents of SCD-initiators reported increased grocery expenses. For one family, cost presented enough of a hardship they stopped following the SCD with their daughter. Other parents could afford the extra expense, but recognized cost would likely be a barrier for lower-income families. Primary drivers of increased grocery costs were organic produce and specialty ingredients. Specifically, many SCD recipes include nut flours or milks, which can be double the cost of wheat flour and dairy milk.

Parents utilized a variety of strategies to reduce financial burden such as buying SCD ingredients in bulk (n=6). Additionally, while organic foods are perceived by many parents to be healthier, they are not required, and one mother was able to save money by purchasing a mix of conventional and organic produce. As a longer-term solution, one parent suggested, “maybe there would be a way… you could submit some of your grocery receipts for eligible items for Flexible Spending Account reimbursement, or your insurance, or some kind of financial help to help people make it feasible for them.”

Time Commitment

Parents of all SCD-initiators, even those who cooked frequently prior to the SCD, spent more time planning and preparing meals. One factor contributing to this was the need to invest more time in food preparation, because many pre-made items (e.g., broths, sauces) contain ingredients not allowed by the SCD. Parents of two patients specifically noted increases in time

spent baking and three parents noted lunches and snacks were challenging. One parent described, “the toughest transition was figuring out what I could send for lunch, because before he was diagnosed we just always got him a school lunch.” Additionally, two patients’ parents needed to shop more frequently, and at a wider variety of stores, due to the need for more fresh produce and special ingredients. Parents of six patients spent more time in stores because they had to read product labels closely to ensure ingredients were allowed by the SCD.

Parents utilized Facebook groups (n=6), online resources (n=3), and cookbooks (n=2) for recipe ideas. One parent reported, “I just found all these websites and people that are doing SCD and just started following them and finding recipes.” Another parent found success “keep[ing] things really simple in the beginning.” She advised parents not to “fixate on trying to recreate their child’s favorite foods.” Other parents (n=3) found it easier to substitute ingredients (e.g., adding more vegetables to soup in place of rice) than to design new meal plans.

One solution for the need to visit multiple stores is that mainstream grocery stores are starting to carry more SCD-legal foods. One parent said, “these days it seems easier to find it locally than to have to drive to those specific stores.” Ordering ingredients online also helped reduce time spent grocery shopping.

Psychosocial Impact

Four patients’ parents spoke about psychosocial impacts of the SCD on their kids. For some patients, the SCD was difficult because they missed specific foods. For example, one child “was quite unhappy that she couldn’t eat bread.” Other children felt left out in social situations when food was present.

Two parents highlighted the role of social support to lessen the psychosocial difficulty of following the SCD. One patient’s extended family makes an effort to cook things he can eat when he visits. His mother said, “It’s really nice to have that level of support.” Another patient’s

siblings, who do not follow the SCD, each “had a recipe that they would make for her.” This helps the patient feel supported by her family even if she cannot eat the same foods they eat.

One parent whose child was initially opposed to the SCD spoke about the importance of the child being on board. She did not think it would have been successful had she forced her daughter to follow the diet. She shared her strategy for helping her daughter cope with the psychosocial difficulties, saying “I want to be realistic, but also frame it in a positive light… we’re putting stuff in that is healing and that we’re eating real foods. And so rather than feeling like completely left out, I have also tried to talk about wow, we’re so lucky and we’re kind of privileged that we get to eat these real foods that are not as processed.” This parent and another recounted success bringing their own food to restaurants or social gatherings. One patient’s parents called restaurants ahead of time to inquire about ingredients and often found that menu options that could easily be adjusted to be SCD-friendly.

Additional Themes

Adapting to the SCD

All parents expressed that while the SCD initially seemed overwhelming, it gets easier over time. One parent described, "you just get used to the new way of doing stuff." Initially, the diet involves a lot of experimentation and learning in the kitchen, but “it’s not nearly as overwhelming after you get it figured out and get the base ingredients down.” Once parents identified recipes and successfully created dishes the child enjoyed, preparing and planning meals became less time-consuming and burdensome.

Spillover Effects

Parents of six children said the SCD improved their own health and understanding of nutrition. Specifically, reading labels led parents to make dietary changes for themselves as well

as for their child. One father following the SCD with his son lost weight and felt his digestion improved.

Desire for More Information

Parents of five patients expressed desire for more research into the SCD and other dietary therapy. The mother whose son did not use it because of severe disease at diagnosis said, “if it worked for him, I would choose that, in a heartbeat over the bucket of medication that he’s getting today… I would love … if your research shows that… it does work on someone that’s got his kind of case.” She wanted to know if there was a way to “phase into” the SCD for patients using pharmacotherapy to avoid risking a scary and perhaps dangerous disease flare.

Parents of two siblings who discontinued the SCD also wanted more data. The father said, “what works, and how to kind of space it with other treatments and how to monitor it etc., it’s far from clear.” The mother added, “the hardest part is following something that you’re not sure if it is proven.” Similarly, the mother of the child who did not initiate the SCD due to food allergies is hopeful for research into dietary therapy options better suited to children with food allergies. A parent whose son had success with the SCD underscored how important research is to establish the SCD as a “legitimate treatment.” She explained, “having published data out there is hugely important for the success of, and a widespread knowledge of, the diet.” These parents are strong proponents of the role of diet in IBD but feel more research is needed.

Discussion

With knowledge of clinical and anti-inflammatory impacts of the SCD in IBD continuing to grow, understanding barriers to initiating and maintaining dietary therapy is essential to achieving better patient outcomes. In our study, parents of children diagnosed with IBD primarily chose to try the SCD due to concerns about medication safety. This finding is in accordance

with a 2015 case series of 50 adult IBD patients that reported 82% (n=41) of patients opted to follow the SCD due to fear of long-term medication consequences.

Three major barriers to utilizing the SCD emerged from the interviews: cost, time commitment, and psychosocial impact. Lack of research on this topic makes it difficult to compare to prior studies, however, evidence from other populations supports the plausibility of these findings. For example, research shows processed foods, such as those not permitted by the SCD, are less expensive than their unprocessed alternatives.[32] Additionally, a cross-sectional population-based survey from 2008-2009 found more frequent intake of vegetables and fruits, and lower intake of convenience foods were associated with greater amount of time spent preparing food at home.[33] In adult IBD patients, diets that restrict grains/carbohydrates are associated with decreased food-related quality of life compared to either no dietary therapy or other dietary therapies (mean Food-Related Quality of Life [FRQol-29] score 71.0 vs 84.8 [scale 29-145, higher = better], p=0.02).[34]

Multiple policy changes could facilitate wider-spread adoption of dietary interventions such as the SCD and lessen the impact of the barriers we identified. Incorporation of dietary therapies into clinical guidelines from medical entities like the American Gastroenterological Association would enhance clinical knowledge of the diet's therapeutic potential. An "SCD-legal" label from the Food and Drug Administration might increase awareness and encourage more SCD-friendly options at school cafeterias and workplaces (in addition to options for inpatient food services at hospitals), similar to the impact of the FDA's "gluten free" label.[35] This would also make it easier for patients to quickly identify safe items in grocery stores. Additionally, many countries either offer free gluten-free staples or subsidies to patients with celiac disease.[36,37] In the US, patients with celiac disease can deduct costs of gluten-free foods from their taxes and/or use Flexible Spending Account provisions to pay for the incremental cost of foods, including shipping expenses.[37] A policy similar to this for the SCD would help diminish

any economic barrier for patients, thereby improving adherence and leading to improved health outcomes.

Limitations

Much of the burden associated with the SCD (i.e., cost and food preparation time) falls on parents. Many IBD patients are still at an age at which they rely on parents for food, and parents tend to shoulder the burden of transporting children to and from infusion, and managing oral medication administration.[38] However, while interviewing parents provides important insight into logistical and practical aspects of adopting the SCD as a treatment option, it does not allow for direct assessment of the patient perspective. This is an important consideration and is an area that should be explored in future research.

The patient population served by Seattle Children's Hospital is not representative of the national population of pediatric IBD patients and parents. Thus, these results may not be generalizable to the broader population of families with children with IBD. Specifically, there is significant national geographic variation in affordability and access to fruits and vegetables in the US,[39] so some of the potential barriers identified in this study may be more salient for families in other parts of the country.

Conclusion

To our knowledge, this is the first study examining barriers to the SCD among pediatric IBD patients. Our results suggest cost, time commitment, and psychosocial factors are the primary concerns impacting patients' ability to adhere to the diet. Further research is needed to develop interventions or strategies to diminish these barriers and enable more patients to benefit from the SCD.

References

1. Dahlhamer J, Zammitti E, Ward B, Wheaton A, Croft J. Prevalence of Inflammatory Bowel Disease Among Adults Aged ≥18 Years - United States, 2015. *Morb Mortal Wkly Rep.* 2016;65:1166-1169.
2. Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. *Inflammatory bowel diseases.* 2011;17(1):423-439.
3. Heuschkel R, Salvestrini C, Beattie RM, Hildebrand H, Walters T, Griffiths A. Guidelines for the management of growth failure in childhood inflammatory bowel disease. *Inflammatory bowel diseases.* 2008;14(6):839-849.
4. Nasiri S, Kuenzig ME, Benchimol EI. Long-term outcomes of pediatric inflammatory bowel disease. *Seminars in Pediatric Surgery.* 2017;26(6):398-404.
5. Heaton PC, Tundia NL, Schmidt N, Wigle PR, Kelton CM. National burden of pediatric hospitalizations for inflammatory bowel disease: results from the 2006 Kids' Inpatient Database. *Journal of pediatric gastroenterology and nutrition.* 2012;54(4):477-485.
6. Sin AT, Damman JL, Ziring DA, et al. Out-of-pocket Cost Burden in Pediatric Inflammatory Bowel Disease: A Cross-sectional Cohort Analysis. *Inflammatory bowel diseases.* 2015;21(6):1368-1377.
7. Fondell AW, Mosha MH, Frank CR, Brangi JM, Hyams JS. Health Care Cost for Children Newly Diagnosed With Inflammatory Bowel Disease. *Inflammatory bowel diseases.* 2020;26(4):635-640.
8. van der Valk ME, Mangen MJ, Leenders M, et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFalpha therapy: results from the COIN study. *Gut.* 2014;63(1):72-79.
9. Floyd DN, Langham S, Severac HC, Levesque BG. The economic and quality-of-life burden of Crohn's disease in Europe and the United States, 2000 to 2013: a systematic review. *Dig Dis Sci.* 2015;60(2):299-312.
10. El-Matary W, Kuenzig ME, Singh H, et al. Disease-Associated Costs in Children With Inflammatory Bowel Disease: A Systematic Review. *Inflammatory bowel diseases.* 2020;26(2):206-215.
11. Ghersin I, Khateeb N, Katz LH, Daher S, Shamir R, Assa A. Comorbidities in adolescents with inflammatory bowel disease: findings from a population-based cohort study. *Pediatric Research.* 2020;87(7):1256-1262.
12. Ludvigsson JF, Büsch K, Olén O, et al. Prevalence of paediatric inflammatory bowel disease in Sweden: a nationwide population-based register study. *BMC Gastroenterol.* 2017;17(1):23-23.
13. Karve S, Candrilli S, Kappelman MD, Tolleson-Rinehart S, Tennis P, Andrews E. Healthcare utilization and comorbidity burden among children and young adults in the United States with systemic lupus erythematosus or inflammatory bowel disease. *The Journal of pediatrics.* 2012;161(4):662-670.e662.
14. Stallmach A, Hagel S, Bruns T. Adverse effects of biologics used for treating IBD. *Best practice & research Clinical gastroenterology.* 2010;24(2):167-182.
15. Haas SV, Haas MP. *Management of celiac disease.* Philadelphia: Lippincott; 1951.
16. Gottschall E, Gottschall EG. *Breaking the vicious cycle: intestinal health through diet.* Kirkton, Ont.: Kirkton Press; 1994.
17. Personalized Research on Diet in Ulcerative Colitis and Crohn's Disease (PRODUCE). ClinicalTrials.gov Identifier NCT03301311. Accessed March 17, 2020.
18. Suskind DL, Wahbeh G, Gregory N, Vendettuoli H, Christie D. Nutritional therapy in pediatric Crohn disease: the specific carbohydrate diet. *Journal of pediatric gastroenterology and nutrition.* 2014;58(1):87-91.

19. Suskind DL, Cohen SA, Brittnacher MJ, et al. Clinical and Fecal Microbial Changes With Diet Therapy in Active Inflammatory Bowel Disease. *Journal of clinical gastroenterology.* 2018;52(2):155-163.
20. Cohen SA, Gold BD, Oliva S, et al. Clinical and mucosal improvement with specific carbohydrate diet in pediatric Crohn disease. *Journal of pediatric gastroenterology and nutrition.* 2014;59(4):516-521.
21. Cohen SA, Stallworth AN, Koch BM, Mason DH, Blumenthal J, Gold BD. Sa1992 Mucosal Healing With the Specific Carbohydrate Diet in Pediatric Crohn's Disease: Preliminary Results of a Prospective Pilot Study. *Gastroenterology.* 2012;142(5):S-376.
22. Suskind DL, Wahbeh G, Cohen SA, et al. Patients Perceive Clinical Benefit with the Specific Carbohydrate Diet for Inflammatory Bowel Disease. *Dig Dis Sci.* 2016;61(11):3255-3260.
23. Kaplan HC, Opipari-Arrigan L, Schmid CH, et al. Evaluating the Comparative Effectiveness of Two Diets in Pediatric Inflammatory Bowel Disease: A Study Protocol for a Series of N-of-1 Trials. *Healthcare (Basel).* 2019;7(4):129.
24. Adams KM, Kohlmeier M, Powell M, Zeisel SH. Nutrition in medicine: nutrition education for medical students and residents. *Nutr Clin Pract.* 2010;25(5):471-480.
25. Levine BS, Wigren MM, Chapman DS, Kerner JF, Bergman RL, Rivlin RS. A national survey of attitudes and practices of primary-care physicians relating to nutrition: strategies for enhancing the use of clinical nutrition in medical practice. *Am J Clin Nutr.* 1993;57(2):115-119.
26. Soltesz KS, Price JH, Johnson LW, Tellijohann SK. Family physicians' views of the preventive services task force recommendations regarding nutritional counseling. *Archives of family medicine.* 1995;4(7):589-593.
27. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful Sampling for Qualitative Data Collection and Analysis in Mixed Method Implementation Research. *Adm Policy Ment Health.* 2015;42(5):533-544.
28. Fusch PI, Ness LR. Are we there yet? Data saturation in qualitative research. *The qualitative report.* 2015;20(9):1408.
29. Guest G, Bunce A, Johnson L. How many interviews are enough? An experiment with data saturation and variability. *Field methods.* 2006;18(1):59-82.
30. *Taguette* [computer program]. Zenodo; 2020.
31. Thomas DR. A general inductive approach for qualitative data analysis. 2003.
32. Gupta S, Hawk T, Aggarwal A, Drewnowski A. Characterizing Ultra-Processed Foods by Energy Density, Nutrient Density, and Cost. *Front Nutr.* 2019;6:70-70.
33. Monsivais P, Aggarwal A, Drewnowski A. Time spent on home food preparation and indicators of healthy eating. *American journal of preventive medicine.* 2014;47(6):796-802.
34. Guadagnoli L, Mutlu EA, Doerfler B, Ibrahim A, Brenner D, Taft TH. Food-related quality of life in patients with inflammatory bowel disease and irritable bowel syndrome. *Qual Life Res.* 2019;28(8):2195-2205.
35. Three Years Later, What is the Impact of the Gluten-Free Labeling Standard? *Conversations with Experts on Food Topics* 2017; https://www.fda.gov/food/conversations-experts-food-topics/three-years-later-what-impact-gluten-free-labeling-standard. Accessed February 20, 2021.
36. See JA, Kaukinen K, Makharia GK, Gibson PR, Murray JA. Practical insights into gluten-free diets. *Nature reviews Gastroenterology & hepatology.* 2015;12(10):580-591.
37. Pinto-Sanchez MI, Verdu EF, Gordillo MC, et al. Tax-deductible provisions for gluten-free diet in Canada compared with systems for gluten-free diet coverage available in various countries. *Canadian journal of gastroenterology & hepatology.* 2015;29(2):104-110.

38. Hommel KA, Odell S, Sander E, Baldassano RN, Barg FK. Treatment adherence in paediatric inflammatory bowel disease: perceptions from adolescent patients and their families. *Health & social care in the community.* 2011;19(1):80-88.
39. Sturm R, Datar A. Regional price differences and food consumption frequency among elementary school children. *Public Health.* 2011;125(3):136-141.

Tables

Table 1. Characteristics of pediatric patients with inflammatory bowel disease included in the study

	SCD-Initiators (n=8)		Non SCD-Initiators (n=2)
	Current users (n=4)	Past users (n=4)	
Sex, n (%)			
Male	3 (75%)	1 (25%)	2 (100%)
Age (years), median (range)	13.5 (11-15)	15.5 (13-18)	15.5 (13-18)
Duration of disease (years), median (range)	3.5 (0.5-4)	1.5 (0.6-6)	6 (3-9)
Disease type, n (%)			
Crohn's Disease	2 (50%)	1 (25%)	1 (50%)
Ulcerative Colitis	2 (50%)	3 (75%)	
Indeterminate Colitis			1 (50%)
Current therapy, n (%)			
SCD only	3 (75%)		
SCD plus pharmacotherapy	1 (25%)		
Pharmacotherapy only		4 (100%)	2 (100%)

SCD: Specific Carbohydrate Diet

Table 2. Key barriers to initiating the Specific Carbohydrate Diet among families of pediatric patients with inflammatory bowel disease and example quotes from interviewed parents

Potential Barrier	Example Quotes
Cost	*You know, but a barrier, and this is, this is the part that breaks my heart a little bit, and I, is that the barrier for some families is the cost. Not only, I mean yes, there's a time investment, but there's also just the cost of good quality produce and good quality food is higher."* *It just got to a point when I was just like ok, um, I don't think we can do this, all of us do this diet because it was just getting too expensive.* *I could see how a low income family might struggle with it. Especially at first you're just buying a lot of the whole foods aren't cheap.* *It definitely got more expensive because of just trying to buy all the good fruits and vegetables I think was the main problem…and I forget the name of the bread, but it was made out of cashews, and buying organic cashews were expensive, and that bread was like three cups of cashews for each loaf, and I was just buying these bags from amazon and it was like $50 each, and also like making her almond milk and buying good almonds to make the almond milk, and then also like, I would just try to like, I was just trying to find her good snacks that she could enjoy that I wasn't preparing all the time, that she could just grab from the pantry and go, and just purchasing um some of the SCD stuff that they were selling online, those were very pricey.* *Because all those nut flours and milks that are not cow milk, they are very expensive.* *We're lucky 'cause we can spend the money on the groceries and stuff. It'd be interesting to see if you had a low income family where generally you're going to buy cheaper, more processed stuff.* *I think it's the organic, like the organic vegetables. I think that's it, and then when we order stuff online, it is so much money to have stuff shipped to us, especially if it needs to be in a cooler or something, so that costs a lot, so we don't do that too often. But yeah I think it's the organic. And then I think it's the organic vegetables like organic fruit that costs a lot.*
Time Commitment	*We used to do a lot of premixes, canned goods, that kind of stuff that we just throw together. Now everything's from scratch, so, it's an hour or two depending on the meal.* *Quite a bit more baking with those special recipes for him and it mainly just takes time to figure them out rather than to make them. I mean some of them are harder to bake, but finding them and then you know, there are a lot of flour, or almond flour based breads that turn out horrible, and then there's the ones she's recently made are*

	really good. *I go twice a week now, I don't find that produce lasts long enough to go only once a week. And his diet is a lot of produce. There are items that we find that work for us, and then the store will stop carrying it, so I'll have to shop around to try to find it somewhere else.* *It made me have to go to more stores. Because not one, there was no one store that carried everything.*
Psychosocial Impact	*I think it was, it was also hard, because he was in a, you know it's a sensitive part of your life when from uh, you're going from uh 12, well you know, that's tough. I mean it's almost easier when you're little. Right. And then if you're a young adult I think it's easier. But when you're right in the middle it's hard. So I think it was challenging for him when he was in school and stuff.* *It's emotionally difficult for ***. When he goes to school and there's a birthday party, and everybody else has cupcakes and he can't have that. Um. He's been great with it, but it's difficult for him to not be able to eat some of the things that even siblings are able to eat, but he's not.* *When I read the diet, I'll be honest, my stomach turned and I felt like I was going to throw up because I was like this is everything he loves. This kid ate rice like crazy. He ate, he loved, he would guzzle milk. I mean, it was like, he's gonna lose everything he loves and I was like oh my gosh.*

Conclusion

The objective of this study was to assess the potential health outcomes and economic impact of the SCD as a therapeutic option for pediatric patients with IBD. In Aim 1, we evaluated the comparative effectiveness of the SCD as an adjunct to pharmacotherapy using data from the PRODUCE study and an external control arm from the ICN registry. In the full population, the difference in differences in sPCDAI score from baseline to eight weeks was neither statistically, nor clinically, significant comparing the SCD plus pharmacotherapy to pharmacotherapy alone. In the subgroup of patients with active disease (sPCDAI ≥15) at baseline, the difference in differences in sPCDAI was statistically significant, but did not reach clinical significance.

In Aim 2, we developed a hybrid decision tree Markov model to assess the VBP of the SCD for induction of remission in pediatric patients with active CD. To our knowledge, this is the first study to estimate the potential cost-effectiveness of the SCD for treatment of pediatric CD. Even at an effectiveness of only 50%, we found that the VBP of the SCD was close to $20,000, which far exceeds the likely cost of the diet, suggesting that the SCD has the potential to be a highly cost-effective treatment option.

In Aim 3, we conducted a qualitative study of parents of patients with IBD treated at Seattle Children's Hospital to assess perceived barriers to initiating and/or maintaining the SCD. We found that parents of children diagnosed with IBD primarily chose to try the SCD due to concerns about medication safety. Additionally, we identified that cost, time commitment, and psychosocial impact are three major barriers to utilizing the SCD.

There is a need for new treatments for pediatric IBD that offer therapeutic benefits comparable to current pharmaceutical options while decreasing health care costs. The results of these analyses indicate that the SCD has the potential to fulfill this need. Even with moderate effectiveness, the value-based price of the SCD far exceeds the average grocery expenditures

for a family of four in the US. Because there is currently no reimbursement from health insurance companies for the SCD (or other dietary therapies), the added cost of SCD compliant foods can present a barrier for families with children with IBD. Financial assistance for patients on the SCD would help diminish any economic barrier to the SCD for patients, thereby improving adherence and leading to improved health outcomes. However, policy action will require demonstrating long-term value. Long-term studies are needed to provide evidence that the SCD improves IBD-related outcomes, such as lowering incidence of disease flares and hospitalizations, as well as decreasing incidence of toxicities associated with IBD pharmacotherapy (i.e., malignancies and infections).

This work provides a foundation for further research into the population health and economic impacts of dietary therapy for IBD. Future studies are needed to assess both the direct and indirect costs of the SCD, as well as the effectiveness of the SCD as a stand-alone therapy and as an adjunct to pharmacotherapy. These data would enable more robust evaluation of the SCD as a therapeutic option, therefore providing essential information for clinicians, patients, payers, and policy-makers.