Hindawi
GastroHep
Volume 2022, Article ID 1192547, 12 pages
https://doi.org/10.1155/2022/1192547

Review Article

Improving the Treatment Response of Patients with Irritable Bowel Syndrome: Implementing a Second-Generation Artificial Intelligence System for Overcoming Resistance

Anat Hershko-Moshe,[1] Yaako'v Hasin,[1] Anat Nevo-Shor,[2,3] Ohad Etzion,[2,3] and Yaron Ilan[1]

[1]*Faculty of Medicine, Department of Medicine, Hebrew University, Hadassah Medical Center, Jerusalem, Israel*
[2]*Department of Gastroenterology and Liver Diseases, Soroka Medical Center, Israel*
[3]*Faculty of Health Sciences, Ben-Gurion University of the Negev, Israel*

Correspondence should be addressed to Yaron Ilan; ilan@hadassah.org.il

Received 16 June 2022; Accepted 12 September 2022; Published 26 September 2022

Academic Editor: Soe Thiha Maung

Irritable bowel syndrome (IBS) is a common functional disorder. The syndrome's multifactorial pathophysiology makes it challenging to design effective therapies. The present paper reviews several therapeutic approaches to treating IBS, highlighting the challenges of losing response over time to therapies. Here, we present the relevance of chronobiology in biological systems focusing on the potential of chronotherapy for IBS. Artificial intelligence- (AI-) based approaches have been developed over the last few years to improve the diagnosis, therapeutic approaches, and monitoring of patients with various diseases. We discuss the use of first-generation AI platforms and their limitations in clinical practice and present the establishment of a second-generation system designed to overcome obstacles in managing these patients. The system identifies costly patients and those who do not respond to therapies and may benefit from algorithm-based therapies. We present a patient-tailored approach for improving the response to therapy in IBS using an AI-based algorithm. This system provides a tool for a patient-tailored monitoring system. The second-generation AI system can provide a comprehensive tool for improving the diagnosis and therapy and monitoring of patients with IBS.

1. Introduction

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder. IBS is diagnosed according to patterns of gastrointestinal symptoms as described by the Rome diagnostic criteria [1]. IBS is characterized by abdominal pain and altered bowel habits without specific organic pathologies. Patients with IBS are classified into four subtypes: IBS with predominant constipation (IBS-C), predominant diarrhea (IBS-D), mixed bowel habits (IBS-M), and the unclassified subtype (IBS-U) [2]. IBS affects between 5% and 10% of healthy individuals at any point in their lives [3]. In most patients, it has a relapsing and remitting course. IBS has considerable effects on quality of life. A combination of environmental, infectious, genetic, microbiome, immune, diet, and gut-brain interaction-associated parameters underlies the pathogenesis of IBS [1]. These factors result in motility disturbances, visceral hypersensitivity, and altered central nervous system (CNS) processing. Both nonpharmacological and pharmacological therapies can help control IBS symptoms but do not provide relief to a significant proportion of patients [4–11].

In the present paper, we review some therapeutic approaches to treating IBS, highlighting the loss of response over time to therapies. We discuss the relevance of chronobiology in patients with IBS. The use of artificial intelligence-

(AI-) based approach was described. We focus on establishing a second-generation algorithm to overcome some of the main obstacles in treating IBS.

2. Treatment for IBS: Lack of Curable Therapies, Drug Resistance, and Low Response Rates

IBS therapy is aimed at providing symptomatic relief for diarrhea, constipation, and pain. While some patients respond well to nonpharmacological treatment, many require pharmacological treatment. Symptom-oriented pharmacological treatment algorithms manage many patients with IBS who fail to improve their lifestyle or follow psychological interventions [12]. Notably, single-agent therapy rarely relieves the symptoms in all patients [4, 13–17].

2.1. Pharmacological Treatments. Antidepressants and central neuromodulators can treat IBS. IBS is a disease caused by multifactorial elements linked with psychological disorders. Patients with IBS suffer from higher rates of anxiety and depression [18]. Psychological components may alter pain thresholds and cause visceral hyperalgesia [19]. Disturbance in the brain-gut axis is associated with IBS symptoms. The autonomic nervous system connects the CNS to the enteric nervous system (ENS). Disruption of this pathway may lead to constipation and diarrhea [20]. Antidepressants are a second-line treatment for IBS. Tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRIs) affect the CNS and gastrointestinal motility through serotonin receptor activation and lead to symptom relief [21]. Relief in somatic but not in psychiatric symptoms was described with a lower dosage of TCA [20, 22]. TCA was more favorable for symptom relief in IBS-D and SSRI in IBC-C [23]. The long-term beneficial effects of antidepressant therapies on IBS are yet to be determined.

Vitamin D deficiency is associated with IBS symptoms, and its supplementation may be beneficial. However, the use of vitamin D in patients with IBS remains controversial. A case-control study showed a significantly higher prevalence of vitamin D deficiency in patients with IBS than in healthy individuals (82% vs. 31%). A randomized double-blinded study reported significant improvement in symptoms with vitamin D supplementation [24]. The mechanism of this effect may be attributed to the role of vitamin D as an immune modulator and anti-inflammatory agent, reducing the release of proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, and stimulating the function of T regulatory cells [25, 26]. It also affects the gut microbiome [27]. In contrast, a recent randomized, double-blind, placebo-controlled trial showed no advantages in administering vitamin D to patients with IBS, even those with vitamin D deficiency [28]. Long-term follow-up of patients treated with vitamin D supplementation in IBS has not been reported [29].

The gut microflora is a contributing factor in the pathogenesis of IBS. It is affected by gastroenteritis, surgery, and antibiotics, precipitating IBS symptoms. The fecal flora of patients with IBS is different from healthy controls, showing reduced numbers of coliforms, lactobacilli, and bifidobacterial spp. [30]. The use of nonabsorbable antibiotics has been suggested to target alterations in the microbiota in IBS [31]. Rifaximin is a broad-spectrum nonabsorbable antibiotic that appears beneficial after two weeks of treatment, alleviating abdominal pain and bloating and relieving diarrhea [32]. This effect appears to decrease at ten weeks of follow-up; however, repeat treatment with rifaximin showed improvement of symptoms [33, 34].

Probiotics are living organisms that comprise different types of streptococci, lactobacilli, bifidobacteria, and yeast. Probiotics seem to be effective in relieving IBS symptoms and stabilizing immune dysregulation [35]. However, their long-term effects remain uncertain [36]. Two meta-analyses assessing probiotics in IBS showed that long-term use of probiotics is associated with reduced efficacy and no improvement in IBS symptoms [37, 38].

Abnormal gastrointestinal motility is an essential pathophysiological mechanism in IBS, with increased motility reported in IBS-D and decreased motility in IBS-C [39]. Antispasmodics reduce gastrointestinal contractility by acting on the gastrointestinal smooth muscles. A meta-analysis assessing IBS symptoms using antispasmodics compared with placebo showed a short-term benefit [40]. Peppermint oil acts as an antispasmodic, anti-inflammatory, serotonergic, and opioid agonistic property. It has a significant benefit over placebo [41]. However, the most prolonged follow-up period in these trials was 15 weeks.

Intestinal secretagogues regulate intestinal water and electrolyte transport. Linaclotide and Plecanatide are agonists of the luminal receptor guanylyl cyclase C, which activates apical CFTR chloride channels via cGMP production [42]. Linaclotide improves stool frequency, ease of defecation, and symptoms, such as abdominal pain, discomfort, and bloating in 33% vs. 14% [43]. Lubiprostone activates type 2 chloride channels in enterocytes. A study of 1,171 patients showed that its use led to the relief of symptoms in patients with IBS-C over 12 weeks [44]. Tenapanor inhibits gastrointestinal sodium-hydrogen exchanger three that increases the fluid volume of stool by reducing sodium absorption, improves stool pattern, and reduces abdominal pain. In a study of 356 patients, tenapanor improved stool frequency and abdominal symptoms over 12 weeks [45].

Opioid receptors are located throughout the paleospinothalamic pathway from the cerebral cortex until the peripheral myenteric and submucosal plexus and play a role in the gut-brain axis. Moreover, opioid receptors are responsible for chronic pain [46]. Morphine decreases lower esophageal sphincter pressure, delays gastric emptying, and relieves pain through its function in the CNS. Fedotozine has the same antinociceptive qualities as morphine, increasing bowel motility [46]. Different opiates can treat diverse types of IBS. In IBS-D, loperamide, which induces constipation, reduces episodes of incontinence [47]. In IBS-C, fedotozine, a K-receptor agonist, was suggested to alleviate symptoms of abdominal pain and bloating [48], but clinical trials have shown a lack of efficacy [49]. Phase II clinical trials showed that asimadoline, a selective K-receptor agonist, was beneficial in IBS-D [49, 50].

5-HT receptors play a role in the gut-brain axis due to their effect on the CNS and ENS. The enteric system can cause bowel contractions or smooth muscle relaxation [51]. 5-HT3 receptor antagonists alleviate IBS-D, and 5-HT4 receptor agonists assist IBS-C. 5-HT3 receptor antagonists, such as alosetron and ondansetron, delay colonic transit time in patients with IBS. Stasi et al. and Johanson relieve symptoms in patients with IBS-D. 5-HT4 agonists, such as tegaserod and prucalopride, increase colonic transit time and improve symptoms in up to 70% of patients [51, 52].

2.2. Nonpharmacological Treatments. IBS treatment is challenging for both patients and caregivers due to the lack of curative treatments and its multifactorial pathophysiology [14–17, 53]. The relationship of patients with their health care provider is essential to optimize patient care in IBS and improve the patients' quality of life [54]. Due to its chronic nature, patient education is essential for IBS management. Structured patient education was beneficial in improving symptom severity and quality of life [55]. Both multidisciplinary patient education and nurse-based education were effective in improving symptoms [56]. Education using digital methods can reduce health expenses. Moreover, webinars prepared using dietary management guidelines improve patient knowledge and are cost-effective [57].

Psychological therapies, including cognitive-behavioral therapy (CBT), are used in patients with IBS. Sustained stress can persistently increase central stress circuits' responsiveness and vulnerability to functional disorders. Studies showed a relationship between IBS and stressful or traumatic life events and comorbidity with anxiety disorders [58]. In a Cochrane review of 25 controlled trials, CBT, stress management, relaxation therapy, and interpersonal psychotherapy were superior to usual care. Studies comparing interpersonal therapy with placebo and one study comparing CBT with placebo showed significant improvement. A systematic meta-analysis of 41 RCTs of CBT showed that gut-directed hypnotherapy, dynamic psychotherapy, and group therapies effectively alleviated IBS symptoms. In patients with refractory symptoms, only CBT and gut-directed hypnotherapy were effective [59]. The sustained benefits of these treatments remain unelucidated. Studies with up to 15 months of follow-up showed a loss of treatment effect over time [60].

Patients with IBS report symptoms related to food ingestion, making dietary approaches attractive [61]. Patients with IBS show higher small intestinal bacterial overgrowth (SIBO) associated with IBS symptoms [62, 63]. A reduction in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP), found in foods containing lactose and fructose, which are poorly absorbed, is beneficial in IBS [62, 64]. A high FODMAP diet worsened the symptoms of IBS [65]. Restriction of FODMAP reduces bacterial count and changes intestinal microbiome [66]. A randomized controlled crossover trial showed reduced symptoms in half of the patients [66, 67]. The long-term effects of low FODMAP diets (LFD) on symptoms and the microbiome are yet to be determined [61, 68, 69].

Both soluble and insoluble fibers can alleviate the IBS symptoms. Insoluble fibers have a laxative effect by increasing fecal mass, secretion, and peristalsis via mechanical stimulation of the colonic mucosa. Short-chain fibers can be fermented by increasing the colonic biomass and fecal mass, altering the microbiota composition, and affecting the oro-anal transit time. Fermentation of by-products lowers the intestinal pH, affecting the gastrointestinal neuroendocrine system. Soluble viscous long-chain dietary fibers are minimally fermented and form a gel that normalizes stool form [70]. A meta-analysis of 11 RCTs showed a significant improvement in the global assessment of IBS symptoms. However, no improvement in abdominal pain, severity risk scores, and quality of life scores have been demonstrated [71]. There appears to be no long-term follow-up data on treatment with soluble fibers.

Acupuncture stimulates the somatic nervous system and vagus nerve, causing alterations in intestinal motility [72]. Several systemic reviews failed to show a significant benefit compared to sham treatment but showed improvement related to a placebo effect [73–75]. In contrast, a meta-analysis of six randomized controlled trials showed significantly favorable outcomes of acupuncture compared to placebo [76]. A study evaluating acupuncture in the primary care setup alleviated IBS symptom severity score (IBS-SSS) for up to 12 months duration [77], but not sustained for 24 months [78].

Taken together, the major drawback of both pharmacological and nonpharmacological therapies is the lack of sustainability of their effects [14–17, 79, 80].

Guidelines use a stepwise approach for the treatment of IBS [13]. Step 1 comprises behavioral modification, diet therapy, and gut-targeted pharmacotherapy for four weeks. For nonresponders, step 2 suggests a combination of several mechanism-based gut-targeted agents and psychopharmacological agents and psychotherapy for four weeks. For nonresponders, step 3 comprises combined gut-targeted pharmacotherapy, psychopharmacological treatments, and a more specific psychotherapy [13]. Overall, the treatment of IBS remains a challenge, and improving the quality of life is difficult in many chronic patients.

3. The Role of Chronobiology in the Pathogenesis of IBS

The circadian clock is a regulator of multiple biological processes [81]. The endogenous clock is a highly conserved timekeeper that supports the daily cycle of physiological processes and maximizes the proper functions of biological systems. Circadian rhythms coordinate cellular reactions, organ function, and body homeostasis [82]. In the intestine, the circadian rhythm regulates the transcriptional and translational feedback loops that culminate in the rhythmic expression of a set of clock genes and related hormones [83]. The suprachiasmatic nucleus and peripheral core molecular clocks oscillate every 24 h, regulating the periodic activity of the gut endocrine, immune, and nervous systems controlling intestinal functions and transit. Circadian rhythms are linked to energy balance regulation and nutrition. The circadian clocks showing lowered nocturnal activity regulate the motility of the colon. Healthy humans have

normal bowel motility following awakening or a meal, with minimal activity during the night [83].

The circadian clock regulates several potential mechanisms underlying IBS. Disturbed gut circadian rhythms lead to constipation and IBS [83]. Microbes contribute to the maintenance of clock function [82]. Disruption of the circadian system alters the microbiome to alter host metabolism, energy homeostasis, and inflammatory pathways [84]. Clock disruption and microbiota alterations exert reciprocal effects on brain function, further affecting the brain-gut axis [82]. Circadian-controlled dynamic neuroimmune routes in the gut regulate the association between innate immune protection mediated by IL-22 and food absorption [85].

Circadian rhythms are also associated with diet. The host circadian rhythm and timing of feeding are cross-regulated, hence controlling multiple physiological functions, including host immunity and metabolic health [86]. Diurnal shifting of the diet-microbiome-host immune axis is relevant to the gut, nervous system, and endocrine physiology. They also impact the gut-brain interactions [86, 87]. A high-fat diet disturbs the circadian rhythm of the microbiome. Morning soy protein intake led to greater microbiota diversity and a decrease in the cercal pH resulting from the production of short-chain fatty acids in mice [88]. The circadian hormone melatonin can improve lipid metabolism by reprogramming the gut microbiota, exhibiting rhythmicity in a light/dark cycle. Melatonin regulates the gut microbiota circadian rhythms in mice [89].

In preclinical models, poor sleep altered the gut microbiome and fecal metabolome, identifying sleep disruption-sensitive bacterial taxa and metabolites [90]. In humans, the day and night cycles underlie the function of the central and gut clocks. Sleep disorders are associated with diet and IBS [91]. Short sleep durations disrupt the intestinal gut microbiota, contributing to an inflammatory state, intestinal dysmotility, and alterations in metabolism associated with shift work [92]. In a clinical trial of healthy volunteers, rotational day and night shift work disturbed the circadian rhythm, altering the abundance of gut microbiota, which may be associated with intestinal pathology [93].

A clinical trial of 170 volunteers determined the association between the CLOCK 3111T/C single nucleotide polymorphism and the Period3 (PER3) variable-number tandem-repeat polymorphism with morning gastric motility. The data showed that minor polymorphisms of the circadian rhythm genes CLOCK and PER3 are linked to poor morning gastric motility [94]. Participants with the CLOCK C allele showed a significantly lower frequency of gastric motility.

While chronobiology plays a role in the pathophysiology of IBS, chronotherapy, the provision of therapies based on the circadian rhythm, has not yet been applied to optimize treatment in these patients.

4. Using the First-Generation Artificial Intelligence Systems in IBS

Selection of the treatment is a challenge in patients with IBS due to the low response rate and dynamic nature of this relapsing and remitting syndrome [13].

First-generation gastroenterology-directed AI systems may assist in diagnosing, selecting appropriate therapies, and predicting disease prognosis and outcome of diseases [95, 96]. Most first-generation systems evolve from the notion of collecting big datasets for identifying patterns and implementing them to improve diagnosis and management. The diagnosis of many gastrointestinal conditions relies on image-based procedures, making AI systems ideal for increasing the accuracy of diagnosis using AI-assisted image analysis. AI can also assist in integrating genomic, epigenetic, and metagenomic data, improving the accuracy of diagnosis of gastrointestinal malignancies [97–99]. AI platforms can assist in managing relapsing and remitting diseases, such as IBS, inflammatory bowel disease, or peptic ulcer bleeding, as a complex neural network may formulate models to predict disease outcome and enhance treatment efficacy [96]. However, while treatment algorithms are more straightforward for the last two examples, enabling closed-loop systems in designing large dataset-based treatment schemes, the case is different for IBS.

Being a multifactorial syndrome and the lack of biochemical or image-based criteria for establishing diagnosis limits the incorporation of first-generation AI platforms in diagnosing IBS. Patients with IBS show low response rates to most therapies, require combination therapies, and show dynamic changes in disease patterns and severity over time, which are obstacles for most currently developed AI systems [95].

Psychological and biological disease models assist in the diagnosis of IBS. A symptom network and an adaptive network may assist in specifying and covariation of symptomatology [100]. Only the adaptive network model, which assumes that a network of biological mechanisms has emergent properties and can exhibit adaptation, was able to explain the covariation of somatic symptoms of IBS. A recent study determined the prediction of symptoms with pathology in patients with IBS. It showed that network connection strengths vary with pathology, supporting the notion that functional disorders are associated with network adaptation. Using a machine learning analysis on surveys from 1,751 people reporting IBS, fibromyalgia, and chronic fatigue syndrome identified eleven symptoms. The strength of the associations between clusters varied due to symptom frequency. The data suggested an ability to diagnose IBS based on clusters of symptoms. The results imply that the body uses complex adaptation and that functional disorders, such as IBS, result when maladaptive changes occur to rules that generally improve adaptation [100].

A recent trial determined the feasibility of quantifying small bowel motility using magnetic resonance imaging (MRI) in a larger population with a spectrum of GI conditions with impaired small bowel motility. Motility quantitation showed marked differences in the motility of the terminal ileum in patients with small bowel Crohn's disease but not in patients with IBS [101].

Dietary adherence to a low FODMAP diet (LFD) is difficult. Heali is an AI-based dietary application designed to improve adherence to LFD, IBS symptoms, and quality of life outcomes. In a trial of 58 patients with IBS, the reduction

in symptom severity score was 24% greater in the study group than in the control group, although this difference was not significant [102].

In summary, the attempts to implement first-generation AI systems in patients with IBS did not lead to a validated diagnostic or therapeutic scheme that could assist in managing IBS in most patients.

5. Establishing a Second-Generation AI System to Improve the Management of Patients with IBS

The second-generation AI system provides a comprehensive solution for the three gaps in the management of IBS in patients. These include difficulties in diagnosing, treating, and monitoring these patients.

Table 1 summarizes some of the barriers in diagnosing, treating, and monitoring patients with IBS and the solutions offered using second-generation AI systems.

5.1. Use of a Second-Generation System to Improve IBS Diagnosis. The lack of validated tests for IBS diagnosis makes it challenging to design diagnostic algorithms. The second-generation system can select subgroups of patients that require further evaluation by colonoscopy or motility tests. The system also assists in searching datasets for identifying costly patients who do not respond to therapies and may benefit from second-generation algorithm-based therapies [95, 103]. This subgroup of patients is a significant burden on the health care system, and targeting them may alleviate the burden on caregivers and payers while improving their overall quality of life and response rates of patients with IBS.

5.2. A Patient-Tailored Approach for Improving Response to Therapy in IBS. The Digital Pill comprises any type of pharmacological therapy for IBS regulated by a second-generation algorithm [104] and improves therapies' effectiveness and patient adherence [95, 105, 106]. The patient receives the medication as prescribed by the physician with an app that has predefined therapeutic regimens dictated by the physician.

The Digital Pill system for patients with IBS is being developed in a stepwise manner comprising three levels [104]. In the first level, an application is provided to patients and reminds them of the dose and time of administration of the selected treatment. Physicians enter into the application ranges of dosages and administration times of each drug and other interventions within the approved ranges [104]. The embedded algorithm introduces variabilities in dosing and times within predetermined ranges [95, 104]. Treatment regimens based on aperiodic routines of taking the medication at irregular intervals and strengths may improve responsiveness [87, 103, 105, 107–113].

In contrast to first-generation systems, the second-generation system provides a means for a continuous dynamic feedback loop that accounts for changes in patient outcomes, response to therapy, disease manifestations, and environmental factors [95]. The system can also be applied to nonpharmacological therapies and assist in improving the response to sports activities, diets, and other interventions in patients with IBS [87, 103, 104, 113–115].

The Digital Pill is a simple system that can improve the response to the currently used treatment methods in patients with IBS. It may overcome drug resistance in multiple chronic diseases and conditions, including inflammatory bowel diseases [111], arthritis [111], epilepsy [116], cancer [108], metabolic diseases [87], obesity [113], pancreatitis [110], microbiome-based disorders [117], infections [109, 118], microtubule-linked disorders [119–121], chronic pain [112], rare diseases [103], and chronic inflammation [122].

Variability is inherent to biological systems and responses to medications. It partially underlies the partial or complete loss of response to chronic drugs [123–125]. Studies showed a high degree of inter- and intrapatient variability for drug metabolism, pharmacodynamics, and drug responsiveness [104–106, 126, 127]. Regular administration of a daily dose at fixed times is associated with drug resistance [107], while drug holidays can improve it [105, 128].

The first level of the Digital Pill can assist in overcoming the partial or complete loss of the effect of chronic drugs used for IBS. While first-generation platforms suffer from a lack of adherence by patients, the second-generation system is aimed at improving clinically meaningful outcomes, ensuring improved adherence [95]. Improving the clinical symptoms when using the application ensures a continuous motivation for using the drug based on the regimen provided by the application.

The second level of the system includes a closed-loop system directed to alter the variability in dosages and administration times based on the response to therapy. It implements chronobiology variables for the pharmacotherapy of IBS. The system receives feedback from the patient and caregivers and implements data collected from other patients. Endpoints for the algorithm are predefined clinical outcomes and are patient-tailored [104]. The algorithm alters the variability in dosing and times of administration of drugs based on the patient's clinical response. The system continuously personalizes each subject's therapeutic regimen based on predefined outcome measures [95, 104].

At the third level, the system implements variability signatures relevant to the disease into the treatment algorithm [95, 104]. Examples are evident for other chronic diseases: variability in cytokine profiles in patients with inflammatory bowel diseases or arthritis [111], heart rate variability in patients with chronic heart diseases [105], and electroencephalogram-derived variability data in patients with epilepsy [116]. For patients with IBS, implementing inherent variabilities associated with the immune system (e.g., cytokine patterns), microbiome-signatures, patterns associated with the autonomic nervous system (e.g., heart rate variability), and motility test-derived parameters can improve the therapeutic regimen and hence the clinical outcome [104]. The algorithm can select the appropriate variability patterns in a patient-tailored way by continuously comparing inputs of different variability signatures on the output of the therapeutic schedule in a way that adapts itself to the selected outcome (e.g., improvement in bloating, pain, and diarrhea).

Table 1: Overcoming significant gaps in the diagnosis, treatment, and monitoring of patients with IBS using second-generation artificial intelligence systems.

	Barrier	Solution
Diagnosis	(i) Multifactorial nature of IBS	(i) A digital system that collects and integrates different datasets
	(ii) Lack of validated tests	(ii) Identification of patient subgroups that require further evaluation by colonoscopy and motility tests
		(iii) Identification of patients who do not respond to treatment and may cause high health care costs
Treatment	(i) Low response rates (ii) Require combination therapy (iii) Changes in IBS pattern over time	(i) A digital system with continuous dynamic feedback helps improve patient adherence, management of symptoms, and adaptation to the changing nature of the disease
Monitoring	(i) Chronicity imposes a health care challenge to monitor patients	(i) A tool in the digital system to collect data of symptoms, the effectiveness of therapy, and side effects
	(ii) Changes in IBS pattern over time	(ii) Provides a valid tool for caregivers to follow patients' adherence and responsiveness
		(iii) The dynamic nature of the artificial intelligence system helps both patients and caregivers to tailor the relevant follow-up variables

Dysregulation of the brain-gut axis is associated with IBS. A recent clinical trial applied multivariate pattern analysis to identify an IBS-related morphometric brain signature that could serve as a biomarker. Parcellation of 165 cortical and subcortical regions used FreeSurfer and Destrieux and Harvard-Oxford atlases. The study used a training set of 160 participants consisting of 80 healthy controls and 80 patients with IBS for modeling. The predictive accuracy of the classification algorithm was 70% based on regional brain morphometry. While the algorithm's accuracy may be insufficient, it suggests the potential of using brain-derived signatures to improve the algorithm [129].

The second-generation system has several advantages for patients with IBS and can overcome several obstacles first-generation systems face. The system evolves from an $n = 1$ concept, ideal for patients with IBS for whom large, validated datasets are not always available. The marked phenotypic differences among patients with IBS make it inappropriate to "force averages" resulting from accessible datasets on an individual patient [130]. The system continuously adapts the therapeutic schedule to the dynamicity of the symptoms, which is common in patients with IBS, and adapts itself to alterations in the degree of responsiveness to therapies [104].

Figure 1 demonstrates a schematic presentation of a second-generation artificial intelligence system for improving diagnosis, treatment, and follow-up of IBS patients. The system is designed to improve diagnosis and identify optimal treatment regimens with continuous feedback and better monitoring of outcomes.

5.3. Patient-Tailored Monitoring System for Patients with IBS. The second-generation system provides a method to monitor patients with IBS based on a dynamic outcome approach, leading to improved care and saving costs [103, 131]. The application provides patients with a tool to collect data on their symptoms, effectiveness of therapy, and side effects. Physicians can adhere to the therapy and responsiveness. As a dynamic monitoring tool, the system allows patients and caregivers to adapt the variables to be followed [95, 104]. Patients with IBS are heterogeneous in terms of their phenotypes and the dynamicity of the disease, which manifests as significant inconsistencies in symptoms, remissions, and exacerbations. The ability of the second-generation system to continually adapt itself to different variables is mandatory for making it a proper monitoring tool.

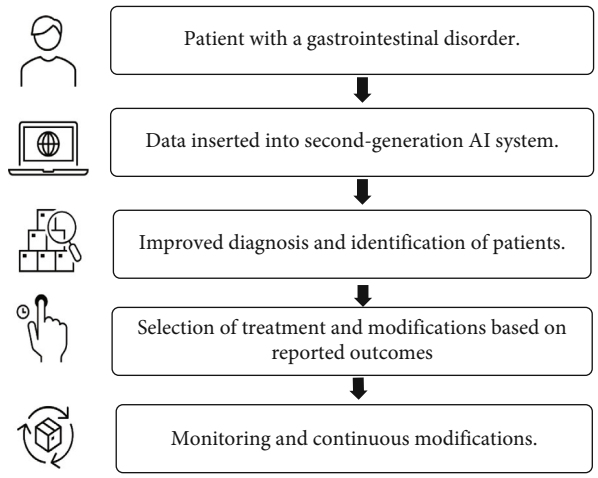

Figure 1: A schematic presentation of a second-generation artificial intelligence system for improving diagnosis, treatment, and follow-up of patients with irritable bowel syndrome (IBS). Data is inserted for a patient with a gastrointestinal disorder to improve diagnosis and identify optimal treatment regimens with continuous feedback, modifications, and better monitoring.

Overall, the second-generation AI system provides a comprehensive tool for improving the diagnosis, therapy, and monitoring of patients with IBS. It provides an added value to all players in the health care system. For patients, the algorithm can improve the outcome and quality of life. The system offers physicians a simple tool and a patient-

tailored monitoring tool to improve therapeutic regimens. It also benefits healthcare systems by reducing costs due to improved outcomes. A continuous closed-loop machine learning system that adapts itself to changes in symptoms and response to therapy in an individualized manner ensures the sustainability of the effects.

Insurance coverage is an essential factor in choosing treatment for IBS in many countries. A recent study conducted multilevel microsimulation tracking costs and outcomes among 10 million hypothetical moderate-to-severe patients with IBS modeling. Over one year, the analysis included all possible algorithms, including common IBS pharmacological and nonpharmacological treatments. The data showed that routine and algorithmic prescription drug coverage restrictions requiring failure of low-cost behavioral, dietary, and off-label treatments are cost-effective. Routinely, using a central neuromodulator, low fermentable oligo-, di-, monosaccharides, polyols, and cognitive behavioral therapy saved costs [132]. While algorithm-based prescription can lower costs, implementing algorithms for detecting costly patients and increasing responsiveness to relatively low-cost medications (e.g., rifaximin for IBS-D and linaclotide for IBS-C) may increase savings.

6. Summary

Treatment of patients with IBS remains a challenge. The use of second-generation AI systems can provide an inclusive solution to improve the diagnosis and classification of patients for appropriate therapies. The system provides a tool for overcoming the loss of response to therapies, ensuring a sustainable effect and increased patient adherence while providing an outcome-based monitoring tool. Ongoing trials are aimed at validating the system in patients with IBS and enabling the upscaling of the algorithm.

Abbreviations

IBS: Irritable bowel syndrome
AI: Artificial intelligence
IBS-C: IBS with predominant constipation
IBS-D: IBS with predominant diarrhea
IBS-M: IBS with mixed bowel habits
IBS-U: Unclassified IBS
CNS: Central nervous system
ENS: Enteric nervous system
TCA: Tricyclic antidepressants
SSRI: Selective serotonin reuptake inhibitors
GAD: Generalized anxiety disorder
IL: Interleukin
TNF: Tumor necrosis factor
CFTR: Cystic fibrosis transmembrane conductance regulator
cGMP: Cyclic guanosine monophosphate
5-HT: 5-Hydroxytryptamine
CBT: Cognitive-behavioral therapy
SIBO: Small intestinal bacterial overgrowth
FODMAP: Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols
LFD: Low FODMAP diet
QOLS: Quality of life scores
IBS-SSS: IBS symptom severity score
PER3: Period 3
MRI: Magnetic resonance imaging.

Data Availability

This is a review, and all data is available in PubMed.

Conflicts of Interest

The authors declare that they have no conflicts of interest. YI is the founder of Oberon Sciences.

Authors' Contributions

Anat Hershko-Moshe and Yaako'v Hasin contributed equally to this work.

References

[1] C. J. Black and A. C. Ford, "Global burden of irritable bowel syndrome: trends, predictions and risk factors," *Nature Reviews. Gastroenterology & Hepatology*, vol. 17, no. 8, pp. 473–486, 2020.

[2] B. Radovanovic-Dinic, S. Tesic-Rajkovic, S. Grgov, G. Petrovic, and V. Zivkovic, "Irritable bowel syndrome - from etiopathogenesis to therapy," *Biomedical Papers of the Medical Faculty of the University Palacky, Olomouc, Czech Republic*, vol. 162, no. 1, pp. 1–9, 2018.

[3] A. C. Ford, A. D. Sperber, M. Corsetti, and M. Camilleri, "Irritable bowel syndrome," *Lancet*, vol. 396, no. 10263, pp. 1675–1688, 2020.

[4] R. Gendi and N. Jahan, "Pharmacological and non-pharmacological treatments of irritable bowel syndrome and their impact on the quality of life: a literature review," *Cureus*, vol. 12, article e9324, 2020.

[5] N. M. Roudsari, N. A. Lashgari, N. Zandi et al., "PPARγ: a turning point for irritable bowel syndrome treatment," *Life Sciences*, vol. 257, p. 118103, 2020.

[6] P. B. Miner, "Plecanatide for the treatment of constipation-predominant irritable bowel syndrome," *Expert Review of Gastroenterology & Hepatology*, vol. 14, no. 2, pp. 71–84, 2020.

[7] J. M. Maixent, O. Pons, S. R. Sennoune, and S. Sadrin, "Clinical effects of lactobacillus strains as probiotics in the treatment of irritable bowel syndrome. Results from the LAPIBSS trial: future objectives," *Cellular and Molecular Biology*, vol. 66, no. 3, pp. 211–214, 2020.

[8] V. N. Madia, A. Messore, F. Saccoliti et al., "Tegaserod for the treatment of irritable bowel syndrome," *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry*, vol. 19, no. 4, pp. 342–369, 2020.

[9] M. Kurin and G. Cooper, "Irritable bowel syndrome with diarrhea: treatment is a work in progress," *Cleveland Clinic Journal of Medicine*, vol. 87, no. 8, pp. 501–511, 2020.

[10] U. C. Ghoshal, "Marshall and Warren Lecture 2019: a paradigm shift in pathophysiological basis of irritable bowel syndrome and its implication on treatment," *Journal of*

Gastroenterology and Hepatology, vol. 35, no. 5, pp. 712–721, 2020.

[11] D. M. Brenner and G. S. Sayuk, "Current US Food and Drug Administration-approved pharmacologic therapies for the treatment of irritable bowel syndrome with diarrhea," *Advances in Therapy*, vol. 37, no. 1, pp. 83–96, 2020.

[12] E. Colomier, J. Algera, and C. Melchior, "Pharmacological therapies and their clinical targets in irritable bowel syndrome with diarrhea," *Frontiers in Pharmacology*, vol. 11, article 629026, 2021.

[13] S. Fukudo, T. Okumura, M. Inamori et al., "Evidence-based clinical practice guidelines for irritable bowel syndrome 2020," *Journal of Gastroenterology*, vol. 56, no. 3, pp. 193–217, 2021.

[14] E. V. Wechsler and E. D. Shah, "Diarrhea-predominant and constipation-predominant irritable bowel syndrome: current prescription drug treatment options," *Drugs*, vol. 81, no. 17, pp. 1953–1968, 2021.

[15] C. Gillan, "Review article: the effectiveness of group and self-help hypnotherapy for irritable bowel syndrome and the implications for improving patients' choice and access to treatment," *Alimentary Pharmacology & Therapeutics*, vol. 54, no. 11-12, pp. 1389–1404, 2021.

[16] S. Patel, B. Doerfler, K. Boutros, S. Ng, M. Manuel, and E. DeSimone, "Review of treatment options for irritable bowel syndrome with constipation and chronic idiopathic constipation," *International Journal of General Medicine*, vol. Volume 14, pp. 1457–1468, 2021.

[17] M. Camilleri, "Diagnosis and treatment of irritable bowel syndrome," *JAMA*, vol. 325, no. 9, pp. 865–877, 2021.

[18] G. Fond, A. Loundou, N. Hamdani et al., "Anxiety and depression comorbidities in irritable bowel syndrome (IBS): a systematic review and meta-analysis," *European Archives of Psychiatry and Clinical Neuroscience*, vol. 264, no. 8, pp. 651–660, 2014.

[19] S. Elsenbruch, "Abdominal pain in irritable bowel syndrome: a review of putative psychological, neural and neuro-immune mechanisms," *Brain, Behavior, and Immunity*, vol. 25, no. 3, pp. 386–394, 2011.

[20] M. Friedrich, S. E. Grady, and G. C. Wall, "Effects of antidepressants in patients with irritable bowel syndrome and comorbid depression," *Clinical Therapeutics*, vol. 32, no. 7, pp. 1221–1233, 2010.

[21] C. Xie, Y. Tang, Y. Wang et al., "Efficacy and safety of antidepressants for the treatment of irritable bowel syndrome: a meta-analysis," *PLoS One*, vol. 10, no. 8, article e0127815, 2015.

[22] A. Kułak-Bejda, G. Bejda, and N. Waszkiewicz, "Antidepressants for irritable bowel syndrome—a systematic review," *Pharmacological Reports*, vol. 69, no. 6, pp. 1366–1379, 2017.

[23] D. J. Cangemi and B. E. Lacy, "Management of irritable bowel syndrome with diarrhea: a review of nonpharmacological and pharmacological interventions," *Therapeutic Advances in Gastroenterology*, vol. 12, article 1756284819878950, 2019.

[24] A. Abbasnezhad, R. Amani, E. Hajiani, P. Alavinejad, B. Cheraghian, and A. Ghadiri, "Effect of vitamin D on gastrointestinal symptoms and health-related quality of life in irritable bowel syndrome patients: a randomized double-blind clinical trial," *Neurogastroenterology and Motility*, vol. 28, no. 10, pp. 1533–1544, 2016.

[25] Y. Zhang, D. Y. Leung, B. N. Richers et al., "Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1," *The Journal of Immunology*, vol. 188, no. 5, pp. 2127–2135, 2012.

[26] B. H. Chung, B.-M. Kim, K. C. Doh et al., "Suppressive effect of 1α, 25-dihydroxyvitamin D3 on Th17-immune responses in kidney transplant recipients with tacrolimus-based immunosuppression," *Transplantation*, vol. 101, no. 7, pp. 1711–1719, 2017.

[27] R. V. Luthold, G. R. Fernandes, A. C. Franco-de-Moraes, L. G. D. Folchetti, and S. R. G. Ferreira, "Gut microbiota interactions with the immunomodulatory role of vitamin D in normal individuals," *Metabolism*, vol. 69, pp. 76–86, 2017.

[28] C. E. Williams, E. A. Williams, and B. M. Corfe, "Vitamin D supplementation in people with IBS has no effect on symptom severity and quality of life: results of a randomised controlled trial," *European Journal of Nutrition*, vol. 61, no. 1, pp. 299–308, 2022.

[29] Y. Khayyat and S. Attar, "Vitamin D deficiency in patients with irritable bowel syndrome: does it exist?," *Oman Medical Journal*, vol. 30, no. 2, pp. 115–118, 2015.

[30] J. Madden and J. Hunter, "A review of the role of the gut microflora in irritable bowel syndrome and the effects of probiotics," *British Journal of Nutrition*, vol. 88, no. S1, pp. s67–s72, 2002.

[31] I. Posserud, P. O. Stotzer, E. S. Björnsson, H. Abrahamsson, and M. Simrén, "Small intestinal bacterial overgrowth in patients with irritable bowel syndrome," *Gut*, vol. 56, no. 6, pp. 802–808, 2007.

[32] M. Pimentel, A. Lembo, W. D. Chey et al., "Rifaximin therapy for patients with irritable bowel syndrome without constipation," *New England Journal of Medicine*, vol. 364, no. 1, pp. 22–32, 2011.

[33] H. L. Koo, S. Sabounchi, D. B. Huang, and H. DuPont, "Rifaximin therapy of irritable bowel syndrome," *Clinical Medicine Insights: Gastroenterology*, vol. 5, pp. 31–41, 2012.

[34] A. Lembo, M. Pimentel, S. S. Rao et al., "Repeat treatment with rifaximin is safe and effective in patients with diarrhea-predominant irritable bowel syndrome," *Gastroenterology*, vol. 151, no. 6, pp. 1113–1121, 2016.

[35] C. Dai, C.-Q. Zheng, M. Jiang, X. Y. Ma, and L. J. Jiang, "Probiotics and irritable bowel syndrome," *World Journal of Gastroenterology*, vol. 19, no. 36, pp. 5973–5980, 2013.

[36] P. Moayyedi, A. C. Ford, N. J. Talley et al., "The efficacy of probiotics in the treatment of irritable bowel syndrome: a systematic review," *Gut*, vol. 59, no. 3, pp. 325–332, 2010.

[37] T. Didari, S. Mozaffari, S. Nikfar, and M. Abdollahi, "Effectiveness of probiotics in irritable bowel syndrome: updated systematic review with meta-analysis," *World Journal of Gastroenterology*, vol. 21, no. 10, pp. 3072–3084, 2015.

[38] L. V. McFarland and S. Dublin, "Meta-analysis of probiotics for the treatment of irritable bowel syndrome," *World Journal of Gastroenterology*, vol. 14, no. 17, pp. 2650–2661, 2008.

[39] N. Manabe, B. S. Wong, M. Camilleri, D. Burton, S. McKinzie, and A. R. Zinsmeister, "Lower functional gastrointestinal disorders: evidence of abnormal colonic transit in a 287 patient cohort," *Neurogastroenterology and Motility*, vol. 22, no. 3, p. 293, 2010.

[40] P. Clavé, M. Acalovschi, J. Triantafillidis et al., "Randomised clinical trial: otilonium bromide improves frequency of abdominal pain, severity of distention and time to relapse in patients with irritable bowel syndrome," *Alimentary Pharmacology & Therapeutics*, vol. 34, no. 4, pp. 432–442, 2011.

[41] A. C. Ford, N. J. Talley, B. M. Spiegel et al., "Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis," *BMJ*, vol. 337, no. nov13 2, p. a2313, 2008.

[42] M. Simrén and J. Tack, "New treatments and therapeutic targets for IBS and other functional bowel disorders," *Nature Reviews Gastroenterology & Hepatology*, vol. 15, no. 10, pp. 589–605, 2018.

[43] W. D. Chey, A. J. Lembo, B. J. Lavins et al., "Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety," *American College of Gastroenterology*, vol. 107, no. 11, pp. 1702–1712, 2012.

[44] D. A. Drossman, W. D. Chey, J. F. Johanson et al., "Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome–results of two randomized, placebo-controlled studies," *Alimentary Pharmacology & Therapeutics*, vol. 29, no. 3, pp. 329–341, 2009.

[45] W. D. Chey, A. J. Lembo, and D. P. Rosenbaum, "Tenapanor treatment of patients with constipation-predominant irritable bowel syndrome: a phase 2, randomized, placebo-controlled efficacy and safety trial," *The American Journal of Gastroenterology*, vol. 112, no. 5, pp. 763–774, 2017.

[46] E. Corazziari, "Role of opioid ligands in the irritable bowel syndrome," *Canadian Journal of Gastroenterology*, vol. 13, suppl a, pp. 71A–75A, 1999.

[47] M. Camilleri, A. Lembo, and D. A. Katzka, "Opioids in gastroenterology: treating adverse effects and creating therapeutic benefits," *Clinical Gastroenterology and Hepatology*, vol. 15, no. 9, pp. 1338–1349, 2017.

[48] H. U. De Schepper, F. Cremonini, M. I. Park, and M. Camilleri, "Opioids and the gut: pharmacology and current clinical experience," *Neurogastroenterology and Motility*, vol. 16, no. 4, pp. 383–394, 2004.

[49] L. Chen, S. J. Ilham, and B. Feng, "Pharmacological approach for managing pain in irritable bowel syndrome: a review article," *Anesthesiology and Pain Medicine*, vol. 7, no. 2, p. e42747, 2017.

[50] A. W. Mangel, J. D. Bornstein, L. R. Hamm et al., "Clinical trial: asimadoline in the treatment of patients with irritable bowel syndrome," *Alimentary Pharmacology & Therapeutics*, vol. 28, no. 2, pp. 239–249, 2008.

[51] C. Stasi, M. Bellini, G. Bassotti, C. Blandizzi, and S. Milani, "Serotonin receptors and their role in the pathophysiology and therapy of irritable bowel syndrome," *Techniques in Coloproctology*, vol. 18, no. 7, pp. 613–621, 2014.

[52] J. Johanson, "Options for patients with irritable bowel syndrome: contrasting traditional and novel serotonergic therapies," *Neurogastroenterology and Motility*, vol. 16, no. 6, pp. 701–711, 2004.

[53] E. Dimidi and K. Whelan, "Food supplements and diet as treatment options in irritable bowel syndrome," *Neurogastroenterology and Motility*, vol. 32, no. 8, article e13951, 2020.

[54] A. Halpert, "Irritable bowel syndrome: patient-provider interaction and patient education," *Journal of Clinical Medicine*, vol. 7, no. 1, p. 3, 2018.

[55] G. Ringström, S. Störsrud, I. Posserud, S. Lundqvist, B. Westman, and M. Simrén, "Structured patient education is superior to written information in the management of patients with irritable bowel syndrome: a randomized controlled study," *European Journal of Gastroenterology & Hepatology*, vol. 22, no. 4, pp. 420–428, 2010.

[56] G. Ringström, S. Störsrud, and M. Simrén, "A comparison of a short nurse-based and a long multidisciplinary version of structured patient education in irritable bowel syndrome," *European Journal of Gastroenterology & Hepatology*, vol. 24, no. 8, pp. 950–957, 2012.

[57] M. Williams, Y. Barclay, L. Harper, C. Marchant, L. Seamark, and M. Hickson, "Feasibility, acceptability and cost efficiency of using webinars to deliver first-line patient education for people with irritable bowel syndrome as part of a dietetic-led gastroenterology service in primary care," *Journal of Human Nutrition and Dietetics*, vol. 33, no. 6, pp. 758–766, 2020.

[58] L. Chang, "The role of stress on physiologic responses and clinical symptoms in irritable bowel syndrome," *Gastroenterology*, vol. 140, no. 3, pp. 761–765.e5, 2011.

[59] C. J. Black, E. R. Thakur, L. A. Houghton, E. M. M. Quigley, P. Moayyedi, and A. C. Ford, "Efficacy of psychological therapies for irritable bowel syndrome: systematic review and network meta-analysis," *Gut*, vol. 69, no. 8, pp. 1441–1451, 2020.

[60] I. L. Zijdenbos, N. J. de Wit, G. J. van der Heijden, G. Rubin, A. O. Quartero, and Cochrane IBD Group, "Psychological treatments for the management of irritable bowel syndrome," *Cochrane Database of Systematic Reviews*, 2009, https://www.cochrane.org/CD006442/IBD_psychological-treatments-for-the-management-of-irritable-bowel-syndrome.

[61] W. S. Nanayakkara, P. M. Skidmore, L. O'Brien, T. J. Wilkinson, and R. B. Gearry, "Efficacy of the low FODMAP diet for treating irritable bowel syndrome: the evidence to date," *Clinical and Experimental Gastroenterology*, vol. 9, pp. 131–142, 2016.

[62] S. Magge and A. Lembo, "Low-FODMAP diet for treatment of irritable bowel syndrome," *Gastroenterology & Hepatology*, vol. 8, no. 11, pp. 739–745, 2012.

[63] A. C. Ford, B. M. Spiegel, N. J. Talley, and P. Moayyedi, "Small intestinal bacterial overgrowth in irritable bowel syndrome: systematic review and meta-analysis," *Clinical Gastroenterology and Hepatology*, vol. 7, no. 12, pp. 1279–1286, 2009.

[64] S. J. Shepherd and P. R. Gibson, "Fructose malabsorption and symptoms of irritable bowel syndrome: guidelines for effective dietary management," *Journal of the American Dietetic Association*, vol. 106, no. 10, pp. 1631–1639, 2006.

[65] D. K. Ong, S. B. Mitchell, J. S. Barrett et al., "Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome," *Journal of Gastroenterology and Hepatology*, vol. 25, no. 8, pp. 1366–1373, 2010.

[66] E. P. Halmos, V. A. Power, S. J. Shepherd, P. R. Gibson, and J. G. Muir, "A diet low in FODMAPs reduces symptoms of irritable bowel syndrome," *Gastroenterology*, vol. 146, no. 1, pp. 67–75.e5, 2014.

[67] S. S. C. Rao, S. Yu, and A. Fedewa, "Systematic review: dietary fibre and FODMAP-restricted diet in the management of constipation and irritable bowel syndrome," *Alimentary Pharmacology & Therapeutics*, vol. 41, no. 12, pp. 1256–1270, 2015.

[68] E. P. Halmos, C. T. Christophersen, A. R. Bird, S. J. Shepherd, P. R. Gibson, and J. G. Muir, "Diets that differ in their FODMAP content alter the colonic luminal microenvironment," *Gut*, vol. 64, no. 1, pp. 93–100, 2015.

[69] E. Altobelli, V. Del Negro, P. Angeletti, and G. Latella, "Low-FODMAP diet improves irritable bowel syndrome symptoms: a meta-analysis," *Nutrients*, vol. 9, no. 9, p. 940, 2017.

[70] M. El-Salhy, S. O. Ystad, T. Mazzawi, and D. Gundersen, "Dietary fiber in irritable bowel syndrome (review)," *International Journal of Molecular Medicine*, vol. 40, no. 3, pp. 607–613, 2017.

[71] N. Nagarajan, A. Morden, D. Bischof et al., "The role of fiber supplementation in the treatment of irritable bowel syndrome: a systematic review and meta-analysis," *European Journal of Gastroenterology & Hepatology*, vol. 27, no. 9, pp. 1002–1010, 2015.

[72] K. Tillisch, "Complementary and alternative medicine for functional gastrointestinal disorders," *Gut*, vol. 55, no. 5, pp. 593–596, 2006.

[73] A. J. Lembo, L. Conboy, J. M. Kelley et al., "A treatment trial of acupuncture in IBS patients," *The American Journal of Gastroenterology*, vol. 104, no. 6, pp. 1489–1497, 2009.

[74] A. Forbes, S. Jackson, C. Walter, S. Quraishi, M. Jacyna, and M. Pitcher, "Acupuncture for irritable bowel syndrome: a blinded placebo-controlled trial," *World Journal of Gastroenterology*, vol. 11, no. 26, pp. 4040–4044, 2005.

[75] E. W. L. Manheimer, K. Cheng, S. M. Li, X. Shen, B. M. Berman, and L. Lao, "Acupuncture for irritable bowel syndrome: systematic review and meta-analysis," *The American Journal of Gastroenterology*, vol. 107, no. 6, pp. 835–847, 2012.

[76] G.-Q. Chao and S. Zhang, "Effectiveness of acupuncture to treat irritable bowel syndrome: a meta-analysis," *World Journal of Gastroenterology*, vol. 20, no. 7, pp. 1871–1877, 2014.

[77] H. T. H. Mac Pherson, J. M. Bland, K. Bloor et al., "Acupuncture for irritable bowel syndrome: primary care based pragmatic randomised controlled trial," *BMC Gastroenterology*, vol. 12, no. 1, 2012.

[78] H. MacPherson, H. Tilbrook, D. Agbedjro, H. Buckley, C. Hewitt, and C. Frost, "Acupuncture for irritable bowel syndrome: 2-year follow-up of a randomised controlled trial," *Acupuncture in Medicine*, vol. 35, no. 1, pp. 17–23, 2017.

[79] D. Qin, Q. F. Tao, S. L. Huang, M. Chen, and H. Zheng, "Eluxadoline versus antispasmodics in the treatment of irritable bowel syndrome: an adjusted indirect treatment comparison meta-analysis," *Frontiers in Pharmacology*, vol. 13, p. 757969, 2022.

[80] J. Daniluk, E. Malecka-Wojciesko, B. Skrzydlo-Radomanska, and G. Rydzewska, "The efficacy of mebeverine in the treatment of irritable bowel syndrome-a systematic review," *Journal of Clinical Medicine*, vol. 11, no. 4, p. 1044, 2022.

[81] H. A. Adeola, S. Papagerakis, and P. Papagerakis, "Systems biology approaches and precision oral health: a circadian clock perspective," *Frontiers in Physiology*, vol. 10, p. 399, 2019.

[82] M. Murakami and P. Tognini, "The circadian clock as an essential molecular link between host physiology and microorganisms," *Frontiers in Cellular and Infection Microbiology*, vol. 9, p. 469, 2020.

[83] H. Duboc, B. Coffin, and L. Siproudhis, "Disruption of circadian rhythms and gut motility: an overview of underlying mechanisms and associated pathologies," *Journal of Clinical Gastroenterology*, vol. 54, no. 5, pp. 405–414, 2020.

[84] F. Bishehsari, R. M. Voigt, and A. Keshavarzian, "Circadian rhythms and the gut microbiota: from the metabolic syndrome to cancer," *Nature Reviews. Endocrinology*, vol. 16, no. 12, pp. 731–739, 2020.

[85] J. Talbot, P. Hahn, L. Kroehling, H. Nguyen, D. Li, and D. R. Littman, "Feeding-dependent VIP neuron-ILC3 circuit regulates the intestinal barrier," *Nature*, vol. 579, no. 7800, pp. 575–580, 2020.

[86] D. Zheng, K. Ratiner, and E. Elinav, "Circadian influences of diet on the microbiome and immunity," *Trends in Immunology*, vol. 41, no. 6, pp. 512–530, 2020.

[87] Y. Kolben, S. Weksler-Zangen, and Y. Ilan, "Adropin as a potential mediator of the metabolic system-autonomic nervous system-chronobiology axis: implementing a personalized signature-based platform for chronotherapy," *Obesity Reviews*, vol. 22, no. 2, article e13108, 2021.

[88] K. Tamura, H. Sasaki, K. Shiga, H. Miyakawa, and S. Shibata, "The timing effects of soy protein intake on mice gut microbiota," *Nutrients*, vol. 12, p. 87, 2019.

[89] J. Yin, Y. Li, H. Han et al., "Administration of exogenous melatonin improves the diurnal rhythms of the gut microbiota in mice fed a high-fat diet," *Msystems*, vol. 5, no. 3, 2020.

[90] S. J. Bowers, F. Vargas, A. González et al., "Repeated sleep disruption in mice leads to persistent shifts in the fecal microbiome and metabolome," *PLoS One*, vol. 15, no. 2, article e0229001, 2020.

[91] F. Vernia, M. Di Ruscio, A. Ciccone et al., "Sleep disorders related to nutrition and digestive diseases: a neglected clinical condition," *International Journal of Medical Sciences*, vol. 18, no. 3, pp. 593–603, 2021.

[92] A. C. Reynolds, J. L. Paterson, S. A. Ferguson, D. Stanley, K. P. Wright Jr., and D. Dawson, "The shift work and health research agenda: considering changes in gut microbiota as a pathway linking shift work, sleep loss and circadian misalignment, and metabolic disease," *Sleep Medicine Reviews*, vol. 34, pp. 3–9, 2017.

[93] H. Mortas, S. Bilici, and T. Karakan, "The circadian disruption of night work alters gut microbiota consistent with elevated risk for future metabolic and gastrointestinal pathology," *Chronobiology International*, vol. 37, no. 7, pp. 1067–1081, 2020.

[94] M. Yamaguchi, K. Kotani, K. Tsuzaki et al., "Circadian rhythm genes CLOCK and PER3 polymorphisms and morning gastric motility in humans," *PLoS One*, vol. 10, no. 3, article e0120009, 2015.

[95] Y. Ilan, "Second-generation digital health platforms: placing the patient at the center and focusing on clinical outcomes," *Frontiers in Digital Health*, vol. 2, p. 569178, 2020.

[96] J. J. Sung and N. C. Poon, "Artificial intelligence in gastroenterology: where are we heading?," *Frontiers in Medicine*, vol. 14, no. 4, pp. 511–517, 2020.

[97] R. A. Sutton and P. Sharma, "Overcoming barriers to implementation of artificial intelligence in gastroenterology," *Best Practice & Research. Clinical Gastroenterology*, vol. 52-53, p. 101732, 2021.

[98] R. W. Stidham, "Artificial intelligence for understanding imaging, text, and data in gastroenterology," *Gastroenterology & Hepatology*, vol. 16, no. 7, pp. 341–349, 2020.

[99] J. S. Cao, Z. Y. Lu, M. Y. Chen et al., "Artificial intelligence in gastroenterology and hepatology: status and challenges," *World Journal of Gastroenterology*, vol. 27, no. 16, pp. 1664–1690, 2021.

[100] C. Melidis, S. L. Denham, and M. E. Hyland, "A test of the adaptive network explanation of functional disorders using a machine learning analysis of symptoms," *Biosystems*, vol. 165, pp. 22–30, 2018.

[101] A. Åkerman, S. Månsson, F. T. Fork et al., "Computational postprocessing quantification of small bowel motility using magnetic resonance images in clinical practice: an initial experience," *Journal of Magnetic Resonance Imaging*, vol. 44, no. 2, pp. 277–287, 2016.

[102] A. J. Rafferty, R. Hall, and C. S. Johnston, "A novel mobile app (Heali) for disease treatment in participants with irritable bowel syndrome: randomized controlled pilot trial," *Journal of Medical Internet Research*, vol. 23, no. 3, article e24134, 2021.

[103] N. Hurvitz, H. Azmanov, A. Kesler, and Y. Ilan, "Establishing a second-generation artificial intelligence-based system for improving diagnosis, treatment, and monitoring of patients with rare diseases," *European Journal of Human Genetics*, vol. 29, no. 10, pp. 1485–1490, 2021.

[104] Y. Ilan, "Improving global healthcare and reducing costs using second-generation artificial intelligence-based digital pills: a market disruptor," *International Journal of Environmental Research and Public Health*, vol. 18, no. 2, p. 811, 2021.

[105] Y. Ilan, "Overcoming compensatory mechanisms toward chronic drug administration to ensure long-term, sustainable beneficial effects," *Molecular Therapy-Methods & Clinical Development*, vol. 18, pp. 335–344, 2020.

[106] Y. Ilan, "Overcoming randomness does not rule out the importance of inherent randomness for functionality," *Journal of Biosciences*, vol. 44, no. 6, 2019.

[107] M. Kyriazis, "Practical applications of chaos theory to the modulation of human ageing: nature prefers chaos to regularity," *Biogerontology*, vol. 4, no. 2, pp. 75–90, 2003.

[108] Y. Ilan and Z. Spigelman, "Establishing patient-tailored variability-based paradigms for anti-cancer therapy: using the inherent trajectories which underlie cancer for overcoming drug resistance," *Cancer Treatment and Research Communications*, vol. 25, article 100240, 2020.

[109] A. Kenig and Y. Ilan, "A personalized signature and chronotherapy-based platform for improving the efficacy of sepsis treatment," *Frontiers in Physiology*, vol. 10, p. 1542, 2019.

[110] A. Kessler, S. Weksler-Zangen, and Y. Ilan, "Role of the immune system and the circadian rhythm in the pathogenesis of chronic pancreatitis: establishing a personalized signature for improving the effect of immunotherapies for chronic pancreatitis," *Pancreas*, vol. 49, no. 8, pp. 1024–1032, 2020.

[111] T. Khoury and Y. Ilan, "Introducing patterns of variability for overcoming compensatory adaptation of the immune system to immunomodulatory agents: a novel method for improving clinical response to anti-TNF therapies," *Frontiers in Immunology*, vol. 10, p. 2726, 2019.

[112] H. Azmanov, E. L. Ross, and Y. Ilan, "Establishment of an individualized chronotherapy, autonomic nervous system, and variability-based dynamic platform for overcoming the loss of response to analgesics," *Pain Physician*, vol. 24, no. 3, pp. 243–252, 2021.

[113] T. Khoury and Y. Ilan, "Platform introducing individually tailored variability in nerve stimulations and dietary regimen to prevent weight regain following weight loss in patients with obesity," *Obesity Research & Clinical Practice*, vol. 15, no. 2, pp. 114–123, 2021.

[114] Y. Ishay, Y. Kolben, A. Kessler, and Y. Ilan, "Role of circadian rhythm and autonomic nervous system in liver function: a hypothetical basis for improving the management of hepatic encephalopathy," *American Journal of Physiology. Gastrointestinal and Liver Physiology*, vol. 321, no. 4, pp. G400–G412, 2021.

[115] A. Kenig, Y. Kolben, R. Asleh, O. Amir, and Y. Ilan, "Improving diuretic response in heart failure by implementing a patient-tailored variability and chronotherapy-guided algorithm," *Frontiers in Cardiovascular Medicine*, vol. 8, article 695547, 2021.

[116] A. Potruch, S. T. Khoury, and Y. Ilan, "The role of chronobiology in drug-resistance epilepsy: the potential use of a variability and chronotherapy-based individualized platform for improving the response to anti-seizure drugs," *Seizure*, vol. 80, pp. 201–211, 2020.

[117] Y. Ilan, "Why targeting the microbiome is not so successful: can randomness overcome the adaptation that occurs following gut manipulation?," *Clinical and Experimental Gastroenterology*, vol. Volume 12, pp. 209–217, 2019.

[118] R. Gelman, A. Bayatra, A. Kessler, A. Schwartz, and Y. Ilan, "Targeting SARS-CoV-2 receptors as a means for reducing infectivity and improving antiviral and immune response: an algorithm-based method for overcoming resistance to antiviral agents," *Emerging Microbes & Infections*, vol. 9, no. 1, pp. 1397–1406, 2020.

[119] E. Forkosh, A. Kenig, and Y. Ilan, "Introducing variability in targeting the microtubules: review of current mechanisms and future directions in colchicine therapy," *Pharmacology Research & Perspectives*, vol. 8, no. 4, article e00616, 2020.

[120] Y. Ilan, "Microtubules: from understanding their dynamics to using them as potential therapeutic targets," *Journal of Cellular Physiology*, vol. 234, no. 6, pp. 7923–7937, 2019.

[121] Y. Ilan, "Randomness in microtubule dynamics: an error that requires correction or an inherent plasticity required for normal cellular function?," *Cell Biology International*, vol. 43, no. 7, pp. 739–748, 2019.

[122] Y. Ilan, "β-Glycosphingolipids as mediators of both inflammation and immune tolerance: a manifestation of randomness in biological systems," *Frontiers in Immunology*, vol. 10, p. 1143, 2019.

[123] A. D. Leino, E. C. King, W. Jiang et al., "Assessment of tacrolimus intrapatient variability in stable adherent transplant recipients: establishing baseline values," *American Journal of Transplantation*, vol. 19, no. 5, pp. 1410–1420, 2019.

[124] I. Gueta, N. Markovits, H. Yarden-Bilavsky et al., "Intrapatient variability in tacrolimus trough levels after solid organ transplantation varies at different postoperative time periods," *American Journal of Transplantation*, vol. 19, no. 2, p. 611, 2019.

[125] A. Del Bello, N. Congy-Jolivet, M. Danjoux et al., "High tacrolimus intra-patient variability is associated with graft rejection, and de novo donor-specific antibodies occurrence after liver transplantation," *World Journal of Gastroenterology*, vol. 24, no. 16, pp. 1795–1802, 2018.

[126] Y. Ilan, "Generating randomness: making the most out of disordering a false order into a real one," *Journal of Translational Medicine*, vol. 17, no. 1, p. 49, 2019.

[127] F. Conti, F. Atzeni, L. Massaro et al., "The influence of comorbidities on the efficacy of tumour necrosis factor inhibitors, and the effect of tumour necrosis factor inhibitors on comorbidities in rheumatoid arthritis: report from a National Consensus Conference," *Rheumatology*, vol. 57, Supplement_7, pp. vii11–vii22, 2018.

[128] W. J. Weiner, W. C. Koller, S. Perlik, P. A. Nausieda, and H. L. Klawans, "Drug holiday and management of Parkinson disease," *Neurology*, vol. 30, no. 12, pp. 1257–1261, 1980.

[129] J. S. Labus, J. D. Van Horn, A. Gupta et al., "Multivariate morphological brain signatures predict patients with chronic abdominal pain from healthy control subjects," *Pain*, vol. 156, no. 8, pp. 1545–1554, 2015.

[130] M. El-Haj, D. Kanovitch, and Y. Ilan, "Personalized inherent randomness of the immune system is manifested by an individualized response to immune triggers and immunomodulatory therapies: a novel platform for designing personalized immunotherapies," *Immunologic Research*, vol. 67, no. 4-5, pp. 337–347, 2019.

[131] Y. Ishay, A. Potruch, A. Schwartz et al., "A digital health platform for assisting the diagnosis and monitoring of COVID-19 progression: an adjuvant approach for augmenting the antiviral response and mitigating the immune-mediated target organ damage," *Biomedicine & Pharmacotherapy*, vol. 143, p. 112228, 2021.

[132] E. D. Shah, L. Chang, J. K. Salwen-Deremer et al., "Contrasting clinician and insurer perspectives to managing irritable bowel syndrome: multilevel modeling analysis," *The American Journal of Gastroenterology*, vol. 116, no. 4, pp. 748–757, 2021.