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POSITION STATEMENT

Perianal Fistulizing Crohn's Disease: Utilizing the TOpClass Classification in Clinical Practice to Provide Targeted Individualized Care

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BACKGROUND & AIMS: **Perianal fistulation is a challenging phenotype of Crohn's disease, with significant impact on quality of life. Historically, fistulae have been classified anatomically in relation to the sphincter complex, and management guidelines have been generalized, with lack of attention to the clinical heterogenicity seen. The recent 'TOpClass classification system' for perianal fistulizing Crohn's disease (PFCD) addresses this issue, and classifies patients into defined groups, which provide a focus for fistula management that aligns with disease characteristics and patient goals. In this article, we discuss the clinical applicability of the TOpClass model and provide direction on its use in clinical practice.**

METHODS: **An international group of perianal clinicians participated in an expert consensus to define how the TOpClass system can be incorporated into real-life practice. This included gastroenterologists, inflammatory bowel disease surgeons, and radiologists specialized in PFCD. The process was informed by the multi-disciplinary team management of 8 high-volume fistula centres in North America, Europe, and Australia.**

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Abbreviations used in this paper: CD, Crohn's disease; EUA, examination under anesthesia; HBOT, hyperbaric oxygen therapy; IBD, inflammatory bowel disease; MDT, multidisciplinary team; MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; PFCD, perianal fistulizing Crohn's disease; PPS, persistent perineal sinus; QoL, quality of life; TDM, therapeutic drug monitoring; TNF, tumor necrosis factor; VAAFT, video-assisted anal fistula treatment.

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RESULTS: **The process produced position statements to accompany the classification system and guide PFCD management. The statements range from the management of patients with quiescent perianal disease to those with severe PFCD requiring diverting-ostomy and/or proctectomy. The optimization of medical therapies, as well as the use of surgery, in fistula closure and symptom management is explored across each classification group.**

CONCLUSION: **This article provides an overview of the system's use in clinical practice. It aims to enable clinicians to have a pragmatic and patient goal-centered approach to medical and surgical management options for individual patients with PFCD.**

Keywords: Crohn's Disease; Multi-disciplinary Management; Perianal Fistula.

Perianal fistulizing Crohn's disease (PFCD) is a phenotype of inflammatory bowel disease (IBD) with high morbidity, which occurs in up to 30% of patients with Crohn's disease (CD).[1] The emergence of perianal fistulae often results in significant symptoms including pain, discharge, and fecal incontinence. The effect of fistulae on patient quality of life (QoL) can be substantial,[2] and optimal management of this group represents a challenge for health care providers. Indeed, PFCD is the IBD phenotype with the highest financial health care burden, and management requires synergistic care involving all members of the multidisciplinary team (MDT).[3]

The complexity of PFCD means that there is marked intra-phenotype heterogeneity, beyond anatomical difference or fistula morphology. This heterogeneity is seen in symptom severity, co-existent luminal disease, response to medical therapy, and variable success rates with surgical intervention. Importantly, there is also heterogeneity among patient and physician treatment goals, which can alter over time, requiring management plans to be dynamic and individualized. Due to this multi-factorial, intra-phenotype heterogeneity, categorizing PFCD in purely anatomical terms is of limited value.

The recent 'TOpClass classification system'[4] (Figure 1) takes a fresh approach to fistula classification by identifying several groups of patients. Key elements of the system include stratification according to disease severity and outcome, as well as synchronization of patient and clinician goals; with a proactive, combined medical and surgical approach on a treat-to-patient-goal basis. The system incorporates an element of flexibility and takes a pragmatic approach allowing clinicians to classify patients into more homogenous cohorts. The clinical utility is in tailoring management in an individual patient.

In the first part of this article (section A), we describe the TOpClass classification groups. Specifically, we discuss therapeutic aims in each class and how, for certain patients, improved symptom control and QoL may be the primary goal of treatment. We also include a real-life case-study to illustrate how patients can transition between classes. In the second part (section B), we present a consensus project offering position statements on management in each TOpClass group.

Section A: An Overview of TOpClass Classification Groups

Class 1: Minimal Disease

Class 1 patients are those with minimal fistula symptoms and anorectal disease burden, requiring minimal intervention over time. In practice, this represents patients with quiescent or asymptomatic perianal disease (ie, minimal drainage or perianal symptoms). In the absence of QoL instrument scores that define 'minimal symptoms,' the definition is patient-driven. In Class 1, the focus of therapy is usually medical, in the form of establishing (or continuing) IBD therapies to prevent disease progression and encourage healing. If any aspect of a fistula is impacting QoL (eg, to the point where patients desire treatment escalation), they enter Class 2.

Class 2: Chronic Symptomatic Perianal Fistulae. Patients in Class 2 have chronic symptomatic fistulae. These patients need a proactive management strategy, including optimizing medical therapies, planned surgical interventions, or a combination. They represent most cases encountered in clinical practice and are categorized into 3 subgroups according to their treatment goals, the impact of disease on QoL, fistula anatomy, and anorectal disease burden. The subgroups are fistulae suitable for repair (2a), fistulae suitable for symptom control only (2b), and fistulae requiring diverting ostomy (2c).

Class 2a: chronic symptomatic fistulae suitable for repair. These patients have symptomatic fistulae suitable for medical and surgical closure or repair and whose goal is fistula closure. Suitability generally includes the absence of proctitis and florid perianal disease (eg, perianal ulceration and fissures). In practice, attempting closure may be as simple as removal of seton in patients on optimized medial therapy. In others, carefully selected reparative procedures can be considered. These procedures may be 'anatomical' (such as ligation of intersphincteric fistula tract and advancement flaps) or 'non-anatomical' (such as curettage and internal opening closure ± biological augmentation). Repair requires suitable fistula anatomy, and highly complex fistulae may fall outside of the Class 2a subgroup due to their morphology (eg, extensive branching, horseshoeing, and multiple internal openings).[5]

Class 2b: chronic symptomatic fistulae suitable for symptom control. For Class 2b patients, the goal of therapy is symptom control, because either: (1) their anorectal disease burden or fistula anatomy precludes fistula closure, or (2) the patient's goal is symptom control. The latter group may have refractory disease, have experienced previous failed attempts at repair, or prefer the security of a seton in a well-controlled tract.

Where anorectal disease, such as proctitis, or complex fistula anatomy preclude repair, medical treatment, or surgical rationalization may be used with the aim to downstage the patient to Class 2a. 'Rationalization' includes draining cavities, eradicating branches, and closing elements of the fistula where multiple tracts or openings exist.

Class 2c: progressive disease. Class 2c patients are differentiated into 2 subgroups based on the velocity of disease progression. Class 2c-i (early, rapidly progressive/destructive disease) are those with rapid disease progression over 3 to 6 months, despite optimized medical and surgical drainage. Class 2c-ii (gradually debilitating disease) have broadly stable disease over the last 3 to 6 months but have experienced background progression in their disease burden, with reducing QoL, over 1 or more years. In both cases, the importance is recognizing that the current therapy alone is not working for the patient. If intensive medical and surgical intervention has failed to achieve control, then a diverting ostomy is recommended. For 2c-i, the therapeutic aim of the ostomy is to urgently halt disease progression. For 2c-ii, the target is restoring patient QoL through diversion.[6] Medical therapy and drainage procedures (if required) should continue after ostomy formation. Unfortunately, subsequent stoma reversal is rarely achieved in these groups.[7] Care should be holistic and include patients' mental health.

What You Need to Know

Background

The heterogenicity of perianal Crohn's disease means a 'one-size-fits-all' approach is impossible for this inflammatory bowel disease phenotype. We discuss the 'TOpClass Classification' of perianal fistula and how it can be translated clinically.

Findings

An international group of perianal Crohn's disease experts describe the classification and provide position statements on best-practice fistula management. These cover optimization of medical and surgical therapy.

Implications for patient care

Our approach could help gastroenterologists when optimizing therapy in fistula patients. We also explain how and when surgery is best deployed alongside medical treatment.

Class 3: Severe Disease With Exhausted Perineum or Adverse Features

In severe, refractory PFCD, ultimately 31% to 49% undergo diverting-ostomy.[8] In two-thirds of these patients, disease will settle and efforts to repair fistulae can be considered.[6,7] However, in one-third, severe symptoms persist and require further medical and surgical optimization.[9] Class 3 patients have severe symptoms, despite defunctioning, with irreversible perineal tissue destruction or symptoms markedly limiting QoL. Proctectomy is required to restore QoL. This procedure is

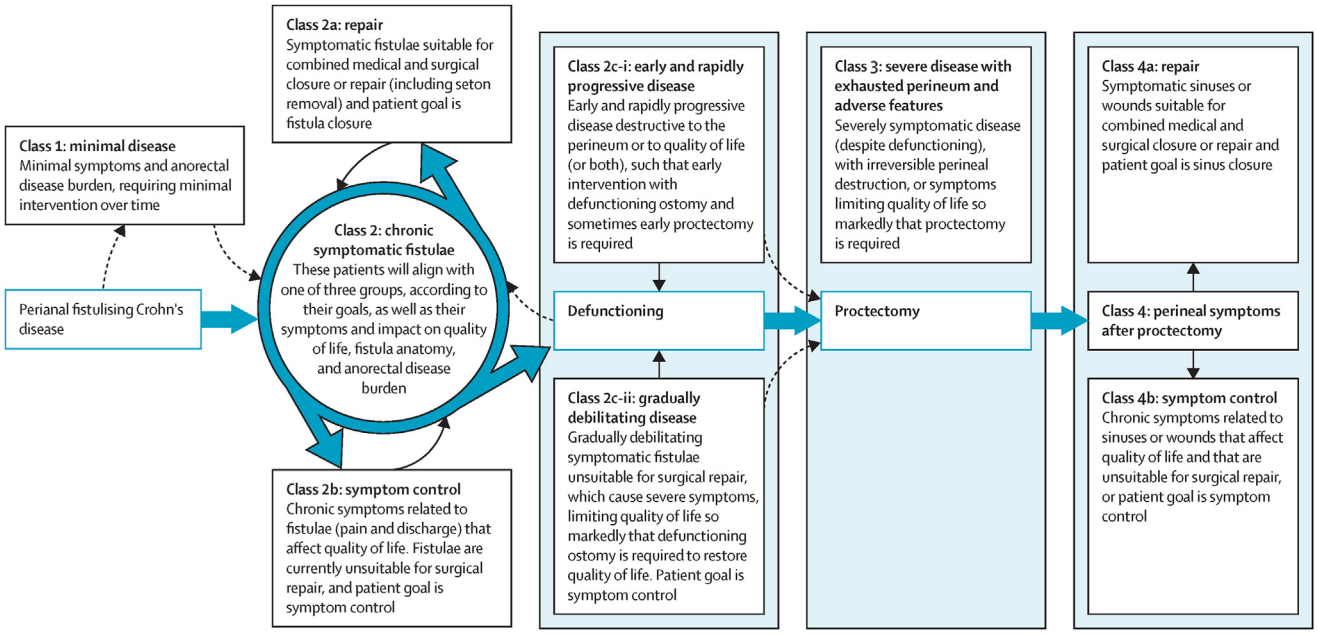

Figure 1. The TOpClass classification system. Reproduced with permission from Elsevier.

highly morbid and results in a permanent ostomy. It requires extensive shared decision-making and therefore should preferably be discussed with patients before it is needed (as with stoma formation in Class 2c).

Class 4: Perineal Symptoms After Proctectomy

Proctectomy in CD is associated with high rates of persistent perineal sinus (PPS) and non-healing wounds (prevalence varying between 23% and 79% in the literature).[10] These patients, with ongoing perineal lesions, are termed Class 4. PPS may be a surgical complication or related to a cavity, but persisting CD-related inflammation can also be present in the perineum.[11] Class 4a and 4b are analogous to Classes 2a and 2b. Class 4a (repair) have a symptomatic sinus or wound, suitable for closure or repair, and whose goal is sinus closure. In contrast, Class 4b (symptom control) have a sinus or wound unsuitable for surgical repair, or the patient goal is symptom control alone. Limited evidence surrounds PPS, but combined medical and surgical treatment can be considered.

Case Study: Downstaging Class 2b Into Class 2a

A 32-year-old male with ileocolonic CD on azathioprine was referred with a symptomatic perianal fistula (pain and discharge). Imaging demonstrated a complex transsphincteric tract with an intersphincteric horseshoe extension, unsuitable for repair. Colonoscopy demonstrated active ileocaecal inflammation and proctitis. A synergistic medical and surgical plan was formulated. He underwent examination under anesthesia (EUA) and seton insertion before being escalated to intravenous infliximab. Repeat endoscopy showed resolution of proctitis. However, his fistula complexity precluded a surgical repair attempt, and he remained in Class 2b, despite his end goal being fistula closure.

A further EUA with video-assisted anal fistula treatment (VAAFT)[12] was performed to eradicate the horseshoe component. Infliximab levels were optimized to $>10\mu g/mL$. Repeat magnetic resonance imaging (MRI) demonstrated complete healing of the horseshoe, simplifying his anatomy to that of a straight tract suitable for surgical repair (2b to 2a transition). As ongoing optimized anti-tumor necrosis factor (TNF) did not achieve the goal of healing; at this point, gastroenterologists may assume loss of response to anti-TNF and consider a switch in therapy. However, in view of the improved anatomy suggesting suitability for surgical repair, this was undertaken with infliximab continued as medical therapy. The result was fistula healing. Figure 2 shows sequential MRI images exhibiting downstaging of the fistula from Class 2b to Class 2a (following optimized medical therapy and VAAFT), with ultimate resolution of the main tract after final surgical repair. This outcome would have been unlikely without a joint medical and surgical approach.

Section B: Expert Consensus Project

To provide guidance on management of the above classes, we performed an expert consensus project. To inform this process, we probed MDT management of PFCD by asking high-volume IBD centers to discuss their approach to treating fictional cases written to illustrate each classification group.

Methods

The project used a modified nominal group technique[13] (Figure 3). First, a systematic review was conducted to evaluate current evidence on management of PFCD (Supplementary Appendix A). The results informed provisional statements that were presented to the expert panel for open discussion and refinement, followed by voting (strongly agree [A+], agree with minor reservation [A], undecided [U], disagree [D], strongly disagree [D+]), and consensus agreement was predefined as 80% voting as "strongly agree" (A+) or "agree with minor reservation" (A). The participants were members of the TOpClass consortium. This is a large, international, group of perianal clinicians and/or researchers, which has developed following the project reclassifying PFCD.[4] The group includes gastroenterologists, colorectal surgeons, and gastrointestinal radiologists who have active research output in the field of PFCD and/or high-volume clinical practices in PFCD care. Details of the expert panel are shown in Supplementary Appendix B.

Subsequently, 8 case vignettes were created to simulate 'real-life' PFCD presentations. These cases were used to evaluate the MDT management of PFCD at participating IBD centers (Supplementary Appendix C). Each case corresponded to a TOpClass classification group and can be found in Supplementary Appendix D. Individual MDT responses were collated and used to develop further consensus statements, as well as to refine provisional statements. Finally, a 2-hour virtual consensus meeting of the expert panel, with voting, was held on Microsoft Teams to produce the presented statements below.

Results

Consensus Statements on Optimal Management of PFCD by Classification Group

PFCD specialists from 8 centers conducted 'mini-MDTs' to answer questions related to the management of the case vignettes. The final consensus statements are presented in order of: (1) statements relating to specific TOpClass classification groups; (2) statements relating to

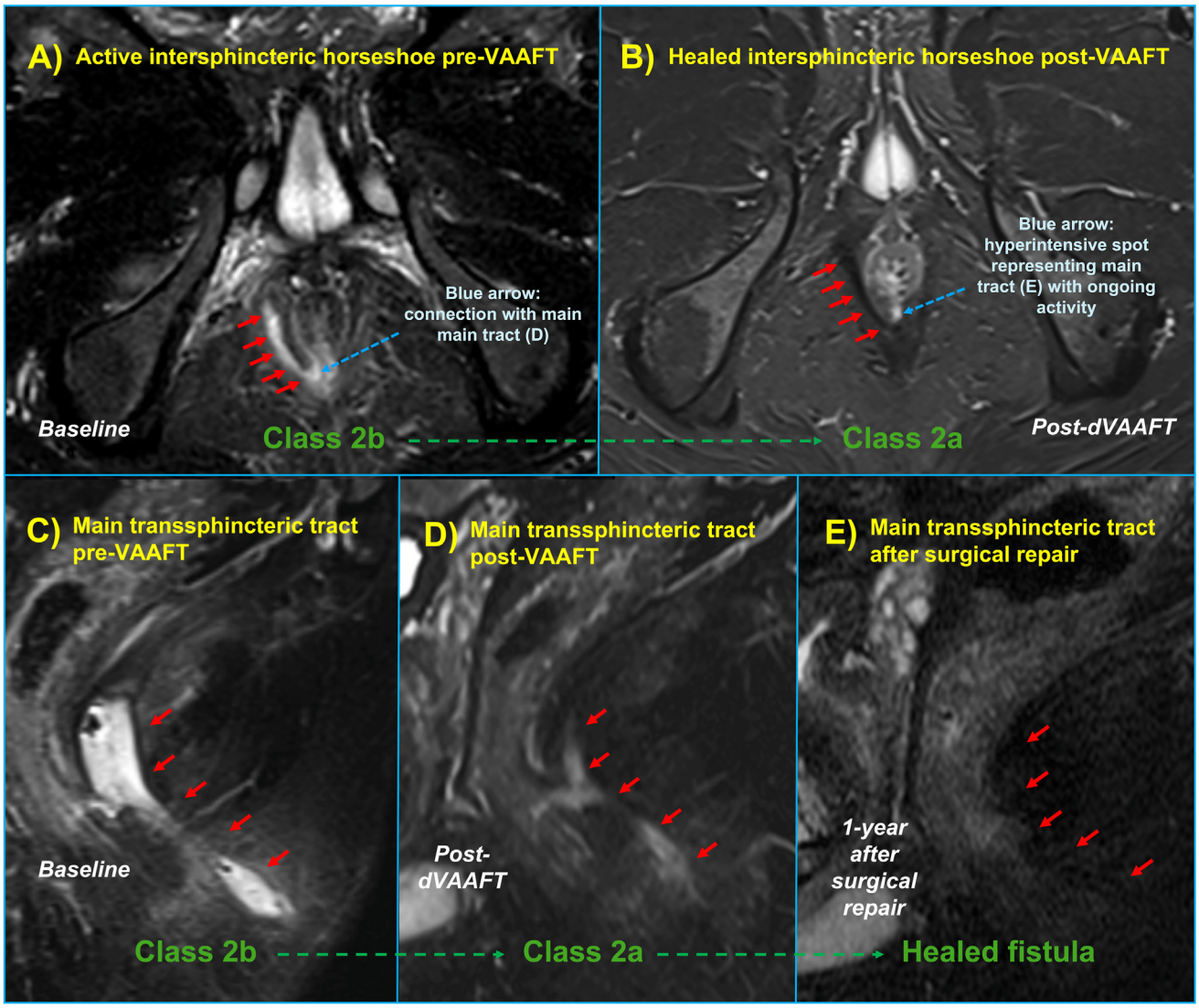

Figure 2. A case of anatomical rationalization and fistula downstaging from Class 2b to 2a. (*A*), Active intersphincteric horseshoe extension at presentation; (*B*), Healed (fibrosed) horseshoe following intensive VAAFT; (*C*), Main fistula tract at presentation; (*D*), Main tract with reduced but ongoing activity following VAAFT; (*E*), Radiological healing (fibrosis) of main tract following definitive surgical repair.

optimized medical management of symptomatic fistulae; and (3) a statement on the psychological burden of PFCD.

Class 1: minimal disease. The role of setons and radiological monitoring in Class 1 was intensively discussed. The panel agreed that, given the lack of symptoms, there is no role for seton insertion in Class 1 patients ([A+] 50%, [A] 50%), and no role for routine monitoring with MRI scans in the absence of new fistula symptoms ([A+] 46%, [A] 54%). Escalation of medical therapy was also explored in the panel's discussions. In our vignette, the Class 1 patient was on azathioprine for luminal disease, and there was uncertainty about escalating medical therapy. Six of 8 centers indicated they would continue with optimized thiopurine monotherapy, whereas 2 of 8 suggested escalating to anti-TNF, highlighting the lack of data and uncertainty on progression of Class 1 disease. Although preventing progression is important, the panel felt decisions to escalate medical therapies should be individualized—balancing the risk:-benefit ratio of therapies in quiescent disease.

Class 2a: chronic symptomatic fistulae suitable for repair. Statements regarding suitability for surgical repair in Class 2 are listed in Table 1. Proctitis and florid perianal disease are signs of an active inflammatory ("hostile") environment, unlikely to support post-operative healing.[14] Additionally, anal stricture is associated with poorer outcomes in PFCD.[15] Although individual surgeons may consider repair outside these parameters, evidence for doing so sparse, meaning it is key that these factors are at least considered before deeming a patient suitable. Importantly, optimizing medications for proctitis, dilating strictures, or rationalizing fistula morphology can move a patient into the 2a subgroup and facilitate a repair attempt. The level of anatomical complexity that precludes 'real-world' non-anatomical repair is unknown, although the ADMIRE-

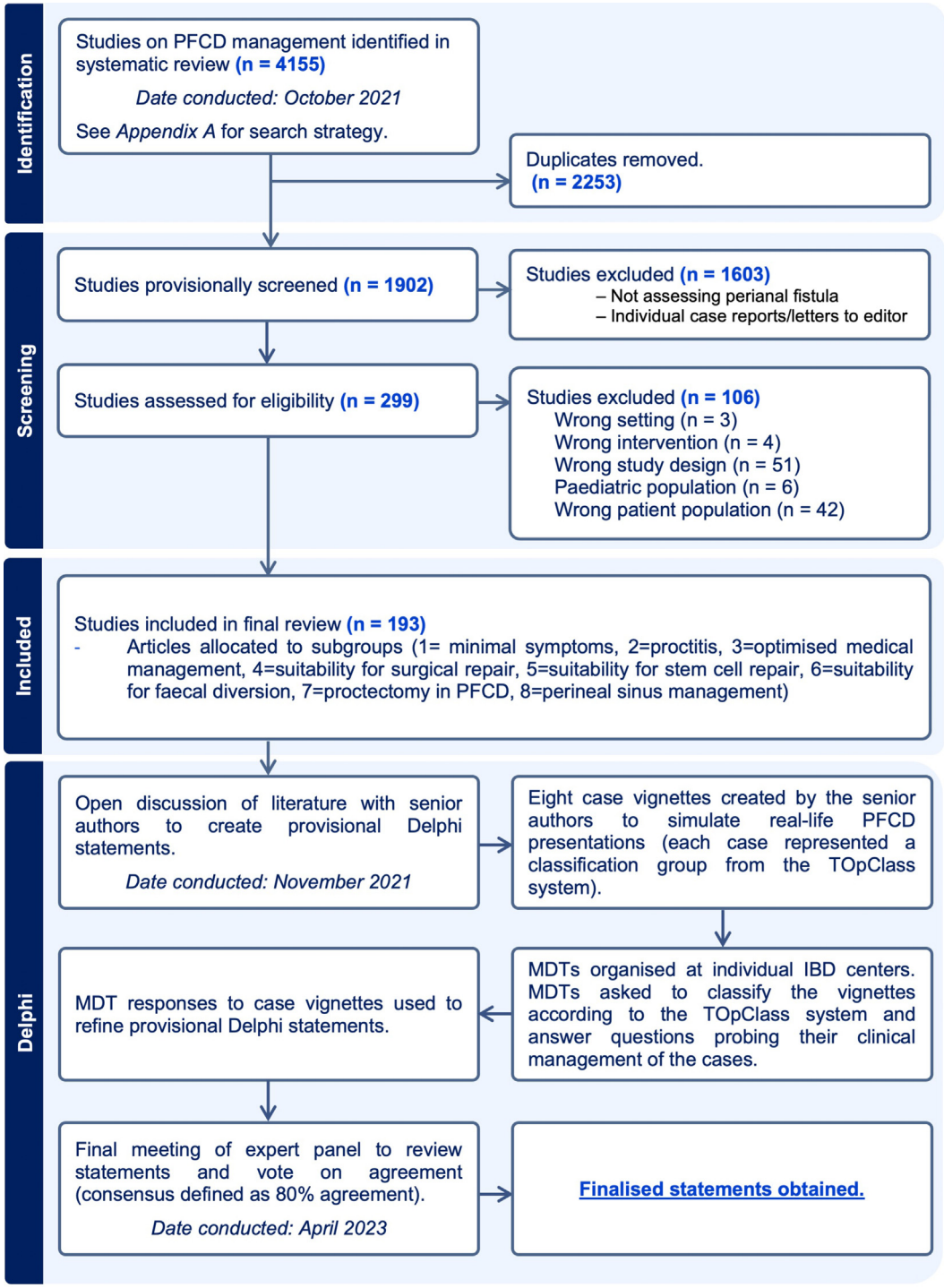

Figure 3. Flow chart showing the methodology of the systematic review and consensus process.

CD[16] (mesenchymal stem cell [MSC] trial) inclusion criteria provides a framework for evidence-based selection (Table 2 footnote). Alternatively, for anatomical repair, >1 internal opening will usually preclude suitability, except in rare circumstances, such as 2 internal openings close enough together to be covered by a single flap.

Statements regarding the proactive surgical management of 2a fistulae are listed in Table 2. The role of seton insertion prior to surgical repair was a particular consideration. Seton placement is established practice in PFCD, is thought to improve recurrence and healing rates of patients starting biological therapy,[17–19] and may aid certain repair modalities (particularly ligation of intersphincteric fistula tract). However, it was felt that a preparatory seton is not always required before fistula repair, and therefore, the recommendation of seton insertion prior to repair is not absolute.

Table 1. Position Statements Relating to the Suitability of Class 2 Fistulae for Surgical Repair

Presence of proctitis	In Class 2a, criteria for suitability of surgical repair includes absence of proctitis ([A+] 50%, [A] 50%) • The diagnosis of proctitis on MRI can be of equivocal significance ([A+] 11%, [A] 89%) • MRI findings of proctitis should be confirmed with endoscopy prior to decision about suitability of surgical repair ([A+] 44%, [A] 56%) • Proctitis is defined as endoscopically visible active mucosal inflammation, a single ulcer > 5 mm in the rectum or 3 ulcers <5 mm ([A] 89%, [U] 11%)
Presence of anal stricture	In Class 2a, criteria for suitability of surgical repair includes absence of anal stricture ([A+] 33%, [A] 56%, [D] 11%) • An anal stricture is a known poor prognostic parameter for surgical fistula closure ([A+] 57%, [A] 43%) • Anal stricture is a relative but not an absolute contraindication for repair in a well-consented patient ([A+] 50%, [A] 50%)
Perianal disease activity	In Class 2a, criteria for suitability of surgical repair includes absence of florid perianal disease ([A+] 67%, [A] 33%) • We define florid perianal disease as the presence of multiple lesions such as suppuration, active fissures, and ulcers ([A+] 25%, [A] 75%)

MRI, Magnetic resonance imaging.

Class 2b: chronic symptomatic fistulae suitable for symptom control. Commonly, a focus of therapy in Class 2b is optimizing drainage at EUA. In real-world practice, this often is limited to curetting the tract, draining collections, and siting setons. The panel discussed how increased access to VAAFT is enhancing the management of this group.[12] They agreed Class 2b fistula tracts with single or multiple internal openings can be considered for 'symptom control' VAAFT during EUA ([A] 100%). Joint care between IBD gastroenterologists and surgeons might be considered when managing challenging 2b cases.

Despite 2b patients not wanting or not being suitable for repair, removal of their setons could be considered if

Table 2. Position Statements Relating to the Surgical Repair of Class 2a Fistulae

Anatomical surgical repair strategies	• Advancement flap repair is best reserved for tracts with a single internal opening with pliable tissues ([A+] 29%, [A] 71%) • Ligation of intersphincteric fistula tract is best reserved for thin transsphincteric tracts without intersphincteric complexity or internal sphincter loss ([A+] 29%, [A] 71%) • Surgical repair utilizing laser fistula treatment is experimental only at this stage ([A] 83%, [U] 17%) • We do not recommend fistula plugs and glues for fistula closure ([A+] 57%, [A] 43%)
Non-anatomical surgical repair strategies (eg, MSCs)	• Fistula tracts with single or multiple internal openings, and no undrained perianal collections, can be considered for operations that debride the tract and close the internal opening ([A] 100%) • Fistula tracts with single or multiple internal openings, and no undrained perianal collections, can be considered for stem cell repair ([A] 100%) • Fistula tracts too complex to be considered for anatomical repair may be treated by stem cell repair, if they meet the appropriate criteria ([A] 80%, [U] 20%)[a]
Role of setons and medical therapy prior to repair attempt	• Surgical repair attempts should only be considered after optimization of medical therapy ([A] 100%) • Surgical repair attempts should *usually* only be considered after insertion of seton ([A] 91.6%, [D] 8.3%)
Seton removal as a repair attempt	• The removal of setons alone can be considered as an attempt at repair once a patient is established on optimised medical therapy ([A+] 80%, [A] 20%) • There is inadequate evidence to support a firm time of seton removal. However, in a well-drained fistula treated with medical therapy, the timing of removal should be considered after induction therapy if there is evidence of local response to therapy. ([A+] 17%, [A] 83%)

MSC, Mesenchymal stem cell.

[a]The ADMIRE-CD inclusion criteria (largest published non-anatomical repair trial) included non- or mildly active luminal disease, ≤2 internal and ≤3 external fistula openings, and the absence of anal stricture or perianal collections >2 cm or rectovaginal fistulation. The efficacy of stem cell repair outside these parameters is unknown. Our proposed criteria for repair suitability (Table 1) includes the absence of proctitis, anal stricture, and severe associated perianal disease. Unlike ADMIRE-CD, we have not included morphological factors, such as the number of fistula openings, as the level of anatomical complexity to preclude a 'real-world' non-anatomical repair attempt is unknown.

they are impacting QoL. Negative experiences of seton drainage have been reported, with patients specifically citing seton- and knot-related pain.[2] However, setons can deliver psychological reassurance (in addition to the known protection against cyclical abscess, and symptom reduction in the long-term), with a small study reporting improvements in global QoL and the mental composite score on the Short Form-12 with seton placement.[20] The panel felt that seton removal in Class 2b patients is uncommon and should be an individualized decision, taken in discussion with the patient, noting removal must be balanced against fistula activity and abscess risk. If long-term setons are sited, a preference for finer material with fewer/smaller knots was suggested from a qualitative study.[2]

Class 2c: progressive disease. The panel agreed rapidly progressive (2c-i) disease must be rapidly identified and intensively managed. They recommended optimizing medical therapy and repeating EUAs until adequate drainage can be achieved ([A+] 91%, [A] 9%). Proactive therapeutic drug monitoring (TDM) of anti-TNFs was discussed, targeting high levels (see 'optimizing medical therapy'). If tissue destruction and QoL do not respond within 3 to 6 months of these measures, consider offering a stoma for defunctioning ([A+] 64%, [A] 36%). Given the intense management Class 2c-i patients require in a short timeframe, it was recommended treating clinicians consider early referral to a high-volume fistula centre ([A+] 85%, [A] 15%).

For Class 2c-ii, the panel felt this group should be offered diverting-ostomy when efforts to improve QoL via optimized medical therapy and surgical disease control fail. It was noted that recognizing this timepoint can be difficult in an individual's disease journey. In patients with long-standing refractory PFCD, building good rapport and assessing QoL impact is essential to identifying 2c-ii patients. It was noted that the psychological burden of PFCD may be particularly high in this group (see 'psychological burden of disease').

Class 3: severe disease with exhausted perineum or adverse features. Although Class 3 patients need consideration of proctectomy, the panel agreed no new management statements specific to this group. The role for perineal surveillance imaging post-proctectomy is unknown. There is modest evidence to suggest biologic immunotherapy, following fecal diversion, is associated with a lower risk of ultimately requiring a proctectomy in severe PFCD.[9] However, there is no evidence regarding the impact of biologics post-proctectomy in attenuating post-proctectomy sinus risk. From our collated MDT responses, 3 of 8 centers suggested they would continue biologics post-proctectomy in PFCD for perineal disease protection (independent of the activity of luminal disease). However, due to lack of any evidence for efficacy of post-proctectomy biologics, no formal statement could be made to support their use or duration.

Class 4: perineal symptoms after proctectomy. The panel agreed that, in Class 4a and 4b patients, there is a major unmet need to improve their management ([A+] 80%, [A] 20%). Additionally, it was agreed that currently there are a variety of potential management options available for Class 4 patients, all with limited supporting evidence ([A+] 55%, [A] 45%). Despite the limited evidence, it was felt reasonable to consider optimizing the perineal tissue in these patients with medical therapy ([A+] 42%, [A] 58%). 'Medical therapy' primarily relates to biologics or small molecules. However, hyperbaric oxygen therapy (HBOT) may also be utilized, although evidence is sparse. Lansdorp et al reported some success with HBOT in 3 patients with biopsy-proven granulomas in their non-healing perineal wounds.[21] A further small case series by Chan et al showed HBOT, combined with PPS excision and perineal reconstruction, led to complete perineal healing in all 4 included patients.[22]

For Class 4a patients, the repair of a perineal sinus would be dependent on its anatomy ([A+] 46%, [A] 54%). In these patients, we recommend optimization of perineal tissues prior to surgical repair of the sinus ([A+] 55%, [A] 45%). Surgical optimization of the perineal tissues prior to repair of the sinus includes drainage of any presacral or pelvic collections and consideration of excision of the mesorectum ([A+] 33%, [A] 67%). Conversely, for Class 4b patients, no formal statements relating to their specific surgical management were made. However, the panel would recommend offering interventions for symptom control, and to induce suitability for sinus repair (where possible), including sinus drainage (eg, debridement and VAAFT) and anatomical rationalization, similar to Class 2b fistulae. Finally, for both subgroups, it was agreed that, in patients with a persistent sinus, imaging with MRI is useful in preoperative planning, monitoring response to medical therapy, and in identifying underlying pathology such as collections, osteomyelitis, and malignancy. The timing of the scan will depend on the indication and clinical status ([A+] 90%, [A] 10%). For instance, a change in symptoms could trigger the need for urgent imaging. Alternatively, imaging could be considered 6 to 12 months post medical or surgical intervention (to assess disease response).

Optimizing Medical Therapy in PFCD (Applicable Within All of Class 2)

The panel made several statements regarding the medical management of chronic symptomatic fistulae (ie, Class 2 patients), listed in Table 3.

First-line therapy (anti-TNF). Anti-TNF therapy is preferred first-line, given the evidence for these medications in PFCD.[17,23,24] The panel specifically preference infliximab, although meta-analyses suggest equivalent remission rates may be obtained with adalimumab in PFCD.[25,26]

Table 3. Position Statements Relating to Medical Management of Perianal CD

First-line therapy (anti-TNF)	• For medical treatment, infliximab is the preferred first-line biological therapy ([A+] 80%, [A] 20%) • When optimizing anti-TNF medical therapy: o There is a role for therapeutic drug monitoring of anti-TNFs ([A] 100%) o Combination use of immunomodulators with anti-TNF can be beneficial ([A+] 14%, [A] 86%) o Higher drug levels may be needed for improved outcomes ([A] 100%)
Starting first-line therapy	• Optimized medical management includes patients having an EUA ± seton insertion prior to starting biologic therapy ([A+] 50%, [A] 50%) • Patients should start anti-TNF therapy as soon as possible after EUA ± seton insertion ([A+] 17%, [A] 83%) • Ideally, the first dose of biologic should be given within 30 days of EUA ([A+] 100%) • Short-term combination use of antibiotics with biologic therapy (eg, for 3 months) can be beneficial when starting medical therapy ([A] 100%)
Switching therapies	• Optimized medical management involves early assessment of clinical response, although it can take up to 6 months before a therapeutic effect can be fully assessed, or the need for a switch in therapy fully appreciated ([A+] 20%, [A] 80%) • Prior to assuming loss of response to a biologic therapy, consider MRI and/or surgical review to exclude the need for surgical intervention ([A+] 17%, [A] 83%)[a] • Following failure of optimized anti-TNF, both ustekinumab and vedolizumab can be considered as second-line medications ([A+] 17%, [A] 83%)[b] • In comparing ustekinumab with vedolizumab, there is not enough data to support the preference of one drug over the other ([A] 100%) • Following a switch in medical therapy, it would be reasonable to monitor response to the change with an MRI in 6 to 12 months ([A+] 56%, [A] 33%, [U] 11%)
Perioperative medical therapy	• Delays to biologic doses should be minimized while awaiting, and following, surgical drainage ([A+] 100%)
Topical therapy	• Despite limited evidence in patients with PFCD, topical therapy can be considered as an adjunct to optimized biologic therapy in patients with proctitis. ([A+] 55, [A] 45%)

CD, Crohn's disease; EUA, examination under anesthesia; MRI, magnetic resonance imaging; PFCD, perianal fistulizing Crohn's disease; TNF, tumor necrosis factor.

[a]For example, to incise undrained cavities and place setons.

[b]Selective anti-IL-23 agents (ie, risankizumab) were not included in our statements as they were not licensed for use in CD at the time of the consensus. Janus kinase-inhibitors (eg, upadacitinib) were also not included, given they were not licensed in certain countries at the time of the consensus.

Timing of induction. The panel felt therapy should be commenced early following initial EUA ± seton insertion. Evidence supporting this includes Bouguen et al's analysis showing the optimal time-point, associated with fistula closure, for commencement of infliximab is within 6 weeks of surgery.[27] However, Zhu et al's retrospective cohort study did not find a clear benefit for fistula healing when comparing early infliximab induction post-surgery (<6 weeks) vs delayed (>6 weeks) [61.6% vs 65.9%; $P = .64$].[28] Although evidence is equivocal, the panel recommend commencement within 30 days of initial EUA.

Optimization of anti-TNF. Optimization of anti-TNFs with immunomodulators is well-known and recommended in PFCD to preserve the effect of therapy against immunogenicity.[23,24] TDM is encouraged with the aim of high anti-TNF drug levels where possible. Indeed, multiple retrospective studies have suggested high infliximab trough levels are associated with increased rates of remission in PFCD,[29,30] as has a sub-analysis of the ACCENT-II trial.[31] Similarly, higher adalimumab levels have correlated with improved fistula outcomes.[29,30,32] However, optimal drug levels are not always consistent between studies, and a specific cutoff value is not recommended in our statements. Furthermore, 'real-world' target levels probably vary substantially, both internationally and between centers. From our MDT responses, suggested optimisation of infliximab drug levels (in refractory fistulae) ranged from >7 μg/ml to >20 μg/mL between the centers taking part. Proactive TDM studies in PFCD are underway and may provide evidence regarding the benefits of early escalated dosing (at <12 weeks) of infliximab therapy.[33] Finally, the panel agreed short-term combination therapy with antibiotics can be beneficial when commencing anti-TNF therapy, based on the ADAFI trial's finding of improved clinical response to adalimumab in patients treated with 12 weeks of contemporaneous ciprofloxacin therapy.[34]

Loss of response to first-line biologic. During discussion, emphasis was placed on the importance of surgical drainage of any perianal collections, when considering possible loss of response to medical therapy. The aim should be for minimal, if any, disruption to the flow of medical treatment, with antibiotics and rapid drainage

being used to minimise or avoid missed/delayed doses. Should a patient lose response to infliximab, our MDT responses indicated choice of second-line therapy would depend on drug and antibody levels. All centers (8/8) would consider adalimumab in immunogenic loss of response with high antibody levels. However, if loss of response was seen in the context of high (optimized) drug levels, all centers preferred a switch out-of-class.

Following anti-TNF failure, both ustekinumab and vedolizumab are viable second-line options with evidence of efficacy in PFCD. Risankizumab and Janus kinase inhibitors were also considered in MDT responses, although they do not feature in our statements (see Discussion). In terms of choice, meta-analyses have not demarcated a clear favourable second-line agent in PFCD.[25,26] However, a recent small study has suggested vedolizumab is more likely to be discontinued within 1-year of prescription in PFCD compared with ustekinumab therapy.[35]

Topical therapy in perianal CD. Despite a paucity of evidence regarding their efficacy, the panel did suggest topical therapy (eg, 5-ASAs and steroids) can be considered as an adjunct to biological therapy in PFCD, as it was felt topical therapy is an often overlooked tool to control proctitis in patients with fistulae. Certain topical therapies can also be applied directly to the perianal/perineal tissue in PFCD. An example is tacrolimus, although the efficacy for this for perianal fistula is doubtful.[36] Yet this can be used outside of Class 2 (for instance, in PPS) and 1 of 8 centers suggested this in their MDT management plan for our Class 4a case vignette.

Psychological Burden of Disease

The impact of PFCD on psychological health is substantial, with 73% of patients self-reporting periods of depression and 13% suicidal ideation while living with PFCD.[37] Sexual function and body image are also affected.[2,37,38] The expert panel discussed the psychological burden of disease within patients in all classification groups and agreed: in all patients with PFCD, the burden of psychological morbidity is high, and we recommend screening for these comorbidities and treating ([A+] 58%, [A] 42%).

Discussion

We would encourage gastrointestinal specialists to consider the TOpClass classification in stratification of patients with PFCD. In this project, all MDTs agreed on the classification of the case vignettes, which corresponded exactly with the authors' intended classification of the fictional patients. This article illustrates how this classification model can be employed clinically when treating fistulae.

There are several limitations to be considered. Our position statements are based on opinion and the combined experience of an international panel, informed by evidence, including systematic reviews, where it is available. As with leading society guidelines,[17,23,24,39] the lack of quality evidence impacted the panel's ability to make bold statements on topics such as the preferable second-line agent following anti-TNF failure. However, from our MDT responses, 5 of 8 centers (63%) preferred ustekinumab over vedolizumab in this setting. Furthermore, in patients with suboptimal response to 8-weekly ustekinumab (having previously failed anti-TNFs), 5 of 8 centers would consider escalating ustekinumab to 4- to 6-weekly dosing prior to switching to vedolizumab. However, evidence regarding dose-escalation of ustekinumab in PFCD is conflicting.[40,41] Although the MDT responses glimpsed aspects of real-world practice that fall outside the evidence base, the panel felt formal position statements could not be integrally developed on this pretext alone.

Additionally, a meta-analysis was not conducted as part of this work, although meta-analyses have recently been published on medications in PFCD.[25,26] Risankizumab is not mentioned in these, although it is licensed for CD in many countries and can be utilized in PFCD.[42] It was not included in our statements, given the minimal usage of this drug for IBD in Europe at the time of the consensus. However, it was considered a second-line option following anti-TNF failure by gastroenterologists who had experience and access to this drug. Additionally, due to limited data,[43,44] small molecules (ie, Janus kinase inhibitors) were not included in our recommendations; however, 2 of 8 centers listed them as an option for an out-of-class switch following anti-TNF therapy.

Finally, the role of combination biologics/immunotherapy[45] in PFCD is not addressed in our statements. This has the potential to optimize IBD treatment and could see patients on one drug for luminal CD and another for their perianal disease. In our MDT responses, 2 of 8 teams suggested they would consider adding ustekinumab or vedolizumab to anti-TNF therapy if a patient had partial response to infliximab. Moreover, 3 of 8 MDTs considered continuing thiopurine following a switch from anti-TNF to ustekinumab in refractory presentations. There are no trials presently assessing combination biologics or non-anti-TNF biologics with immunomodulators in PFCD. However, if combination biologics become mainstream practice in IBD, this strategy may be especially attractive in patients with fistulae. Particularly in the setting of patients with active fistulae but quiescent luminal disease (when a switch in biological therapy risks flaring luminal IBD).

The role of biological augmentation in non-anatomical repair (eg, MSC injection) is in question following the failure of Alofisel (darvadstrocel) to meet its primary endpoint of combined remission at week 24 in the phase III multicentre ADMIRE-CD-II study (NCT03279081). Presently, full study results are not published, and

considering the positive findings of ADMIRE-CD,[16] where MSCs induced combined clinical and radiological remission in 50% to 60% of fistulae corresponding to our Class 2a group, its implications for the future of MSC therapy are unknown.

Importantly, the comparator arm in both studies underwent curettage and internal opening closure (ie, non-anatomical repair without MSC injection), not placebo. There are no major safety concerns regarding the therapy, and the consensus group decided not to retract their statements on stem cell repair (Table 2). However, we acknowledge emerging data and the fact that international access to MSCs is jurisdiction-dependent. Biological augmentation using regenerative therapies in fistulae may well persist, even if their current place in clinical practice is re-evaluated as evidence evolves and particular agents disappear from use.

The TOpClass classification has demonstrated utility with regards to different MDTs being able to independently allocate patients appropriately to each class. The guidance given here takes a step beyond published guidelines to enable clinicians to have a pragmatic and patient-goal centred approach to medical and surgical management options for individual patients with PFCD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2024.06.047.

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Data Availability

We have included a document of supplementary materials alongside the manuscript for submission. Given the nature of the project, no advanced data analysis was conducted as part of this work. Members of the public can contact the corresponding author regarding enquiries relating to the project's consensus process; however, key information is included in the main article and online supplementary materials.