

Future is ready for swallowable sensors

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You may have noticed that even just before the onset of a simple cold or a minor fever, disordered gut function may be experienced. In addition to coryzal symptoms and fever, abdominal discomfort or altered bowel function are not uncommon as accompanying symptoms, such as bloating, abdominal pain, nausea, vomiting, constipation or diarrhea. It is not surprising, as the gut walls are porous, allowing the absorption of nutrients from food intake. The gut mucosa very rapidly exchanges certain chemicals in body fluid compartments with gut liquid and gaseous contents. It is likely that imbalance of the body chemical contents, as a result of a health disorder, rapidly shows itself as changes in gut contents.

Despite the common observations that the modulation of gut functionality almost always occur during sickness, the changes in gut functionality are rarely used by medical and health experts as an input for therapeutic actions; prevention, diagnostics and monitoring of the diseases.

Considering the above, swallowable sensors can be potentially very impactful. In a normal visit, a doctor generally obtains measures of body temperature, blood pressure, heart rate and respiratory rate as vital indicators of general health. It is suggested that future medical care could soon be complemented by swallowable sensors (*Figure 1*) at the hand of medical experts (1,2). These swallowable sensors can provide essential information that can be easy to obtain due to their non-hazardous nature (2-11).

The magic of wearables for decades were heavily promoted and they attract enormous base investments. Yet, wearables cannot offer the powerful prospects for prevention, diagnostics and monitoring that can even

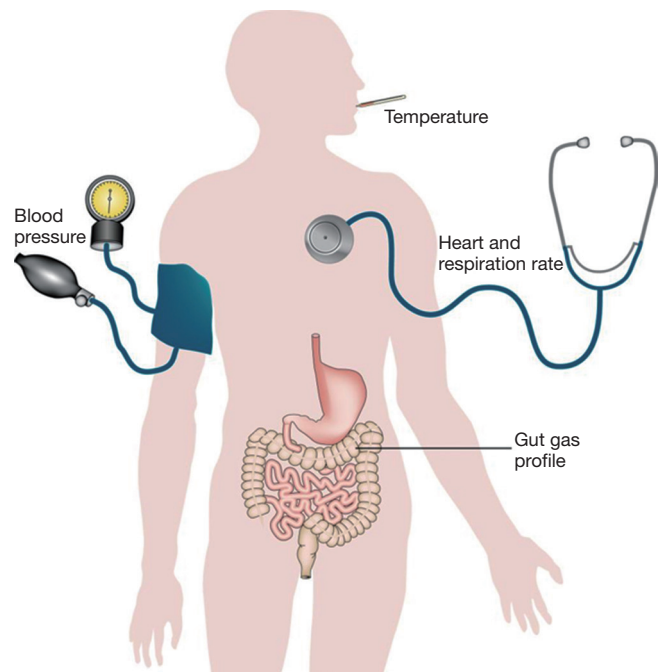


Figure 1 A schematic depiction of body temperature, blood pressure, heart rate and respiratory measurements. In the future, they may be accompanied swallowable sensors. Reproduced from (1) with permission from Nature Publishing Group.

remotely rival swallowable, as continuous monitoring of body fluid chemicals is challenging with wearables. Accessible body liquids for wearables are sweat, tears and saliva, analysis of which provides limited information in comparison to gut content (12). More common wearables can only measure physical signals that pass through the skin.

The skin barrier is the hindrance, which does not allow the access to the chemicals inside the body. By contrast, swallowable provide efficient, easy and safe tools to measure these chemicals internally. When a swallowable is taken, it is immersed into the liquid of the gastrointestinal tract and is in touch with gaseous content of the gut and also provides the possibility of continuous monitoring of chemicals that are generally present in large concentrations inside the gut. The high concentration of chemicals means that by using low cost sensors, swallowable sensors can provide very valuable data.

These days swallowable are widely used in endoscopic imaging, while they are still in their infancy for chemical sensing (2). The development of a swallowable is still challenging and many different aspects require consideration. For example, the content of the stomach is highly acidic, while the rest of the gut environment is more neutral. Mechanical agitations are also diverse. Such different chemical and physical environments pose certain challenges for creating a swallowable with the needed longevity and functionality. The sensors and electronic systems should be able to tolerate the caustic environment of the stomach, endure extreme mechanical vibrations and have the right dimensional, morphological and mass properties to show no retention. The operation of a swallowable should last the duration of its transition through the gut and not fail before its excretion.

Chemical contents of the gut include, but are not limited to, electrolytes, enzymes, metabolites, hormones, and gases. The alimentary tube is a long system of diverse ecosystems: the esophagus, stomach, small intestine, and large intestine. Additionally, a very important issue is the presence of the microbiome in the gut that are in symbiotic life with the gastrointestinal tract. These microbiomes can also produce chemicals that significantly impact health. So either the human body or the commensal microbial communities of the gut are the origins of the chemicals to be sensed. As such, an incredible wealth of knowledge regarding the functionality and state-of-health of individuals through measuring and sensing key gut biomarkers can be obtained. A swallowable chemical sensor should be able to monitor one of a few of the chemicals as biomarkers. There are many questions though. The first critical question is what should be measured. The other important one is how this biomarker can be measured.

It is important to separate imaging capsules from swallowable chemical sensors. Imaging capsules for endoscopy and colonoscopy have been long in the market.

Their significance is immense but they are physical and rely on the observations of images inside the dark gastrointestinal tract that generally contains food. As such, the gut is needed to be cleansed before the imaging capsule can be taken. This is burdensome for patients, and it also reduces the clinical value based on the point that the natural state of the gut is when it is filled partly or fully. This is where imaging capsules may fail to provide correct information. Other physical sensors such as temperature and pressure sensors are suitable as continuous monitoring tools, but they are very limited in the information they can provide.

So far a few swallowable chemical sensors have successfully passed human tests and shown their remarkable value. The initial one is pH sensor. These capsules are routinely used for assessing gut motility and the acidity of the stomach (2). Another novel swallowable has been shown to be sensitive to changes in the gut gases, which are related to the secreted chemicals and the enzymatic activities of the gut microbiome. These gases have been shown to be associated with the measures of pathogenesis in the gut. They can be used for monitoring carbohydrate malabsorptions and also gut motility disorders (1,3,4,6,11). Many more tests should be conducted to reveal other possibilities that the gas sensors can offer, especially for unpleasant symptoms of irritable bowel syndrome.

There are also more chemical sensor concepts that have only passed the animal trial stage. There are capsules for visible and ultraviolet range spectroscopy (2). For instance, a recent report on integrated optical sensors demonstrated utility for monitoring of bleeding within the gut (9,10). They used proteins that could enhance the intensity of the optical measurements. Electrochemical sensors should play an important role in the future of swallowable (2). However, they are Nernst type sensors and intrinsically suffer from high noise that should be addressed. There are also many other opportunities that need to be considered for chemical sensing in the gut.

It is very important to remember that swallowable sensors will impact fields other than in the diagnosis and monitoring of clinical disorders, as they can also produce data that will improve public health. They can provide information regarding the effect of food intake for establishing the base for the creation of the concept of 'individualised diet'. This will create 'big data' of the greatest value that will revolutionize our understanding about our body and the relation between its health and diet. This will eventually lead to new market opportunities that can in return feed more information into clinical and

medical fields and markets.

For the advancement of swallowable sensors, regulatory bodies should assist by removing unnecessary barriers and re-classifying swallowable as low risk medical devices. The current tough classifications only impose costly approval processes that do not help public accessibility to these essential tools of the future. Swallowable sensors will offer the paradigm of accurate point-of-care with remote monitoring and administration, providing accessibility with intelligent and correct diagnostics for individuals. The gut is integral to our health, and the information it provides should not be ignored. We have to change traditional thinking and look inside.

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Footnote

Conflicts of Interest: K Kalantar-Zadeh is the lead scientific advisor for Atmo Biosciences, a company with the patents of swallowable capsules for profiling gases within the gut. SA Ward has no conflicts of interest to declare.

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