Institution: University of Cambridge		
Unit of Assessment: UOA1		
Title of case study: Cytosponge®-TFF3: A new cost-effective, minimally-invasive approach to reduce population mortality from oesophageal cancer.		
Period when the underpinning research was undertaken: September 2002 to present		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Rebecca C. Fitzgerald	Professor of Cancer Prevention	September 2001- present
Period when the claimed impact occurred: August 2013 to present		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact (indicative maximum 100 words)

The incidence of oesophageal adenocarcinoma (OAC) has increased sixfold since the 1990s. Only 12% of these patients live more than five years. But at least 4,500 of the 9,000 cases of OAC diagnosed each year in the UK could be prevented by detection of Barrett's oesophagus (BE) – a precancerous lesion caused by gastro-oesophageal reflux (heartburn) that can be cured with endoscopic treatment. Cambridge researchers conceived, invented and validated at population-scale, Cytosponge®-TFF3: the first diagnostic test for BE that can be deployed in primary care. Cytosponge®-TFF3 is US FDA and CE approved, and is licensed to the US company Medtronic, making it widely available in routine clinical practice in the UK and Europe. Cytosponge®-TFF3 is now an NHS Scotland commissioned service and is being implemented in NHS England. Use of the test has increased exponentially during the Covid-19 pandemic since its application has reduced demands on endoscopy services. The decrease in OAC mortality and morbidity from the use of Cytosponge®-TFF3 is highly cost-effective, with an incremental cost-effective ratio (ICER) of GBP4,752 per quality-adjusted life year (QALY) gained.

2. Underpinning research (indicative maximum 500 words)

Around 9,200 new oesophageal adenocarcinoma (OAC) cases are diagnosed in the UK every year (source: Cancer Research UK), and cases are on the increase due in part to increasing gastro-oesophageal reflux caused by obesity and poor diet. OAC can be prevented in up to 60% of cases by endoscopic treatment of dysplastic Barrett's oesophagus (BE) - the precursor lesion of OAC. But patients with gastro-oesophageal reflux (the main risk factor for BE and OAC) are rarely and sporadically referred by GPs for endoscopy, and population-scale endoscopic screening of BE is prohibited by cost and workforce limitations, contributing directly to poor outcomes from OAC (Shawihdi *et al*., Gut 2014). Therefore, there is great need for an accurate, relatively low-cost test for BE that can be deployed in primary care.

Invention of the Cytosponge®-TFF3 test: In 2001 Fitzgerald conceived, designed and patented a simple, cost-effective device that collects BE cells from the oesophagus. This was then coupled with a robust, immunohistochemical assay for a BE-specific protein – Trefoil Factor 3 (TFF3) – discovered and patented by Fitzgerald [1]. The patient swallows the pill-sized Cytosponge® capsule whilst holding an attached thread. After five minutes, the capsule dissolves in the stomach releasing a spherical sponge. The sponge is then retrieved using the thread, collecting stomach and oesophageal cells along its passage. The sponge is transferred to the laboratory in a standard preservative pot where cells are shaken from the sponge, centrifuged and analysed by TFF3 immunohistochemistry. The presence of TFF3 is then scored by a pathologist, which can be assisted using machine learning to assess samples at scale [2]. TFF3 positive patients are referred for an endoscopy and treatment as required.

***Safety and acceptability of the Cytosponge®-TFF3*:** Fitzgerald led the **B**arrett's o**E**sophagus **S**creening **T**rials 1 (BEST1, 2007-2009) and BEST2 (2011-2014). These studies performed 2,672 Cytosponge procedures among 2,418 individuals in primary and secondary care across UK, Australia and USA. Together, these studies confirmed that Cytosponge®-TFF3 detects a range of oesophageal pathologies in patients with reflux symptoms [3], and is well tolerated and accurately detects BE within the primary care setting [4,5,6,7].

Validation of the Cytosponge®-TFF3 as a frontline, diagnostic test of BE: To complete the translation of Cytosponge®-TFF3 into routine clinical practice, Fitzgerald led a third clinical trial – BEST3 (2017-2019). This multi-site, randomised controlled trial involved 109 GP practices across the UK. It randomised 13,514 patients aged >50 years taking acid-suppressants for >1 year to either the Cytosponge®-TFF3 test (n=6,983) or current standard of care (n=6,531) [7]. The study showed that Cytosponge®-TFF3 diagnoses 10 times more patients with BE (n=140) than does standard GP care (n=13; p<0.0001). Furthermore, Cytosponge®-TFF3 identified nine patients with dysplasia or early cancer, eight of whom received curative endoscopic treatment or minimally invasive surgery. All cases of cancer detected in the standard-care arm (n=3) were at an advanced stage requiring palliative care or systemic chemotherapy and surgery. Thus, Cytosponge®-TFF3 testing results in improved detection of BE and early OAC compared with usual care, establishing the first alternative care pathway to prevent OAC [8].

Health Economics: Cost-benefit ratio is important for the wide adoption of cancer screening tools. Therefore, Fitzgerald and colleagues conducted a microsimulation model analysis to show that screening 50-year-old men with symptoms of reflux disease by Cytosponge®-TFF3 is both cost effective – producing an incremental cost-effectiveness ratio (ICER) of USD15,700 per quality adjusted life year – and would reduce mortality from OAC compared with no screening [9]. This finding was confirmed by an independent Health Economics Consortium (Heberle *et al*., 2017). Following completion of BEST3, a new Markov model with a cycle-length of one year and a lifetime time horizon showed that one round of Cytosponge screening generated an ICER of GBP4,752 per QALY gained. This predicts a cost-effectiveness relative to usual care of >99% against the National Institute for Health and Care Excellence (NICE) willingness-to-pay threshold of GBP20,000 per QALY.

3. References to the research (indicative maximum of six references)
Evidence of research quality: *Research published in peer-review journals. Research was supported by competitively won grants.

[1] *Lao-SirieixP…..**Fitzgerald RC**. Non-endoscopic screening biomarkers for Barrett's oesophagus: from microarray analysis to the clinic. ***Gut*** 2009;8(11): 1451-1459.doi:10.1136/gut.2009.180281. PMID: 19651633.
[2] Triage-driven diagnosis of Barrett esophagus for early detection of esophageal adenocarcinoma 3 using deep learning Gehrung M….**Fitzgerald RC**, Markowetz F Nature Medicine 2021 *in press* https://www.medrxiv.org/content/10.1101/2020.07.16.20154732v1
[3] *Paterson AL….**Fitzgerald RC**; BEST and BEST2 study groups. Range of pathologies diagnosed using a minimally invasive capsule sponge to evaluate patients with reflux symptoms. ***Histopathology***. 2017 Jan;70(2):203-210. doi: 10.1111/his.13039. Epub 2016 Oct 12.
[3]* Kadri SR….**Fitzgerald RC**. Acceptability and accuracy of a non-endoscopic screening test for Barrett's oesophagus in primary care: cohort study. ***BMJ***. 2010 Sep 10;341:c4372. doi: 10.1136/bmj.c4372. PMID: 20833740.
[5]* Ross-Innes CS….**Fitzgerald RC**; BEST2 Study Group. Evaluation of a minimally invasive cell sampling device coupled with assessment of trefoil factor 3 expression for diagnosing Barrett's esophagus: a multi-center case-control study. ***PLoS Med***. 2015 Jan 29;12(1):e1001780. doi: 10.1371/journal.pmed.1001780. eCollection 2015 Jan. PMID:25634542.
[6] *Tan WK….**Fitzgerald RC**. A cross sectional analysis of Facebook comments to study public perception of a new diagnostic test called the Cytosponge. ***Dis Esophagus***. 2019 Jan 1;32(1). doi: 10.1093/dote/doy085. PMID: 30239646.
[7] *Januszewicz W…**Fitzgerald RC**; BEST1 and BEST2 study investigators. Safety and Acceptability of Esophageal Cytosponge Cell Collection Device in a Pooled Analysis of Data From Individual Patients. ***Clin Gastroenterol Hepatol***. 2019 Mar;17(4):647-656.e1. doi: 10.1016/j.cgh.2018.07.043. Epub 2018 Aug 9. PMID: 30099104.
[8] ***Fitzgerald RC**, …. on behalf of the BEST3 Trial team, Sasieni P. Cytosponge-trefoil factor 3 versus usual care to identify Barrett's oesophagus in a primary care setting: a prospective, multicentre, pragmatic, randomised controlled trial. **The Lancet** 2020 Aug;396(10247):333-344. doi: 10.1016/S0140-6736(20)31099-0.
[9] ***Fitzgerald RC***et.al.* Cytosponge-trefoil factor 3 versus usual care to identify Barrett's oesophagus in a primary care setting: a multicentre, pragmatic, randomised controlled trial. ***The***

Lancet. 2020 Aug 1;396(10247):333-344. doi: 10.1016/S0140-6736(20)31099-0. PMID: 32738955.
[10] *Benaglia…**Fitzgerald RC**, Lyratzopoulos G.Health benefits and cost effectiveness of endoscopic and nonendoscopic cytosponge screening for Barrett's esophagus.. ***Gastroenterology***. 2013 Jan;144(1):62-73.e6. doi: 10.1053/j.gastro.2012.09.060. Epub 2012 Oct 3. PMID: 23041329.

Patents: US State Patent: US1032774B2 - Relates to a device design by Fitzgerald that collects BE cells from the oesophagus.US State Patent US9632099B2: Relates to the use of an immunohistochemical assay for Trefoil Factor 3 (TFF3), a BE-specific protein discovered by Fitzgerald,in the diagnosis and detection of BE.

Funding sources (PI: Fitzgerald):
- Medical Research Council Core Funded Programme Grants: initial development of the device, the laboratory biomarkers and the first trial: (2003-2015), GBP3,901,000.
- Cancer Research UK Population Research Committee Programme Award in 2016: GBP1,226,736 (BEST2); 2017: GBP1,304,400 (BEST3)
- Funding for ongoing biomarker research: Evelyn Trust: GBP94,000; Rosetrees Trust:GBP335,400
- East of England Cancer Alliance: implementation of Cytosponge in primary care: GBP40,000
- Innovate UK: implementation of Cytosponge in primary and secondary care across the UK:(2020-2023), GBP2,545,334

4. Details of the impact (indicative maximum 750 words)

Impact on the health and wellbeing of people

Re-inventing the primary-tertiary care pathway to prevent OAC: Cytosponge®-TFF3 has provided patients at risk of OAC with a simple, convenient test in primary care allowing earlier intervention; thereby improving likelihood of survival and reducing both treatment side-effects and healthcare costs. The BEST3 trial was conducted in 109 GP surgeries, covering a patient population of >800,000 and this led to curative treatment for early cancer that would not have been identified otherwise [A]. Cytosponge®-TFF3 has been licensed to Medtronic to commercialise the technology and make it widely available: it received FDA marketing approval in 2018 and CE mark status in 2020 [B]. Medtronic figures indicate that Cytosponge®-TFF3 has now been used in the management of >1,000 patients in addition to those treated on clinical trials and will be administered to >10,000 patients by end of 2021[B], with expansion to Canada and Western Europe reaching >40,000 individuals by 2022 and >100,000 by 2023.

Patient and public involvement has been critical in developing Cytosponge®-TFF3. Over 4,000 people have now had the Cytosponge®-TFF3 test and their feedback has been overwhelmingly positive, for example*: "If I hadn't taken the Cytosponge test, I would now be walking around with cancer… the fact I am clear of cancer is fantastic… I believe this trial saved my life."* [A]. A video demonstrating the test received over 22,500,000 views and 2,837 comments on Facebook within a four-month period [A]. Fitzgerald has ongoing, long-term support of Heartburn Cancer UK, which *"is a passionate advocate of the Cytosponge…the device will reduce the need for unnecessary endoscopies, an invasive procedure, which can only be of benefit to patients and an overburdened health system."*[A]

Impact on practitioners and the delivery of professional services

***Clinical implementation in primary care*:** Cytosponge®-TFF3 is the first diagnostic test for BE available to GPs in primary care. Therefore, following support by Eastern Academic Health Science Network [D], Innovate UK funded the 'Delta Project' to accelerate the use of Cytosponge™-TFF3 in primary and secondary care and to make the identification of patients eligible for Cytosponge®-TFF3 clearer to GPs. This system alerts GPs to test patients with Cytosponge®-TFF3 who request repeat prescription for acid-suppressants [C] –1,300,000 patients in the UK are on long-term proton pump inhibitor (PPI) medication. To ensure further that clinicians are widely informed about Cytosponge®-TFF3, in December 2020, NICE published a Medtech Innovation Briefing, designed to support NHS and social care commissioners and staff who are considering using new medical devices and other medical or diagnostic technologies [D].

Cytosponge®-TFF3 has also been promoted as simple cost-effective test for BE by the Canadian Agency for Drugs and Technologies in Health, *"Use of the Cytosponge with biomarker analysis could improve identification of individuals with BE through a test that is less onerous for patients than endoscopy, as well as less costly*" [D]. Cytosponge is also an exemplar for the 2020 Early Detection and Diagnosis Roadmap produced by Cancer Research in collaboration with the Department of Health and Social Care [D]**.**

Maintaining services during the Covid-19 pandemic*:* The Covid-19 pandemic disrupted routine NHS services and screening on an unprecedented scale. Routine endoscopy lists – an 'aerosol generating procedure' – presented a high COVID-risk and were subject to major delays and cancellations. Therefore, Cambridge University Hospital NHS Trust accelerated commissioning of the Cytosponge®-TFF3 during the pandemic demonstrating its value to investigate patients who could not access endoscopy [E]. This led the Scottish Government from October 2020 to invest GBP500,000 to implement Cytosponge®-TFF3 across all ten of its mainland health boards [E]. By the end of December 2020, NHS Scotland were performing 100 Cytosponge procedures/week and NHS Scotland have stated they are scaling up these services with the expectation that 40% of the >65,000 patients undergoing upper gastrointestinal endoscopy each year will meet the criteria to undergo Cytosponge. Scottish Health Secretary Jeane Freeman stated: *"Cytosponge is part of an accelerated roll-out of innovative technologies being embraced by Scotland's NHS to support the resumption and recovery of vital health services that had to be paused because of the pandemic. It is a much simpler and more patient friendly test than endoscopy that enables faster diagnosis of patients at risk of pre or early cancer, without the need for them to undergo a more invasive procedure. The Scottish Government is working at pace with Health Boards, National Services Scotland (NSS), and industry partners to safely resume NHS services and this new tool further strengthens our ability to provide vital health services, and protect patients across Scotland*"**.** NHS England are also implementing Cytosponge®-TFF3 through a pilot project to reduce the Covid-19 related backlog in secondary care. 700 patients (phase 1) will be tested first, expanding to 30,000 in 2021/22 [E], with a clear path to NICE approval and commissioning. Testing in a mobile van will start in 2021 to pilot the community implementation which will fulfil the recommendation to move routine diagnostics out of secondary care, and assist in providing a Covid-19 safe service during the pandemic [E]**.**

Impact on commerce and the economy

Established a companion diagnostics company: To commercialise the sample processing and reporting of cells obtained through Cytosponge®-TFF3, in 2018 Fitzgerald co-founded the Cambridge spin-out Cyted that secured GBP8,700,000 investment from Morningside Capital Management. Cyted is providing the sample processing and reporting for Cytosponge procedures, and pioneering AI innovations for smart reporting [F]. In October 2020 Cyted acquired Pathognomics Limited, a provider of digital pathology and clinical diagnostic laboratory services, bringing the total number of Cyted employees to 23 [F].

Healthcare savings for the NHS: The cost of using Cytosponge®-TFF3 is approximately GBP280 – two thirds the cost of standard endoscopy (GBP407 [D(i)]). Based on 2016 UK population data (Office of National Statistics), assuming an uptake of the test in 50% of the 16,500,000 people aged 50-70 years who have gastro-oesophageal reflux (10% of a given age bracket), at least 800,000 people will be tested resulting in an estimated GBP240,000,000 screening savings to the NHS [G]**.**

5. Sources to corroborate the impact (indicative maximum of 10 references)

[A] Evidence of patient and public support for Cytosponge®-TFF3:
(i) Clinical trial found my cancer and saved my life, CRUK website, 18 Dec 2018 (ii) Taking part in a clinical trial was the "luckiest day of my life", Healthwatch Torbay, 2 July 2019 (iii) Tan WK, Muldrew B, Khan Z, Fitzgerald RC. A cross sectional analysis of Facebook comments to study public perception of a new diagnostic test called the Cytosponge. *Dis Esophagus*. 2019 Jan 1;32(1). doi: 10.1093/dote/doy085. (iv) Testimonial from Heartburn Cancer UK
[B] Cytosponge licensing and approvals:(i) Testimonial from Medtronic (ii) FDA approval, 2018 (iii) CE mark status approval, 2020
[C] About the Delta Project: https://www.deltaproject.org/about
[**D] Impact on clinical practice:**
(i) NICE Medtech innovation briefing on Cytopsonge for detecting abnormal cells in the oesophagus, 15 December 2020
(ii) EASTERN alliance supports roll-out of Cytosponge, Eastern AHSN, 31st July 2020
(iii) Early Detection and Diagnosis of Cancer Roadmap (2020). Cytosponge highlighted as a case study, page 63
(iv) Canadian Agency for Drugs and Technology for Health, The Cytosponge: An Alternative to Endoscopy in Detecting Barrett Esophagus, October 2015, page 3
[E] Cytosponge to alleviate endoscopy backlog during Covid-19 pandemic:
(i) Use of Cytosponge as a triaging tool to upper gastrointestinal endoscopy during the COVID-19 pandemic. di Pietro M, Modolell I, O'Donovan M, Price C, Pilonis ND, Debiram-Beecham I, Fitzgerald RC. Lancet Gastroenterology & Hepatology 5, Issue 9, p 805-809
(ii) Scottish Government commissioning of Cytosponge, October 2020
(iii) NHS Innovation has commissioned a pilot across England. Press release from NHS England. Evidence available upon request.
(iv) Diagnostics: Recovery and Renewal – Report of the Independent Review of Diagnostic Services for NHS England, 27 November 2020, page 66.
[F] Cyted commercial information:
(i) Cyted: From Cambridge start-up to digital pathology front-runner in one year, Cambridge Independent, 11 December 2020.
(ii) Cyted website: Cyted acquires Pathognomics Ltd, 19 October 2020
[G] Health economics of Cytosponge:(i) Benaglia…**Fitzgerald RC**, Lyratzopoulos G.Health benefits and cost effectiveness of endoscopic and nonendoscopic cytosponge screening for Barrett's esophagus. *Gastroenterology*. 2013 Jan;144(1):62-73.e6. doi: 10.1053/j.gastro.2012.09.060.
(ii) Heberle CR, Omidvari AH, Ali A, Kroep S, Kong CY, Inadomi JM, Rubenstein JH, Tramontano AC, Dowling EC, Hazelton WD, Luebeck EG, Lansdorp-Vogelaar I, Hur C. Cost Effectiveness of Screening Patients with Gastroesophageal Reflux Disease for Barrett's Esophagus With a Minimally Invasive Cell Sampling Device.*Clin Gastroenterol Hepatol.* 2017 Sep;15(9):1397-1404.e7.