

Challenges in IBD Research: Update on Progress and Prioritization of the CCFA's Research Agenda

Lee A. Denson, MD,¹ Millie D. Long, MD, MPH,² Dermot P. B. McGovern, MD, PhD,³ Subra Kugathasan, MD,⁴ Gary D. Wu, MD,⁵ Vincent B. Young, MD, PhD,⁶ Theresa T. Pizarro, PhD,⁷ Edwin F. de Zoeten, MD, PhD,⁸ Thaddeus S. Stappenbeck, MD, PhD,⁹ Scott E. Plevy, MD,² Clara Abraham, MD,¹⁰ Asma Nusrat, MD,¹¹ Christian Jobin, PhD,^{2,12} Declan F. McCole, PhD,¹³ Corey A. Siegel, MD, MS,¹⁴ Peter D. R. Higgins, MD, PhD,¹⁵ Hans H. Herfarth, MD, PhD,² Jeffrey Hyams, MD,¹⁶ William J. Sandborn, MD,¹³ Edward V. Loftus, Jr, MD,¹⁷ Michael D. Kappelman, MD, MPH,¹⁸ James D. Lewis, MD, MSCE,¹⁹ Charles A. Parkos, MD, PhD,²⁰ and R. Balfour Sartor, MD² for the Challenges Workgroup

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EXECUTIVE SUMMARY

The Crohn's and Colitis Foundation of America (CCFA) convenes meetings of leading basic, translational, and clinical researchers every 4 to 5 years to update progress on the foundation's research agenda and prioritize goals in inflammatory bowel diseases (IBDs) research. These multidisciplinary meetings are designed to identify crosscutting goals across basic and clinical research arenas. The goal of each meeting is to define the

overarching integrative global research mission and priorities of the CCFA for the ensuing 4 to 5 years.

The first such meeting was in 1990, at which time a white paper entitled "Challenges in IBD Research" was produced naming research priorities and resources necessary to reach these goals. Updated "Challenges" documents have been produced at regular intervals since this time. The most recent Challenges document was published in 2008.¹ This document described advances in basic and

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From the ¹Division of Pediatric Gastroenterology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, Cincinnati, Ohio; ²Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; ³F. Widjaja Inflammatory Bowel and Immunobiology Research Institute, Cedars-Sinai Medical Center, Los Angeles, California; ⁴Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia; ⁵Division of Gastroenterology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; ⁶Infectious Diseases Division, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan; ⁷Department of Pathology, Case Western Reserve University School of Medicine, Cleveland, Ohio; ⁸Children's Hospital Colorado, Digestive Health Institute, Denver, Colorado; ⁹Department of Pathology and Immunology, Washington University School of Medicine, St Louis, Missouri; ¹⁰Department of Medicine, Yale University, New Haven, Connecticut; ¹¹Department of Pathology, Emory University School of Medicine, Atlanta, Georgia; ¹²Department of Microbiology and Immunology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; ¹³Division of Gastroenterology, University of California San Diego, La Jolla, California; ¹⁴Inflammatory Bowel Disease Center, Section of Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; ¹⁵Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan; ¹⁶Department of Pediatrics, Connecticut Children's Medical Center, Hartford, Connecticut; ¹⁷Division of Gastroenterology & Hepatology, Mayo Clinic, Rochester, Minnesota; ¹⁸Division of Gastroenterology and Hepatology, Department of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; ¹⁹Raymond and Ruth Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; and ²⁰Epithelial Pathobiology and Mucosal Inflammation Research Unit, Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, Georgia.

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Reprints: Millie D. Long, MD, MPH, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina at Chapel Hill, Campus Box 7080, Chapel Hill, NC 27599-7080 (e-mail: millie_long@med.unc.edu).

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clinical research for the preceding interval years and identified major themes in research priorities to emphasize in the near future. During this interval, advances were made in identification of genes, in understanding the association between IBD and abnormal host responses to commensal bacterial flora, in the contribution of the innate immune system to mucosal homeostasis, and elucidation of the cellular populations and their mediators that drive and regulate immune responses. This document identified important themes for research priorities from 2008 to 2012, including improved tools for rapid identification of genes associated with IBD, enhanced tools for microbiome analysis, genetically determined variances in responses to drugs and prognosis, and improvement in therapeutic options for IBD management.

In June 2012, leading researchers representing committees composed of multidisciplinary investigators drawn from a variety of research areas relevant to IBD pathogenesis and treatment convened to review progress since the last document and identify new global research priorities for the CCFA. The group concluded that since 2008, advances in basic research have principally included:

- Significant and rapid progress has been made in identifying additional genetic loci in Crohn's disease (CD) and ulcerative colitis (UC), with over 160 published susceptibility loci/genes to date.
- Fundamental insights into enteric microbiota community structure and genetic, immunologic, and microbial interactions have been made possible through rapid advances in high-throughput DNA sequencing and bioinformatics technology. These tools have allowed for identification of immunologic properties of individual species and groups of bacteria and have provided evidence that host-associated bacterial communities are more complex in their interactions and biochemistry than previously thought.
- The interaction of the intestinal microbiota and innate immune cells with the mucosal adaptive immune system has been shown to play an important and required role for the development of Th17 and regulatory T cells.
- There has been further discovery of novel functions and regulation for previously recognized innate immune cells, and the discovery and characterization of novel innate immune cell types such as innate lymphoid cells.

Significant advances in clinical research have also occurred, with the following major themes:

- Large cohort studies have been initiated to identify clinical or biological variables that predict treatment outcome and risk stratification in pediatric IBD (e.g., RISK Stratification Study and Predicting Response to Standardized Pediatric Colitis Therapy "PROTECT").
- Multicenter registries have been developed to determine the incidence of short-term and long-term adverse effects of medical therapies used to treat pediatric IBD.

- Prospective cohort studies have provided a better understanding of risks and benefits of medical and surgical therapies in key subpopulations (e.g., Pregnancy in IBD and Neonatal Outcomes study "PIANO").

Based on these advances in the past 5 years, with further understanding of disease pathogenesis and therapy, leading researchers developed a new research agenda for the CCFA. This agenda is divided into 8 subgroups with a discrete research agenda for each section. These sections include genetics, epidemiology and environmental factors, microbiome, epithelial cell biology, innate immunity, adaptive immunity, IBD diagnoses, and optimizing medical therapy.

Genetics

Much progress has been made in the arena of IBD genetics over the past 5 years. Over 160 susceptibility loci/genes for CD and UC have been discovered to date. Included are genes involved in IL23/Th17 signaling (*IL23R*, *IL12B*, *JAK2*, *TYK2*, and *STAT3*) and *IL10*, *IL1R2*, *REL*, *CARD9*, *NKX2.3*, *ICOSLG*, *PRDM1*, *SMAD3*, and *ORMDL3*. For CD, gene discoveries have focused on the areas of defective processing of intracellular bacteria, autophagy, and innate immunity.²⁻⁴ For UC, genetic evidence has demonstrated the importance of barrier function.⁵ Emerging data also show an overlap of susceptibility loci with other immune-related diseases. However, data are lacking in very early-onset IBD (onset <10 years old) and non-European origin IBD cohorts. Therefore, further research is needed in these specific groups. These genetic discoveries are a first step toward an ultimate goal of personalized medicine in IBD.

Translation of these advances into the clinical sphere will include the use of genetic information in diagnostics, predicting risk, individualizing therapy, and development of novel therapeutics that correct abnormal pathways. This will require the collection and characterization of large, robustly phenotyped prospective studies.

Genome-wide association and linkage association studies have yielded important insights and highlighted relevant pathways in the pathogenesis of CD and UC. However, genome-wide association approaches only identify regions that harbor risk genes, requiring follow-up studies to discover the precise disease-causing gene variants and their function. Genome-wide association studies describe only a small fraction (about 25%) of inherited disease risk. Therefore, additional studies of epigenomics, gene-environment interactions, chromatin structure, copy number variants, and micro-RNAs are needed in the coming years. It will be necessary to recruit well-characterized, multiply affected family-based cohorts to explain both heritable traits and identify rare but high effect variants. Further understanding of gene-microbial interactions is also of utmost importance, particularly the role of host genomic variation in determining microbial patterns.

Several approaches to bridging the bench to bedside divide have been proposed: making genomics-based diagnostics routine, defining the genetic components of disease, and developing practical systems for clinical genomic informatics.⁶ It is also important to define the functions of IBD risk alleles. These are areas where researchers should focus their efforts in IBD.

Epidemiology and Environmental Factors

Over the past 2 decades, epidemiological data have suggested that environmental factors play a key role in the pathogenesis of IBD. However, conclusive evidence on the role of specific environmental factors in either triggering or protecting against disease onset or progression has been limited.

Methodological challenges within the field of IBD epidemiology have limited the ability to draw firm conclusions from epidemiological studies. These challenges include inconsistent measurement (misclassification) of exposures and outcomes, the difficulty in recruiting and following sufficient numbers of subjects for long enough time periods, and the inability (until now) to measure and account for gene–environment interactions.

To account for the lack of large population-based cohort studies of IBD, an increasing number of pharmacoepidemiological studies have been performed. These studies, although limited by factors such as lack of clinical data or incomplete capture of events, have led to important advances in aspects of IBD management. We now have evidence of the long-term effectiveness of biological anti-tumor necrosis factor α (TNF- α) α therapy in CD,⁷ the relative and absolute risks of unintended outcomes including infection^{8,9} and malignancy (non-Hodgkin's lymphoma,¹⁰ nonmelanoma skin cancer,^{11,12} and melanoma¹³) associated with these and other medications, and preliminary evidence of the safety and effectiveness of these agents in populations not initially studied in randomized trials.^{14,15}

With the above-mentioned advances and limitations in mind, well-designed epidemiological studies are needed in 3 major arenas. First, studies of disease etiology are needed, with a particular focus on gene–environment interactions. These studies should incorporate the simultaneous measurement of environmental and genetic factors before disease onset. Second, studies of the natural history of disease are needed to evaluate the role of environmental factors on flares/disease progression. Third, pharmacoepidemiological studies of the absolute risks and benefits of available treatment options used under real-world conditions and in diverse populations are needed to further inform treatment algorithms.

Microbiome

The enteric microbiota is now accepted as an important etiologic factor in the pathogenesis of human IBD and immune-mediated chronic experimental intestinal inflammation.¹⁶ Over the past 5 years, there has been an explosive increase in understanding the fundamental composition and community structure of the intestinal microbiota and how these enteric bacterial species and their metabolic products interact with the host to mediate mucosal homeostasis versus chronic intestinal inflammation. Insights into genetic, immunologic, and microbial interactions have flourished with identification of immunologic properties of individual species and groups of bacteria.^{17,18}

These dramatic advances have been made possible because of corresponding advances in sequencing technology and the development of computational pipelines to handle these larger data sets. These sequencing platforms permit a more comprehensive

analysis of the microbiota community structure, their genes, and metabolic potential (through metagenomics, metabolomics, and metatranscriptomics) on a more affordable relatively rapid basis. Many of these advances were made possible through the CCFA Microbiome Initiative and the National Institutes of Health's Human Microbiome Project.

Evidence suggests that host genes affect microbiota profiles and that specific commensal microbes (either viruses or bacteria) selectively interact with host genes to influence intestinal inflammation. Investigations using genetics/microbiome/immunologic integration hold great promise for the prospect of personalized medical care.

To further the understanding of microbiota in the pathogenesis of IBD, the knowledge base must be expanded beyond broad descriptions of enteric bacterial taxonomy to include individual bacterial species, functionally active strains, and other microbes, including viruses, fungi, and parasites. Of utmost importance is further comprehension of how host genetics and environmental factors shape microbiota composition and function. We also need to determine whether we can influence human disease outcomes in a durable fashion by altering the composition and function of the gut microbiota using standard therapeutic interventions, diet, or fecal transplant. Ultimately, these findings may influence clinical care through improved diagnosis, prediction of clinical course, treatment, prevention, and identification of clinically relevant disease subsets to achieve the hope of a personalized medical approach for each individual with IBD.

Epithelial Cell Biology

The gastrointestinal epithelium and associated secreted products (mucus, antimicrobial peptides, antibodies, etc.) serve as a selective permeable barrier that restricts access of luminal antigens and viable microbes to underlying tissue compartments, thereby playing a pivotal role as a gatekeeper that controls overall mucosal homeostasis. Over the past 5 years, advances in epithelial cell biology have included further understanding of mechanisms of epithelial barrier compromise, the role of epithelia in controlling the intestinal immune response, and new insights into epithelial cross talk with microbiota in IBD. CCFA-funded projects have demonstrated changes in intercellular junction proteins (occludin, claudins, cadherins) that contribute to perturbed epithelial homeostasis and compromised barrier function observed in IBD. It is now apparent that cytokines such as TNF- α , IFN γ , IL-1 β , and IL-13 have potent regulatory effects on expression and function of epithelial intercellular junction proteins, polarity complexes, and pattern recognition receptors that directly translate to the barrier compromise observed in patients with IBD. Lamina propria lymphocytes play an important role in not only contributing to the mucosal barrier defense but also in directly modulating epithelial differentiation and barrier function.

Gene linkage studies have provided new insights into epithelial dysfunction in CD. Additionally, innate immune receptors such as Dectin-1 have now been linked to mucosal responses to commensal fungal microorganisms that may play a role in pathobiology of UC.¹⁹ The biology of other epithelial cell types, such as Paneth cells, and their roles in intestinal host

defense and homeostasis has been illuminated. Importantly, dysfunction of Paneth cells is now thought to increase susceptibility to pathologic chronic intestinal inflammation as seen in IBD.

Over the next 4 to 5 years, an emphasis on understanding the mechanisms that influence mucosal barrier function (and malfunction) is warranted. The outcome of such studies will have important implications in defining IBD pathophysiology and potential therapeutic targets in IBD. In particular, it is important to understand what regulates intestinal epithelial barrier function and how compromise of this function contributes to IBD pathogenesis. Beyond understanding the barrier function, we need to determine how this function can then be restored. Additionally, the interaction between the microbiota, epithelial homeostasis, and wound healing needs to be characterized. Further appreciation of the contributions of inflammation and intrinsic epithelial growth regulatory signaling pathways to colitis-associated carcinoma is also needed. Finally, the CCFA is interested in determining which experimental models could contribute to the generation of basic cellular and molecular understanding of intestinal epithelial cell biology.

Innate Immunity

Research in the field of innate immunity and mucosal immunology has been expanding rapidly over the past 5 years, with the potential to dramatically impact future IBD pathogenesis and management. Novel functions and regulation for previously recognized innate immune cells have been discovered. Additionally, ongoing discovery and characterization of novel innate immune cell types, such as innate lymphoid cells, has continued.²⁰

Advances in other fields have contributed to these discoveries. For example, genetics and microbiological analysis have affected the direction of innate immunity research. Functions of genes have begun to be uncovered within specific innate immune cell types, such as monocyte-derived cells and Paneth cells. Our understanding of microbial-associated molecular patterns (MAMPs, aka PAMPs) has significantly expanded our knowledge of their related signaling pathways. In addition, the massive expansion of knowledge of the intestinal microbiome has helped us identify potential microbes that normally interact with and shape the innate immune system.

To this end, goals for the CCFA research agenda over the next 5 years include defining new functional roles of known innate cell types and elucidating the roles of emerging innate immune cells. A deeper understanding of how IBD susceptibility polymorphisms and IBD gene mutations affect innate immune function and intestinal immune homeostasis is also needed. In particular, we need to clarify whether these mutations identify specific pathways that can be explored experimentally and therapeutically. Finally, appreciating the nature of the cross talk of host innate immune cells with the microbiome is a fundamental question and understanding these interactions will have a profound impact on IBD.

Adaptive Immunity

The adaptive immune system includes the antigen-specific immune responses mediated primarily by T cells and B cells.

Although significant progress has been made in our understanding of the role of the adaptive immune system in IBD pathogenesis, we have an incomplete understanding of the pathways involved in the regulation of the adaptive immune response to commensal bacteria and pathogens in the intestine. For example, the role of Th17 effector cells in the pathogenesis of experimental IBD seems to be more complicated than initially observed, with some studies suggesting a pathogenic role, whereas others demonstrating a protective or regulatory role.²¹

Discoveries have also been made in understanding the relationship of the intestinal microbiota and innate immune cells with the mucosal adaptive immune system. This relationship has been reported to play an important and required role for the development of Th17 cells.^{22–24} Specific microbes, or phyla of microbes, that are important for activating Th17 immune responses have also been defined.²⁵ It has also been suggested that stimulation of Th17 is required for the beneficial, as well as the pathogenic, effects of gut immune responses.

Although significant progress has been made within the past 5 years in identifying potential mechanisms involving the adaptive immune system in the pathogenesis of IBD, more work is needed. In particular, knowledge gained thus far needs to be translated into clinically relevant applications and appropriate tools (i.e., novel animal models) to address emerging questions.

The CCFA is interested in supporting further efforts to define the precise phenotypic and functional properties of T-effector and Treg/emerging regulatory subsets that distinguish different forms of IBD. In addition, concepts generated from experimental models of IBD need to be translated to the clinical setting. This can be accomplished through identification of potential biomarkers for active disease or characterization of novel cytokines/mediators involved in IBD pathogenesis that may be future therapeutic targets. To accomplish these goals, there is an urgent need for development of humanized mouse models.

IBD Diagnoses: Clinical Classification and Prognostic Models

We have learned that both CD and UC patients have heterogeneous genetic profiles. Therefore, using genetic data in combination with other factors (clinical criteria, immune profiles, intestinal gene expression patterns, and microbiome community structure) may serve as an important prognostic tool to determine factors such as drug toxicity or response to therapy. An important step in furthering this understanding is ongoing; the development and follow-up of the prospective pediatric RISK cohort. This study examines the relationship between genetic, serological, immunologic, and microbiological factors and clinical course of CD. Enrollment of the cohort was completed in 2011, and prospective 3-year follow-up is ongoing. This cohort is an important step toward developing a tool, or series of tools, to define prognosis in pediatric IBD.

Important advances have also been made in improving classification of IBD. A series of 3 meetings took place in 2009 to define a new Paris classification system for pediatric-onset IBD.²⁶

This system can be used in conjunction with the existing Montreal classification system. The 2 main additions include a definition of very early-onset IBD as less than age 10 at onset and early-onset IBD as less than age 17 at onset. In addition, modifiers for extensive small bowel CD, growth failure, and severe UC were defined. A consensus definition for “early” CD was also derived and validated over the past 2 years.²⁷ The primary features include duration of disease of not >2 years, no significant gastrointestinal dysfunction or fibrotic or penetrating complications, and no exposure to immune modulators or biologics. This definition could be used to define a more homogenous patient population for clinical trials of new disease-modifying therapies.

Little progress has been made in defining risks of rare adverse events of medical therapy. Emerging cases of serious complications, such as hepatosplenic T-cell lymphoma²⁸ and progressive multifocal leukoencephalopathy,²⁹ have emphasized the importance of understanding the individualized risks of therapies. Ongoing cohort studies will seek to better define these long-term risks.

To further the advances made over the past 5 years, the most important research questions in the arena of IBD diagnostics focus on developing better ways to classify patients for prediction of natural history, response to therapy, and adverse effects of therapy. Large prospective cohort studies are needed to validate factors that predict those at risk of severe disease or complications, and conversely, those patients with predicted mild courses. We also need to understand the accuracy of diagnostic imaging modalities in monitoring inflammation and/or fibrosis and to determine whether these studies can predict clinical outcomes. Cost-effectiveness studies comparing strategies for disease management and monitoring should be performed, along with implementation of tools for shared decision making with patients.

Optimizing Medical Therapy

Progress has been made over the past 5 years in improving outcomes in children and adults with IBD. In particular, strides have been made toward identifying variables that predict treatment outcomes and allow for risk stratification of children with IBD. Currently, the CCFA-sponsored RISK Stratification Study is ongoing, which will also provide important information on therapeutic outcomes. The PROTECT study will examine the relationship between similar genetic, serological, immunologic, and microbiological factors and the likelihood of children newly diagnosed with UC maintaining remission on standard doses of mesalamine. The results of this study may allow for avoidance of unnecessary medications (and ensuing side effects) in a subgroup of patients. Other registry studies have also been initiated to identify the incidence of adverse effects in IBD. In particular, we now have a better understanding of the risks and benefits of medical and surgical therapies in population subgroups, such as pregnant women with IBD.¹⁵

The research priorities for the CCFA in optimizing medical therapy in adults include a focus on individualized therapy. For example, individualization of anti-TNF therapy in IBD may improve outcomes. A better understanding of the role of customized dosing frequencies and adjustments in anti-TNF

therapy and concomitant immunosuppressants is warranted. Better prediction models for monitoring disease course and activity are needed. Along these lines, objective instruments to validate CD activity in clinical trials are also considered necessary. Importantly, a better understanding of when therapies can be reduced, or “stepped-down,” during a lifetime of disease is warranted, as well as determination of optimal therapies in specific subpopulations, such as the elderly.

Specific challenges in the management of pediatric IBD are also a focus for the CCFA. Of particular importance is the ideal method of using anti-TNF therapy in pediatric CD populations, including the role for and risks of combination therapy in patient subgroups. Additionally, data are needed as to the best method to monitor success of therapies in the pediatric population. For UC, an important emphasis over the next 5 years will be the development of new strategies for the treatment of fulminant UC.

Summary of Global Priorities

The participants in the 2012 Challenges meeting identified the following integrative global priorities for the CCFA’s research agenda:

- Define clinically relevant subsets of patients with IBD using genetic, immunologic, microbial, tissue expression, and clinical profiles (including drug metabolism and pharmacokinetics) that will predict aggressiveness of disease, complications, and response to treatment.
- Understand how environmental factors enhance the risk of IBD through effects on microbial, epigenetic, immunologic, and mucosal barrier influences.
 - A specific focus on the role of diet is warranted.
- Determine which environmental triggers initiate, perpetuate, and/or reactivate disease.
- Further understand reciprocal interactions (cross talk) between genes, microbiota, epithelial cells, and innate and adaptive immune responses that determine pathways mediating mucosal homeostasis versus inflammation.
 - Determine critical rate-limiting cell/cellular pathways for communication with the microbiota.
 - Definition of critical cell types and the functional pathways leading to further understanding of homeostasis versus inflammation, with an ultimate goal of identifying putative (therapeutic) targets.
- Determine optimal treatment approaches and strategies through comparative effectiveness studies.

To carry out this research agenda, the following resources are needed:

- Centralized and distributable infrastructure for biobanking, data warehouse, and tissue/cell/microbial repositories for integrated human investigation.
- Prospective cohort studies of pediatric and adult patients with IBD with serial biospecimens collected throughout the course of their diseases.

- Infrastructure to recruit and follow patients from childhood to adult life.
- Access to data and biospecimens collected before and following treatment with established and novel therapeutics.
- Improved tools for measuring disease activity in IBD.
- More specific in vivo tools including humanized mice and lineage-specific models for mechanistic research.
- Availability of new methodology for improved cell lines and freshly isolated and viable mucosal cells.
- Implementation of a series of workshops to improve IBD research methodology and promote integrative multidisciplinary approaches and resources.

Since 1990, there has been remarkable progress in our understanding of the pathogenesis and therapeutic targets in IBD, but further strides are needed. The CCFA has played a central role in advancing this research. Through development of the ambitious research goals outlined in this document, the CCFA has again led the effort to further the understanding of IBD. The CCFA is keen to advance this research agenda in 2012 and beyond.

For more detailed information, see Supplemental Digital Content 1, <http://links.lww.com/IBD/A77>.

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