Institution: Newcastle University		
Unit of Assessment: UoA5		
Title of case study: Peptest, a quick and simple test for reflux		
Period when the underpinning research was undertaken: 2002-2013		
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:**
Prof Jeff Pearson	Professor of Molecular Physiology	1/8/90 to present
Prof Chris Ward	Professor of Respiratory Physiology	1/4/01 to present
Prof Iain Brownlee	Assistant Professor	1/8/11 to 30/4/16
Dr David Bulmer	Experimental Scientific Officer	1/10/04 to present
Dr Ian Forrest	Associate Clinical Researcher	1/10/06 to present
Dr Desmond Murphy	Clinician Research Fellow	2004 to 2007
Emeritus Prof Paul Corris	Professor of Thoracic Medicine	1/5/86 to present
Prof John Dark	Professor of Cardiothoracic Surgery	1/10/87 to present
Dr Rachel Stovold	PhD Student	1/2/06 to 30/4/09
Period when the claimed impact occurred: 2014–present		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Gastro-oesophageal reflux disease (GORD) is a chronic disease with an estimated worldwide prevalence of 13.98%. Current methods for diagnosing GORD are highly invasive and lack sensitivity and specificity. Newcastle research confirmed that pepsin was a suitable biomarker of reflux events and was responsible for damage during reflux events. However no test existed to easily and accurately detect pepsin in patients. Newcastle research in collaboration with Technostics led to the development of Peptest, a sensitive and non-invasive measure of pepsin presence and reflux events. Peptest has achieved regulatory approval in several countries, including FDA approval in the US; has generated £1.2 million in revenue in 46 countries; since 2019 is being actively used in at least 6 NHS trusts.

2. Underpinning research

Reflux events and current diagnosis methods

Gastro-oesophageal reflux disease (GORD), commonly called heartburn, is the repeated movement of stomach acid up from the stomach to the throat, damaging the mucus layer in the throat and oesophagus. GORD is a chronic disease affecting all age groups with an estimated worldwide prevalence of 13.98%[1]. From the mid-1980s, GORD was gradually recognised to be linked to several diseases of the upper airways and lungs including asthma, voice disorders and idiopathic pulmonary fibrosis[2]. The recognition was slow because of the lack of strong evidence for reflux events or that refluxate was damaging.

GORD is now recognised as a major burden on primary care resources with estimates of £750 million[3] in the UK and $1.2 billion[4] in the USA spent on diagnosis, treatment, prescriptions and

[1] Nirwan JS, et al. (2020) Global Prevalence and Risk Factors of Gastro-oesophageal Reflux Disease (GORD): Systematic Review with Meta-analysis. *Sci Reports.* 10:5814. DOI: 10.1038/s41598-020-62795-1
[2] Vakil et al. (2006) The Montreal Definition and Classification of Gastroesophageal Reflux Disease A Global Evidence-Based Consensus. *American Journal of Gastroenterology*. 101(8):1900-1920. ISSN: 0002-9270.
[3] Mason J, Hungin APS. (2005) Review article: gastro- oesophageal reflux disease – the health economic implications. *Alimentary Pharmacology and Therapeutics* 22(1):20-31. DOI: 10.1111/j.1365-2036.2005.02606.xC
[4] Everhart JE, Ruhl CE. (2009) Burden of Digestive Diseases in the United States Part I: Overall and Upper Gastrointestinal Diseases. *Gastroenterology* 136(2):376–386. DOI: 10.1053/j.gastro.2008.12.015

sick leave. Many patients are treated with expensive and inappropriate medication without having a confirmed diagnosis. Current tests for reflux disease, such as PPI trials or endoscopy, suffer from a lack of specificity or sensitivity[5] while others such as upper gastrointestinal endoscopy, 24 hour pH monitoring (BRAVO) or high-resolution manometry, are highly invasive. There was therefore a clear unmet need for a simple, rapid, accurate and non-invasive diagnostic test to confirm the presence of GORD and direct future treatment. Such a test would considerably improve resource spending and patient QOL.

Pepsin as a biomarker for reflux events and as a source of damage during events

A biomarker for reflux was needed, the importance of which would be increased if it was also responsible for the progression of diseases associated with GORD. One suggested biomarker was pepsin protein. However at the outset of research, no assay for pepsin protein was available. Newcastle demonstrated that pepsin could be used as a biomarker as it can be detected in sputum samples, indicating its presence outside the stomach and a reflux event (R1, R2, R3). In addition Newcastle research demonstrated that pepsin can retain tissue damaging activity up to pH 6.5 indicating that pepsin itself has the potential to be a causative agent in disease (R4, R5). This increases the need for a sensitive and non-invasive test for pepsin.

ELISA development and creation of Peptest

Newcastle developed an assay with specificity and sensitivity for pepsin in the ng/ml range, by designing an ELISA with a polyclonal antibody to pepsin isolated from human pepsin from human gastric juice (R3). This ELISA was then further developed and commercialised by Technostics who, in collaboration with Newcastle University, developed a monoclonal antibody for the test. This eventually led Technostics to develop Peptest, a lateral flow test to measure pepsin, to be used as a diagnostic tool. Peptest was given an EU-wide CE mark in January 2011.

3. References to the research

SciVal field-weighted citation impact (FWCI) as of December 2020. Newcastle researchers in **bold.**

R1. Tasker A, Dettmar PW, Panetti M, Koufman JA, Birchall JP, **Pearson JP**. (2002) Reflux of gastric juice and glue ear in children. *The Lancet*. 359(9305):493. DOI: 10.1016/S0140-6736(02)07665-1. FWCI: 11.84.

R2. **Ward C**, **Forrest IA**, Brownlee IA, Johnson GE, **Murphy DM**, **Pearson JP**, Dark JH, **Corris PA**. (2005) Pepsin like activity in bronchoalveolar lavage fluid is suggestive of gastric aspiration in lung allografts. *Thorax.* 60(10):872-4. DOI: 10.1136/thx.2004.036426. FWCI: 1.5.

R3. **Stovold R**, **Forrest IA**, **Corris PA**, **Murphy DM**, Smith JA, Decalmer S, **Johnson GE**, **Dark JH**, **Pearson JP**, **Ward C.** (2007) Pepsin, a biomarker of gastric aspiration in lung allografts: a putative association with rejection. *American Journal of Respiratory Critical Care Medicine.* 175(12):1298-303. DOI: 10.1164/rccm.200610-1485OC. FWCI: 3.02.

R4. Bulmer D, Ali M, Brownlee I, Dettmar P, **Pearson JP**. (2010) Laryngeal mucosa: Its susceptibility to damage by acid and pepsin. *Laryngoscope*. 120(4):777-782. DOI: 10.1002/lary.20665. FWCI: 4.15.

R5. Ali M, Parikh S, Chater P, **Pearson JP**. (2013) Bile acids in laryngopharyngeal refluxate - will they enhance or attenuate the action of pepsin? *Laryngoscope.* 123(2):434-439. DOI: 10.1002/lary.23619. FWCI: 1.95.

4. Details of the impact

Development of Peptest

Peptest is a non-invasive lateral flow test for pepsin developed by Technostics Ltd. who confirm that Newcastle research "*described the first ELISA for pepsin, including a key polyclonal pepsin antibody, which informed development of our monoclonal antibody and ultimately led us to develop Peptest, a world class lateral flow test for pepsin*" (EV1). Peptest is now manufactured and distributed by the UK based company RD Biomed [Redacted for publication] (EV1).

[5] Bytzer et al. (2012) Limited ability of the proton-pump inhibitor test to identify patients with gastroesophageal reflux disease. *Clinical Gastroenterology and Hepatology*. 10(12):1360-6. DOI: 10.1016/j.cgh.2012.06.030.

This is the only test available non-invasive for pepsin and operates much like the COVID-19 lateral flow test. Approximately 1ml of saliva is applied to a custom sample chip containing two unique and specific human pepsin monoclonal antibodies (EV2). Visible reaction of the antibodies to pepsin presence provides a qualitative pepsin positive/negative result within 10 minutes. When used in clinic, the test can be conducted at the bedside, quantified further within 15 minutes by simply inserting into an in-house Peptest reader, or if a reader is not present at the healthcare centre, in depth quantitative analysis can be completed at RD Biomed, usually within one business day (EV1).

Peptest is highly regarded in the diagnosis of GORD events and is considered an '*industry leading gold standard assay*' (EV1). In the diagnosis of GORD and laryngopharyngeal reflux (stomach content reaching the larynx and pharynx), Peptest has 95% and 81% sensitivity, and an 89% and 100% specificity respectively (EV1).

Impacts on the NHS

The UK is not the primary market for Peptest so in 2019, RD Biomed assigned a new UK distributor (Biohit UK) to grow the number of NHS hospitals and trusts supplied. As of the end of 2020, 6 NHS trusts are now using Peptest in everyday practice [Redacted for publication] (EV1).

Increased Peptest use is expected to lead to savings for the NHS. [Redacted for publication] (EV3). Gastroenterology referrals, gastroscopy sessions and impedance of pH monitoring are noted as all avoidable following a positive Peptest result, leading to concurrent savings.

Impacts on Technostics and RD Biomed

The primary markets for Peptest have been Asia and Oceania, North America and the rest of the EU. Distribution to these markets has been facilitated by registration as an in vitro diagnostic device (EV2), its initial CE certification in 2011 and further regulatory approvals in several countries. It was registered as a low-risk Class 1 medical device by the FDA in 2017 (EV4) and approved by the Chinese health authorities in 2019 (EV5). It is also approved in Canada, Brazil, Australia, Germany and France (EV1). Chinese approval is especially important as diagnosis of reflux has increased in Asian populations[6]. Indeed, a Chinese validation study of Peptest, which analysed samples from 709 GORD patients from 7 Shanghai and 2 Beijing hospitals, found that reflux disease in China was likely much higher than previously estimated (EV6).

While not required, regulatory approval of Peptest has encouraged international sales to healthcare providers. Peptest is also available privately, sold directly to patients through the Peptest website. These distribution routes have led to [Redacted for publication] sales since January 2014 in 46 countries in Europe, Sub-Saharan and North Africa, the Middle East, Asia and Oceania, North America and Latin America and the Caribbean (EV1). Tests are sold in 50, 10 or single test formats, along with required consumables and an additional sample reader is also available (the PEPCube). [Redacted for publication] (EV1).

[Redacted for publication] (EV1). A 2014 survey of Peptest customers conducted by the manufacturers, reported that 79% of respondents were happy with their diagnosis and 91% said that they would buy Peptest again. Customers especially praised "fast and efficient" service and quick test turnaround (EV1, EV7).

Summary

Newcastle development of the first ELISA against pepsin, including a key polyclonal antibody, led to the development and international commercialisation of the fast and non-invasive Peptest by RD Biomed, with significant markets in Asia, Europe and US.

[6] El-Serag HB, et al. (2014) Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut*. 63(6):871–880. DOI: 10.1136/gutjnl-2012-304269.

5. Sources to corroborate the impact

EV1. Letter of support from the Director of Technostics. PDF

EV2. NICE Medtech innovation briefing. 'Peptest for diagnosing gastro-oesophageal reflux'. 2015. Page 5, "About the technology". PDF. https://www.nice.org.uk/advice/mib31/resources/peptest-for-diagnosing-gastrooesophageal-reflux-63499100556229

EV3. [Redacted for publication]

EV4. Peptest registered with US Food and Drug Administration. 16th August 2017. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/rl.cfm?lid=518958&lpcd=JLL PDF

EV5. Peptest celebrates official launch in China. 21st November 2019. https://www.peptest.co.uk/peptest-celebrates-official-launch-in-china/ PDF

EV6. Wang YF, et al. (2019) Validation in China of a non-invasive salivary pepsin biomarker containing two unique human pepsin monoclonal antibodies to diagnose gastroesophageal reflux disease. *Journal of Digestive Diseases*. 20:278–287. DOI: 10.1111/1751-2980.12783

EV7. "Peptest customer survey 2014 … The Results are in". 26th September 2014. https://www.peptest.co.uk/peptest-customer-survey-2014the-results-are-in/ PDF