IBD&me: Optimizing Selection of Biologic and Small Molecule Therapies in IBD

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COVER PAGE

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ABSTRACT:
Biologics remain the mainstay of treatment for those with moderate-to-severe inflammatory bowel disease (IBD). However, drug development in IBD is dynamic; many additional therapies with novel mechanisms of action are in the pipeline. For example, a novel oral Janus kinase inhibitor called tofacitinib was recently shown to be efficacious in ulcerative colitis.

Currently, there are multiple first-line IBD therapies, and it can be difficult for patients to navigate the array of treatment options. Moreover, the decision-making process will become even more complex as additional effective therapies are developed, tested, and approved for use in clinical practice. To facilitate shared decision-making (SDM) focused on IBD treatments, our research group created IBD&me (ibdandme.org) – a free, online, unbranded resource that offers an immersive and interactive decision aid that supports patients in selecting a treatment that is congruent with their preferences and beliefs. IBD&me also uses conjoint analysis to generate a unique personalized report designed to help doctors efficiently and effectively understand their patients' treatment preferences.

As part of this study, we aim to assess the impact of IBD&me on patient perceptions of SDM and satisfaction when compared to a standardized education arm in a multicenter randomized controlled trial in partnership with IBD Qorus. Moreover, in a separate aim, we will assess how IBD patients navigate and make decisions when selecting among current and emerging IBD therapies (i.e., small molecules) using conjoint analysis; these results will inform future updates to the IBD&me decision tool as new therapies are approved for use in clinical practice.

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MAIN PROPOSAL

OVERALL GOALS & OBJECTIVES

Inflammatory bowel disease (IBD) is a chronic condition that leads to significant morbidity and decreased health-related quality of life (HRQOL).[1,2] Although there are many treatment options available for patients with ulcerative colitis (UC) and Crohn's disease (CD), biologic therapies remain the mainstay of treatment for those with moderate-to-severe IBD.[3,4] However, drug development in IBD is dynamic; many additional therapies with novel mechanisms of action are in the pipeline. For example, tofacitinib, an oral small molecule Janus kinase inhibitor, was shown to be effective in inducing and maintaining remission in UC vs. placebo.[5]

While the available biologics and small molecule therapies are effective in treating IBD, there have been few major head-to-head trials of these commonly-prescribed therapeutics. Because of the lack of comparative effectiveness data, IBD care pathways endorse several first-line therapies.[6,7] As a result, it is often difficult for patients to navigate the array of treatment options with their physician and to choose a therapy that aligns with their unique treatment preferences. Moreover, the decision-making process will become even more complex as additional effective therapies are developed, tested, and approved for use in clinical practice.

Because there are multiple first-line IBD therapies, it is vital to elicit patient preferences by engaging in shared decision-making (SDM), a process in which clinicians and patients make healthcare choices together by balancing risks and expected outcomes with the patient's preferences and values.[8-11] In IBD, employing SDM has potential to strengthen the patient-provider dialogue in a way that facilitates alignment between treatment decisions and patient preferences. When effectively employed, SDM can improve medication adherence, enhance HRQOL and clinical outcomes, and lower healthcare costs compared to a less personalized approach of assigning therapy.[12-15]

To facilitate SDM focused on IBD treatments, our research group created IBD&me (ibdandme.org) – a free, online, unbranded resource that offers an immersive and interactive decision aid that supports patients in selecting a treatment that is congruent with their preferences and beliefs. IBD&me enables patients to explore biologic risks and benefits, and then guides them through a survey called the IBD&me Decision Tree. Once patients complete the survey, which is based on an underlying conjoint analysis software program, the website generates a unique personalized report designed to help doctors efficiently and effectively understand their patients' treatment preferences. Based on the SDM literature, we hypothesize that use of IBD&me and its tailored reports can facilitate a more informed discussion in clinic between patients and clinicians, improve SDM, and better align medical care with patients' unique preferences and values.[16,17] Of note, IBD&me will be featured at a continuing medical education symposium at the Crohn's & Colitis Congress in January 2018 and is in revision for the upcoming "Putting Patients First" special issue of the *American Journal of Gastroenterology*.

While SDM tools have potential to enhance patient-centered care and improve the patient-provider interaction,[18] IBD&me has not yet been subject to prospective validation. **As part of this study, Aim 1 will assess the impact of IBD&me on patient perceptions of SDM and**

satisfaction when compared to a standardized education arm in a multicenter randomized controlled trial (RCT). Here, we will partner with and recruit patients through IBD Qorus, a ground-breaking initiative by the Crohn's & Colitis Foundation with 30 community-based and academic IBD centers committed to improving the quality of care delivered to IBD patients. Please see accompanying Letter of Support from IBD Qorus leadership (Dr. Corey Siegel, Co-Principal Investigator; Alandra Weaver, Director of IBD Qorus, Crohn's & Colitis Foundation).

In addition to testing the impact of IBD&me on patient-reported outcomes, we have an opportunity through this grant to prepare the tool for wider dissemination and applicability to upcoming therapeutic options. As with any SDM tool, IBD&me must stay relevant over time, particularly in IBD given the growing pipeline of IBD therapies and increasing global prevalence of CD and UC. To achieve this, we will assess whether there are cultural differences in decision making when patients navigate among current and emerging IBD therapies; these results will allow future updates to the tool. **Specifically, Aim 2 will use conjoint analysis, a technique that determines how respondents make complex decisions under conditions of uncertainty, to examine how patients with moderate-to-severe IBD both inside and beyond North America select among available biologic as well as upcoming small molecule therapies.** This information will inform updates to IBD&me as well as other decision aids once new medications become available for use in everyday clinical practice.

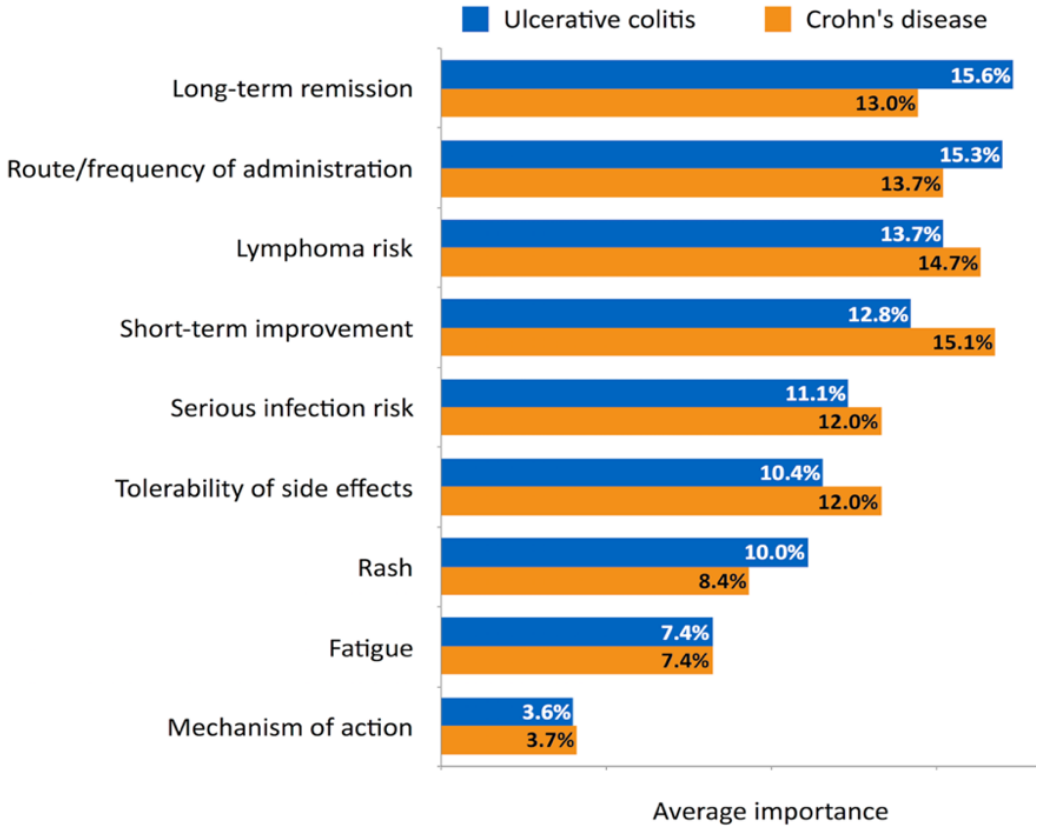
CURRENT ASSESSMENT OF NEED IN TARGET AREA

While the tested biologics and small molecule therapies are effective in treating IBD compared to placebo, there is still a lack of comparative effectiveness data, resulting in care pathways that endorse several first-line therapies.[6,7] Adding to the complexity is the substantial variation among biologics and upcoming small molecules with respect to mechanism of action, mode of administration, and side effects, among other attributes. For example, the therapies can be categorized as anti-tumor necrosis factor (TNF), anti-integrin, anti-interleukin (IL) 12/anti-IL 23 agents, or Janus kinase inhibitors.[5,19,20]

Aside from mechanism of action, IBD therapies also differ in both the route (intravenous vs. subcutaneous vs. oral) and frequency of use. IBD therapeutics also have varying side-effect profiles, as there are differential rates of fatigue, skin rash, lymphoma, infections, and hyperlipidemia.[5,21] As a result, it is often difficult for patients to navigate the array of treatment options with their physicians and to choose a therapy that aligns with their unique treatment preferences. Moreover, the decision-making process will become more complex as additional drugs are developed and approved.

Our group recently conducted a study using conjoint analysis – a technique that determines how respondents make complex decisions under conditions of uncertainty – that found systematically different approaches to biologic therapy decision making between patients with UC and CD (manuscript in revision at *Am J Gastroenterol*) (**Figure 1**).[22] Moreover, across conditions we found widely divergent individual patient preferences when selecting among biologics. In attempting to identify predictors of individual patient choice, we found that demographic and IBD characteristics were largely unhelpful; 98% of respondents had unique decision-making profiles, again emphasizing the highly personalized nature of decision making.

FIGURE 1. Average attribute importance for UC and CD patients. The average importance of each biologic attribute is based on part-worth utilities. For UC patients, remission, mode of administration, and lymphoma risk accounted for 15.6%, 15.3%, and 13.7% of decision making. For CD patients, short-term improvement (15.1%), lymphoma risk (14.7%), and mode of administration (13.7%) were most important (N=336 CD; 334 UC; data in revision at *Am J Gastroenterol*).



Because of the highly-individualized nature of decision making in IBD, along with healthcare's increased emphasis on SDM, it is critical for clinicians to identify what matters most to patients when choosing among therapeutic options; this enables patients to select therapies that align with their values – a need that is recognized by patients and physicians alike.[23,24] Yet, it can be challenging to accurately establish a patient's unique preference profile in the context of a brief clinic visit because no two IBD patients are alike. In the face of burgeoning administrative and clinical tasks, gastroenterologists often lack time and resources to engage in detailed discussions around therapies' risks, benefits, and tradeoffs. Thus, there is a need for simple and efficient tools that elicit individual preferences and support the patient-provider interaction.

To address this gap, we converted our conjoint analysis into a decision aid called IBD&me (ibdandme.org). IBD&me is a novel, online tool to enhance SDM between IBD patients and their providers when navigating among the available IBD therapies. The program enables patients to explore the risks and benefits of the different therapies, and then guides them through a conjoint survey called the IBD&me Decision Tree. Once patients complete the survey, the website generates a unique personalized report that can be shared with a doctor. See below for full details on IBD&me.

While decisions aids have been shown to increase participants' knowledge and accuracy of risk perceptions, decrease decisional conflict, and positively impact patient-clinician communication,[18] the capacity of IBD decision aids, such as IBD&me, to improve patient outcomes is less well defined. We aim to address this gap by conducting a pragmatic, multicenter RCT in partnership with IBD Qorus institutions comparing the impact of IBD&me on SDM and patient satisfaction when compared to standardized education.

AIM 1. RCT OF IBD&ME VS. STANDARDIZED EDUCATION.

TARGET AUDIENCE

We will recruit IBD patients from participating IBD Qorus institutions to participate in an RCT comparing use of IBD&me vs. standardized education. IBD Qorus is a consortium of 30 community-based and academic IBD centers committed to improving the quality of care delivered to IBD patients and provides access to over 1,000 potential study participants. Eligible patients will include those who are: (i) age ≥18 years; (ii) have moderate-to-severe UC or CD; and (iii) considering starting or switching biologics for treating his or her IBD. Individuals with mild IBD or who are stable on their biologic therapy will be ineligible. Please see the "Project Design and Methods" section for details on recruitment plan.

PROJECT DESIGN AND METHODS

Approach. To measure the efficacy of IBD&me in clinical practice, we will conduct a pragmatic, multicenter RCT comparing provision of IBD&me vs. standardized education. We will recruit patients seen in centers that have consented to be part of IBD Qorus. Eligible patients will be offered participation in the study 1 week prior to their next scheduled appointment – a period when they normally complete a standardized IBD Qorus questionnaire. Patients interested in participating will be directed to the study website where they will electronically consent and then undergo randomization to access either one of two websites: (i) IBD&me; or (ii) standardized, high-quality educational material from the Crohn's & Colitis Foundation. See below for full descriptions of the two arms. We hypothesize that IBD&me, through optimizing SDM and improving the patient-provider interaction, will provide incremental benefits beyond those provided by high-quality educational material without an SDM tool.

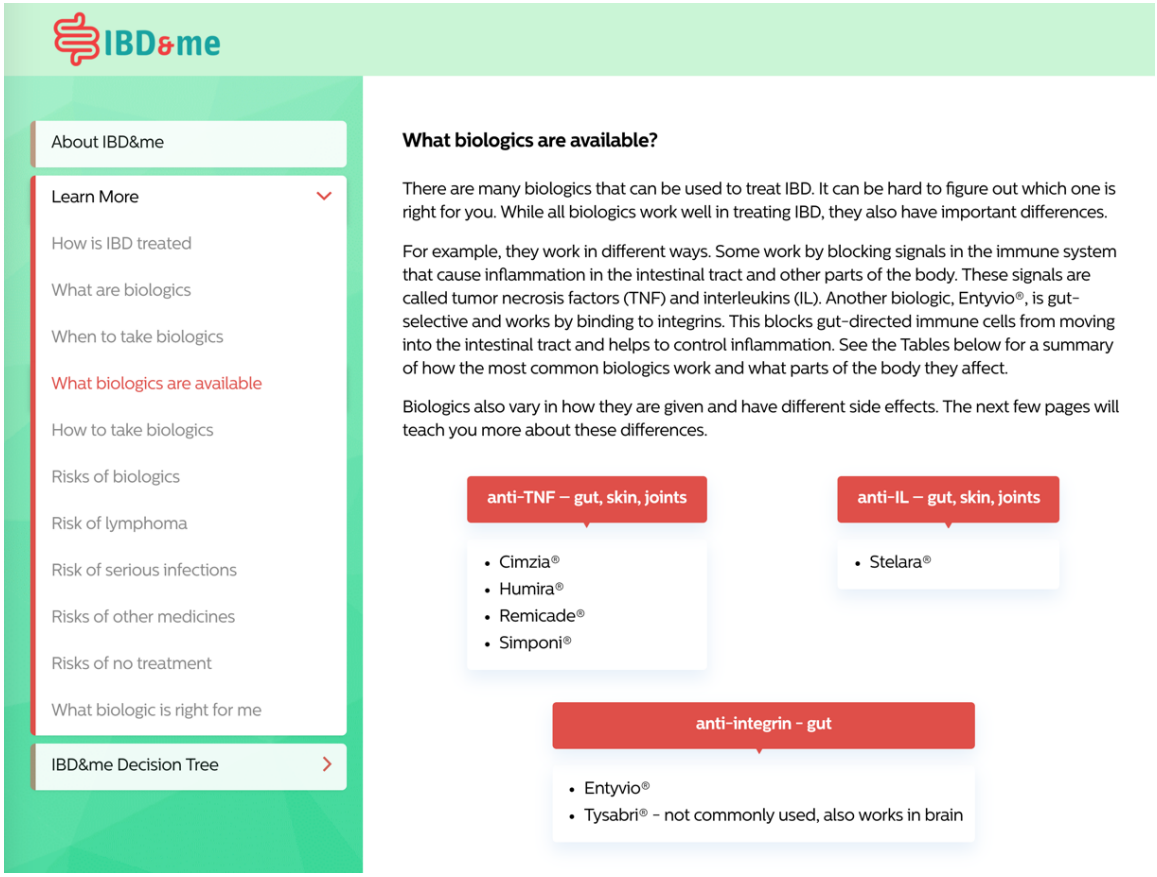
Patients randomized to IBD&me will be directed to complete the IBD&me Decision Tree prior to their appointment. By presenting the site to patients in this manner, rather than requesting that patients complete the SDM tool in clinic immediately preceding their visit, we intend to allow for sufficient time to review the education content and complete the conjoint survey at home, at their own pace. This recruitment process will also bypass the busy clinician office and not rely on providers enrolling patients – a pragmatic design we have developed from other trials we have performed of pre-clinic online tools.[25-27] Patients who complete IBD&me will be asked to print out their personalized report and bring it with them to their upcoming visit. As a pragmatic trial, we will track all patients who enroll using an intention-to-treat principal, including those who decide not to use the site, or those who do not bring their report with them to the visit. As a secondary analysis, we will also evaluate per-protocol subjects, focusing on those who completed the Decision Tree and brought the report to their appointment.

One day after the visit, subjects will receive a follow-up email to ask about their perception of SDM during the visit, their satisfaction during their visit, whether they completed and brought their personalized report to the visit, and the perceived utility of IBD&me in facilitating the discussion and/or impacting therapeutic decisions. Two months later, a follow-up email will direct subjects to report changes in treatment, and in clinical outcomes including disease activity and HRQOL. See the "Evaluation Design" section below for additional details on the outcome measurements and related psychometrics.

***Intervention: IBD&me – A Digital Tool to Enhance SDM for IBD Biologics*.** IBD&me (ibdandme.org) is an online, freely-available tool that allows patients to explore decision making around biologic therapies for IBD at their own pace. Funding for the development of the site was through collaborative research and educational grants managed by the Cedars-Sinai Office of Continuing Medical Education, which oversaw development of the content using a fair and balanced, peer-review process.

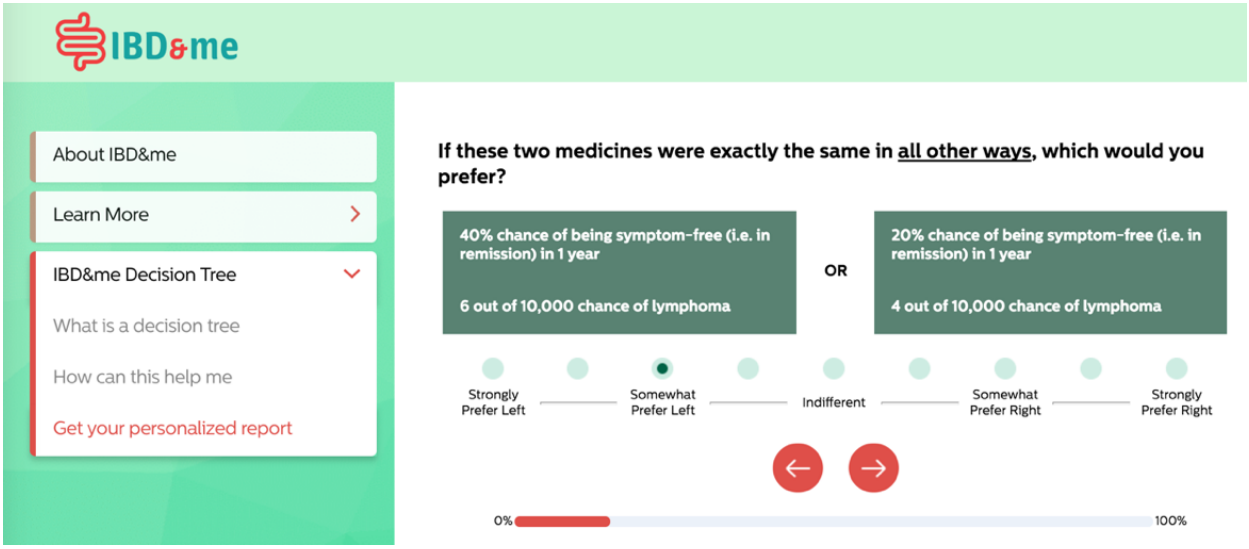
IBD&me enables patients to explore biologic risks and benefits by first introducing users to a "Learn More" section, which was iteratively developed by content experts at CS-CORE and the Cedars-Sinai IBD Center (**Figure 2**). Here, the site addresses common questions like: What are biologics? How to take biologics? And, what is the risk of lymphoma?

FIGURE 2. In the IBD&me "Learn More" section, patients learn about important terms and concepts related to biologics. In the page below, individuals are informed of the clinically-available biologic therapies and their mechanisms of action.



Afterwards, users complete a conjoint survey called the IBD&me Decision Tree; see **Figure 3** for a sample screenshot. Based on the respondent's answer to the first comparison, an algorithm selects a new side by side comparison and asks the respondent to select the preferred profile. The process continues until the respondent reveals internal consistency and the technique collects sufficient data to rank preferences.

FIGURE 3. In this example from the IBD&me Decision Tree, a patient needs to weigh the tradeoff of increased effectiveness of the biologic in inducing remission with an increased risk of lymphoma.



Once users complete the Decision Tree, the website then generates a unique IBD&me personalized report that they can review and share with their doctor. No two reports are the same. The report has been designed to help clinicians efficiently understand what is most important to their patient when selecting a biologic medicine. The example report in **Figure 4** reveals the type of information available to patients and their providers, and has 4 sections: (1) About This Report; (2) My Importance Scores; (3) What Does This Mean?; and (4) Other Helpful Information. The "About This Report" section describes how the report may be useful to patients and also instructs them to print it out and bring it to their next clinic visit (an email option is also available). The "My Importance Scores" section includes the patients' part-worth utility scores for the different biologic characteristics; the higher the score, the more important the characteristic is to the patient when choosing among medicines. In the example in **Figure 4**, mode of administration is the most important factor as it accounts for 19% of this patient's biologic decision making. In the "What Does This Mean?" section, patients see their top 3 most important factors in the decision-making process. It also highlights the patient's preferred route of administration and how often the patient prefers to receive the medicine. Finally, in the "Other Helpful Information" section, both patients and clinicians can review relevant, tailored information that may be helpful when discussing the different biologic options in clinic. For instance, in the provided example, the report describes how each of the currently available biologics are administered since the patient prioritized mode of administration when navigating the IBD&me Decision Tree.

FIGURE 4. Sample IBD&me Personalized Report that details the patient's priorities when selecting an IBD therapy.

IBD&me
www.ibdandme.org

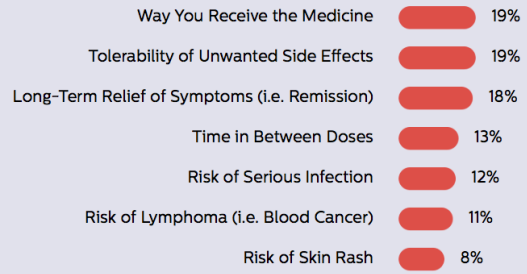
MY IBD&ME PERSONALIZED REPORT

ABOUT THIS REPORT

This is your IBD&me Personalized Report. It shows what was most important to you as you were deciding among the different biologic medicines. You can print out the Report and bring it with you to the doctor, or you can send it in an email to your doctor.

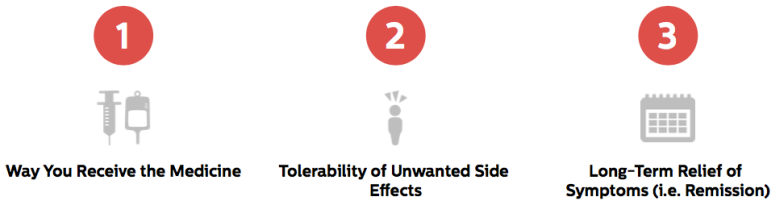
Below, you will see your "Importance Scores" for the seven biologic characteristics from the IBD&me Decision Tree. The higher the score, the more important the characteristic is to you when choosing among medicines. If you want to learn more about Importance Scores or how you can use this report, please visit the FAQs.

MY IMPORTANCE SCORES



WHAT DOES THIS MEAN?

Based on your responses, these were the top 3 most important factors for you as you were choosing among the different biologic medicines. It also seems that you prefer to receive the medicine injected under the skin in your home and want it given every 8 weeks



IBD&me
www.ibdandme.org

OTHER HELPFUL INFORMATION

WAY YOU RECEIVE THE MEDICINE

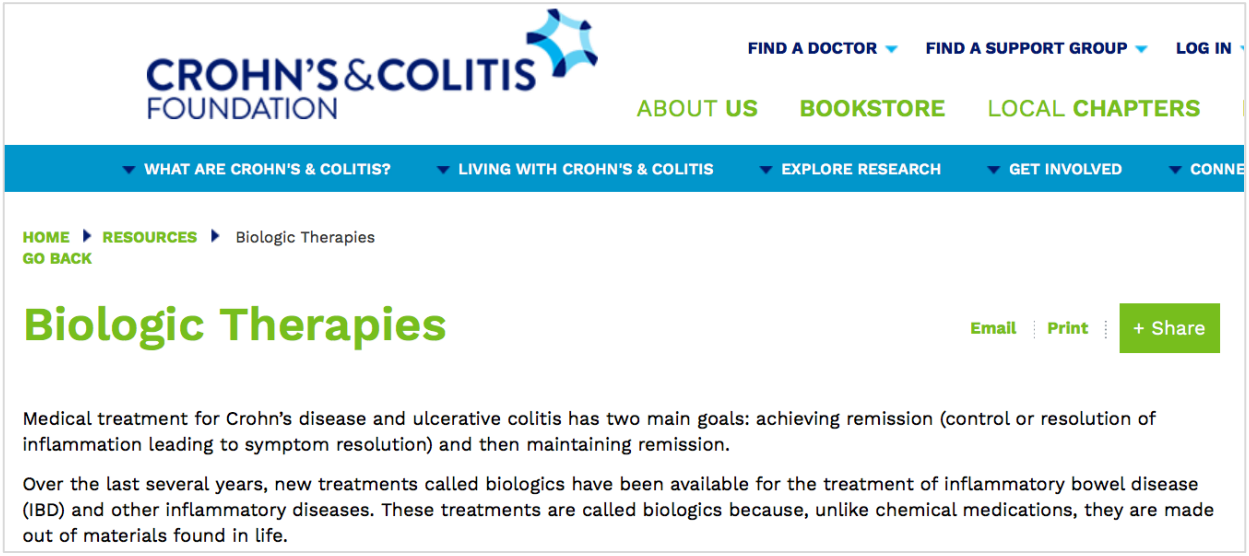
The Table shows how the currently available biologics are given. One option is to give it through an IV into the vein either in a clinic or at home. Another option is to inject the medicine yourself under the skin at home.

Give through an IV into the vein	Injected under the skin
Entyvio® (vedolizumab)	Cimzia® (certolizumab pegol)
Remicade® (infliximab)	Humira® (adalimumab)
Stelara® (ustekinumab) - starting dose *	Simponi® (golimumab)
	Stelara® (ustekinumab) - maintenance doses *

* When taking a biologic, there are two phases – the induction (i.e. starting) period followed by the maintenance period. During induction, higher and more frequent doses are generally given to improve your chances of responding to the medicine. If your IBD symptoms improve during induction, then you later receive maintenance doses that are more spaced out.

***Comparator: Crohn's & Colitis Foundation Education Material*.** The purpose of the RCT is to determine whether provision of an SDM tool like IBD&me offers incremental benefits over and above high quality educational material in the absence of an SDM tool. Thus, we will compare IBD&me against an active control that employs standardized, high-quality educational material from the Crohn's & Colitis Foundation. We will use the Foundation's Biologic Therapies online resource (www.crohnscolitisfoundation.org/resources/biologic-therapies.html), which is a well-researched and clearly presented overview of IBD biologic therapies, but without an active SDM component. See **Figure 5** for a screenshot of the site, which includes information on the different biologics, their mechanisms of action, and frequency of dosing. The site also describes the risks and special considerations for biologic therapies.

FIGURE 5. Crohn's & Colitis Foundation Biologic Therapies educational material.



Covariate Data. In addition to outcomes data (see "Evaluation Design" section for details), we will collect patient demographics, including age, gender, race/ethnicity, education, marital status, employment status, and income. We will also ask questions regarding participants' IBD, including the type of IBD (UC or CD), duration of IBD, prior IBD-related surgery, IBD-related symptoms experienced in the past 30 days, IBD severity as determined by the Short Inflammatory Bowel Disease Questionnaire (SIBDQ),[28] and current and prior IBD therapy use (steroids, aminosalicylates, immunomodulators, antibiotics, biologics, and small molecules).

EVALUATION DESIGN

Primary and Secondary Outcomes. Our primary outcome will be SDM as measured by the validated 9-item Shared Decision Making Questionnaire (SDM-Q-9; **Appendix 1**).[29] Patient satisfaction as measured by the short-form Patient Satisfaction Questionnaire (PSQ-18; **Appendix 2**) will serve as a secondary outcome.[30] One day after the clinic visit, patients will be sent an email by research staff inviting them to complete the SDM-Q-9 and PSQ-18 on REDCap, a secure web application for managing online surveys and databases. They will be instructed to

answer the questions thinking about discussions that took place during the visit, if any, regarding biologic therapeutic options. Two months later, a follow-up email will direct subjects to report changes in treatment, and in clinical outcomes including disease activity (SIBDQ) and HRQOL (NIH PROMIS 10 Global Health questionnaire).

Statistical Analysis. All analyses will be conducted from an intention-to-treat perspective. As randomization will balance measurable and unmeasurable variables between groups, we will use Student's t-test to assess for significant differences in SDM-Q-9 scores between the IBD&me and standardized education groups. We will also perform multivariable linear regression to identify patient (age, sex, race/ethnicity, education level, etc.), provider (years of experience, level of training [physician, nurse practitioner, physician assistant]), and process (IBD&me vs. education material comparator) characteristics that are independent predictors of higher SDM-Q-9 scores.

Sample Size. While the SDM-Q-9 is a widely used, validated measure, we are unaware of data measuring the minimally clinically important difference on the scale. Therefore, the sample size was calculated to achieve a moderate effect size of 0.5 (a half standard deviation difference, which generally correlates with the minimally clinically important difference) in mean SDM-Q-9 scores between groups.[31,32] Assuming a two-tailed 5% significance level with 80% power, the minimum sample size needed to show an effect size of 0.5 is 64 patients per group.

Plans for Dissemination. Upon completion of the study, we will disseminate the findings through abstracts submitted to either the Crohn's & Colitis Congress or Digestive Disease Week (DDW). We will also prepare and submit a manuscript for peer-review at a high-impact medical journal, employ our social media channels at Cedars-Sinai (12K+ followers) and the PI (Dr. Spiegel ~5.6K followers), and work with our media contacts to drive awareness about the trial results.

DETAILED WORKPLAN AND DELIVERABLES SCHEDULE

For Aim 1, we anticipate a 12-month timeline. This will begin with a kickoff in-person meeting that will include all members of the research team at Cedars-Sinai, principal investigators of IBD Qorus, and representation from the Crohn's and Colitis Foundation including the Director of IBD Qorus. This meeting will serve as the launch of the study, ensure all personnel roles are clarified, and that the timeline and study plan are reviewed. Immediately following this meeting, we will develop patient recruitment materials, and update the IBD&me site for use in a research capacity. We will then develop and test outcome surveys to clarify determinants of success. Regulatory documents will be prepared and submitted for review through the usual mechanisms of IBD Qorus regulatory submission, utilizing Dartmouth-Hitchcock as the central Institutional Review Board (IRB) for the majority of sites, and any additional interested sites not relying on Dartmouth will be provided the relevant regulatory documents for local submissions. We anticipate a rapid approval for this low-risk study based on our prior experience with IBD&me, and expect patient enrollment to begin within 4 months of study kickoff after requisite regulatory approvals. Patient enrollment will continue for 5 months, during which time, enrollment will be actively monitored and strategies for boosting enrollment will be sought as needed, with active collaboration with the IBD Qorus leadership team. Patients will

complete all study-related surveys 2 months following enrollment, for a total of 7 months of data collection from the first patient enrolled to the last patient for whom data is collected. We then anticipate a 2-3 month data analysis period, followed by abstract and manuscript preparation for submission to an international GI meeting and a high-impact medical journal.

AIM 1: Timeline and Milestones.

Task	Month											
	1	2	3	4	5	6	7	8	9	10	11	12
Kickoff meeting	○											
IRB submission and approval	○	○	○									
Develop patient recruitment strategy and materials	○	○										
Develop and test outcome surveys	○	○										
Recruit patients through IBD Qorus				○	○	○	○	○				
Data collection and analyses				○	○	○	○	○	○	○		
Prepare and submit abstracts & manuscript										○	○	○

AIM 2. EXAMINING IBD PATIENTS' MAIN DRIVERS OF DECISION MAKING WHEN SELECTING AMONG BIOLOGICS AND SMALL MOLECULES.

TARGET AUDIENCE

In addition to testing the impact of IBD&me on patient-reported outcomes, we also aim to prepare the tool for wider dissemination and applicability to upcoming therapeutic options. As with any SDM tool, IBD&me must remain relevant over time, especially given the growing pipeline of IBD therapies and increasing worldwide prevalence of IBD. To achieve this, we will use conjoint analysis to assess how IBD patients both within and beyond North America choose among both current and future IBD therapeutic profiles. Eligible patients will include those with IBD recruited through Cint (www.cint.com), an international survey research firm, the Cedars-Sinai Gastrointestinal Patient Reported Outcome Measurement Information System (PROMIS®) research database,[33] and the Mucosal Immunology Repository for Inflammatory and Digestive Diseases (MIRIAD) database. Eligible individuals will be those who are 18 years of age or older with evidence of recently active IBD symptoms in the past 30 days, including abdominal pain, diarrhea, constipation, bowel incontinence or leakage, nausea and/or vomiting, joint pain, and/or blood in stool.

PROJECT DESIGN AND METHODS

Conjoint Analysis – Overview. Conjoint analysis is a form of tradeoff analysis that elucidates how people make complex decisions by balancing competing factors.[34] It was first widely used in marketing,[35] but the technique has since spread to product design, social sciences, and healthcare. Recent studies from our group and others have used conjoint to examine clinical decision making in rheumatology,[36] surgery,[37] diabetes management,[38] use of transfusions in dialysis-related anemia,[39] and even IBD.[40-45] Given the penetration of this technique into healthcare, the International Society for Pharmacoeconomic and Outcomes Research (ISPOR) created a task force to develop guidelines for healthcare conjoint analysis,[34] indicating broad acceptance of this approach for quantifying how patients make difficult decisions under conditions of uncertainty.

Conjoint analysis poses a series of side by side comparisons of competing product profiles and asks respondents to select which profile is preferable (**Figure 3**). Based on the respondent's answer to the first comparison, an algorithm selects a new side by side comparison and asks the respondent to select the preferred profile. The process continues until the respondent reveals internal consistency and the technique collects sufficient data to rank preferences.

Conjoint Analysis Survey for Biologic and Small Molecules Decision Making. To quantify and rank preferences regarding use of biologics and small molecules in IBD, we will use the adaptive conjoint analysis platform developed by Sawtooth Software (Sawtooth, North Orem, Utah). Conjoint analysis assumes that decision making depends upon attributes, each of which has levels. For example, selecting among IBD biologics and small molecules may depend upon many attributes, including mechanism of action, route of delivery, frequency of administration, efficacy at inducing remission, tolerability of side effects, and risks for lymphoma, serious infection, rash, fatigue, and hyperlipidemia. Each attribute can be measured across several levels. As an example, levels for mechanism of action are anti-TNF, anti-integrin, anti-IL 12/23, and Janus kinase inhibitors. For mode of administration, levels can include oral, intravenous, and subcutaneous. Of note, our original conjoint analysis focused solely on biologics,[22] and did not include oral administration of medications; this may be a priority for many patients with moderate-to-severe IBD when selecting among the different therapy options.

Once the attributes and levels are defined, the conjoint analysis software displays sets of side by side therapeutic profiles, each with varying levels for each attribute (**Figure 3**). For each therapeutic profile in these pair comparisons, respondents decide which therapy is preferable, if any. The comparisons become increasingly complex as the respondent progresses and continues until responses achieve internal consistency.

In addition to conjoint vignettes, the survey will include stand-alone questions regarding patient demographics, including age, gender, race/ethnicity, education, marital status, employment status, and income. We will also ask questions regarding participants' IBD, including the type of IBD (UC or CD), duration of IBD, prior IBD-related surgery, IBD-related symptoms experienced in the past 30 days, IBD severity as determined by the SIBDQ,[28] and current and prior IBD therapy use (steroids, aminosalicylates, immunomodulators, antibiotics, biologics, and small molecules). The responses to these questions will be used to identify potential demographic or clinical predictors of decision making. We hypothesize that biologic

and small molecule preferences might vary predictably, for example, by IBD severity, patient age, or country.

Approach. We will recruit eligible patients to complete the conjoint analysis survey through Cint, a global survey research firm, and through the Cedars-Sinai Gastrointestinal PROMIS® and MIRIAD databases. Cint partners with panel companies and research panels across the world, and all together has access to over 40 million potential research participants in over 80 countries. For this study, we will focus on recruiting patients from North American and European countries with a high prevalence of IBD, including the U.S., Canada, and United Kingdom.[46] The PROMIS® database includes over 150 IBD patients evaluated in clinics at Cedars-Sinai Medical Center, the West Los Angeles Veterans Affairs Medical Center, the University of Michigan, and UCLA.[33] The MIRIAD database includes over 15,000 IBD patients who have consented to be contacted for future research studies including surveys.

Cint will send potential subjects a message through the Cint portal inviting them to complete the conjoint survey. After they provide online informed consent, participants will then be shown a "blinded" screener question that asks them if they have been diagnosed by a physician with one or more of the following medical conditions: (i) UC; (ii) CD; (iii) rheumatoid arthritis; (iv) ankylosing spondylitis; (v) psoriasis; (vi) psoriatic arthritis; or (vii) none of the above. Only those who click UC or CD will be allowed to proceed through the conjoint exercise. By using a "blinded" screener that includes UC and CD along with other inflammatory conditions, it will help maximize the likelihood that respondents had, in fact, been diagnosed with IBD and are not simply seeking compensation by participating in a survey. As for the patients included in our PROMIS and MIRIAD databases, all of whom have physician-confirmed IBD, research staff will directly email potential participants a link to the conjoint analysis survey.

EVALUATION DESIGN

Conjoint Analysis Outcomes – Part-Worth Utilities and Importance Scores. After respondents complete the survey, the conjoint software uses hierarchical Bayes regression to estimate individual-level utility coefficients.[41,47] These coefficients are called part-worth utilities, and they are generated for each attribute level. Levels that have greater importance in the decision-making process are associated with higher part-worths, and the part-worth utilities for the levels within each attribute sum to zero. In addition to calculating part-worth utilities, the conjoint software also generates importance scores, which are derived by calculating the delta between the part-worths for the most important and least important level of each attribute.[41] The larger the delta in part-worth utilities, the larger the importance of the attribute in the decision-making process. As an example, see **Figure 1** for average attribute importance scores for UC and CD patients in our recent study focused on biologic decision making.[22]

Statistical Analysis*.* For the entire cohort, we will calculate mean importance scores for each therapy attribute (e.g., mechanism of action, mode of administration, efficacy, etc.), and list them in rank-order from highest to lowest relative importance. We will then compare group-level (e.g., male vs. female, racial/ethnic group comparisons, U.S. vs. Canada vs. United Kingdom comparisons) rankings, followed by patient-level ratings to assess the uniqueness of individuals' decision profiles.

We will then perform multivariable logistic regression models on our outcomes to adjust for confounding. The outcomes in the models will be whether individuals reported the following attributes as the most important factor in their decision-making process: (i) mechanism of action; (ii) mode of administration; (iii) efficacy; and (iv) side-effect profile (i.e., tolerability of side effects, fatigue, rash, risk of serious infection, risk of lymphoma, or hyperlipidemia). All patient-level demographic (age, gender, race/ethnicity, education, marital status, employment status, household income, country) and clinical (type of IBD, duration of IBD, prior surgery for IBD, IBD severity as determined by the SIBDQ, current and prior IBD therapy use) variables will be included in the regression models.

Sample Size. Based on conjoint analysis sample size recommendations from Sawtooth Software and to allow for adequately powered subgroup comparisons,[48] we will recruit 300 respondents from each country (U.S., Canada, United Kingdom) through Cint to complete the survey. From the PROMIS and MIRIAD databases we will recruit another 300 patients combined. Therefore, the study will include a total of 1,200 IBD patients from across the globe.

Plans for Dissemination. Upon completion of the study, we will disseminate the findings through abstracts submitted to either the Crohn's & Colitis Congress or DDW. We will also prepare and submit a manuscript for peer-review at a high-impact medical journal, employ our social media channels at Cedars-Sinai, and work with our media contacts to drive awareness about the study results.

DETAILED WORKPLAN AND DELIVERABLES SCHEDULE

For Aim 2, we anticipate a 12-month timeline. This will begin with a kickoff in-person meeting that will include all members of the research team at Cedars-Sinai. This meeting will serve as the launch of the study, ensure all personnel roles are clarified, and that the timeline and study plan are reviewed. Immediately following this meeting, we will develop and update the conjoint survey to expand the attributes and options to reflect up-to-date treatment options, safety profiles, and efficacy estimates of available and emerging therapies. Regulatory documents will be prepared and submitted for review through the usual mechanisms at the Cedars-Sinai IRB. We anticipate a rapid approval for this low-risk study based on our prior conjoint analysis-based studies, and expect patient enrollment to begin within 4 months of study kickoff after requisite regulatory approvals. Patient enrollment will continue for up to 5 months, during which time, enrollment will be actively monitored and strategies for boosting enrollment will be sought as needed. After data collection is complete, we then anticipate a 2-3 month data analysis period, followed by abstract and manuscript preparation for anticipated submission to an international GI meeting and a high-impact medical journal, respectively.

AIM 2: Timeline and Milestones.

Task	Month											
	13	14	15	16	17	18	19	20	21	22	23	24
Kickoff meeting	○											
IRB submission and approval	○	○										

Develop and test conjoint analysis survey	○	○	○	○								
Recruit IBD subjects globally and collect data				○	○	○	○	○				
Data collection and analyses				○	○	○	○	○	○	○		
Prepare and submit abstracts & manuscript										○	○	○

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