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Review

Ingestible electronic capsules for *in situ* sensing of diverse biomarkers

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THE BIGGER PICTURE Electronic capsules have emerged as an important tool for the diagnosis of gastrointestinal (GI) diseases in recent years. Technologies such as capsule endoscopy, temperature-sensing capsules, and pH-sensing capsules have successfully transitioned from laboratory research to clinical application. However, the diagnostic capability of these capsules is often constrained by their primary reliance on physical parameters, because such parameters inherently lack the specificity required for the precision diagnosis of GI diseases. With the deep convergence of microelectronics, biosensing technologies, and medical sciences, the role of electronic capsules in disease diagnostics is entering a new developmental stage. These devices are evolving from simple observers of physical parameters into precise diagnostic platforms capable of *in situ* molecular recognition. This review systematically summarizes key technological advances in biochemical biomarker sensing of electronic capsules, aiming to provide a comprehensive and forward-looking perspective on their application in precision diagnostics.

SUMMARY

Electronic capsules have emerged as a transformative technology in the diagnosis of gastrointestinal (GI) diseases, achieving remarkable progress over the past three decades. Although existing capsule systems based on the monitoring of physical parameters have been successfully translated into clinical practice, they remain limited by insufficient disease specificity, constraining their utility for precision diagnosis of GI disorders. Next-generation electronic capsules, by incorporating biochemical biomarker-sensing capabilities, are poised to significantly enhance diagnostic accuracy and accelerate the transition of the field toward molecular-level, *in situ* detection. Moreover, the growing recognition of the gut microbiota as a critical predictor of systemic diseases positions electronic capsules as a revolutionary platform for dynamic, whole-body health assessment. This review systematically explores the applications and limitations of electronic capsules in monitoring physical parameters and summarizes recent technological advances in biochemical biomarker detection, highlighting the transformative role of electronic capsules in precision medicine and their prospects.

INTRODUCTION

In clinical practice, the diagnosis of gastrointestinal (GI) diseases primarily relies on endoscopic and imaging techniques, such as X-ray, computed tomography (CT), and magnetic resonance imaging (MRI), as well as analyses of body fluid samples, including blood, urine, and feces.[1,2] Endoscopic and imaging approaches provide essential structural and functional insights into the GI

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mucosa and internal architecture, offering critical support for initial disease identification and localization. However, endoscopy is inherently invasive and limited in anatomical coverage, particularly within the small intestine, which remains difficult to access and monitor consistently, whereas external imaging, although non-invasive, suffers from constrained spatial resolution, often failing to detect early or subtle lesions.[3,4] Moreover, although advanced endoscopic technologies, such as narrow-band imaging and fluorescence endoscopy, have already begun to integrate functional and molecular-level information,[5] mainstream diagnostic approaches still primarily rely on the interpretation of tissue morphological features. Therefore, while mainstream imaging modalities provide intuitive anatomical visualization, their sensitivity to pathological changes at the molecular level remains limited. In contrast, body-fluid analyses offer a non-invasive and operationally convenient means of capturing pathological signals from the GI tract through detection of nucleic acids, proteins, and metabolites secreted into the systemic circulation. Nevertheless, these circulating biomarkers are frequently subjected to dilution, metabolic degradation, and systemic noise, thereby diminishing their spatiotemporal relevance to local lesions and limiting their utility in early screening or precise *in situ* disease assessment.[6,7]

Electronic capsule technologies, as rapidly evolving non-invasive GI-interfacing platforms, offer the unique capability of direct contact with luminal contents and real-time *in situ* monitoring, thereby overcoming the inherent limitations of conventional diagnostic modalities.[8,9] Since the first wireless capsule endoscope was approved by the Food and Drug Administration (FDA) in 2001, capsules designed to measure physical parameters such as pH, temperature, and pressure have been successively developed and approved for clinical use. Representative sensing-oriented ingestible capsule devices that have been developed and approved by the FDA, ranging from early-generation to recent innovations, are summarized in Table 1. These devices have demonstrated substantial diagnostic value in evaluating structural and functional abnormalities of the GI tract.[10,11] However, their dependence on physical parameters, which generally lack biochemical specificity, has constrained their utility in precision diagnostics.[10,12,13] Since 2010, considerable research has focused on endowing electronic capsules with the capacity for *in situ* biochemical sensing (Figure 1). Notably, the HemoPill developed by Ovesco was the first capsule to be tested in human volunteers in 2016, demonstrating the capability to detect blood in the GI tract.[14] In 2023, PillSense became the first capsule endoscope approved by the FDA for blood detection, marking a pivotal milestone in the clinical translation of biomarker-sensing capsule technologies.

It is increasingly recognized that the GI tract functions not only in digestion but also in immune regulation, metabolic homeostasis, endocrine signaling, and neurophysiological communication. As a central hub in systemic disease pathophysiology, the GI tract offers a valuable window for diagnostic insights.[15–17] By integrating sensitive biosensors with miniaturized electronics, next-generation electronic capsules enable specific detection of systemic conditions, including neurological, cardiovascular, metabolic, and oncological diseases, thus establishing a new paradigm in non-invasive precision medicine.

At present, several high-quality reviews have been published in the field of electronic capsules, focusing respectively on macro-scale engineering challenges[10]; the broad application landscape in diagnosis, therapy, and sampling[12]; as well as end-to-end design guidelines.[8] These works have collectively provided a broad theoretical framework for the development of ingestible electronic capsule technologies. However, when sensing is considered a central function, existing discussions have primarily centered on imaging techniques and physical biomarker detection,[5] whereas the sensing of biochemical biomarkers has largely been limited to preliminary summaries or to discussions framed from clinical and engineering perspectives with a focused thematic orientation.[5,8,10,12,18,19] To address this critical gap, this review systematically outlines the developmental trajectory of sensing-oriented ingestible capsules, for the first time elucidating their transition from physical-parameter detectors to platforms capable of *in situ* molecular recognition. We further examine structural and functional alterations of the GI tract in systemic diseases, highlight key biochemical biomarkers, and focus on recent advances in sensing mechanisms and capsule-based diagnostics. Finally, we discuss the translational potential and future directions of these platforms as emerging tools for non-invasive molecular diagnostics. Given the interdisciplinary nature of ingestible capsule technologies, key terminology used in this review is defined in Table S1.

THE GI TRACT AS A DIAGNOSTIC WINDOW FOR SYSTEMIC DISEASES

In recent years, increasing evidence has revealed that the GI tract is not only a central organ for digestion and nutrient absorption but also a critical hub for immune modulation, metabolic regulation, and neural communication, positioning it as a key regulator of systemic health.[15,16] The integrity of the mucosal barrier, enteroendocrine signaling, enteric nervous system, and gut microbiota jointly contribute to maintaining systemic health.[20] In particular, the gut microbiome influences multiple organs through a network of inter-organ axes, including the gut-brain, gut-liver, gut-lung, gut-heart, and gut-kidney axes, positioning the GI tract as a promising biological window for systemic disease diagnostics (Figure 2).[21,22]

Physical biomarkers

Given that the GI tract is a central hub for multi-system interactions, the occurrence of various systemic diseases is often accompanied by GI complications.[23,24] For example, diabetes is often associated with symptoms such as gastroparesis, constipation, and diarrhea.[25] Parkinson's disease is frequently accompanied by symptoms such as dysphagia and delayed gastric emptying.[26] In addition, gastroesophageal reflux disease (GERD), nausea, vomiting, bloating, dyspepsia, and cholecystitis are also common GI complications.[27] The occurrence of these symptoms generally indicates certain structural and functional abnormalities, which can be categorized as morphological changes, local temperature fluctuations, electrophysiological activity abnormalities, GI motility disorders, and GI pressure variations. Morphological changes usually indicate structural abnormalities of the GI tract and provide direct pathological

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Table 1. FDA-approved first-generation and recently developed sensing-oriented ingestible capsules

FDA classification name (product code)	Device name	Submission number	Requester/applicant	Biomarkers	Unique features	Decision (date)
System, Imaging, Gastrointestinal, Wireless, Capsule (NEZ)	GIVEN DIAGNOSTIC IMAGING SYSTEM	DEN010002 K010312	Given Imaging	morphology	first-generation small bowel capsule endoscopy system	granted (08/01/2001)
System, Imaging, Gastrointestinal, Wireless, Capsule (NEZ)	PillCam SB?? 3 capsule endoscopy system	K211684	Given Imaging (Medtronic)	morphology	adaptive frame rate technology suspected blood indicator function	substantially equivalent (08/27/2021)
System, Imaging, Gastrointestinal, Wireless, Capsule (NEZ)	NaviCam Small Bowel Capsule Endoscopy System	K221590	ANKON Technologies	morphology	clinically equivalent diagnostic performance to PillCam SB3	substantially equivalent (12/02/2022)
System, Imaging, Gastrointestinal, Wireless, Capsule (NEZ)	PillCam SB 3 capsule endoscopy system	K230991	Given Imaging (Medtronic)	morphology	cloud-based remote data management platform	substantially equivalent (06/30/2023)
System, Imaging, Gastrointestinal, Wireless, Capsule (NEZ)	NaviCam Small Bowel Capsule Endoscopy System with NaviCam SB Capsule and NaviCam Tether	K233229	AnX Robotica Corporation	morphology	combined esophagus and small bowel examination via tether accessory	substantially equivalent (01/05/2024)
System, Imaging, Gastrointestinal, Wireless, Capsule (NEZ)	CapsoCam (SV-1)	K151635	CapsoVision	morphology	first 360° panoramic imaging with four lateral cameras	substantially equivalent (02/09/2016)
System, Imaging, Gastrointestinal, Wireless, Capsule (NEZ)	CapsoCam Plus (SV-3) Capsule Endoscopy System	K192662	CapsoVision	morphology	cloud-based software platform	substantially equivalent (02/14/2020)
System, Imaging, Gastrointestinal, Wireless, Capsule (NEZ)	CapsoCam Plus (SV-3) Capsule Endoscopy System	K242643	CapsoVision	morphology	expanded indication for patients aged 2 years and older	substantially equivalent (12/04/2024)
System, Imaging, Esophageal, Wireless, Capsule (NSI)	GIVEN DIAGNOSTIC SYSTEM WITH M2A ESO CAPSULE	K041149	GIVEN IMAGING	morphology	first esophageal imaging capsule	substantially equivalent (10/25/2004)
Colon Capsule Imaging System (PGD)	GIVEN PILLCAM COLON 2 CAPSULE ENDOSCOPY SYSTEM	DEN120023 K123666	Given Imaging	morphology	first colon-imaging capsule	granted (01/29/2014)
Electrode, Ph, Stomach (FFT)	BRAVO PH MONITORING SYSTEM	K002028	ENDONETICS	pH	first catheter-free wireless pH monitoring system	substantially equivalent (09/29/2000)
Gastrointestinal Motility System, Capsule (NYV)	SMARTPILL GI MONITORING SYSTEM	K053547	THE SMARTPILL CORPORATION	pH, pressure, temperature	first wireless motility monitoring capsule with pH, pressure, and temperature sensing	substantially equivalent (07/18/2006)

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Table 1. *Continued*

FDA classification name (product code)	Device name	Submission number	Requester/applicant	Biomarkers	Unique features	Decision (date)
Gastrointestinal Motility System, Capsule (NYV)	SMARTPILL GI MONITORING SYSTEM, VERSION 2.0	K092342	THE SMARTPILL CORPORATION	pH, pressure, temperature	expanded motility indications to include chronic constipation	substantially equivalent (10/30/2009)
Blood Detection Capsule	Pill Sense System	DEN220065	Enterasense	blood	first capsule for blood detection	granted (02/24/2023)

These include GI capsule endoscopes; 360° panoramic capsule endoscopes; esophageal capsule endoscopes; colon capsule endoscopes; pH-monitoring capsules; multimodal capsules capable of sensing pH, pressure, and temperature; as well as blood-sensing capsules. Notably, while PillSense is the first FDA-approved capsule for blood detection, the HemoPill developed by Ovesco was the first to successfully demonstrate this capability in human subjects.[14]

information, especially for the identification of mucosal surface lesions.[28] Common examples include erosion, ulcers, and polyps, which can be visually observed and preliminarily assessed by endoscopy.[29] GI temperature is jointly maintained by local metabolic activity, blood circulation, and neurohumoral regulatory mechanisms.[30] Under inflammatory conditions, enhanced local metabolism and increased blood flow can lead to temperature elevation at affected sites within the GI tract.[30–32] Conversely, in cases of circulatory disturbance or reduced local metabolism, local GI temperature may decrease, which is commonly observed in diseases such as intestinal ischemia and hypothyroidism.[33,34] GI electrophysiological signals are closely associated with GI motility and subsequently regulate the dynamic fluctuations of intraluminal pressure.[35,36] Therefore, diseases related to motility disorders, such as gastroparesis, functional dyspepsia, and diabetes, often present with abnormalities across multiple physical domains, including electrophysiological activity, motility, and intraluminal pressure.[37,38] In addition, neurological disorders such as Parkinson's disease, autism, and stroke can affect enteric nervous system (ENS) function through the gut-brain axis, leading to disturbances in GI electrical and motor function.[39,40] In general, these physical characteristics provide important physiological information, but their diagnostic specificity is limited. This means that the detection of a single physical parameter is often insufficient to determine a specific disease type and can only offer preliminary diagnostic guidance. In contrast, molecular-level biomarkers exhibit high specificity; can reveal pathological mechanisms; and are applicable to early screening, disease classification, and therapeutic response prediction across a wide range of conditions.

Chemical biomarkers

pH

The GI tract displays a pronounced dynamic pH gradient that is essential for the physiological functions of the entire digestive system. This gradient begins in the stomach, where parietal cells, regulated by neural, endocrine, and paracrine signals, secrete hydrochloric acid and maintain a mean intragastric pH of about 2.7, with individual instantaneous fluctuations ranging from 1.0 to 8.0.[41] A low-pH environment facilitates food digestion and absorption, clearance of pathogens, and mucosal self-protection.[42] After chyme enters the small intestine, pancreatic and biliary secretions buffer the acidity, bringing the pH in the proximal small intestine to a range of approximately 5.9–6.3. The pH then progressively increases to 7.4–7.8 as it moves distally through the intestine. Upon entering the large intestine, the pH typically decreases again due to bacterial fermentation and the production of short-chain fatty acids, resulting in an average pH of 6.5, with fluctuations between 5.0 and 8.0.[43] When the regulatory pathways are disrupted or the mucosal structure is damaged, an imbalance in pH throughout the GI tract can occur. For example, excessive excitation of the vagus nerve can enhance acetylcholine release, thereby promoting parietal cell activity and leading to gastric acid hypersecretion.[44] In contrast, reduced mucosal renewal capacity or structural damage may result in hyposecretion of gastric acid, which is commonly observed in atrophic gastritis and *Helicobacter pylori* infection.[45]

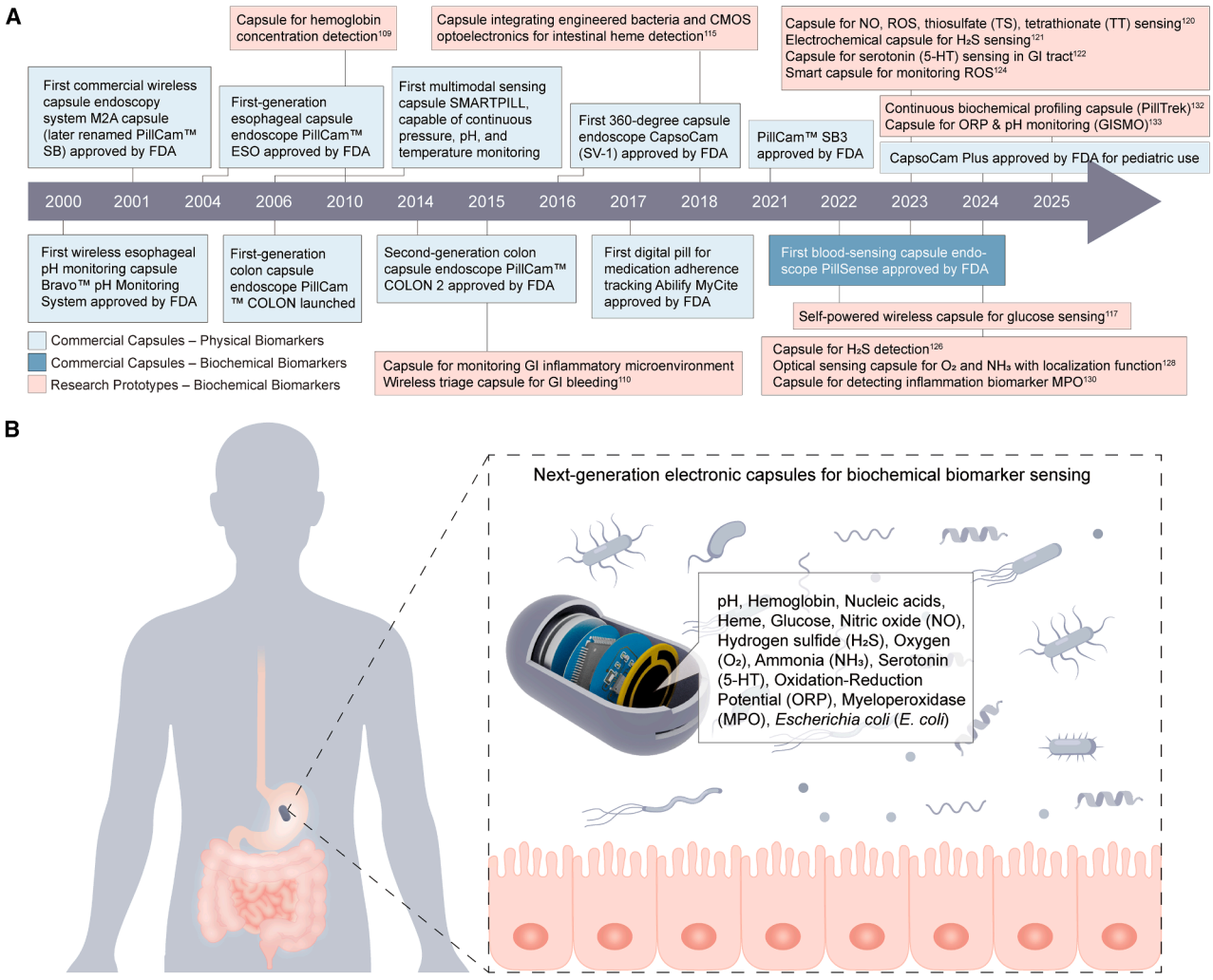

Figure 1. Evolution and application of electronic capsules for biomarker sensing

(A) Timeline of developmental milestones for commercial and research capsules.

(B) Schematic of a next-generation capsule sensing various biochemical biomarkers within the GI tract.

Small molecules

Small molecules in the GI tract originate from various sources, including secretory products of epithelial cells and metabolites generated through microbial fermentation. Their synthesis and release are regulated by neural signals, endocrine hormones, and the intestinal microecological environment.[46] These small molecules not only provide energy for local cells but also play critical roles in maintaining mucosal barrier integrity, modulating immune responses, and regulating GI motility. For instance, short-chain fatty acids (SCFAs), especially butyrate, promote intestinal epithelial cell proliferation, maintain mucosal barrier function, and suppress intestinal inflammation. Studies have shown that decreased SCFA levels are closely associated with the development of inflammatory bowel disease (IBD) and colorectal cancer.[47] Bile acids participate in lipid digestion and absorption, and their metabolic disorders are also associated with GI diseases such as colorectal cancer and enteritis.[48] In addition, pepsinogen, as a sensitive marker of gastric mucosal functional status, is commonly used in the auxiliary diagnosis of gastritis, peptic ulcers, and gastric cancer.[49]

Notably, beyond reflecting local physiology, several key small molecules in the GI milieu also serve as indicators of systemic disease states. For example, neurotransmitters in the GI tract are primarily localized within the ENS, where they not only regulate local physiological functions such as motility, secretion, and absorption but also influence systemic health via the gut-brain axis, including modulation of mood, metabolism, and immune responses.[50,51] Among them, serotonin (5-HT) is a particularly pivotal neurotransmitter. Approximately 95% of total serotonin is produced by enterochromaffin cells in the intestine, and it acts across multiple domains, including GI motility and secretion, sensory signaling and immune modulation, central regulation of mood and metabolism, and vascular function.[50,52] Dysregulation of 5-HT is therefore closely linked to GI disorders, and elevated 5-HT levels can drive diarrhea-predominant

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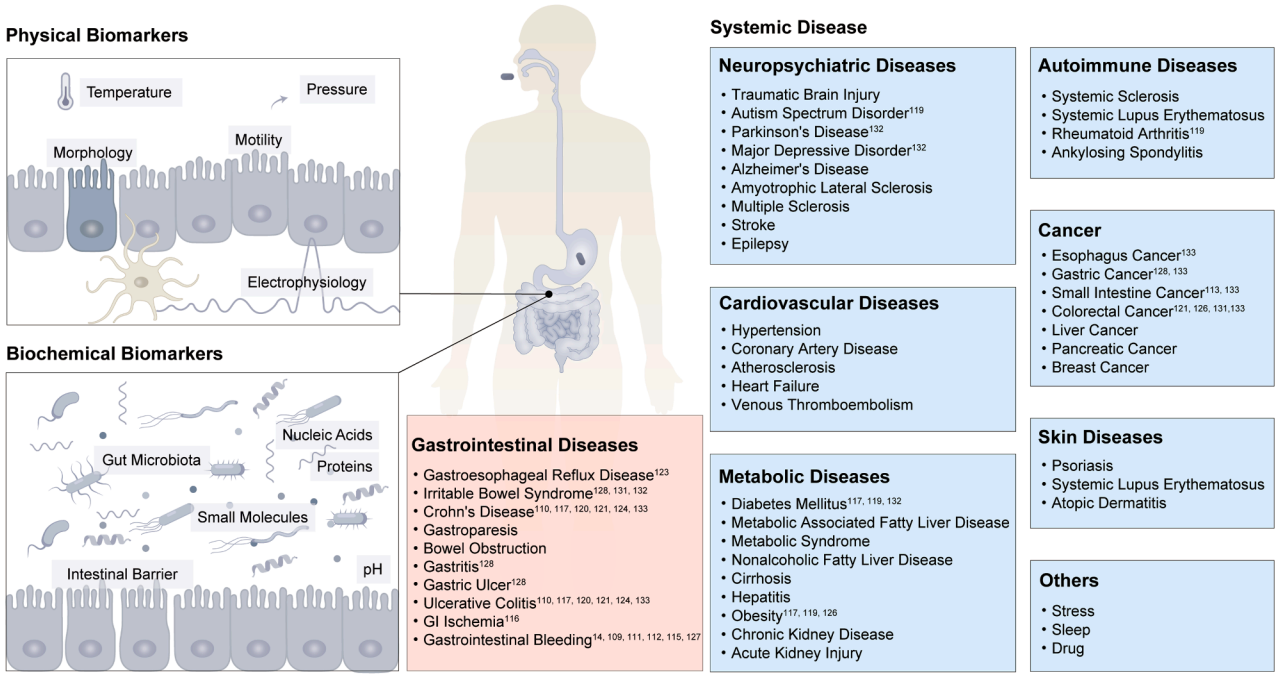

Figure 2. GI biomarkers and their potential in diagnosing related systemic diseases

The biomarkers include morphology, temperature, electrophysiology, motility, pressure, pH, small molecules, nucleic acids, proteins, gut microbiota, and intestinal barrier. Associated diseases span GI disorders, neuropsychiatric diseases, cardiovascular diseases, metabolic diseases, autoimmune diseases, cancer, skin diseases, and others.

irritable bowel syndrome (IBS).[53] Through the gut-brain axis, 5-HT is further associated with systemic conditions including depression, anxiety, autism spectrum disorders, and metabolic syndrome, supporting its use as a diagnostic biomarker and a molecular-sensing target.[54,55] In addition, this class of small molecules encompasses other critical categories. For example, SCFA metabolic disorders are closely related to obesity, type 2 diabetes, and metabolic syndrome.[56] Bile acid dysregulation is associated with non-alcoholic fatty liver disease, atherosclerosis, and increased cardiovascular disease risk.[57] Therefore, GI small-molecular metabolites can serve as diagnostic biomarkers for local diseases and also represent potential chemical targets for early screening and diagnosis of systemic diseases.

Biological biomarkers

Intraluminal biological biomarkers in the GI tract are mainly present in gastric juice, intestinal fluid, mucus, and mucosa, and they include nucleic acids, proteins, and gut microbiota. These biomarkers may be secreted by local cells or regulated via systemic signal transduction.[58] Some GI diseases can release disease-specific biomarkers directly into the lumen, while systemic diseases may influence the GI microenvironment through blood, lymphatic, or neural pathways, leading to abnormal expression of biomarkers.[59]

Proteins and nucleic acids

Nucleic acids and proteins play central roles in the initiation and progression of GI diseases. As carriers of genetic information, nucleic acids can precisely reflect cellular functional states and pathological changes, while proteins directly participate in and execute biological functions, providing an intuitive representation of physiological and pathological conditions. These biomarkers mainly originate from GI epithelial cells, tumor cells, or pathogens and are typically released via cell secretion or exosomal transport, thus enabling diagnosis of GI tumors, inflammation, and infections.[60,61]

Tumor cells often exhibit specific DNA mutations or aberrant methylation. For example, methylation sites such as BARHL2, MINT25, and RORA in gastric juice have been found to be closely associated with gastric cancer.[62] In addition, non-coding RNAs, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), are also present in gastric juice. These molecules are involved in key biological processes such as apoptosis, proliferation, differentiation, and angiogenesis, and they play critical roles in the development of gastric cancer.[63] Studies have shown that the expression levels of circulating miR-21 and miR-106a in gastric juice are significantly lower in patients with gastric cancer compared to those with benign gastric diseases.[64] In intestinal mucus, the loss of expression of MUC5AC mucin can serve as an indicator of colorectal cancer.[65] Calprotectin, found in the intestinal mucosa and fluid, is closely associated with inflammatory damage.[66] In addition, urease positivity in the gastric mucosa is often indicative of *H. pylori* infection.[67]

Gut microbiota

As a critical component of the human microecosystem, the gut microbiota is involved in regulating metabolism, immunity, and inflammation, and it establishes interactive relationships with multiple organ systems through complex networks and signaling

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pathways, including the gut-brain axis, gut-liver axis, gut-heart axis, and gut-immune axis. These axes render the gut microbiota not only essential for maintaining host homeostasis but also central to the development and progression of various diseases.

With the advancement of high-throughput omics technologies, including 16S rRNA sequencing, metagenomics, metabolomics, and proteomics, as well as the widespread application of data-analysis approaches such as machine learning, an increasing number of gut-microbiota-derived biomarkers associated with disease states have been identified. These discoveries have significantly enhanced early screening and risk-prediction capabilities for multi-system diseases such as neurological disorders, cardiovascular diseases, metabolic dysfunctions, and cancer.[68] For example, in patients with Parkinson's disease, a significant reduction has been observed in the abundance of Prevotellaceae, Lachnospiraceae, and *Faecalibacterium*, whereas Verrucomicrobiaceae, Bifidobacteriaceae, Christensenellaceae, and Ruminococcaceae are significantly elevated.[69] Bacteria belonging to the genus *Oscillibacter* are closely associated with decreased fecal and plasma cholesterol levels and may serve as potential biomarkers for cardiovascular health.[70] In studies on metabolic diseases, genera such as *Anaerostipes*, *Blautia*, and Erysipelotrichaceae UCG-003 have been identified as early diagnostic and risk-stratification indicators for type 1 diabetes.[71] Additionally, the gut microbiota is also strongly linked to autoimmune diseases, cancer, dermatological conditions, psychological stress, and sleep disorders, gradually emerging as a critical biomarker system for a wide range of complex diseases.[72]

Intestinal barrier

The intestinal barrier is a multilayered defense system essential for maintaining intestinal homeostasis and systemic health. It is composed of the gut microbiota, mucus layer, epithelial cells and their tight junctions, and mucosal immune components. As such, it does not fall under a single conventional biomarker category but rather represents a complex and dynamic protective network. This barrier functions to prevent the translocation of pathogens and toxins, regulate molecular permeability, and sustain mucosal immune tolerance, thereby serving as a critical interface between the GI tract and the systemic environment.[20,73] Damage to specific layers of the barrier can compromise its integrity and contribute to the pathogenesis of various diseases. For instance, in IBD, decreased expression of tight-junction proteins such as claudins and occludin, along with increased epithelial cell apoptosis, results in elevated intestinal permeability, facilitating the translocation of bacterial components and triggering excessive immune responses.[74] In colorectal cancer, a weakened barrier permits carcinogenic bacteria to penetrate the epithelium and activate pro-tumorigenic signaling.[75] In neurological disorders such as Parkinson's disease and Alzheimer's disease, increased gut permeability allows microbial metabolites and inflammatory mediators to access the central nervous system via the gut-brain axis, contributing to neurodegenerative processes.[76] Therefore, the intestinal barrier not only is essential for maintaining local ecological balance but also reflects early pathophysiological alterations in multiple disease states. The integrity of the intestinal barrier can be assessed through surrogate molecular markers such as zonulin, claudin-1, and occludin, which reflect the structural status of epithelial tight junctions.[73,77] In addition, intestinal impedance measurement, an emerging biophysical parameter indicative of barrier permeability, represents another critical approach, although it has thus far been primarily validated in *in vitro* settings.[78,79]

ELECTRONIC CAPSULES FOR GI BIOMARKER DETECTION

Electronic capsules have emerged as a transformative tool for the diagnosis of GI diseases, achieving a significant transition from basic research to clinical application over the past three decades.[8] Capsule endoscopy has been recommended by clinical guidelines as a first-line diagnostic tool for a variety of small-bowel disorders.[80,81] Similarly, the catheter-free Bravo pH-monitoring system is also endorsed by clinical guidelines as a standard method for prolonged esophageal acid exposure assessment in the diagnosis of GERD.[82] Additionally, the SmartPill motility capsule, which assesses GI transit time based on physiological parameters such as temperature, was once widely used as a reference standard in clinical studies evaluating GI motility.[83] However, it has since been discontinued, underscoring the practical challenges faced by capsule-based diagnostic technologies in sustaining long-term market adoption. These systems primarily focus on the acquisition of physical parameters. However, physical biomarkers inherently lack sufficient specificity, limiting their utility in precision diagnostics. Recently, next-generation electronic capsules integrated with biosensing capabilities for biomarker detection are propelling the field toward a new phase of high-accuracy and early-stage disease screening.[84] The following section systematically reviews the implementation and advancement of various biomarker-sensing technologies in capsule platforms.

Electronic capsules based on physical biomarkers

Conventional tools for intraluminal morphological observation of the GI tract include endoscopes, whose white-light imaging (WLI) technology has been miniaturized into capsule form, constituting the earliest generation of capsule endoscopes.[13] Since the first capsule endoscope was approved for clinical use in 2001,[85] the technology has undergone multiple iterations: from passive locomotion systems to today's magnetically actuated navigation[86–88]; from limited-resolution single-ended imaging to panoramic multi-camera arrays, such as the CapsoCam capsule, which employs four cameras to achieve 360° imaging, with its feasibility validated in multiple clinical studies.[89,90] More recently, propeller-driven autonomous capsules have been developed to eliminate the need for bulky driving platforms, enabling portable, controllable, and home-based monitoring. PillBot, a representative system developed by Endiatx, utilizes four micro-propellers to enable multidirectional propulsion and rotational control within the gastric cavity, while transmitting high-definition images in real time. Currently, the system is primarily designed for gastric inspection, as the propeller-based locomotion faces inherent limitations in maneuvering through narrower and longer segments of the GI tract, thereby restricting

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its applicability beyond the stomach. Although WLI is mostly confined to the mucosal surface, emerging multimodal imaging techniques such as autofluorescence imaging, ultrasound imaging, optical coherence tomography, and X-ray imaging are progressively being adapted for capsule integration, expanding the diagnostic dimensions.[5]

In terms of temperature monitoring, integrating miniature thermosensitive sensors with signal processing and wireless transmission via a microcontroller unit (MCU) represents a relatively mature technical solution, and several commercial products have already been launched. Current leading products in the market include BodyCap's e-Celsius Performance[91] and e-Celsius Medical System (CE medical qualification under review), as well as the SmartPill multisensor platform,[92,93] in which temperature sensing serves as a secondary function. Additionally, earlier systems such as Philips' VitalSense capsule[94] and HQ's CorTemp ingestible sensor,[95] which were representative of the initial generation of temperature-monitoring capsules, are no longer active in the current market. In GI electrophysiological monitoring, whether performed *in situ* or *ex vivo*, effective signal acquisition requires reliable contact between sensing electrodes and mucosal tissue. This necessitates stringent demands on electrode design adaptability, biocompatibility, flexibility, and signal-to-noise ratio. Various configurations of contact-mode electrophysiological sensors have been reported. For example, Oldroyd et al. developed a soft, stretchable, multimodal sensor capable of simultaneously measuring electrical signals and mechanical deformation while conformally interfacing with tissue. This device underwent comprehensive functional validation on *ex vivo* mouse colon and human stomach tissues, providing a powerful *ex vivo* research tool for investigating the pathophysiological mechanisms of complex disorders such as IBS and gastroparesis.[96] To enable *in vivo* monitoring, Xue et al. integrated a 3D electrode array with an inflatable balloon, effectively addressing the electrode-tissue contact challenge in colonic electrophysiology, and they demonstrated its capability to generate high-resolution colonic electrical activity maps in *in vivo* rabbit models.[97] Similarly, Srinivasan et al. employed the inflatable balloon approach to develop a high-resolution intraluminal electrophysiological mapping system, which successfully distinguished normal from diseased bowel segments in *in vivo* mouse models, demonstrating its substantial potential as a neural signature analysis tool for the precise diagnosis of neuromuscular disorders such as Hirschsprung's disease.[98] A key step toward clinical translation in this field was achieved by You et al., who developed the ingestible device MIGUT, a fully untethered capsule system incorporating a coiled flexible electrode ribbon that autonomously deploys in the stomach. This device has undergone extensive multi-day testing in large, freely moving swine models, maintaining stable signal acquisition even during feeding and sleeping, thus demonstrating the feasibility of long-term, dynamic monitoring under realistic physiological conditions.[99] GI motility, a composite measure of propulsion, mixing, storage, and emptying functions, is commonly evaluated via intraluminal pressure sensing. Strategies employed in electronic capsules include piezoelectric,[100] capacitive,[101] piezoresistive,[102] and LC resonant pressure sensors.[103] Some studies have proposed multi-parametric fusion approaches that simultaneously monitor temperature, pH, and pressure variations, along with transit time across different GI segments, to indirectly characterize gastric motility profiles.[104,105]

Electronic capsules based on biochemical biomarkers

In clinical settings, endoscope-assisted assays such as the rapid urease test,[106] mucosal inflammatory cytokine profiling, and optical imaging techniques have been employed for the auxiliary diagnosis of *H. pylori* infection, IBD, and GI tumors.[107] However, these methods are inherently invasive and rely on *ex vivo* sample analysis, rendering continuous *in situ* monitoring of target regions challenging. With the advancement of microelectromechanical systems (MEMSs) and miniaturized sensor technology, the integration of biochemical sensors into ingestible capsule platforms provides a novel avenue for non-invasive, *in situ* diagnostics. The fundamental working principle of biochemical sensing capsules lies in specific molecular recognition, such as enzyme-substrate reactions or antigen-antibody binding, which are converted into measurable signals via a transducer unit and wirelessly transmitted in real time to external receivers.[108] Relevant ingestible capsules designed for biochemical biomarker monitoring are summarized in Table 2. According to the signal-transduction modality, biochemical sensing capsules can be broadly categorized into electrochemical and optical types (Figure 3). A comparison of the core attributes and performance characteristics of different sensing technologies is provided in Table S2.

Electrochemical biosensing electronic capsules

Electrochemical biosensing technology transduces molecular-recognition events into quantifiable electrical signals, offering substantial potential for integration within electronic capsule platforms.[134] The core mechanism involves changes induced by target analyte recognition, including generation or consumption of electroactive species, interfacial charge density, electron transfer efficiency, ion concentration, and the thickness of the covering layer, thereby triggering current, potential, or impedance signal responses. Electrochemical biosensors are favored for their high sensitivity, compact structure, and broad applicability.[135] Traditional electrochemical analysis relies on benchtop workstations incorporating components such as MCUs, digital-to-analog and analog-to-digital converters, potentiostats, current sources, and impedance analyzers. However, the size, power, and complexity of these systems pose significant challenges for direct integration into capsule-based platforms. Recent advances in microelectronic systems and low-power integrated circuits have enabled the embedding of simplified electrochemical modules into capsule systems in the form of miniaturized sensors and low-power transducers.[136] Currently, the most widely adopted sensing types include amperometric, potentiometric, and impedance-based transducers. Corresponding electrochemical measurement strategies include amperometry, voltammetry, potentiometry, and electrochemical impedance spectroscopy (EIS).

Amperometry. Amperometric analysis is based on applying a constant potential and quantitatively measuring the current generated or consumed during the electrochemical reaction involving the target molecule.[137] In electronic capsules, a miniature potentiostat is typically integrated to maintain the desired potential while simultaneously measuring the current intensity

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Table 2. Target biomarkers, associated diseases, sensor types, detection principles, capsule dimensions, power-management strategies, operational lifetimes, performance metrics, *in vivo* validations, and publication years of ingestible capsules developed for biochemical monitoring

Target biochemical biomarkers	Associated diseases	Sensor types	Detection principles	Capsule dimensions	Power management	Lifetime	Performance metrics	*In vivo* validation	Year	Reference
Hemoglobin	GI bleeding	optical sensor	absorbance	11.0 mm (diameter) × 26.0 mm (length)	powered by three button cells; uses a sleep-wake strategy, activating RF?? transmission only upon positive detection	not explicitly quantified	identifies GI bleeding by detecting hemoglobin concentrations at or above 0.05 g/mL	No	2010	Liu et al.[109]
Inflammatory markers	Crohn's disease, ulcerative colitis	electrochemical sensor	voltammetry	12.0 mm (diameter) × 28.0 mm (length)	powered by a lithium manganese dioxide cell; manages power via a "sense-transmit-sleep" three-mode duty cycle	72 h	performs electrochemical analysis for GI disease diagnosis, with proven reliability of over 500 measurement cycles	no	2015	Caffrey et al.[110]
Fluorescein	GI bleeding	optical sensor	fluorescence	11.0 mm (diameter) × 27.0 mm (length)	powered by a Li-polymer battery; optimizes endurance using an ultra-low sleep current and an adjustable operational frequency	1.7–3.3 days	detects active bleeding by measuring a fluorescein tracer with an LOD of 20 nM	no	2015	Nemiroski et al.[111]
Hemoglobin	GI bleeding	optical sensor	absorbance	electronics on a 10-mm-diameter PCB; overall capsule size not explicitly stated	powered by two silver-oxide batteries; employs an intermittent "work-sleep" cycle to reduce average power consumption	6–8 h	identifies bleeding by analyzing a color-sensitive film in HSL space, with recognition conditions of $3 \leq H \leq 25$ and $0.3 \leq S \leq 0.8$	no	2016	Qiao et al.[112]

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Table 2. *Continued*

Target biochemical biomarkers	Associated diseases	Sensor types	Detection principles	Capsule dimensions	Power management	Lifetime	Performance metrics	*In vivo* validation	Year	Reference
Hemoglobin	GI bleeding	optical sensor	absorbance	6.5 mm (diameter) × 25.5 mm (length)	powered by an internal battery; performs near-continuous real-time monitoring at a fixed 4-s sampling interval	51–129 h	detects blood by calculating the absorption ratio of two wavelengths (415 nm and 720 nm), allowing risk stratification based on the resulting quotient	yes	2016	Schostek et al.[14]
ICG-labeled neoplastic lesions	small intestine tumors	optical sensor	fluorescence	13.0 mm (diameter) × 25.0 mm (length)	powered by silver-oxide batteries; uses an accelerometer-dependent sampling rate and internal data storage to maximize endurance	about 9 h	screens for early cancer by measuring ICG fluorophore, capable of detecting concentrations in the nM to μM range	no	2016	Demosthenous et al.[113]
DNA/RNA	respiratory infections	optical sensor	fluorescence	not applicable (Unpackaged)	externally powered; total consumption of 118 mW during DNA/RNA testing and thermal cycling	not applicable (externally powered)	performs high-sensitivity fluorescence measurement for DNA/RNA testing, featuring a photodetector with a dynamic range of 116 dB (10 fA to 10 nA)	no	2017	Manickam et al.[114]
Heme	GI bleeding	optical sensor	chemiluminescence	13 mm (diameter)	powered by a 5-mAh button cell; the core strategy utilizes a nanowatt-level ultra-low-power luminometer circuit	about 1.5 months	detects GI bleeding by measuring bioluminescence from engineered bacteria, with an *in vitro* detection limit as low as 32.5 ppm blood	yes	2018	Mimee et al.[115]
Glucose	GI ischemia	electrochemical sensor	amperometry	not applicable (Unpackaged)	not applicable (sensor study only)	not applicable	enables stable glucose detection for over 90 min in a highly acidic environment (pH 1.5) by using an edible carbon paste to protect the enzyme	no	2019	Ruiz-Valdepeñas Montiel et al.[116]

(*Continued on next page*)

Table 2. *Continued*

Target biochemical biomarkers	Associated diseases	Sensor types	Detection principles	Capsule dimensions	Power management	Lifetime	Performance metrics	*In vivo* validation	Year	Reference
Glucose	diabetes, obesity, IBD	electrochemical sensor	amperometry	9.0 mm (diameter) × 26.0 mm (length)	battery free; self-powered by a glucose BFC and uses magnetic human body communication for low-power wireless transmission	not applicable (self-powered)	achieves self-powered sensing by measuring glucose, with a detection limit of 4.66 mM and a dynamic range of 3–90 mM	yes	2022	De la Paz et al.[117]
NO	inflammation	electrochemical sensor	amperometry	16.0 mm (diameter) × 5.0 mm (height) (tethered module)	externally/tethered power; proposes a duty-cycling strategy for future battery-powered applications to maintain sensor performance	not applicable (Tethered)	performs *in situ* detection of the inflammatory biomarker NO via an electrochemical method, with a sensor response time of 3 s	yes	2022	Huang et al.[118]
DNA	obesity, autism, diabetes, rheumatoid arthritis	optical sensor	fluorescence	9.0 mm (diameter) × 23.0 mm (length)	powered by a coin-cell battery; employs bidirectional wireless communication, allowing an external base station to reconfigure the sensor for power-sensitivity optimization	about 24 h (capable of about 500 measurements)	performs multiplexed biomolecular detection via a CMOS fluorescence sensor array, with a DNA detection limit of 100 pM to 1 nM	no	2023	Zhu et al.[119]
NO, ROS, thiosulfate (TS), tetrathionate TT)	IBD, intestinal inflammation, oxidative stress-related disorders	optical sensor	chemiluminescence	14.25 mm (diameter) × 8.5 mm (length)	powered by a coin-cell battery; employs a custom low-power CMOS photodetector and readout circuit to convert the bioluminescent signal	1 month	performs *in situ* detection of inflammatory biomarkers by measuring bioluminescence from engineered bacteria, achieving 100% sensitivity and specificity for tetrathionate in a porcine model	yes	2023	Inda-Webb et al.[120]

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Table 2. *Continued*

Target biochemical biomarkers	Associated diseases	Sensor types	Detection principles	Capsule dimensions	Power management	Lifetime	Performance metrics	*In vivo* validation	Year	Reference
H_2S	IBD, colorectal cancer	electrochemical sensor	amperometry	14.0 mm (diameter) × 34.0 mm (length)	the sensor is designed for integration with a previously reported battery-powered capsule electronics platform	not applicable	performs electrochemical detection of H_2S gas in the GI tract, with a linear sensing range of 0.9–9 ppm	no	2023	Stine et al.[121]
5-HT	GI motility disorders, gut-localized inflammatory response	electrochemical sensor	voltammetry	15.0 mm (diameter) × 29.0 mm (length)	powered by two SR44W batteries in series; wirelessly transmits CV data via a Bluetooth module	not explicitly stated	performs real-time electrochemical detection of 5-HT in the GI tract, with a dynamic range of 2–10 μM	no	2023	Straker et al.[122]
pH	IBD, pancreatitis, GERD	electrochemical sensor	potentiometry	9.0 mm (diameter) × 22.1 mm (length)	powered by two silver-oxide batteries; employs a "work-sleep" mode and stores data locally on electrically erasable programmable read-only memory (EEPROM) to avoid high-power wireless transmission	about 103 h	performs pH monitoring via a flexible, thread-based electrochemical sensor using polyaniline (PANI), achieving a sensitivity of −59.73 mV/pH in standard buffers	no	2023	Asci et al.[123]
ROS	IBD	electrochemical sensor	potentiometry	11.0 mm (diameter) × 22.0 mm (length)	powered by two button-cell batteries; performs real-time wireless data transmission via Bluetooth and optimizes sampling frequency to ensure lifetime covers the full GI transit time	48 h	monitors GI inflammation via a dual pH and ORP sensor, with a pH sensor sensitivity of −43.2 mV/pH	no	2023	Gopalakrishnan et al.[124]
NH_4^+	protein fermentation-associated gut metabolic dysregulation	electrochemical sensor	potentiometry	not applicable (Unpackaged)	not applicable (Sensor study only)	not applicable	directly measures NH_4^+ ions in digesta via an ion-selective electrode, capable of discriminating a >2-fold concentration change (from 180–400 ppm) caused by different diets	no	2023	Leonardi et al.[125]

(*Continued on next page*)

Table 2. ***Continued***

Target biochemical biomarkers	Associated diseases	Sensor types	Detection principles	Capsule dimensions	Power management	Lifetime	Performance metrics	*In vivo* validation	Year	Reference
H_2S	IBD, colorectal cancer, obesity, halitosis, pouchitis, periodontitis	electrochemical sensor	amperometry	14.0 mm (diameter) × 34.0 mm (length)	powered by a lithium coin-cell battery; employs a bluetooth low energy module for wireless data transmission and a magnetic switch for power control	about 29 h	performs electrochemical detection of H_2S gas with a linear range of 0.21–4.5 ppm and high selectivity against hydrogen (H_2S:H_2 = 1340)	no	2024	Stine et al.[126]
Hemoglobin	GI bleeding	electrochemical sensor	EIS	not explicitly stated	powered by two coin-cell batteries; employs a low-cost electronic interface based on a direct-digital synthesizer and an analog lock-in amplifier	not explicitly stated	performs immunosensing of hemoglobin via electrochemical EIS, with an LOD of 2.31 mg/mL in simulated intestinal fluid	no	2024	Demirhan et al.[127]
O_2, NH_3	*H. pylori* infection, peptic ulcers, gastritis, gastric cancer, IBD, IBS, food intolerances	optical sensor	fluorescence	10.0 mm (diameter) × 26.0 mm (length)	powered by two silver-oxide batteries in series (28 mAh); employs bluetooth low energy for wireless communication	16 h	performs optical gas sensing via fluorescence quenching to measure oxygen (0%–20%) and ammonia (0–100 ppm)	no	2024	Abdigazy et al.[128]
E. coli	chronic diarrhea, malabsorption, IBD, sepsis	optical sensor	fluorescence	7.0 mm (diameter) × 15.0 mm (length)	not applicable	not applicable	performs fluorescence-based immunosensing of *E. coli* with a linear range of 2.0×10^3 to 14.0×10^3 CFU/mL and LOD of 400 CFU/mL	yes	2024	Khachornsakkul et al.[129]
MPO	IBD	optical sensor	chemiluminescence	11.0 mm (diameter) × 26.0 mm (length)	powered by two 1.55V batteries; uses bluetooth for wireless data transmission and forwards data to a station via Wi-Fi	>8 h	performs paper-based chemiluminescent immunosensing of MPO with a linear range of 0–7 U/mL and a sensitivity of 6.14 $\mu J/U{\cdot}mL^{-1}$	no	2024	Kadian et al.[130]

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Table 2. ***Continued***

Target biochemical biomarkers	Associated diseases	Sensor types	Detection principles	Capsule dimensions	Power management	Lifetime	Performance metrics	*In vivo* validation	Year	Reference
pH	colorectal cancer, IBD, IBS, *H. pylori* infection	electrochemical sensor	amperometry	6.2 mm (diameter) × 17.0 mm (length)	powered by a 100 μAh solid-state battery; utilizes an ultra-low-power (32 μW) wireless transmitter in the medical implant communication service (MICS) band (402–405 MHz)	not explicitly stated	performs electrochemical pH detection, featuring a core chip with a minimum detectable current of 150 pA within a ±29 μA range	no	2024	Abdigazy et al.[131]
Serotonin, glucose, pH, ionic strength, temperature	IBS, depression, anxiety, Parkinson's disease, diabetes, malabsorption, gut microbiome dysbiosis	electrochemical sensor	voltammetry, amperometry, potentiometry, EIS	7 mm (diameter) × 25 mm (length)	powered by 16-mAh silver-oxide batteries and communicating wirelessly via a bluetooth low energy module with an average power consumption under 350 μW	>22 h	integrates a versatile electrochemical workstation capable of synchronously detecting multiple biomarkers, featuring a nanomolar-level (50 nM) detection limit for serotonin and covering a millimolar physiological range (0–50 mM) for glucose	yes	2025	Min et al.[132]
ORP, pH	Crohn's disease, ulcerative colitis, oxidative stress-related conditions, gut microbiome dysbiosis, GI cancers	electrochemical sensor	potentiometry	7.5 mm (diameter) × 21 mm (length)	Driven by 12.5-mAh silver-oxide batteries, maintaining an exceptionally low average current consumption of only 28 μA in its normal operational mode	>5 days (normal mode) + 9 additional days (ultra-low power mode)	features highly stable ORP and pH-monitoring capabilities with a high temporal resolution of one sample every 20 s, and its safety and reliability have been confirmed in a human clinical trial	yes	2025	Even et al.[133]

LOD, limit of detection

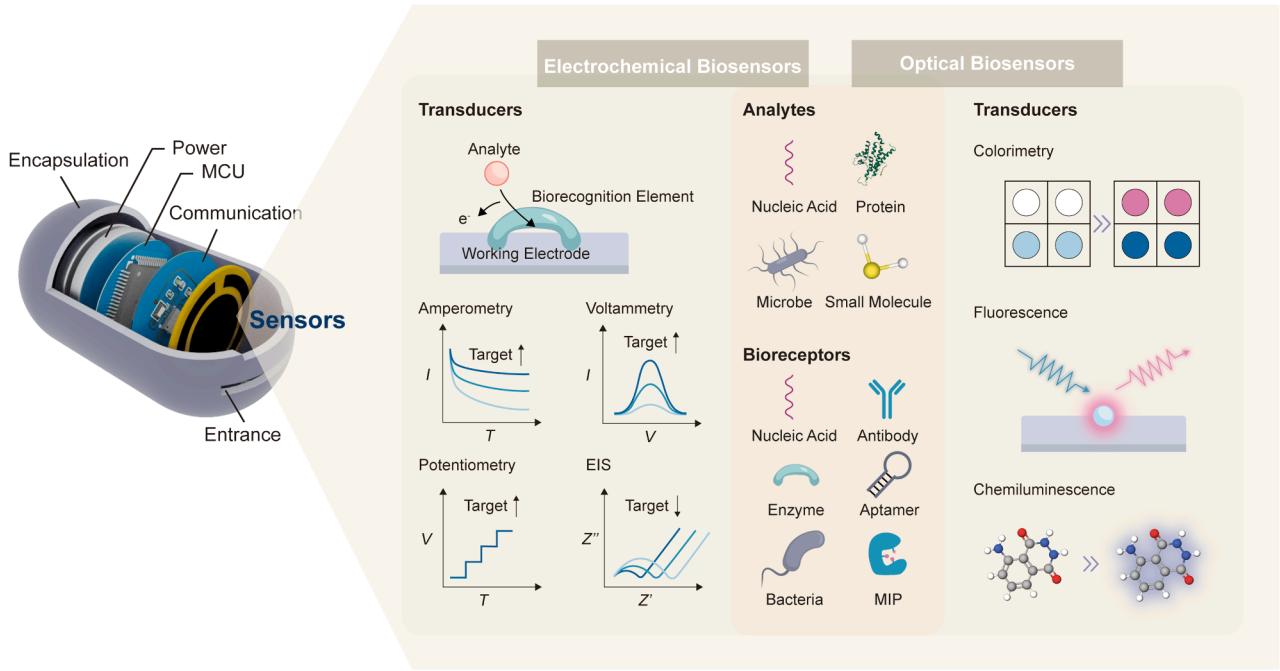

Figure 3. Sensing technologies integrated into electronic capsules

An electronic capsule typically consists of encapsulation, entrance module, power supply, MCU, communication module, and sensors. The sensors can be categorized into electrochemical and optical types.

in real time, thereby outputting information on the concentration variation of the target molecule.[138] This technique has been employed for monitoring of glucose in the intestine, where the current signal generated by the glucose oxidation reaction serves as a quantitative indicator.[116] De la Paz et al. proposed a self-powered electronic capsule based on a biofuel cell (BFC), in which the voltage generated from glucose metabolism is converted into a frequency signal via a voltage-controlled oscillator. The BFC functions not only as a sensor but also as a power-supply unit, eliminating the need for a traditional battery module and significantly reducing the overall system size while enhancing biosafety and energy efficiency.[117] For other molecular targets, a flexible three-electrode system combined with a Nafion solid-state electrolyte membrane has been used for detection of hydrogen sulfide (H_2S) in the intestine, enabling early screening of IBD and colorectal cancer (Figure 4A).[121,126] Huang et al. integrated a commercial electrochemical nitric oxide (NO) sensor with a gas-permeable membrane and a duty-cycle control strategy to achieve dynamic tracking of NO concentrations in inflammatory regions in a porcine model.[118] Furthermore, amperometry has also been applied for monitoring pH variations in the GI tract. By co-constructing an electrode system with PEDOT:PSS and a proton-selective membrane, the research team achieved highly sensitive detection of hydrogen ion concentration changes, providing a novel strategy for continuous analysis of GI acid-base status.[131]

Voltammetry. Voltammetry is an electrochemical detection technique that records current-voltage curves under a sweeping potential. By analyzing the peaks and current intensities in the voltammogram, the type of analyte can be identified and quantified. Common techniques include linear sweep voltammetry (LSV), cyclic voltammetry (CV), and differential pulse voltammetry (DPV).[137] Although methodologically more complex than amperometry, voltammetry offers superior resolution in multicomponent systems and is particularly suitable for analyzing and investigating unknown components in complex matrices.[139] McCaffrey et al. developed an electronic capsule platform integrating a miniature potentiostatic control system and a transimpedance amplifier, enabling the amplification and wireless transmission of weak current signals for real-time electrochemical detection of inflammatory environments in the GI tract, such as Crohn's disease and ulcerative colitis (Figure 4B).[110] Straker and colleagues employed CV and used an Au-CNT working electrode to enhance sensitivity, achieving real-time electrochemical detection of 5-HT in the GI tract. This allowed genuine dynamic monitoring of neurotransmitters and offers a promising tool for investigating the regulatory mechanisms of neurotransmitters in the gut-brain axis and neurogastroenterological disorders.[122,140]

Potentiometry. Potentiometry is an electrochemical detection technique that enables quantitative analysis based on the Nernst equation by measuring the influence of ion concentration on the potential of an indicator electrode. This method does not require the application of an external current and features a simple device structure with ultra-low power consumption, making it highly suitable for miniaturization and integration.[141] These attributes are particularly advantageous for *in situ* sensing applications within electronic capsule platforms. At present, various electrodes, such as glass electrodes,[142] polyaniline/carbon thread composite electrodes,[123] and iridium oxide (IrOx)

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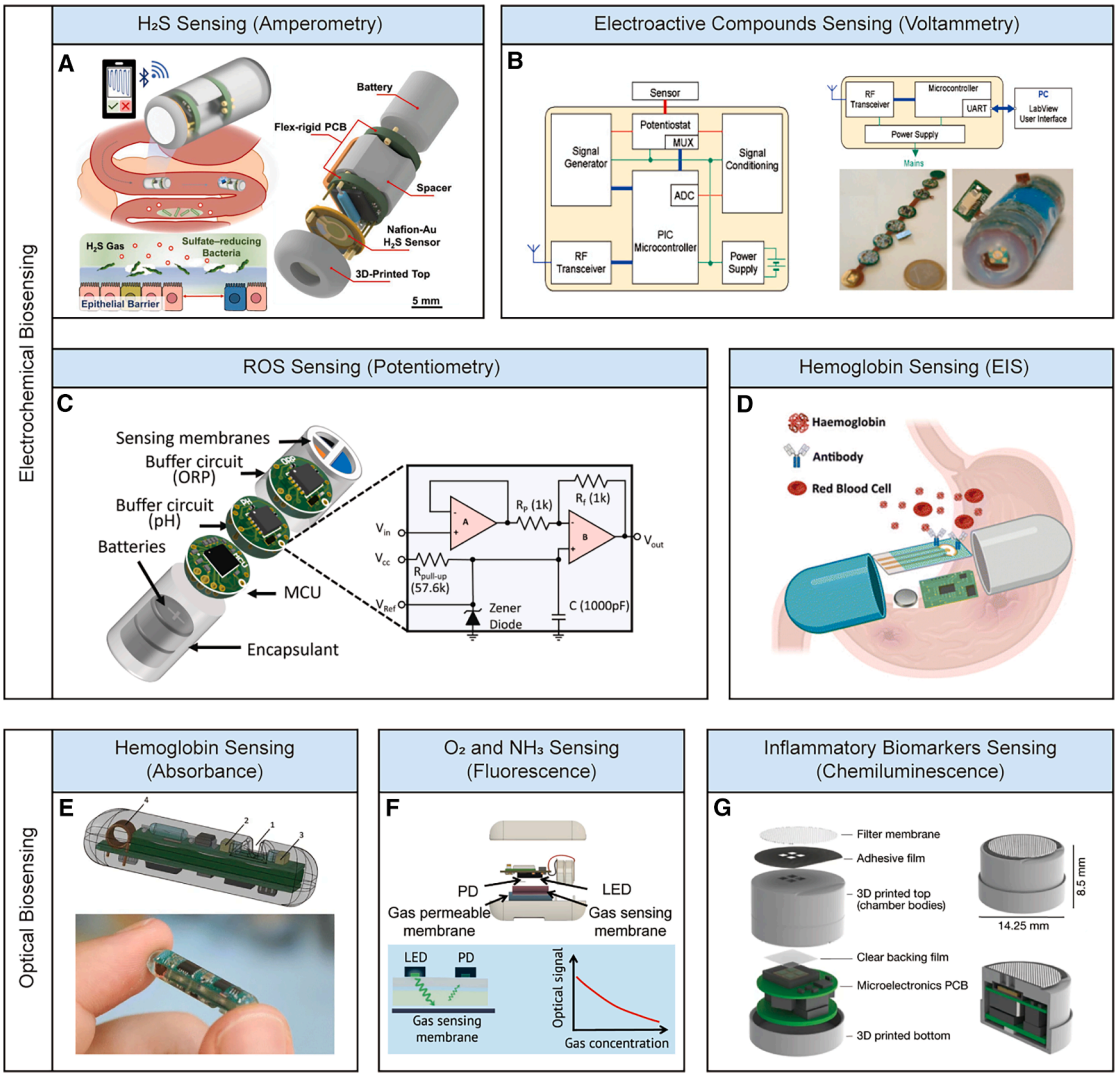

Figure 4. Electronic capsule for biochemical biomarker sensing

(A) Wireless capsule for real-time GI H_2S detection via amperometry.[126] Reproduced with permission.

(B) Wireless capsule enabling electrochemical detection of GI fluids via voltammetry.[110] Copyright 2015, Elsevier.

(C) A smart capsule integrating ORP and pH sensors for electrochemical tracking of ROS throughout the GI tract to assess inflammation status.[124] Reproduced with permission.

(D) A miniaturized immunosensor using EIS detects hemoglobin as an early marker of GI bleeding.[127] Reproduced with permission.

(E) The HemoPill capsule detects upper GI bleeding through optical absorption ratio sensing.[14] Copyright 2016, Springer Nature.

(F) An ingestible capsule with fluorescence-quenching sensors detects O_2 and NH_3 in the GI tract.[128] Reproduced with permission.

(G) A wireless capsule integrating engineered bacteria and optical electronics enables *in situ* detection of labile inflammatory biomarkers.[120] Copyright 2023, Springer Nature.

electrodes,[143,144] have been widely applied for real-time monitoring of GI pH. Among them, IrOx electrodes have undergone preliminary validation in *in vivo* models of pigs and beagle dogs, demonstrating excellent stability and biocompatibility. In addition, potentiometry has been extended to detection of oxidation-reduction potential (ORP), serving as an indirect indicator of reactive oxygen species (ROS) levels and offering a novel strategy for continuous monitoring of IBD (Figure 4C).[124] Recently, this approach was successfully translated to humans with the GISMO smart capsule, which performed the first-in-human continuous ORP measurements along the entire GI tract, establishing a foundational redox profile in healthy volunteers.[133] In applications related to nutritional metabolism, Leonardi et al. integrated ion-selective electrodes to dynamically detect ammonium (NH_4^+) concentrations in digesta within the porcine GI tract, enabling assessment of the relationship between protein fermentation levels and dietary composition. This study highlights the considerable potential of potentiometric sensors in intestinal functional monitoring, nutritional evaluation, and metabolic research.[125]

EIS. EIS is a non-steady-state detection technique based on alternating-current excitation, which measures the response of materials or biological tissues to current or voltage stimuli at varying frequencies. This method enables the acquisition of key electrochemical parameters, such as interfacial charge-transfer resistance, capacitance, and resistance. Compared with traditional electrochemical techniques, EIS exhibits higher sensitivity to subtle changes at the interface, making it particularly suitable for dynamic assessment of microenvironmental parameters such as biological barrier function, cellular permeability, and tissue integrity.[145] In GI-barrier monitoring, Balakrishnan et al. designed a flexible dual-electrode structure based on a gelatin capsule shell to track impedance changes induced by acid erosion or tissue injury at low frequencies, effectively validating the feasibility of EIS in intestinal barrier evaluation.[78] Holt et al. further developed a four-electrode capsule platform modified with PEDOT:PSS to precisely capture changes in tissue impedance over a frequency range of 100 Hz to 200 kHz, thereby enabling dynamic monitoring of epithelial barrier function.[79] Both studies demonstrate the broad prospects of EIS for non-invasive assessment of intestinal mucosal barrier integrity and provide novel approaches for disease screening, including IBD and leaky gut syndrome. In addition, EIS has been applied to the early detection of GI bleeding. Demirhan et al. developed a miniaturized immunosensing system based on EIS, in which immobilized antibodies recognize hemoglobin molecules within the intestinal lumen and record the resulting changes in interfacial impedance in real time, enabling non-invasive screening of trace bleeding events (Figure 4D).[127]

Furthermore, some pioneering technologies have expanded the scope of traditional electrochemical sensing, with the Atmo gas-sensing capsule serving as a representative example. The core of this platform is a dual-sensor system that integrates a semiconducting sensor based on the chemiresistive effect, which detects changes in electrical resistance caused by gas-molecule adsorption and converts them into direct electrical signals. Concurrently, it harnesses the unique thermal conductivity of H_2 for selective detection via a thermal-conductivity sensor. By combining active temperature modulation with this dual-channel sensing architecture, the system captures the dynamic response fingerprints of target gases, which are subsequently identified and analyzed by a backend algorithm. This approach offers a novel strategy for real-time monitoring of complex gaseous environments within the body.[146] In addition, the PillTrek capsule showcases the versatility of electrochemical sensing. It functions less as a single sensor and more as a miniaturized analytical platform capable of executing multiple electrochemical techniques. This allows it to leverage different sensing principles for a comprehensive analysis of diverse biomarker types, including hormones, metabolites, and electrolytes.[132]

Optical biosensing electronic capsules

Optical biosensors are a class of sensing devices that respond to specific biological recognition events through changes in optical signals and are widely applied in the *in situ* analysis of various target molecules.[147] The integration of optical biosensing technologies into ingestible electronic capsules offers advantages such as high sensitivity, low power consumption, and high spatial resolution, making them particularly suitable for real-time monitoring in complex GI environments. According to their transduction mechanisms, they can be categorized into absorbance-based, fluorescence-based, and chemiluminescence-based types. These systems typically consist of miniaturized light sources, such as light-emitting diodes (LEDs) or laser diodes,[113] and photodetectors, such as photodiodes or CMOS image sensors. Benefiting from advances in semiconductor manufacturing and packaging technologies, these key components have been highly miniaturized and are now capable of system-level integration.[148,149] Optical biosensing technologies are gradually becoming promising diagnostic modules within electronic capsule platforms, especially for clinical scenarios involving bleeding, inflammation, and tumors.

Absorbance. Absorbance-based detection is founded on the Beer-Lambert law, which enables quantitative analysis of target molecule concentrations by monitoring the attenuation of light at specific wavelengths through a target medium. This method does not rely on fluorescent labeling, features a simple structure, and provides rapid response, making it suitable for colorimetric reaction systems.[150] It has been widely employed in GI bleeding detection, enzymatic reactions, and spectral-absorbance analysis. Liu et al. designed a swallowable sensing system based on optical absorbance, capable of dynamically monitoring hemoglobin concentration by detecting color changes in intestinal fluid. The system integrates a white-light LED excitation source and a TCS230D color light-to-frequency conversion module, demonstrating high-sensitivity bleeding recognition and showing strong potential for *in situ* diagnostics.[109] Subsequently, Qiao et al. developed an intelligent recognition algorithm based on HSL color-space analysis. The system captures color changes of an absorbent membrane and interprets variations in the H/S parameters to enable intelligent identification of GI bleeding signals.[112] In addition, the HemoPill capsule developed by Ovesco Endoscopy employs an absorbance-based detection method that integrates dual light sources at 415 and 720 nm. By calculating the transmission ratio, the system evaluates bleeding severity and transmits the results in real time to external devices. This method does not rely on image processing or operator experience, significantly improving diagnostic consistency and automation. Critically, its clinical feasibility and safety have been validated in a multicenter study involving 61 patients with suspected GI bleeding across 12 international hospitals, in which the capsule achieved a technical success rate of 98%. Compared with single-wavelength detection, dual-wavelength colorimetry offers advantages in reducing background interference, enhancing detection sensitivity, and improving signal stability (Figure 4E).[14,151]

Fluorescence. Fluorescence is a photoluminescent phenomenon widely applied in biosensing due to its high sensitivity, rapid response, and strong molecular-recognition capabilities.[152] Constructing an integrated "excitation-emission-detection" optical system within ingestible electronic capsules enables dynamic and visualized analysis of target molecules in the GI tract. Nemiroski et al. reported a miniature fluorometer integrating a 465-nm blue LED, photodiode, high-gain low-noise amplifier, and digital lock-in filter module for real-time detection of gastric fluorescence signals, enabling early identification and

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quantitative detection of GI bleeding.[111] However, the system relies on intravenous administration of fluorescent markers, which limits its non-invasiveness. Subsequent studies extended fluorescence techniques to tumor screening. Researchers used ICG dye for targeted labeling of early neoplastic lesions in the small intestine, and they integrated an array of near-infrared laser diodes, filtered photodiodes, and data-processing modules to enable tumor screening of the intestinal wall.[113] Distinct from methods relying on exogenous markers, a complementary strategy utilizes the autofluorescence of endogenous molecules for completely label-free detection. Cumming's group first demonstrated a wireless capsule with a high-sensitivity single-photon avalanche diode (SPAD). to detect weak, intrinsic fluorescence signals in biological tissues.[153,154] They subsequently advanced this technology from a single-point sensor to a miniaturized fluorescence imager. This advanced system, built upon a 64 × 64 SPAD array, successfully imaged *ex vivo* human colorectal cancer tissues, revealing a marked decrease in autofluorescence in malignant areas versus healthy tissue, a result that corroborates clinical findings.[155] Zhu et al. developed a fluorescence biosensing capsule based on CMOS technology, incorporating nanophotonic filters, a multi-channel sensor array, and a bidirectional wireless communication module, achieving picomolar-level detection sensitivity and supporting high-precision fluorescence detection at the DNA molecular level.[119] Manickam et al. fabricated a fully integrated continuous-wave fluorescence chip using CMOS processes, achieving high-sensitivity and high-throughput analysis of DNA/RNA based on reverse-quenching principles.[114] Abdigazy et al. combined fluorescence sensing with wearable technologies, implementing optical sensing and millimeter-scale 3D localization of GI O_2 and NH_3 gases based on fluorescence-quenching mechanisms (Figure 4F).[128] Khachornsakkul et al. further combined gold nanocluster fluorescent probes with molecularly imprinted polymers to develop a passive sensing capsule for quantitative detection of *Escherichia coli*, providing a scalable template for gut microbiota monitoring.[129] In addition, Biora Therapeutics has developed a Smart Capsule Bacterial Detection System (SCBDS) based on fluorescence sensing for the diagnosis of small-intestinal bacterial overgrowth (SIBO). In a pivotal multicenter clinical study, the fluorescence-based analytical method employed by SCBDS demonstrated an overall agreement of 82%–92% with conventional total bacterial count (TBC) culture methods. This fluorescence-enabled capsule technology holds great promise as an accurate, convenient, and non-invasive diagnostic tool for SIBO.[156]

Chemiluminescence. Chemiluminescence is a light-emitting process initiated by chemical reactions without the need for external excitation light, including both pure non-enzymatic chemiluminescence and luciferase-based bioluminescence.[157] With no excitation source required, low background noise, and minimal power consumption, it is highly suitable for integration into electronic capsules. In pure chemiluminescence applications, Kadian et al. developed a paper-based chemiluminescent capsule combining a myeloperoxidase (MPO)-UHP-luminol reaction system. This device integrates a luminescence-sensing module and photodetection unit to enable detection of the inflammatory biomarker MPO within the GI tract, offering a non-invasive and personalized screening approach for chronic inflammatory diseases such as IBD.[130] In the field of bioluminescence, Mimee et al. proposed an ingestible biotic-electronic platform integrating genetically engineered bacterial circuits with a CMOS photodetection readout system. Upon detection of heme in the intestine, the engineered bacteria initiate autonomous bioluminescence, and signals are captured and wirelessly transmitted via a low-power readout array.[115] Liu et al. further optimized the readout circuitry using duty-cycling control and time-to-digital conversion techniques, achieving ultra-low power consumption of only 59 nW and a minimum detection limit of 59 fA, which was successfully integrated into a millimeter-scale capsule for high-sensitivity detection of bacterial signals.[158] Inda-Webb et al. engineered various bioluminescent bacteria via synthetic biology to detect short-lived molecules such as NO, ROSs, and sulfate (Figure 4G). This approach exemplifies the integration of synthetic biology with microsystem technologies to develop next-generation biosensing platforms that function as living diagnostics within the host.[120]

TRANSLATIONAL CHALLENGES AND EMERGING PATHWAYS

Despite their transformative potential in disease diagnostics, ingestible sensing capsules face substantial barriers on the path from laboratory prototypes to clinical deployment. These challenges stem from the need to operate safely, reliably, and over extended durations within the complex and dynamically changing GI environment while achieving precise localization at target sites and, when required, integrating therapeutic functionalities. At the same time, they must comply with stringent regulatory standards and be designed to ensure a positive user experience for both patients and healthcare providers (Figure 5).

Safety

During transit through the GI tract, capsules are exposed to harsh physiological conditions, including steep pH gradients, digestive enzymes, shear stresses, and peristaltic compression.[159] Failure of encapsulation integrity or inappropriate material selection can lead to serious complications, such as chemical leakage or electrothermal injury. Mechanical impaction may also occur in cases of anatomical abnormalities or luminal strictures. From a materials perspective, the capsule shell must meet stringent biocompatibility standards to prevent chemical or immune irritation to the mucosal lining. Early devices primarily employed medical-grade rigid polymers such as polycarbonate and polyether ether ketone, with shells fabricated via computer numerical control (CNC) precision machining.[109,110] With advances in high-resolution stereolithography, biocompatible photopolymeric resins such as BioMed Clear and BioMed Amber have been widely adopted for rapid prototyping, markedly accelerating design and optimization.[123,128] In parallel, biodegradable and edible polymers are being integrated into next-generation platforms to mitigate the risks of fragment retention and long-term toxicity.[10,116] Retention risk is primarily reduced by stringent control of capsule geometry and profile. A widely accepted design principle is to ensure that the capsule dimensions do not

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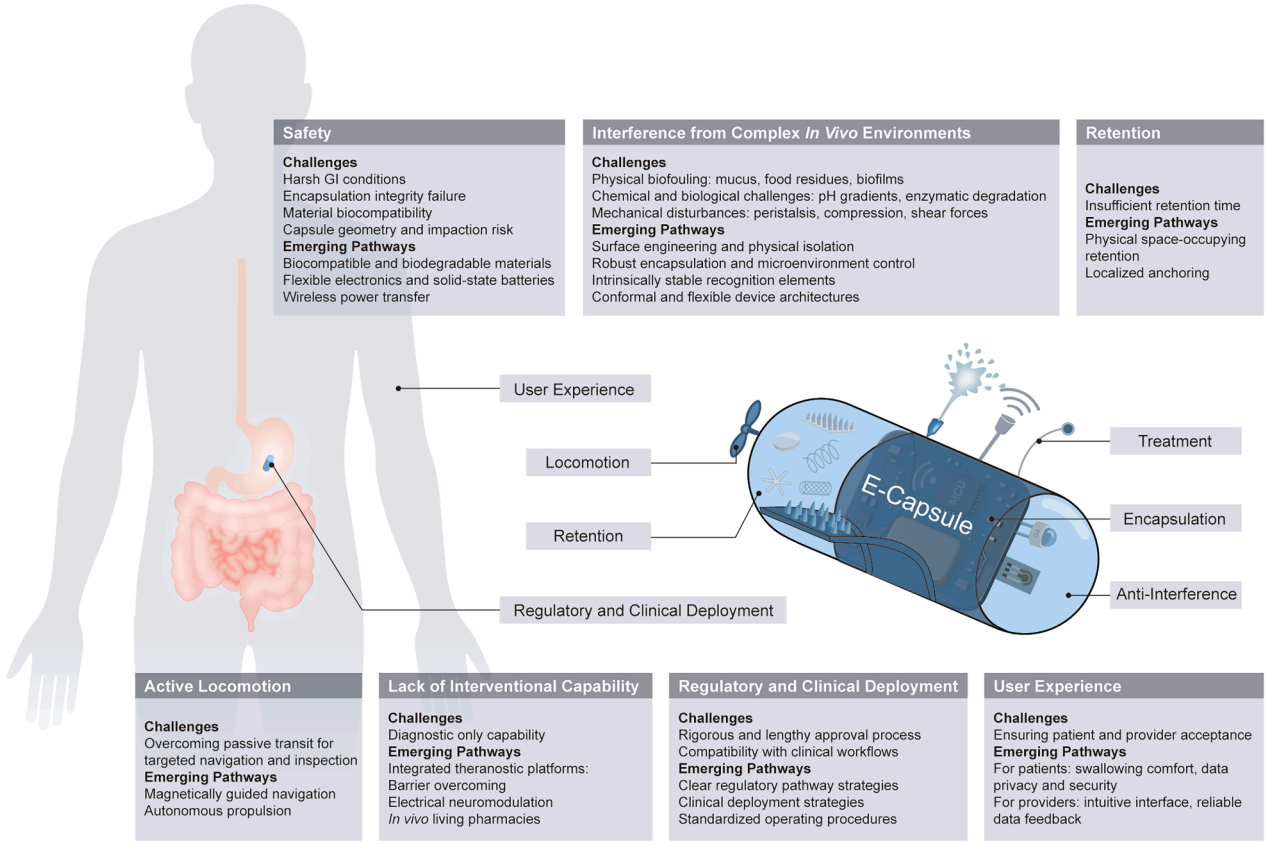

Figure 5. Translational challenges and emerging pathways for ingestible electronic capsules

exceed those of typical commercial video capsules, such as the PillCam SB3, which measures 11.4 mm in diameter and 26.2 mm in length, or the 000-size capsule, which measures approximately 26.14 by 9.91 mm. Capsules that are too large may become lodged at the pylorus, ileocecal valve, or within strictured segments, whereas those that are too small may transit too rapidly, limiting dwell time in target regions. An optimal approach is to match the dimensions to those of a size 00 capsule, approximately 23.30 × 8.53 mm, balancing GI passage efficiency with adequate retention time. Clinically, in patients at risk of intestinal stricture, such as those with Crohn's disease, a patency capsule of matching dimensions is often ingested for pre-screening; successful natural passage indicates eligibility for deployment of the functional capsule.[160] To further reduce dependence on rigid volumes and eliminate internal chemical hazards, emerging strategies incorporate flexible electronics, solid-state microbatteries, and wireless power-transfer modules,[131,161] thereby markedly decreasing or eliminating the need for traditional wet-chemical batteries and mitigating the risks of electrolyte leakage, thermal runaway, and prolonged capsule retention.

Interference from complex *in vivo* environments

The functional stability and diagnostic reliability of electronic capsules are fundamentally challenged by the harsh and dynamically changing conditions of the GI tract.[159] These challenges are primarily attributed to biofouling and mechanical disturbances. Biofouling typically manifests as nonspecific adhesion of mucus, food residues, exfoliated epithelial cells, or bacterial biofilms to the sensing interface, combined with chemical challenges such as steep pH gradients, enzymatic degradation, and interference from diverse nonspecific molecules.[162,163] Physical obstruction layers not only hinder the diffusion of target analytes but may also substantially delay sensor response times and attenuate signal intensity. For example, Rajan et al. demonstrated that mucins in the GI tract can markedly delay the response of pH probes.[142] One core strategy to address this issue is surface-engineering optimization. Holt et al. coated impedance electrodes with the conductive polymer PEDOT:PSS to create a soft and hydrophilic interface, effectively reducing interfacial impedance while improving signal stability.[79] Another approach employs physical isolation through semipermeable membranes. Inda-Webb et al. encapsulated engineered bacterial-sensing elements within microchambers sealed by semipermeable membranes, allowing small-molecule target analytes to diffuse freely while physically blocking large molecules, mucus, and food residues, thus preventing contamination of the internal sensing components. This protective design enabled continuous monitoring for up to 4 h within an *in vivo* porcine intestinal model and demonstrated stability exceeding 24 h in

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simulated intestinal fluid *ex vivo*.[120] To mitigate challenges arising from the chemical environment, material-based encapsulation strategies have been implemented. Ruiz-Valdepeñas Montiel et al. embedded glucose oxidase within an olive-oil-based hydrophobic carbon-paste matrix, effectively shielding the enzyme from degradation in aqueous media. This approach enabled the sensor to operate stably for over 90 min in simulated gastric fluid at pH 1.5, representing a 19-fold improvement in stability compared with conventional sensors.[116] Kadian et al. proposed a more advanced strategy by coating the capsule exterior with a pH-responsive enteric layer that dissolves only upon reaching the small intestine, thereby activating the internal multilayer paper-based sensor. The outermost layer incorporated a strong buffering system capable of automatically adjusting the sample microenvironment to the alkaline conditions required for chemiluminescent reactions, ensuring reaction stability in dynamic biological settings.[130] Khachornsakkul et al. introduced molecularly imprinted polymers as recognition elements. These synthetic antibody mimics exhibit excellent chemical tolerance and intrinsic resistance to enzymatic degradation, making them highly promising candidates for *in vivo* sensing.[129] Mechanical disturbances such as GI peristalsis and intraluminal fluid flow constitute another major physical challenge to stable capsule retention and signal consistency. One mitigation strategy is to employ flexible and conformal designs. Li et al. developed the NeuroString system using soft, stretchable, biomimetic materials that allow the device to bend and conform synchronously with GI peristalsis, thereby avoiding stress concentration and loss of contact.[164] In addition, certain retention mechanisms are discussed in the subsequent section, and it is noteworthy that prolonged retention may result in more severe biofouling, thereby imposing stricter requirements on the long-term fidelity of sensor signals.

Retention

Beyond addressing the challenges posed by mechanical disturbances in the GI tract, sustained monitoring of *in vivo* biomarkers by electronic capsules also requires the capability to remain in the GI tract for extended periods. Current GI retention strategies can be broadly categorized into two types. The first is physical space-occupying retention, in which structural expansion or inflation prevents passage through the pylorus or intestinal segments.[165–170] The second is localized anchoring, in which physical adhesion or chemical crosslinking to the mucosa enables site-specific retention.[161,171–173] A more comprehensive summary of these strategies is available in our previous review.[174]

Active locomotion

Passive locomotion remains one of the main limitations of current capsule technologies, preventing precise detection in regions of interest. Granting capsules the capability for active locomotion is a pivotal step toward intelligent operation. Current active-locomotion strategies can be broadly classified into two categories. One approach leverages external magnetic-field manipulation, offering precise control and clinical stability, as demonstrated by magnetically guided capsule endoscopy. However, this strategy depends on bulky and expensive magnetic-field generators, limiting its portability and broader adoption. As a result, the development of autonomously propelled capsule systems that operate independently of external devices has emerged as a key research frontier. Based on propulsion mechanisms, self-propelled capsules can be further classified into wall-interacting locomotion and fluid-mediated locomotion. The former relies on direct mechanical interaction with the GI wall to generate propulsion or anchoring forces, as seen in legged locomotion,[175] paddle-based locomotion,[176] wheel-based rolling,[177] and peristaltic motion systems.[178,179] The latter, exemplified by propeller-driven designs, enables swimming-like motion through luminal fluids. For instance, Liang et al. developed a motor-powered capsule robot that uses a miniature propeller to convert rotational energy into axial thrust, allowing stable navigation in complex GI environments with mucus, food residue, and luminal debris.[180]

Lack of interventional capability

In clinical practice, the absence of real-time interventional capability means that abnormalities detected cannot be immediately treated, thereby diminishing the potential clinical value. Future ingestible capsules must evolve from single-purpose diagnostic tools into fully integrated theranostic platforms. In terms of therapy, beyond drug loading and region-specific release, recent efforts have focused on overcoming GI barriers and enhancing bioavailability. Several therapeutic modules have been proposed for capsule integration, including mucus-clearing mechanisms,[181] direct injection,[182] jet injection,[183] ultrasound-assisted delivery,[184] and iontophoresis.[185] In addition, ingestible devices equipped with electrical stimulation capabilities have demonstrated promising potential in neuromodulation, with effective applications in the treatment of gastroparesis and appetite regulation.[161,186] This opens a hopeful avenue for addressing disorders of the nervous system. Meanwhile, the use of electronic capsules as *in vivo* living pharmacies, by encapsulating engineered microbes or other biologics, represents another highly promising strategy. Such an approach holds promise for enabling modulation of the gut microbiota to therapeutically intervene in disease. More importantly, it offers a potential solution to the long-standing disconnect between the external production and internal demand of biologic therapeutics.[187–189] In the future, as capsule systems continue to evolve toward greater functional integration, electronic capsule platforms will truly usher in a new era of integrated medicine that unifies precision diagnosis and targeted intervention.

Regulatory and clinical deployment

All electronic capsules intended for human use must undergo rigorous regulatory approval. If an electronic capsule demonstrates substantial equivalence in use and technological characteristics to an existing legally marketed device, it may be classified by the FDA as a class II medical device, allowing for market clearance via the 510(k) premarket notification pathway. This process requires the submission of sufficient safety and effectiveness data to establish comparable performance and risk profiles. For devices introducing fundamentally new technological principles or indications with no existing predicate, classification may instead proceed via the *De Novo* pathway for moderate-risk devices or the more rigorous Premarket Approval (PMA)

pathway for high-risk class III devices.[190,191] Following regulatory clearance, strategies for clinical deployment become critical to the widespread adoption of electronic capsules. This includes systematic evaluation of operational compatibility across diverse healthcare environments, such as integration with electronic medical records (EMRs) and hospital communication infrastructures, data transmission reliability, and potential wireless interference in clinical settings. Standardized operating procedures and training protocols must also be established to ensure that healthcare personnel can reliably initiate, monitor, and manage the devices with safety and efficiency.

User experience

Ultimately, the clinical translation of electronic capsule technologies will hinge on the overall end-user experience. For patients, the capsule must demonstrate multi-dimensional safety, including ease of swallowing, biocompatibility, and protection against electrical or thermal risks. Its *in vivo* behavior should minimize the sensation of a foreign body to enhance patient compliance. In parallel, the system must ensure strict protection of patient privacy and data security.[192] For healthcare providers, the device should feature an intuitive human-machine interface, stable system performance, clear visual feedback, and explicit alerts for abnormal conditions, thereby facilitating efficient operation and informed clinical decision-making. Therefore, systematically and proactively incorporating considerations of clinical translation challenges at the early stages of technology development will drive the progression of electronic-capsule technologies from proof of concept to clinical utility, accelerating their implementation in real-world medical settings.

CONCLUSIONS AND OUTLOOK

With the rapid advancements in MEMS, biosensors, and nanomaterials technologies, electronic capsules are undergoing a profound transformation from physical-parameter observers to *in vivo* molecular-recognition platforms. This paradigm shift offers new possibilities for the role of the GI tract in the diagnosis of systemic diseases, positioning it not merely as a tool for assessing local lesions but as a potential diagnostic hub connecting multiple systems, including the central nervous, metabolic, immune, and oncological networks. Although current research on electronic capsules targeting GI microecology or molecular signals related to systemic diseases remains in its infancy, the maturation of relevant technologies is expected to make GI-based *in situ* diagnostics an integral component of future precision medicine. Realizing this vision will require deep interdisciplinary collaboration across biomedical engineering, materials science, integrated circuit design, mechanical systems, multi-omics analytics, and clinical translation.

At the biomarker level, current monitoring remains limited to a small set of known targets. Future advances require systematic identification of candidate molecules that display defined spatiotemporal expression, remain stable in GI fluids, and are highly specific to disease states.[193] Such molecules provide the foundation for building highly specific diagnostic models and impose explicit requirements on capsule dwell time and active locomotion. In sensor design, achieving high sensitivity and high selectivity is equally critical. This depends on constructing molecular-recognition interfaces capable of detecting trace targets such as nucleic acids, proteins, and small molecules, coupled to signal-amplification schemes that include enzymatic reactions, nanocatalysis, nucleic acid amplification, and immune-bridging amplification, thereby enabling a high signal-to-noise ratio and dynamic response.[194] At the same time, interference from the *in vivo* environment must be addressed through strategies such as surface engineering, physical isolation, and tissue adhesion to resist both physical and chemical perturbations. At the system-integration level, electronic capsules must tightly couple sensing, signal acquisition, energy supply, and wireless communication within a highly miniaturized form factor. This directly affects device safety and user experience and places stringent demands on ultra-low-power circuit design, wireless power transfer, and mechanical architecture. In addition, materials and encapsulation must be optimized to ensure long-term structural stability and biosafety, which is the essential prerequisite for regulatory approval and eventual clinical adoption. Looking ahead, ingestible capsules will evolve from single-purpose diagnostic tools into fully integrated theranostic platforms. By incorporating therapeutic modules such as micro-drug delivery, electrical stimulation units, or engineered microbes, electronic capsule platforms will inaugurate a new era of integrated precision diagnostics and targeted interventions in medicine.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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