Digital biomarkers in human excreta

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Traditionally underutilized human excreta have emerged as a rich source of digital biomarkers for disease prevention and early detection. In this Comment, we highlight the breadth of digital biomarkers that can be extracted from human excreta and their potential uses in the context of 'precision health'.

In 2021, consumer devices to track basic health parameters are found increasingly in our phones, on our wrists, and in our bedrooms, but not in our bathrooms. For example, the concept of a 'smart toilet' to analyse urine and stool has been around since the 1970s, but its execution has been limited by privacy concerns and the challenges of working with human excreta[1].

Precision health

Such devices can have a significant role in the concept of precision health, which emphasizes disease prevention and early detection via individualized, longitudinal monitoring. It is the proactive counterpart to precision medicine, which individualizes treatment and intervention for disease that has already manifested[2]. Precision health, by its nature of detecting subtle clinical signs before disease manifestation, relies on continuous health monitoring using wearable, implantable or home-based devices rather than measurements in the clinic. Precision health relies on digital biomarkers, which are physiological, biochemical and behavioural data collected by smart devices[3]. This is in contrast to traditional 'analogue' biomarkers, which are subjectively generated and manually recorded by the patient. Digital biomarkers are inherently quantitative, can be collectively analysed with predictive modelling and artificial intelligence for pattern recognition, and enable actionable response determination. The coronavirus disease 2019 (COVID-19) pandemic has also accelerated the trend towards remote health-care ecosystems. One study[4] analysed continuous smart-watch data (for example, heart rate, step count and sleep duration) to detect pre-symptomatic COVID-19 infection. Nonetheless, current clinical care, obtained through periodic doctor's visits and laboratory testing, provides only snapshots of a patient's disease. Digital biomarkers and longitudinal monitoring will record over longer timespans to enable deeper understanding of disease.

Digital biomarkers in human excreta

There is a wealth of information to be found in biofluids such as blood, breath, sweat, saliva, urine and stool. Although blood is by far the most well characterized, the requirement for needles precludes it from being an ideal candidate for repeated longitudinal monitoring. An ideal precision health biomarker should be monitored both non-invasively and passively, as devices that require behavioural modification (for example, remembering to put on a wearable) will ultimately limit user adoption. A smart toilet could seamlessly integrate urine and stool analysis as part of routine toileting events.

Urine and stool contain many 'analogue' biomarkers that could benefit from conversion to digital biomarkers for more accurate monitoring. For example, the Bristol Stool Form Scale (BSFS)[5] is a visual classification of stool morphology used in the Rome diagnostic criteria for irritable bowel syndrome[6], a common and debilitating disease in which stool diaries are important in guiding symptomatic treatment of either diarrhoea or constipation. However, analogue diaries are limited by variations in BSFS interpretation by patients, and by a general lack of interest in recording one's stool on a regular basis. Objective and automated methods using computer vision and artificial intelligence would generate valuable digital biomarkers that are more comprehensive and reliable for clinical interpretation, overcoming the inaccuracy of patient-reported outcomes. The smart toilet could collect additional digital biomarkers such as time spent on the toilet or duration of a bowel movement to help diagnose disorders related to pelvic outlet dysfunction or constipation. Digital diaries can also collect and digitize symptomatic outcome data for conditions that are difficult to define due to their functional nature, as they can track the variability of defecation symptoms related to mixed-type irritable bowel syndrome, inflammatory bowel disease, and bowel habit changes after colorectal cancer surgery.

Similarly, voiding diaries and urine flow measurements are routinely recommended for evaluation of common urological conditions such as benign prostatic hyperplasia and overactive bladder. For voiding diaries, patients are asked to record the time and volume of each urination using a urinal or special container placed in the toilet. Compliance towards completion of a voiding

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diary as short as 24 hours is a recognized challenge. Image-based analysis of the urine stream using a smart toilet could digitize data collection of the urinary flow rate, volume and frequency to improve the quality of the diagnostic study[7]. A simple bidet-style attachment could also deploy urine test strips, which can measure biochemical contents ranging from urinalysis markers (for example, of infection) to other urine tests (for example, pregnancy and fertility hormones) and interpret the colorimetric readouts[7]. As new point-of-care tests are developed, they can be integrated into the toilet and tailored to each individual's health needs.

New clinical insights from digital biomarkers

These candidates for digital biomarkers are simple and easily implemented, but they do not even begin to cover the breadth of health data that can be mined from human excreta. Urine metabolites are associated with nearly 600 human health conditions, ranging from cancer to obesity[8]. Real-time monitoring of urine metabolites has the potential to identify individual phenotypes related to exercise, nutrition and sleep. The microbiota–gut–brain axis is one of the most compelling recent developments in precision medicine and it has been implicated in an increasing number of conditions including motility disturbances and visceral hypersensitivity in functional gastrointestinal disorders, alterations in mucosal and immune function in inflammatory bowel disease, and alterations in the enteric nervous system in neuropsychiatric diseases such as anxiety, schizophrenia and Alzheimer's disease[6,9]. Although it is an emerging field, it is evident that understanding its high inter-individual variation will benefit from digitized, individualized and longitudinal monitoring of human excreta.

Automated passive monitoring can also lead to early disease detection. Bladder and colon cancer are typically diagnosed and surveilled with cystoscopy and colonoscopy, respectively, which are time-consuming and invasive. Monitoring of supplemental digital biomarkers such as haematuria, changes in stool form, bloody or mucoid stool, and eventually nucleic acid and protein biomarkers could lead to earlier diagnosis. Biomarkers derived from excreta can also be helpful in screening for infectious diseases. SARS-CoV-2 viral RNA has been found in the stool of both symptomatic and asymptomatic patients with COVID-19, and gastrointestinal symptoms such as diarrhoea often precede respiratory symptoms in SARS-CoV-2 infection[10]. High-frequency measurements of these biomarkers might better elucidate individual phenotypic signatures, improving diagnosis and informing about variance in human health and disease.

Challenges

There are dozens of devices capable of monitoring physiological parameters such as heart rate and activity, but very few devices offer biochemical measurements, such as continuous glucose monitoring systems. This asymmetrical development is likely related to the invasive nature of measuring serum-based biomarkers; the absence of predictive, validated biomarkers in non-serum biofluids; and the requirement for behavioural modification and active sample collection by the patient. The ideal digital biochemical marker can be measured passively and non-invasively, but there will be significant challenges in identifying such a biomarker (if it exists) and in adapting and scaling bulky biochemical analysis platforms such as mass spectrometry and PCR in non-clinical settings.

Digital biomarkers and continuous health monitoring might lead to overdiagnosis and harmful outcomes such as false alarms, alert fatigue and unnecessary medical treatment[2]. Sophisticated back-end analytics are required to minimize false positives and alleviate alert fatigue. More monitoring is not always better or even necessary to improve diagnosis, and large-scale clinical studies to optimize user interface are necessary to evaluate an optimal balance between monitoring frequency, performance accuracy and associated cost. Digital biomarkers are also inherently tied to privacy and security concerns, especially when combined with the taboo around human excreta. Multiple devices represent multiple opportunities for cybersecurity breaches, which can both invade privacy and threaten patient care. Thus, this field of medicine must be cautiously cultivated. It is crucial to properly validate new digital biomarkers and their benefits, and to define appropriate ethical guidelines for good medical practice and social care.

Although there are many challenges to developing digital biomarkers from human excreta, technological advances and efforts to overcome privacy concerns show immense promise to turn such analysis into an integral tool in the new era of precision health.

1. Nature Microbiology. We need to talk about crapping. *Nat. Microbiol.* **3**, 1189 (2018).
2. Gambhir, S. S., Ge, T. J., Vermesh, O. & Spitler, R. Toward achieving precision health. *Sci. Transl. Med.* **10** eaao3612 (2018).
3. Coravos, A., Khozin, S. & Mandl, K. D. Developing and adopting safe and effective digital biomarkers to improve patient outcomes. *NPJ Digit. Med.* **2**, 14 (2019).
4. Mishra, T. et al. Pre-symptomatic detection of COVID-19 from smartwatch data. *Nat. Biomed. Eng.* **4**, 1208–1220 (2020).
5. Lewis, S. J. & Heaton, K. W. Stool form scale as a useful guide to intestinal transit time. *Scand. J. Gastroenterol.* **32**, 920–924 (1997).
6. Drossman, D. A. Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features and Rome IV. *Gastroenterology* **150**, 1262–1279.e2 (2016).
7. Park, S. M. et al. A mountable toilet system for personalized health monitoring via the analysis of excreta. *Nat. Biomed. Eng.* **4**, 624–635 (2020).
8. Miller, I. J. et al. Real-time health monitoring through urine metabolomics. *NPJ. Digit. Med.* **2**, 109 (2019).
9. Cryan, J. F. et al. The Microbiota-Gut-Brain Axis. *Physiol. Rev.* **99**, 1877–2013 (2019).
10. Xu, Y. et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat. Med.* **26**, 502–505 (2020).

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Competing interests

The authors declare no competing interests.