# Variation Among Patients With Crohn's Disease in Benefit vs Risk Preferences and Remission Time Equivalents

Meenakshi Bewtra,[*,‡,§] Shelby D. Reed,[‖] F. Reed Johnson,[‖] Frank I. Scott,[*,¶] Erin Gilroy,[*] Robert S. Sandler,[#] Wenli Chen,[#] and James D. Lewis[*,‡,§]

*Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, Pennsylvania; ‡Division of Gastroenterology, University of Pennsylvania, Philadelphia, Pennsylvania; §Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, Pennsylvania; ‖Duke Clinical Research Institute, Duke University, Durham, North Carolina; ¶Division of Gastroenterology, University of Colorado Anschutz Medical Campus, Aurora, Colorado; and #Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

**BACKGROUND & AIMS:** **Patients with Crohn's disease (CD) must make decisions about their treatment. We aimed to quantify patients' preferences for different treatment outcomes and adverse events. We also evaluated the effects of latent class heterogeneity on these preferences.**

**METHODS:** **An online stated-preference survey was completed by 812 individuals with CD in the Crohn's and Colitis Foundation Partners cohort (IBD Partners). Patients were given information on symptoms and severity of active disease; duration of therapy with corticosteroids; and risks of serious infection, cancer and surgery. Patients were asked to assume that their treatment was not working and to choose an alternative therapy. The primary outcome was remission-time equivalents (RTE) of a given duration of symptom severity or treatment-related risk. Latent class choice models identified groups of patients with dominant treatment-outcome preferences and associated patient characteristics with these groups.**

**RESULTS:** **Latent class analysis demonstrated 3 distinct groups of survey responders whose choices were strongly influenced by avoidance of active symptoms (61%), avoidance of corticosteroid use (25%), or avoidance of risks of cancer, infection or surgery (14%) when choosing a therapy. Class membership was correlated with age, sex, mean short CD activity index score and corticosteroid avoidance. RTEs in each latent class differed significantly from the mean RTEs for the overall sample, although the symptom-avoidant class most closely approximated the overall sample.**

**CONCLUSIONS:** **In an online survey of patients with CD, we found substantial heterogeneity in preference for medication efficacy and risk of harm. Physicians and regulators should therefore not assume that all patients have mean-value preferences—this could result in significant differences in health-technology assessment models.**

*Keywords:* Anti-TNF; Discrete Choice Experiments; Biologic; Corticosteroids.

Traditionally, regulators and physicians have been responsible for evaluating therapeutic benefit-risk tradeoffs of medications, with regulators responsible for approving drugs for marketing and physicians for the decision of to whom to prescribe the drug. Because treatment decisions directly affect patients, there is increasing support, including from the Food and Drug Administration, for explicitly incorporating patients' evaluations of the relative benefits and risks of medical technologies in regulatory and clinical decision-making.[1]

Heterogeneity in patients' preferences may also impact clinical practice. The degree to which patients' preferences contribute to substantial variability in care among patients with Crohn's disease (CD) has not been well studied.[2,3] These patients often face difficult treatment decisions. One such decision is the choice between taking repeated short courses of corticosteroids, with a number of potential serious adverse events (SAEs) including increased serious infection risks and increased mortality,[4] or corticosteroid-sparing agents such as anti-

*Abbreviations used in this paper:* CD, Crohn's disease; CI, confidence interval; DCE, discrete choice experiment; IBD, inflammatory bowel disease; QALY, quality-adjusted life-years; RTE, remission-time equivalents; SAE, serious adverse event.


1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2019.05.010

TNF agents, anti-integrins, thiopurines, or methotrexate for a longer term. Growing evidence supports earlier initiation of steroid-sparing drugs and accelerating treatments as needed to achieve both symptomatic and endoscopic remission; however, these therapies have their own associated risks.[5,6] Patient-centered preferences about the relative risks and benefits of these treatment options have not previously been measured.

Here, we quantified variability in patients' preferences around CD symptom severity and duration, steroid use and key adverse outcomes of cancer, serious infection, and surgery through latent class analysis of choice-experiment data obtained from a web-enabled survey.[7] We hypothesized that patients would have very different treatment preferences and understanding driving forces for these preferences will assist physicians in counseling patients regarding the tradeoffs among different treatment strategies and tailoring treatment decisions that align with patients' preferences.

### What You Need to Know

#### Background

We aimed to quantify preferences of patients with Crohn's disease (CD) patients for different treatment outcomes and adverse events. We also evaluated the effects of latent class heterogeneity on these preferences.

#### Findings

In an online survey of patients with CD, we found substantial heterogeneity in preference for medication efficacy and risk of harm. We demonstrated 3 distinct groups whose preferences for CD treatments were strongly influenced by 1) avoidance of disease activity, 2) avoidance of corticosteroids, and 3) avoidance of therapy risks.

#### Implications for patient care

Physicians and regulators should not assume that all patients with CD have mean-value preferences: there is significant variability in disease therapy risk-tolerance thresholds, and these preferences may vary over time and disease experience. These findings have direct implications for treatment strategies and health decision analyses.

## Materials and Methods

### *Survey Sample*

Invitation emails were sent to CD members of the Crohn's and Colitis Foundation Partners cohort (IBD Partners).[8] The cohort has been shown to be similar to other IBD populations, albeit with a larger proportion of women.[8] Members of IBD Partners update disease information every 6 months. Following completion of the semiannual questionnaire, patients were asked if they would be willing to complete an additional survey regarding their preferences for therapies for CD. Patients indicating a willingness to participate were emailed a separate invitation and a link to the online survey.

### *Survey Development*

A discrete choice experiment (DCE) survey was performed. DCE is a nonexpected utility theory method that recognizes that interventions (eg, medical or surgical treatments) derive value from specific attributes (eg, treatment efficacy, potential SAEs). In turn, these attributes have varying levels (eg, efficacy rates, risk rates). By measuring systematic tradeoffs, DCE generates choice data that quantifies implicit decision weights indicating relative utility for treatment attributes and treatments overall. Because it is based in nonexpected utility theory, it avoids inaccurate assumptions of preference behavior in expected utility theory-based methods (eg, time tradeoff or standard gamble) (Supplementary Methods).[9–17]

A choice-experiment survey was developed using best-practice methods to elicit patients' willingness to accept tradeoffs among various medication and surgical therapies.[18] Baseline demographics and recent disease history from the IBD Partners' database were augmented by additional questions regarding specific history related to the risks and therapies assessed in the study.

Treatment attributes shown in choice-experiment scenarios were determined from literature review, expert consultation, focused interviews with IBD patients and piloting in 9 CD patients. Patients were asked to assume that their current treatment was not working to control their CD and they need to choose an alternative therapy. Patients were offered choices between 2 medical therapy profiles. Attributes of each profile included number of months per year of specified disease severity ranging from 12 months of remission to 12 months of mild, moderate or severe disease activity; and number of months of steroid usage each year (Supplementary Figure 1). Symptoms descriptions were adapted from the Crohn's Disease Activity Index. For each treatment, the risks were described for 3 serious adverse events (SAEs): the increased risk of cancer, serious infection and need for intestinal surgery. Each SAE and its treatment were described in nontechnical language (see Supplementary Survey example). Hypothetical risk levels for a 10-year period ranged from 0%–8% for cancer and surgery; and 0%–30% for serious infections. Pretest interviews and pilot data indicated these ranges yielded trade-off information required to quantify the upper limits of risk that most participants would accept for improvements in disease severity. All treatment benefits were described as certain and all treatment risks were described as known probabilities. Consistent with best practices, specific risk levels were shown.[18] SAE

probabilities were presented both graphically and numerically (Supplementary Figure 2).[19] See Supplementary Materials for further details of the survey design.

### Statistical Analysis

Latent GOLD 5.0 Choice was used to estimate latent class relative importance weights from the choice data (see Supplementary Materials for additional details of model development).[20] To give utility differences a clinically relevant metric, we used the marginal utility of 1 month of remission to derive the remission-time equivalent (RTE), of a given duration of symptom severity or treatment-related risk. Thus, RTE is the loss in remission time that has the equivalent utility loss as a given amount of symptom-severity time; or the loss in remission time that has the equivalent utility loss as bearing a given level of SAE risk.

Time profiles in the choice questions were specified as number of months with specified symptom severity and number of months of remission over a 12-month period. Thus the utility gains from 1 less month of mild, moderate or severe disease corresponds to the marginal utility of 1 more month of time in remission.

Variables were also examined to determine clinically-relevant predictors of latent class membership. Clinically-relevant covariates were added and removed sequentially from latent class models based on significance at a $P$ value of $\leq$.10.

The study was approved by the University of Pennsylvania's Institution Review Board.

## Results

1753 CD patients were invited to participate of whom 81% (1422/1753) agreed to learn more about the study, 1409 were sent the consent page, and 58% of those (812/1409) consented and completed the full choice-experiment survey (Supplementary Figure 3). Five respondents failed the test for internal validity. Given the low number, they were not excluded from final analysis.

The majority of respondents were female, consistent with the IBD Partner's population (Table 1).[8] The majority were not in a self-reported remission, although the median Short Crohn's Disease Activity Index score was 142. Approximately one-third were currently taking immunosuppressant medications and one-third had used oral corticosteroids in the prior year.

### Scaled Preference Utilities

Figure 1 shows the average relative importance of attributes for the overall population. Relative importance of each attribute is indicated by the distance between zero and the greatest level of each attribute and is dependent on attribute level range. All severity levels

**Table 1.** Baseline Characteristics of the Study Population

| Variable | Patients (n = 812) |
|---|---|
| Age, y | 44 ± 15, 43 |
| Age ≥50 y | 290 (36) |
| Gender | |
| Male | 204 (25) |
| Female | 608 (75) |
| Ethnicity/race[a] | |
| Caucasian | 751 (95) |
| African American | 10 (1) |
| Asian | 5 (<1) |
| American Indian or Alaskan Native | 4 (<1) |
| More than 1 race | 14 (2) |
| Other | 3 (<1) |
| Hispanic[b] | 19 (2) |
| Length of time with Crohn's disease[c] | 16.4 ± 13.4, 12 |
| Complications of Crohn's disease | |
| History of fistula | 312 (38) |
| History of stricture | 322 (40) |
| History of abscess | 259 (32) |
| History of surgery for Crohn's disease[d] | 412 (51) |
| History of hospitalization for Crohn's disease[e] | 551 (68) |
| Short Crohn's Disease Activity Index[f] | 150.8 ± 90.3, 142 |
| Patient-reported disease activity[g] | |
| Remission | 329 (40) |
| Mild | 331 (41) |
| Moderate | 128 (16) |
| Severe | 21 (3) |
| Months with symptoms in last year[h] | |
| 0 | 148 (18) |
| 1–2 | 148 (18) |
| 3–11 | 270 (34) |
| 12 | 239 (30) |
| Months with symptoms in last year[h] | 5.8 ± 4.8, 5 |
| Most recent flare[i] | |
| Mild | 342 (42) |
| Moderate | 312 (38) |
| Severe | 153 (19) |
| History of hospitalization for serious infection[j] | 231 (29) |
| Personal history of cancer[k] | 80 (10) |
| Family or friend who died from cancer | 499 (62) |
| Corticosteroid (oral) use[l] | |
| Never | 62 (8) |
| In past 1–2 mo | 126 (16) |
| In past 3–11 mo | 133 (17) |
| 12 or more months ago | 465 (59) |
| Willing to take corticosteroids again[m] | 510 (70) |
| Current immunosuppressant use[n] | 258 (32) |

Values are mean ±SD, median; or n (%).
[a]25 missing.
[b]15 missing.
[c]5 missing.
[d]3 missing.
[e]5 missing.
[f]4 missing;
[g]3 missing.
[h]7 missing.
[i]5 missing.
[j]2 missing.
[k]4 missing.
[l]26 missing.
[m]26 missing and 62 had not previously taken corticosteroids (510 of 724 =70%.
[n]1 missing, inclusive of thiopurine analogs, biologics, and methotrexate.

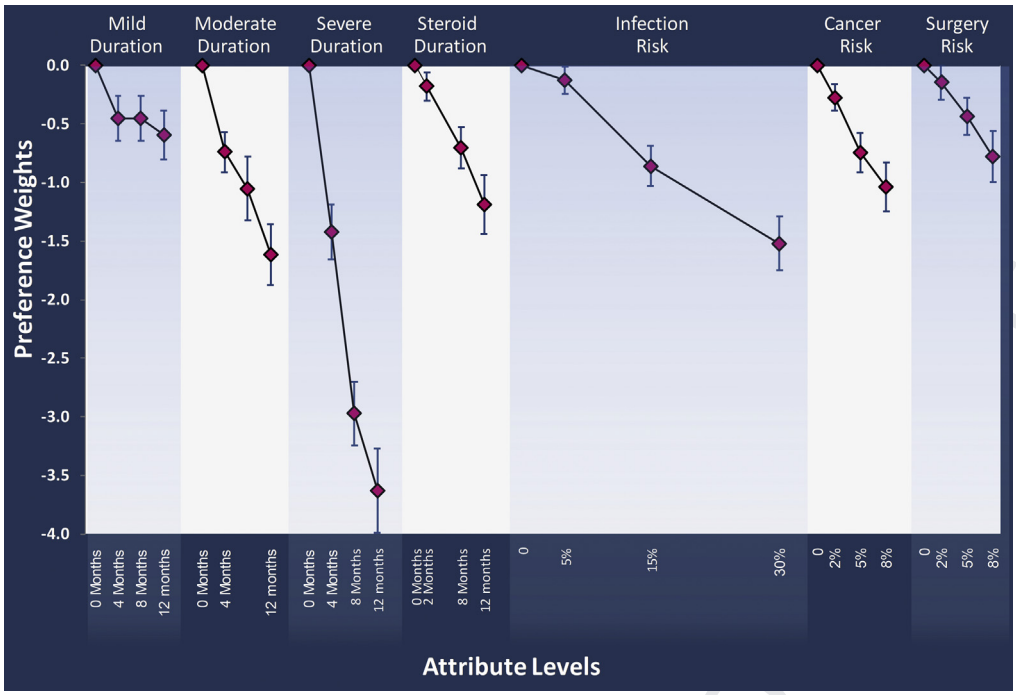



**Figure 1.** Categorical preference weights for overall sample. Preference weights for overall study population. The vertical axis shows utility loss and the horizontal axis shows attributes and their respective levels.

and corticosteroid use were evaluated over 12 months; infection risk ranged as high as 30%, while the maximum value of other risks was only 8%. Preference weights showed logically ordered utility losses with increasing levels of disease activity and risk. Differences among symptom severity and risk levels generally were statistically significant. An exception was mild-disease durations, in which respondents were insensitive to differences in durations >0, similar to prior studies.[21]

Severe disease duration was the most important attribute, with the lowest utility assigned to severe disease lasting for 1 year. Up to an 8% risk of surgery was considered less important. Four months of severe disease was considered 3.2-fold more important than moderate disease and 1.6-fold more important than mild disease of equal duration. The differences in importance were larger for longer durations of active disease. At the 5% risk level, cancer risk was about twice as important as surgery risk and about 6-fold more important than infection risk. Avoiding 12 months of steroid use, with perceived side effects, was more important than avoiding an 8% risk of surgery.

### *Latent Class Analysis of Choice Data*

Using latent class analysis the best fit model included 3 latent classes which described 3 dominant decision-making patterns. Classes were termed symptom avoidant, steroid avoidant, and risk avoidant to describe the characteristics of each class. Figures 2 and 3 compare the relative importance and illustrate the preference weights of the attributes by latent class, respectively. The symptom-avoidant class constituted 61% of the overall sample and had stronger preference for avoiding moderate and severe disease. The corticosteroid-avoidant class represented 25% of the sample and had a stronger preference for avoiding corticosteroids, even at the cost of lower medication efficacy. The risk-avoidant class constituted 14% of the overall sample and had a stronger preference for avoiding therapeutic risks, especially cancer risks.

We calculated RTE values corresponding to losses in months of remission for various severity and risk levels (Figures 3 and 4). The RTEs for the symptom avoidant class most closely approximated the RTEs for the overall sample (Supplementary Table 1; Figure 4). However, in

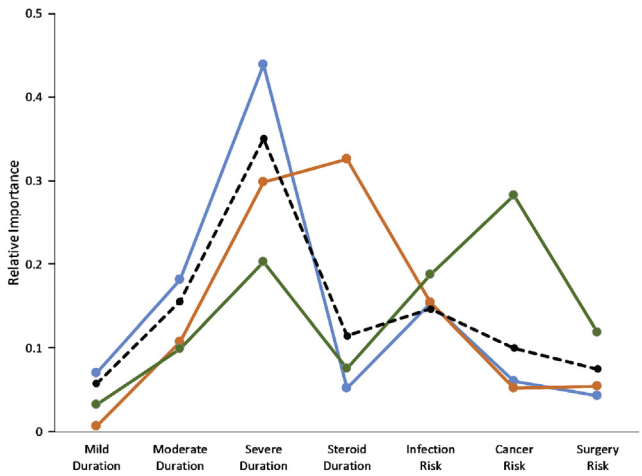



**Figure 2.** Relative attribute importance by latent class. Relative importance of attributes for overall population (black dashed line) and latent class membership: symptom avoidant (blue), corticosteroid avoidant (red), and risk avoidant (green). Relative importance is the difference between the worst level and an omitted zero category for each attribute, with scaling to sum to 1.

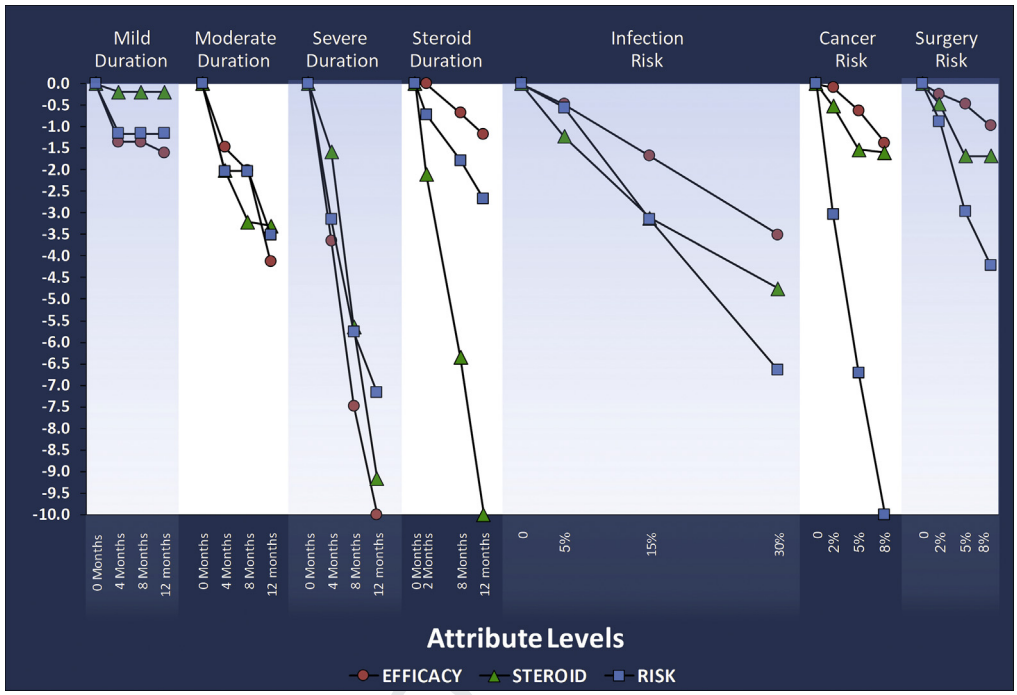



**Figure 3.** Preference weights for varying attribute levels by latent class membership. The vertical axis is utility loss and the horizontal axis shows the attributes and their respective levels: symptom avoidant (blue), corticosteroid avoidant (red), and risk avoidant (green).



each level of attributes of SAE risks, the mean RTEs for the overall sample underestimated the RTEs for at least 1 of the latent class groups.

The heterogeneity in treatment preferences resulted in markedly different valuation of durations of active CD (Supplementary Table 1). For example, the symptom-avoidant class valued 3 months of moderate disease (–4.1 RTEs; 95% confidence interval [CI], 5.3 to 2.9), similar to the corticosteroid-avoidant class, which valued 5 months of moderate disease (–3.8 RTEs; 95% CI, –6.4 to 1.2), and the risk-avoidant class, which valued 9 months of moderate disease (–3.9 RTEs; 95% CI, –8.1, 0.2).

### *Characteristics of Latent Class Membership*

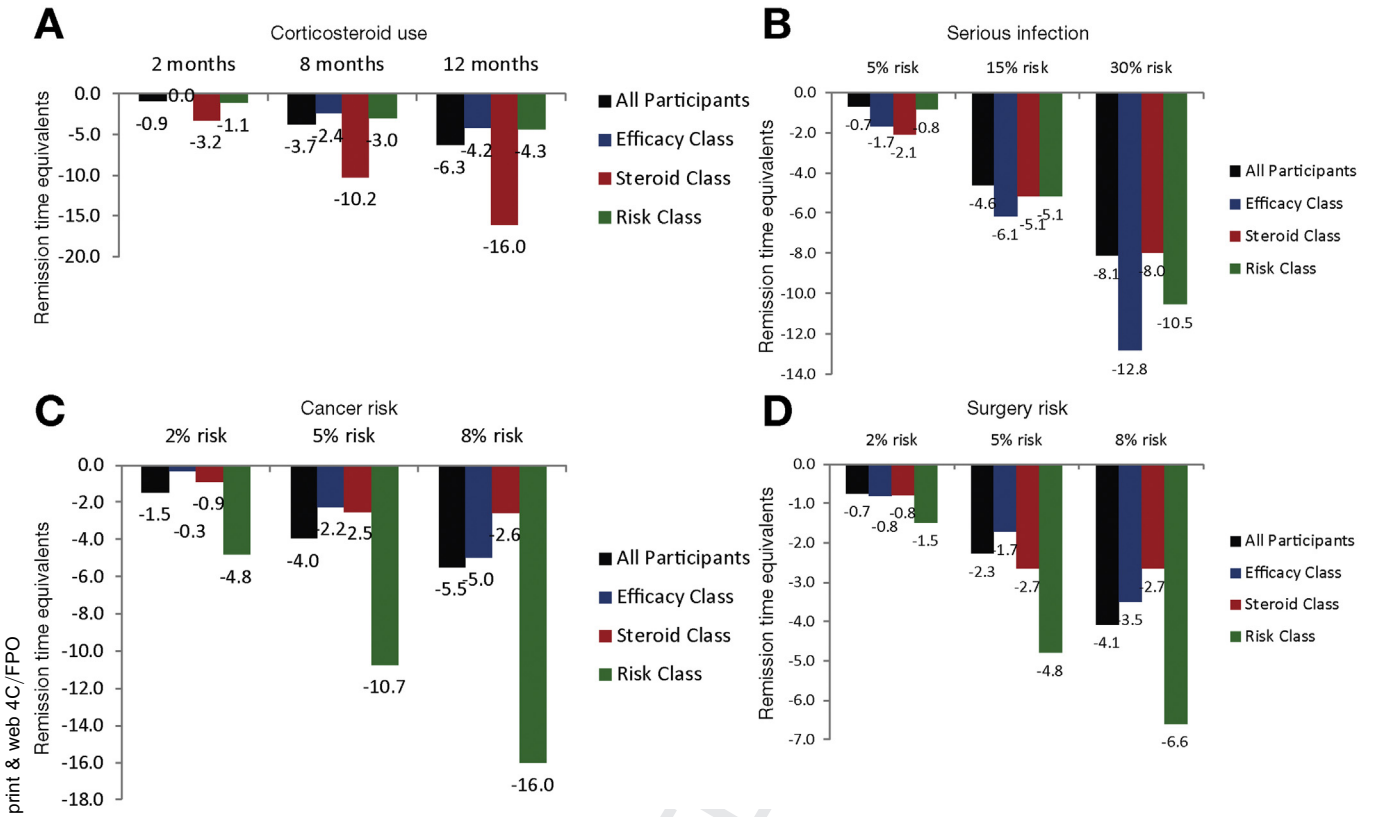
Regression modeling identified 4 patient characteristic covariates that retained significance across models predicting likelihood of membership in each latent class of decision-making patterns (Table 2), although an individual may use components of each in making health decisions. The corticosteroid-avoidant class tended to be women with greater disease activity as indicated by mean short Crohn's Disease Activity Index scores, whereas the symptom-avoidant class tended to be younger and with lower disease activity.

## Discussion

In response to the increasing call for patient preference information in clinical decisions and public policy, this study was designed to quantify how CD patients value treatments and outcomes. The study demonstrated substantial variability in patient preference. Three groups were identified within our sample who valued treatment outcomes and side-effect risks differently. The largest group placed a premium on minimizing the time spent with moderate to severe disease activity and was relatively less concerned with corticosteroid use and SAE risks associated with medication or surgery.

However, 39% of our sample differed substantially from the largest group and from the overall average in their priorities for treatment outcomes. These patients belonged to 1 of 2 other latent classes: one group was primarily concerned about corticosteroid use whereas the other focused primarily on risks of SAEs. For example, the risk-avoidant class viewed a 5% risk of cancer as equivalent to losing 16 months of symptom-free time compared with an average of 4 months for the entire study population. The corticosteroid-avoidant class assessed 2 months of corticosteroid exposure as equivalent to losing nearly 3.2 months of remission compared with the less than 1 month for the full study sample.

Preference estimates based on aggregate samples are used throughout health care, at the individual, societal, and regulatory levels. Our data demonstrate that policies and guidelines that consider all CD patients as a single group could be inconsistent with the concerns of more than one-third of the patient population. Health technology assessment models may differ because they ignore differences in population members. Similarly, when regulators make decisions about the balance of potential benefits and harms of therapies, and when manufacturers develop risk-management plans, it is important to consider that subpopulations of patients have different risk-tolerance thresholds. Our findings




print & web 4C/FPO

**Figure 4.** Remission-time equivalents by latent class. Black indicates all participants; colored columns indicate groups of latent class membership, by preference: symptom avoidant (blue), corticosteroid avoidant (red), and risk avoidant (green).

also point to potential variables associated with membership in these subpopulations of different risk-tolerance thresholds and provide insight into the trade-offs these subpopulations are willing to make between the benefits and risks of therapies based on their preferences.

Similarly, practice guidelines are typically based on average response rates derived from clinical trials. However, some patients are reluctant to follow established guidelines. Our data help to explain why certain patients have a strong desire to avoid certain therapies; and how patients' preference for therapies could change over time as they age and their disease experiences change. Providers may need to address varying concerns over the disease history; both providers and patients may find it useful in directing goals of clinical visits and education in a more personalized nature.

These findings have direct implications for evolving treatment strategies that target mucosal healing in addition to control of disease-related symptoms, often referred to as treat to target. Concerns regarding these approaches include the perception that proactive escalation of therapy based on endoscopic or laboratory findings in the absence of symptoms ignores patient preferences for therapies; and that patients could be reluctant to accept increased therapy risk to prevent future complications of disease. Prior work has shown that patients value medication efficacy and are willing to accept risk levels comparable to, or even higher than, actual medication SAE risks to achieve durable clinical remission.[22] However, accepting risks to improve current symptoms is different than accepting risks to reduce the risk of future adverse outcomes.

This research extends the findings of prior studies in several ways. By including the risks of surgery and medication-related adverse events, this research allows for direct comparisons of the relative importance patients place on avoiding surgery or adverse events related to medical therapy. In general, patients prioritized avoidance of cancer more than avoidance of surgery, and avoidance of serious infections was prioritized least. Further, by including duration of symptoms, the importance of the risk of surgery could be compared with the importance of the risk of future symptoms. Patients perceived a 5% risk of surgery as having comparable importance to having 2–3 months of moderate symptoms, but viewed this surgical risk as less important than the risk of 8 months of corticosteroids. These findings are consistent with many clinicians' anecdotal experience of patients choosing not to take medication or discontinuing a medication once their current flare symptoms resolve, even if this increases the risk of future relapses and surgery, and points to critical areas to prioritize for discussion and education regarding the natural history of disease and risks of therapy.

A treat-to-target strategy is likely to be preferred by patients who prioritize avoiding future disease relapse and the related need for corticosteroid use and surgery.

**Table 2.** Participant Characteristics by Latent Class Membership

| Characteristics | Overall | Latent Class | | | Wald *P* value |
|---|---|---|---|---|---|
| | | Symptom Avoidant | Corticosteroid Avoidant | Risk Avoidant | |
| Mean age, y | 44 | 42 | 44 | 50 | <.001 |
| Male, % | 25 | 30 | 15 | 32 | .007 |
| Willing to use corticosteroids again, % | 65 | 77 | 43 | 64 | <.0001 |
| Mean sCDAI | 151 | 130 | 172 | 167 | <.0001 |

Baseline demographics were not adjusted for each other. Covariate interactions were interpreted relative to the symptom-avoidant as the omitted category.
sCDAI, short Crohn's Disease Activity Index.

Somewhat surprisingly, relative to other features of CD therapy, avoiding surgery was valued somewhat similarly across latent class groups and generally less than avoiding moderate and severe disease. Thus, the most important evidence that would lead these patients to pursue a treatment strategy consistent with treat to target may be evidence that achieving mucosal healing minimizes the amount of time that patients will have active symptoms in future years. This should be an important outcome for future studies comparing alternative treatment strategies.

Two additional novel aspects of this study were the ability to compute RTEs for different health states and to examine how preferences vary for different durations of active symptoms. Unlike standard health-state utility assessments that use utilities bound between 0 and 1 and assume linearity across time (eg, quality-adjusted life-years [QALYs]), our approach avoids restrictive assumptions of cardinality, linearity, proportionality, and separability required for calculating QALYs.[9–11,15,23] We impose no functional-form requirements, allow severity and duration to logically interact in determining utility, and are able to construct the RTE values for both symptom-duration combinations and utility losses from anticipating possible treatment-related risks. Rather than requiring respondents to evaluate outcomes relative to death and perfect health over a lifetime, we elicited trade-off preferences using choices among simulated actual treatments for clinically relevant health states and durations. Moreover, computations using utility estimates such as QALYs are difficult to interpret. Healthy time equivalents, RTEs in the case of IBD, provide an alternative metric that may be easier to understand by patients, providers and policy makers.

This study provides a unique insight into how patients value different levels of disease activity and duration of living with these symptoms. For example, patients who generally prioritized avoiding corticosteroid use were very accepting of up to 4 months of symptoms but had a stronger aversion to longer periods of active symptoms (Supplementary Figure 1). In contrast, the 2 other subgroups had significant utility losses for the first 4–8 months of symptoms, but this often plateaued after that period. Across all latent classes, the importance of symptom duration was nonlinear and increased substantially as the severity of the symptoms increased.

There are several limitations to our work. Stated preferences are elicited from a controlled experiment on hypothetical treatment choices. Real-world choices are complicated by physician intermediation, reimbursement and insurance coverage, and other factors not accounted for in our controlled experiment. Thus, actual treatment decisions could be different than those predicted by our data. Also the use of the relatively more motivated and engaged IBD Partners population, while preserving internal validity, may limit generalizability and affect the relative proportions in latent class analysis.

Several features of the study design were implemented to implement best-practice DCE methodology and limit the potential for bias due to the challenges inherent in DCE.[24] Scenarios were presented as realistically as possible; and the survey emphasized the value of the research to help CD patients and their physicians, and the importance of full concentration when answering the questions. The number of questions each respondent answered was limited in consideration of cognitively challenging choice questions. Internal validity testing demonstrated excellent understanding of the choice tasks. Owing to potential confusion over conditional probabilities, outcomes and SAEs risks were presented as certain. However, risks were presented over a plausible range of levels to facilitate quantification of clinically relevant risk tolerance.

In conclusion, this study defined values for RTEs for mild, moderate, and severe symptoms of CD over the course of 1 year. We identified 3 groups of patients with treatment preferences driven by differing emphasis on avoiding symptoms, avoiding corticosteroid use, and avoiding risk. At a societal level, these data emphasize that regulatory decisions and treatment guidelines need to acknowledge the heterogeneity in patients' preferences related to CD. The duration-specific assessment of patient preferences combined with the latent class analysis demonstrating heterogeneity provides an entirely new framework for decision and cost-effectiveness analyses related to CD.

At an individual patient level, physicians may need to tailor their discussions with patients according to these preference patterns. The largest group placed the greater emphasis on avoiding symptoms than avoiding the risk of future surgery. Similarly, a second group emphasized avoiding corticosteroid use much more than avoidance of surgery. As such, when physicians are communicating potential treatment strategies to patients, it may be more effective to focus discussions on the potential to reduce the amount of future time with active disease and ability to avoid future corticosteroid use more so than reducing the risk of future surgeries. For the subset of patients who most prioritize avoiding the risk of cancer, it may be important to emphasize that while some medications increase the risk of cancer, active inflammation also increases the risk of cancer. Tailoring educational materials and communication to the individual patient's priorities could help patients with CD to make treatment decisions that have the greatest potential to meet their personal goals and to preserve adherence to therapy once remission has been achieved.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.05.010.

## References

1. Hunter NL, O'Callaghan KM, Califf RM. Engaging patients across the spectrum of medical product development: view from the US Food and Drug Administration. JAMA 2015; 314:2499–2500.
2. Weaver KN, Kappelman MD, Sandler RS, et al. Variation in care of inflammatory bowel diseases patients in Crohn's and Colitis Foundation of America partners: role of gastroenterologist practice setting in disease outcomes and quality process measures. Inflamm Bowel Dis 2016;22:2672–2677.
3. Esrailian E, Spiegel BM, Targownik LE, Dubinsky MC, Targan SR, Gralnek IM. Differences in the management of Crohn's disease among experts and community providers, based on a national survey of sample case vignettes. Aliment Pharmacol Ther 2007;26:1005–1018.
4. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. Clin Gastroenterol Hepatol 2006;4:621–630.
5. Grijalva CG, Chen L, Delzell E, et al. Initiation of tumor necrosis factor-alpha antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. JAMA 2011; 306:2331–2339.
6. Lemaitre M, Kirchgesner J, Rudnichi A, et al. Association between use of thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. JAMA 2017;318:1679–1686.
7. Greene WH. Econometric Analysis. Englewood Cliffs, NJ: Prentice Hall, 2011.
8. Long MD, Kappelman MD, Martin CF, et al. Development of an internet-based cohort of patients with inflammatory bowel diseases (CCFA Partners): methodology and initial results. Inflamm Bowel Dis 2012;18:2099–2106.
9. Bleichrodt H, Pinto JL. The Validity of QALYs under non-expected utility. Econ J 2005;115:533–550.
10. Brazier J, Rowen D, Yang Y, Tsuchiya A. Comparison of health state utility values derived using time trade-off, rank and discrete choice data anchored on the full health-dead scale. Eur J Health Econ 2012;13:575–587.
11. Hauber AB. Healthy-years equivalent: wounded but not yet dead. Expert Rev Pharmacoecon Outcomes Res 2009; 9:265–269.
12. Johnson FR. Editorial: moving the QALY forward or just stuck in traffic? Value Health 2009;12(Suppl 1):38.
13. Nord E, Daniels N, Kamlet M. QALYs: some challenges. Value Health 2009;12(Suppl 1):10.
14. Deaton A, Muellbauer J. Economics and Consumer Behavior. Cambridge, UK: Cambridge University Press, 1980.
15. Starmer C. Developments in non-expected utility theory: the hunt for a descriptive theory of choice under risk. J Econ Lit 2000;38:332–382.
16. Van Houtven G, Johnson FR, Kilambi V, Hauber AB. Eliciting benefit-risk preferences and probability-weighted utility using choice-format conjoint analysis. Med Decis Making 2011; 31:469–480.
17. Bewtra M, Johnson FR. Assessing patient preferences for treatment options and process of care in inflammatory bowel disease: a critical review of quantitative data. Patient 2013; 6:241–255.
18. Bridges JF, Hauber AB, Marshall D, et al. Conjoint analysis applications in health–a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. Value Health 2011;14:403–413.
19. Visschers VH, Meertens RM, Passchier WW, de Vries NN. Probability information in risk communication: a review of the research literature. Risk Anal 2009;29:267–287.
20. Vermunt JK, Magidson J. Latent GOLD 5.0 Upgrade Manual. Belmont, MA: Statistical Innovations Inc, 2013.
21. Bewtra M, Kilambi V, Fairchild AO, Siegel CA, Lewis JD, Johnson FR. Patient preferences for surgical versus medical therapy for ulcerative colitis. Inflamm Bowel Dis 2014; 20:103–114.
22. Bewtra M, Fairchild AO, Gilroy E, et al. Inflammatory bowel disease patients' willingness to accept medication risk to avoid future disease relapse. Am J Gastroenterol 2015; 110:1675–1681.
23. Beresniak A, Medina-Lara A, Auray JP, et al. Validation of the underlying assumptions of the quality-adjusted life-years outcome: results from the ECHOUTCOME European project. Pharmacoeconomics 2015;33:61–69.
24. Johnson FR, Reed S, Gonzalez JM. Letter to the editor regarding optimizing selection of biologics in inflammatory bowel disease: development of an online patient decision aid using conjoint analysis. Am J Gastroenterol 2018; 113:1720.

**Reprint requests**
Address requests for reprints to: Meenakshi Bewtra, Division of Gastroenterology, University of Pennsylvania,423 Guardian Drive, 724 Blockley Hall, Philadelphia, PA 19104. e-mail: mbewtra@pennmedicine.upenn.edu; fax: (215) 573-5325.

**Acknowledgments**
The authors thank James Tarver, PhD; Jackie Spencer, MSW, Robert Baldassano, MD; and Diane Burkhardt for their input during design and interpretation phases of this study.

**Conflicts of interest**
These authors disclose the following: Meenakshi Bewtra reports research funding from Janssen, GlaxoSmithKline, and Takeda; having served as a consultant for Janssen and AbbVie; and having received honorarium for participation in a CME program sponsored by AbbVie. Frank I. Scott reports having grants from Takeda Pharmaceuticals USA and having received personal fees from Evidera Inc. James D. Lewis reports having received personal fees from Shire, Janssen Pharmaceuticals, AbbVie, Immune Pharmaceuticals, AstraZeneca, Amgen, MedImmune, Merck, Nestle Health Science, Takeda Pharmaceuticals North America, Pfizer, Lilly, Gilead, Samsung Bioepis, and Johnson and Johnson; and has research funding from Takeda Pharmaceuticals North America and Nestle Health Science and nonfinancial research support from AbbVie. The remaining authors disclose no conflicts.

**Funding**
This work was supported by the Crohn's and Colitis Foundation and from a contract from a Patient-Centered Outcomes Research Institute grant number NCT02316678. The funder was not involved with the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

## Supplemental Methods

### Survey Development and Implementation

Survey participants were offered pairs of constructed treatment profiles that specified how much efficacy, steroid use, and various side-effect risks are associated with each treatment alternative. An experimental design identified pairs of treatment alternatives that would produce choice patterns that could be statistically analyzed to identify the relative importance weights attached to each attribute level.

We developed an online discrete choice experiment survey instrument with appropriate programming code using best-practice methods[1] to elicit Crohn's disease (CD) patients' willingness to accept trade-offs among medical and surgical interventions for CD.[2] We tailored language and format to a sixth-grade reading level; obtained published data and expert opinion to clearly delineate attributes and levels; and conducted 1-on-1 piloting with 9 CD patients to ensure cognitive suitability, refine language, determine potential effect modifiers, and tailor length.

To motivate evaluation of the series of pairwise comparisons of constructed treatment options, participants were asked to assume that their current treatment was not working to control their CD and they needed to choose between two alternative medical therapies. Medical therapy attributes included number of months per year of specified disease severity ranging from 12 months of remission to 12 months of mild, moderate, or severe disease activity; and number of months of steroid usage each year. Symptom descriptions were adapted from the Crohn's Disease Activity Index. For each treatment, the risks were described for 3 serious adverse events (SAEs): the increased risk of lymphoma, serious infection, and need for intestinal surgery. Each SAE and its treatment were described in nontechnical language.

Hypothetical risk levels for a 10-year period ranged from 0% to 8% for lymphoma and surgery and from 0% 30% for serious infections. Pretest interviews and pilot data indicated these ranges yielded trade-off information required to quantify the upper limits of risk that most participants would accept for improvements in disease severity. Attribute levels also included outcomes in the clinically relevant ranges to facilitate mapping benefit-risk preferences to actual treatments. The 10-year time frame has been deemed to be appropriate from conceptual, methodological, and patient cognitive perspectives, and has been previously described in the literature.[3–5]

To limit cognitive and numeracy concerns, all treatment benefits and risks are described as certain or with known probabilities. Consistent with best practices, specific risk levels were shown.[1] Additionally, SAE probabilities are presented graphically in an icon array with shaded elements indicating the number of patients out of 100; and numerically as fractions (counts out of 100) and percentages. The survey includes tests for numeracy and internal tests for subject-level validity through logic testing. A commonly used algorithm in SAS (SAS Institute, Cary, NC) was used to construct D-efficient experimental designs resulting in the least number of scenarios to efficiently estimate MARs.[6–10] To reduce respondent burden, the trade-off scenarios are typically blocked into sets of 8–12 questions with their order randomized to avoid sequence effects.

### Survey Validation

The choice-experiment surveys included tests for numerical understanding and an internal test for subject-level validity through logic testing. To assess understanding of the numerical information in the survey, subjects were shown a series of risks, presented as percentages, fractions and risk-grid graphics, and subsequently tested on their understanding of these numeric concepts. Logic testing was assessed to evaluate if respondents understood and were attentive to the choice task to indicate a preference for the treatment profile with better efficacy and lower risks across all attributes (the "dominant treatment"). The statistical model was tested to evaluate the influence of respondents who failed one or both of these tests.

### Statistical Analysis

Latent GOLD 5.0 Choice (Statistical Innovations, Belmont, MA) was used to estimate latent class relative importance weights from the choice data.[11] The choice model estimates separate parameters and class-membership probabilities for a specified number of classes. We estimated models for 1–5 classes to evaluate the optimal number of latent classes. Fully categorical models were specified to avoid imposing functional-form assumptions for continuous variables. All severity duration interactions were estimated to avoid the implausible, but common, assumption that health-state utility and durations are linear and proportional. The Bayesian information criterion was used to compare relative fit of the models and Wald tests were used to determine whether coefficient differences were significant among classes.[12] We also evaluated whether model classes represented reasonably large fractions of the total sample, were distinctly different from other classes, and had logical and clinically meaningful interpretation.[13]

The absolute scale of the preference-utility parameter estimates has no intuitive meaning; only comparisons of differences are meaningful. To facilitate comparisons among classes, we rescaled each set of parameters for each class to range between 0 (best) and −10 (worst) outcome levels. The resulting relative-importance score indicates the overall influence each attribute had on choice evaluations.

To convert relative importance estimates to a clinically relevant metric, we used the marginal utility of one month of remission to rescale the preference estimates in terms of equivalent remission-time equivalents (RTEs), of a given duration of symptom severity or treatment-related risk. Thus, RTE is the loss in remission time that has the equivalent utility loss as a given amount of symptom-severity time, or the loss in remission time that has the equivalent utility loss as bearing a given level of SAE risk.

Time profiles in the choice questions were specified as number of months with specified symptom severity and number of months of remission over a 12-month period. The marginal utility of 1 more month of time in remission depends on whether the additional month comes from 1 fewer month of mild, moderate, or severe disease. For calculating RTEs we rescale reductions in severity durations using the negative of the mean marginal utility loss over all severity duration levels as the average marginal utility of 1 month in remission. We calculated RTE losses by dividing symptom duration utility losses by this value.

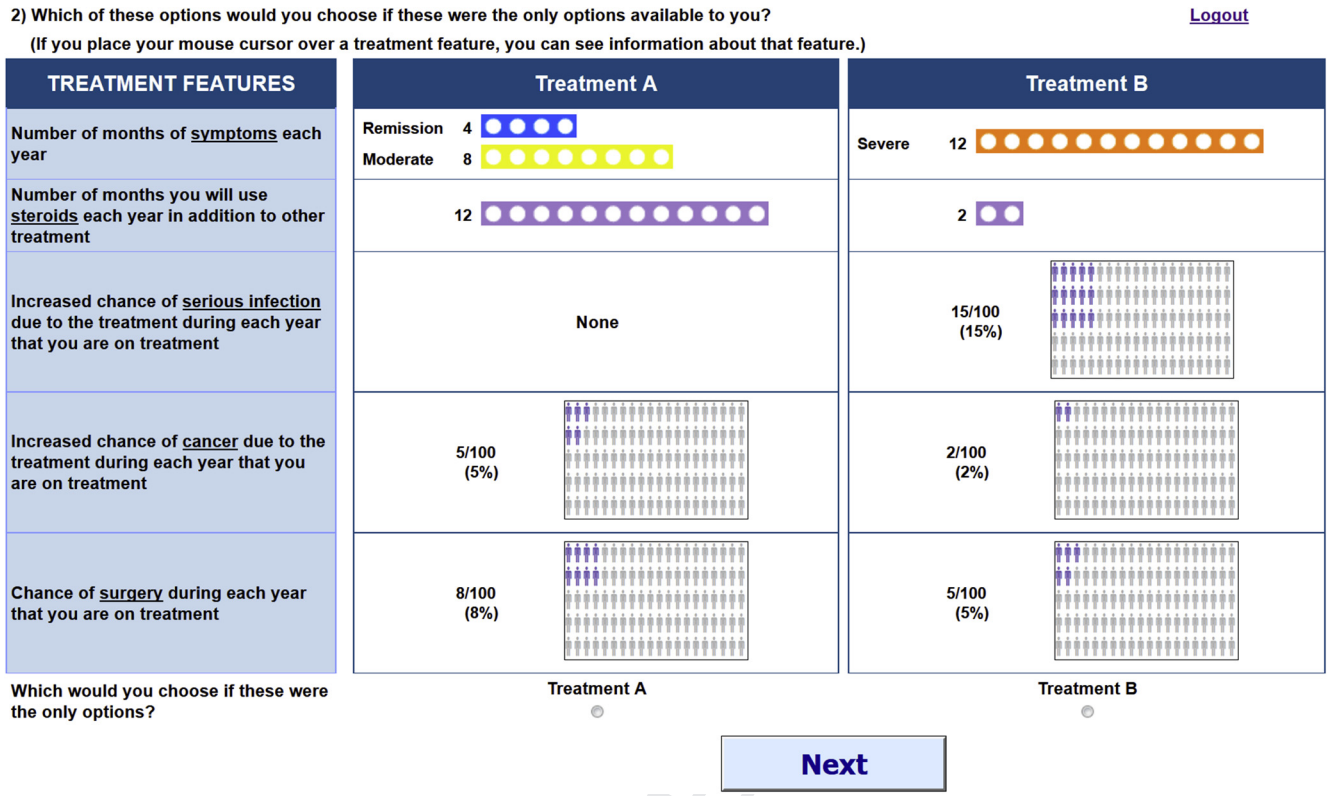
Variables also were examined to determine clinically relevant predictors of latent class membership. Clinically-relevant covariates were added and removed sequentially from latent class models based on significance at a $P$ value of $\leq .10$.

## References

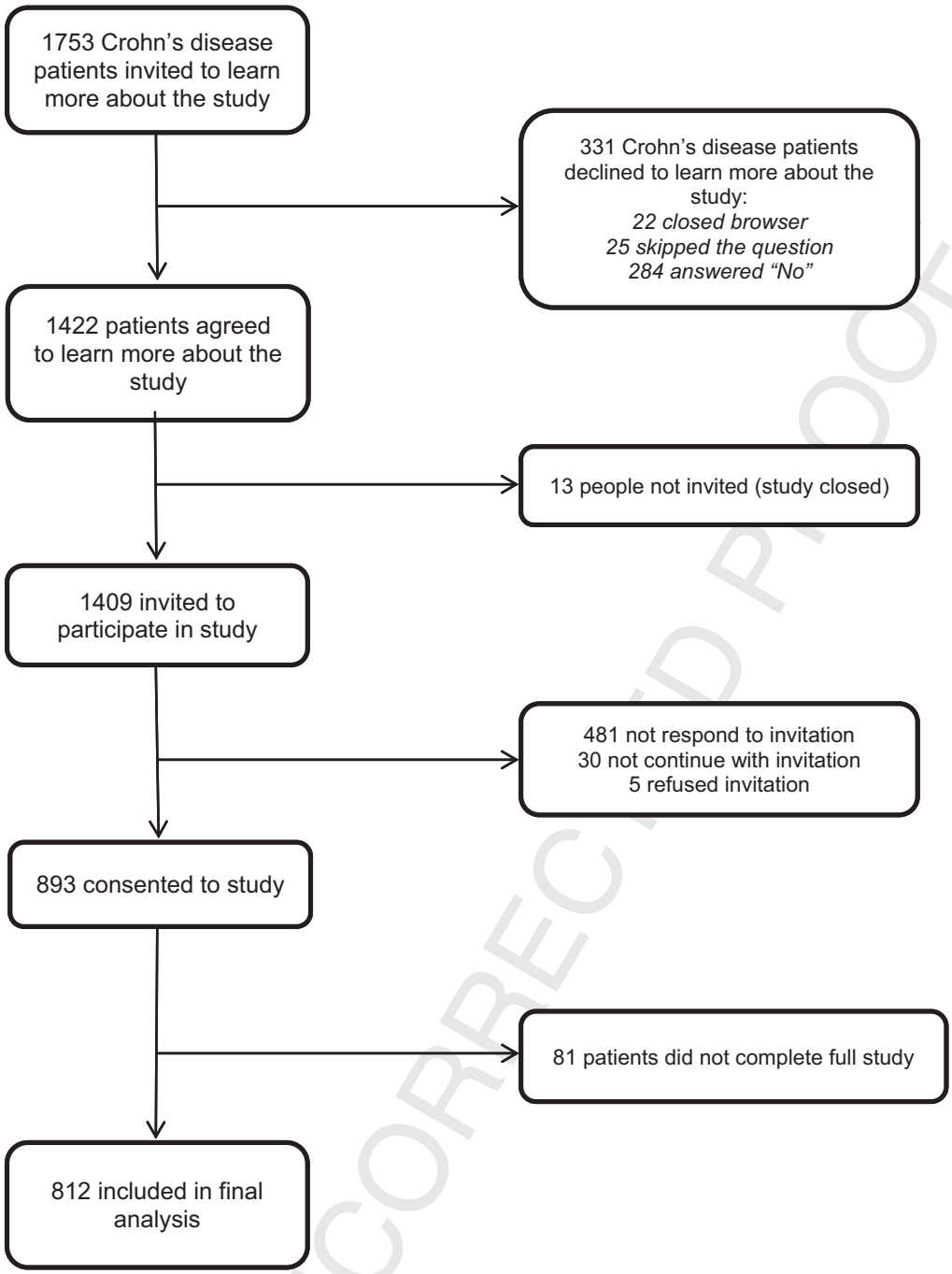

1. Bridges JF, Hauber AB, Marshall D, et al. Conjoint analysis applications in health–a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. Value Health 2011;14:403–413.
2. Bewtra M, Kilambi V, Fairchild AO, et al. Patient preferences for surgical versus medical therapy for ulcerative colitis. Inflamm Bowel Dis 2014;20:103–114.
3. Johnson FR, Ozdemir S, Mansfield C, et al. Crohn's disease patients' risk-benefit preferences: serious adverse event risks versus treatment efficacy. Gastroenterology 2007; 133:769–779.
4. Johnson FR, Ozdemir S, Mansfield C, et al. Are adult patients more tolerant of treatment risks than parents of juvenile patients? Risk Anal 2009;29:121–136.
5. Johnson FR, Hauber B, Ozdemir S, et al. Are gastroenterologists less tolerant of treatment risks than patients? Benefit-risk preferences in Crohn's disease management. J Manag Care Pharm 2010;16:616–628.
6. Kanninen BJ. Optimal design for multinomial choice experiments. J Market Res 2002;39:214–227.
7. Kuhfeld WF. Experimental design: efficiency, coding, and choice designs 2010 (MR-2010C). Available at: http://support.sas.com/techsup/technote/mr2010c.pdf: Accessed •••.
8. Kuhfeld WF. Marketing research methods in SAS 2010 (MR-2010). Available at: http://support.sas.com/techsup/technote/mr2010.pdf: Accessed •••. Q6
9. Huber J, Zwerina K. The Importance of utility balance and efficient choice designs. J Market Res 1996;33:307–317.
10. Dey A. Orthogonal Fractional Factorial Designs. Hoboken, NJ: Wiley, 1985.
11. Vermunt JK, Magidson J. Latent GOLD 5.0 Upgrade Manual 2013. Belmont, MA: Statistical Innovations, 2013.
12. Vermunt J, Magidson J. Latent GOLD 4.0 User's Guide. Belmont, MA: Statistical Innovations, 2005.
13. Lanza ST, Rhoades BL. Latent class analysis: an alternative perspective on subgroup analysis in prevention and treatment. Prev Sci 2013;14:157–168.

| Feature | Levels | | | |
|---|---|---|---|---|
| Severity and duration [a] | Severity: 0 Months | Severity: 4 Months | Severity: 8 Months | Severity: 12 Months |
| | Remission: 12 | Mild: 4<br>Remission: 8 | Mild: 8<br>Remission: 4 | Mild: 12 |
| | | Moderate: 4<br>Remission: 8 | Moderate: 8<br>Remission: 4 | Moderate:12 |
| | | Severe: 4<br>Remission: 8 | Severe: 8<br>Remission: 4 | Severe: 12 |
| Months of steroids [b] | Steroids: 0 | Steroids: 2 | Steroids: 8 | Steroids: 12 |
| Increased chance of serious infection [b] | None | 5 out of 100 (5%) | 15 out of 100 (15%) | 30 out of 100 (30%) |
| Increased chance of cancer | None | 2 out of 100 (2%) | 5 out of 100 (5%) | 8 out of 100 (8%) |
| Increased chance of surgery [a] | None | 2 out of 100 (2%) | 5 out of 100 (5%) | 8 out of 100 (8%) |

**Supplemental Figure 1.** Attributes and levels.




**Supplemental Figure 2.** Example of survey scenario.




**Supplemental Figure 3.** Patient accrual.

**Supplemental Table 1.** Remission-Time Equivalents

| Attribute | Overall | Symptom Avoidant | Corticosteroid Avoidant | Risk Avoidant |
|---|---|---|---|---|
| Severe duration | | | | |
| 1 mo | −1.9 (−2.2 to −1.6) | −3.3 (−4.0 to −2.7) | −0.7 (−1.6 to 0.3) | −1.3 (−2.3 to −0.4) |
| 2 mo | −3.8 (−4.4 to −3.1) | −6.7 (−8.0 to −5.3) | −1.3 (−3.3 to 0.6) | −2.6 (−4.5 to −0.7) |
| 3 mo | −5.7 (−6.7 to −4.7) | −10.0 (−12.0 to −8.0) | −2.0 (−4.9 to 0.9) | −3.9 (−6.8 to −1.1) |
| 4 mo | −7.6 (−8.9 to −6.3) | −13.3 (−15.9 to −10.7) | −2.7 (−6.5 to 1.2) | −5.2 (−9.0 to −1.5) |
| 5 mo | −9.6 (−10.9 to −8.3) | −16.8 (−19.6 to −14.1) | −4.3 (−8.3 to −0.3) | −6.3 (−10.1 to −2.6) |
| 6 mo | −11.6 (−13.0 to −10.3) | −20.4 (−23.3 to −17.4) | −5.9 (−10.1 to −1.8) | −7.4 (−11.4 to −3.5) |
| 7 mo | −13.7 (−15.1 to −12.3) | −23.9 (−27.2 to −20.5) | −7.6 (−12.0 to −3.2) | −8.5 (−12.8 to −4.2) |
| 8 mo | −15.7 (−17.2 to −14.2) | −27.4 (−31.2 to −23.6) | −9.2 (−13.9 to −4.5) | −9.6 (−14.4 to −4.8) |
| 9 mo | −16.6 (−18.1 to −15.0) | −29.7 (−33.6 to −25.7) | −10.7 (−15.4 to −5.9) | −10.1 (−14.8 to −5.4) |
| 10 mo | −17.4 (−19.1 to −15.8) | −32.0 (−36.3 to −27.6) | −12.1 (−17.0 to −7.2) | −10.6 (−15.4 to −5.7) |
| 11 mo | −18.3 (−20.1 to −16.5) | −34.3 (−39.1 to −29.4) | −13.5 (−18.7 to −8.4) | −11.0 (−16.2 to −5.9) |
| 12 mo | −19.2 (−21.2 to −17.1) | −36.6 (−42.0 to −31.1) | −15.0 (−20.5 to −9.5) | −11.5 (−17.1 to −5.9) |
| Moderate duration | | | | |
| 1 mo | −1.0 (−1.2 to −0.7) | −1.4 (−1.8 to −1.0) | −0.8 (−1.5 to −0.1) | −0.8 (−1.8 to 0.1) |
| 2 mo | −1.9 (−2.4 to −1.5) | −2.7 (−3.5 to −1.9) | −1.7 (−3.1 to −0.3) | −1.6 (−3.5 to 0.3) |
| 3 mo | −2.9 (−3.7 to −2.2) | −4.1 (−5.3 to −2.9) | −2.5 (−4.6 to −0.4) | −2.5 (−5.3 to 0.4) |
| 4 mo | −3.9 (−4.9 to −2.9) | −5.5 (−7.1 to −3.8) | −3.3 (−6.1 to −0.6) | −3.3 (−7.1 to 0.5) |
| 5 mo | −4.3 (−5.2 to −3.4) | −5.9 (−7.6 to −4.3) | −3.8 (−6.4 to −1.2) | −3.3 (−6.7 to 0.1) |
| 6 mo | −4.7 (−5.8 to −3.7) | −6.4 (−8.3 to −4.5) | −4.3 (−7.1 to −1.5) | −3.3 (−6.6 to 0.1) |
| 7 mo | −5.2 (−6.4 to −4.0) | −6.8 (−9.2 to −4.5) | −4.8 (−8.1 to −1.5) | −3.3 (−7.0 to 0.4) |
| 8 mo | −5.6 (−7.1 to −4.1) | −7.3 (−10.2 to −4.4) | −5.3 (−9.2 to −1.3) | −3.3 (−7.6 to 1.1) |
| 9 mo | −6.3 (−7.8 to −4.9) | −9.2 (−12.1 to −6.4) | −5.3 (−9.1 to −1.6) | −3.9 (−8.1 to 0.2) |
| 10 mo | −7.1 (−8.5 to −5.7) | −11.2 (−14.1 to −8.3) | −5.3 (−9.0 to −1.7) | −4.6 (−8.6 to −0.6) |
| 11 mo | −7.8 (−9.2 to −6.4) | −13.2 (−16.3 to −10.1) | −5.4 (−9.1 to −1.7) | −5.3 (−9.3 to −1.2) |
| 12 mo | −8.6 (−10.1 to −7.1) | −15.1 (−18.5 to −11.8) | −5.4 (−9.3 to −1.5) | −5.9 (−10.1 to −1.7) |
| Mild duration | | | | |
| 1 mo | −0.6 (−1.3 to 0.1) | −1.2 (−2.2 to −0.3) | −0.1 (−33.9 to 33.6) | −0.5 (−2.0 to 1.0) |
| 2 mo | −1.2 (−2.5 to 0.2) | −2.5 (−4.3 to −0.6) | −0.3 (−67.8 to 67.2) | −0.9 (−3.9 to 2.0) |
| 3 mo | −1.8 (−3.8 to 0.3) | −3.7 (−6.5 to −0.9) | −0.4 (−101.7 to 100.8) | −1.4 (−5.9 to 3.1) |
| 4 mo | −2.4 (−5.0 to 0.3) | −4.9 (−8.7 to −1.2) | −0.6 (−135.6 to 134.4) | −1.9 (−7.8 to 4.1) |
| 5 mo | −2.4 (−4.4 to −0.4) | −4.9 (−7.7 to −2.2) | −0.6 (−101.8 to 100.7) | −1.9 (−6.3 to 2.6) |
| 6 mo | −2.4 (−3.8 to −1.0) | −4.9 (−6.8 to −3.1) | −0.6 (−68.1 to 66.9) | −1.9 (−5.5 to 1.7) |
| 7 mo | −2.4 (−3.5 to −1.3) | −4.9 (−6.5 to −3.4) | −0.6 (−34.4 to 33.2) | −1.9 (−5.7 to 2.0) |
| 8 mo | −2.4 (−3.6 to −1.2) | −4.9 (−6.9 to −3.0) | −0.6 (−3.9 to 2.7) | −1.9 (−6.9 to 3.1) |
| 9 mo | −2.6 (−3.6 to −1.6) | −5.2 (−6.9 to −3.4) | −0.6 (−3.4 to 2.3) | −1.9 (−5.9 to 2.2) |
| 10 mo | −2.8 (−3.7 to −1.9) | −5.4 (−7.1 to −3.6) | −0.6 (−3.3 to 2.2) | −1.9 (−5.3 to 1.6) |
| 11 mo | −3.0 (−4.0 to −2.0) | −5.6 (−7.5 to −3.6) | −0.6 (−3.6 to 2.5) | −1.9 (−5.1 to 1.4) |
| 12 mo | −3.2 (−4.3 to −2.0) | −5.8 (−8.1 to −3.4) | −0.6 (−4.2 to 3.0) | −1.9 (−5.5 to 1.8) |
| Steroid duration | | | | |
| 1 mo | −0.4 (−0.8 to −0.2) | 0.0 (−0.7 to 0.7) | −1.6 (−2.7 to −0.6) | −0.6 (−1.6 to 0.5) |
| 2 mo | −0.9 (−1.6 to −0.3) | 0.0 (−1.3 to 1.3) | −3.2 (−5.4 to −1.1) | −1.1 (−3.2 to 0.9) |
| 3 mo | −1.4 (−2.1 to −0.8) | −0.4 (−1.8 to 1.0) | −4.4 (−6.6 to −2.2) | −1.4 (−3.5 to 0.6) |
| 4 mo | −1.9 (−2.6 to −1.2) | −0.8 (−2.3 to 0.6) | −5.6 (−7.9 to −3.2) | −1.7 (−3.9 to 0.4) |
| 5 mo | −2.3 (−3.1 to −1.9) | −1.2 (−2.8 to 0.4) | −6.7 (−9.2 to −4.2) | −2.0 (−4.3 to 0.2) |
| 6 mo | −2.8 (−3.6 to −2.0) | −1.6 (−3.4 to 0.1) | −7.9 (−10.5 to −5.2) | −2.3 (−4.8 to 0.1) |
| 7 mo | −3.3 (−4.2 to −2.4) | −2.0 (−4.0 to −0.1) | −9.0 (−11.9 to −6.2) | −2.7 (−5.3 to 0.0) |
| 8 mo | −3.8 (−4.8 to −2.8) | −2.4 (−4.6 to −0.3) | −10.2 (−13.2 to −7.2) | −3.0 (−5.8 to −0.1) |
| 9 mo | −4.4 (−5.5 to −3.3) | −2.9 (−5.3 to −0.5) | −11.7 (−15.0 to −8.3) | −3.3 (−6.4 to −0.3) |
| 10 mo | −5.0 (−6.2 to −3.9) | −3.3 (−6.0 to −0.7) | −13.1 (−16.8 to −9.4) | −3.7 (−7.0 to −0.3) |
| 11 mo | −5.7 (−7.0 to −4.4) | −3.8 (−6.7 to −0.8) | −14.6 (−18.6 to −10.5) | −4.0 (−7.6 to −0.4) |
| 12 mo | −6.3 (−7.7 to −4.9) | −4.2 (−7.5 to −1.0) | −16.0 (−20.5 to −11.6) | −4.3 (−8.3 to −0.3) |
| Infection risk | | | | |
| 1% | −0.1 (−0.3 to 0.0) | −0.3 (−0.6 to −0.1) | −0.4 (−0.8 to −0.1) | −0.2 (−0.5 to 0.2) |
| 2% | −0.3 (−0.5 to 0.0) | −0.7 (−1.2 to −0.2) | −0.8 (−1.5 to −0.1) | −0.3 (−1.1 to 0.4) |
| 3% | −0.4 (−0.8 to 0.0) | −1.0 (−1.8 to −0.2) | −1.2 (−2.3 to −0.2) | −0.5 (−1.6 to 0.6) |
| 4% | −0.5 (−1.0 to −0.1) | −1.4 (−2.4 to −0.3) | −1.7 (−3.0 to −0.3) | −0.7 (−2.2 to 0.8) |
| 5% | −0.7 (−1.3 to −0.1) | −1.7 (−3.0 to −0.4) | −2.1 (−3.8 to −0.3) | −0.8 (−2.7 to 1.1) |
| 6% | −1.1 (−1.7 to −0.4) | −2.2 (−3.5 to −0.8) | −2.4 (−4.2 to −0.6) | −1.3 (−3.2 to 0.7) |
| 7% | −1.5 (−2.1 to −0.8) | −2.6 (−3.9 to −1.3) | −2.7 (−4.5 to −0.8) | −1.7 (−3.7 to 0.3) |
| 8% | −1.9 (−2.5 to −1.2) | −3.0 (−4.4 to −1.7) | −3.0 (−4.9 to −1.1) | −2.1 (−4.2 to 0.0) |
| 9% | −2.2 (−3.0 to −1.5) | −3.5 (−4.9 to −2.1) | −3.3 (−5.3 to −1.3) | −2.6 (−4.7 to −0.4) |
| 10% | −2.6 (−3.4 to −2.0) | −3.9 (−5.4 to −2.5) | −3.6 (−5.7 to −1.5) | −3.0 (−5.3 to −0.7) |

**Supplemental Table 1.** Continued

| Attribute | Overall | Symptom Avoidant | Corticosteroid Avoidant | Risk Avoidant |
|---|---|---|---|---|
| 11% | –3.0 (–3.8 to –2.2) | –4.4 (–5.9 to –2.8) | –3.9 (–6.2 to –1.7) | –3.4 (–5.8 to –1.0) |
| 12% | –3.4 (–4.2 to –2.6) | –4.8 (–6.4 to –3.2) | –4.2 (–6.6 to –1.9) | –3.8 (–6.4 to –1.3) |
| 13% | –3.8 (–4.7 to –2.9) | –5.3 (–6.9 to –3.6) | –4.5 (–7.0 to –2.0) | –4.3 (–7.0 to –1.6) |
| 14% | –4.2 (–5.1 to –3.3) | –5.7 (–7.4 to –4.0) | –4.8 (–7.5 to –2.2) | –4.7 (–7.6 to –1.8) |
| 15% | –4.6 (–5.6 to –3.6) | –6.1 (–8.0 to –4.3) | –5.1 (–7.9 to –2.4) | –5.1 (–8.2 to –2.1) |
| 16% | –4.8 (–5.8 to –3.8) | –6.6 (–8.5 to –4.7) | –5.3 (–8.1 to –2.5) | –5.5 (–8.6 to –2.4) |
| 17% | –5.1 (–6.1 to –4.1) | –7.0 (–8.9 to –5.1) | –5.5 (–8.4 to –2.7) | –5.9 (–9.0 to –2.8) |
| 18% | –5.3 (–6.3 to –4.3) | –7.5 (–9.5 to –5.5) | –5.7 (–8.6 to –2.9) | –6.2 (–9.4 to –3.1) |
| 19% | –5.5 (–6.6 to –4.5) | –7.9 (–10.0 to –5.9) | –5.9 (–8.8 to –3.0) | –6.6 (–9.8 to –3.4) |
| 20% | –5.8 (–6.8 to –4.7) | –8.4 (–10.5 to –6.3) | –6.1 (–9.0 to –3.2) | –6.9 (–10.2 to –3.7) |
| 21% | –6.0 (–7.1 to –4.9) | –8.8 (–11.0 to –6.6) | –6.3 (–9.2 to –3.3) | –7.3 (–10.6 to –4.0) |
| 22% | –6.2 (–7.3 to –5.1) | –9.3 (–11.5 to –7.0) | –6.5 (–9.4 to –3.5) | –7.7 (–11.0 to –4.3) |
| 23% | –6.5 (–7.6 to –5.3) | –9.7 (–12.0 to –7.4) | –6.6 (–9.7 to –3.6) | –8.0 (–11.4 to –4.6) |
| 24% | –6.7 (–7.8 to –5.5) | –10.2 (–12.5 to –7.8) | –6.8 (–9.9 to –3.8) | –8.4 (–11.9 to –4.9) |
| 25% | –6.9 (–8.1 to –5.7) | –10.6 (–13.1 to –8.1) | –7.0 (–10.1 to –3.9) | –8.7 (–12.3 to –5.2) |
| 26% | –7.2 (–8.3 to –6.0) | –11.0 (–13.6 to –8.5) | –7.2 (–10.4 to –4.0) | –9.1 (–12.7 to –5.5) |
| 27% | –7.4 (–8.6 to –6.2) | –11.5 (–14.1 to –8.9) | –7.4 (–10.6 to –4.2) | –9.5 (–13.2 to –5.7) |
| 28% | –7.6 (–8.9 to –6.4) | –11.9 (–14.7 to –9.2) | –7.6 (–10.9 to –4.3) | –9.8 (–13.6 to –6.0) |
| 29% | –7.9 (–9.1 to –6.6) | –12.4 (–15.2 to –9.6) | –7.8 (–11.1 to –4.4) | –10.2 (–14.1 to –6.3) |
| 30% | –8.1 (–9.4 to –6.8) | –12.8 (–15.7 to –9.9) | –8.0 (–11.4 to –4.6) | –10.5 (–14.5 to –6.6) |
| Cancer risk | | | | |
| 1% | –0.7 (–1.0 to –0.4) | –0.2 (–0.6 to 0.3) | –0.4 (–1.2 to 0.3) | –2.4 (–3.4 to –1.4) |
| 2% | –1.4 (–2.0 to –0.9) | –0.3 (–1.3 to 0.6) | –0.9 (–2.4 to 0.6) | –4.8 (–6.9 to –2.8) |
| 3% | –2.3 (–2.9 to –1.7) | –1.0 (–1.9 to –0.1) | –1.4 (–3.0 to 0.1) | –6.8 (–9.0 to –4.6) |
| 4% | –3.1 (–3.8 to –2.4) | –1.6 (–2.7 to –0.5) | –2.0 (–3.8 to –0.1) | –8.8 (–11.4 to –6.2) |
| 5% | –4.0 (–4.8 to –3.1) | –2.2 (–3.8 to –0.7) | –2.5 (–4.7 to –0.3) | –10.7 (–13.8 to –7.6) |
| 6% | –4.5 (–5.4 to –3.6) | –3.1 (–4.7 to –1.6) | –2.5 (–4.9 to –0.1) | –12.5 (–15.9 to –9.1) |
| 7% | –5.0 (–6.0 to –4.0) | –4.1 (–5.8 to –2.3) | –2.5 (–5.3 to 0.3) | –14.2 (–18.2 to –10.3) |
| 8% | –5.5 (–6.6 to –4.3) | –5.0 (–7.0 to –2.9) | –2.6 (–5.9 to 0.7) | –16.0 (–20.5 to –11.5) |
| Surgery risk | | | | |
| 1% | –0.4 (–0.8 to 0.0) | –0.4 (–1.5 to 0.7) | –0.4 (–1.4 to 0.6) | –0.7 (–1.9 to 0.4) |
| 2% | –0.8 (–1.5 to 0.0) | –0.8 (–3.0 to 1.4) | –0.8 (–2.7 to 1.2) | –1.5 (–3.7 to 0.8) |
| 3% | –1.3 (–2.0 to –0.5) | –1.1 (–3.0 to 0.7) | –1.4 (–3.4 to 0.6) | –2.6 (–4.8 to –0.3) |
| 4% | –1.8 (–2.5 to –1.0) | –1.4 (–3.0 to 0.2) | –2.0 (–4.2 to 0.2) | –3.7 (–6.2 to –1.2) |
| 5% | –2.3 (–3.2 to –1.4) | –1.7 (–3.2 to –0.2) | –2.7 (–5.2 to –0.1) | –4.8 (–7.7 to –1.9) |
| 6% | –2.9 (–3.8 to –2.0) | –2.3 (–4.0 to –0.6) | –2.7 (–5.5 to 0.2) | –5.4 (–8.4 to –2.4) |
| 7% | –3.5 (–4.5 to –2.5) | –2.9 (–4.9 to –0.9) | –2.7 (–6.0 to 0.7) | –6.0 (–9.4 to –2.6) |
| 8% | –4.1 (–5.3 to –2.9) | –3.5 (–5.9 to –1.1) | –2.7 (–6.5 to 1.2) | –6.6 (–10.5 to –2.7) |