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Autonomic Function in Inflammatory Bowel Disease: A Narrative Review of Objective Assessment and Physiological Monitoring

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Abstract

Introduction and purpose: Autonomic alterations may contribute to the physiological heterogeneity of inflammatory bowel disease (IBD). This review examines objective autonomic assessment in Crohn disease and ulcerative colitis, focusing on physiological phenotyping and longitudinal monitoring.

Methods: This focused narrative review synthesizes 25 included studies. Evidence on heart rate variability (HRV), Holter monitoring, cardiovascular reflexes, orthostatic responses, baroreflex function, sudomotor testing, and wearable-derived signals was organized by modality and relationship with disease activity.

Brief description of the state of knowledge: HRV was the most studied modality and was associated with clinical, biochemical, and endoscopic activity in selected cohorts. Autonomic alterations may persist during remission and do not consistently correspond to symptoms or inflammatory markers. Reduced HRV alone does not establish autonomic neuropathy. Multimodal testing assesses complementary physiological domains and may yield discordant findings. Wearables offer opportunities for repeated assessment alongside sleep and physical activity, while neuromodulation remains investigational. Heterogeneous protocols, small cohorts, and limited external validation constrain clinical interpretation.

Conclusions: Objective autonomic assessment may complement established IBD evaluation in selected patients. The proposed Clinical Algorithm and Physiological Framework are hypothesis-generating and require prospective validation. Standardized multimodal protocols and longitudinal studies are needed. Current evidence does not support autonomic biomarkers as stand-alone tools for disease monitoring or exercise prescription.

Keywords: inflammatory bowel disease; autonomic function; heart rate variability; physiological monitoring; wearable devices; clinical phenotyping.

1. Introduction

Inflammatory bowel disease (IBD), encompassing Crohn disease and ulcerative colitis, is a chronic relapsing inflammatory disorder characterized by complex interactions among immune, microbial, environmental, and neural pathways. Although contemporary treat-to-target strategies emphasize biochemical, endoscopic, and increasingly histological control, patients may continue to experience fatigue, palpitations, dizziness, sleep disturbance, gastrointestinal symptoms, and impaired quality of life despite apparently satisfactory inflammatory control. This discordance has increased interest in physiological systems that are not captured directly by conventional inflammatory biomarkers. [1].

The autonomic nervous system is a plausible component of this broader disease phenotype. Through sympathetic, parasympathetic, enteric, cardiovascular, and neuroimmune pathways, autonomic regulation participates in cardiovascular homeostasis, gastrointestinal function, stress responses, and bidirectional brain-gut signalling. In IBD, objective autonomic abnormalities have been investigated using heart rate variability (HRV), 24-hour Holter monitoring, cardiovascular autonomic reflex tests, baroreflex measures, orthostatic testing, sudomotor assessment, and, more recently, wearable-derived physiological signals. [1, 2, 3].

However, the literature remains difficult to translate into clinical practice. HRV protocols vary markedly in recording duration and analytic approach, symptom burden does not consistently correspond to objective dysfunction, and autonomic abnormalities may differ between active disease and remission. Moreover, individual modalities assess different physiological domains and should not be considered interchangeable. Consequently, the clinical meaning of an isolated abnormal autonomic result remains uncertain. [4, 5, 6, 7].

These limitations suggest that the key question is no longer simply whether dysautonomia occurs in IBD. A more clinically relevant question is whether objective autonomic testing can identify reproducible physiological phenotypes, complement established measures of inflammatory activity, and help characterize patients with persistent or otherwise unexplained symptoms. [6].

The aim of this narrative review is therefore to critically synthesize the evidence on objective autonomic assessment in IBD, with particular emphasis on physiological modalities, relationships with inflammatory activity, clinical phenotyping, and longitudinal monitoring. We additionally propose an evidence-informed Clinical Algorithm and Physiological Framework to organize current findings and define priorities for future validation. These frameworks are intended to be hypothesis-generating rather than diagnostic guidelines or validated clinical classification systems.

2. Methods

2.1. Review Design and Scope

This work was designed as a focused narrative review rather than a systematic review or meta-analysis. The review was structured to provide a clinically oriented synthesis of objective autonomic assessment in IBD and to integrate heterogeneous physiological modalities that would not be appropriately summarized through a single quantitative effect estimate. Particular attention was given to objective cardiovascular and peripheral autonomic testing, relationships with disease activity, clinical consequences, longitudinal monitoring, digital biomarkers, and neuromodulation.

2.2. Evidence Identification and Study Selection

The evidence base was assembled through structured literature screening focused on patients with inflammatory bowel disease and studies evaluating autonomic function or autonomic-related physiological biomarkers. Search terms covered inflammatory bowel disease, autonomic dysfunction, heart rate variability, cardiovascular autonomic testing, orthostatic function, sudomotor assessment, wearable physiology, and related autonomic biomarkers. Study selection prioritized reports providing objective physiological or autonomic data relevant to the scope of the review, while symptom-only studies were retained only when they provided clinically informative context. Following screening and removal of one duplicate record, 25 included studies formed the core evidence base for the present review. Studies without relevant autonomic information were excluded from the manuscript evidence set.

2.3. Evidence Extraction and Standardization

Each included study was reviewed individually using standardized working notes. Extracted domains included study design and population, IBD subtype and activity, autonomic modality, acquisition protocol, HRV parameters where applicable, orthostatic or reflex findings, sudomotor and peripheral autonomic findings, inflammatory biomarkers, endoscopic outcomes, symptoms, quality of life, longitudinal outcomes, clinical implications, methodological strengths, and limitations. Findings were subsequently harmonized in a structured evidence database to permit modality-level comparison across heterogeneous studies. Detailed study characteristics are provided in the Supplementary Appendix (Supplementary Table S1).

2.4. Evidence Synthesis

Because substantial heterogeneity was present in autonomic protocols, populations, disease-activity definitions, and reported endpoints, findings were synthesized narratively. Autonomic modalities were interpreted according to the physiological domain assessed rather than pooled as a single construct of dysautonomia. Particular emphasis was placed on distinguishing symptom-based autonomic burden from objectively demonstrated dysfunction and on separating clinical disease indices from biochemical, endoscopic, or histological inflammatory activity.

Study-level characteristics and modality-, HRV-, biomarker-, clinical-, and research-priority syntheses are presented in the Supplementary Appendix (Supplementary Tables S1-S6).

2.5. Development of the Clinical and Physiological Frameworks

The proposed Clinical Algorithm and Physiological Framework were developed through evidence-to-manuscript mapping of the included studies. Components were retained when supported by convergent evidence or when they represented a clinically relevant gap requiring explicit future validation. The resulting frameworks are evidence-informed and hypothesis-generating; they should not be interpreted as validated diagnostic pathways, formal clinical guidelines, or established IBD phenotypes.

3. Objective Assessment of Autonomic Function in Inflammatory Bowel Disease

Objective assessment of autonomic function in inflammatory bowel disease (IBD) has evolved from conventional electrocardiographic and cardiovascular reflex testing toward continuous wearable monitoring and multimodal physiological phenotyping. Across the available literature, the most frequently investigated modality is heart rate variability (HRV), assessed using recordings ranging from ultra-short 10-second electrocardiograms to standardized five-minute resting recordings, 24-hour Holter monitoring and consumer wearable devices. A smaller body of evidence has incorporated cardiovascular reflex testing, orthostatic challenge, baroreflex assessment, beat-to-beat haemodynamics, electrodermal or sudomotor measurements, and multimodal autonomic batteries. This methodological diversity is both informative and problematic: it demonstrates that autonomic abnormalities in IBD can be detected across several physiological domains, but it also limits direct comparison between studies and precludes the use of a single autonomic parameter as a validated diagnostic marker (Supplementary Tables S1 and S2). The objective autonomic modalities used across the evidence base are summarized in Supplementary Table S2.

A central distinction is required between **autonomic modulation** and **autonomic dysfunction**. Reduced HRV, for example, indicates altered cardiac autonomic regulation but does not by itself establish autonomic neuropathy or generalized dysautonomia. This distinction is illustrated by multimodal studies in which different autonomic tests produced discordant results. In a highly selected cohort of adults with Crohn disease, Wasserbauer et al. found abnormalities on cardiovascular reflex testing in more than half of participants, whereas spectral HRV was abnormal in only one patient and Sudoscan abnormalities were present in approximately one third. The poor concordance between symptoms, HRV, cardiovascular reflex testing and sudomotor assessment indicates that these methods interrogate related but non-equivalent components of autonomic physiology.

3.1. Heart Rate Variability

Heart rate variability (HRV) is the most extensively studied objective autonomic measure in IBD. Available studies have assessed time-domain indices such as SDNN and RMSSD, frequency-domain measures including LF and HF, and derived parameters such as LF/HF. Their interpretation depends on recording duration, posture, respiration, and analytic methodology. Accordingly, LF/HF is treated cautiously throughout this review rather than as a stand-alone index of autonomic state. [8, 4, 7].

Several studies suggest that HRV is sensitive to IBD activity. Wang et al. assessed 84 adults with Crohn disease using standardized five-minute resting ECG recordings. Patients with clinically active disease had lower SDNN (35.09 ± 16.12 vs 46.99 ± 22.18 ms; $p=0.006$) and HF power (214.12 ± 233.51 vs 494.02 ± 673.87 ms²; $p=0.015$) than those with inactive disease. [8].

Differences were more pronounced when disease activity was defined endoscopically. Endoscopically active Crohn disease was associated with lower SDNN (34.69 ± 15.83 vs 47.73 ± 22.00 ms; $p=0.002$), lower HF (209.00 ± 252.17 vs 506.65 ± 670.02 ms²; $p=0.011$), and higher LF/HF (2.67 ± 2.12 vs 1.38 ± 0.78 ; $p<0.001$). SES-CD correlated positively with heart rate and LF/HF and inversely with SDNN, HF, and VLF, with HF showing the strongest HRV correlation ($r=-0.395$; $p<0.001$). [8].

Evidence from ulcerative colitis is directionally similar. Guo et al. derived HRV from routine 10-second 12-lead ECGs in 91 patients and observed lower SDNN, SDSD, and RMSSD in those with more severe endoscopic disease. SDNN was 18.54 ms in the severe endoscopic-activity group compared with 29.33 ms in patients with milder disease, while RMSSD was 12.31 versus 21.42 ms. [4].

An internally derived RMSSD threshold below 15.516 ms was associated with severe mucosal inflammation. This threshold should be regarded as exploratory rather than clinically validated because it originated from a single retrospective cohort. Moreover, HRV was not significantly associated with histological healing, indicating that endoscopic associations cannot automatically be extrapolated to microscopic inflammatory activity. [4].

Autonomic abnormalities may also persist outside overt inflammatory activity. Zawadka-Kunikowska et al. examined patients with Crohn disease in clinical and endoscopic remission using HRV alongside haemodynamic, baroreflex, orthostatic, and deep-breathing assessments. Resting LF/HF was higher and baroreflex effectiveness lower than in healthy controls, whereas cardiovagal and orthostatic reflex responses were largely preserved. This pattern supports the presence of subtle, domain-specific autonomic alterations rather than generalized autonomic failure. [5].

The relationship between HRV and IBD activity is further complicated by stress and behavioural influences. In the longitudinal UC cohort of Sauk et al., higher baseline fecal calprotectin was associated with higher LF/HF and lower RMSSD, but baseline HRV responses did not predict subsequent clinical or biochemical flares. High perceived stress was associated with increased electrodermal activity and greater clinical flare risk, whereas RMSSD and HF did not differ significantly between stress groups. [9].

Overall, the available evidence supports HRV as a promising adjunct physiological biomarker and phenotyping tool in IBD. Associations with disease activity—particularly objective inflammatory activity—are increasingly evident, but methodological heterogeneity and limited external validation currently preclude diagnostic thresholds or stand-alone clinical use (Supplementary Table S3). [8, 4, 5, 9].

3.2. Short-Term and Ultra-Short-Term ECG-Derived HRV

Recording duration is a major methodological determinant of HRV interpretation. Within the IBD literature, short-term recordings of approximately five minutes and ultra-short recordings derived from routine 10-second ECGs represent distinct approaches and should not be considered interchangeable. [8, 10, 4].

Standardized five-minute HRV offers a practical compromise between physiological validity and clinical feasibility. In Wang et al., seated, awake, resting participants underwent five-minute ECG recording with continuous RR-interval analysis. The resulting HRV indices were associated with clinical and, more strongly, endoscopic Crohn disease activity, supporting further evaluation of standardized short-term HRV as a low-burden physiological adjunct. [8, 10].

Ultra-short HRV offers a different potential clinical application. Guo et al. demonstrated that HRV indices derived from a routine 10-second 12-lead ECG were associated with endoscopic severity in ulcerative colitis. Because standard ECGs are already widely obtained in clinical practice, this approach could allow autonomic information to be extracted with essentially no additional procedural burden. [4].

However, ultra-short recordings provide substantially less physiological information and less stable HRV estimates than conventional short-term recordings. The internally derived RMSSD threshold reported by Guo et al. therefore requires independent validation before any clinical application. Ultra-short HRV should currently be regarded as an opportunistic physiological signal, rather than a substitute for standardized HRV assessment. [8, 4].

At present, **standardized five-minute HRV appears the more physiologically robust candidate for clinic-based autonomic phenotyping**, whereas ultra-short ECG-derived HRV may ultimately provide a

scalable screening or risk-enrichment signal. Neither approach has yet reached the level of validation required for stand-alone diagnostic or disease-monitoring use in IBD.

3.3. Twenty-Four-Hour Holter ECG and Circadian HRV Assessment

Twenty-four-hour Holter ECG extends autonomic assessment beyond short resting recordings by capturing cardiac rhythm and HRV during daily activity, sleep, and circadian transitions. This may be particularly relevant in IBD, where autonomic abnormalities may vary with posture, activity, and time of day. However, prolonged monitoring also introduces variability related to physical activity, meals, sleep, stress, and environmental exposures. [7, 11]. Representative HRV findings across acquisition strategies are summarized in Supplementary Table S3.

Mouzas et al. evaluated 27 patients with IBD—16 with ulcerative colitis and 11 with Crohn disease—in clinical and endoscopic remission and compared them with 28 matched healthy controls. Twenty-four-hour HRV analysis included SDNN, SDANN, RMSSD, pNN50, LF, HF, and LF/HF. Patients showed lower LF and LF/HF, with a tendency toward higher HF, particularly during daytime recordings. The authors interpreted this pattern as relative parasympathetic predominance driven predominantly by sympathetic withdrawal. [7].

Supportive evidence comes from Gunterberg et al., who studied 41 patients with newly diagnosed ulcerative colitis in remission and 31 healthy controls. Global time-domain indices, including SDNN and RMSSD, were preserved, whereas LF/HF during standing was lower in patients with UC. Although interpreted as attenuated sympathetic responsiveness, this finding requires caution because the study was reported only as a conference abstract and LF/HF is an imperfect surrogate of sympathovagal regulation. [12].

Holter monitoring may additionally identify rhythm abnormalities. In a conference study of 67 adults with IBD, Yürekli et al. reported frequent arrhythmias and lower several Holter-derived HRV indices among patients with active disease. However, the absence of a healthy control group, limited methodological detail, and lack of multivariable analysis preclude interpretation of the reported arrhythmia frequency as a population-level estimate. [7, 11].

Overall, 24-hour Holter monitoring provides complementary information to short-term HRV by capturing circadian autonomic patterns and simultaneously enabling rhythm surveillance. Current evidence is insufficient to define IBD-specific Holter thresholds or demonstrate superiority over

standardized short-term HRV. Its most defensible position within an objective assessment pathway is therefore as a second-line, phenotype-directed modality, particularly when prolonged autonomic characterization or concurrent arrhythmia assessment is clinically relevant.

3.4. Cardiovascular Autonomic Reflex Testing

Cardiovascular autonomic reflex testing assesses dynamic responses to standardized physiological challenges rather than autonomic modulation at rest. In IBD, the principal approaches include head-up tilt, orthostatic testing, deep breathing, the Valsalva maneuver, and Ewing-type cardiovascular reflex batteries. These tests interrogate partially distinct cardiovagal and adrenergic domains and may therefore identify abnormalities not captured by HRV alone. [5, 6].

Zawadka-Kunikowska et al. evaluated 30 adults with Crohn disease in clinical and endoscopic remission and 29 healthy controls using beat-to-beat haemodynamics, HRV, baroreflex assessment, 70° head-up tilt, and deep breathing. Patients had higher resting LF/HF and lower baroreflex effectiveness, while baroreflex sensitivity was reduced during the final phase of tilt. In contrast, the deep-breathing E/I ratio and overall orthostatic heart-rate responses were largely preserved. [5].

A complementary pattern was reported by Wasserbauer et al. in 30 adults with historically severe Crohn disease receiving long-term anti-TNF therapy. An Ewing battery identified abnormalities in deep breathing, Valsalva, and orthostatic R-R responses, whereas no participant met the study threshold for a pathological systolic blood-pressure fall. Ten patients were classified as borderline and seven as having manifest cardiovascular autonomic abnormalities. [6].

Importantly, autonomic modalities showed substantial discordance. Spectral HRV was pathological in only one participant, whereas Ewing-test abnormalities were considerably more frequent and Sudoscan was abnormal in approximately one third. This finding supports multimodal assessment and indicates that normal resting HRV should not be used to exclude abnormalities in other autonomic domains. The reported frequency of abnormal tests, however, cannot be generalized beyond this small and highly selected severe Crohn disease cohort. [5, 6].

Orthostatic testing may have particular clinical value in symptomatic patients. Kamogashira et al. used serial heart-rate and blood-pressure measurements during the Schellong test in IBD patients referred for dizziness or vertigo. Orthostatic dysregulation was identified in approximately half of the 10 IBD patients and was more frequent than in non-IBD comparators. Because of the very small and highly selected sample, these findings should support targeted orthostatic assessment rather than estimates of prevalence in the general IBD population. [13].

Collectively, these studies show that autonomic abnormalities in IBD may emerge only during physiological challenge and may affect different reflex domains unequally. Simple orthostatic HR and blood-pressure assessment is therefore reasonable in patients with postural symptoms, whereas head-up tilt, deep breathing, Valsalva, or broader autonomic batteries are better positioned as phenotype-directed second-line investigations. Current evidence does not support a universal IBD-specific reflex-testing battery or diagnostic threshold. [5, 6, 13].

3.5. Baroreflex Function and Blood-Pressure Regulation

Baroreflex assessment provides information beyond conventional HRV by examining the coupling between beat-to-beat changes in arterial pressure and compensatory heart-rate responses. Despite its physiological relevance, this domain remains markedly understudied in IBD. Detailed baroreflex sensitivity (BRS), baroreflex effectiveness index (BEI), and blood-pressure variability have been reported primarily by Zawadka-Kunikowska et al. [5].

In 30 adults with Crohn disease in clinical and endoscopic remission and 29 healthy controls, continuous ECG and beat-to-beat blood pressure were integrated with impedance cardiography, HRV, BRS, BEI, deep breathing, and head-up tilt. At rest, BEI was lower in Crohn disease than in controls ($70.2 \pm 14.9\%$ vs $76.6 \pm 8.5\%$; $p < 0.05$). During the final phase of tilt, BRS was also reduced (9.2 ± 4.1 vs 12.8 ± 9.5 ms/mmHg; $p < 0.05$). [5].

BRS, BEI, and continuous beat-to-beat haemodynamics therefore remain specialist physiological phenotyping tools rather than established clinical biomarkers in IBD. Their principal contribution to the current evidence base is to demonstrate that preserved conventional reflex responses do not necessarily imply normal cardiovascular autonomic control. Future studies should integrate baroreflex and BPV measurements with standardized HRV, orthostatic testing, and synchronized inflammatory endpoints to determine their clinical and prognostic value. [5].

3.6. Sudomotor and Peripheral Autonomic Assessment

Sudomotor testing evaluates sympathetic pathways controlling sweat-gland function and may provide information complementary to cardiovascular autonomic testing. Evidence in IBD is limited, with the most direct data coming from Wasserbauer et al., who combined Sudoscan with an Ewing battery, spectral HRV, autonomic symptom assessment, and peripheral sensory examination. [6].

Among 30 adults with historically severe Crohn disease, Sudoscan was abnormal in 10 patients (33.3%). In the same cohort, cardiovascular reflex abnormalities were more frequent than pathological spectral HRV, and Sudoscan findings did not significantly correlate with either domain. This discordance suggests

that sudomotor and cardiovascular tests may capture partially independent components of autonomic physiology. [6].

Importantly, Sudoscan was not validated against QSART or skin biopsy with intraepidermal nerve fiber density assessment. Abnormal Sudoscan should therefore be interpreted as evidence of sudomotor dysfunction rather than definitive small-fiber neuropathy. [6].

Overall, sudomotor assessment remains an underdeveloped domain in IBD. Existing data suggest that peripheral autonomic abnormalities may not parallel cardiac HRV or cardiovascular reflex findings, supporting multimodal phenotyping. However, the lack of robust QSART and skin-biopsy studies represents a major knowledge gap. Sudomotor testing should therefore be considered a complementary, phenotype-directed modality rather than a stand-alone diagnostic tool. [6, 9].

3.7. Wearables and Continuous Physiological Monitoring

Wearable devices extend autonomic assessment from episodic laboratory measurements to continuous, real-world physiological monitoring. In IBD, this approach is particularly attractive because autonomic signals can be evaluated longitudinally alongside inflammatory and symptomatic disease states. Recent studies have focused primarily on wearable-derived HRV, resting heart rate, sleep, and activity metrics. [3, 14, 15].

The strongest evidence comes from Hirten et al., who used continuous wearable monitoring to characterize physiological changes associated with inflammatory and symptomatic flares. HRV, particularly SDNN, differed across disease states, including periods of objectively defined inflammation, supporting the concept that longitudinal autonomic signals may capture physiological changes accompanying IBD activity. Importantly, inflammatory and symptomatic flares were not physiologically identical, suggesting that wearable monitoring may help distinguish inflammation-related changes from symptom burden alone. [3].

Smaller studies provide supportive evidence. Imai et al. demonstrated the feasibility of nighttime wearable HRV monitoring in ulcerative colitis and reported associations between HRV and clinical disease activity, although the pilot sample was very small and objective inflammatory validation was limited. Wearable ECG-derived HRV has also differentiated active from quiescent UC in preliminary conference data, further supporting the feasibility of ambulatory autonomic monitoring. [14, 15].

Wearable monitoring should therefore be regarded as a longitudinal digital-biomarker platform rather than a diagnostic test for dysautonomia. Its near-term value may lie in identifying physiological deviations that

prompt confirmatory inflammatory assessment, while standardization and external validation remain prerequisites for routine use. [3].

4. Relationship Between Autonomic Dysfunction and IBD Activity

A central question is whether autonomic abnormalities in IBD reflect intestinal inflammatory activity, clinical symptom burden, or a partially independent physiological phenotype. Available studies suggest that these domains overlap but are not interchangeable. Associations have been demonstrated with clinical, biochemical, and endoscopic activity, but the strength and consistency of these relationships vary across endpoints. [8, 4, 9, 3]. Relationships between autonomic measures and inflammatory biomarkers or disease-activity endpoints are summarized in Supplementary Table S4.

4.1. Clinical Disease Activity

Several studies report associations between cardiac autonomic modulation and clinical disease activity. In Wang et al., patients with clinically active Crohn disease defined by CDAI ≥ 150 had higher heart rate and lower SDNN and HF than those with inactive disease. Heart rate correlated positively with CDAI ($r=0.406$; $p<0.001$), whereas SDNN ($r=-0.270$; $p=0.013$) and LF ($r=-0.222$; $p=0.042$) showed weaker inverse relationships. HF and LF/HF were not significantly correlated with CDAI. [8].

Prospective pediatric evidence provides additional support. Yerushalmy-Feler et al. reported higher RMSSD in patients in clinical remission than in those with active IBD (67.72 ± 27.81 vs 45.76 ± 22.04 ms; $p=0.022$). Lower baseline RMSSD was also associated with subsequent exacerbation, although the cohort included only 34 patients. These findings are relevant longitudinally but should not be directly extrapolated to adult IBD. [16].

Clinical activity may also diverge from objective inflammation. In the longitudinal UC study by Sauk et al., higher perceived stress was associated with greater electrodermal activity and 3.6-fold higher odds of clinical flare, but not with a significantly increased frequency of biochemical flare. This illustrates why symptom-defined exacerbation and inflammatory recurrence should remain separate outcomes when evaluating autonomic biomarkers. [9].

4.2. Systemic Inflammatory Biomarkers

Wang et al. reported associations between selected HRV parameters and several systemic inflammatory indices in Crohn disease, including an inverse relationship between HF and the neutrophil-to-lymphocyte ratio. However, associations were not uniform across all inflammatory markers. These findings are compatible with coupling between systemic inflammatory burden and cardiac autonomic modulation, but they do not support a reproducible blood-biomarker/HRV diagnostic threshold. [8].

The relationship is also evident in interventional studies, although these data require different interpretation. In refractory Crohn disease treated with implanted vagus nerve stimulation, D'Haens et al. reported concurrent improvements in clinical activity, fecal calprotectin, inflammatory cytokines, and HRV-derived autonomic balance. Such parallel changes are compatible with neuroimmune coupling but cannot establish that autonomic modulation directly caused the inflammatory improvement because the study was small and uncontrolled. [17].

4.3. Fecal Calprotectin and Intestinal Inflammatory Activity

In the longitudinal UC cohort of Sauk et al., increased fecal calprotectin was associated with cardioautonomic measures consistent with lower parasympathetic activity. However, autonomic responses did not reliably predict subsequent biochemical flares. This distinction is important: an autonomic measure may correlate with contemporaneous inflammatory burden without necessarily functioning as a prospective predictor of inflammatory relapse. [9].

Longitudinal neuromodulation studies provide complementary evidence. In the VNS study by D'Haens et al., fecal calprotectin decreased substantially during treatment alongside improvement in clinical and autonomic measures. Again, these parallel changes support physiological coupling but do not demonstrate that autonomic normalization is a validated surrogate for reduction in intestinal inflammation. [17].

4.4. Endoscopic and Histological Activity

The strongest direct evidence linking autonomic physiology with objective IBD activity comes from studies using endoscopic reference standards. This is particularly relevant because endoscopy provides direct assessment of mucosal disease activity and avoids part of the ambiguity inherent in symptom-based indices. [8, 4].

In Crohn disease, Wang et al. found consistent associations between five-minute HRV and SES-CD. Heart rate correlated positively with SES-CD ($r=0.388$; $p<0.001$), while SDNN ($r=-0.325$; $p=0.003$), HF ($r=-0.395$; $p<0.001$), and VLF ($r=-0.363$; $p=0.001$) were inversely correlated. LF/HF was positively associated with endoscopic activity ($r=0.292$; $p=0.007$). [8].

Comparable evidence exists in ulcerative colitis. Guo et al. found that patients with MES 2–3 had lower SDNN, SDSD, and RMSSD and higher heart rate than those with MES 0–1. An RMSSD value below 15.516 ms was independently associated with severe endoscopic inflammation (OR 5.21; 95% CI 1.12–24.14), although the threshold was internally derived and requires external validation. [4].

Importantly, the relationship did not extend consistently to histological activity. No HRV parameter significantly differentiated histological healing or activity according to Geboes score in the same cohort.

This discordance indicates that autonomic associations observed at the endoscopic level cannot be assumed to reflect microscopic inflammatory resolution. [4].

5. Clinical Phenotypes of Autonomic Dysfunction in IBD

The available evidence does not support a single, uniform autonomic phenotype in IBD. Instead, objective abnormalities appear across several partially overlapping domains, including cardiac autonomic modulation, cardiovascular reflex control, orthostatic regulation, baroreflex function, and sudomotor pathways. Importantly, these abnormalities may occur during active inflammation, persist during remission, or remain clinically silent. [5, 6, 7, 13].

5.1. Subclinical Autonomic Dysfunction

Objective autonomic abnormalities may occur in patients without overt neurological or autonomic complaints. Wasserbauer et al. studied 30 neurologically asymptomatic adults with historically severe Crohn disease and identified abnormalities across cardiovascular reflex and sudomotor domains. The Ewing battery was abnormal or borderline in 17 patients, while Sudoscan was pathological in 10 and spectral HRV in only one. [6].

5.2. Symptomatic Autonomic Dysfunction and Orthostatic Phenotypes

Orthostatic dysfunction represents a potentially distinct phenotype. Kamogashira et al. found orthostatic dysregulation in 5 of 10 IBD patients referred for dizziness or vertigo, compared with 11% of non-IBD patients. Vestibular dysfunction did not differ significantly between groups. Although the IBD subgroup was extremely small and highly selected, the findings support targeted orthostatic testing when postural symptoms are prominent. [13].

5.3. Autonomic Dysfunction, Symptom Burden and Quality of Life

The clinical relevance of autonomic dysfunction extends beyond abnormalities detected during physiological testing. Ananthakrishnan et al. compared 43 IBD patients with clinically manifest autonomic dysfunction against 129 disease-matched controls. Autonomic dysfunction was diagnosed using a standardized laboratory battery, although modality-level details were insufficient for direct comparison with the other protocols reviewed here. [2].

Patients with autonomic dysfunction had longer small-bowel transit (92.7 vs 62.9 minutes) and an adjusted SIBDQ score 7.5 points lower than controls. They also had greater odds of more than three annual gastroenterology visits (OR 2.84) and IBD-related hospitalization (OR 2.49). [2].

5.4. Discordance Between Autonomic Phenotype and Inflammatory Activity

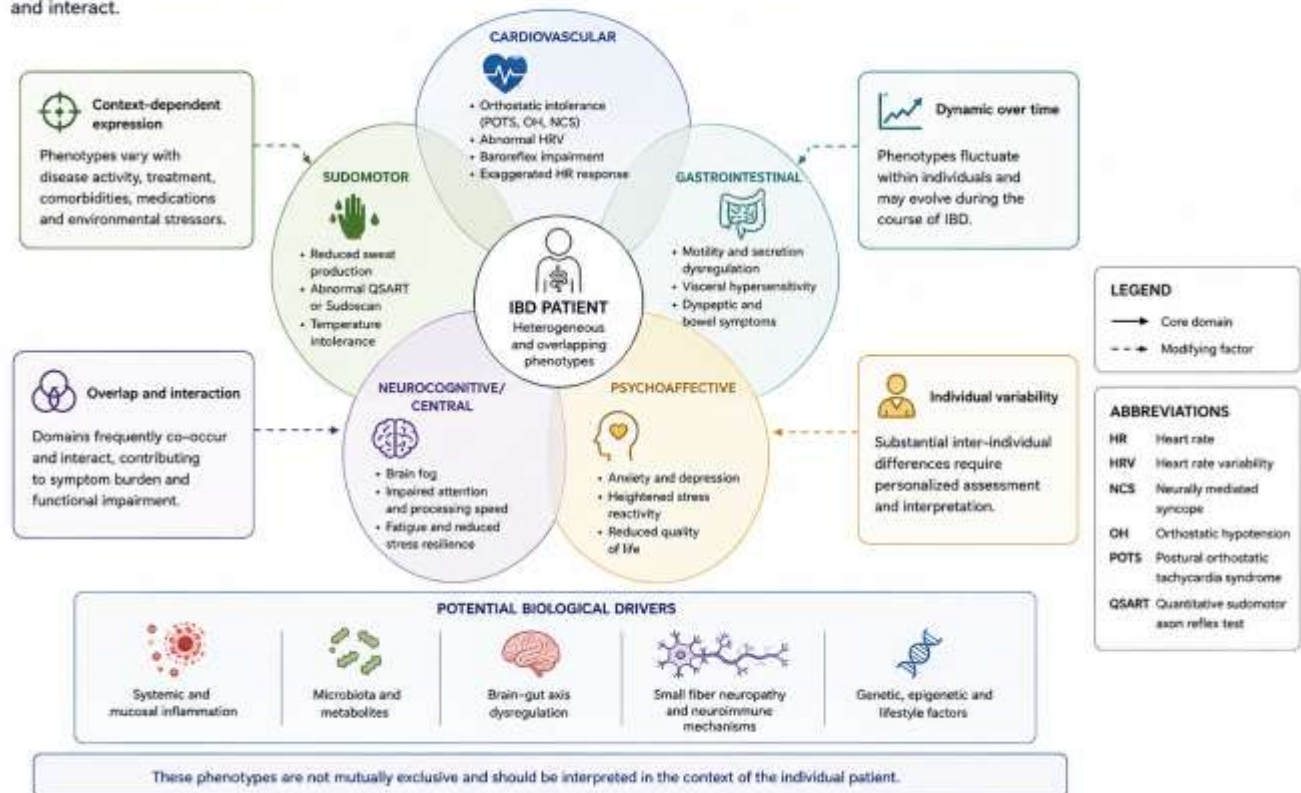
Sauk et al. provide a clear example. Among 110 adults with UC in clinical remission, high perceived stress was associated with greater electrodermal activity and a 3.6-fold higher odds of subsequent clinical flare. However, biochemical flare rates did not significantly differ between high- and low-stress groups, and baseline autonomic responses did not predict clinical or biochemical flares. [9].

5.5. Toward Multidimensional Autonomic Phenotyping in IBD

Taken together, the evidence supports moving beyond a binary question of whether an IBD patient 'has dysautonomia' toward identifying which autonomic domain is abnormal and in what inflammatory and clinical context. No single measurement captures this complexity. [6, 5, 13]. The proposed multidimensional phenotype concept is summarized in Figure 3.

Figure 3. Multidimensional phenotypes of autonomic dysfunction in IBD.

Autonomic dysfunction in IBD is heterogeneous and affects multiple domains that often coexist and interact.



6. Proposed Clinical Algorithm for Objective Autonomic Assessment in IBD

6.1. Who Should Be Evaluated?

Within the proposed framework, testing may be considered in selected patients with persistent dizziness, orthostatic symptoms, presyncope, palpitations, unexplained tachycardia, sweating abnormalities, or other

symptoms suggestive of autonomic involvement. Persistent fatigue or exercise intolerance may also justify assessment when not explained by active inflammation or other common causes. Autonomic symptoms alone should not establish the diagnosis; objective confirmation is required before symptoms are attributed to dysautonomia. [13, 2, 6, 18].

6.2. Step 1: Clinical Screening and Context

The first step is to define the symptom pattern and identify factors that may influence autonomic measurements or mimic dysautonomia. Relevant context includes inflammatory activity, treatment exposure, nutritional status, stress, and sleep. Questionnaires such as COMPASS-31 may identify autonomic symptom burden and help select patients for further assessment, but they should remain screening tools rather than diagnostic tests. [20, 21, 9, 19].

6.3. Step 2: First-Line Objective Testing

Initial objective assessment should favor low-burden physiological measures in selected patients. These may include resting heart rate and blood pressure, standard ECG, standardized short-term HRV where available, and orthostatic heart-rate and blood-pressure measurements. This step is intended to orient further phenotype-directed assessment, not to establish an IBD-specific autonomic diagnosis or apply unvalidated cut-offs. [8, 4, 5, 13].

6.4. Step 3: Phenotype-Directed Testing

Further testing should be selected according to the suspected physiological domain. Orthostatic symptoms may prompt structured standing assessment or head-up tilt testing; suspected cardiovascular reflex dysfunction may justify deep breathing, Valsalva, or Ewing-type testing. Sudomotor testing can be considered when sweating or peripheral sensory symptoms are prominent, while persistent multisystem or discordant presentations may justify specialist autonomic laboratory assessment. No evidence supports performing the full battery in every patient. [5, 6, 13, 11].

6.5. Step 4: Integration With IBD Activity

Autonomic findings should be interpreted alongside objective measures of IBD activity. Symptoms, CRP or ESR, fecal calprotectin, and endoscopy provide different information and should not be treated as equivalent. Autonomic testing should therefore complement, not replace, established inflammatory assessment. [8, 4, 9, 3].

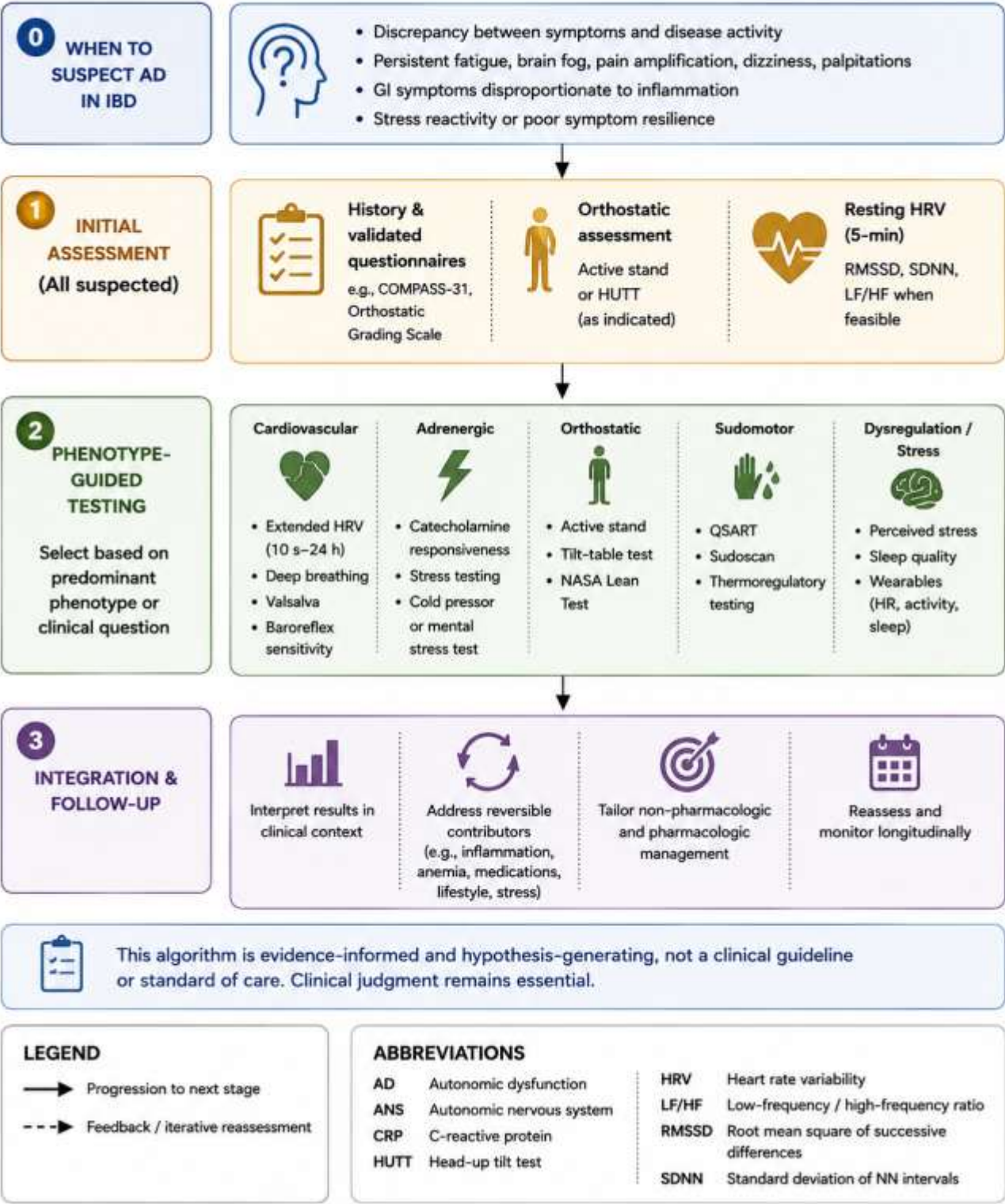
6.6. Step 5: Longitudinal Monitoring

Repeated measurements may ultimately be more informative than isolated autonomic values, particularly for HRV. Longitudinal monitoring should focus on within-patient trajectories rather than unvalidated IBD-specific cut-offs. HRV, Holter, or wearable-derived signals may support follow-up in selected patients, but abnormal trends should prompt clinical or inflammatory reassessment rather than directly determine treatment. [3, 14, 7].

6.7. Interpreting Discordant Results

Discordance should be expected. Patients may report autonomic-type symptoms without objective abnormalities, show objective abnormalities without prominent symptoms, or demonstrate autonomic alterations despite inflammatory remission. Interpretation should therefore integrate symptoms, inflammatory activity, and the physiological domain demonstrated by testing. The proposed algorithm ends with an integrated autonomic phenotype rather than a binary diagnosis. [6, 5, 7, 9]. The proposed staged clinical assessment pathway is shown in Figure 2.

Figure 2. Evidence-informed, staged algorithm for objective assessment of autonomic dysfunction in adults with IBD.



7. Physiological Framework: Autonomic–Immune Interactions in IBD

7.1. The Brain–Gut–Autonomic Axis

The brain-gut axis integrates central, autonomic, enteric, endocrine, and immune signalling. Gut-derived inflammatory and microbial signals can influence neural activity, while autonomic output participates in gastrointestinal motility, barrier regulation, and immune signalling. Within this network, HRV and other objective autonomic measures are indirect markers of systemic autonomic regulation rather than direct measures of intestinal neural function. [1].

7.2. Vagal Regulation and the Inflammatory Reflex

The vagus nerve provides a biologically plausible interface between autonomic regulation and intestinal inflammation, including the cholinergic anti-inflammatory pathway. Small clinical neuromodulation studies provide preliminary translational support, with changes in clinical, inflammatory, and autonomic endpoints occurring in parallel. These data support biological plausibility but do not establish the inflammatory reflex as a validated clinical mechanism in IBD. [1, 17, 22, 23, 24].

7.3. Inflammation as a Driver of Autonomic Alteration

The relationship may also operate in the opposite direction. Objective inflammatory activity has been associated with altered HRV and other physiological signals, suggesting that intestinal or systemic inflammation may influence autonomic regulation. Reduced HRV in active IBD may therefore accompany the inflammatory state rather than represent an independent autonomic disorder. Cross-sectional associations cannot establish direction of causality. [8, 4, 3].

7.4. Stress and Autonomic–Inflammatory Coupling

Psychological stress provides an additional modifying pathway. Stress-related autonomic activation should not be equated with intestinal inflammation. In prospective UC data, perceived stress and electrodermal sympathetic arousal related more clearly to symptom-defined flare than to biochemical flare, supporting partially separable stress, symptom, autonomic, and inflammatory domains. [9].

7.5. Persistent Autonomic Alterations During Remission

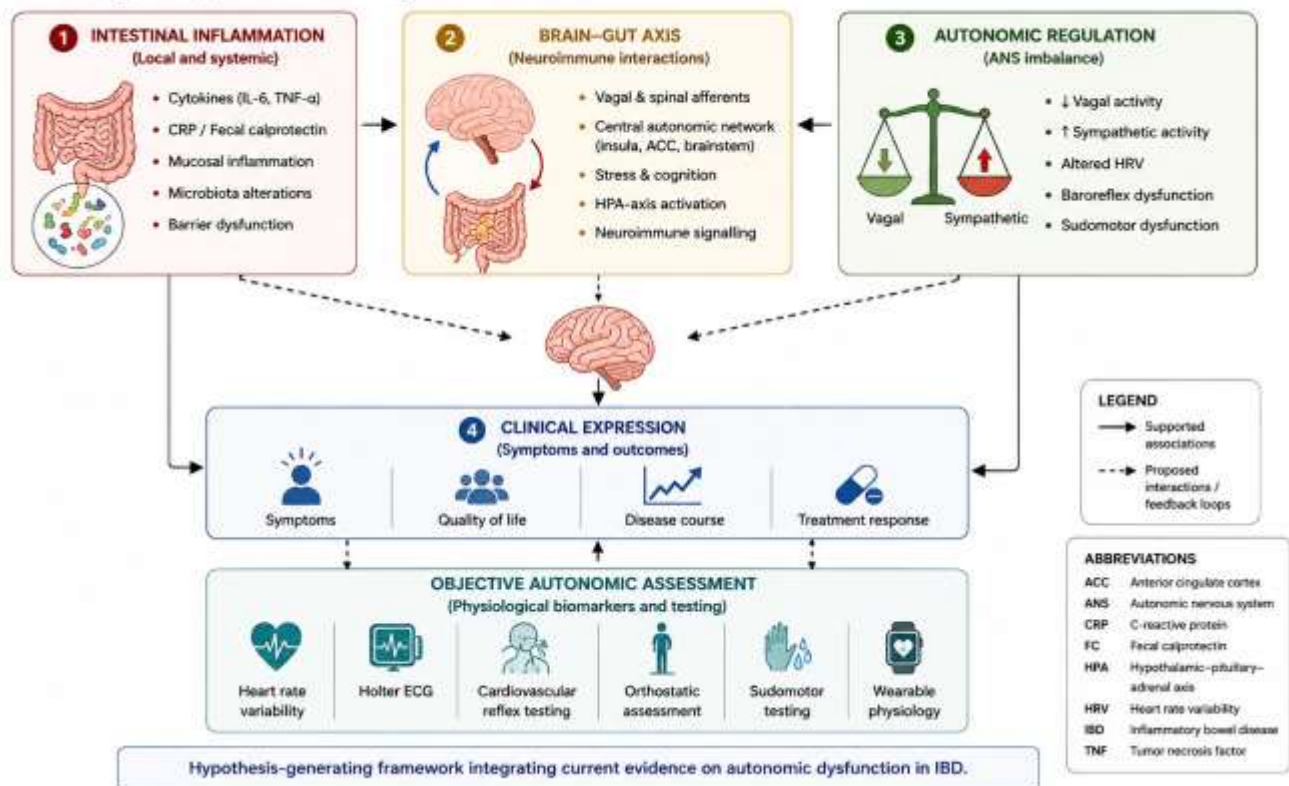
Autonomic abnormalities are not confined to active IBD. Altered HRV, resting autonomic balance, and baroreflex-related findings have been reported during clinical or endoscopic remission. These observations indicate that inflammatory remission does not necessarily coincide with autonomic

normalization. The mechanisms of persistence remain uncertain and cannot be resolved by current observational studies. [7, 5].

7.6. An Integrated Physiological Framework

We therefore propose a bidirectional, hypothesis-generating framework in which intestinal inflammation, autonomic regulation, and brain-gut signalling interact dynamically rather than sequentially. Disease history, treatment exposure, nutritional status, stress, sleep, and individual physiology may modify the observed autonomic phenotype. This framework organizes convergent observations but should not be interpreted as a validated causal model or formal disease classification. [1, 8, 5, 6, 3]. The proposed bidirectional physiological framework is illustrated in Figure 1.

Figure 1. Hypothesis-generating physiological framework linking intestinal inflammation, the brain-gut axis, and autonomic dysfunction in IBD.



8. Clinical Implications

Objective autonomic testing may add physiological context in selected patients with persistent, orthostatic, cardiovascular, or otherwise unexplained symptoms, but it should complement rather than replace established assessment of intestinal inflammation. HRV remains the most studied modality; phenotype-directed reflex, orthostatic, Holter, or sudomotor testing may be appropriate when clinically indicated. Wearable monitoring is promising for longitudinal within-patient assessment, whereas neuromodulation

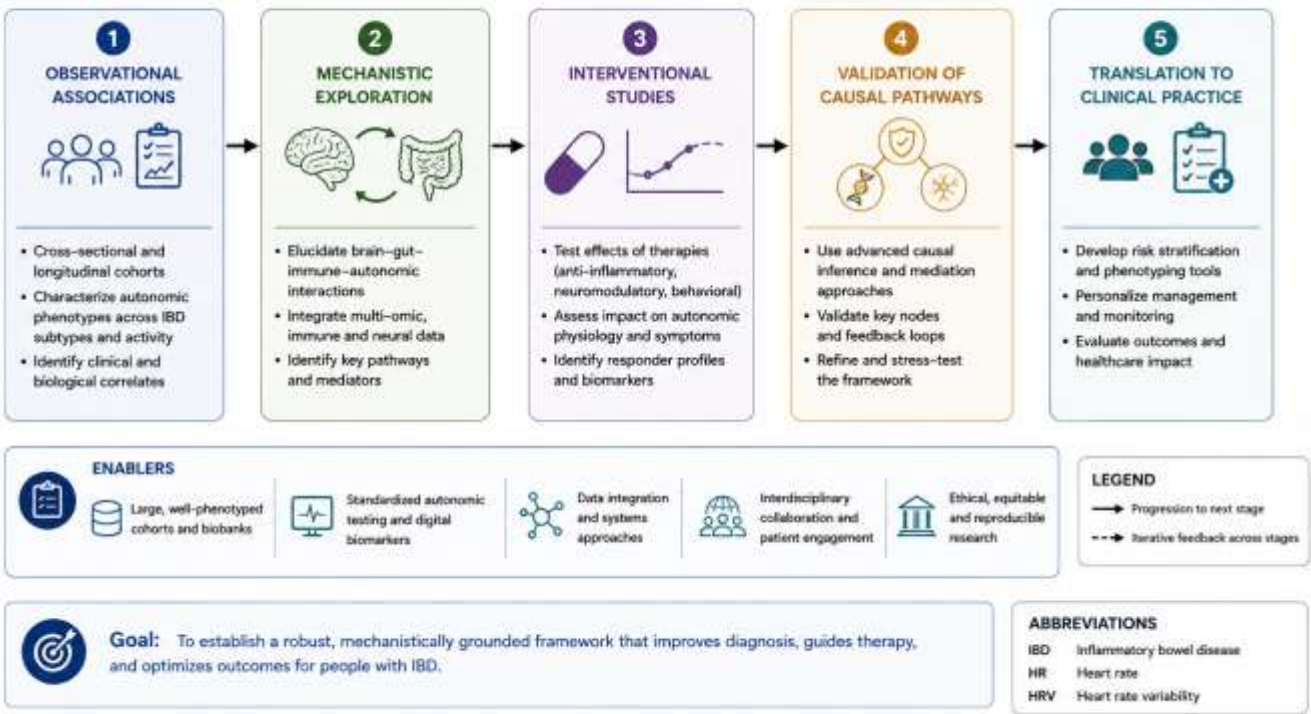
remains investigational. Potential clinical applications are summarized in the Supplementary Appendix (Supplementary Table S5). [8, 4, 6, 3, 14, 17, 22].

9. Knowledge Gaps and Future Directions

The principal priorities are methodological standardization, validated reference values, multimodal phenotyping, synchronization with objective inflammatory endpoints, and longitudinal within-patient assessment. Wearable biomarkers require external validation across devices and populations, peripheral autonomic dysfunction remains insufficiently characterized, and neuromodulation requires adequately powered controlled trials. The full research agenda is provided in the Supplementary Appendix (Supplementary Table S6). [4, 8, 7, 3, 6, 5, 17, 22]. The integrated research framework is shown in Figure 4.

Figure 4. Proposed research roadmap for validating an integrative neuroimmune–autonomic framework in IBD.

A stepwise strategy to advance from observational associations to causal mechanisms and clinical implementation.



Note: This roadmap is hypothesis-generating and not a prescriptive guideline. Iterative feedback between stages is essential.

10. Discussion

10.1. Principal Findings

The available evidence supports objective autonomic involvement in IBD across cardiac, reflex, orthostatic, baroreflex, sudomotor, and digital physiological domains, but not a single uniform autonomic disorder. HRV has the largest evidence base, while multimodal studies show that normal findings in one

domain do not exclude abnormalities in another. Autonomic alterations may also persist during remission, indicating that inflammatory control and autonomic normalization are not necessarily synchronous. [25, 8, 4, 6, 5, 7].

10.2. From Dysautonomia to Multidimensional Physiological Phenotyping

This heterogeneity favors multidimensional physiological phenotyping over a binary dysautonomia label. The relevant question is which domain is abnormal and how that finding relates to symptoms and inflammatory state. We therefore use cardiac modulation, cardiovascular reflex/baroreflex function, orthostatic regulation, and peripheral/sudomotor involvement as overlapping physiological domains rather than validated diagnostic categories. [6, 5, 13].

10.3. Relationship With Inflammation and Clinical Relevance

Autonomic physiology and inflammation are related but non-interchangeable. Associations are most consistent for selected HRV measures and endoscopic activity, whereas relationships with symptoms, systemic biomarkers, fecal calprotectin, and histology are less uniform. Stress-related autonomic signals may also track symptom-defined flare without equivalent biochemical inflammation. Autonomic testing may therefore add context in selected patients, but cannot substitute for established inflammatory assessment. [8, 4, 9, 3, 7].

10.4. Clinical Translation

Current evidence does not support universal screening or treatment decisions based on autonomic biomarkers alone. A staged, phenotype-directed approach is more defensible, with low-burden testing followed by specialized assessment when clinically indicated. Wearables are promising for longitudinal within-patient monitoring, whereas neuromodulation remains investigational. Both require further validation before routine clinical integration. [13, 6, 8, 3, 14, 17, 22].

10.5. Strengths and Limitations of the Evidence

Major limitations include heterogeneous autonomic protocols, small and often cross-sectional cohorts, inconsistent characterization of disease activity and treatment exposure, few multimodal head-to-head studies, and reliance on selected referral populations or conference abstracts. Pediatric findings also cannot be translated directly into adult thresholds. These constraints preclude robust prevalence estimates, IBD-specific cut-offs, and causal inference. A strength of this review is the integration of multiple autonomic modalities with objective inflammatory endpoints within a single physiological framework. [25, 6, 11, 16].

10.6. Overall Perspective

Overall, autonomic dysfunction is best regarded as a measurable but heterogeneous physiological dimension of IBD. No autonomic biomarker currently has validated performance for independent clinical use. The proposed Physiological Framework and Clinical Algorithm are therefore evidence-informed, hypothesis-generating tools whose clinical value requires prospective multicentre validation with standardized multimodal testing. [8, 4, 6, 5, 7, 3].

11. Conclusions

Objective autonomic abnormalities are measurable in at least some patients with IBD, but their expression is heterogeneous and cannot be characterized by a single test. HRV has the largest evidence base, while cardiovascular reflex, orthostatic, baroreflex, Holter, and sudomotor findings show that autonomic involvement extends beyond cardiac variability alone. [25, 8, 6, 5].

Autonomic alterations may accompany active disease or persist during remission, and symptoms, autonomic physiology, and intestinal inflammation do not consistently correspond. This supports hypothesis-generating multidimensional autonomic phenotyping that integrates objective physiology with symptoms and established measures of IBD activity. Autonomic testing should complement, not replace, conventional inflammatory assessment. [7, 5, 6, 9, 8, 4].

Future studies should prioritize standardized multimodal protocols, longitudinal within-patient monitoring, synchronized inflammatory endpoints, and external validation of wearable-derived biomarkers. The proposed Clinical Algorithm and Physiological Framework are not clinical guidelines; prospective multicentre studies must establish incremental clinical utility before autonomic assessment can become part of personalized IBD care. [3, 14, 16, 13, 6].

Declarations

Author Contributions

Jakub Marcel Korowicki: Conceptualization, Project administration, Supervision. Marta Labon: Methodology. Julia Beata Woźniak: Data curation, Formal analysis. Helena Strzelka: Visualization, Writing – original draft. Milena Dziejna: Writing – original draft. Bartosz Seroczyński: Writing – review & editing. Anna Zyskowska: Conceptualization, Methodology.

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The authors declare no conflicts of interest.

Declaration of the Use of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT (OpenAI) for text formatting, and verification of bibliographic style. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the substantive content of the publication.

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