HHS Public Access

Author manuscript

Aliment Pharmacol Ther. Author manuscript; available in PMC 2023 March 17.

Published in final edited form as:

Aliment Pharmacol Ther. 2022 May ; 55(9): 1179–1191. doi:10.1111/apt.16853.

A United States expert consensus to standardise definitions, follow-up, and treatment targets for extra-intestinal manifestations in inflammatory bowel disease

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Author contributions: All authors participated in the modified Delphi consensus panel. KF and FR wrote the manuscript. All authors revised and edited the manuscript. All authors approved the final version of the article, including the authorship list.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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Summary

Background and aims: Extra-intestinal manifestations (EIMs) are a common complication of inflammatory bowel diseases (IBD), affecting up to half of the patients. Despite their high prevalence, information on standardised definitions, diagnostic strategies, and treatment targets is limited.

Methods: As a starting point for a national EIM study network, an interdisciplinary expert panel of 12 gastroenterologists, 4 rheumatologists, 3 ophthalmologists, 6 dermatologists, and 4 patient representatives was assembled. Modified Delphi consensus methodology was used. Fifty-four

candidate items were derived from the literature review and expert opinion focusing on five major EIMs (erythema nodosum, pyoderma gangrenosum, uveitis, peripheral arthritis, and axial arthritis) were rated in three voting rounds.

Results: For use in a clinical practice setting and as part of the creation of a prospective registry of patients with EIMs, the panel developed definitions for erythema nodosum, pyoderma gangrenosum, uveitis, peripheral arthritis, and axial arthritis; identified the appropriate and optimal subspecialists to diagnose and manage each; provided methods to monitor disease course; offered guidance regarding monitoring intervals; and defined resolution and recurrence.

Conclusions: Consensus criteria for appropriate and optimal means of diagnosing and monitoring five EIMs have been developed as a starting point to inform clinical practice and future trial design. Key findings include straightforward diagnostic criteria, guidance regarding who can appropriately and optimally diagnose each, and monitoring options that include patient and physician-reported outcomes. These findings will be used in a national multicenter study network to optimise the management of EIMs.

1 | INTRODUCTION

Extra-intestinal manifestations (EIMs) represent a significant yet understudied complication of inflammatory bowel diseases (IBD). EIMs are diagnosed in up to 50% of IBD patients[1] and are associated with morbidity, markedly decreased quality of life, increased complexity of decision-making for providers, and at times even mortality.[2,3]

Despite their prevalence and significance for patients, the diagnosis and management of EIMs have received only limited attention in the literature, especially in the United States (US). Consistent definitions have yet to be established and can vary widely based on whether the gastroenterology or subspecialty literature is followed.[4,5] Retrospective studies often rely on metrics like patient reports or the International Classification of Disease (ICD) code for diagnosis and are inherently limited by their retrospective nature.[6–9] Subanalyses of clinical trials lack standardised definitions of EIMs, are heterogeneous, and are of limited sample size.[10] There have been few randomised control trials (RCTs), and prospective studies have only been carried out for some of the EIMs, which typically are of small sample size and use widely different definitions of EIMs and treatment success.[11–16] None of the indices for EIMs in IBD have been developed following accepted methodologies. A 2017 systematic review of the use of biologics to treat all EIMs, including metabolic bone disease and anemia, only identified 22 studies, the majority of which were noninterventional.[17] The heterogeneity of EIM definitions and outcomes meant that grading studies or conducting a meta-analysis was not possible and led the authors to identify EIMs as a significant unmet need in the literature.[17]

This scattered and nonsystematic approach has led to conflicting reports and ongoing uncertainties in clinical practice. For example, a retrospective study found a higher rate of EIMs in patients on vedolizumab, whereas a subanalysis of the GEMINI trial reported a decreased likelihood of joint-related EIMs.[10,12] Diagnosis and management of EIMs is thus largely based on the expert opinion of individual providers as opposed to rational data-driven management, as indicated in the first guideline published in 2015 in Europe.[13] Although a

very important and useful guide, this work does not comment on several items critical for clinical practice. Due to limitations in the literature itself, how and by whom these entities should be diagnosed and treated is often vague, and the means of assessing for improvement or worsening, resolution, and recurrence are not always clearly outlined. In addition, there is little guidance regarding monitoring intervals for EIMs. At the time, this consensus was initiated, no guidelines in the United States had been published.

To address this unmet need, we assembled a multidisciplinary panel of experts across the US and conducted a modified Delphi consensus panel to standardise definitions and treatment targets of five major EIMs in the clinical practice setting. The manifestations included in this study are erythema nodosum (EN), pyoderma gangrenosum (PG), uveitis, peripheral arthritis, and axial arthritis, which were selected based on prevalence and impact on quality of life. This work intends to provide clarity for the practicing provider, set the groundwork for a national multicenter EIM study network, and facilitate future, much-needed prospective studies and clinical trials of EIMs that will impact most IBD patients in their lifetime.

2 | MATERIALS AND METHODS

2.1 | Review of literature

In order to better understand possible means of diagnosis and monitoring for each EIM, a thorough review of literature was conducted. Given the lack of published controlled or prospective data in this field, a full systematic review was not performed. Instead, a search of Ovid, MEDLINE, Cochrane Library, EMBASE, and Web of Science was conducted with the assistance of a trained medical librarian. Three search strings were used with the first encompassing all English language articles published on EN, PG, uveitis, peripheral arthritis, and axial arthritis, regardless of the presence of IBD in the past 5 years, the second all articles published on these five EIMs using the medical subject heading inflammatory bowel disease, and the third restricted solely to systematic reviews (Figure S1).[17–22] The European Crohn's and Colitis Organisation (ECCO) EIM consensus guidelines were also closely reviewed along with the article reference list. Clinical features, previous methods of identifying EIMs (ICD codes, subspecialty diagnosis), and diagnostic systems developed both in the EIM literature and in the subspecialty literature were considered.[5,17,23,24] For example, we considered the type I versus type II classification system for arthritis (type I is pauci-articular, classically involves fewer than five joints, is self-limited, and follows the course of IBD, whereas type II is polyarticular, classically involves >5 joints, is persistent, and runs independently from the course of IBD) as well as the Assessment in SpondyloArthritis International Society (ASAS) classification criteria for peripheral and axial arthritis and the Standardisation of Uveitis Nomenclature criteria for uveitis. Similarly, the means of tracking EIMs previously employed in open-label studies, post hoc analyses, and RCTs were assessed along with the scoring systems utilised. We also reviewed clinical trials that were not designed specifically for patients with IBD but did include some patients with IBD in their analysis to determine monitoring strategies.[8,13,14,15,25] The conclusion of this exercise was that currently, no broad consensus exists on how to diagnose and monitor EIMs but the presence of such tools is critical for progress in this field. Those articles that proposed new, practice-changing definitions for EIMs were disseminated to

panelists for their review prior to voting, along with commonly utilised scoring systems or quality of life indices (Table S1). Materials were selected for dissemination by KF and FR with any disagreements resolved via discussion with BC. All panelists were also given the opportunity to suggest any additional articles they felt were relevant during the introductory panel meeting and via email.

2.2 | Expert consensus process

2.2.1 | Expert selection—For the purposes of conducting a modified Delphi consensus network followed by the creation of a national multicenter EIM study network, eight centers within the Crohn's and Colitis Foundation Clinical Research Alliance network were selected. Each site was carefully chosen to ensure an ethnically and geographically diverse patient population as well as site principal investigators (PIs) with national recognition in the field of IBD who were committed to the study of EIMs and had already established multidisciplinary EIM working groups. Site PIs from each center then helped us to identify dermatology, ophthalmology, and rheumatology subspecialists, all of whom were collaborators in centers with a high patient volume of IBD EIMs. Publication record, national reputation, experience in clinical epidemiology, trial design and modified Delphi consensus panels, and expertise in EIMs were incorporated into the selection process. The final selection of participants was performed by KF, BC, and FR. At least one gastroenterologist from each center was included for a total of 12 panelists from gastroenterology. Not all centers had an ongoing working relationship with all subspecialists, and so a number of participants across the other subspecialties varied, with three ophthalmologists, four rheumatologists, and six dermatologists ultimately included. Given that 5–10 experts are considered sufficient for a modified Delphi consensus panel and the challenges associated with too large a group, a total of 25 voting members was felt to be sufficient, and additional subspecialty voting members were not sought out. In order to promote patient-centered care and begin the process of developing patient-reported outcomes, four patient representatives were also asked to comment on the items and offer any feedback prior to the final voting round. These representatives were selected based on their personal experience with at least one of each of the EIMs in question as well as their national reputation for patient advocacy.

The modified Delphi consensus appropriateness methodology was used to assess the validity and feasibility of items designed to identify appropriate means of diagnosing and monitoring EIMs.[26–29] The modified Delphi approach combines the best available evidence with the clinical experience of relevant experts and is iterative, evidence-based, and widely accepted in the literature.[26–29] The consensus was framed as a way to create definitions relevant for use in clinical practice that could also later be used in the creation of a prospective registry of patients with EIMs.

2.2.2 | First-panel meeting and initial survey—Fifty-one items were identified via review of literature as summarised above and in collaboration with focus groups with the nationally recognised heads of Cleveland Clinic interdisciplinary IBD EIM subspecialty clinics. These items were then discussed during an introductory panel meeting on May 21, 2021 including all experts, revised accordingly, and circulated via an online survey

to all panelists (Table S2). Panelists anonymously rated the appropriateness of each item on a scale from 1 (strongly disagree) to 10 (strongly agree). Panelists were also given the opportunity to provide commentary on each item. Gastroenterologists voted on all items, whereas the subspecialists voted only on items pertinent to their subspecialty (e.g., dermatologists voted only on EN and PG). A priori rules dictated that a statement be deemed appropriate if at least 75% of participants rated the item at a score of 7 or higher.

2.2.3 | Subsequent panel meetings and surveys—Results of Round 1, including commentary on items, were distributed to all panelists (Table S2). These results were discussed in a moderated face-to-face teleconference on June 11, 2021 and further feedback was also solicited from each participant via individual emails. All responses were reviewed and items for which no consensus was reached or items with opportunities to clarify phrasing were revised based on feedback and prepared for Round 2 of voting (Table S2). All items reached a consensus in Round 2. Following this round, feedback regarding the consensus items was solicited from the four patient representatives. Another panel teleconference was then held on January 4, 2022 in preparation for a third round of voting to review patient commentary, vote on three additional candidate items, and provide guidance regarding optimal diagnostic and monitoring strategies in scenarios in which multiple items were deemed appropriate. Of note, more than one item could be deemed optimal, and it was also possible for no item to be deemed optimal if items did not meet the prespecified threshold.

2.2.4 | Ethical considerations—No Institutional Review Board approval for this study was necessary.

3 | RESULTS

3.1 | Erythema nodosum

Appropriate and optimal consensus items regarding EN are summarised in Table 1 and Table S3, respectively. The optimal definition of EN is the characteristic appearance of erythematous nodule(s) plus patient report of tenderness, with biopsy demonstrating septal panniculitis only if there is diagnostic uncertainty in a physical exam. A key panel discussion point for EN centered around the need for dermatology involvement in the diagnosis and management of this EIM. This may be especially desired in a prospective clinical trial with EN as a primary endpoint. However, in current clinical practice, the scenario of this consensus, dermatology involvement was not considered the standard of care, and both gastroenterologists and dermatologists felt confident in the ability of an IBD specialist to diagnose EN. In addition, by our panel's definition, any uncertainty on physical exam necessitates a biopsy, which then would provide diagnostic clarity. Thus, it was determined that it was not only appropriate but also could be considered optimal for an IBD specialist to both diagnose and manage EN, with the monitoring interval dependent on the severity of EN as outlined in Table 1 and Table S3. Changes in size and number of nodules as well as physician global assessment—defined for all EIMs with 100% consensus as the overall status of EIM based on patient symptoms, physical exam, and any relevant testing (imaging, laboratory data)—were considered appropriate ways to assess for improvement

or worsening, with no one monitoring strategy deemed superior to the others. No quality of life indices was considered appropriate for monitoring EN. Notably, photographs were not deemed sufficient for monitoring in part due to difficulty assessing a nodule in one dimension, though patients did note that they find this to be an important part of care especially when access to subspecialists is challenging due to distance, transportation, cost, or other barriers (Table S2). Recurrence was defined as patient or physician assessment of nodule(s) returning any time after the resolution, with physician assessment deemed optimal.

3.2 | Pyoderma gangrenosum

Appropriate and optimal consensus items regarding PG are summarised in Table 2 and Table S4. Panelists concluded that both dermatologists and IBD specialists should be able to recognise PG, while a diagnosis of PG should be reserved for dermatologists. This was a notable departure from our conclusions regarding EN. However, given that diagnosis of PG can be challenging even for dermatologists coupled with the significantly increased complexity in managing and successfully treating this cutaneous manifestation, our panel reasoned that dermatologists should be involved in care. Acceptable means of diagnosis include expert assessment of an ulcerated and tender lesion with the exclusion of other etiologies, ulcerated lesion with biopsied edge demonstrating neutrophilic infiltrate and exclusion of other etiologies, or any lesion meeting the 2018 PG-modified Delphi consensus criteria or PARACELSUS score criteria.[30,31] Of note, although the classic teaching is to avoid biopsy of PG due to pathergy, a biopsy is the only major criteria in the 2018 PG-modified Delphi Consensus criteria, a part of the PARACELSUS score criteria and a central tenet of one of the new definitions created by our panel. Interestingly, however, the optimal strategy was considered expert assessment of an ulcerated and tender lesion with the exclusion of other etiologies, which is the only definition not prominently featuring biopsy results. A variety of outcomes were deemed appropriate for monitoring for improvement or worsening but the optimal strategy was physician assessment of objective change in size or ulceration (Table 2 and Table S4). Unlike for EN, for PG photographs demonstrating a change in size and/or degree of ulceration as per dermatology were also considered appropriate ways to assess for improvement or worsening. Panelists again concluded that monitoring should occur based on the severity of PG, as outlined in Table 2, and determined that the IBD specialist is the optimal provider to monitor for recurrence, with referral back to dermatology if needed. No quality of life indices was judged appropriate for monitoring PG.

3.3 | Uveitis

Consensus items regarding uveitis are summarised in Table 3. Only two rounds of voting were needed for this manifestation as only one response in each item category was deemed appropriate. Interestingly, uveitis was the only EIM the panel determined should be recognised, diagnosed, and monitored by ophthalmology, highlighting a lack of comfort with this condition among IBD specialists. Although a regular visit with ophthalmology is not currently standard of care for all IBD patients, these findings do demonstrate the need for prompt referral to ophthalmology for any IBD patient with concerning ocular complaints. The patient representatives all noted that more involvement from gastroenterology in at least the recognition of this condition would be beneficial. Panelists agreed with the utilisation of the Standardisation of Uveitis Nomenclature criteria,

which defines uveitis as more than 1 cell in the anterior chamber, vitreous haze, or the presence of choroidal or retinal inflammation, for diagnosis and for monitoring, as outlined in Table 3.[24] No quality of life indices were deemed appropriate for monitoring uveitis. Recurrence is defined as a new episode in either eye with inflammation occurring after >3 months regardless of IBD therapy.

3.4 | Peripheral arthritis

Appropriate and optimal consensus items regarding peripheral arthritis are summarised in Table 4 and Table S5. Notably, panelists concluded that peripheral arthritis could be recognised, clinically diagnosed, and monitored by IBD specialists *or* rheumatologists. As for EN, there was significant discussion during each voting round regarding whether rheumatology input was a necessity. Both the rheumatologists and gastroenterologists on the panel concluded that currently, peripheral arthritis is often managed by an IBD specialist and that the agreed-upon definitions from our panel could be comfortably applied by a rheumatologist or an IBD specialist with limited risk of misdiagnosis. However, given their expertise rheumatologists were consistently voted as the optimal managing provider, with the practical limitations in having all patients with peripheral arthritis followed by rheumatology noted by panelists and patient representatives alike. Appropriate definitions include (1) joint pain and swollen/tender joints on the exam; (2) morning stiffness, joint pain, and swollen/tender joints on the exam; and (3) swollen/tender joints on exam with the exclusion of other etiologies. No one definition was deemed superior to the others, underscoring the lack of a single, validated definition for this EIM (Table S2). Monitoring intervals were again determined based on the severity of peripheral arthritis. Changes in joint exam and symptoms as noted by a physician have deemed the optimal means of assessing for improvement or worsening, as outlined in Table S5. None of the included quality of life indices reached consensus for use in monitoring peripheral arthritis. Of note, imaging modalities, including X-ray, MRI, or ultrasound, were discussed but not felt to be sufficiently validated nor practical enough to endorse their use in clinical practice currently. Resolution can be appropriately assessed by the rheumatologist, IBD specialist, or patient. Recurrence is defined as recurrent joint involvement in the same anatomic location or in a new anatomic location any time after resolution. Monitoring for recurrence should occur as part of standard of care visits with rheumatology and the IBD specialist.

3.5 | Axial arthritis

Optimal and appropriate consensus items regarding axial arthritis are summarised in Table 5 and Table S6. Panelists determined that both IBD specialists and rheumatologists can recognise axial arthritis. However, unlike peripheral arthritis, the panel concluded that axial arthritis can only be appropriately diagnosed and monitored by a rheumatologist. This was consistent with the panel conclusions regarding the included cutaneous EIMs as well —manifestations that are more challenging to diagnose and/or more debilitating require subspecialty involvement. While an appropriate definition for axial arthritis is patients who meet Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axial arthritis as per rheumatology, the optimal definition was determined to be the panel-developed definition of patients with IBD, inflammatory back pain, and consistent MRI findings as per rheumatology.[5] This decision was based on the lack of validation

of ASAS criteria in an IBD patient population. Patients with axial arthritis should be monitored via visits to rheumatology and should be seen at least every 3 months until symptoms improve or resolve. Consistently appropriate ways to monitor for improvement or worsening included patient reports of change in pain or overall symptoms and physician global assessment, with no one method deemed superior to the others. None of the included quality of life indices reached consensus for use in monitoring axial arthritis, nor did any scoring systems (Bath Ankylosing Spondylitis Disease Activity Index, Ankylosing Spondylitis Disease Activity Index), which were again not deemed appropriate due to the lack of validation in an IBD patient population. In addition, while MRI was felt to be appropriate in diagnosis, due to cost and other appropriate means of monitoring for improvement/worsening, it was not recommended as a standard monitoring tool. As axial arthritis is a chronic condition, we did not vote on overall resolution or recurrence as we did for the other EIMs but instead on the more applicable clinical resolution and recurrence, which should be based on rheumatology assessment.

4 | DISCUSSION

IBD is a systemic illness with manifestations that reach far beyond the gut. Despite the systemic nature of the disease, research on EIMs has been limited in scope and depth, with definitions and management strategies inconsistent or not specific to the IBD patient population.[5,24,30,31] Patient panelists also note the lack of consistent and reliable messaging for patients regarding EIMs, such that many are unaware of the need to bring EIMs to the attention of their providers. Our patient panelists emphasised the importance of developing guidance for clinicians that can help raise awareness of this issue.

Following a comprehensive review of the available literature and the identification of current practice patterns and limitations, we assembled a multidisciplinary panel of 25 experts from gastroenterology, dermatology, ophthalmology, and rheumatology along with four patient representatives. A modified Delphi consensus, a validated approach commonly employed in the literature, was performed to arrive at appropriate definitions and management strategies for five EIMs. The purpose of this exercise was to create definitions for the clinical practice setting while establishing a framework that could later be utilised in the creation of a prospective registry of patients seen at the included centers.

Based on the appropriateness rating, the group has devised recommendations regarding EIMs in IBD agreed upon by both gastroenterologists, the appropriate subspecialists, and four patient advocates. Overall, the panel concluded that some of the more common EIMs (e.g. EN and peripheral arthritis) can be appropriately diagnosed and managed by gastroenterologists alone, while other EIMs that are potentially progressive/debilitating or require extended testing to diagnose (e.g. PG, uveitis, axial arthritis) require input from the appropriate subspecialist. Integrated multidisciplinary care clinics represent the gold standard, as subspecialty input was consistently deemed to be optimal in the majority of EIMs. However, based on resource availability IBD specialists may need to assume a leadership role in the managing select EIMs and can do so appropriately as needed to advance patient care. In fact, the patient representatives on the panel emphasised the challenges associated with gaining access to and navigating complex care requiring multiple

subspecialists and expressed the desire for gastroenterologists to take an active role in management of EIMs as much as possible within their practice capabilities. They also noted the importance of increased awareness of EIMs across care providers, including primary care providers, an important future direction for this work.

Appropriate and when possible optimal definitions for each EIM were established, utilising some combination of physical exam findings, symptoms, previously validated scoring systems, and imaging/tissue biopsy results. Monitoring intervals tailored to the EIM sub-type, activity, and severity were established. Appropriate and when possible optimal ways to assess for improvement, worsening, resolution, and recurrence were also established via a combination of physical exam findings, reported symptoms, patient reports, photographs, and physician global assessment (Tables 1–5 and Tables S3–S6).

In many ways, our definitions build upon the current literature, taking previously used broad definitions and tailoring them specifically to the IBD patient population. Per European Crohn's and Colitis Organisation (ECCO) guidelines, EN can be diagnosed clinically or with a biopsy in atypical cases, and our definition agrees with this statement while providing some guidance to the practicing clinician on what exactly constitutes a clinical diagnosis (Table 1).[13] For conditions that can be more challenging to diagnose, such as PG, ECCO guidelines are understandably more vaguer, pointing to clinical diagnosis based on characteristic features without explicitly outlining what these might be. In this regard, the subspecialty literature proved especially beneficial. Our panel concluded that definitions previously proposed in the subspecialty literature for PG and uveitis but not specific to IBD patients could be appropriately applied to the IBD patient population, while also developing our own diagnostic criteria for PG specifically designed for an IBD patient population that was ultimately deemed the optimal diagnostic approach by our panel (Tables 2, 3 and S4).[24,30,31]

Notably, for peripheral and axial arthritis, there were some meaningful departures from the literature (Tables 4 and 5). Much of the gastroenterology literature, including the ECCO consensus guidelines, utilises type I (pauci-articular) and type II (polyarticular) definitions for peripheral arthritis.[13] However, type I and type II peripheral arthritis definitions are not supported in the rheumatology literature and were strongly opposed by our rheumatology panelists during initial discussions regarding proposed definitions of peripheral arthritis. Therefore, these definitions were not considered in our original voting round. Meanwhile, the rheumatology literature provides separate guidelines on how to define peripheral and axial arthritis in all patient populations.[5] These criteria were voted on during the initial round of the panel, and there were concerns regarding their applicability to our IBD patient population. While deemed appropriate but not optimal for axial arthritis, these criteria never reached consensus with regard to peripheral arthritis. Both gastroenterology and rheumatology panelists noted that the proposed criteria were not created with IBD patients in mind and include components that are difficult to meaningfully interpret in an IBD patient population. Thus, the proposed definitions for peripheral arthritis laid forth by our group are unique and represent the first truly multidisciplinary approach to defining this entity in IBD patients.

The literature is also limited with regard to how to assess for improvement, worsening, resolution, or recurrence of these entities, especially specific to the IBD patient. The findings outlined by our panel are thus important to the practicing clinician to determine if treatment efforts are successful and for the selection of endpoints in prospective trials. There is also little published guidance regarding how frequently these patients need to be seen and by whom, an important clinical question addressed by this work. For each EIM, we attempted to identify quality of life or functional disease activity indices that could be utilised to monitor for improvement or worsening but none were deemed appropriate by the panel due to their limitations and lack of applicability to the IBD patient population specifically. This remains an unmet need and the development of quality of life indices and scoring systems in conjunction with patient representatives for this patient population is necessary. In addition, the role of imaging beyond MRI for the diagnosis of axial arthritis has not yet been defined in the spondyloarthritis patient population, and further prospective studies to clarify the role of this and other imaging modalities, including ultrasound, are planned by our group.

Of note, in parallel to this consensus panel, the International Organisation for the Study of Inflammatory Bowel Disease (IOIBD) conducted the Endpoints for Extra-Intestinal Manifestations in Inflammatory Bowel Disease (EXTRA) initiative, which was recently published.[32] This excellent manuscript provides guidance regarding endpoints for clinical trials developed by a panel of 41 international experts. Although the panel size was larger, it included fewer ophthalmologists, dermatologists, and rheumatologists than our panel and also did not include patient representatives. Many of our findings do align—for example, a definition of axial arthritis that includes typical MRI findings and back pain and a timepoint assessment of every 3 months. However, there are also substantial differences, highlighting the need for further research to move forward from expert opinion to data-driven practice. The most prominent differences are related to peripheral arthritis and erythema nodosum. As outlined above, our panel does not require subspecialty input for these EIMs, while the EXTRA initiative does and defines each based on subspecialty expertise and subsequent subspecialty follow-up assessment. Our guidelines may lose some degree of specificity and robustness given that subspecialty input is not required, but they also are far more practical to implement in clinical practice. The EXTRA initiative on the other hand was geared toward clinical trials in which a higher specificity is warranted. In addition, our consensus definitions may prove more useful for the clinician or the researcher looking for more specific guidance on how to diagnose EIMs, more granular ways to assess improvement or worsening across EIMs (notably, the EXTRA initiative did not reach a consensus for assessment of axial arthritis treatment response), and for more nuanced timepoint assessments based on the severity of EIM.

We feel that this research provides much-needed initial guidance and standardisation in the field of EIMs for the practicing gastroenterologist. Strengths of our study are the inclusion of an expert multidisciplinary panel, adoption of a rigorous methodology to minimise bias, and the creation of tools that can be of benefit in clinical practice and research alike for multiple common EIMs that significantly influence the IBD patient population.

Our study has several important limitations. Given that research in EIMs is limited and definitions vary widely, our recommendations cannot be based on high-level evidence.

While this was the trigger for this consensus, the results are vulnerable to bias. It is also important to note that peripheral arthritis especially can be heterogeneous and difficult to characterise in IBD patients, with presentations ranging from inflammation of the entire joint to solely enthesitis, or inflammation at the insertion of tendons or ligaments to the joints. While an important step forward, our current definition of peripheral arthritis remains broad and will not capture these subtle distinctions.

In addition, our panel has several important limitations with regard to representation. First, our panel was composed solely of physicians practicing in the United States, as it was created in order to form a national study network. This means that international applicability will need to be confirmed. Second, all gastroenterologists on our panel are also IBD specialists. This was done on purpose to be able to present a “gold standard” for interdisciplinary care of EIM, but at the same time, it may limit the generalizability of our conclusions to all practicing gastroenterologists. Third, the majority of participants work in tertiary academic settings. Fourth, our total number of panel participants was above those common for a Delphi consensus panel, but the topic of this consensus is broad. While a higher number of subspecialty experts (anywhere from 3 to 12 were used in this program) would be desirable, doing so would exceed the typical size of a Delphi consensus considering the number of needed subspecialties. For this reason, we also did not include pathologists or radiologists.

Finally, our conclusions have not yet been validated, reliability tested, or undergone responsiveness testing. For this reason, we have set in motion a program for this purpose for each individual EIM.

5 | CONCLUSION

We performed a multidisciplinary consensus process using modified Delphi methodology to standardise definitions and monitoring strategies for five EIMs. This work will serve as the basis to develop a prospective cohort of patients with EIMs utilising the definitions identified in this project, which is currently underway. The ultimate goal is the development of a fully validated set of criteria for use in clinical practice and in therapeutic trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We would like to acknowledge our four patient representatives for their substantial and meaningful contributions to this manuscript:

- Tina Aswani-Omprakash, MPH Candidate 2023. Mount Sinai School of Medicine, Founder of Own Your Crohn’s, Co-Founder of South Asian IBD Alliance and IBDesis
- Jessica Caron, MS, Founder of Chronically-Jess.com
- Gaylyn Henderson, Founder of Gutless and Glamorous, Inc.
- Alison Rothbaum, Founder of Empowering Patients, LLC. Their insights are greatly appreciated.

Declaration of personal interests:

AA has served on the scientific advisory boards of Gilead, Ikena therapeutics, and Sun Pharma. Ananthakrishnan is supported by grants from the National Institutes of Health, Crohn's and Colitis Foundation, and Chleck Family Foundation. APF is an investigator for Pfizer, Corbus, Mallinckrodt, and Novartis and receives personal research support from Mallinckrodt and Novartis; honorarium from AbbVie, BMS, Novartis, Alexion, UCB, Boeringer-Ingelheim, and Mallinckrodt for consulting and advisory board participation, and honorarium from AbbVie, Novartis, Kyowa Kirin, and Mallinckrodt for teaching and speaking. ELB is a consultant for AbbVie, Gilead, Pfizer, and Target RWE. BLC receives the following financial support: Advisory Boards and Consultant for Abbvie, Celgene-Bristol Myers Squibb, Pfizer, Sublimity Therapeutics, Takeda, TARGET RWE; CME Companies: Cornerstones, Vindico; Speaking: Abbvie; Educational Grant: Pfizer. RKC receives income from consulting and participation in advisory boards from Abbvie, Bristol Myers Squibb, Eli Lilly, Janssen, Pfizer, Samsung Bioepis, and Takeda. JFC reports receiving research grants from AbbVie, Janssen Pharmaceuticals, and Takeda; receiving payment for lectures from AbbVie, Amgen, Allergan, Inc., Ferring Pharmaceuticals, Shire, and Takeda; receiving consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Celgene Corporation, Eli Lilly, Ferring Pharmaceuticals, Galmed Research, Glaxo Smith Kline, Geneva, Iterative Scopes, Janssen Pharmaceuticals, Kaleido Biosciences, Landos, Otsuka, Pfizer, Prometheus, Sanofi, Takeda, TiGenix; and hold stock options in Intestinal Biotech Development. KF is supported by a grant from the Crohn's and Colitis Foundation. CH is on the advisory board for Abbvie, Janssen, Genentech, InDex Pharmaceuticals, Takeda, Pfizer, and Bristol Myers Squibb. She has research collaborations (nonfunded) with Abbvie, Genentech, Lilly, and Pfizer. She receives grant support from Pfizer. She is on the speakers' bureau for Abbvie. HH receives research support from Allakos, Artizan, NovoNordisk, Pfizer, and consulting fees from Alivio, BMS, Boehringer, ExeGi Pharma, Finch, Gilead, Janssen, Pfizer, Pure Tech, and Otsuka. SH has served as a consultant for Abbvie, Janssen, UCB, Takeda, and Gilead. JH has received research funding from Redhill Biosciences, Janssen, Abbvie, Celgene, Genentech, Eli-Lily, Lycera, and Pfizer Inc. JH is supported in part by resources at the VA HSR&D Center for Innovations in Quality, Effectiveness and Safety (#CIN 13-413), at the Michael E. DeBakey VA Medical Center, Houston, TX. The views expressed in this article are those of the author(s) and do not necessarily represent the views of the Department of Veterans Affairs. GRM serves on Scientific Advisory Boards for Almirall, Incyte, Pfizer, Lilly, UCB, Dermavent, Trevi, Abbvie, Bristol Meyers Squibb (BMS), Celgene, and LEO; is a consultant for Pfizer, Almirall, Abbvie, Lilly, Biofrontera, UCB, Galderma, Scientist, Dermavent, Bausch/Ortho, Incyte, BMS, Celgene, and LEO; is a speaker for Incyte, UCB, LEO; and owns stock in Doc Martins of Maui Sunscreen Company. FR is on the advisory board for or consultant to Adnovate, Agomab, Allergan, AbbVie, Arena, Boehringer Ingelheim, Celgene/BMS, CDISC, Cowen, Ferring, Galmed, Genentech, Gilead, Gossamer, Guidepoint, Helmsley, Index Pharma, Jannsen, Koutif, Mestag, Metacrine, Morphic, Organovo, Origo, Pfizer, fPliant, Prometheus Biosciences, Receptos, RedX, Roche, Samsung, Surmodics, Surrozen, Takeda, Techlab, Theravance, Thetis, UCB, Ysios, and 89Bio. FR is supported by grants from the National Institutes of Health (K08DK110415 and R01DK123233), Crohn's and Colitis Foundation, Rainin Foundation, and the Helmsley Charitable Trust through the Stenosis Therapy and Anti-Fibrotic Research (STAR) Consortium. CS has received honoraria as a speaker from Abbvie and Novartis, honoraria for consulting from Abbvie, Novartis, and UCB. Investigator fees are paid to the institution by Abbvie, Novartis, UCB, InflaRx, Incyte, and Chemocentryx. Consulting fees are paid to the institution by UCB.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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TABLE 1

EN items reaching consensus

Item	Responses	Proportion agreement (%)
In a clinical practice setting, IBD-associated EN should be recognised by	Dermatologist	100
	An IBD specialist	100
IBD-associated EN should be clinically diagnosed by	Dermatologist	100
	An IBD specialist	94
IBD-associated EN should be defined in the clinical practice setting based on	Characteristic appearance of erythematous nodule(s) plus patient report of tenderness	100
	A lesion with features of septal panniculitis on biopsy if there is diagnostic uncertainty on physical exam	100
The average patient with IBD-associated EN can be monitored via	Visits to IBD specialist	88
	Visits to Dermatologist	88
The average patient with IBD-associated EN should be seen	At the time of scheduled assessment of IBD with mild disease and every 1–3 months for moderate to severe disease requiring active intervention	88
Appropriate ways to assess for improvement or worsening in IBD-associated EN include	Patient report of a change in size and/or number of nodules	88
	Patient global assessment	82
	Physician assessment demonstrating change in size	75–83[a]
	Physician assessment of change in the number of nodules	76–82[a]
	Physician global assessment[b]	76–94[a]
Resolution of IBD-associated EN is defined as	Patient report of resolution	88
	Physician assessment demonstrating no nodule(s)	88
Recurrence of IBD-associated EN is defined as	Nodule(s) that develop anywhere	100
Timeline of recurrence of IBD-associated EN is defined as	Patient report of the nodule(s) returning any time after resolution	82
	Physician assessment of nodule(s) returning any time after resolution	88
Patients with IBD-associated EN should be monitored for recurrence	As part of standard of care visits with their IBD specialist	94
	As part of standard of care visits with dermatology	88

Abbreviations: EN, erythema nodosum; IBD, inflammatory bowel disease.

[a]Range in percentage is due to the inclusion of percentage agreement for improvement and for worsening (see Table S2 for a breakdown of percentages by individual items).

[b]Physician global assessment was defined by our panel with 100% consensus as the overall status of EIM based on patient symptoms, physical exam, and any relevant testing (imaging, laboratory data).

TABLE 2

PG items reaching consensus

Item	Responses	Proportion agreement (%)
In a clinical practice setting, IBD-associated PG should be recognised by	An IBD specialist	88
	Dermatologist	94
IBD-associated PG should be clinically diagnosed by	Dermatologist	100
IBD-associated PG can be defined in the clinical practice setting via	Expert assessment of ulcerated and tender lesions with the exclusion of other etiologies	94
	Ulcerated lesions with biopsy of edge demonstrating neutrophilic infiltrate AND exclusion of other etiologies	75
	Any lesion meeting either 2018 Modified Delphi Consensus OR Paracelsus score criteria[a]	75
The average patient with IBD-associated PG should be monitored via	Visits to IBD specialist	88
	Visits to Dermatologist	88
The average patient with IBD-associated PG should be seen	At the time of scheduled assessment of IBD with mild disease and every 1–3 months for moderate to severe disease requiring active intervention	88
Appropriate ways to assess for improvement or worsening of IBD-associated PG include	Patient report of change in size (measured with a tape measure) and/or degree of ulceration	81
	Physician assessment of subjective change in size	81
	Physician assessment of objective change in size	100
	Physician assessment of change in ulceration	88–94[b]
	Physician global assessment[c]	76–92[b]
	Photographs demonstrating a change in size and/or degree of ulceration as per dermatology	94
Resolution of IBD-associated PG can be defined as	Patient report of absence of ulceration	94
	Physician assessment demonstrating no lesion(s)	100
	Photographs demonstrating no lesions as per dermatology	94
Recurrence of IBD-associated PG is defined as	A lesion that recurs anywhere	100
Timeline of recurrence of IBD-associated PG is defined as	Physician assessment of lesions returning any time after resolution	76
Patients with IBD-associated PG should be monitored for recurrence	As part of the standard of care visits with their IBD specialist	88
	As part of the standard of care visits with dermatology	88

Abbreviations: IBD, inflammatory bowel disease; PG, pyoderma gangrenosum.

[a]The 2018 Modified Delphi criteria are one major criterion – biopsy of ulcer edge demonstrating neutrophilic infiltrate and eight minor criteria: (1) exclusion of infections; (2) pathergy; (3) history of inflammatory bowel disease or inflammatory arthritis; (4) history of papule, pustule, or vesicle ulcerating within 4 days of appearing; (5) peripheral erythema, undermining border, and tenderness at ulceration site; (6) multiple ulcerations at least one on the anterior lower leg; (7) cribriform or "wrinkled paper" scar(s) at healed ulcer sites; and (8) decreasing ulcer size within 1 month of initiation immunosuppressive medication(s).[30] The Paracelsus Criteria are *P*rogressing disease (defined as clinically evident ulcer developing within <6 weeks), *A*ssessment of relevant differential diagnoses, *R*eddish-violaceous wound border, *A*melioration by immunosuppressant drugs, *C*haracteristically irregular (bizarre) ulcer shape, *E*xtreme pain >4/10 on the visual analog scale, *L*ocalization of lesion at the site of trauma (pathergy phenomenon), *S*uppurative inflammation in histopathology, *U*ndermined Wound Border, *S*ystemic disease associated.[31]

[b] Range in percentage is due to the inclusion of percentage agreement for improvement and for worsening (see Table S2 for a breakdown of percentages by individual items).

[c] Physician global assessment was defined by our panel with 100% consensus as the overall status of EIM based on patient symptoms, physical exam, and any relevant testing (imaging, laboratory data).

TABLE 3

Uveitis items reaching consensus

Item	Responses	Proportion agreement (%)
In a clinical practice setting, IBD-associated uveitis should be recognised by	An ophthalmologist	100
IBD-associated uveitis should be clinically diagnosed by	An ophthalmologist	100
IBD-associated uveitis should be defined as	More than one cell in the anterior chamber, vitreous haze, or the presence of choroidal or retinal inflammation	75
In a clinical practice setting, IBD-associated uveitis should be monitored by	An ophthalmologist	100
Improvement of IBD-associated uveitis is defined as	Two-step decrease in the level of inflammation or decrease to Grade 0 as per ophthalmologists	77
Worsening of IBD-associated uveitis is defined as	Two-step increase in the level of inflammation or increase from Grade 3 to 4 as per ophthalmologists	86
Recurrence of IBD-associated uveitis is defined as	New episode in either eye	92
Timeframe of recurrence of IBD-associated uveitis is defined as	Inflammation recurring after >3 months regardless of IBD therapy	93
Patients with history of IBD-associated uveitis should be monitored for recurrence	As part of the standard of care visits with ophthalmology	93

Abbreviation: IBD, inflammatory bowel disease.

TABLE 4

Peripheral arthritis items reaching consensus

Item	Responses	Proportion agreement (%)
In a clinical practice setting, IBD-associated peripheral arthritis should be recognised by	An IBD specialist	92
	A rheumatologist	93
IBD-associated peripheral arthritis should be clinically diagnosed by	An IBD specialist	85
	A rheumatologist	100
In a clinical practice setting, IBD-associated peripheral should be defined as	Joint pain + swollen/tender joints on exam	77
	Morning stiffness + joint pain + swollen/tender joints on exam	85
	Swollen/tender joints on the exam with the exclusion of other etiologies	92
In a clinical practice setting, IBD-associated peripheral can be monitored via	Visits to IBD specialist	85
	Visits to rheumatologist	100
The average patient with IBD-associated peripheral arthritis should be seen	At the time of scheduled assessment of IBD with mild disease and every 1–3 months for moderate to severe disease requiring active intervention	85
Appropriate ways to assess for improvement or worsening in IBD-associated peripheral arthritis include	Patient report of change in morning stiffness	75
	Patient report of the change in joint pain with movement	75
	Patient report of change in swelling/tenderness	81–88[a]
	Patient report of change in number of involved joints	75
	Patient report of overall improvement/worsening	75–81[a]
	Physician report of change in swelling/tenderness/redness	100
	Physician report of change in number of involved joints	86–100[a]
	Physician global assessment[b]	86–88[a]
Resolution of IBD-associated peripheral arthritis can be defined as	Patient report of resolution	75
	IBD specialist assessment demonstrating resolution	86
	Rheumatology assessment demonstrating resolution	100
Recurrence of IBD-associated peripheral arthritis is defined as	Recurrent joint involvement in the same anatomic location(s)	88
	New joint involvement in any anatomic location	100
Timeline of recurrence of IBD-associated peripheral arthritis is defined as	Patient report of joint symptoms returning any time after resolution	75
	Physician assessment of joint symptoms returning any time after resolution	88
Patients with IBD-associated peripheral arthritis should be monitored for recurrence	As part of the standard of care visits with their IBD specialist	94
	As part of the standard of care visits with rheumatology	100

Abbreviation: IBD, inflammatory bowel disease.

[a] Range in percentage is due to the inclusion of percentage agreement for improvement and for worsening (see Table S2 for a breakdown of percentages by individual items).

[b] Physician global assessment was defined by our panel with 100% consensus as the overall status of EIM based on patient symptoms, physical exam, and any relevant testing (imaging, laboratory data).

TABLE 5

Axial arthritis items reaching consensus

Item	Responses	Proportion agreement (%)
In a clinical practice setting, IBD-associated axial arthritis should be recognised by	An IBD specialist	86
	A rheumatologist	100
IBD-associated axial arthritis should be clinically diagnosed by	A rheumatologist	100
In a clinical practice setting, IBD-associated axial arthritis should be defined as	Patient who meets ASAS classification criteria for axial arthritis as per rheumatologists[c]	93
	Patients with IBD, inflammatory back pain, and consistent MRI findings as per rheumatologists	93
In a clinical practice setting, IBD-associated axial arthritis can be monitored via	Visits to rheumatologist	100
The average patient with IBD-associated axial arthritis should be seen	At least every 3 months until symptoms improve or resolve	81
Appropriate ways to assess for improvement or worsening of IBD-associated axial arthritis include	Patient report of change in back pain	75
	Patient report of overall improvement or worsening	75–76[a]
	Physician global assessment[b]	86
In a clinical practice setting, clinical resolution of symptoms of IBD-associated axial arthritis can be defined as	Rheumatology assessment demonstrating resolution of clinical symptoms	94
In a clinical practice setting, clinical recurrence of symptoms of IBD-associated axial arthritis can be defined as	Rheumatology assessment demonstrating recurrence of clinical symptoms anytime after resolution	88
The average IBD patient with axial arthritis should be seen	As part of the standard of care visits with their IBD specialists	81
	As part of the standard of care visits with rheumatology	100

Abbreviation: IBD, inflammatory bowel disease.

[a]ASAS criteria for spondyloarthritis include patients with ≥3 months of back pain with or without peripheral manifestations and age at onset <45 years who have sacroiliitis on imaging plus ≥1 spondyloarthritis feature of HLA-B27 plus ≥2 other spondyloarthritis features. Spondyloarthritis features include inflammatory back pain, arthritis, enthesitis (heel), uveitis, dactylitis, psoriasis, Crohn's/Ulcerative colitis, good response to nonsteroidal anti-inflammatory drugs, family history for spondyloarthritis, HLA-B27, and elevated C-reactive protein.[5]

[b]Range in percentage is due to the inclusion of percentage agreement for improvement and for worsening (see Table S2 for a breakdown of percentages by individual items).

[c]Physician global assessment was defined by our panel with 100% consensus as the overall status of EIM based on patient symptoms, physical exam, and any relevant testing (imaging, laboratory data).