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Review

Ingestible Sensors and Sensing Systems for Minimally Invasive Diagnosis and Monitoring: The Next Frontier in Minimally Invasive Screening

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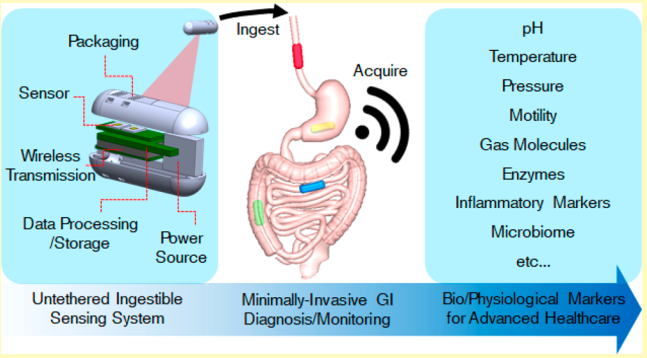
ABSTRACT: Ingestible electronic systems that are capable of embedded sensing, particularly within the gastrointestinal (GI) tract and its accessory organs, have the potential to screen for diseases that are difficult if not impossible to detect at an early stage using other means. Furthermore, these devices have the potential to (1) reduce labor and facility costs for a variety of procedures, (2) promote research for discovering new biomarker targets for associated pathologies, (3) promote the development of autonomous or semiautonomous diagnostic aids for consumers, and (4) provide a foundation for epithelially targeted therapeutic interventions. These technological advances have the potential to make disease surveillance and treatment far more effective for a variety of conditions, allowing patients to lead longer and more productive lives. This review will examine the conventional techniques, as well as ingestible sensors and sensing systems that are currently under development for use in disease screening and diagnosis for GI disorders. Design considerations, fabrication, and applications will be discussed.



KEYWORDS: *swallowable sensors, ingestible capsules, wireless electronics, sensing systems, microsystems, minimally invasive diagnosis, chronic disease monitoring, gastrointestinal monitoring*

THE NEED FOR IMPROVED HEALTH SCREENINGS

The United States spends far more on healthcare than any other industrialized nation with little, if any, measurable benefit in health outcomes (as compared to peer nations).[1] The reasons behind this include (1) a lack of focus on prevention of illness and (2) the more prevalent use of higher cost healthcare technologies, such as magnetic resonance imaging (MRI), as compared to other industrialized nations.[1] A focus on prevention and disease intervention at early stages could therefore lead to better health outcomes with decreased costs for society as a whole. The population-based screening techniques applied for colon cancer screenings (i.e., colonoscopy) are an excellent example, leading to as much as a 67% reduction in disease incidence (according to one study).[2,3]

As will be discussed throughout this review, there are many opportunities that can be addressed by ingestible capsule systems including gastrointestinal (GI) tract disease screening, local delivery of drugs to the GI tract, easier administration of systemic therapies, and possibly even screening for diseases in other abdominal organs. A great deal of work is needed in the development of both sensors and associated systems to make these technologies a reality. These technologies truly represent a new frontier in ambulatory care and have the potential to reduce both the burden to patients with chronic diseases that require periodic surveillance as well as the cost to the healthcare system. As noted, there are a myriad of clinical problems that can benefit from swallowable sensors and sensing systems. An analysis of the ingestible capsule market indicates significant growth in the future, due to both the advanced capabilities being achieved with newly developed technologies for diagnosis and monitoring along with the increasing occurrence of GI conditions. A recent report specifies an expected $627.1 M increase and a compound annual growth rate of approximately 21.2% during 2015−2020.[4] The report discusses approaches including capsule

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endoscopes and GI monitoring technologies; both are further elaborated in this review.

OPPORTUNITIES FOR INGESTIBLE DEVICES

Early Diagnosis and Screening for Disease. Secretions of the gut consist primarily of digestive enzymes and the means for ensuring their proper function, such as ions to maintain appropriate pH balance (i.e., HCO_3^- from the pancreas); other ions (i.e., H^+, K^+, Cl^-, and Na^+) also ensure proper nutrient transport across the GI tract wall. Additional contents include mucus, for lubrication and protection, and bile, which emulsifies lipids aiding in absorption. These compounds (and proteins) are one class of potential biomarkers of GI function.

Cancer screening and early detection within the GI tract and its accessory organs is of particular interest. In addition to the aforementioned colon cancer screening, pancreatic cancer is a disease that would benefit from GI-targeted, population-based screening. Treatment is possible if found early; this is often not possible, however, as the pancreas lies behind most of the abdominal contents in the retroperitoneum, where a tumor can grow for long periods of time without causing symptoms.[5] Currently, the only way to effectively screen for pancreatic cancer is through imaging (i.e., MRI, computed tomography (CT), and endoscopic ultrasound (EUS)). Using these imaging techniques for screening on a population basis would be prohibitively expensive, especially given that pancreatic cancer is relatively rare. Pancreatic cancer is therefore a prime example of a disease process where the development of a cost-effective swallowable sensor or capsule for screening could be beneficial. There is not currently a cost-effective screening method, but if detected early, the prognosis is much more favorable.

Disease Surveillance. In addition to screening or early detection of difficult-to-diagnose cancers, ingestible technologies have potential applications in chronic disease surveillance. Three specific examples of chronic diseases of the GI tract that require periodic surveillance are Barrett's esophagus, Crohn's disease, and ulcerative colitis (UC), of which the latter two are often grouped together as inflammatory bowel disease (IBD). Both IBD and Barrett's esophagus are inflammatory conditions where tissue changes over time can eventually lead to cancer development. IBD comprises a spectrum of diseases that can affect the entire GI tract. Specifically, Crohn's disease can affect the gut anywhere from the mouth to the anus, usually in a noncontinuous fashion, while UC only affects the colon, with the disease progressing up the GI tract from the rectum in a continuous fashion.[6] There is a degree of overlap between both disease processes, specifically that they are multifactorial, as each involves interaction of the bowel wall, bacteria within the bowel lumen, and the immune system.[6] Barrett's esophagus is due to repeated exposure of the esophagus to stomach acid and is associated with gastresophageal reflux disease (GERD).[7] GERD is a chronic condition where, for several different reasons, stomach acid is able to exit the stomach and enter the esophagus. This irritates esophageal tissue, leading to what is commonly known as heartburn. If the condition persists over time, it can lead to histological changes in the esophageal tissue, such as replacement of normal esophageal cells with cells that resemble those in the intestine, eventually leading to abnormal cell growth (dysplasia) and cancer.[7−9]

In both Barrett's esophagus and IBD, repeated screening is needed to detect precancerous lesions so that they can be treated or, if the extent of the lesions is great enough, the esophagus or colon can be removed to prevent cancer development.[7,10] For example, the recommendation for Barrett's esophagus is to perform two endoscopies with biopsy within one year of the initial diagnosis and then repeat the screening endoscopy every one to three years if no dysplasia is found. If dysplasia is present, particularly high grade, screenings must be repeated as often as every 3 months.[7] There is interest in using an endoscopy capsule for screening Barrett's esophagus patients, though there are concerns about the cost of the endoscopy capsules.[7] A cost-effective capsule screening technology for Barrett's esophagus could help aid in more timely diagnosis as well as improved quality of life for patients, who would no longer need anesthesia for repeated screening.

In UC and Crohn's colitis, a colonoscopy to screen for cancer is recommended to be performed within 8−10 years of initial diagnosis. Further screenings are performed every 1−2 years depending on the disease severity and even more often (as frequently as 3 month intervals) if dysplasia is found.[10] Additional requirements may include tissue biopsy for monitoring dysplasia (i.e., presence of precancerous cells).[6] A screening option bypassing such requirements that could be performed in ones' home or in an outpatient setting could greatly reduce the burden to patients with these diseases, as well as expected facility and labor costs. Ingestible sensors could find numerous applications in the repeated monitoring that is needed for these patients. In both, real-time surveillance of treatment effectiveness as well as fewer requirements for anesthesia during screening procedures have the potential to greatly improve patient quality of life.

Novel Insights into Disease Biology and Pathogenesis. The unknown (or not fully understood) etiology of IBD highlights another potential application area for ingestible systems: that of trying to understand the complex system biology that underlies disease. For instance, understanding the interaction between the gut microbiome and inflammation may offer insights into the pathogenesis of IBD. More specifically, mapping areas of inflammation within the gut to changes in pro-inflammatory markers released by commensal bacteria could be one potential direction in understanding how Crohn's disease or other associated IBD pathologies are related to gut microbiome activity. Furthermore, the ability to map these inflammatory changes could improve treatment strategies and facilitate more frequent monitoring of IBD patients without the burden of repeated endoscopies.[11,12] A review on IBD and various methods to address its further challenges can be found in ref 13.

Another example of a potential clinical application for swallowable and ingestible diagnostics is GI motility and pressure monitoring. These parameters are of interest in several different disease processes, including the diagnosis of constipation and gastroparesis.[14−18] Constipation is defined by the inability to move ones' bowels or incomplete emptying of the bowels, while gastroparesis is a condition where the contents do not move through the stomach properly, leading to discomfort, indigestion, and poor nutrition.[6] Gastroparesis in particular is likely to become more prevalent because it is associated with diabetes, the incidence of which is also growing due to the obesity epidemic.[19−24] Despite the high prevalence of these disorders, there are no simple and inexpensive systems to render the diagnosis. More importantly, knowledge of the underlying pathophysiology in most of these disorders has

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been stymied by the lack of technologies that can more directly measure nerve and muscle function rather than rely on surrogate markers such as transit time. These gaps in our knowledge have proven to be a major obstacle in the development of rational pharmacological treatments.

Overall, it is clear that there are many disease processes, chronic disease surveillance applications, and population-based screening needs that require lower-cost and minimally invasive solutions. Imaging techniques and conventional endoscopy are unable to meet all demands of these applications. A major advantage of swallowable sensors and sensing systems is their ability to reach areas of the GI tract not easily accessible by traditional endoscopy. Improving access to these regions will inherently broaden the ability to screen for other conditions as well as other organs in the body that are adjacent to or drain secretions into the GI tract (i.e., the pancreas, liver, and spleen). As a result, ingestible devices could provide opportunities for accessing information from secretions of these other organs, offering utility for diagnostic/screening purposes.

This review will cover (1) the conventionally used endoscopic techniques, (2) commercially available ingestible capsule products, and (3) ingestible sensors and sensing systems that are currently under development to meet the stringent demands of this application.

EXAMPLES OF CONVENTIONAL GI INTERVENTIONS

A common conventional GI intervention technique, as mentioned earlier, is endoscopy, where a camera attached to a flexible fiber-optic tube is inserted into the GI tract to allow for interior examination of the organ. The location of insertion is dependent on the portion of the tract that warrants inspection. For upper GI endoscopy, the tube is inserted into the mouth, whereas a colonoscopy requires insertion through the anus. Upper GI endoscopy is typically used to examine the esophagus, stomach, and duodenum, while colonoscopy is used to examine the colon (the colon is typically ∼1 m long in most patients). Both techniques can be augmented with balloon endoscopy where balloons can be inflated, fixing the endoscope in the bowel and allowing the bowel to be drawn toward and pleated over the endoscope.[25] This can extend endoscopy into examination of portions of the small bowel, though these methods are complex and time-consuming. Endoscopy generally requires some form of sedation, limiting its use to hospitals or clinics with the appropriate expertise and patient monitoring equipment. Figure 1 contains a diagram of basic GI anatomy which can be used as a reference for the following discussion.

Endoscopy is used for a variety of purposes, such as detecting bleeding, inflammation, and neoplasms.[27] The most attractive features of endoscopy are its ability to intervene within the GI tract with minimal pain, quick post-procedure recovery, and a low risk of mortality. Endoscopy is often used for disease screening and the treatment of inflammatory conditions and precancerous lesions, including the detection and removal of polyps in the colon or the surveillance and treatment of Barrett's esophagus.[28] Endoscopes are designed with ports that allow the insertion of instruments through the scope for removal of biopsy specimens or treatment of identified lesions. EUS is an additional adjunct to endoscopy which can be particularly useful for further staging and treatment planning once a lesion has been found, as well as for

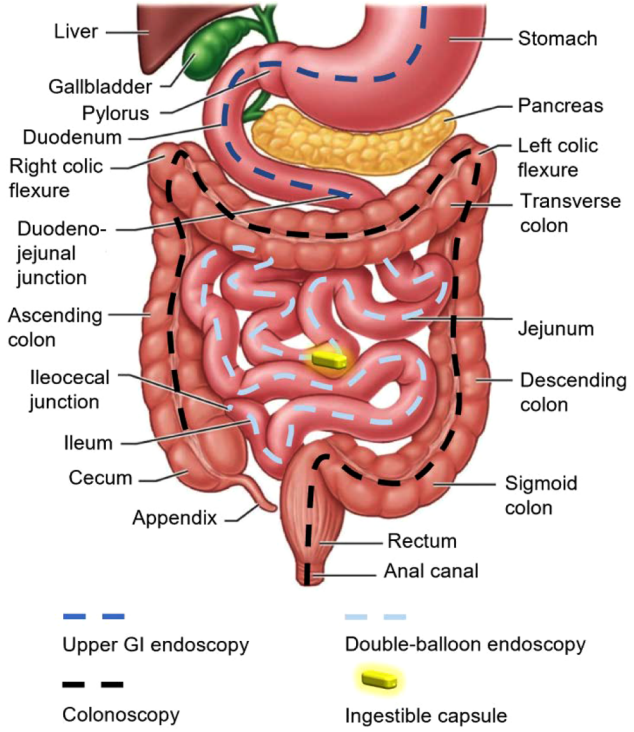

Figure 1. Relevant anatomy for GI monitoring (Reprinted with permission from ref 26. Copyright 2017 Jotscroll.com.) with indications of accessible GI regions for different methods.[26]

investigating the extent of tumor invasion or lymph node involvement.[29,30]

Endoscopy is often combined with other imaging and diagnostic methods to expand its utility and access to more areas of the body. For example, in endoscopic retrograde cholangiopancreatography (ERCP), the sphincter of Oddi (where the common bile duct intersects the duodenum, allowing products from the liver and pancreas to be injected into the GI tract) is cannulated using an endoscope, allowing for the injection of radiocontrast into the common bile duct or pancreatic duct; fluoroscopy is then used as an additional means to look for abnormalities.[6] ERCP is useful for detecting choledocholithiasis (gallstones) or strictures, whereas for pancreatic diseases ERCP is capable of diagnosing chronic pancreatitis, pancreatic duct leakage, pseudocysts (fluid collection), or even later stage pancreatic cancer.[31] In most cases, newer imaging methods such as magnetic resonance cholangiopancreatography (MRCP) are replacing ERCP for diagnostic purposes, and ERCP is increasingly becoming an exclusively therapeutic procedure.[31−33]

As with any other method, endoscopy has limitations. Most notably, it can only readily image several feet into the GI tract, while most humans have ∼7.5 m (25 feet) feet of intestine.[34] Although enteroscopy, a technique using a very long scope with ancillary features to advance the instrument to greater lengths, is available, inspection is typically not thorough and the procedure is time-consuming and requires a high degree of skill. Capsule endoscopes, such as the PillCam (Medtronic, Minneapolis MN), are tools that have been developed to address these limitations. Camera-based imaging in pills has been used for a variety of purposes,[35−38] but principally to detect bleeding or neoplastic lesions in the small intestine that cannot be readily reached using traditional endoscopy. Capsule

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endoscopy devices have been developed for imaging the small intestine and colon but are most commonly applied to the small intestine.[39,40] The location of the capsule in the GI tract can be determined by several methods, including GI transit time, combining information from pH and pressure sensors, identifying unique morphology of different GI regions, magnetic methods, and radiographic tracking (i.e., using X-rays).[41] A thorough review of capsule endoscopy and its uses can be found in ref 42.

One final commonly encountered application of the current minimally invasive GI intervention methods is esophageal pH and motility monitoring.[6] These studies are performed in patients suffering from GERD or, in the latter case, who are having trouble swallowing. Monitoring of esophageal contraction is performed using a catheter containing pressure sensors inserted into the esophagus to measure the pressure waveform of the esophageal contraction.[6] Monitoring pH can be accomplished using a catheter that is inserted and stays in place (in similar fashion to monitoring esophageal contractions) as well as using an endoscopically placed wireless-based capsule that sloughs off spontaneously over the course of the next few days.[6]

Currently used methods are effective but are not without risk. The most feared, although uncommon, major complications of both upper and lower GI endoscopy are bleeding and perforation. Interestingly, the most common complication of such procedures is a cardiopulmonary event (such as an arrythmia or a heart attack), often due to the sedation that is required to perform the procedure.[43,44] Furthermore, endoscopy is labor-intensive, requires the use of advanced facilities, and involves patient sedation. This can be particularly burdensome when repeated surveillance is required, for example, in Barrett's esophagus[7] or UC.[45,46] In addition, improved techniques are needed to locate neoplastic lesions or other abnormalities within the small intestine that are difficult to reach using traditional endoscopy.[47] Capsule-based endoscopy technologies address some of these shortcomings.

As will be covered below, low-cost, real-time sensors and sensing systems need to be specifically tailored to a disease process and a patient population to be fully effective. Instead of a one-size-fits-all approach, different methods must be developed for specific applications. Several sensing devices are commercially available, while others are under development. Both will be covered in the sections below, as well as microsystem and biosensor design principles underlying their development.

DESIGN CONSIDERATIONS FOR INGESTIBLE SENSORS AND SENSING SYSTEMS

There are many requirements to consider in designing ingestible systems, and they accumulate with increasing complexity. Several of them include size, power consumption, sampling rate, packaging, data storage/transmission, and materials compatibility.[48] The sensor or sensing system must be small enough to be swallowed and capable of passing through the GI tract without causing obstruction.[39,40] The swallowability of the capsule likely may not only hinge on its size but also on other factors such as its texture or shape. The materials comprising the capsule system are a key consideration for both functionality and biocompatibility. A review of materials for ingestible electromechanical systems, which covers a variety of areas, can be found in ref 49. A key specification in the design is the overall size of the device. As mentioned in Figure 2, some of the commercially available swallowable systems range in length from 24.5 to 28 mm and in diameter from 10.8 to 13 mm.

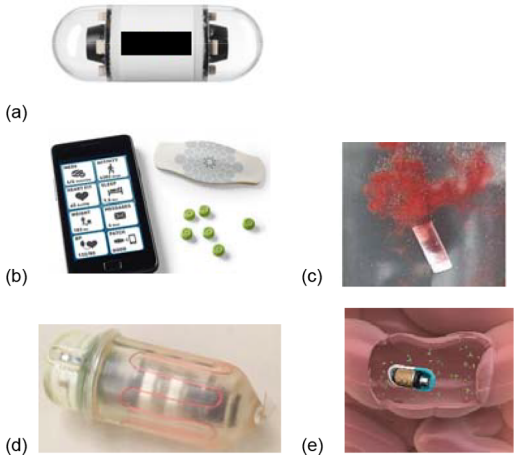

Figure 2. Images of commercial, off-the-shelf swallowable sensing systems: (a) PillCam (Medtronic, Minneapolis MN) (Reprinted with permission from ref 97. Copyright 2020 Medtronic).[97] (b) The Proteus Digital Health Feedback System (Proteus Digital Health, Redwood City CA) (Reprinted with permission from ref 71. Copyright 2009 IEEE).[71] (c) The IntelliSite Capsule (Casper Associates, Sanford NC) (Reprinted with permission from ref 98. Copyright 2016 Scintipharma/Casper Associates).[98] (d) Wireless Motility/pH Capsule ((Medtronic, Minneapolis MN), (Reprinted with permission from ref 99. Copyright 2011 Gastroenterology & Hepatology). (e) Atmo Gas Capsule (Atmo BioSciences, Box Hill, Victoria, Australia) (Reprinted with permission from ref 100. Copyright 2018 Atmo Biosciences).[100] For a size comparison, the commercially available endoscopic capsules for small bowel imaging such as the PillCam (shown above) range in length from 24.5 to 28 mm and in diameter from 10.8 to 13 mm.[39]

Power management and power consumption are key considerations given the stringent size requirements for capsule sensing systems, as well as the limited availability of small batteries that can produce large amounts of current for sustained periods of time. A review of power sources for implantable systems can be found in ref 50. In the research setting, a variety of different batteries have been utilized. Lithium ion or lithium polymer coin cells are often used when higher currents are needed.[51] Energy harvesting is an additional means that is under investigation for powering ingestible capsule systems. One example of a developed power harvesting scheme is generating current from stomach acid using a zinc−copper galvanic cell.[52] Others are also possible, such as those requiring motion from biomechanical energy.[53−55] In addition, the intestines are a major site of diverse chemical reactions involved in the digestion of food, which can also serve as a source of harvestable energy for generating electrical currents.

Sensors and actuators are the main functional components of these ingestible systems, as they perform measurements and tasks to address underlying symptoms of disease. Ingestible sensors can be designed to measure specific biomarkers (e.g., gas,[56,57] blood,[58−60] molecules[61,62]) or physiological conditions (e.g., temperature, pH, pressure[63]) or perform location tracking using O_2 levels[56] or magnetic sensing.[64] These sensors all function as transducers, converting molecular, mechanical, electromagnetic, or thermal energy (among others) into

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electrical currents for integration with downstream electronics. pH sensors are commonly used in ingestible systems, taking advantage of the distinct pH gradient along the GI tract for health monitoring or region-targeted actuation. ISFETs (ion sensitive field effect transistors) are an alternative to glass electrodes, which measure the effect of H+ ions on current through a p/n channel.[65] The response of these transducers can be tuned for sensitivity and specificity to a given input by engineering the sensor interface.

Molecular biosensors are also useful for detecting the presence of specific compounds within the GI tract. Biosensor design generally follows a common scheme, in which a biorecognition element (e.g., receptor, selective membrane) specifically, interacts with a biological analyte of interest (e.g., gas, molecular biomarkers). A transduction element (e.g., some form of transducer) then detects the analyte through interaction with the biorecognition element, creating an electrical signal for data processing, quantification, and communication. A range of different micro- and nanoscale biosensors and transducers have been developed for a variety of applications.[66] The selection of transducer will depend on the analyte of interest and the desired transduction mechanism. Basic transducer types include gravimetric (mass-sensitive), capacitive, electrochemical, impedimetric, resistive/conductive, field-effect, and optical among others.[66,67] Different types of analytes are more readily detectible using some types of sensors but not others. For example, compounds that undergo oxidation/reduction reactions (e.g., ascorbic acid, biomarker of oxidative stress[68,69]) are readily detectable by electrochemical methods. Alternatively, analytes that induce a large change in dielectric constant at the surface of a sensor (e.g., an enzyme dissolving a specific coating) may be readily detectable by capacitive sensors. Often, an analyte can be detected by more than one method and the selection of transducer in this case will have to be considered alongside the circuit and system design. For example, a system that is battery-powered where highly specific analyte detection is required may be best-equipped with an electrochemical sensor, while a capacitive transducer may be more readily incorporated into a passive system.

Microfabricated sensors and actuators are of particular interest because of their small size, low power consumption, and potential for batch fabrication, which reduces the per-unit cost. An overview of microfabrication methods can be found in several texts including refs 66 and 70. In addition, microfabricated sensors that are made using materials and tooling from the semiconductor electronics industry have the potential for integration with complementary metal oxide semiconductor (CMOS) electronics, reducing the needed tooling to fabricate these types of sensors. One commercialized sensor has already taken advantage of integration with CMOS electronics.[71] Several examples of microfabricated sensors and actuators for ingestible systems are discussed below.

The sensor types and circuitry to run the sensor is, in many ways, the most important consideration when designing an ingestible sensing system. The discussion of the electrical interface circuity for the sensor is tightly linked to the discussion of the sensor selection, since different circuits are needed depending on the employed sensor. For example, an electrochemical sensor requires a potentiostat for its readout, which is a circuit that applies specific voltages and measures the resulting current, while an impedimetric sensor requires a circuit which is able to excite the sensor with an electrical signal at a specific frequency and then measure the resulting voltage signal. The chosen back-end electronics must be able to interface with the sensor circuit. Some circuits produce a simple analog output, which can, for example, be read using an analog-to-digital converter on a microcontroller, while other types of readout circuitry (particularly commercially available integrated circuits (ICs)) may require a specific type of serial interface (i.e., serial peripheral interface or a universal asynchronous receiver transmitter).

Data sampling and storage are a major consideration for any sensing system. Trade-offs to consider in ingestible systems include whether to use an active (i.e., internally powered system that can measure, receive, and transmit data) or a passive system (i.e., a passive LC resonant based system), whether to store the data locally or transmit it later, and the sampling rate requirements (i.e., at what rate data must be collected in order to properly reconstruct the signal of interest). Passive systems have the advantage that they do not need to be powered; however, they have the limitation that external equipment is needed to interrogate their signals, and it can be difficult to add multiple channels.[72,73] Active systems tend to be larger due to the battery and are limited by their battery life. Both systems face the challenge of transmission efficiency through body tissue.

Sampling rate is important to consider due to the significant trade-off between power consumption and sampling rate (i.e., sampling at higher rates will burn more power). Furthermore, radiofrequency (RF) transmission can consume large amounts of power, though this can be mitigated with intermittent sampling and the use of lower power modes of operation in between sampling or data transmission periods. The sampling consideration is generally clinically driven depending on the biological signals being investigated. Finally, the questions of where to store the data and whether to transmit it in real time are both clinically and technically driven.

Real-time data transmission can be very attractive in clinical situations where rapid intervention may be needed (i.e., in localizing major bleeding), but it requires a compact and efficient RF system. The United States Federal Communications Commission has specified the Medical Device Radiocommunications Service lying approximately between 401 and 457 MHz. Thus, this frequency band is approved specifically for communicating with implantable medical devices.[74] Several of the commercial video endoscopy capsules are capable of real-time data transmission to a vest that the patient wears. However, the use of other commercial communications frequencies have been utilized to interface with ingestible sensors. Compact antenna designs for commonly used frequencies (i.e., 433 MHz and 2.4 GHz) can be a challenge because, in terms of efficiency, the optimal antenna size is one-half the wavelength for a given transmission frequency, often making the antenna much larger than the system. Higher frequencies are therefore desirable for compact systems because of the potentially reduced system size. However, there are several additional trade-offs to consider. First, the selected frequency should ideally be associated with a commonly used signal band to allow the design to take advantage of existing transmitter and receiver technologies. Second, the absorbance of water differs at different frequencies. For example, water has a high absorbance at 2.4 GHz, the frequency for Bluetooth data transmission, making this frequency somewhat less desirable. In one case, the optimal antenna design for miniaturized capsule systems was

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investigated as well as tested in several phantoms that imitate live tissue.[75] Local storage can be performed reliably using a variety of available compact memory integrated circuits (ICs) but requires recovery of the capsule for data analysis and cannot provide real-time information.

The STORM Lab Open Source Architecture for Capsules (SMAC) is an open source platform that integrates several different modules that can perform many of the functions listed above, including sensor interface electronics and wireless data transmission. The modules can be connected using connectors that plug into a flexible interconnect. The entire system offers a starting place for capsule design.[76,77]

Mechanical actuator design is necessary for applications that require placement of sampling and delivery modules at targeted locations, especially for those that require close proximity to the epithelium interface, where a high concentration of biomolecules/microbiome activities can be found with high therapeutic absorption efficacy.[78] An effective actuation design needs sufficient displacements and forces to the local geometric and peristaltic demands. Additionally, the effects of food and GI liquid must be considered as well. Specifically, the stomach offers more opportunities for the actuation design as it is relatively larger and easier to access[6] compared to the small intestine and colon at the lower GI tract. Peristaltic contractions occur in wave patterns traveling down short lengths of the GI tract from one section to the next. The measured small intestine peristaltic contact pressure, contraction pressure, and propagation speed are of 0.29 kPa, 1.08 kPa, and 0.08−2 cm/s, respectively.[79−83] A preferable actuation design targeting the lower GI tract should have a small form factor and reduced power consumption or a passive mechanism. Commonly used actuators include precompressed springs[84−87] and flexures,[88,89] balloons,[90,91] and magnets.[92−94]

A key consideration from both an engineering and medical perspective are the materials requirements to meet both the specifications of the system as well as the stringent biocompatibility requirements for medical devices. Materials to be used must be tested for toxicity, genotoxicity, and carcinogenicity, among other concerns.[95] In addition, the packaging materials need to meet the requirements of the device, including adequate sealing of components, protection from corrosive GI contents, and proper electrical insulation of components to protect both the patient and the system. In addition, electronics and other components may dissipate heat, which could cause the temperature of the capsule itself to rise. Proper thermal management is important to ensure that the capsule temperature does not rise to unsafe levels, which could cause burns to the GI tract. These are important considerations from the outset of the device development process. Different manufacturing processes are only compatible with certain materials, for example. This can be especially true for chemical processing as it occurs in micro/nanomanufacturing, where specific material properties (i.e., photo-cross-linking) may be needed.[96]

Ultimately, the success of any devices hinges on, first, the development of relevant design requirements based on a specific clinical problem that needs to be solved, and then, the development of a system based on these specifications where each of the components work cohesively to achieve the desired goal.

COMMERCIALLY AVAILABLE INGESTIBLE SENSING SYSTEMS

Additional commercially available ingestible diagnostic systems are available for a variety of purposes; Table 1 provides a summary of the commercially available devices. Capsule endoscopy (e.g., PillCam) is mentioned above and has been extensively covered in previous reviews and, therefore, will not be focused on here.[48,101−103]

During physiology experiments or work/competition in extreme environments (among others), it can be desirable to easily measure a person's core body temperature. This is to ensure that they are not becoming hypo/hyperthermic. Using an ingestible sensor, these values can readily be obtained compared to the traditional methods (i.e., rectal thermometer), providing a more desirable method for patients/participants. Two examples are the CorTemp, made by HQinc (Palmetto, FL) and the VitalSense Jonah capsule, made by Phillips (Amsterdam, Netherlands). These pills can potentially be used for noninvasive core temperature monitoring in a variety of settings where individuals may be working or competing in athletic events.[104−107]

The Proteus Discover, produced by Proteus Digital Health (Redwood City, CA), addresses the burdensome problem of medication compliance. Fewer than 50% of patients take their medication every day or as directed.[108−111] This is a major issue as chronic diseases, which often require daily medication use for adequate management, are becoming more prevalent. Specifically, noncompliance with medication is estimated to cost the US healthcare system $289 billion every year.[71] Proteus uses a microfabricated device that can be inserted into a conventional medication capsule during manufacturing. When the pill with the Proteus sensor reaches the stomach, the metal layers on the surface of the microfabricated chip react with stomach acid and produce a voltage through electrochemical reactions. The voltage is used to power a CMOS circuit, which transmits a unique code to an external patch, indicating that the pill has been ingested. The signal transmission is accomplished by conduction of the current generated by the pill through the tissue of the body. The patch then relays the information to a smartphone or tablet.[71]

There are also commercial capsule systems that are capable of measuring specific physiological parameters. The SmartPill, made by Medtronic (Minneapolis, MN), can measure pH, temperature, and pressure from within the GI tract, though it has mainly been used to measure transit time in different regions of the gut.[99] Prolonged esophageal pH monitoring can be useful in the diagnosis of GERD and in deciding whether additional treatment or surgery is necessary.[6] The Bravo Capsule, also made by Medtronic, is attached endoscopically with the assistance of vacuum suction to the esophageal wall and is held into place using a steel pin deployed from the capsule. It is capable of extended esophageal pH monitoring toward obtaining a better understanding of reflux symptoms.[112−114] Both devices are for use in the upper GI tract and are aimed at improving chronic disease management.

A capsule system has also been commercialized to treat patients who suffer from chronic constipation. The Vibrant capsule (Vibrant, Ltd., Hakochav, Yokneam, Israel) uses vibration to induce peristalsis in the intestine to allow material to continue moving through the GI tract, thereby relieving constipation; it is currently undergoing clinical trials. The

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Table 1. Summary of Specifications for Commercially Available Swallowable Sensing Systems

device name	manufacturer	medical application	sensor/actuator type	dimension	power details	sample/operation frequency	operating range	references
PillCam	Medtronic	Morphological Imaging	Miniature video camera	11 mm × 26 mm (SB Video)	Battery Lifetime: 10 h (PillCam Crohn's Capsule)	Video/434 MHz	20–40 °C (specific model dependent)	116−118
Vital Sense Jonah	Philips	Core Body Temperature	Thermometer	23 mm × ϕ8.7 mm	Battery Lifetime: 10 d	Sampling: 1/15 Hz	−10 to 60 °C	104,106,107
CorTemp	HQinc	Core Body Temperature	Thermometer	22.4 mm × ϕ10.9 mm	Battery Lifetime: 7−10 d	Sampling: <0.1 Hz	30−45 °C	104,107
Bravo	Medtronic	GERD, Acid Reflux	pH sensor, Vacuum-based esophageal attachment	25 mm × 6 mm × 5.5 mm	Battery Lifetime: Up to 4 d	Sampling: 1/3 Hz	pH: 1−7	112−114
Proteus Pill	Proteus Digital Health	Medication Compliance Tracking	Stomach acid-dependent battery	5 mm × 5 mm × 0.6 mm	Acid activation	Sampling: 2 Hz; Operation: 10−30 kHz	N.A.	71,119−121
Vibrant Capsule	Vibrant Ltd.	Constipation Relief	Vibrational actuator	24.2 mm × ϕ11.3 mm	Electromagnetic actuation	N.A.	240 cycles	115,122
IntelliSite Capsule	Scintipharma	Drug Delivery	RF-triggered release of shape memory alloy spring	35 mm × ϕ10 mm	RF actuation	Operation: 6.78 MHz	N.A.	98,123
SmartPill	Medtronic	Gastroparesis, GI/Colonic transit time	Temperature sensor, pH sensor, Intraluminal pressure sensor	26.8 mm × ϕ11.7 mm	Battery Lifetime: >5 d	Sampling: 1/20 Hz (0−24 h); 1/40 Hz (>24 h); Operation: 434 MHz	Temp.: 25−49 °C; pH: 0.05−9.0; Pressure: 0−350 mmHg	99,124
Atmo Gas Capsule	Atmo Biosciences	Region-specific gut microbiome fermentation activity	Gas Sensors: CO_2, H_2, O_2 Temperature sensor	26 mm × ϕ9.8 mm	>1 d	Operation: 433 MHz	Not Available	56

capsule can receive data from an external base unit (also made by Vibrant) which is able to activate the capsule.[115]

The last example of a commercially available capsule system we discuss here is the IntelliSite Capsule (Casper Associates, Sanford, NC). The IntelliSite is meant to deliver pharmaceuticals under development to specific areas of the GI tract for the purpose of studying their absorption and distribution. The capsule is controlled via a radiofrequency link and when the desired location with the GI tract is reached, an RF signal actuates a spring-loaded mechanism to release the contents of a reservoir within the capsule. The IntelliSite capsule is meant more as a research and development tool to tailor drug delivery rather than a clinical treatment.[98]

Thus, it can be seen that although commercialized devices are available for a few indications, they are limited in their ability to provide the kind of information that is necessary to address all the unmet needs described in Opportunities for Ingestible Devices. For example, there are no currently available systems that can screen for specific molecules or compounds within the GI tract. Furthermore, there are few examples of active systems that are able to both sense an abnormality, such as a lesion, and then take action to intervene. These active systems have the potential to intervene in areas of the GI tract that are beyond the reach of traditional endoscopic techniques. A full understanding of the medical problem/need is a key step in delivering a usable device to the clinic, but present devices have not yet taken advantage of the transformative advances made in electronics, sensors, packaging, powering, and systems integration tools. A key consideration in this front is the fabrication and packaging methods that make the system integration and assembly possible.

INGESTIBLE SENSORS

Single sensor devices are a class of ingestible diagnostics that can come in many forms and can perform a variety of functions. They are distinct from the commercialized capsule systems presented previously as well as the capsule systems under development that are presented below in that they are sensors with little electronics integration and are not fully implemented systems capable of data processing and storage. However, there is some overlap between the single sensors and the capsule systems. The distinction made here is that the single sensors only perform one function (i.e., magnetic tracking), regardless of shape. Nonetheless, these systems are useful because of their simplicity in comparison to capsule systems and can offer specific advantages, such as being biodegradable.

Edible devices fabricated from food-based materials represent an interesting class of sensors for ingestible applications.[125,126] Transforming food materials into electronics is a field unto itself. In some cases, edible materials can also be used as a biomaterials interface with traditional electronics; for example, films made from gelatin over impedance sensors have been used to sense pancreatic enzymes such as trypsin.[127] Additionally, preliminary trials with composite films made from triglycerides and glycerol have indicated that these films will dissolve in response to varying concentrations of duodenal contents such as pancreatic lipase and bile salts via hydrolysis and emulsification reactions, respectively. The deposition of these films over MEMS capacitance sensors and the resulting change in capacitance in response to enzymatic film removal is a method of

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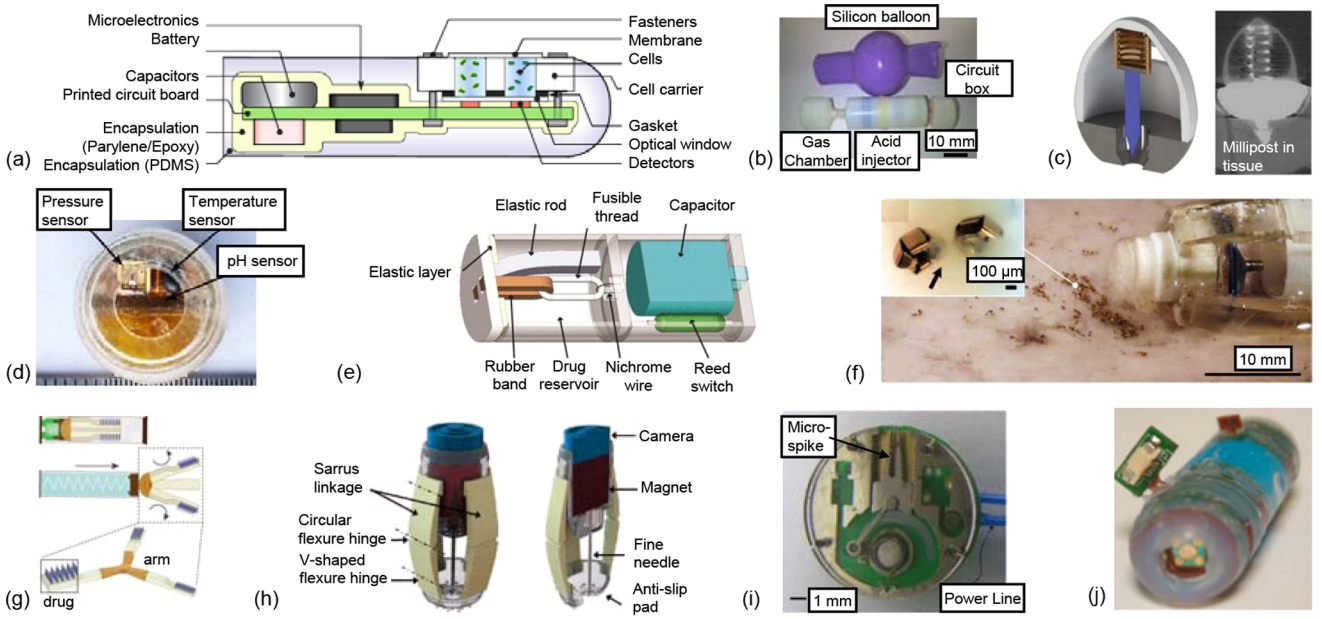

Figure 3. Examples of capsule systems from the published literature: (a) Image of a capsule using live bacteria to detect hemoglobin within the GI tract (Reprinted with permission from ref 59. Copyright 2018 Science).[59] (b) Ingestible capsule with an inflatable balloon for tamponade of GI hemorrhage (Reprinted with permission from ref 90. Copyright 2016 IEEE).[90] (c) Bioinspired, self-orienting applicator for active insulin delivery (Reprinted with permission from ref 89. Copyright 2019 Science).[89] (d) Ingestible capsule system integrating a MEMS pH sensor and an ASIC (Reprinted with permission from ref 63. Copyright 2017 IEEE).[63] (e) Smart capsule for targeted GI tract drug delivery (Reprinted with permission from ref 163. Copyright 2015 IEEE).[163] (f) Ingestible capsule capable of releasing a retrievable microgripper for tissue biopsy (Reprinted with permission from ref 157. Copyright 2013 IEEE).[157] (g) Passive folded microneedle drug delivery device that is released from the capsule by the dissolution of an enteric coating and the release of a compressed spring (Reprinted with permission from ref 164. Copyright 2019 Nature Medicine).[164] (h) Magnetic actuation mechanism for a capsule needle biopsy device (Reprinted with permission from ref 94. Copyright 2017 IEEE).[94] (i) Nickel-plated torsional spring actuated mechanism for obtaining biopsies in an endoscopic capsule (Reprinted with permission from ref 159. Copyright 2008 Journal of Micromechanics and Microengineering).[159] (j) Ingestible electrochemical sensing system encapsulated in PEEK (Reprinted with permission from ref 58. Copyright 2015 Elsevier).[58]

quantifying the concentration of these enzymes.[128] Current research in this area has been reviewed in several recent articles.[129,130] Items ranging from discrete electrical components to piezoelectric components, such as microphones for listening to bowel sounds, have been constructed using edible materials.[130] An additional class of sensors, made from ingestible materials but directed toward detecting food spoilage, have been demonstrated using silk proteins.[131] These sensors are of interest because of the applicability of the same materials for use in other ingestible applications. Along those lines, Kim et al. demonstrated a fully edible electrochemical sensor that can be placed on a variety of foods. The sensor consists of activated conductive carbon held together using an oil binder.[132]

Along similar lines, Ruiz-Valdepeñas Montiel et al. developed an ingestible electrochemical glucose sensor that is targeted to regions of interest within the GI tract via pH-responsive polymer coatings. The electrode for the electrochemical sensor is made from edible carbon and olive oil. The investigators were able to demonstrate glucose sensing in the 2−10 mM range in simulated fluids with a range of pH values using a benchtop potentiostat and chronoamperometry measurements for this initial investigation. Though, the response of the sensor was somewhat pH-dependent.[61]

Several different sensing systems have been developed to address GI motility, including pill-shaped sensor magnets, which can be tracked using external magnetic sensors.[64,133,134] In assessing GI motility, it is also desirable to measure the pressures that develop within different sections of the alimentary canal. Microelectromechanical systems (MEMS) based pressure sensors have been developed for a variety of applications, and some have even been commercialized for implantable applications, though not for the GI tract in this particular case (CardioMEMS HF Sensor, Abbott Medical, Abbott Park, IL). Passive RLC circuits are a commonly used topology which can be used to construct pressure sensors. In these circuits, the measured pressure alters the capacitance of the circuit, often by changing the distance between the plates/fingers of a capacitor, and this, in turn, changes the resonant frequency of the circuit.[72,73] Annese et al. demonstrated a sensor based on this principle which was fabricated on a biodegradable polycaprolactone (PCL) substrate.[135]

The deformation of a piezoelectric material can also be used to detect pressure. When piezoelectric material deforms, a change in the voltage across the device can be measured. Dagdevirin et al. developed a flexible pressure sensor based on this principle using lead zirconate titanate (PZT) on a Kapton substrate.[136] The device was fabricated by a multilayer deposition and etch process, where the metal and piezoelectric layers for the sensor are deposited on a silicon wafer and then coated with gold. The top gold layer and the lower metal layers are then wet etched. The entire structure is transferred onto a spin-coated polymer film using a PDMS stamp and then subsequently sealed.[55] This represents a wafer-level system integration process which is in contrast to the discrete component integration that will be discussed later. Although this device is implantable within the stomach, it requires

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Table 2. Examples of Ingestible Devices Reported in Academic Publications, Categorized Based on Key Functionalities

category	key functionality	applications	novel components/technical specifications	evaluation platform	refs
Sensing	Electrochemical sensing	Monitoring redox species in GI fluid for diagnosis	- Integration of electronic tongue concept into capsule development	In vivo fecal solution samples	58
			- Capability to run cyclic voltammetry with integrated potentiostat		
			- tested in .1 M H_2SO_4; 0−1.5 V potential window; 10.5 mA consumption		
	Optical sensing (colorimetric, fluorescence, luminescence)	Cancer cell detection	- Infrared fluorometer to detect weak fluorescence emitted by cancer cell labeling fluorophores	Benchtop	152
			- Data storage		
			- 7 pA to 30 nA photocurrent range; 129 nM to 645 μM detection range; 6.3 mA consumption		
		Monitoring GI bleeding	- Design of miniaturized fluorometer for integration with swallowable capsules	Benchtop	146
			- 20 nM fluorescein detection limit; 0.01−1.0 mM range; 1.5 pA/μM sensitivity		
			- Use of engineered heme-sensitive bacteria as biosensors	In vivo model/Porcine GI tract	59
			- Luminescence from bacteria upon absorption of target molecules detected by an integrated photodetector		
			- 115 ppm sensitivity in blood, 83.3% at 60 min and 100% at 120 min specificity; 32.5−250 ppm range		
	Multimodal physiological monitoring (pH, temperature)	Monitoring physiological conditions associated with pathological states	- Custom ASIC design	In vitro GI model	162
			- Studied impact of biofouling on exposed pH sensor surfaces		
			- 20 mV/M sensitivity, ∼15.5 mW (active), 4.5 mW (standby) consumption		
	Multimodal physiological monitoring (pH, temperature, pressure)		- Low-power ASIC integration with multiple MEMS Sensors	In vitro stomach model	63
			- Resolutions of the pH sensor are 0.0066 for pH 1.0 to 2.0, 0.0114 for pH 2.0 to 3.0, and 0.0430 for pH 3.0 to 4.0		
			- Resolutions of the pressure sensor are 0.69 kPa for 101 to 200 kPa, 1.17 kPa for 80 to 101 and 2.5 kPa for 50 to 80 kPa		
			- Temperature values ranging from 25 to 50 °C, resolution of 0.087 °C		
			- 1.08 μW (sleep) and 7.38 mW (active) consumption		
	Magnetic coils/sensors	Motility tracking/analysis	- Low power, simplified magnetic capsule IC with pediatric-application compatible capsule size	Benchtop	134
			- 250 μW consumption; 48 h operation time; 125 kHz signal, 3 magnetic transmitter coils		
		Location tracking, GI Transit time analysis	- New mathematical model and a tracking algorithm	In vivo model/Porcine GI tract	64
			- Simplification of magnetic GI tracking system		
			- 4 × 3-axis magnetic sensors, highest sampling rate of 2.4 kHz/Axis, ∼1.4 mG resolution; lowest sampling rate of 300 Hz/Axis, ∼0.15 mG resolution; 5 mm error localization		
	Acoustic sensing	Heart rate and respiratory rate monitoring	- Studied impact of device contact with GI wall and ingested food to acoustic data quality	In vivo model/Porcine GI tract	161
			- Developed a robust signal processing algorithm for waveform analysis		
			- 5 bpm heart rate error, 97%, 95%, 98% concordance for esophagus, stomach, duodenum; 95% confidence overall for R−R, −45 dB ± 4 dB sensitivity		
	Piezoelectric sensing	Mechanical energy harvesting, motility disorder diagnostic, ingestion monitoring	- Development of flexible piezoelectric device to sense mechanical deformation within GI tract	In vivo model/Porcine GI tract	136
			- PZT based strain sensor on polyimide resists up to 10 000 bending cycles and stable over 48 h in simulated gastric fluid		
			- Measures stomach pressure (swine model) in the range of 0−1 psi		
	Thermo-resistive sensing	Gas sensing	- Human trial measuring gas (O_2-equivalent, H_2, CO_2) and temperature profiles in correlation with daily digestions and activities	In vivo model/Human GI tract	181
			- Sensing accuracy: >0.2% for O_2 and H_2, and >1% for CO_2		
			- Selectivity between O_2 and H_2 enhanced by an advanced gas profile extraction algorithm based on heat modulation		
			- Two different mode operations (physisorptive, chemisorptive) widening gas response spectrum		

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Table 2. continued

category	key functionality	applications	novel components/technical specifications	evaluation platform	refs
Imaging/ Biopsy	Thermoresponsive microgrippers	Untethered GI sampling coupled with optical imaging	- Magnetically actuated capsule design for controlled release and collection of microgrippers - Thermoresponsive actuation of microgrippers	In vivo model/Porcine GI tract	157
	Electromagnetic rotor-based tissue cutting razor unit		- Use of active locomotive intestinal capsule endoscope - Externally controlled electromagnetic force to actuate capsule integrated permanent magnet coupled with a tissue cutting razor unit	Ex vivo using porcine intestine tissue	93
Delivery	Drug delivery via passive, pH-based activation	Oral delivery of therapeutic doses of macromolecules Insulin is used as a model drug	- Luminal unfolding actuator - Microneedle injector for intestinal tissue drug delivery - Fast pharmacokinetic insulin uptake, higher than that of a subcutaneous injection (25 min vs 120 min) - Systemic bioavailability >10% of subcutaneous delivery (4 h sampling period)	In vivo model/Porcine GI tracts; Ex vivo human GI tissue	164
	Drug delivery via self-orienting system to attach to and penetrate the gastric wall	Oral delivery of therapeutic doses of macromolecules in stomach Insulin is used as a model drug	- Gravity-based self-orienting millimeter-scale applicator (SOMA) 50−100 ms orientation time from tilt angles up to 135° - Automatic actuation to let a micropost penetrate the gastric wall to insert active pharmaceutical ingredient (API) into the mucosa - Demonstrated administration of insulin (0.5 mg loaded), as well as lysozyme and glucose-6-phosphate - Near zero-order release rate over 30 h	In vivo model/Porcine and Rat	89
	Electronically controlled drug delivery and monitoring	Targeted delivery of substances to well-defined areas of the GI tract	- Good correlation between GI landmark identification based on pH and temperature recordings (10 s measurement frequency), as compared to scintigraphy - Remotely controlled payload release	In vivo model/Human GI tract	170
	Electrically activated micropositioning and delivery	Targeted drug delivery in the small intestines	- Rotational needle positional system - Compact form factor to be incorporated into commercial capsule systems for multifunctional sensing - 4 mm needle extension over ∼2.5 s - 12.16 J consumed per extension (3.3% battery energy capacity)	Benchtop	173
GI indwelling	Chemical reaction-based silicone balloon inflation	Indwelling of ingestible devices in GI tract for long-term monitoring/treatment	- Leveraging gastric reaction in GI/stomach to activate inflation of balloon using CO_2 - Target volume of 50 mL with 250 mL volume reached after 140 s - Electrophoresis-based actuation of needle to puncture and deflate balloon - Operation range: 3−5 V; Current consumption: 7−40 mA	Benchtop	91
	Spring-loaded tissue attachment mechanism	Attaching modular sensors on GI walls	- Use of negative pressure-based tissue anchoring mechanism with a novel sucker hole/needle element - 0.35 cm^3 vacuum volume generates ∼6 N of attachment force - Success rate: aspiration 100%; in vitro separation 78.6% and in vivo separation 42.9% - In vivo attachment lasted 40 h with detachment after 52 h	In vivo model/Porcine GI tract	84
	pH-responsive hydrogel based activation of locking element	Long-term drug release	- Use of pH responsive degradation of hydrogels for location-targeted actuation in the stomach - Use of 3-D printed elastic thermoplastic and poly(L-lactic acid) (PLA) for actuation - Averaged gastric residence of 30 d and operational lifetime of 15.3 d achieved in vivo - Demonstrated controlled release of levonorgestrel over 6 d; average release of 106 $\mu g\ d^{-1}$	In vivo model/Porcine skin	185

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connection to external electronics using a percutaneous endoscopic gastrostomy (PEG) tube.

As described above, pH measurement within the GI tract is important diagnostically, particularly the pH value in the esophagus and stomach where high acidity from the stomach can cause damage to other organs, such as the esophagus. An example of a single chip pH sensor that was packaged for ingestible sensors was developed by Zhu et al., who demonstrated a system on a chip (SoC) with a wireless transceiver.[137] The pH sensor was implemented as a ion sensitive field effect transistor (ISFET), where the gate of a metal oxide semiconductor field effect transistor (MOSFET) is coated with a special membrane to make it sensitive to only hydrogen ions, and thus pH.[66,137]

INGESTIBLE CAPSULE SYSTEMS UNDER DEVELOPMENT

Considerable research and development work has been devoted to the creation of capsule sensing systems with capabilities beyond that which are already commercially available.[48,138] These systems generally consist of a sensing apparatus which is operated by a small form factor circuit/electronic back end. These capsules can transmit data wirelessly or store data onboard for later analysis. Here, we make the distinction between capsule systems and the ingestible sensors presented in the previous section by noting that the capsules are true integrated systems with sensors, control systems, data storage/transmission, and a power source. While the ingestible sensors are simpler, consisting of devices that can sense a single analyte, they are not as robust in terms of data processing and storage as the ingestible capsule systems. Figure 3 and Table 2 contain images and a summary of the devices discussed in this section, respectively.

GI Indwelling Systems. A first application of capsule systems that ties into the previous section is the development of devices capable of immobilizing a biosensor at a specific location within the GI tract. In work by Xie et al., a spring-loaded fixture actuated by a vacuum chamber is used to attach a sensor to the gut wall. The system is created using 3D printed parts. The melting of wax at the target location within the GI tract causes the seal of the integrated vacuum/low-pressure chamber to break, drawing tissue into an orifice of the device and releasing a spring-loaded mechanism to propel the sensor to be placed onto the wall of the intestine.[84] Similarly, Quaglia et al. developed a spring-loaded mechanism to release an adhesive patch from an ingestible capsule.[85] The same group also developed a capsule that could release a clip which one could envision being used for a variety of purposes, including sensor attachment and hemorrhage control.[86]

Balloon inflation has been employed in medical device applications as a relatively simple way to provide actuation for an ingestible capsule.[139−142] Balloons have the advantage that they can be stored compactly within the capsule system before deployment. The work by Nakamura et al. demonstrated balloon-based actuation utilizing a sodium bicarbonate reaction with stomach acid to inflate a balloon from a capsule system to allow the capsule to temporarily reside in the stomach. A gelatin plug is designed in the system which will liquefy at body temperature to expose an onboard sodium bicarbonate reservoir to gastric acid. Subsequently, an electrolysis reaction creates gas pressure that drives a needle into the silicone balloon causing it to deflate for a retrieval process.[91] This work also used a flexible PCB to integrate a flexible antenna in the device,[143] providing an innovative packaging technique suitable for the stringent system requirement. Additional actuation devices/mechanisms have been incorporated in ingestible capsule systems, including the design of mechanical legs, the use of compressed air, and the application of an external magnetic field to steer the system.[144]

GI Bleeding. One potential use of capsule systems is to detect traces of blood as a result of GI hemorrhaging. GI bleeding is of particular interest because, due to the large surface area of the GI tract, it can be difficult to locate the source using conventional endoscopy.[145] In one example of a capsule developed for this application, Nemiroski et al. constructed a swallowable device with an integrated fluorometer to enable fluorescent detection of GI bleeding. One potential trade-off with this approach is that the fluorescent dye must be injected into the patient's bloodstream to allow for the detection scheme to function. This capsule is also compatible with Zigbee communication (a low data rate 2.4 GHz transmission technology), allowing it to transmit data wirelessly.[146] This is a key consideration when trying to perform a time critical intervention on a life-threatening condition.

A second optically based capsule for GI bleeding was developed by Qiao et al. and uses an optical sensor and an absorptive film to detect hemoglobin. The hemoglobin binds to and dyes the absorptive film, leading to signal detection.[147] This wireless capsule autonomously detects bleeding and then transmits an alarm signal in response. An additional fluorescent approach uses specifically engineered bacteria that fluoresce in the presence of hemoglobin. An onboard fluorescence detector is used to read the signal from the bacteria instead of an absorptive film, where the data is again transmitted wirelessly. This approach was also used to detect thiosulfate (an inflammatory biomarker) as well as acyl-homoserine lactone (a marker of gut microbiome activity).[59] A semipermeable membrane is used to prevent the bacteria within the capsule from being released into the gut. Additional work has also been performed on algorithms to detect GI bleeding using capsule endoscopy.[148−150]

A third optical bleeding detection approach uses light emitting diodes (LEDs) to compare the transmission of light at two different wavelengths (415 and 720 nm) and to then use this ratio to properly identify bleeding. Increased absorption at 415 nm indicates the presence of blood. This system was demonstrated using a wireless capsule operating at 433 MHz.[151]

A natural extension of automatic lesion detection is identification followed by intervention. Leung et al. developed a wireless capsule that is capable of both transmitting recorded images and then analyzing the data using an onboard microcontroller to detect bleeding lesions. A set of training images was used to train an algorithm that could run on the microcontroller within the device to identify bleeding regions within the GI tract. The capsule goes one step further by inflating a balloon, achieved by combining two chemicals with a linear actuator, to tamponade the bleeding.[90] Several of the hemorrhage detection concepts above were tested in simulated tissue models in the lab but still need further testing for full characterization in animal models or humans.

Small Bowel Cancer. Tumors, especially those of the small bowel, can be difficult to screen for using conventional endoscopy.[47] One method of lesion detection, similar to those for bleeding, would be to fluorescently tag the cancer cells,

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then detect the fluorescent signal. This entails that, before ingesting the capsule, the patient would need to swallow a solution containing fluorescent antibodies that would attach to the cancer cells. This approach was demonstrated by Demosthenous et al., who developed a near-infrared fluorometer on a capsule platform to detect indocyanine green-labeled cancer cells. The capsule and electronics are assembled on PCBs with a flexible interconnect between different boards within the device. Using the onboard accelerometers, the capsule adjusts the sampling rate for data collection from the photodiode to account for the rate at which the capsule moves through the GI tract.[60,152] This work is specifically aimed at detecting small intestinal tumors at an early stage, and the authors report that the demonstrated method, where the capsule detects whether the signal from the dye exceeds a specific threshold, removes the necessity of analyzing hours of video (as would be the case with conventional capsule endoscopy).

Biopsy. Several other techniques have been developed to biopsy limited-access GI regions or to perform tissue diagnosis without having to extract tissue samples that must be sent to a lab. Along these lines, Gora et al. developed a tethered confocal microscopy system that could be used for GI tract diagnostics.[153] Although some could argue that this work does not represent a true capsule system, it is worth mentioning because of the streamlines that the system adds to the diagnostic process, as it avoids traditional sample removal for conventional microscopy. There are several other examples of tethered capsuled endoscopy, others of which can be found in refs 154−156.

Capsule systems have also been demonstrated that use microgrippers for tissue extraction and retrieval.[157] The entire system consists of a magnetically actuated capsule and can be induced to release a payload using the change in strength on an applied external magnetic field. In this work, the payload was self-folding microgrippers.[157] The microgrippers were fabricated on a silicon wafer on top of a poly(vinyl alcohol) release layer; the gripper hinges contain chromium and copper covered in positive photoresist. The fingers of the grippers were made using electrodeposited nickel and gold. Heating of the photoresist within the hinges above 37 °C causes the grippers to close. A detailed description of the grippers and their fabrication can be found in ref 158. In their integrated capsule system, a polyurethane post structure impregnated with a silicone oil adheres to the microgrippers for retrieval.[157]

Several additional methods have been developed for biopsy using a swallowable capsule. Kong et al. developed a spring-loaded biopsy device that is held in place using a paraffin block. Heating the paraffin releases a torsional spring, launching a cutting device into the lesion to perform a biopsy. The heating mechanism is triggered externally from the capsule.[87] Also, Park et al. demonstrated a torsional spring plated from nickel using a PMMA mold. The spring is loaded into the capsule and then thermally triggered by melting a polymer wire. A barbed fixture on the end of the torsional spring grabs tissue when the spring is released. The action of the torsional spring is able to both release and retrieve the barbed fixture.[159] External magnets can also be used to actuate a rotating cutting device to obtain biopsy samples.[92−94]

Many of the sensors that have been developed for screening GI tract diseases are very useful, but it is important to note that histological examination of the tissue is often required to reach a diagnosis, even after the screening test has detected a concerning lesion.

Physiological Monitoring and pH. As mentioned above with some of the ingestible technologies, to measure body temperature, monitoring and collection of physiological data are highly desirable in many different healthcare or field settings. Traverso et al. developed a wireless capsule for measuring heart and respiratory rate which transmits data in the 433 MHz range. The capsule, called the EnteroPhone (MIT Lincoln Laboratories/Harvard Medical School)[160] uses tiny electret microphones and a specifically designed algorithm to detect the signals from heart rate and respiration, tested within a porcine model.[161] There are various other capsule systems that have been developed for physiological monitoring incorporating multiple sensor types including those for detecting pH and temperature.[63,162] Of note, several of these use analog ICs to reduce the footprint of the readout circuitry.

Additionally, a GI tract physiological monitoring capsule, developed by Arefin et al., features a flexible PCBs fabricated on polyimide with flexible interconnects linking a series of boards containing the necessary electronics for facile assembly. An antenna that can be folded is fabricated on a flexible substrate to reduce the footprint as well.[63] This saves space while simultaneously allowing for efficient wireless transmission. The resulting form factor for the completed capsule was 28 mm long by 13 mm in diameter.[63]

A key consideration in any of these fabrication processes is the integration of biocompatible materials. Johannessen et al. examined the biocompatibility of a fabricated wireless capsule. The capsule that was tested consisted of a custom application-specific circuit and a pH-sensitive ISFET. The capsule containing the circuit, sensor, and batteries was encapsulated in an epoxy resin. Testing was completed in simulated gastric juice (a low-pH ionic solution), simulated intestinal juice (near-neutral pH solution containing ions and small intestine enzymes), and then simulated food-containing solutions. The food-containing solutions were similar to the simulated gastric/intestinal fluids but had pet food or milkshake solution added to them.[162] The same investigators also incorporated a permanent magnet into the capsule system for location tracking using magnetoresistive sensors and were able to perform measurements in the porcine GI tract (in a fresh carcass not a live animal) with data transmission at 433 MHz.[165]

Additional examples of innovative fabrication techniques for physiological monitoring transducers have involved the development of miniaturized pH sensors for ingestible systems.[166] In one example, Shoa et al. used a reaction between antimony and hydrogen ions to create an electrical current which correlates with solution pH. The sensor is fabricated by solidifying metal powders in a glass tube. The silver/silver chloride reference electrode necessary for electrochemical measurements is fabricated again using metal powder, then sealed with paraffin wax. A wireless capsule containing a similar antimony-based pH sensor to the one above has been investigated for esophageal pH monitoring with the addition of magnetic holding (via external magnets) to keep the capsule in place.[167]

Drug Delivery. Drug delivery directly into the GI tract may be desirable for several reasons. First, certain drugs, particularly those based on a particular protein structure (insulin is an example of a peptide), cannot generally be administered orally because proteases in the GI tract will break down the proteins

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into individual amino acids, preventing the drug from ever taking effect. Using a swallowable device to inject the drug directly into the GI vasculature may be one method to replace repeated injections or lengthy infusions. In addition, several GI tract diseases, particularly IBD, often require systemic therapies, which can carry considerable side effects including increased susceptibility to infections and cancers.[168,169] Local administration of therapeutic agents at affected locations within the bowel may be one method to reduce the need for systemic treatment.

GI capsule systems integrating both sensors and actuators have been investigated for GI drug release applications. These have the potential advantage of detecting certain conditions or locations in the GI tract, with the added functionality of releasing a drug.[163,170] Some of these technologies are advanced enough that they are beginning to be studied in clinical trials. A capsule using the GI tract pH profile to bypass the hostile gastric and proximal small bowel environment has demonstrated controlled drug delivery functionality suitable for nanomedicine.[170] In a more system-development-related investigation, Wuyang et al. demonstrated a magnetic-thermal release mechanism where an external magnetic field closes a reed switch, heating and melting a band which holds the drug reservoir closed. When the band melts, the capsule opens, releasing the drug it contains.[163] Spring loading is another actuation mechanism that has been investigated recently. Abramson et al. developed a spring-loaded folded structure that is held in place by an enteric coating. When the coating dissolves, the compressed spring propels the folded hierarchical microneedle structure out of its container to release its contents into the wall of the GI tract.[164] This group also developed an ingestible self-orienting system and demonstrated *in vivo* oral delivery of insulin with animal studies.[89] The spring-loaded device has the advantage that it is completely passive and does not require additional onboard power to operate.

These capsule systems employing sensing and actuation are significant as they entail a complete closed-loop device for targeted/on-demand operations, where sensors detect the release location and then trigger actuators to release the drug. Along the lines of complete microrobot systems, Woods et al. investigated capsule systems for drug delivery applications that include micromotors and computerized numerical control (CNC) machined gears. The investigators developed a microneedle injection system and also examined issues such as the possibility for the capsule to resist peristalsis.[171−173] The developed system was also investigating microsurgery using the gear-driven capsule.[174]

Along the lines of positioning, investigators have demonstrated a magnetic positioning system for a drug delivery capsule.[175] A magnetic actuation mechanism, similar to one discussed above, for the biopsy capsule has also been investigated for drug delivery. In this system, an external magnetic field is used to compress the capsule lengthwise, compressing a drug reservoir releasing the drug.[176] Additional investigations have used ultrasonic transducers mounted within an ingestible capsule to drive drugs into certain regions of the wall of the GI tract.[177]

Additional Examples. Additional sensor types have been included in capsule systems for a variety of additional applications. Capacitive micromachined ultrasonic transducer arrays (CMUT) have been employed in wireless capsules for ultrasound imaging.[178] Lay et al. provides further discussion of ultrasound systems for capsule endoscopy as well as multimodal sensing within capsule systems.[179] Thermoresistive and electrochemical sensors have also been utilized.[180] Kalantar-Zadeh et al. reported a human trial of a GI gas sensing capsule, capable of measuring oxygen, hydrogen, and carbon dioxide levels.[181] These sensors were used to look at bacterial fermentation of dietary fiber within the gut microbiome. Further, Berean et al. report the measurement of hydrogen production in the gut for detecting small intestinal bacterial overgrowth.[182] An additional potential application of gas sensors may be for cancer detection with an initial investigation using trained dogs to detect odors suggestive of cancer.[183]

Electrochemical sensing, on the other hand, has been widely used for a variety of potential applications. McCaffrey et al. developed an electrochemical sensing capsule which transmits data wirelessly at 433 MHz.[58] Their work describes the system development and construction using commercially available components coupled to an "E-tongue" electrochemical sensor. The entire system is packaged as a series of circular PCBs connected via a flexible interconnect, encapsulated within a polyether ether ketone (PEEK) shell.[58]

As discussed above, the standard of care for colon cancer screening is colonoscopy, but this requires swallowing and then defecating a large amount of bowel prep solution to clean any material off the walls of the colon. This bowel prep process is a deterrent to patients undergoing screening. Kimchy et al. describes the operation of a colon cancer screening capsule that uses radiofrequency positioning and an X-ray-based imaging to map the contours of the bowel wall without the need for the patient to take any bowel prep. The patient does need to swallow small amounts of iodine-based contrast for the capsule to work. If a lesion is detected, then it can be investigated further using colonoscopy or appropriate imaging.[184]

Having a capsule that operates effectively within different regions of the GI tract is important given the variety of diseases that affect different parts of the gut and the diverse physiology of different regions. Along those lines, Carta et al. developed a capsule for operation in the stomach that includes power transfer via electromagnetic induction and contains four propellers for locomotion.[186]

3D printing is an exciting technique, which is being increasingly utilized to overcome materials and manufacturing challenges.[187−189] Various technologies such as fused deposition modeling (FDM) or stereolithography (SLA) are increasingly employing materials that achieve biocompatibility requirements, thereby promoting their use for creating structural components in medical devices. Recent work suggests that this utility extends to capsule devices as well.[190] In our recent work, 3D-printed capsules are used to package sensors that verify sampling of simulated GI environments. This is achieved by leveraging pH-soluble coatings, specifically, varying formulations of Eudragit (E PO, L100, and S100) commonly used in pharmaceuticals and drug delivery for targeting specific GI regions.[191,192] Demonstrated to be effective when coated over 3D-printed capsules, efforts have continued in testing these polymer coatings, both with varying thicknesses and when combined and subsequently exposed to dynamic pH sequences. In this work, coating dissolution was detected using a capacitive sensor contained within a capsule.[193] The results indicate the potential for control over sensor exposure to surrounding environmental cues, i.e., pH,

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using these coatings as a passive method for targeting, therefore enabling more specific onboard sensing modalities with reduced interference from nonspecific regions as well as more efficient power distribution to additional tasks.

DISCUSSION AND FUTURE OUTLOOK

The current commercialized ingestible sensing technologies do not extend beyond imaging and the measurement of a few physiological parameters, such as temperature and pH. Ingestible sensing systems have a potential well beyond these few applications. One point that does deserve mention is that the use of any medical technology/medical intervention is not without risk. For example, capsule endoscopy use has determined that capsule systems hold a nontrivial risk of bowel obstruction, which is as high as 2% in the published literature.[194,195] Capsule retention, where the capsule does not pass through the GI tract but is retained somewhere in the path, represents an additional risk. Further complications include bowel perforation, infection, and device failure, potentially leading to the release of harmful materials into the alimentary canal, among others.[196,197] The key to the further successful translation of swallowable sensing systems is the identification of medical conditions where the benefit of intervention with a swallowable system outweighs the risk.

The current state-of-the-art commercialized systems do not include any kind of biochemical marker or tissue diagnosis. Systems under development have examined some of these types of capabilities, including in the area of bleeding detection and biopsy, but more work is needed to translate these technologies. With the advent of personalized diagnosis and personalized medicine (for example, treating a patient's tumor based on a specific biomarker that it expresses), platform sensing technologies are needed that can identify these markers and match patients to appropriately tailored interventions.

Two major hurdles for ingestible sensing systems are (1) the identification of relevant biomarkers that can be detected in the ingestible setting (noting that they may be different than those that are identified in stool samples for example) and (2) the development of sensing systems that are able to filter out and amplify small amounts of analyte from all of the different material that is normally found in the human GI tract. In addition, the sensitivity of the ingestible sensing systems as well as their overall size and battery life will all need to be addressed so that they can function as needed. The literature contains numerous examples of relevant back-end platforms (i.e., power electronics, RF transmitters, microcontroller systems and packaging), but a great deal of work is needed on developing front-end sensing technologies for biomarker identification.

From a healthcare systems perspective, low-cost devices based on batch fabricated sensors and electronics could allow one to take full advantage of the developments in miniaturization and integration that have occurred over the past several decades and could allow for swallowable sensing technologies to be developed that are lower in cost compared to other technologies. More importantly, further development of ingestible technologies has the potential to (1) reduce the cost of current screening methods by greatly reducing labor costs and (2) provide new screening capabilities made possible by the system integration of microscale sensors with application specific circuits, made possible by state-of-the-art microelectronics technologies.[198]

In addition to autonomous operation within the GI tract, one can envision the same concept applied to other organ systems such as the central nervous system (CNS) or the circulatory system. For example, invasive procedures requiring large doses of radiation can be required to diagnose arterial blockages. Autonomous systems that can screen for and potentially even treat these conditions would further reduce associated procedural and hospital time as well as labor costs and could potentially improve screening availability on a population basis. The GI tract is an effective stepping stone toward the development of devices that can operate in other regions of the body due to its more forgiving nature. For example, an arterial blockage can begin to cause life/limb threatening ischemia within minutes, while a GI tract blockage can occur over hours or even days before it will be life-threatening, increasing the window of time for correction.[6,194,199] Additionally, an arterial injury leading to bleeding can kill in under an hour, while a GI tract perforation can be life-threatening but can be tolerated for several hours allowing time for appropriate intervention.[6]

A key component to successfully translating the promising results reviewed above is identifying the relevant clinical problem and then weighing the following: (1) the risks/benefit to the patient and (2) the added efficiency or burden on the healthcare system. Devices that are most likely to translate effectively are the ones that provide multiple randomized trial-proven benefits to the patient or improved healthcare decision-making without greatly increasing the risks or costs. However, it should also be noted that FDA requirements for randomized controlled trials for devices are different than those for pharmacological agents and, in many cases, also simpler. Identifying diseases that are difficult to screen, and for which a robust system can be developed to improve screening for that matter, is an excellent place to start because catching deadly diseases at earlier stages could hold tremendous potential benefits for patients. Furthermore, there are a myriad of GI pathologies that require frequent surveillance to either assess treatment efficacy or assess for disease progression. Ingestible technologies are not at the point where they can really be used for these surveillance applications, but getting ingestibles to this point could help to make these screenings less burdensome and disruptive for patients.

As mentioned above, some disease processes that require frequent screenings, currently performed by endoscopy are Barrett's esophagus and inflammatory bowel disease, in particular, ulcerative colitis. The aim of the screening performed in these conditions is to detect precancerous lesions before they progress to become life-threatening. A swallowable system that could identify and diagnose neoplastic lesions without the need for sedation, for example, could reduce the cost to both the patient and the healthcare system.

However, designing a single system to address these complex medical problems is a formidable task. A possible middle ground, allowing earlier adoption of ingestible technology while still addressing a medically relevant problem, is to identify medical settings where a screening test in the form of an ingestible capsule would be useful to identify patients that would then benefit from a screening endoscopy. For example, the current screening guidelines for colon cancer recommend that a screening colonoscopy be performed starting at either age 45 or 50 (the current guidelines differ between agencies).[200,201] This may not be necessary for all patients. A capsule that could first screen for concerning lesions could

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then identify patients who actually need to undergo colonoscopy.

An additional setting where these minimally invasive technologies could potentially find first applications are in resource-poor environments where endoscopy or other procedures may not be possible because of a lack of equipment or providers. A swallowable capsule that could identify GI bleeding, precancerous lesions, or additional interventions requiring more complex facilities could then inform which patients need to be transported to higher levels of care.

There is an opportunity for lower-cost, autonomous sensing systems that collect data in the outpatient setting and do not require higher level facilities for equipment or sedation. These sensing, and potentially interventional, systems should be able to both detect and transmit data as well as collect and analyze samples in real time within the GI tract. Such systems would have use in both medical diagnostics as well as better understanding the complex systems biology involved with diseases.

One of the key issues in global healthcare systems is to identify ways to deliver ever-improving health outcomes without greatly increasing the costs of care. Ingestible sensing technologies that rely on batch fabricated MEMS and microsystems technologies and that do not require constant user direction/intervention for safe operation raise the potential to reduce cost by leveraging the low cost per unit for batch manufactured devices and the potential for these systems to operate autonomously or semiautonomously.

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Notes

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