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## Tethered capsule endomicroscopy enables less-invasive imaging of gastrointestinal tract microstructure

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### Abstract

Here, we introduce “tethered capsule endomicroscopy,” that involves swallowing an optomechanically-engineered pill that captures cross-sectional, 30  $\mu\text{m}$  (lateral)  $\times$  7  $\mu\text{m}$  (axial) resolution, microscopic images of the gut wall as it travels through the digestive tract. Results in human subjects show that this technique rapidly provides three-dimensional, microstructural images of the upper gastrointestinal tract in a simple and painless procedure, opening up new opportunities for screening for internal diseases.

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Diseases of the gastrointestinal (GI) tract are commonly diagnosed by endoscopy, where a flexible video-imaging probe is advanced through a natural orifice into the luminal digestive organs. If an abnormal region is identified, endoscopic biopsy forceps are used to extract a small amount of tissue from the suspect area. The biopsy is then processed and reviewed under a microscope by a pathologist who renders the final diagnosis. It is estimated that

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#### AUTHOR CONTRIBUTIONS

Device design: MG, RC, KG, MS, BB, MR, GT

Study design: JS, MG, MR, LK, GT

Conduct of the study: JS, NN, LK, KG, MG, GT

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approximately 15 million such biopsies are excised and analyzed every year in the United States<sup>1</sup>.

While endoscopy has significantly improved health outcomes, it has certain inefficiencies that limit its impact. For most endoscopic procedures, subjects are sedated, requiring a specialized setting, equipment, and medical staff to monitor for adverse reactions. Transnasal endoscopy, which has been gaining in popularity in some endoscopy communities<sup>2</sup>, does not require sedation, yet necessitates a trained endoscopist to conduct the procedure. Endoscopy is therefore time-consuming and costly, making population-based screening for most conditions difficult to justify. Some GI diseases involve microscopic features that manifest below the tissue surface. Because video imaging only provides information about the superficial mucosal structures, these features cannot be seen with conventional endoscopy or even higher resolution forms of endoscopy such as high-definition magnification endoscopy<sup>3</sup>. For these cases, the physician must randomly biopsy multiple portions of the organ with the hope of sampling the correct spot, which, unfortunately, is often missed.

We have created a novel, tethered optomechanical pill<sup>4</sup> (Figs. 1a–c, Supplementary Fig. 1) that captures three-dimensional microscopic images of the digestive organs after it has been swallowed. The tethered capsule employs optical frequency domain (OFDI) imaging<sup>5</sup> technology to provide cross-sectional architectural morphologic data that has previously been shown to enable the diagnosis of Barrett's and high-grade neoplastic changes in the esophagus<sup>6–8</sup>. The capsule portion of the device is connected to a thin, string-like tether (Figs. 1a–c, Supplementary Fig. 1) that allows the operator to control the position of the capsule in the GI tract<sup>9</sup>, effectuates a circumferential scan of the miniature focusing optics in the pill, and transceives light to and from the capsule. Once swallowed, the luminal organs constrict around the pill and gradually push it down the GI tract under the natural propulsion force of peristalsis. Once the capsule has reached the distal-most region of interest, it is pulled back using the tether, again while imaging. During its transit, multiple 30  $\mu\text{m}$  (lateral)  $\times$  7  $\mu\text{m}$  (axial) resolution OFDI cross-sections of the luminal organ (Figs. 1d, f, h and Supplementary Movies 1, 2) are acquired enabling the visualization of normal squamous mucosa (Figs. 1e, 2c), stomach (Figs. 1g, 2a), and Barrett's epithelia (Figs. 1i, 2b). Sequential cross-sections may also be compiled to reconstruct a three-dimensional microscopic representation of the entire luminal organ (Figs. 2d–f and Supplementary Movie 3). After the procedure, the capsule is withdrawn through the mouth and disinfected for reuse. In a study of 13 subjects (normal volunteers (n=7), volunteers with known Barrett's esophagus (n=6)), we found that the mean transit time for imaging ~15 cm length of esophagus was only 58 sec. For four imaging passes (two up and two down), resulting in four complete datasets, the entire procedure lasted an average of approximately 6 minutes (6 min 18 sec) from capsule insertion to extraction. There were no complications of tethered capsule endomicroscopy. Following the procedure, the majority (12/13) of the subjects reported that they would prefer tethered capsule endomicroscopy to conventional endoscopy.

Tethered capsule endomicroscopy has the opportunity to open up new possibilities for medical screening and diagnosis of GI tract organs. Because these images are obtained from

singly scattered light rather than the multiply scattered color reflectance of endoscopy, they carry architectural microscopic image information that is spatially correlated with histopathology from corresponding locations<sup>6–8</sup>. The device furthermore acquires three-dimensional microscopic image data from large segments of luminal tissues, enabling the comprehensive assessment of subsurface microstructures that are not evident and can be missed by endoscopy. Since the tethered endomicroscopy pill traverses the GI tract without visual guidance, the training required to conduct the procedure is minimal. This and the brevity and ease with which the procedure is performed will enable internal microscopic imaging in almost any health care setting, including in the primary care physician's office. In addition, because the device can be retrieved and disinfected, tethered capsule endomicroscopy could be inexpensive<sup>9</sup>, making it feasible to screen large populations for upper digestive diseases. A somewhat surprising finding of this first foray into capsule endomicroscopy was the degree to which the esophagus remained close to the outer surface of the pill in a manner such that high quality images were obtained (an average of 94.5% of all frames). This result indicates that other in vivo endomicroscopy technologies, such as confocal microscopy<sup>10,11</sup>, could also be effective when implemented using a capsule. Looking towards the future, the full potential of capsule endomicroscopy will truly come to light through the implementation of tether-free pills, the addition of video imaging for guidance and the incorporation of externally-controlled locomotion<sup>12,13</sup> and concomitant biopsy and therapy<sup>14</sup> functionalities.

## METHODS

### OFDI technology

OFDI is a cross-sectional, interferometric microscopic imaging technique that records light reflected as a function of depth within tissue<sup>15</sup>, information that may be used to accurately render pathologic diagnoses in digestive tract tissues such as the esophagus<sup>6</sup>. The OFDI system utilized in this study illuminated tissue using near-infrared (NIR) wavelengths sweeping from 1250–1380 nm. We acquired circumferential, cross-sectional images at 20 frames second<sup>-1</sup> using a total of 2048 axial (depth) scans per image. Axial resolution was 7  $\mu\text{m}$  in tissue (estimated refractive index  $n=1.4$ ) and the sensitivity was  $\sim 110$  dB. During the procedure, we recorded all raw data in real time and also displayed subsampled versions of the images in real time. Immediately following the imaging session, we reconstructed the images at full resolution ( $2900 \times 2900$  pixels) and displayed them using an inverse gray scale lookup table. We automatically aligned frames and rotationally registered them using cross-correlation in ImageJ. We removed signals from the capsule's inner and outer surfaces prior to three-dimensional volume rendering (Osirix 4.0). We measured the percentage of frames where the capsule was in proximity to the esophagus by dividing the number of frames in which the esophageal wall was clearly visible for greater than 50% of its circumference by the total number of frames.

### Tethered capsule endomicroscope device

The capsule comprises a 12.8 mm (diameter)  $\times$  24.8 mm (length) transparent, cylindrical shell bounded by hemispherical end caps (Supplementary Fig. 1). The shell encloses miniature optics that redirect focused (FWHM diameter 30  $\mu\text{m}$ ) light outside the capsule.

The capsule is connected to a flexible, 0.96 mm diameter sheath, which serves as a tether<sup>9</sup> (Supplementary Fig. 1). The sheath encloses a driveshaft and an optical fiber; the fiber transmits light to and receives light from the miniature optics inside the capsule. The driveshaft conveys rotational torque from the system's optical rotary junction to the capsule's optics (Supplementary Fig. 1). Circumferential, cross-sectional images are acquired as the rotary junction and thus the optical beam in the capsule continuously spins. Three-dimensional images are obtained while acquiring cross-sectional images as the tethered capsule moves up and down the digestive tract.

### Imaging procedure

Healthy, unsedated volunteers were enrolled in the study. Subjects were asked to swallow the capsule endomicroscope and then take a sip of water. While the operator held the tether, the capsule was gently allowed to descend through the esophagus to the stomach. The distance between the capsule and the incisors was recorded using 5-cm-spaced marks on the tether. We visualized images in real time to determine when the capsule had reached the stomach. Once in the stomach, we gradually pulled back the pill up through the esophagus to the mouth while imaging. We performed a total of four imaging passes (two up and two down) in each subject. Following imaging, we removed the tethered capsule and disinfected it for reuse in accordance with the standard procedure for the disinfection of GI endoscopes (submersion in Cidex OPA for 12 minutes). Immediately after the pill was withdrawn, we asked each subject whether or not procedure was preferable to endoscopy. The Partners IRB approved the study (Protocol #2011P002619).

### Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

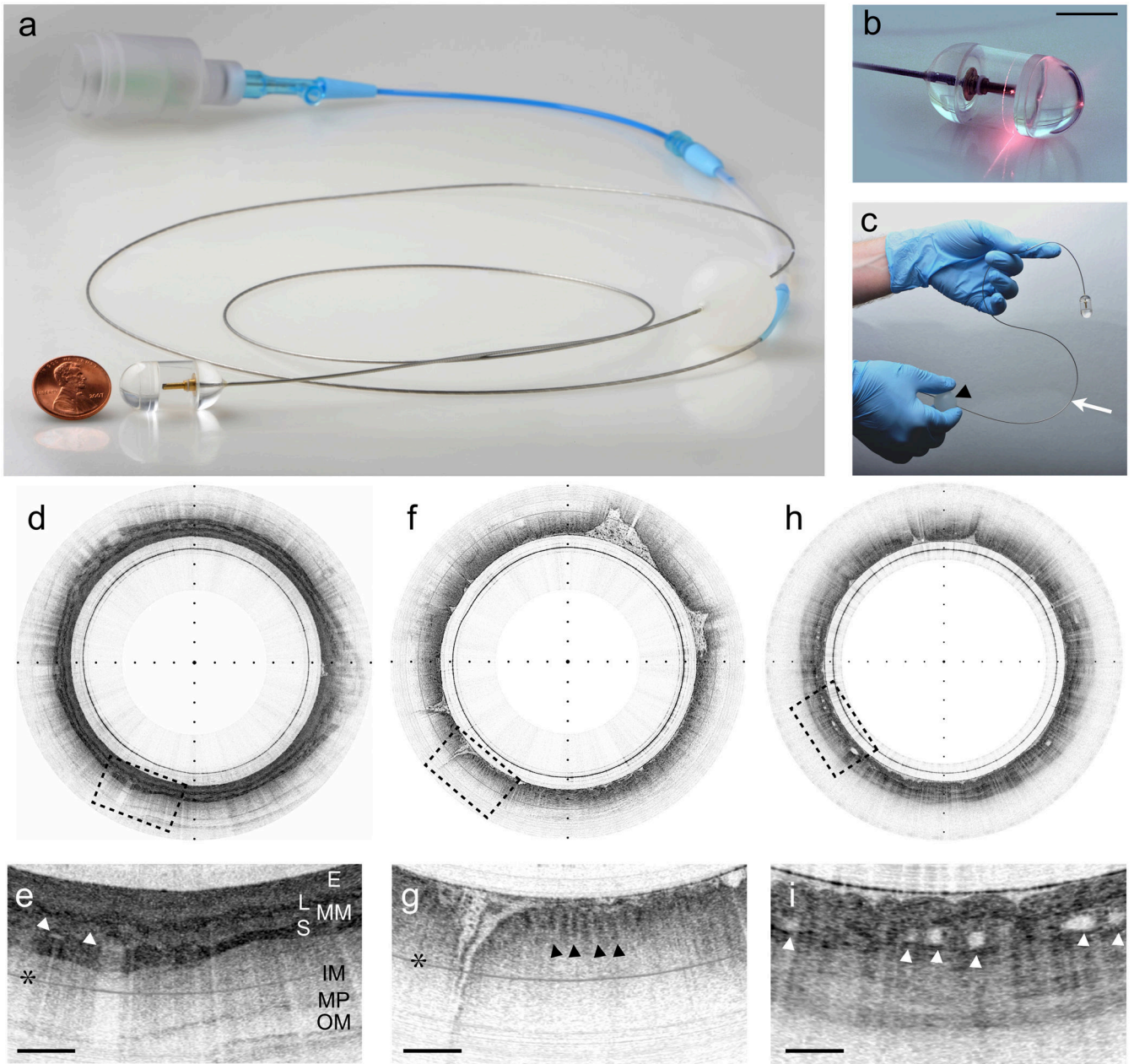
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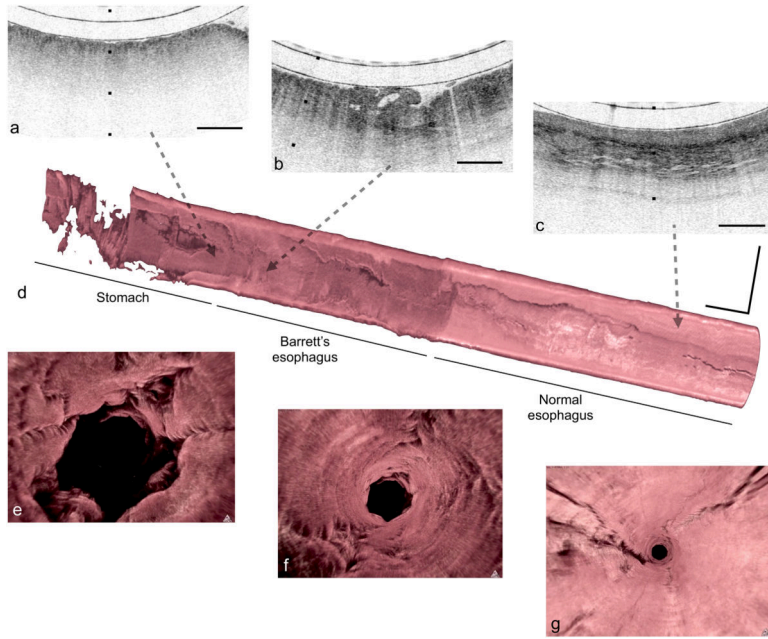
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**Figure 1. Tethered capsule endoscopy**

(a) Photograph of the entire tethered capsule endoscopy device, showing the capsule portion adjacent to a penny for scale. (b) Close-up, time-integrated photograph of the tethered capsule endoscope, transmitting red light as the internal optics rotate. (c) The tether (arrow) is very flexible and a plastic ball, attached to the tether (arrowhead), facilitates manipulation of the device. (d) Tethered capsule endoscopy image of the normal esophagus, obtained from a normal volunteer *in vivo*. (e) 3x expanded view of (d) demonstrates the normal esophageal wall architectural morphology, including the squamous epithelium (E), muscularis mucosa (MM), lamina propria (L), submucosa (S), containing blood vessels (arrowheads), inner and outer muscularis (IM and (OM), and myenteric

plexus (MP). **(f)** Tethered capsule endomicroscopy cross-sectional image of the stomach, obtained from a normal volunteer *in vivo*, with a 3x expanded view in **(g)** displaying characteristic glandular “pits” (arrowheads). **(h)** Image obtained from a patient with histopathologically-confirmed Barrett’s esophagus *in vivo*. **(i)** The 3x-magnified view of **(h)** shows an irregular luminal surface, heterogeneous backscattering, and glands within the mucosa (arrowheads). Tick marks in **(d, f, h)** - 1 mm; scale bars in **(e, g, i)** denote 0.5 mm. \* multiple reflection artifact.



**Figure 2. Tethered capsule endomicroscopy data from a patient with a diagnosis of Barrett’s esophagus and high-grade dysplasia/intramucosal carcinoma**  
 Portion of a cross-sectional tethered capsule microscopy image of stomach (a), Barrett’s with architectural atypia suggestive of high-grade dysplasia (b), and squamous mucosa (c) can be seen at the distal, mid, and proximal ends of the esophagus, respectively. (d) A three-dimensional representation of the tethered capsule endomicroscopy dataset shows a 4 cm segment of Barrett’s esophagus with multiple raised plaques/nodules, one of which corresponds to the features shown in (b). (e–g) Three-dimensional flythrough views of the stomach, Barrett’s segment, and squamous mucosa, respectively, demonstrating a clear difference between the superficial appearance of the rugal folds of the stomach, the crypt pattern of Barrett’s esophagus, and the smooth surface of the squamous mucosa. Tick marks and scale bars in (a–c) represent 1 mm. Scale bars in (d) represent 1 cm.