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| **Institution: University College London** | | |
| **Unit of Assessment: 1 - Clinical Medicine** | | |
| **Title of case study: National implementation of MR enterography (MRE) and intestinal ultrasound (US) for more effective diagnosis and management of Crohn's disease: reducing harm and providing quantitative biomarkers of disease activity for clinical trials** | | |
| **Period when the underpinning research was undertaken: 2012 - 2020** | | |
| **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:** |
| **Stuart Taylor** | **Professor of Medical Imaging** | **2006 - present** |
| **Steve Halligan** | **Professor of Gastrointestinal Radiology** | **2006 - present** |
| **Period when the claimed impact occurred: 2013-2020** | | |
| **Is this case study continued from a case study submitted in 2014?** N | | |

## 1. Summary of the impact

Research led by UCL has changed the way patients with Crohn's disease are diagnosed and monitored, reducing their exposure to harmful X-radiation and providing new quantitative biomarkers to measure treatment efficacy. The UCL team has developed and clinically validated MR enterography (MRE) as a diagnostic tool and developed non-invasive quantitative markers for Crohn's disease activity, which are endorsed by national and international guidelines; have been adopted by pharmaceutical companies in clinical trials of novel therapeutics; and resulted in a software spin-out, Motilent. The research has led to a 79% increase in use of MRE by the NHS in 6 years, reducing exposure of young patients to harmful X-ray radiation by 50% and preventing at least 25 radiation-induced deaths each year, in the UK alone.

## 2. Underpinning research

At least 115,000 people are diagnosed with Crohn's disease (CD) in the UK each year, generally in young adulthood. It is a life-long condition and can cause debilitating symptoms including pain, fatigue, weight loss and malnutrition and life-threatening complications such as severe infections and bowel obstruction and perforation. Small bowel involvement ranges from superficial ulceration to deep penetrating disease, characterised by strictures, fistulae and abscesses. Disease management requires regular monitoring and knowledge of the extent and location of disease, inflammatory activity and any additional complications. Radiological imaging is fundamental to diagnosis and management as the small bowel is relatively inaccessible. Several small bowel imaging techniques are used within the NHS: barium fluoroscopy (BaF), CT enterography (CTE), ultrasound (US) and magnetic resonance enterography (MRE – a specialised MRI for the bowel). However, both BaF and CT expose patients to significant x-rays and carry an accumulating increased cancer risk with repeat imaging over the patient's lifetime.

**Validating magnetic resonance enterography (MRE) and ultrasound (US) to diagnose and assess Crohn's disease (CD)**

In 2011, Taylor and colleagues undertook the first national survey of radiological imaging in CD, revealing wide variation in use of various small bowel imaging tests across the NHS. They found extensive use of CT and X-Ray fluoroscopy (**R1**), which subject young patients to increased cancer risk due to repeated radiation exposure over their lifetime. In contrast,

implementation of safer techniques such as MRE and US that do not use X-radiation, was ad hoc, partly due to lack of published evidence to support their use. To guide NHS implementation, the NIHR commissioned Taylor, Halligan and colleagues to elucidate and then directly compare the diagnostic accuracy of MRE and US for small bowel CD. They carried out the METRIC trial, recruiting 284 patients with newly diagnosed or relapsing CD across 8 NHS hospitals between 2013 and 2016 (**R2**).

METRIC is the largest prospective multicentre study directly comparing diagnostic accuracy of MRE and US in CD. The primary outcome was the per-patient difference in sensitivity between MRE and US for correct identification and localisation of small bowel CD. Secondary outcomes included specificity for disease extent, identification of active disease, influence on patient management, cost-effectiveness and comparative patient experience. The trial showed that both MRE and US achieved high accuracy for detecting and localising small bowel CD, but MRE was significantly superior to US. Both tests were cost effective (judged by NICE criteria), and detailed health psychology evaluation (**R3**) found both were well tolerated by patients, who rated accuracy as the most important test attribute.

**Validating MRE analysis in Crohn's patients against histological reference material for disease activity scoring**

Further research by Taylor and colleagues has validated MRE as a noninvasive marker of CD activity which can be used to guide and monitor anti-inflammatory therapy. To develop the scoring system, the team performed MRE in 16 patients undergoing small bowel resection. Mural thickness, T2 signal, contrast enhancement, and perimural oedema were scored qualitatively (0–3) at 44 locations. Transmural histopathological scoring of acute inflammation (AIS) was performed at all locations (score 0–13). MRI parameters best predicting AIS were derived using multivariate analysis. The MRI activity index was applied to 26 Crohn's patients and correlated to terminal ileal biopsy scores of acute inflammation. The study confirmed that a simple qualitative MRE Crohn's disease activity score is predictive against a histopathological standard of reference and the disease activity scoring system can be easily employed in routine clinical practice (**R4**) and is sensitive to responses to therapeutic interventions.

**Software development to quantify small bowel motility as a biomarker for CD activity**

In CD, bowel motility is related to disease activity. In collaboration with experts in medical imaging at UCL between 2012 and 2019, Taylor pioneered software for quantification of small bowel motility measured using MRE that now provides a novel responsive biomarker of CD disease activity (**R5**) and can be used to monitor the effectiveness of medical interventions (**R6**).

## 3. References to the research

**R1** Hafeez R, Greenhalgh R, Rajan J, Bloom S, McCartney S, Halligan S. Taylor SA (2011) Use of small bowel imaging for the diagnosis and staging of Crohn's disease--a survey of current UK practice. *The British journal of radiology*; 84(1002): 508-17. DOI: 10.1259/bjr/65972479

**R2** Taylor SA, Mallett S, Bhatnagar G, Baldwin-Cleland R, Bloom S, Gupta A, Hamlin PJ, Hart AL, Higginson A, Jacos I, McCartney S, Miles A, Murray CD, Plumb AA, Pollok RC, Punwani S, Quinn L, Rodriguez-Justo M, Shabir Z, Slater A, Tolan D, Travis S, Windsor A, Wytie P, Zealley I, Halligan S on behpaf of the METRIC study investigators (2018). Diagnostic accuracy of magnetic resonance enterography and small bowel ultrasound for the extent and activity of newly diagnosed and relapsed Crohn's disease (METRIC): a multicentre trial. *The lancet Gastroenterology & hepatology* 2018; **3**(8): 548-58. DOI: 10.1016/S2468-1253(18)30161-4

**R3** Miles A, Bhatnagar G, Halligan S, Gupta A, Tolan D, Zealley I, Taylor SA on behalf of the METRIC investigators. (2018) Magnetic resonance enterography, small bowel ultrasound and colonoscopy to diagnose and stage Crohn's disease: patient

acceptability and perceived burden. *European radiology*. DOI: 10.1007/s00330-018-5661-2

**R4** Steward MJ, Punwani S, Proctor I, Halligan S, Rodriguez-Justo M, Taylor SA. (2012) Non-perforating small bowel Crohn's disease assessed by MRI enterography: derivation and histopathological validation of an MR-based activity index. *European journal of radiology*; 81(9): 2080-8. DOI: 10.1016/j.ejrad.2011.07.013

**R5** Odille F, Menys A, Ahmed A, Punwani S, Taylor SA, Atkinson D. (2012) Quantitative assessment of small bowel motility by nonrigid registration of dynamic MR images. *Magnetic resonance in medicine*; 68(3): 783-93. DOI: 10.1002/mrm.23298

**R6** Plumb AA, Menys A, Russo E, Prezzi D, Bhatnagar G, Vega R, Halligan S, Orchard TR, Taylor SA (2015). Magnetic resonance imaging-quantified small bowel motility is a sensitive marker of response to medical therapy in Crohn's disease. *Alimentary pharmacology & therapeutics*; 42(3): 343-55. DOI: 10.1111/apt.13275

## 4. Details of the Impact

Research at UCL to compare the clinical accuracy and potential risks of harm between tests for diagnosing Crohn's Disease (CD) that do or do not expose patients to X-radiation has resulted in changes to recommendations in national and international clinical guidelines. These changes have in turn improved clinical practice and patient outcomes through the reduction of harm caused by repeated exposure to X-rays during diagnostic imaging. Based on the UCL research, clinical guidelines now also recommend the use of MRI to monitor response to treatment in people with CD, including in clinical trials. In addition, software developed at UCL to exploit this application of the research has been licensed via a successful spin-out company.

### Updated National and international clinical guidelines for the diagnosis and management of CD

The UCL-led research demonstrating high diagnostic accuracy and patient acceptability of MRE and US in CD has directly influenced both national (**S1**) and international clinical practice guidelines (**S2**) and is included in new guidance on training curriculums. The British Society of Gastroenterology guidelines are the leading multi-disciplinary guidelines for those dealing with patients with inflammatory bowel disease in the NHS and influence NICE guidance on CD management. The current version has been downloaded 51,983 times in 11 months with an Altmetric score of 244) (**S3**). The European Crohns and Colitis Organisation (ECCO) guidelines fulfil a similar role in Europe and have had 42,643 views or downloads in the 23 months since their publication (**S2**).

Both these widely implemented guidelines now recommend first line MRE (and US) rather than ionizing alternatives such as CTE. For example, the 2019 BSG guidelines state, "Cross-sectional imaging...has largely replaced conventional barium fluoroscopic and nuclear medicine techniques and has the advantage of evaluating both luminal and extraluminal disease. Emphasis should be placed on MR enterography and ultrasound as they do not expose patients to ionising radiation". The METRIC trial is quoted as the key reference. The METRIC trial is also specifically highlighted by the ECCO/ESGAR guideline (**S2, Part 2**), which states, 'All newly diagnosed CD patients should undergo small bowel assessment [intestinal ultrasound, MR enterography and/or capsule endoscopy]' and 'Endoscopic or cross-sectional reassessment in CD should be considered in cases of relapse, persistent disease activity, new unexplained symptoms, and prior to switch of therapy'.

There are approximately 78,000 new diagnoses of CD in Europe annually to whom this guidance directly applies. A gastroenterologist representing Amsterdam University Medical Centers said: "These guidelines (**S2**) are highly influential to the practice of gastroenterologists across Europe and directly impact the care of patients with Crohn's disease….In my practice in 2019 we performed >200 MRE examinations and just 2 barium fluoroscopic investigations. Ultrasound has been introduced as a 'point-of-care' technique at

the outpatient clinic offered every day of the week...This transition is replicated across European hospitals treating patients with IBD" (**S4**).

Taylor also officially advises IBD UK, a charity led alliance whose remit is to raise standards of care for those living with IBD in the UK. Access to appropriate imaging has now been added to their national service benchmarking tool (**S5**).

**Impact on NHS practice and patient benefit**

Results from the UCL-led METRIC trial have changed NHS practice. MRE use in the NHS has increased by 79% from 26,560 examinations in 2013 to 47,570 in 2019 (**S6**). At the same time, barium fluoroscopy has fallen by 63% from 11,380 to 4,310 annually. In response to the METRIC trial, the British Society of Gastrointestinal and Abdominal Radiology has set up a national program of training in MRE, and the European Society of Gastrointestinal and Abdominal Radiology has created a technical standards document (**S7**). It is estimated that fluoroscopic examinations induce around 70 cancers per year in the UK (**S8**), and abdominal CT induces approximately one cancer for every 500 scans performed in 20-year olds (conservatively equating to an extra 10-15 cancers annually from CT use in the UK Crohn's population) (**S8, S9**). Based on the METRIC trial data, the transition to MRE and US from other techniques is already reducing diagnostic radiation-induced malignancy, almost halving ionising radiation exposure in these young patients, and potentially preventing 25 to 30 radiation-induced cancers per year in the UK.

**MRI activity scores included as clinical trials endpoints**

UCL research has led to changes in international guidelines recommending MRE as a biomarker of disease activity, which were introduced in 2018. The joint ECCO/ESGAR guidelines (**S2**) state "Magnetic resonance [MR] enterography-based indexes have high accuracy for assessing luminal CD activity and can be used in clinical trials for measuring activity and response to pharmacological interventions." Specifically, the MRE activity score developed by Taylor's research was one of just two scores recommended as sufficiently validated for use in this context.

As a result, Pharma now specifically includes the activity score developed at UCL (the so called 'London score') as an endpoint in trials of novel anti-inflammatory therapies in CD (**S10**). The technique is also being applied to clinical trials investigating other gastroenterological conditions including idiopathic constipation (**S11**).

**Spin-out company established to licence software to quantify small bowel motility as a measure of CD disease activity**

In 2018, the software developed and validated by the UCL team to quantify small bowel motility in CD using MRI was commercialised by an SME (Motilent), set up by a former PhD student (Alex Menys) in Taylor's research group (**S12**). The company employs 12 FTE and has doubled its turnover in 12 months. It attracted more than GBP400,000 investment from the Enterprise Investment Scheme (EIS) in 2020 and is rolling out its CE marked flagship product GI Quant across 7 NHS sites. GI Quant helps clinicians identify at an early stage when patients stop responding to immunotherapy. The company has to-date processed over 400,000 images for over 40 R&D projects across the EU and US. The company was recently awarded a GBP2,700,000 grant funding from NIHR i4i and Innovate UK in a joint commercial academic collaboration with UCL, Great Ormond Street Hospital and the University of Nottingham.

**5. Sources to corroborate the impact**

**S1** Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, Hayee BH, Lomer MCE, Parkes GC, Selinger C, Barrett KJ, Davies RJ, Bennett C, Gittens S, Dunlop MG, Faiz O, Fraser A, Garrick V, Johnston PD, Parkes M, Sanderson J, Terry H, IBD guidelines eDelphi consensus group, Gaya DR, Iqbal TH, Taylor SA, Smith M, Brookes M, Hansen R, Hawthorne AB. (2019). British Society of Gastroenterology consensus guidelines on the

management of inflammatory bowel disease in adults. *Gut*; 68(Suppl 3): s1-s106. doi: 10.1136/gutjnl-2019-318484.

**S2** ECCO-ESGAR Guideline for Diagnostic Assessment in IBD **Part 1**: Initial diagnosis, monitoring of known IBD, detection of complications. Journal of Crohn's & colitis 2019; 13(2): 144-64. Maaser C et al. **Part 2**: IBD scores and general principles and technical aspects J Crohns Colitis . 2019 Mar 26;13(3):273-284 .Sturm A et al. doi: 10.1093/ecco-jcc/jjy114

**S3** Altmetric scores for guidelines https://gut.bmj.com/content/68/Suppl_3/s1.altmetrics

**S4** Testimonial from gastroenterologist representing Amsterdam Universities Medical Centers.

**S5** IBD Standards Document: https://ibduk.org/ibd-standards/the-ibd-service/investigations

**S6** Data from the Diagnostic Imaging Database, provided by NHS Digital.

**S7** Taylor SA, Avni F, Cronin CG, Hoeffel C, Kim SH, Laghi A, Napolitano M, Petit P, Rimola J, Tolan DJ, Torkzad MR, Zappa M, Bhatnagar G, Puylaert CAJ, Stoker J (2017) The first joint ESGAR/ ESPR consensus statement on the technical performance of cross-sectional small bowel and colonic imaging. *European radiology*; 27(6): 2570-82. doi: 10.1093/ecco-jcc/jjy113

**S8** Smith-Bindman R, Lipson J, Marcus R, Pyo Kim K, Mahesh M, Gould R, Berrington de Gonzalez A, Miglioretti DL (2009). Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Arch Intern Med*. Dec 14;169(22):2078-86. doi: 10.1001/archinternmed.2009.427

**S9** Berrington de Gonzalez A, Darby S. Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries. Lancet (London, England) 2004; 363(9406): 345-51. doi: 10.1016/S0140-6736(04)15433-0

**S10** Jairath V, Ordas I, Zou G, Panes, J, Stoker J, Taylor SA, Santillan C, Horsthuis K, Samaan MA, Shackelton LM, Stitt, LW, Hindryckx P, Khanna R, Sandborn WJ, D'Haens G, Feagan BG, Levesque BG, Rimola J. (2018). Reliability of Measuring Ileo-Colonic Disease Activity in Crohn's Disease by Magnetic Resonance Enterography. Inflammatory bowel diseases; 24(2): 440-9. doi: 10.1093/ibd/izx040

**S11** The causes of constipation. reclassifying consitpation using MRI and high resolution manometry to define mechanism of disease and target treatment. MR/N026810/1 https://gtr.ukri.org/projects?ref=MR%2FN026810%2F1

**S12** Motilent. http://www.motilent.co.uk/