Evaluating a Prediction Tool and Decision Aid for Patients with Crohn's Disease

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ABSTRACT

Purpose: The overall purpose of this project was to validate a model that risk stratifies patients with Crohn's disease, link this model to a web-based decision aid to create a personalized shared decision making program, and to study the impact of this program on patients' choice of therapy and decision quality.

Scope: The prediction tool was calibrated and validated using data from adult patient populations. The Crohn's disease shared decision making program was then tested in adult patients ranging from 18-69 years of age, from 14 gastroenterology practices throughout both urban and rural regions in the United States.

Methods: The prediction tool was developed using data from a single medical center, and then validated in two separate patient cohorts. Then, using system dynamics analysis (SDA) these results were transformed into a simple graphical web-based display to show patients their individualized probability of developing a complication over a 3-year period. This Crohn's disease shared decision making program was then tested prospectively in a cluster randomized controlled trial.

Results: Compared to the control group the intervention group receiving the shared decision making program had more patients select "combination therapy," which has been proven the most effective therapy for the treatment of Crohn's disease. We also showed that in the intervention group fewer patients remained untreated, patients more often received the treatment that they preferred, had lower decision conflict, an increased understanding of their disease and increased trust in their physicians.

Key Words: Crohn's disease, shared decision making, risk, prediction

PURPOSE

Crohn's disease is a chronic inflammatory bowel disease that has significant impact on the quality of life of an estimated 500,000 Americans. Recent studies have taught us that earlier, more intensive therapy with immunomodulator and anti-tumor necrosis factor (TNF) medications soon after diagnosis and before complications occur lead to better patient outcomes. However, these drugs have serious risks including life-threatening infections and an association with lymphoma. There are two major barriers in initiating these medications early in the disease course before patients have proven to have severe disease: (1) we need to choose appropriate patients who will need these drugs without over-treating those destined to have mild disease, and (2) based on fears of side-effects, patients are hesitant to use these medications until they believe their disease is severe enough to deserve them. To address these concerns, we have developed two tools. First, we have created a statistical model using system dynamics analysis (SDA) to predict an individual patient's Crohn's disease course based on clinical, serologic, and genetic factors. Second, we have produced a web-based decision aid to help patients weigh the benefits and risks of available treatments for Crohn's disease. The overall purpose of this project was to validate our currently available prediction model, link this to the web-based decision aid to create a personalized shared decision making program, and to study the impact of this program on patients' choice of therapy for Crohn's disease and decision quality. This proposal responds to the AHRQ health information technology (IT) portfolio priority area to improve health care decision making by developing and implementing health information tools that consider patients' expressed treatment preferences.

SCOPE

Background

Crohn's disease is a chronic inflammatory bowel disease (IBD) primarily causing inflammation of the bowel. Although the pathogenesis is incompletely understood, Crohn's disease is likely caused by a complex relationship between genetics, immune dysregulation, and environmental factors.[1] Crohn's disease affects over half of a million people in the United States, with an incidence and prevalence estimated as high as 10.7 per 100,000 person-years and 246.7 cases per 100,000 person-years, respectively.[2, 3] Patients are most commonly diagnosed in young adulthood, but others may not develop symptoms until they are older.[4] Symptoms range from mildly active disease with occasional diarrhea and rectal bleeding to severely active disease that may result in 10-20 bloody bowel movements per day, associated abdominal pain and the frequent need for bowel surgery as a result of intestinal strictures, perforations, and fistulas. Quality of life is variable with many patients living completely normal active lives, while others are disabled.

Context: Evolving Treatment Algorithms – Early Intensive Therapy

Significant progress has been made for the treatment of IBD over the past decade. In addition to the introduction of the anti-tumor necrosis factor (TNF) and other biologic agents, we are also learning to better optimize the available medications. The treatment algorithm of starting with safe but weaker medications early in the disease course, and only advancing to more potent medications when those treatments fail has been

challenged with recent comparative effectiveness studies. The “top-down” treatment strategy for Crohn’s disease showed us that use of infliximab in combination with the immunomodulator azathioprine early in their disease course led to remission of symptoms, steroid sparing and endoscopic healing more often than patients treated in a standard “step-up” fashion.[5] In the landmark SONIC study, patients with a relatively short disease duration who were naïve to immunomodulators and biologics were randomized to receive azathioprine, infliximab or combination infliximab and azathioprine therapy. The combination therapy group clearly showed superiority for inducing remission and mucosal healing.[6] It has become clear that more patients will respond to therapy and attain remission with this more aggressive “early intensive” approach of using effective medications before patients become dependent on corticosteroids, and before permanent complications of their disease occurs.

Barriers to Early Intensive Therapy

There are two significant barriers to the wide acceptance of early intensive therapy. (1) We need to determine which patients are at the highest risk for disease complications so that we can properly select who is most appropriate for this approach – certainly it is not all patients and (2) due to rare but serious side-effects of immunomodulators and anti-TNF agents (including lymphoma and life-threatening infections), patients and many providers are hesitant to use these medications. To help all of those involved in decisions for treatment we need to better understand the predicted course of disease and how this is balanced by the chance of treatment related adverse events. Although determining the expected benefit and risks of therapy is the first step in helping us make an informed decision, a critical component is to develop methods for clearly communicating these complex data to patients so that they can be meaningful participants in a shared medical decision.

Overcoming Barrier #1: Predicting the Course of Crohn’s Disease

There has been great interest in defining risk factors that predict which patients with Crohn’s disease will have the highest chance of experiencing an aggressive disease course leading to complications, such as strictures or perforations. The simple idea is to identify high-risk patients at or soon after diagnosis so that they can be treated effectively before complications develop. An analogy is to rheumatoid arthritis management. If effective treatments, such as the anti-TNF agents, are given after severe joint deformities develop there is little chance of reversing the damage. However, early treatment with anti-TNFs for at risk patients is a successful strategy to prevent damage before it occurs.[7] For Crohn’s disease, clinical factors predicting severe disease have been identified including age, location of Crohn’s disease involvement (e.g., small bowel, colon, perianal disease), symptoms at the time of diagnosis and requirement for steroids early in the disease course.[8, 9] Serologic markers have also been identified as predictive of disease complications including immune response to microbial antigens and carbohydrates.[10-12] In addition, genetic status appears to play a role in identifying patients at risk for a more rapid progression of their disease.[13, 14] This previous work very nicely shows that we can, in fact, identify patients who are at the most risk to develop complications from Crohn’s disease. At the current time, these independent studies leave us without a clear understanding of how each of these factors interacts with each other. Furthermore, there was no method available to combine these variables to create an individualized risk profile.

Overcoming Barrier #2: Shared Decision Making & Decision Aids

Shared decision making (also called decision support) is defined as the process of interaction with patients who wish to be involved with their health care providers in making medical decisions.[15] In this model, physicians have the responsibility of informing and recommending treatments to patients, but the process of deciding on how to act on this is shared. The goal is to enhance patient involvement, and on the basis of the available evidence, facilitate "evidence - based patient choice."[16] The fairly new and increased attention to shared decision making derives from a number of different factors.[15] These factors include a move from the idea of informed consent to "informed choice," the consumer [patient] rights movement and the changing nature of medical practice (long-term management of chronic disease).[15]

Finding an efficient and effective method to clearly communicate data to our patients is not easy, but decision aids are showing great promise to meet this goal**.** Decision aids are interventions developed for preparing patients for decision making about specific treatment choices.[17, 18] These are not patient education materials given to patients after a prescription has been written or a surgery is scheduled, but a presentation of information before a choice of therapy has been made. Decision aids are essentially the presentation of evidence-based information in a patient-friendly format to allow patients to understand how treatment options fit with their personal preferences. If the appropriate data are available, and the decision aid is produced effectively, a decision aid is a perfect tool to communicate the results of comparative effectiveness research (studying day-to-day clinical decisions) directly to patients**.**

Improving Clinical Practice

To overcome these two barriers, a decision aid incorporating a risk prediction tool can present a balanced discussion of benefits and risks of therapy and allow patients to see their personalized predicted course of disease. A typical gastroenterology office visit lasts between 15 and 30 minutes, with precious little time to assess, diagnose and develop a treatment plan. The task of discussing complex tradeoffs of different medical therapies is, unfortunately left little or no time. Patients need to learn about their disease, their expected natural history with or without treatment, and the benefits and risks of therapeutic options. A systematically developed, evidence-based and validated tool that is easy for patients to use outside of the office visit would substantially impact the way we communicate with patients and allow them to make informed and shared medical decisions**.**

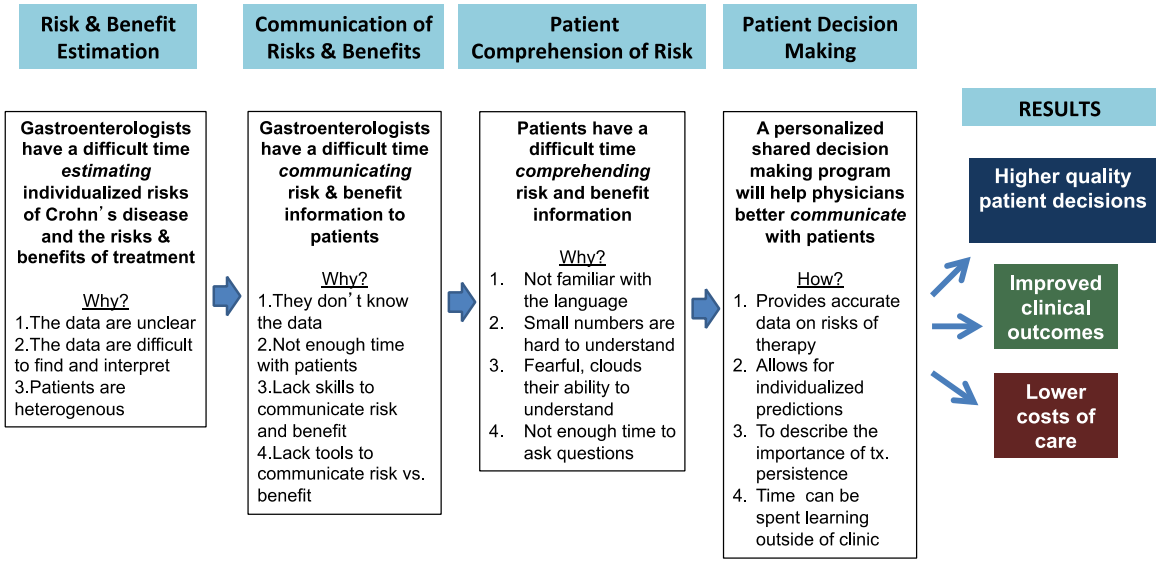
Overall Hypothesis and Project Goal

Hypothesis: A shared decision making program incorporating a web-based decision aid with an individualized risk prediction tool will help patients understand which treatments are right for them and will lead to a higher acceptance of appropriate therapy, improved persistence with chosen therapy, lower costs and improved clinical outcomes.

The overall goal of this project was to develop a web-based decision aid that incorporates a validated Crohn's disease prediction tool, and in the setting of a randomized controlled trial study the impact of the shared decision making program on patients' choices for therapy, decision quality, persistence with chosen medications, cost of care, and clinical outcomes of Crohn's disease**.**

The conceptual framework of our program is shown in **Figure 1**.

Figure 1. Conceptual framework of research program



Participants and Study Setting

The inclusion criteria for patients in the randomized controlled trial included:

1. Patients age 18 years or older
2. Fluent, English speaking
3. Established diagnosis of Crohn's disease based on standard clinical, radiographic, endoscopic and histologic criteria
4. A candidate to receive immunomodulators or anti-TNF therapy based on their provider's recommendation
5. Not currently taking immunomodulators (6-MP, azathioprine, methotrexate) or anti-TNF agents (infliximab, adalimumab, certolizumab pegol)

The exclusion criteria included:

1. Participant in a pilot study/focus group for development of the Crohn's Disease Shared Decision Making Program
2. Currently taking any medication that is contraindicated to take together with an immunomodulator or anti-TNF agent
3. Known intolerance to either immunomodulators or anti-TNF agents
4. Lack of accessibility to telephone or email for follow-up surveys

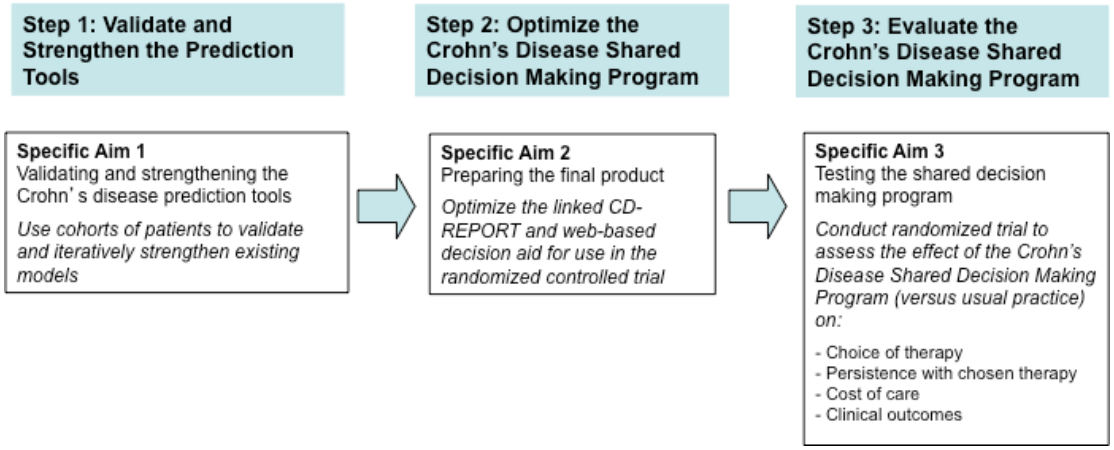
There was a broad practice mix to address priority populations, specifically from rural and urban locations, and from both academic and community practices.

Academic Centers	Community Practices
Dartmouth-Hitchcock Medical Center, Lebanon, NH	Atlanta Gastroenterology, Atlanta, GA
Cedars-Sinai Medical Center, Los Angeles, CA	Dartmouth-Hitchcock Nashua, Nashua, New Hampshire
Brigham and Women's Hospital, Boston, MA	Charlotte Gastroenterology and Hepatology, Charlotte, NC
Jefferson University, Philadelphia, PA	Ohio Gastroenterology and Liver Institute, Cincinnati, OH
Mount Sinai Medical Center, New York, NY	Minnesota Gastroenterology, Minneapolis, MN
University of Chicago, Chicago, IL	Winthrop University Hospital, Winthrop, NY
University of Pittsburgh, Pittsburgh, PA	
University of Maryland, Baltimore, Maryland	

METHODS

The operational framework of the research program is displayed below in **Figure 2.**

Figure 2. Operational framework of research program



Specific Aim 1 – To validate the Crohn's Disease prediction model

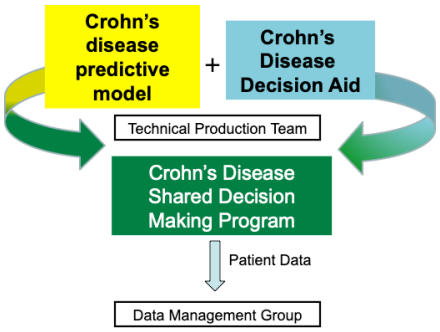
The adult Crohn's disease prediction model was developed using data from the Cedars-Sinai Medical Center in Los Angeles, California. A well-characterized cohort of adult patients with Crohn's disease was analyzed. Available data included: demographics; clinical characteristics; serologic immune responses; *NOD2* status; time from diagnosis to complication; and medication exposure. Cox proportional analyses were performed to model the probability of developing a Crohn's disease complication over time. Two independent cohorts were used for validation of the calibration model. The first cohort included 612 adult Crohn's disease patients from Mount Sinai Hospital in Toronto, Ontario. Identical data to the calibration cohort were captured in the Mount Sinai Hospital database. The second validation cohort included 409 pediatric patients with Crohn's

disease from a multicenter prospective patient registry, described in a previous publication. Using system dynamics analysis (SDA) these results were transformed into a simple graphical web-based display to show patients their individualized probability of developing a complication over a 3-year period. The tool was called PROSPECT (Personalized Risk and Outcome Prediction Tool).

Specific Aim 2 – Optimizing the Crohn's disease shared decision making program

The adult Crohn's disease prediction model and the Crohn' disease decision aid were separate entities that needed to be linked electronically. This link allowed for sequential communication to patients about Crohn's disease and its treatment along with a prediction of that individual patient's disease course. In addition, data collection instruments (e.g., surveys and data collection forms) were developed and incorporated into these web-based tools for purposes of the randomized controlled trial in Specific Aim 3. To build the link between the prediction model and the decision aid, along with the data collection instruments, we worked together with a technical production team responsible for the web-based applications and a data management group to retrieve, record and analyze the results in a secure manner.

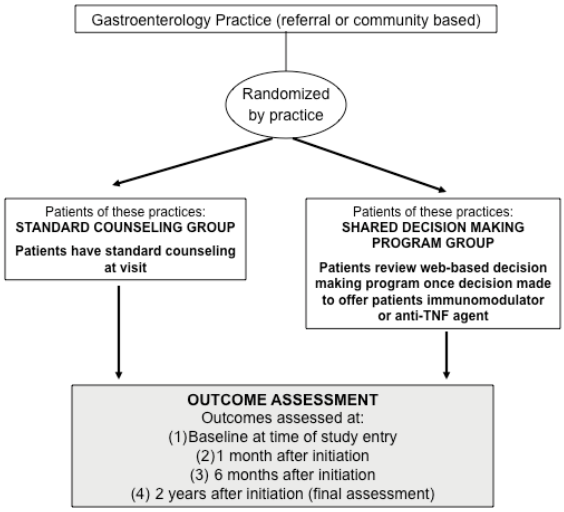
Figure 3. Operationalization of Specific Aim 2



Specific Aim 3 – Evaluate the shared decision making program

Patients with Crohn's disease were prospectively recruited from 14 GI practices across the US. To meet inclusion criteria, all patients had to be within 15 years of diagnosis, without any current or prior disease complications, not currently on IMs or biologics but considered a candidate for these treatments by their provider. This study was a cluster randomized trial stratified by practice type, with 7 practices in the intervention arm (received Decision Aid) and 7 practices in the control arm (standard of care). Questionnaires were administered electronically and via telephone to capture data over different time points, in addition to chart reviews. **Figure 4** shows an overview of the study design.

Figure 4. Overview of the cluster randomized controlled trial



Primary outcome measure

Proportion of patients choosing combination therapy. Rationale: This project proposal was developed with the concept that barriers to using early combination therapy limit its use in practice. Based on data presented in the decision aid and our prior work with the risk prediction model, combination therapy will be the superior treatment strategy for most patients. Due to previously described barriers we expected the standard counseling group to have a relatively low rate of choosing combination therapy allowing our best opportunity to detect a difference in the intervention group. Secondary outcome measures below will include how patient preferences influence these decisions.

Secondary outcome measures

a. Time to initiation of immunomodulator and/or anti-TNF therapy
b. Patient choice of therapy (4 level: no therapy, immunomodulator monotherapy, anti-TNF monotherapy, combination therapy)
c. Persistence (Adherence) with chosen therapy
d. Quality of decision
    i. Decisional conflict (validated scale)
    ii. Decision consistent with patient values (i.e., patient receiving the treatment that they want)
    iii. Trust in physician
e. Cost of care*
    i. Crohn's disease related costs at 2 years
f. Clinical outcomes at 6 months, 1 year and 2 years*
    i. Proportion of patients in clinical remission
    ii. Proportion of patients taking steroids
    iii. Proportion of patients requiring surgery
    iv. Number of hospitalizations

*preliminary data to understand feasibility of these outcomes

RESULTS

Specific Aim 1 – To validate the Crohn's Disease prediction model

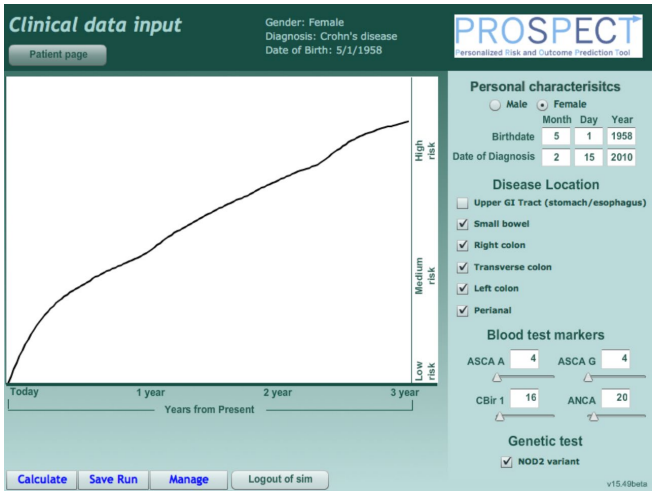
243 CD patients **(Table 1)** were included in the final model of which 142 experienced a complication. Significant variables in the multivariate Cox model included small bowel disease (HR 2.12, CI 1.05-4.29), left colonic disease (HR 0.73, CI 0.49-1.09), perianal disease (HR 4.12, CI 1.01-16.88), ASCA (HR 1.35, CI 1.16-1.58), Cbir (HR 1.29, CI 1.07-1.55), ANCA (HR 0.77, CI 0.62-0.95), and the NOD2 frameshift mutation/SNP13 (HR 2.13, CI 1.33-3.40). The Harrell's C (concordance index for predictive accuracy of the model)=0.73. When applied to the two external validation cohorts (adult n=109, pediatric n=392), the concordance index was 0.73 and 0.75, respectively for adult and pediatric patients.

Table 1. Characteristics of Crohn's Disease Patients Included in the Calibration Cohort

	N=243
Age (median, range)	28 (18-76)
Proportion female	118 (49%)
Years of Crohn's disease (median, range)	6.1 (0.25-15)
Disease location	
Small bowel only	55 (23%)
Colonic only	37 (15%)
Small bowel and colonic	149 (61%)
Perianal	35 (15%)
Disease phenotype	
Stricturing	91 (38%)
Internal Penetrating	46 (19%)
Non-stricturing/Non-penetrating	118 (49%)
Years to complication (median, range)	3.3 (0.3-15.7)
Underwent surgery (non-perianal)	121 (50%)

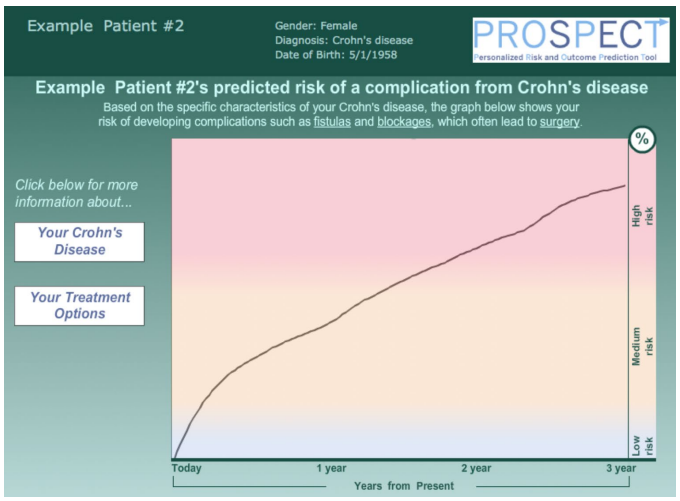
Using system dynamics analysis (SDA) these results were transformed into PROSPECT, the simple graphical web-based display to show patients their individualized probability of developing a complication over a 3-year period. **Figure 5** shows the data input screen for the example patient, and Figure Y shows the patient output screen.

Figure 5. Clinical data input screen for risk prediction tool of example patient



Next, the patient results **(Figure 6)** were sent directly to the patient, linked to the Crohn's disease decision aid video along with follow-up baseline survey.

Figure 6. Example patient output screen

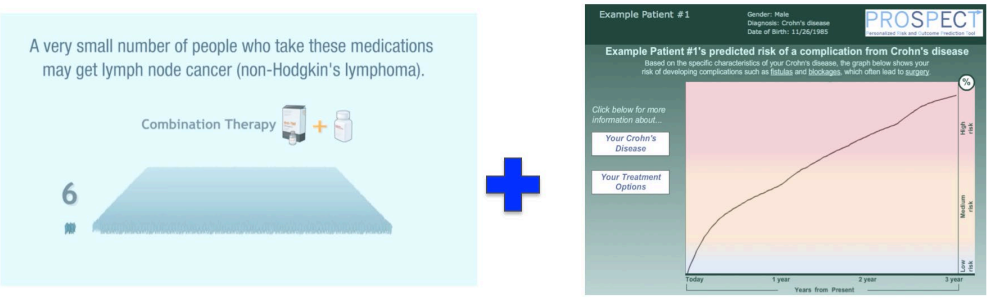


Specific Aim 2 – Optimizing the Crohn's disease shared decision making program

For Specific Aim 2, the results were an operational shared decision making program including the web-based Crohn's decision aid plus the individual results of PROSPECT **(Figure 7)**. This was sent as an email link to patients in the invention group only. Programming allowed for electronic surveys to be administered and all responses were captured for analysis.

Figure 7. Crohn's disease decision aid

Web-Based Crohn's Decision Aid **Individual Risk Prediction Tool**



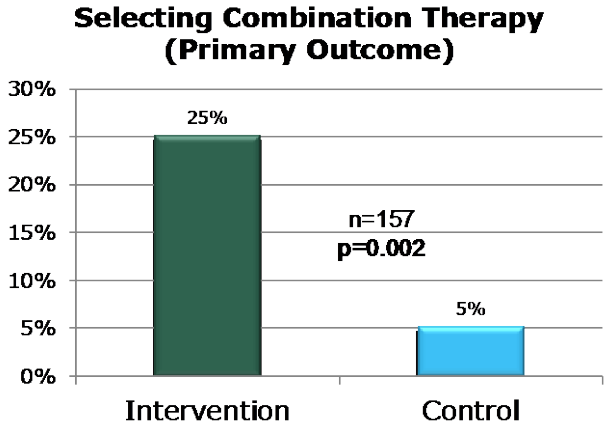
Specific Aim 3 – Evaluate the shared decision making program

A total of 202 patients were recruited over a 3-year period, approximately 2:1 in favor of intervention (133) versus control (69). Demographics were similar between groups **(Table 2)**, with more women in the control group and slightly shorter disease duration in the intervention group. **For the primary outcome, 25% of patients in the intervention group chose combination therapy as compared to 5% in the control group (p=0.002), Figure 8.** In the intervention group, only 1% of patients chose no therapy directed at Crohn's disease versus 17.5% in the control group (p<0.001).

Table 2. Patient characteristics from cluster randomized controlled trial

	Intervention (N=133)	Control (N=69)
% Female	51.9%	65.2%
Median age in yrs (range)	32 (18-69)	31(18-69)
Median time since Diagnosis, yrs (range)	1.38 (0.02-15.07)	2.31 (0-14.25)
Disease Location		
Small bowel only	35%	46%
Small bowel + colon	29%	34%
Colonic only	36%	20%

Figure 8. Primary outcome – Proportion of patients selecting combination therapy



Secondary outcomes showed that there was lower decision conflict in the intervention group (31.4 v 33.9, p=0.04). For the intervention group, patients consistently reported that the PROSPECT tool (87%) and Crohn's disease online program (98%) increased understanding of their disease **(Figure 9)**. Provider trust was higher in the intervention versus the control group (p=0.04), **Figure 10**.

Figure 9. Secondary outcomes

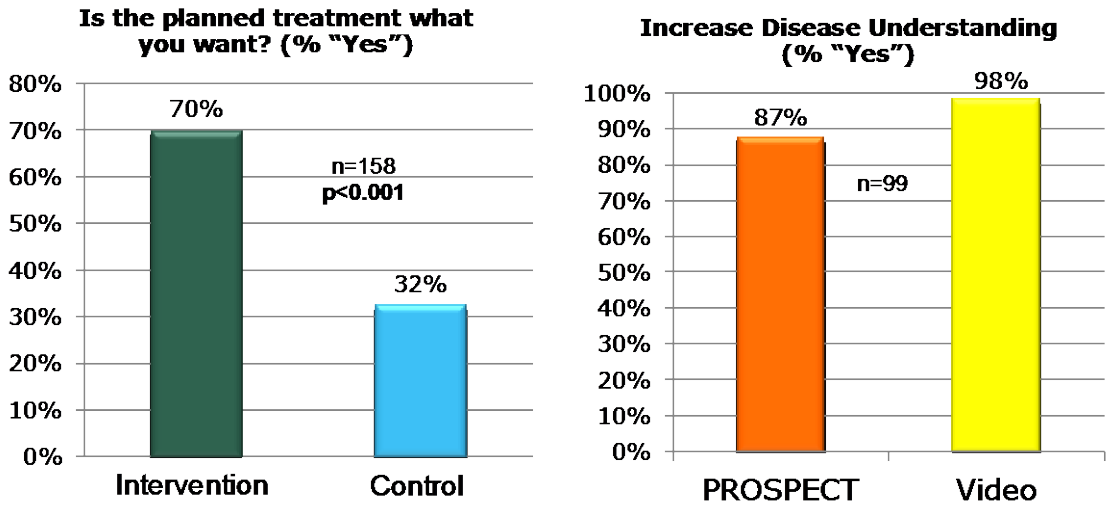
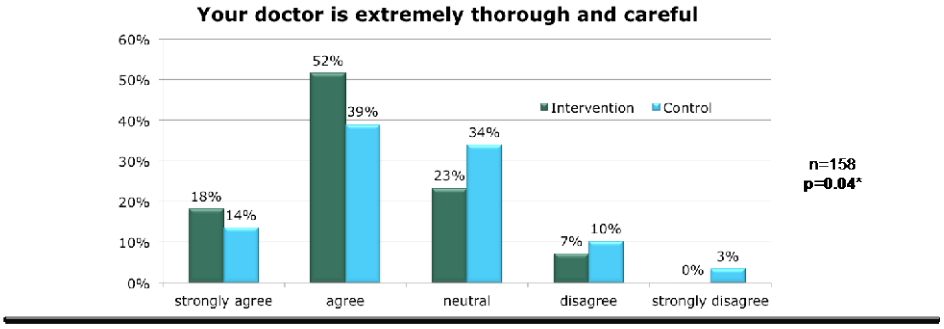
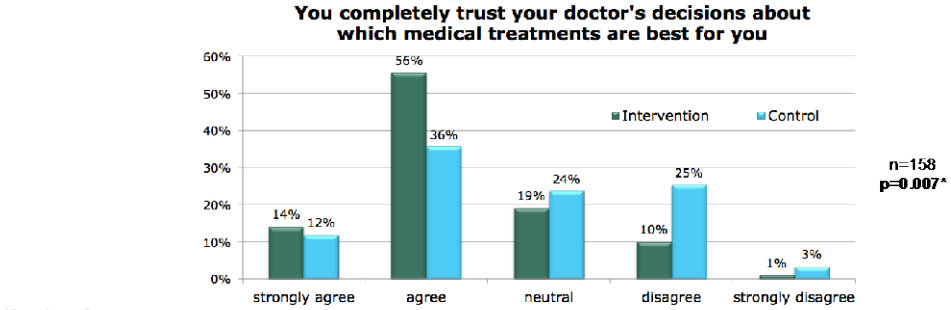


Figure 10. Patients' trust in their providers





*for strongly agree + agree

DISCUSSION

This research program titled “Evaluating a Prediction Tool and Decision Aid for Patients with Crohn’s Disease” allowed for the creation of a novel shared decision making program that was tested in a randomized controlled trial and met its primary endpoint. In addition to showing that this program had more patients select “combination therapy,” which has been proven the most effective therapy for the treatment of Crohn’s disease, we also showed that fewer patients remained untreated, patients more often received the treatment that they preferred, had lower decision conflict, an increased understanding of their disease and increased trust in their physicians.

To the best of our knowledge, this is the first decision aid created for Crohn’s disease that has been implemented and tested, and has shown positive results. We believe that we have established a model not just for inflammatory bowel diseases, but for any chronic disease state where increased information for patients together with a personalized risk prediction tool can help facilitate shared decision making. We hope that others will use similar methodology or be motivated to develop other methods to address the critical patient need for personalized decision making tools.

There were some limitations to our research program. We struggled with control group enrollment, but fortunately were powered enough to find a difference between our two groups. We met resistance from pharmacies when trying to verify active patient medications. We do have both patient reported medication and medications from the chart reviews so we believe that we are accurate in our results, however, a third source from the pharmacies would have been helpful. We have further analyses still planned. Patient adherence to therapy needs to be assessed from our data. We have not yet done the analyses to determine if patient outcomes and cost were influenced. These were exploratory analyses to determine feasibility of understanding if these metrics can be collected in this type of cluster randomized trial. We do have the data from patient reports and chart review, and these analyses are currently underway.

The significance and implications of our results are two-fold. First, we have shown a methodology that could be mirrored by others on how to create and test a personalized shared decision making program. We expect that others could attain similar results in other disease states. Second, we are in the process of allowing for widespread use of PROSPECT, and we have already helped the Crohn’s and Colitis Foundation obtain a link to the web-based Crohn’s disease decision aid video that is now available free to any patient. Therefore, the products of our program can be accessible to all patients who can benefit from this work.

CONCLUSION

In summary, we have successfully created a personalized shared decision making program for patients with Crohn’s disease that positively influenced patient decision making, decisional conflict, understanding of their disease, and trust in their providers. This work can be used as a model for other disease states. We feel confident that we have responded to the AHRQ health IT portfolio priority area to improve health care decision making by developing and implementing health information tools that consider patients’ expressed treatment preferences.

PUBLICATIONS AND ABSTRACTS

Full publication from Aim 1 (risk prediction model validation) and a number of abstracts form interim analyses of the randomized controlled trial (Aim 3). Final publications pending are listed below as "In preparation."

1. **Siegel CA**, Horton H, Siegel LS, et al. A validated web-based tool to display individualised Crohn's disease predicted outcomes based on clinical, serologic and genetic variables. Aliment Pharmacol Ther. 2016;43:262-271. PMID 26567467
2. Thompson KD, Siegel LS, MacKenzie T, Dubinsky M, **Siegel CA**. Crohn's disease risk prediction model appropriately stratifies patients' risk for developing disease related complications. Digestive Disease Week. Chicago, IL, May 6, 2017.
3. Thompson KD, Siegel LS, MacKenzie T, Dubinsky M, **Siegel CA**. Crohn's disease risk prediction model appropriately stratifies patients' risk for developing disease related complications. European Crohn's and Colitis Organisation. Barcelona, Spain, Feb 16, 2017.
4. **Siegel CA**, Horton H, Siegel LS, et al. A validated web-based tool to display individualised Crohn's disease predicted outcomes based on clinical, serologic and genetic variables. Aliment Pharmacol Ther. 2016;43:262-271. PMID 26567467
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In preparation:

1. Main manuscript presenting results of the randomized controlled trials (as described above in results).
2. Manuscript on cost and healthcare utilization in the prospective IBD cohort from this study.
3. Manuscript evaluating patient psychologic factors and their influence on decision making.
4. Manuscript assessing adherence to therapy and any factors that could predict medication adherence.

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