Assessing Patient Preferences for Treatment Options and Process of Care in Inflammatory Bowel Disease: A Critical Review of Quantitative Data

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Abstract

Inflammatory bowel disease (IBD), consisting of both Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory conditions of the intestinal tract. As there is no cure for either CD or UC, these patients face numerous treatment decisions regarding their disease. The aims of this review are to evaluate literature regarding quantitative studies of patient preferences in therapy for IBD with a focus on the emerging technique of stated preference and its application in IBD. Numerous simple survey-based studies have been performed evaluating IBD patients' preferences for medication frequency, mode of delivery, potential adverse events etc., as well as variations in these preferences. These studies are limited, however, as they are purely descriptive in nature with limited quantitative information on the relative value of treatment alternatives. Time trade-off and standard gamble studies have also been utilized to quantify patient utility for various treatment options or outcomes. However, these types of studies suffer from inaccurate assumptions regarding patient choice behavior. Stated preference is an emerging robust methodology increasingly utilized in health care that can determine the relative utility for a therapy option as well as its specific attributes (such as efficacy or adverse side effects). Stated preference techniques have begun to be applied in IBD and offer an innovative way of examining the numerous therapy options these patients and their providers face.

1. Inflammatory Bowel Disease: Overview and Treatment Options

Inflammatory bowel disease (IBD), consisting of two types of disease, Crohn's disease (CD) and ulcerative colitis (UC), are chronic relapsing/remitting inflammatory conditions of the intestinal tract that have no cure. The etiology of IBD is unclear, but is believed to be multifactorial including a dysregulated immune system. IBD affects over 1.3 million Americans and the prevalence and incidence of IBD is increasing.[1] The peak incidence of IBD occurs in the 2nd and 3rd decade of life, and this predominance in a younger population can result in a large economic burden from both chronic treatment as well as lost productivity. In CD, disease can occur anywhere from the mouth to the anus, is progressive over time, and is associated with several complications including abscesses, fistulae, and stricture formation from active disease. In contrast, UC is limited to the colon and therefore surgical removal of the colon, specifically a total proctocolectomy, provides a potential surgical "cure." The two most common procedures performed are a total proctocolectomy with end ileostomy (an external ostomy bag) and restorative ileal pouch anal anastomosis

(IPAA). However, the surgery itself has its own risks of morbidity and mortality; and quality of life after surgery can be compromised.

1.1 Treatment Options in IBD

When evaluating therapy options in IBD, it is important to consider that clinical drug efficacy trials in both UC and CD have traditionally had two different endpoints--clinical response and clinical remission. The former is improvement of clinical symptoms over a baseline score while the latter is an objective improvement to a pre-defined definition of remission based upon a disease severity indice.

In UC, treatment often begins in a "step-up" fashion with mesalamine (5-ASA) therapy, a relatively safe and effective therapy for mild-to-moderate UC. However, 5-ASA fails to induce a clinical remission in 50% or more of UC patients.[2–8] For patients in whom 5-ASA therapy is inadequate to control their disease, the next drug utilized are often corticosteroids. Unfortunately, over 50% of patients either will suffer disease recurrence upon discontinuation of corticosteroids, or be unable to taper off corticosteroids at all due to recurrent disease at lower doses of the drug.[9] Given that both short- and long-term corticosteroid use is associated with a significant number of potential adverse side effects, alternatives to corticosteroid therapy have been developed. These include potent classes of immunosuppressant medications called immunomodulators (including the thioprine analogs azathioprine and 6-MP) and anti-TNF therapies. Cyclosporine and tacrolimus have also been used as a bridge to thiopurines for refractory UC, particularly in patients who have failed to respond to intravenous corticosteroids.[10,11]

Because UC is limited to the colon, surgery offers a possible cure for the disease. The two most common operations performed for UC are total proctocolectomy with end ileostomy and restorative ileal pouch anal anastomsosis (IPAA). While UC patients having had surgery feel, after a period of adjustment, that they are better off than before surgery[12], most patients and physicians who contemplate surgery consider it an option of "last resort." At a national level, surgical rates have not changed significantly over the past decade.[13] It is estimated, however, that 25–30% of UC patients eventually will require colectomy for medication-refractory disease.[14,15]

While many of the same therapies used in UC are utilized in CD, there are significant differences. Even if a patient is clinically asymptomatic, tissue damage can continues to progress and result in numerous complications.[16,17] Up to 80% of CD patients will require intestinal surgery, with 30% requiring a second operation.[1] 50% of patients have perianal involvement (including perianal fistula and abscesses) which risk repeated surgeries and fecal incontinence.[1] Furthermore, because disease can recur post-operatively, the goal of treatment is to avoid bowel resection surgery. Therefore there is no "surgical cure" for CD. Finally, CD itself has an increased overall-mortality compared to the general population, in part due to CD-related complications including malnutrition, post-operative complications, and intestinal cancer.[18,19] Unfortunately, morbidity and mortality rates have not changed over the last 5 decades, despite improvements in medical therapies, as these medications often are not started early enough in disease progression (before irreversible damage occurs); or are not maintained in a regular fashion, allowing for progression of tissue damage during gaps in therapy.

As a result of these prognostic differences in CD, therapies and therapy algorithsm are also different. Mesalamine therapy has not been shown to be effective in CD.[20,21] In patients with perianal disease or certain disease complications may be treated with antibiotic therapy for short amounts of time. Patients with mild disease can be started on corticosteroids or budesonide, a steroid medication with limited systemic absorption. However, given the

potential for disease progression, even if asymptomatic patients, treatment algorithms have evolved over the past decade to emphasize a more aggressive approach to CD care. Studies have shown that a "top down" approach, with initiation of a combination of immunosuppressant medications from disease onset (typically a thiopurine analog plus an anti-TNF therapy), is associated with improved disease remission and decreased CD-related complications.[22,23] While cyclosporine has not been found to be effective in CD, the thiopurine analogs, anti-TNF medications, and methotrexate have been shown to be effective in treating CD.[22,24–31] An additional medication natalizumab, a humanized monoclonal antibody against the cell adhesion molecule α4-integrin, has also been shown to increase rates of remission and prevent disease relapse in refractory CD.[32]

Over the past decade, a greater understanding of the progression of IBD has also led to the increasing belief that a more rigorous endpoint, that of mucosal healing (e.g. endoscopic remission) should be the goal of IBD care.[33] This has endorsed shifts in treatment algorithms to a more early-aggressive approach, especially in CD; and also has implications for how drug efficacy is evaluated in both diseases. However, patients' willingness to accept the risks of additional therapy (see below) in the absence of symptoms can be at odds with such recommendations. Furthermore, certain populations of patients, such as pediatric patients, may be unwilling to accept long-term or lifelong risks of mono- or combination-immunosuppressant therapy, especially if they have never experienced any medical therapy for their disease.

1.2 Risks of Medical and Surgical Therapy in IBD

Medical therapy in IBD carries several potential risks. Corticosteroids are associated with numerous well-characterized side effects including near inevitable occurrence of bone disease and cataracts with long-term use. Furthermore, corticosteroid therapy has been associated with an increased mortality risk.[34,35] Given their effects on the immune system, corticosteroids and the immunosuppressant medications have been associated with serious opportunistic infections. Corticosteroids have been associated with a 2–3 times increased odds of serious infections.[36,37] Rates of infection for those on thiopurine analogs and anti-TNF therapy are as high as 5% per year, including a fatal central nervous system infection called progressive multifocal leucoencephalopathy (PML) with natalizumab.[37–41] The thiopurine analogs and anti-TNF therapies also may increase the risk of certain cancers including an increased risk of cervical dysplasia and non-melanoma skin cancer.[42–44] The risk of lymphoma associated with thiopurine analogs and anti-TNF use that may be as much as four times that of the general population; with combination therapy, this risk increases to 6–10 times that of the general population.[45–48] A particularly aggressive and nearly universally fatal form of lymphoma, called hepatosplenic T-cell lymphoma (HSTCL), is associated with immunosuppression particularly in young adults.[49–51] By virtue of retaining their colon, IBD patients also have a lifetime risk of colon cancer that is as high as three times that of the general population [52]

As with all medications, there is the risk of medication failure for therapy in IBD. Best clinical trial efficacy rates indicate that at least one-third of patients will fail induction or maintenance of remission with these medications at one year.[21,22,26,28,29,31,53–56] During this time, patients are exposed to the risks of medical therapy as well as the risk of continued active disease. The consequences of incompletely treated disease as a result of medication failure are poorly understood. However, indirect evidence suggests that patients are at increased risk of morbidity and mortality including hospitalization, complications of active disease (such as abscess or stricture formation) or emergent surgery which carries a substantially higher morbidity and mortality rate than elective or planned surgery.[1,34,35,57–60].

In UC, the option of surgery also carries risks, related to both the surgery itself and the post-operative quality of life. While the majority of patients will successfully undergo IPAA surgery, a minority will instead have a permanent externally draining ileostomy. Those who do have IPAA surgery still have six bowel movements a day on average. This means that some patients will have more bowel movements than prior to their colectomy. Additionally, patients with IPAA surgery are at risk for having fecal incontinence, impeding quality of life. Mortality rates with elective colectomy range are no higher than 1% at 35 months; and as low as 0.5% at 33 months.[12,61,62] However, with emergent colectomy, mortality is much higher.[57,60,63,64] As with all surgery, there is a risk of post-operative infection following colectomy. Reported rates range of septic complications, pelvic abscesses and wound dehiscence range from 1%–10%, depending on the institution.[12,61,65]

1.3 Decision Making in IBD

As illustrated above, patients with IBD face numerous decisions regarding therapy for their disease. For patients with mild UC, there are decisions about mesalamine therapy, specifically, route and frequency of administration. For the majority of UC patients, mesalamine therapy will be insufficient, and these patients face decisions regarding chronic repeated corticosteroid use, long-term immunosuppressant therapy, or colectomy surgery. Likewise, in CD, patients face decisions regarding chronic repeated corticosteroid use or initiation early in the disease with long-term immunosuppressant therapy, either as a single drug or as a combination of drugs.

Without the ability to predict which patients will respond to which therapies, or how aggressive disease will be, IBD patients and their physicians often find themselves in a variety of challenging clinical decision-making situations with no clear correct solutions. Because all potential therapies (medical and surgical) have potential risks and benefits, and thus implications for patient quantity and quality of life, patient collaboration in this decision-making is therefore essential. The last few decades have seen an increased importance placed on patient preferences in healthcare.[66,67] Patient preferences arguably play a critical role in health care outcomes: patients' preferences for therapies influence adherence, compliance and satisfaction with therapies, which in turn influences overall care. In turn, patient preferences can inform physicians in their daily interaction with patients; regulators in setting thresholds for therapy efficacy and risk; and national organizations in setting treatment guidelines. Thus, rigorous methodologies capable of accurately quantifying patient preferences in large patient populations are needed.

2. Preferences, Health-State Utility, and Patient-Reported Outcomes

The increased focus on patient-centered health care and medical research in recent years has heightened awareness of the importance of patients' perspectives in assessing health-care interventions.[68–71] Patients' perspectives include information on outcomes such as pain that are not clinically observable. These outcomes are quantified using patient-reported outcome (PRO) instruments. For cost-utility studies, it is necessary to identify a common scale for combining and comparing dissimilar oucomes. Methods such as standard gamble (SG) and time-tradeoff (TTO) are widely used to obtain patient-derived health-state utilities for both clinically observable and PRO outcomes. Patients' perspectives also are essential for obtaining values or weights indicating patients' trade-off preferences for health outcomes, health-care processes, and convenience features of treatments. Stated-preference methods including contingent valuation and conjoint analysis or discrete-choice experiments (DCEs) have been increasingly used to quantify these subjective preference weights.

Thus PRO instruments, health-state utility methods, and stated-preference surveys were developed to answer different questions about patient concerns. Unfortunately, there is

considerable misunderstanding about similarities and differences among methods and how these different patient-centered measurement techniques contribute to outcomes research. For example, PROs quantify health outcomes, but do not measure patient preferences.[72] Health-state utility measurement techniques are used to calculate standardized quality-adjusted life years (QALYs) but do not account for the wide range of factors that contribute to patient satisfaction.[73–81]

The focus of this review is to evaluate the literature regarding quantitative studies of patient preferences in therapy for IBD. While most published studies have utilized conventional health-state utility measurement techniques, we evaluate limitations of this literature and explore the growing field of stated preference and its application in IBD.

3. Literature Review

To identify published studies on patient preferences in IBD, a systematic PubMed search was conducted on December 20, 2012. The search used the following keywords and MESH headings: survey preferences or time trade off or standard gamble or conjoint analysis or discrete choice combined with inflammatory bowel disease or ulcerative colitis or Crohn's disease. This approach identified 54 papers published between 1987 and 2012 (Figure 1). Two additional citations were identified through review of references or personal communication. Application of the limitations "English language" and "human studies" yielded 55 papers for analysis. Each study was systematically reviewed to assess for appropriateness for the current review. Studies were excluded because they did not evaluate patient preferences (9); were review or commentary articles (2); were not specific to IBD (5); did not evaluate preferences between treatment options and/or measured utilities for correlation with quality-of-life measurement tools only (6); was primarily a methodology analysis (1) or were cost-effectiveness analyses (4). Twenty-eight articles were evaluated for this review.

4. Survey studies of IBD preferences

The most basic form of assessing patient preferences are simple questionnaire-based surveys. Given the variety of issues facing IBD patients and their providers, a number of studies have utilized survey methods to obtain information on a range of issues. Our search identified 15 survey studies on topics including information needs and delivery for IBD patients; perceptions regarding colorectal cancer screening and recommendations in IBD; preferences for shared decision-making; preferences for potential treatments (administration, efficacy, safety, dosing); adolescent and pediatric IBD preferences; and preferences regarding genetic testing in IBD (Table I).

All of these studies provide some insights regarding attitudes of both patients and physicians toward IBD care. However, these studies generally are descriptive in nature (typically presenting percentages of respondents as results), with limited quantitative information on the perceived value of treatment alternatives. More specifically, while a survey may tell us the average score a given outcome has on a Likert or visual-analog scale, such metrics do not provide valid estimates of intensity of preferences.[72,97] The resulting data thus do not provide information on what patients would be willing to give up to obtain outcome A, or what specifically makes outcome A preferable to outcome B. For example, in the study by Allen et al, the authors evaluated patients' stated preferences for infliximab (an intravenous medication) versus adalimumab (a self-injectable medication), and described a trend in respondents towards a preference for infliximab.[87] However, the authors could not evaluate what features (frequency of infusions, mode of administration, etc) of the drugs evaluated could have explained this finding, the intensity of preference for these features or the drugs themselves, or what would cause patients to change their mind regarding their preferences.

Eliciting patient trade-off preferences in a realistic, although hypothetical, clinical context is more likely to be informative about how patients would evaluate actual therapeutic decisions. For example, researchers in one study asked patients if they would be willing to accept a medication with a 98% remission rate but risks similar to that of infliximab (0.4% mortality risk).[98] Over 60% of patients said the benefits of this drug did not justify its risks. However, it is unclear what implicit alternative treatment patients assumed in answering the question. If patients had been told that they could take this drug or face colectomy surgery because of complications resulting from disease progression, it is possible that a greater number of patients would consider the hypothetical medication to be acceptable.

5. Time trade-off and standard-gamble studies in IBD

Health-state utility is a well-known cardinal index of the quality of a given health state. Utilities can be measured at population or individual levels, and vary as people's health changes. Changes in health states can be expressed as incremental utility elicited by either time-tradeoff or standard-gamble question formats. Utilities can be converted to QALYs that are used in cost-utility analysis. QALYs weight durations in each health state by the average utility of that state and facilitate health-outcome comparisons across groups of people, health outcomes and durations.

In time-trade-off (TTO) studies, respondents evaluate specific treatment-outcome scenarios and are asked how much of a reduction in expected life years they would accept for living in perfect health instead of living the rest of their expected lifetime in the compromised health state. Health-state utility is measured as the ratio of equivalent years in perfect health to years in compromised health.

Standard-gamble studies determines the chance of the worst imaginable health state (usually assumed to be death) that a patient would be willing to accept in return for the best possible health (usually defined as perfect health). The patient typically imagines a treatment that would completely cure their symptoms but involves a risk of immediate death. Setting the utility of death at zero and the utility of best possible health at 1, and assuming that expected utility is the sum of outcomes weighted by probabilities, one minus the indicated risk of death indicates the health-state utility.

A significant number of the TTO and SG studies evaluating health-state utilities for various IBD therapies have been small studies, often with sample sizes of less than 50 patients (Table II). The majority have focused on patients with UC, and specifically preferences for continued medical management of UC versus colectomy surgery. This decision branch lends itself rather elegantly to analysis, as it involves two very different decisions and their corresponding varying health-state utilities. One study directly evaluated utilities for colectomy surgery versus continued medical therapy in UC. Arseneau and colleagues evaluated 48 UC patients' utilities in steroid-refractory UC for colectomy surgery, therapy with infliximab and/or therapy with cyclosporine for use in Markov modeling for these various treatment decisions.[99] However, one prominent finding in their results was the highly variable measure of optimal treatment choice (e.g. that which maximized their QALYs) among patients, with total colectomy being the optimal treatment choice for 37% of their patient sample. When utilizing the average utility for analysis, medical therapy was superior to colectomy surgery. However, in their probabilistic sensitivity analysis utilizing multiple simulations of treatment decisions per patient, only one-third of patients had highly robust and reproducible optimal treatment decisions. The authors concluded that assessing individual patient utilities was important given the significant number of UC patients for which there was no clear superior treatment.

Three studies examined the perceived and actual utility of pre- and post-colectomy outcomes in UC. McLeod et al. examined 20 UC patients' perceptions of their post-operative quality of life prior to surgery and compared this to their realized 1-year post-operative quality of life utilities; and further examined 93 UC patients over one year after colectomy surgeries.[100] They found that mean realized post-operative utilities were significantly higher than perceived utilities and did not vary by colectomy surgery type.[100] Walijee et al also evaluated differences in utility of UC patients with active disease versus those having a colectomy. They surveyed patients without UC, patients with UC without colectomy and post-colectomy UC patients with standardized scenarios for moderately active UC and post-colectomy states.[104] Those without UC viewed both the UC and post-colectomy scenarios equally poorly. UC patients, however, reported similar utilities for both active UC and the post-colectomy scenarios. This was in contrast to those patients who had a colectomy: these patients perceived active UC as significantly worse than the post-colectomy state.[104] Finally, a recent study compared physicians and UC patients' preferences for active UC versus colectomy.[106] They evaluated 17 physicians, 150 UC patients having had a colectomy and 69 patients with moderately active UC with standardized scenarios for active disease and post-surgery. Both the physicians and those patients having a colectomy viewed UC more poorly than the post-colectomy state; however, patients who had not had a colectomy but had moderately active UC indicated that both their active disease and the post-colectomy state had equal utilities.[106]

Taken together, this evidence would seem to suggest that patients with UC who have not undergone colectomy surgery associate this treatment and the post-surgery state with significantly diminished quality of life versus those who have actually had the surgery. A study evaluated this apparent preference by UC patients for more long-term health risks (e.g. immunosuppression) versus short-term health risks (such as colectomy surgery) by focusing on the standard 5% discounted rate for future health traditionally used in TTO/SG studies.[105] The authors determined that this standard discount rate was a substantial underestimation of measured UC patients' discount rate, suggesting that UC patients either have a strong aversion to immediate risks in favor of future risks or place a lower value on future health in favor of more immediate health.[105] However, in all comparisons of pre- and post-colectomy health states, it is important to appreciate that the comparison is not equivalent: those having undergone colectomy surgery more likely did so due to medication-refractory disease. Their disease history (including duration of disease and medication use history) would be expected to impact their risk preferences.

There is no option for a surgically curative procedure in CD. However, up to 80% of CD patients will require intestinal surgery during their disease history, with a significant portion requiring a second operation.[1] A study evaluated CD patients' utilities for various surgical interventions versus medical therapy for their CD, and compared these utilities to those of surgeons and gastroenterologists using scenarios illustrating different surgical outcomes.[103] They found that gastroenterologists were more strongly averse to surgery than either surgeons or CD patients; and in half of the scenarios provided, gastroenterologists' and CD patients' utilities diverged in a significant fashion, most notably regarding an open or laparoscopic ileocolic bowel resection, one of the most common procedures performed in CD.[103] Furthermore, gastroenterologists and colorectal surgeons' utilities were similar in less than half of the scenarios provided.[103]

Given the lack of a surgical cure in CD, disease therapy relies much more heavily on medical management with a goal of preventing first surgeries and/or decreasing the risk of recurrence of disease necessitating subsequent surgeries. In a Markov model examining 1-year cost and utility for infliximab (an infusion medication) compared to the oral medications 6-MP and metronidazole for perianal fistula therapy in CD, utilities were

evaluated from CD and control patients and found no differences in measured utilities for various therapy options.[102] Another study aimed to examine the utilities patients had regarding mesalamine therapy postoperatively to prevent disease recurrence.[101] However, a subsequent letter to the journal editors remarked that the authors of this study were not evaluating utilities per se, but rather actions, an important distinction within the utility theory framework that can lead to miscalculations of actual utilities expected based upon these measured actions.[107]

5.1 Advantages and Disadvantages of Time Trade-off and Standard Gamble

Using traditional methods such as TTG and SG to obtain utility values for QALY estimation is widely accepted for health-technology assessment because these methods allow for a simple method of integrating mortality, morbidity and preferences for therapies into a single estimation representing the equivalent years of perfect health. This allows for relatively simple comparisons with other QALY-based measurements (including some quality of life questionnaires) and utilization of these QALYs for cost-utility analyses.

However, it is exactly this simplicity that can become problematic due to inaccurate assumptions regarding patient preferences. TTO and SG studies suffer from a number of fundamental limitations that have been recognized for several decades.[77–81] The clinically-artificial method of eliciting patient utilities in TTO/SG studies employs cardinal-utility, a ratio-scale metric rejected by nineteenth-century utility theorists in favor of ordinal-utility measures. Ordinal utility is the basis of virtually all subsequent applied-economics research.[108]

Numerous validity tests of QALY studies also have rejected the assumptions of independence, procedural and description invariance, linearity over time and comparability across groups of patients.[109,110] Furthermore, in the interest of simplicity, conventional TTO and SG applications assume that health history or current health state do not affect relative preferences. To the extent that disease attributes (including duration of disease, history of complications and current disease symptoms) would be expected to impact patient preferences, these conventional methodologies may lead to biased comparisons between and within groups of patients. Moreover, conventional health-state utility measurement techniques are unable to capture the impact of acute conditions, treatment risks, or process-related factors such as the method of administration or treatment duration. Such factors can play a significant role in understanding patients' preferences for IBD treatments.

Additionally, TTO and SG studies have been shown to have significant failings in populations with low numeracy. A full discussion regarding numerical issues in patient-preference studies is outside the scope of this review; however treatment decisions and patient preferences do require patients to integrate and weigh pros and cons of medical decisions in a numerical fashion. Several factors have been found to be important in how patients perceive risks. This includes framing, which refers to how risk is presented;[111–113] how numbers are presented (such as frequencies, which have been shown to be easiest to understand, versus proportions or probabilities which are more artificial constructs and require additional conditional math);[114–118] and base-rate neglect (susceptibility to numerators with relative neglect of the corresponding denominator).[114–117,119] These issues are attenuated in low-numeracy populations, a significant issue in the United States.[111,112,114–117,120–124] And patients with low-numeracy skills have proven difficulties appropriately completing SG and TTO tasks appropriately.[122,125,126]

6. Discrete-Choice Experiments in IBD

DCEs, also known as choice-format conjoint analysis, employ a multi-attribute preference-elicitation technique that quantifies the strength of preferences for features of products, services or health-care interventions. Interventions, such as medical or surgical treatments in IBD, derive value from their specific attributes, features or outcomes, including treatment efficacies, tolerability, convenience, and potential serious adverse risks. In turn, each of these attributes has varying levels, such as efficacy rates or adverse risk rates. DCEs systematically elicit tradeoffs among constructed outcome combinations to generate choice data that quantifies implicit decision weights indicating relative utility for both treatment attributes as well as the treatment option as a whole. Because DCEs measure the rate at which patients accept tradeoffs among different treatment attributes, it is also possible to calculate a maximum acceptable risk or maximum probability of an adverse event that participants are willing to tolerate in exchange for a given treatment benefit. DCE increasingly has been applied in the field of healthcare for eliciting patient preferences for a range of medical and surgical therapies across many disease states.[127–133]

Given the numerous treatment options, both medical and surgical, in UC and CD, there are a number of opportunities to evaluate patient and provider preferences (Table III). The majority of published studies have evaluated preferences in CD, and all have utilized larger sample sizes of study participants than prior methodologies. In a DCE examining preferences for therapies in CD, the three most important attributes of medical therapy were achievement of a lasting remission, frequency of medication administration and how quickly the patient achieved a response to therapy.[134] One of the first examined CD patients' preferences for lethal adverse events in exchange for medication efficacy.[135] One of the risks in this study was for the rare but lethal neurological side effect PML associated with natalizumab. At the time that the study was conducted, natalizumab had been removed from the market by the FDA due to concerns regarding cases of reported PML in the approved indication for multiple sclerosis. The authors found that CD patients were willing to accept high levels of PML well above the clinical exposure in exchange for clinically realistic improvements in treatment outcomes.[135] Following this study, natalizumab was approved for CD patients, subject to certain restrictions.

Two further studies in CD have evaluated differences in preferences for medication risks and benefits between populations of patients and/or providers. A study by Johnson and colleagues compared risk preferences between juvenile and adult CD patients, an important issue for providers caring for these patients as they transition between the pediatric and adult health care systems.[136] They found that parents of juvenile CD patients and adult CD patients had similar risk tolerances for medication efficacies in CD therapies.[136] An additional study compared CD patients and gastroenterologists with respect to their willingness to accept therapy risks and benefits.[137] Utilizing DCE methodology, the authors were able to evaluate preferences across varying age groups of CD patients, various risks of medical therapies and various efficacies of the therapies. The authors found that gastroenterologists' risk tolerances differed by the age of their patients, with less risk tolerance for the older IBD patient compared to the middle-aged or younger IBD patient.[137] Furthermore, significant differences existed in disease severity tolerance and various risk tolerance tolerances for resultant drug efficacy: for example, middle-aged patients were significantly more tolerant of the risk of lymphoma than physicians if a medication was completely efficacious and resulted in a disease remission (rather than a clinical improvement but not complete remission).[137]

A multicenter multi-country DCE study evaluated UC patient preferences for various aspects of 5-ASA therapy and further evaluated differences in these preferences for self-

proclaimed "good" versus "poor" medication adherers.[138] The study found that preferences varied by adherence-reporting as well as country for important attributes in 5-ASA therapy. Patients who self-reported good adherence preferred 5-ASA therapies that improved stool frequency and promoted mucosal healing. North Americans (US and Canada) preferred reduced pill quantity or frequency of taking medications. Furthermore, clinical characteristics of the participants (for example, disease activity within the past year) affected importance of preferences regarding therapy efficacy.[138]

6.1 Advantages and Disadvantages of Discrete-Choice Experiments

One of the most powerful advantages of DCE is that it does not require the restrictive assumptions of conventional QALY metrics. By offering realistic benefit-risk tradeoff scenarios within a non-expected utility framework, DCEs more accurately quantify preference data, from which utility is derived. Houtven et al showed how to derive maximum acceptable risk from generalized utility theory with an example using a DCE study in IBD.[110]

DCE also allows for subgroup analysis by health history, current health state or other covariates of interest which may affect risk preferences. For example, Johnson et al. found that duration of disease, proximity of last disease flare and disease history all affected risk preferences for treatment SAEs in exchange for treatment efficacy.[135] As it is reasonable to expect risk preferences to be influenced by patient history, DCE offers a rigorous framework with which to assess this impact.

As patient preferences play a key role in patient satisfaction, which in turn influences adherence and ultimately clinical outcomes, DCE-measured preference data are more patient-centered than QALYs. Furthermore, by measuring preferences for attributes of a medical therapy as well as the therapy overall, DCE also provides information on the total value of an intervention or on the marginal effect of modifying a single factor on the value. By collecting data within carefully devised experimental designs, DCEs can introduce variability and reduce or even completely eliminate collinearity, making possible precise estimates of attribute contributions to therapy utilities. This also allows for preference measurement on future interventions including those that may not be currently available. Finally, within the given choice format, DCE can assess numeracy, present risks in multiple formats, and perform inherent tests of validity and consistenty including logic testing, test-retest and transitivity.

While DCEs stated-preference measures can quantify preferences for both health outcomes and process-related factors, the resulting relative importance weights are not generalizable across therapeutic areas. An important limitation of DCEs include their hypothetical nature: simulated decision-making using hypothetical therapeutic options does not have the same medical, emotional and financial consequences as actual therapeutic decisions. In addition, outcomes in real clinical settings are inherently probabilistic in nature. Eliciting patients' willingness to accept benefit-risk tradeoffs is cognitively challenging because of the low numeracy level of many respondents. Resulting preference data thus may be subject to considerable measurement error. Finally, DCE studies can be difficult to implement, both in terms of design methodologies as well as analysis,[139,140] which can affect comprehension and acceptability among physicians and regulators.

7. Discussion

Understanding patients' preferences for therapies that affect their care is important in every aspect of health care. There is an increased importance placed on patient autonomy within medical decision making, both in health care policy, as well as by patients and physicians.

Furthermore, health-care expenditures are often shouldered wholly or in part by patients themselves, which often results in rationing of care based upon preferences for perceived risks and benefits.[116] This is a particular problem for illnesses such as IBD that disproportionately affect younger patients who may not have access to resources through employment and health insurance.

Additionally, understanding IBD patient preferences takes on particular importance because the most appropriate treatment option in IBD is not always obvious. Therefore, patient preferences for treatment efficacy, potential adverse effects or surgery play an important part of clinical decision making. Understanding those preferences can have far-reaching consequences. For example, surgery in UC is thought of as an option of last resort or a product of medication failure. However, if it is found that UC patients view colectomy surgery as equivalent to long term use of immunosuppressants with their associated risks; or superior to incompletely effective medical therapy, then the conversations physicians have with UC patients as well as society-based practice algorithms may change. Likewise, as seen in CD, patients' preferences for risks of therapies in exchange for durable treatment efficacy can influence acceptability of these drugs including drug approval. Therefore, accurate assessment of patient preferences is important not only in understanding patients' goals in therapy but also in potentially setting benchmarks for therapy guidelines and therapies themselves.

It is clear that IBD patients do have preferences for medical and surgical therapies for their disease. The next challenge, therefore, is accurately describing and quantifying these preferences. Traditional methods of eliciting patient preferences such as SG and TTO have constituted the bulk of studies in IBD. And these studies have offered important insights, such as the discovery that post-surgical UC patients value their surgery after the fact more than they did prior to going to surgery. This has important implications in counseling UC patients who may be facing surgery but wary of its impact on quality of life.

However, clinical decision-making in IBD is more complicated than a single decisionnode. And failure to account for all the attributes that constitute a particular therapeutic option, or the alternative options, can lead to inaccurate assumptions regarding patient preferences for these decisions. For example, if a patient with active disease is facing surgery or life-long immunosuppressant therapy with its potential risks, it is possible that this patient may not discount the surgical alternative as greatly as previously judged using traditional methods of preference elicitation.

A more serious limitation of SG and TTO is the growing recognition that the fundamental axiom of these studies, namely the expected utility theory, may actually be violated in normal human preference behavior. This results in bias in preference assessment when utilizing these techniques. This violation of the expected utility theory has been recognized in economics for some time; but is increasingly appreciated when assessing preferences for health care. As a result, more rigorous methodologies, such as DCE, are being applied to assess preferences for health care, both goods and services. The realistic presentation of clinical scenarios with the ability to quantify maximum acceptable risks for treatment attributes and therapies allows DCE to uniquely handle the myriad of choices and risks facing IBD patients and evaluate preferences across a number of clinical outcomes and risk probabilities. As patient preference studies continue, it is easy to envision DCE studies evaluating a number of critical issues in IBD: how much risk of serious adverse events are UC patients willing to accept from immunosuppressants before they prefer surgical options for their disease? How much additional medication risk (from mono- or combination-therapy) are patients with CD willing to accept to avoid a relapse of their disease? What specific attributes of a medication therapy (injection versus infusion; frequency of dosing,

etc) make one medication preferable to another for a given efficacy? And how do these preferences change with age, gender, disease duration or other clinical features of IBD phenotype? One can easily see how the answers to such questions could facilitate not only interactions between patients and physicians in the office, but also how regulators and society as a whole view therapeutic strategies in IBD.

8. Conclusion

IBD patients face an increasing number of choices regarding care of their chronic illness. These choices range from mode and frequency of drug administration to preferences regarding types of serious potential risks to decisions regarding forgoing medical therapy in favor of surgical interventions. As a result of these increased choices, IBD patient preferences carry a growing importance in the decisions regarding their care, both at a personal and public policy level. Therefore, rigorous methodologies to evaluate patient preferences and willingness to accept risks are needed. SG and TTO have traditionally examined preferences in IBD care, but have inherent flaws that may bias their results. DCE offers the ability to provide systematic, quantifiable measurements of patient preferences, which in turn can inform physicians, surgeons, and public health policy regarding the care of this challenging disease.

Acknowledgments

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Key Points for Decision Makers

Accurately quantifying patient preferences for potential risks and benefits of therapy options is crucial in numerous clinical situations in IBD where no clear correct decision exists, and therefore patient preferences play a critical role in patient-centered decision-making.

Traditional estimates of health-state utilities have several important limitations that can render inaccurate estimations of patient preferences for therapies in IBD. Stated-preference methods, including discrete-choice experiments, employ a non-expected utility framework to more accurately assess patient preferences for overall therapies and therapy-specific attributes (including efficacy and averse effects), and represent a powerful tool to quantify preference data.
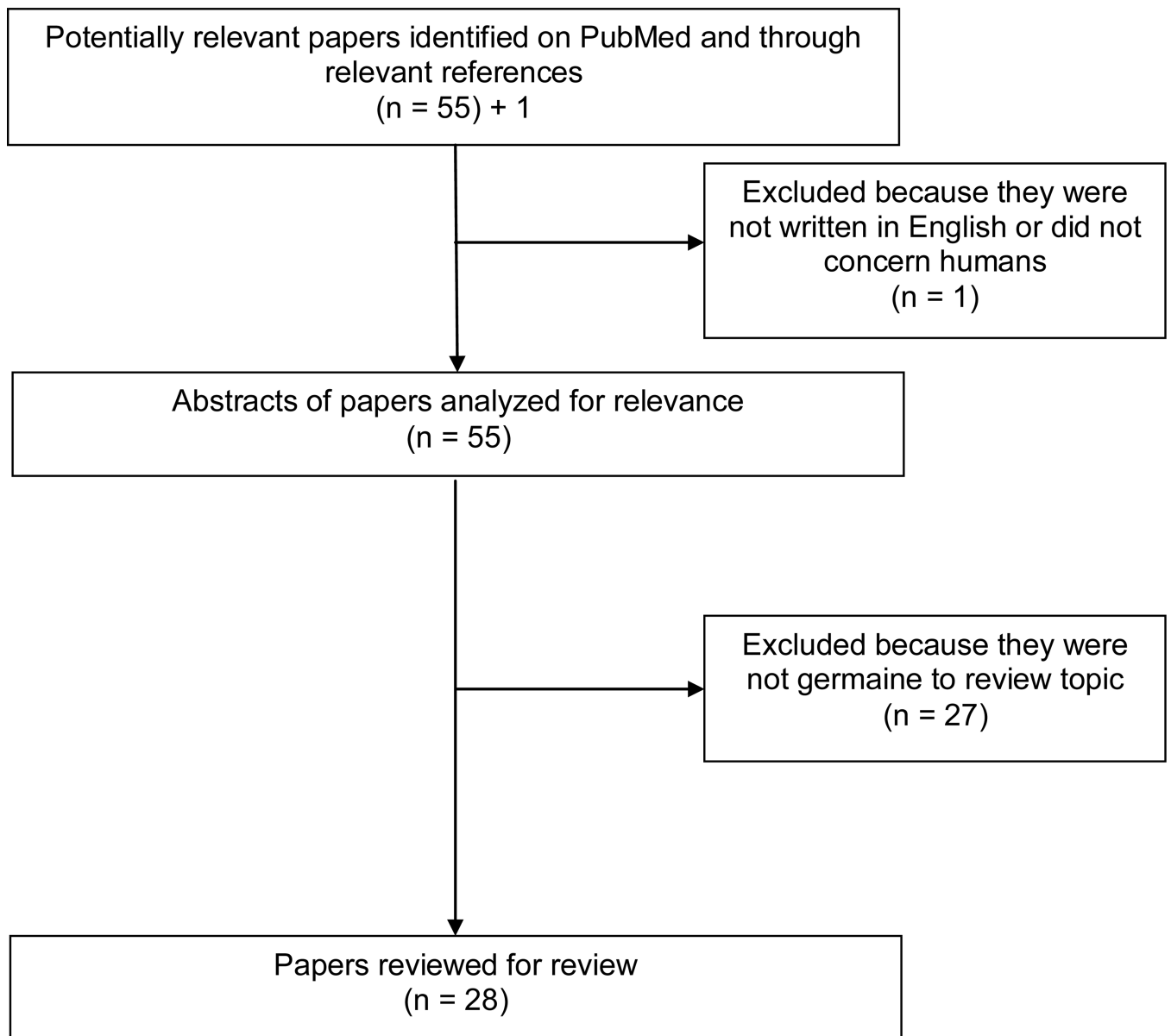
Figure 1.
Identification of Studies

Table I

Survey Studies of IBD Patient Preferences

Study	Study Population and Sample Size	Study Aim
Wong S et al.[82]	241 UC and CD patients	Evaluate the information needs and preferred mode of information delivery in patients with IBD
Conrad S et al.[83]	1056 UC and CD patients	Evaluate information needs, preferred sources of information and preferred role in decision-making
Bernstein KI et al.[84]	74 UC and CD patients (newly diagnosed)	Evaluate information needs and preferred method of information delivery for newly diagnosed IBD patients
Siegel CA et al.[85]	199 UC patients	Evaluate UC patients' perception of colon cancer risk and assess preferences for colectomy surgery in the setting of dysplasia
Baars JE et al.[86]	617 CD patients 450 UC patients	Evaluate IBD patients preferences regarding shared decision-making
Allen PB et al.[87]	125 UC and CD patients	Evaluate preferences for infliximab versus adalimumab
Lewis JR et al.[88]	30 UC and CD patients	Evaluate IBD patient preferences for genetic testing in IBD
Gray JR et al.[89]	100 UC patients	Evaluate patients preferences regarding therapies including efficacy, dosing frequency, cost, etc.
Knopf JM et al.[90]	22 IBD patients and their parents	To determine differences and similarities between pediatric patients and their parents with regards to decision-making
Kennedy ED et al.[91]	127 CD patients	Evaluate patient preferences for postoperative maintenance therapies
Konda V et al.[92]	82 CD patients 25 UC patients 7 other (presumably indeterminant)	Evaluate patient interest in genetic testing and willingness to accept uncertainty of these tests
Rutter MD et al.[93]	281 patients	Evaluate patient preferences and experience with colonoscopy surveillance in UC
Cheung WY et al.[94]	69 general practitioners caring for IBD patients	Evaluate physician preferences for open access outpatient follow-up for their IBD patients
Green TJ et al.[95]	76 CD 49 UC	Evaluate the dietary practices and effectiveness of these diets in pediatric IBD patients
Probert CS et al.[96]	70 UC and CD patients	Evaluate patient preferences for receiving information regarding their disease

Table II

Time trade-off (TTO) and standard gamble (SG) studies in IBD

Study	Study Type	Study Population and Sample Size	Study Aim
McLeod RS et al.[100]	TTO	20 pre- & post-colectomy UC patients 93 post-colectomy UC patients	Evaluate perceived quality of life by UC patients pre-colectomy and post-colectomy surgery
Kennedy ED et al.[101]	SG	65 CD patients	Determine if CD patients value absolute reduction in post-operative disease recurrence attributable to 5-ASA therapy[*]
Arseneau KO et al.[102]	SG	32 CD patients 15 non-CD patients	Determine utilities for CD patients for varying perianal fistula treatments[†]
Arseneau KO et al.[99]	TTO	48 UC patients	Determine utilities for steroid-refractory UC for colectomy versus varying medical therapy[†]
Byrne CM et al.[103]	TTO/SG	41 CD patients 92 colorectal surgeons 74 gastroenterologists	Compare preferences for surgical intervention in CD between patients, gastroenterologists and surgeons
Waljee AK et al.[104]	TTO	150 non-UC patients 150 UC patients 150 UC post-colectomy patients	Evaluate differences in utility of active UC versus post-colectomy state
Waljee AK et al.[105]	SG/TTO	150 UC patients 150 post-colectomy UC patients	Evaluate discount rate used by UC patients when evaluating colectomy
Brown LK et al.[106]	TTO	17 physicians 150 post-colectomy UC patients 69 moderate UC patients	Compare physician and patient preferences for active UC versus colectomy

[*] further discussion in letter to editor[107]

[†] utilities determined for Markov modeling

Table III

Discrete-Choice Experiment studies in IBD

Study	Study Population and Sample Size	Study Aim
Hodgkins P et al.[138]	400 UC patients	To determine preferences for 5-ASA therapy based on self-reported adherence
Johnson FR et al.[137]	315 gastroenterologists 580 CD patients	To measure and compare acceptability of medication risks and benefits between adult CD patients and gastroenterologists
Lichtenstein GR et al.[134]	252 CD patients	To determine treatment preferences for and relative importance of treatment attributes for CD
Johnson FR et al.[136]	345 CD patients > 18 years old 150 parents of CD patients < 18 years old	To measure and compare risk preferences for medical therapy between parents of juvenile patients and adult patients
Johnson FR et al.[135]	580 CD patients	To measure CD patients' willingness to accept serious adverse events in exchange for medication efficacy