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Patient Preferences for Surgical Versus Medical Therapy for Ulcerative Colitis

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Abstract

Background—Therapy options for mesalamine-refractory ulcerative colitis (UC) include immunosuppressive medications or surgery. Chronic immunosuppressive therapy increases risks of infection and cancer, whereas surgery produces a permanent change in bowel function. We sought to quantify the willingness of patients with UC to accept the risks of chronic immunosuppression to avoid colectomy.

Methods—We conducted a state-of-the-art discrete-choice experiment among 293 patients with UC who were offered a choice of medication or surgical treatments with different features. Random parameters logit was used to estimate patients' willingness to accept trade-offs among treatment features in selecting surgery versus medical treatment.

Results—A desire to avoid surgery and the surgery type (ostomy versus J-pouch) influenced patients' choices more than a specified range of 10-year mortality risks from lymphoma or infection, or disease activity (mild versus remission). To avoid an ostomy, patients were willing to accept a >5% 10-year risk of dying from lymphoma or infection from medical therapy, regardless of medication efficacy. However, data on patients' stated choice indicated perceived equivalence between J-pouch surgery and incompletely effective medical therapy. Patient characteristics and disease history influenced patients' preferences regarding surgery versus medical therapy.

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Conclusions—Patients with UC are willing to accept relatively high risks of fatal complications from medical therapy to avoid a permanent ostomy and to achieve durable clinical remission. However, patients view J-pouch surgery, but not permanent ileostomy, as an acceptable therapy for refractory UC in which medical therapy is unable to induce a durable remission.

Keywords

inflammatory bowel disease; IBD; DCE; maximum acceptable risk

Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD) that can be severely debilitating and has no medical cure. Historically, UC was treated with mesalamine and corticosteroids, and if these failed, surgical resection of the colon. Because UC is limited to the colon, surgery offers a theoretical “cure” and eliminates the risk of colon cancer. The 2 most common operations performed are a total proctocolectomy with end ileostomy and restorative ileal pouch anal anastomosis (IPAA). The former entails a permanent ileostomy, whereas the latter avoids this but is associated with frequent bowel movements and the risk of fecal incontinence.

The demonstrated efficacy of thiopurine analogues and antibodies against tumor necrosis factor α has improved our ability to induce and maintain remission. However, at least one-third of the patients will fail to produce a durable remission.[1–3] These patients will often be exposed to repeated or chronic corticosteroid therapy, which is associated with increased morbidity and mortality.[4–6] Furthermore, chronic immunosuppressant maintenance therapy risks serious and opportunistic infections,[4,7,8] and an increased the risk of certain cancers including lymphoma[9,10] and hepatosplenic T-cell lymphoma.[11,12]

If surgery for UC resulted in a completely normal quality of life, the choice between medical and surgical therapy would be obvious. Because this is not the case, physicians and their patients are willing to accept risks of medical therapies, often with the presumption that the patient’s foremost desire is to avoid surgery. However, for some patients, this may not be the case, and in an era that places an increasing premium on patient autonomy and shared decision making, quantifying risk preferences of patients with UC includes their voice in an increasingly complex decision process. Furthermore, quantifying patients’ risk threshold can help physicians, drug manufacturers, and regulators when contemplating appropriate indications for existing and new medical therapies. Previous studies evaluating preferences of patients with UC have been few and used methodologies that make numerous uncertain or inaccurate assumptions about patient preferences.[13,14] In this study, we used an innovative patient preference methodology called discrete-choice experiment (DCE) to quantify the tolerance of patients with UC for life-threatening serious adverse events (SAEs) in exchange for specific treatment benefits. We estimated the mean maximum acceptable risk (MAR) for SAEs associated with immunosuppressant therapy in UC that patients are willing to accept to avoid colectomy with ostomy, IPAA, or IPAA complicated by fecal incontinence. We also evaluated how clinical characteristics affect tolerance for medical therapy risks in preference to surgery.

MATERIALS AND METHODS

DCEs, also known as choice-format conjoint analysis, quantify the strength of preferences for features of products, services, or health care interventions and are increasingly being applied in the health sciences.[15–17] Interventions, such as medical or surgical treatments, derive value from their specific attributes, features, or outcomes including treatment efficacies and potential SAE risks. Each of these attributes can occur at varying levels, such as remission rates or SAE incidence. DCEs recognize that patients have preferences of varying strengths for different attributes and are willing to accept trade-offs among various levels. By systematically eliciting trade-offs among constructed outcome combinations, DCEs generate choice data to quantify implicit decision weights indicating relative utility or satisfaction that patients have for both individual attributes of a treatment (such as the specific risks and benefits) and the treatment as a whole. Because DCEs measure the rate at which patients accept trade-offs among different treatment attributes, it is possible to use these trade-off rates to scale a change in one attribute to equivalent units of another attribute. It is thus possible to calculate time, money, and risk equivalents of a given change in treatment options. In this study, we used estimated tradeoff rates to calculate the MAR as an indication of patients' willingness to accept medication-related SAE risks to avoid surgery.

Survey Development

A DCE survey instrument was developed using best-practice methods[18] to elicit patients' willingness to accept tradeoffs among therapeutic options regarding medical and surgical interventions for UC. The survey instrument assessed respondents' baseline demographics, current disease activity (using the Simple Clinical Colitis Activity Index and the 6-point Mayo score),[19,20] medication use history, and knowledge of colectomy surgery. Numeracy was assessed using test questions.

For the DCE scenarios, attributes were determined from a literature review, IBD expert consultation, focused interviews with patients with IBD, and a pilot study in 127 patients with UC. Based on this information, a decision frame was developed in which respondents assume a moderate to severe UC flare and must select either a new medication or surgery as treatment for the flare (Table 1). Medication treatment attributes included efficacy with levels of remission and incomplete response resulting in mild disease activity for 10 years, described using text from the Mayo score.[21]

Surgery was described as a 1-or 2-step process with a resultant permanent surgical remission. A permanent ostomy (single-stage operation) was described as having a surgical remission with no blood, abdominal pain, fatigue, or interference with job/daily activities and having bowel movements through the ostomy. Pictures of female and male patients with ostomy bags were shown. Two-stage (IPAA) surgery was described as resulting in an average 5 bowel movements per day but otherwise having similar disease activity symptoms as those having an ostomy. Incontinence also was described. All surgery was described as carrying a 1-in-3 chance of having difficulty becoming pregnant for female patients. Pilot testing indicated good understanding of the medical and surgical outcomes.

For nonsurgical options, a 0.3% risk of dying from colon cancer within 10 years was included.[22] Two SAEs were additionally considered. The risk of dying from lymphoma was only associated with selection of medication therapy; the risk of dying from a serious infection was associated with both medication therapy and surgery. Colorectal cancer, lymphoma and serious infections were described using layman terms based in part on descriptions from the American Cancer Society patient information.[23] For each of the SAEs, hypothetical risk levels ranged from 0% to 5% for experiencing the event within the next 10 years. Pretest interviews and pilot data indicated that this range yielded trade-off information required to quantify MAR. The 10-year time frame was determined to be appropriate during piloting and data collection/analysis from conceptual, methodological, and patient-cognitive perspectives. Pretests of the instrument found that 10 years allowed for magnification of annual risks to levels that could be described graphically and were sufficiently salient to induce trade-offs among other attributes.

To limit cognitive burden and numeracy concerns, all treatment benefits were described as certain and all treatment risks were described as known probabilities. To avoid measurement error in preference elicitation and analysis, specific risk levels (rather than ranges) were presented in keeping with best practice methods.[18] To further aid respondents understanding of quantitative risks, the SAE probabilities were presented in 3 ways: graphically as a risk grid of shaded circles indicating the number of patients out of a full grid of 1000 circles who would die from the SAE, and numerically as fractions (counts out of 1000) and percentages (Fig. 1).

The DCE questions in the final survey instrument asked patients to choose between a medication resulting in either complete remission or incomplete remission (i.e., mild disease activity) for 10 years or surgical therapy for their UC disease flare. Figure 1 is an example of the DCE question format. We used a variation of a commonly used algorithm in SAS to construct a D-efficient experimental design resulting in 48 pairs of treatment options.[24–28] To reduce respondent burden, the trade-off scenarios were blocked into 6 sets of 8 questions. Each participant was randomly assigned to receive 1 of the 6 sets of questions. Surveys were mailed using the Dillman method to maximize response rates.[29]

Survey Validation

The design of the DCE survey included tests for numeracy and an internal test for subject-level validity through logic testing. To assess numeracy, subjects were shown a series of numerical examples of risk, presented as percentages, fractions, and an illustrative risk grid, and subsequently tested on their understanding of these numeric concepts. Logic testing was assessed to evaluate if respondents understood the question choice format sufficiently to indicate a preference for a visibly better therapy through an additional trade-off scenario in which medication treatment dominated the surgical treatment for every attribute. The model was tested to evaluate the statistical influence of respondents who failed 1 or both of these tests.

Survey Sample

Patients were eligible if they were 18 years or older with an *ICD-9* code for UC (556.0–556.6 and 556.8–556.9) and an out-patient gastroenterology clinic visit at participating institutions within the previous 2 years. Patients with any *ICD-9* code for Crohn's disease (555.0–555.2 and 555.9) were ineligible. In the survey, patients were asked if they considered themselves to have UC; only respondents who further self-identified as having UC were included in the survey sample. All patients received a small financial compensation for their time and effort.

Statistical Analysis

In DCE studies, the pattern of choices by respondents observed reveals the implicit decision or preference weights respondents used to evaluate the hypothetical treatment tradeoffs. Multivariate random parameters logit was used to estimate preference weights for each attribute level while avoiding potential estimation bias in choice models from unobserved variation in preferences not accounted for by the variables in the model.[30,31] Both a mean value and taste distribution SD parameter are estimated for each preference weight. A flexible correlation structure also accounts for within-sample correlation in the question sequence for each participant.

Effects coding was used so that the mean effect of each attribute is normalized at zero instead of setting all the omitted categories to zero. The omitted-category parameter is the negative sum of the included-category parameters for each attribute. This provides parameter estimates for every attribute-level preference weight, avoids confounding the grand mean with marginal effects, and facilitates subsequent calculations. T-statistics thus are interpreted relative to the mean effect rather than the omitted category.

The resulting mean preference weights are used to estimate the MAR, defined as the specific increase in treatment risk that exactly offsets the therapeutic benefit of a given improvement in treatment outcomes. For example, consider a medication A that has a measured therapeutic benefit $\beta_1 = 0.5$ (versus surgery), and a value of $\beta_i = -0.025$ for each 1% increase in infection risk. The MAR for medication A is the increased risk of infection that exactly offsets the increase in satisfaction from preserving one's colon. Since offering medication A increases patients' satisfaction by 0.5 versus surgery, if medication A increases the risk of infection by 0.5/0.025 = 20%, then the increased infection risk exactly offsets patients' perceived satisfaction from avoiding surgery. However, if medication A increases the risk of infection by <20%, then patients would be better off with medication A than with surgery. In practice, risk levels are fit to a generalized nonlinear function to use all information regarding the shape of the response gradient when determining the level of risk that makes the mean preference weight = 0 between categorical risk-level parameters.

In our model, certain attributes were applicable only to the medication or surgical therapy option. Furthermore, the surgical therapy option was inherently different from the medication therapy option. Interaction terms and constraints in the model account for and measure the effect of surgery versus medical therapy in choice preferences for attributes. The goal of the survey instrument was to calculate respondents' willingness to trade off risk

of SAE for improvements in UC symptoms through either medical or surgical therapy by calculating the MAR which respondents were willing to accept from a given medical therapy of specified efficiency to avoid a specific surgical outcome. Comparisons were made of the MARs for the lymphoma and serious infection SAEs in exchange for treatment efficacy to avoid surgical outcomes of an ostomy, a J-pouch with incontinence, and a perfectly functioning J-pouch. When computation of MAR required extrapolation beyond the upper level of risk presented in the survey, we report risk tolerance as greater than the level of risk shown.

Overall joint tests of parameter differences used the scale-controlled likelihood-ratio test for choice models.[32] Tests of differences of MARs used 2-tailed z-tests for differences of means for independent, normally distributed random variables. Statistical differences between individual parameter estimates were tested using maximum likelihood asymptotic 2-tailed tests at the 95% confidence level. Subgroup analysis was performed using an effects coded model that included an interaction term with the most preferred parameter to maximize the statistical power of the subgroup models. SAS 9.2 was used for data management and tables. Limdep/NLOGIT 7.0 was used for statistical modeling.

Ethical Considerations

The study and final survey instrument were approved by the institution review boards at participating institutions.

RESULTS

Survey Population

Survey instruments were mailed to 662 patients and responses were received from 374 patients (56% response rate). We had limited information on nonresponders, but men were less likely to respond (data not shown). Eight respondents (3%) answered the numeracy questions correctly but failed a test scenario in which there was a clearly dominated treatment choice. Given the small number and their appropriate response to the numeracy questions, these patients remained in the analyzed final sample. After applying the exclusion criteria and excluding patients with missing answers to conjoint questions, 293 respondents were included in the final analysis (Fig. 2). Baseline demographics are shown in Table 2. Notably, most of the respondents was highly educated and had a long-standing history of UC. Over half were in a remission as defined using the SSCAI or 6-point Mayo score. Most of the respondents had previously or was currently taking an immunosuppressant medication, inclusive of thiopurine analog, calcineurin inhibitor, methotrexate, and/or anti-TNFα (Table 2).

Preference Weights

Analysis of respondents' preference weights for the varying levels of mortality from lymphoma or serious infection over 10 years indicated a relatively steep decrease in DCE utility for all attributes when going from 0% to 0.5% risk compared with equivalent increments in levels of risk beyond 0.5% (Figure 3A). This result is inconsistent with the conventional preference elicitation methods that assume linear preferences across

probabilities and indicate that participants perceived a much larger decrease in utility from going from “no risk” to “some risk” (such as 0.5%) than they did from moving from “some risk” to “some additional risk” (such as 2% or 5%). Other researchers have identified similar risk-preference nonlinearities in non-health and health applications.[14,33]

Figure 3B shows the relative preference weight estimates for the risk attributes and medication efficacy. The estimated preference weights for risks and efficacies are consistent with the natural ordering of the levels. The largest effect on DCE utility was for the difference between a J-pouch and ostomy when the participant selected the surgery option: no other change in risk levels was comparable with the perceived benefit of avoiding an ostomy when surgery was chosen as the preferred therapy for a UC flare. This difference in surgery type—J-pouch versus ostomy—influenced patients’ choices more than the risk of dying from lymphoma or serious infection or medication efficacy over the ensuing 10 years when the medical therapy was chosen. At the other extreme was medication efficacy: the difference between a medication-induced remission and an incompletely effective medication that only improves disease activity to a mild state was roughly equivalent only to the difference between a 0% risk of lymphoma and a 0.5% risk. Thus, on average, patients were willing to accept a 0.5% increase in risk of dying from lymphoma over 10 years if the medication put them in a complete remission. However, if the risk of lymphoma mortality over 10 years were higher, patients preferred a less effective medication with 0% risk of lymphoma.

The mean MAR estimates of tolerance for SAE mortality risks respondents were willing to accept for better surgical or medication outcomes are shown in Table 3. To avoid having an ostomy, patients were willing to accept >5% risk of dying from lymphoma over 10 years even if the medication was incompletely effective. In contrast, patients were willing to accept only a 1%–1.6% risk of death from lymphoma or serious infection for improved medication efficacy. Patients were less tolerant of medication risk if the surgical outcome was a J-pouch, and remarkably, patients were equally satisfied with J-pouch surgery as with an incompletely effective medical therapy that left them with mild disease symptoms over 10 years (Table 3).

Effect of Covariates on Benefit–Risk Tradeoff Preferences

Subgroup analysis was performed using an effects coded model and implementing an interaction on the most preferred parameter (Fig. 4). Disease duration, time from last flare (<3 mo), and disease activity overall (including those reporting having had a flare as bad or worse than the one described in the presented scenario, i.e., moderate to severe flare) had no impact on preferences for surgical versus medical therapy. We further evaluated those in a remission defined by a Simple Clinical Colitis Activity Index score <2.5 versus those with active disease (defined by a Simple Clinical Colitis Activity Index score ≥2.5) and found no significant differences in preferences for surgery versus medical therapy. We also specifically evaluated those patients with UC reporting a prolonged remission (>1 yr) and in whom likely the only surgery decisions would be made in the event of dysplasia but found no differences in preferences for surgical and surgical outcomes versus medical efficacy and risks (data not shown). There was a small subgroup of patients currently on

immunosuppressant therapy who reported current active disease symptoms (n = 23), thus representing a compelling sample of patients facing possible surgery. Compared with those not on immunosuppressant therapy, these patients were less willing to accept ostomy surgery ($P = 0.04$) but also less willing to accept the risk of lymphoma with medical therapy ($P = 0.03$). These findings are consistent with our overall findings of equivalent satisfaction with J-pouch surgery (but not ostomy) in the face of ineffective medical therapy and seem to indicate an influence of disease history on risk tolerance.

Desire to have children did not influence the preference for surgical versus medical therapy, but females were significantly less willing to accept ostomy surgery ($P = 0.03$). Previous knowledge of the attributes did influence preferences: patients with either personal or first-hand knowledge of colectomy surgery were more willing to accept surgery overall ($P = 0.002$) and less willing to accept ineffective medical therapies ($P = 0.007$). Those with first-hand knowledge of serious infection, colon cancer, or lymphoma were also more willing to accept surgery overall ($P = 0.006$), although they were also less willing to accept ostomy as an outcome ($P = 0.02$). Additionally, those patients who had discussed surgery with a surgeon or physician were significantly more willing to accept surgery overall ($P = 0.03$).

Impact of Numeracy Skills on Results

Twenty-nine patients (9%) failed 1 or more of the numeracy tests. These patients were excluded from the overall sample of 293 and assessed separately. This group was significantly older than the baseline sample (median age 70 yr), and 21% were African American or described their race/ethnicity as “other.” Fifty-four percent had a high-school/General Education Development (GED) education or less; only 22% had a 4-year college or higher education. More were prior smokers (58%) and fewer (39%) had never smoked. Finally, a large percentage (83%) stated they had never discussed surgical options for their UC with a surgeon or physician, and this low-numeracy group expressed a stronger preference to avoid surgery compared with the remainder of the population ($P = 0.02$, data not shown).

DISCUSSION

To our knowledge, this is the first study using DCE to quantify patients’ trade-off preferences for life-threatening adverse medication risks, surgical options, and symptom relief in UC. Using DCE, we found that patients were willing to accept high levels of serious adverse risk from medical therapy to avoid an ostomy. However, patients also valued medication efficacy; indeed, if a durable clinical remission could not be achieved with medical therapy, patients were equally satisfied with J-pouch surgery. To our knowledge, this is the first empirical demonstration that patients with UC without previous surgery view a well-functioning J-pouch as equivalent to persistent mild disease activity.

Our results have several important implications. First, patients expressed a willingness to accept trade-offs among treatments of varying efficacies, risks of associated SAEs, and surgical options in their responses to the DCE scenarios. As expected, patients’ choices indicated a systematic preference for lower risk of SAEs and improved medication efficacy. However, the preference to avoid surgery or SAEs outweighed concerns regarding

medication efficacy. During piloting, one-on-one interviews elicited a repeated sentiment that a disease flare associated with corticosteroid use was “acceptable” because it was a previously experienced risk, whereas the risks of a lymphoma, serious infection, or surgery were much less familiar. The sentiment that rarer or poorly understood risks are worse than more familiar risks is a well-studied phenomenon, and the consistency of our results with this literature supports the face validity of our findings.[34]

Second, patients expressed a willingness to accept extremely high risks of SAEs to avoid a permanent ostomy or complications of a J-pouch. However, not all surgical options were so strongly disregarded in preference for medical therapy: patients with UC were equally satisfied with an uncomplicated J-pouch surgery because they were with medical therapy, especially if that medical therapy was incompletely effective in maintaining a sustained remission (normal number of daily stools without blood or abdominal pain and a good functional status without interference with work/daily activities) for 10 years. To the best of our knowledge, this is the first documentation of such a finding in UC.

Our study’s finding that patients with UC are willing to accept surgery as a treatment option for their disease is novel and has several important implications. First, it highlights that patient preferences can vary significantly from providers’ assumptions regarding these preferences. Current treatment algorithms have rested on the assumption of UC patients’ aversion to all surgical options, and indeed, previous conventional risk assessment in UC supported this finding.[13,35–38] Our findings underline the need for rigorous methodologies to accurately measure patient preferences and present several potential areas for further inquiry regarding preferences of patients with UC for their disease. As noted below, these findings and our methodological approach also have implications for diseases beyond UC, where physicians often make assumptions about patient preferences for risks and therapies in the absence of guiding data.

Second, our study illustrates a critical unmet need in treatment discussions in patients with UC. Shared decision making and informed consent have increasing importance in the changing treatment algorithms for IBD.[39] Most of the gastrointestinal providers will escalate medical therapy for their patients with UC due to failure of mesalamine to ensure a durable remission.[40,41] However, our survey indicated that approximately 50% of patients with UC had never discussed surgical options for their UC with either a medical or surgical physician, including 39% of patients with current or previous immunosuppressant therapy use (data not shown). Despite this, nearly 75% of our population indicated they felt they understood their surgical options very well or had minimal questions regarding surgery for UC (data not shown), indicating attainment of information from sources outside of their IBD care providers. Therefore, our findings that patients with UC overall were willing to accept J-pouch surgery when faced with incompletely effective medical therapy clearly indicates a potential unmet need in treatment discussions in patients with UC by all providers. Given the low surgery discussion rate in our sample, our findings could also underestimate UC preferences regarding surgical therapy, which may further bolster the importance of both discussions with patients and the acceptability of surgical options.

Finally, this finding has important implications for testing efficacy of novel therapies. These data suggest that for a medication to be preferred over J-pouch surgery, it needs to achieve sustained remission and not just a clinical response. As such, remission may be the preferred outcome for testing efficacy of new therapies.

We also found that clinical history did influence preferences for therapies, including current and previous disease course, gender, knowledge of the attributes, and discussion of surgery with a care provider. It is important to note, however, that the study design was not powered for precise subgroup analysis (as indicated by some large but nonsignificant ratios in the subgroup analysis; Fig. 4). Given the variable distribution of potential clinical characteristics, it is possible that other meaningful differences could not be discerned.

DCE has significant advantages over other approaches to preference assessment. Simple survey instruments that ask patients for their willingness to take medications fail to take into account alternative therapies or outcomes if the therapy is not taken. Simple Likert scale questions on the importance of separate interventions or outcomes do not provide data on clinically relevant trade-off evaluations required in actual treatment decisions. DCE mimics such actual decision making by requiring respondents to evaluate trade-offs in a realistic, although hypothetical, choice context. Alternative techniques such as standard gamble or time trade-off elicit preferences for clinically unrealistic trade-offs and assume that preferences are linear in time, linear in probabilities, and identical across groups of patients, not allowing for health history or current health state to affect the relative importance of outcomes. Our current study has shown that such assumptions are inaccurate for patients with UC.

Our results are subject to several potential limitations and qualifications. DCE is a simulated decision-making experience using hypothetical therapeutic options and therefore does not have the same medical, emotional, and financial consequences of actual therapeutic decisions in real clinical settings. However, the question posed in our experiment is a real decision that patients and physicians do make each time they choose between medical and surgical therapy for the treatment of UC. Additionally, the clinical decision of medical versus surgical therapy is often constrained in real clinical settings by limitations imposed by physicians, regulators, and insurance providers (as illustrated in our findings that more than half of surveyed patients had not discussed surgical options with their physician). DCE provides a more rigorous methodology and more accurate assessment of patient preferences for all potential therapy options and their attributes. DCE is also more clinically realistic, a quality we sought to maximize through a series of patient-level interviews and intense piloting. Our internal validity indicates that surveyed patients demonstrated a high level of attentiveness to the choice questions asked of them, with preferences revealing good internal consistency and face validity. To the extent that such analyses of patient preferences are used by physicians, manufacturers, regulators, national organizations, and patient advocacy groups, DCE represents the most rigorous assessment of these preferences.

The exercise of evaluating trade-offs among multiple therapy options with multiple endpoints may be cognitively challenging. However, we assessed the validity in participant responses through numeracy and logic tests, and most of our respondents (>90%) passed

these evaluations. In particular, our study population had extensive experience with UC, was well educated overall, and included a large proportion with personal knowledge of many of the attributes, thus strengthening the validity of their preferences of choice options in the DCE survey. However, in our study, those participants who failed the numeracy examinations had essentially uninterpretable results. Therefore, extrapolation of our results to low-numeracy populations should be done with caution.

Our patients were seen by a variety of physicians from tertiary- care centers, and the majority had escalated medical therapy. Although this may limit generalizability, our sample would seem to typify the patient with UC who has exhausted 5-ASA therapies and now faces decisions regarding immunosuppressant use versus surgery for further UC flares. Many of these patients are seen by community and local practices; thus, our findings have applicability beyond referral centers.

Both SAEs associated with medical therapies and surgical outcomes are probabilistic in the real clinical setting. However, in piloting, including conditional probabilities (the probability of an SAE conditional on the probability of having the outcome) led to significant patient confusion. This was likely related to known difficulties with conditional probability numeracy skills in the general population. Therefore, to minimize this bias, we presented surgical outcomes as certain and presented SAEs as mortality associated with the SAEs. Our estimates therefore cannot be interpreted as MARs for uncertain benefits or outcomes at the individual patient level, and therefore must be interpreted with caution. However, we sought to evaluate the MARs over the a plausible distribution of potential SAEs related to medical therapy, or over the potential distribution of surgical outcomes, so that despite these simplifying assumptions, these aggregate estimations may be informative for decisions regarding benefit–risk trade-offs for populations of patients with UC.

Similarly, the outcome of pouchitis is a conditional outcome of J-pouch surgery and is further conditional in its chronicity, with some having an isolated episode, whereas others have a more chronic course. To avoid such complicated calculations, we chose not to include the risk of pouchitis as an attribute. However, we did include incontinence which may serve as a surrogate for some of the clinical symptoms of pouchitis (including bowel frequency and incontinence). To the extent that fear of pouchitis might dissuade patients from having pouch surgery, the MAR for infection and lymphoma relative to pouch surgery could be viewed as underestimates. However, for these patients, incontinence would be expected to be a worse outcome than pouchitis, and therefore the estimated MAR for J-pouch surgery with pouchitis can be extrapolated to fall between incontinence and a perfectly functioning J-pouch.

We did not evaluate preferences for possible mild side-effects associated with medical therapy. Although one could envision preferences regarding the milder or common side effects associated with particular immunosuppressant therapies, we aimed in our study to describe a generic immunosuppression medication for interpretation of the overall choice of escalation of medical therapy versus surgery.

Our attributes were within a 10-year time horizon for both risk and efficacy. This helped to avoid requiring respondents to interpret extremely small probabilities. Furthermore, when medical therapies such as thiopurines or anti-TNF therapy are initiated, the plan typically calls for chronic therapy as long as the medication remains effective. Similarly, colectomy is irreversible. Although assuming that UC would remain in remission or mildly active for the full 10 years is an oversimplification of the natural history of medically treated UC, one can view these results as if the average disease activity was mildly active or inactive for the 10-year period. Thus, the 10-year time horizon presented in this discrete choice model provided for improved patient understanding and was consistent with the time frame appropriate for the clinical decision.

In conclusion, we have applied a novel methodology to quantify treatment preferences of patients with UC patients' with striking findings. Patient preferences are most strongly impacted by the type of surgical outcome: patients are willing to accept medications that have relatively high risks of fatal complications to avoid a permanent ostomy or incontinence. Our findings therefore lend quantifiable evidence that support current treatment paradigms that involve pursuance of medical therapies to avoid these surgical outcomes. This rigorous methodology also can aid regulators in understanding patients' evaluation of the risk of SAEs for future medical therapies in the context of potential therapeutic benefit.

Even more striking, however, patients with UC are equally satisfied with an uncomplicated J-pouch because they were with a medication that has very small risks of fatal complications or a medication that is incompletely effective at sustaining a durable clinical remission. Traditionally, clinical trials of new therapies have evaluated 2 endpoints—clinical response and clinical remission. Our findings indicate that when evaluating new therapies or therapeutic algorithms, the primary outcome should be a clinical remission rather than a clinical response. Given that patients are equally satisfied with surgery as with mild disease activity, and the goal of medical therapy was to achieve greater patient satisfaction than with surgery, our findings also indicate a critical unmet need to improve physician–patient communication regarding realistic expectations of medical and surgical therapies.

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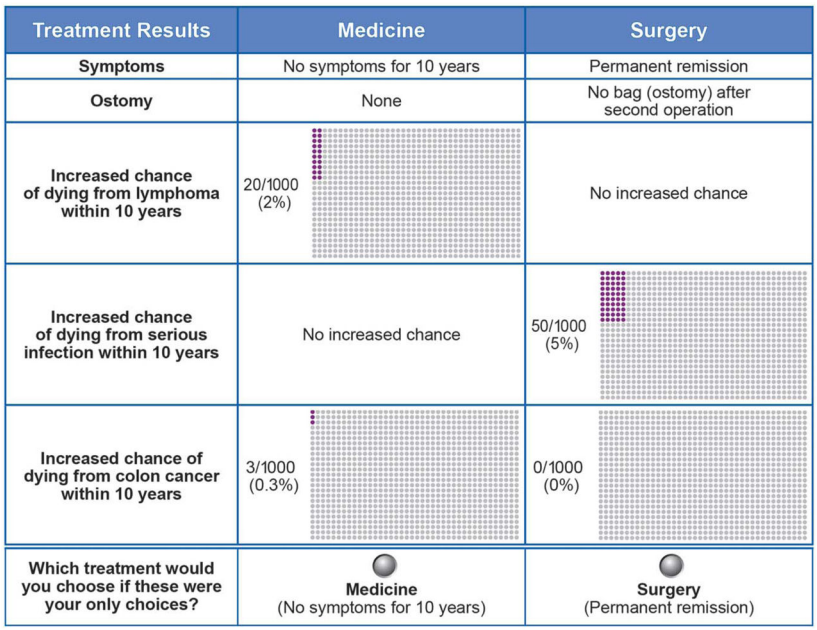

FIGURE 1.

Example of conjoint scenario comparing medication and surgical therapy for UC flare.

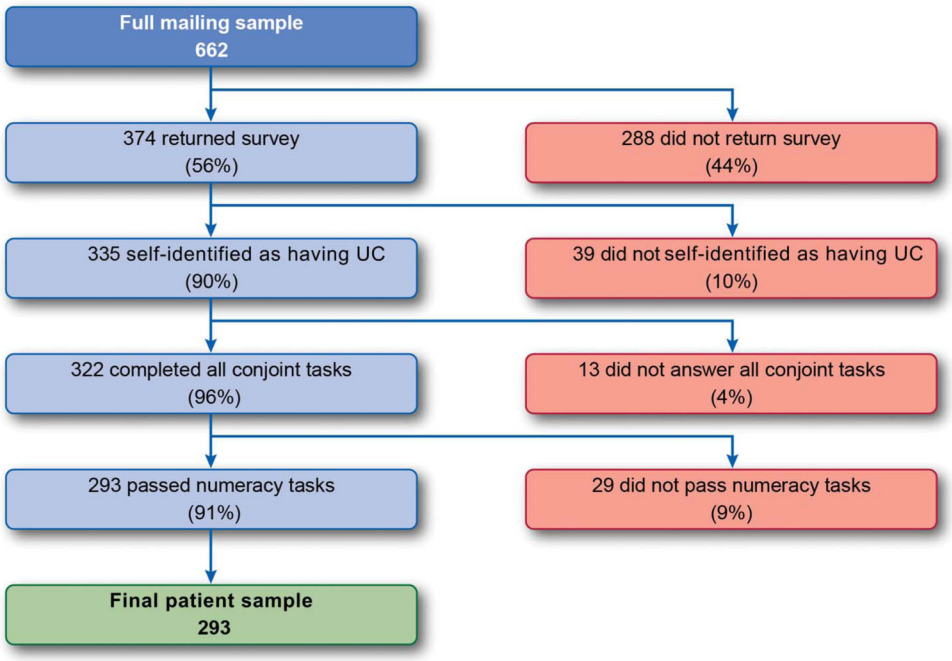

FIGURE 2.
Identification of final patient population.

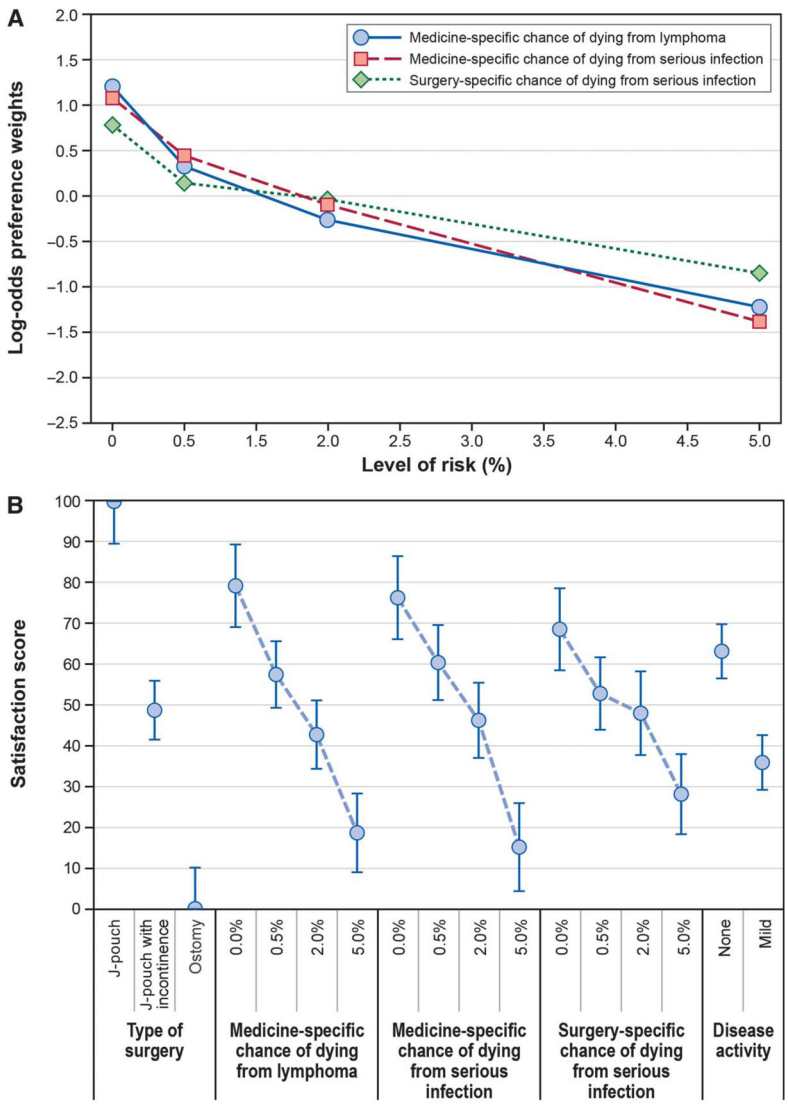

FIGURE 3.

A, Preference weights for varying levels of mortality from lymphoma or serious infection over 10 years. B, Relative preference utility for risk attributes and medication efficacy. The vertical axis shows relative utility/satisfaction (scores scaled between 0 and 100, with 0 corresponding to the smallest satisfaction score across treatment attributes and 100 corresponding to the largest satisfaction score) and the horizontal axis the varying levels of the attributes. Illustrated satisfaction scores at each level of risk take into account the significantly increased preference utility associated with selecting medical therapy in preference of any type of surgery (e.g., satisfaction scores for J-pouch without incontinence are conditional on selecting surgery).

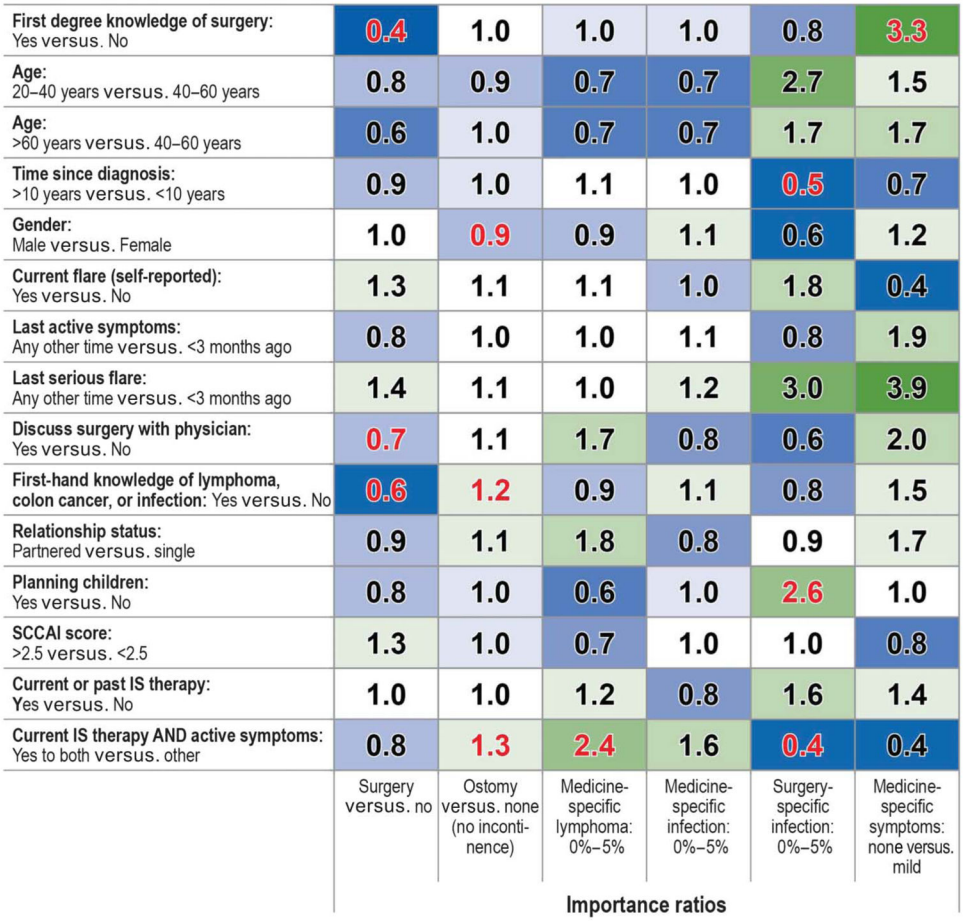

FIGURE 4.

Subgroup analysis of preference utility ratios. Labels on the horizontal axis indicate group A and group B; ratios are interpreted as (attribute importance of group A)/(attribute importance of group B). Numbers <1 and shaded in blue indicates that group A views the option as less important than group B. Numbers >1 and shaded in green indicate that group A cares relatively more than group B about the attribute. Color saturation indicates the distance from 1 relative to other ratios in the figure. Numbers in red indicate a statistically significant difference ($P < 0.05$). Thus, an example would be for those patients who have had a history of surgery versus those who have not, these patients are significantly less concerned with having surgery but are over 3 times more concerned with having a disease remission.

TABLE 1

Treatment Attributes and Levels

Treatment Attribute	Levels
Disease activity	
All patients were asked to assume a constant reference condition of a moderate to severe disease flare defined as: 3–4 stools more than normal per day, obvious blood with stool most of the time, abdominal pain (with or without bowel movements), generally feeling unwell most of the time, difficulty going to work or carrying out normal activities most of the time	Surgical remission (permanent; see surgery attribute)
	Medical remission (for 10 yr)
	Normal number of stools per day
	No blood seen
	No abdominal pain
	Generally feeling well
	No interference with work or normal daily activities
	Mild disease activity (medication only; for 10 yr)
	1–2 stools more than normal per day
	Streaks of blood with stool less than half the time
	Having abdominal pain (with or without bowel movements) a few times each day
	Generally feel unwell 25% of the time
	Having difficulty going to work or carrying out normal activities 3 d per month
Surgical outcomes (surgery option only)	IPAA; IPAA with incontinence during day or night; permanent ostomy bag
Increased chance of dying from colorectal cancer within 10 yr	Medication: 0.3% Surgery: 0%
Increased chance of dying from lymphoma within 10 yr	Medication: 0%, 0.5%, 2%, 5% Surgery: 0%
Increased chance of dying from serious infection within 10 yr	Medication: 0%, 0.5%, 2%, 5% Surgery: 0%, 0.5%, 2%, 5%

TABLE 2

Summary of Patient Characteristics[a]

Characteristic	Patients (N = 293)
Gender, n (%)	
Female	166 (57)
Male	127 (43)
Age, yr	
Median	45
Mean	47
Site, n (%)	
Dartmouth-Hitchcock Medical Center	20 (7)
Hospital of the University of Pennsylvania	273 (93)
Ethnicity/race, n (%)	
Caucasian	256 (87)
African American	17 (6)
Asian	9 (3)
Latino	2 (1)
Other	4 (1)
Highest level of completed education, n (%)	
Less than high school	1 (<1)
High school or equivalent	32 (11)
<4 yr of college	59 (21)
4-yr college degree (e.g., BA, BS)	91 (32)
Post graduate studies	99 (35)
Marital status, n (%)	
Single/divorced/widowed	94 (33)
Married	189 (67)
Desire for children, n (%)	
Would like to have children in future	80 (28)
No desire/plans to have children in future	202 (72)
Smoking status, n (%)	
Current smoker	15 (5)
Past smoker	105 (38)
Never smoked	160 (57)
Length of time with UC	
≤1 years, n (%)	293 (100)
Mean, yr	13
Median, yr	10
Currently having active UC symptoms, n (%)	75 (27)
When last active UC symptoms were experienced, n (%)	
Currently or within last 3 mo	70 (25)
3–6 mo ago	38 (14)

Characteristic	Patients (N = 293)
6 mo to 1 year ago	41 (15)
>1 year ago	131 (47)
Simple clinical colitis activity index <2.5	56%
6-point Mayo score <1.5	64%
5-ASA (oral and/or rectal)	
Current use	57%
Past use	83%
Corticosteroids (oral and/or rectal)	
Current use	10%
Past use	70%
Azathioprine/6-MP	
Current use	16%
Past use	29%
Cyclosporine and/or tacrolimus	
Current use	2%
Past use	2%
Methotrexate	
Current use	<1%
Past use	3%
Anti-TNF therapies (infliximab, adalimumab, certolizumab)	
Current use	15%
Past use	22%
Current or past immunosuppressant use (azathioprine, 6-MP, cyclosporine, tacrolimus methotrexate, anti-TNF)	54%
Personal history of serious infection requiring hospitalization	19%
Knew family member and/or friend with serious infection requiring hospitalization	23%
Personal history of colorectal cancer	1%
Knew family member or friend with colorectal cancer	36%
Personal history of lymphoma	2%
Knew family member or friend with lymphoma	19%
Personally had history of bowel surgery with ostomy	13%
Knew family member or friend with ostomy bag	17%
Never discussed surgical options with medical or surgical physician	51%
Believe colonoscopies will prevent colorectal cancer	74%

[a] Missing data excluded for each category.

TABLE 3

Maximum Acceptable 10-Year Serious Adverse Event Risk (MAR) for Selected Treatment Benefits to Avoid Surgery

Initial Health State	Final Health State	Lymphoma[a] Mean MAR (Lower Bound, Upper Bound)	Serious Infection[a] Mean MAR (Lower Bound, Upper Bound)	To Avoid[b]
Moderate	Medicine with remission	1.04% (0%, 4%)[c]	1.61% (0%, 4%)[c]	J-pouch
Moderate	Medicine with mild symptoms	0.00% (0%, 1%)[c]	0.00% (0%, 1%)[c]	J-pouch
Moderate	Medicine with remission	>5%[d] (4%, >5%)	>5%[d] (4%, >5%)	J-pouch with incontinence
Moderate	Medicine with mild symptoms	3.73% (1%, >5%)	3.93% (2%, >5%)	J-pouch with incontinence
Moderate	Medicine with remission	>5%[d] (>5%, >5%)	>5%[d] (>5%, >5%)	Ostomy
Moderate	Medicine with mild symptoms	>5%[d] (>5%, >5%)	>5%[d] (>5%, >5%)	Ostomy

[a] 10-yr risk of death from lymphoma/infection.

[b] Surgical options assume a mean 10-yr surgery-associated infection mortality risk of 1.87%.

[c] Lower bounds could not be less than 0%, indicating non-significant findings.

[d] All MARs >5% indicate extrapolations outside the range of risks evaluated in the trade-off questions.