

Impact case study (REF3)

Institution: University of Westminster		
Unit of Assessment: 3 Allied Health Professionals		
Title of case study: Enhancing Non-Invasive Diagnosis of Liver Disease		
Period when the underpinning research was undertaken: 2014 - 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): E Louise Thomas Jimmy Bell	Role(s) (e.g. job title): Professor Professor	Period(s) employed by submitting HEI: Oct 2014 ongoing; Aug 2014 ongoing
Period when the claimed impact occurred: June 2015 – Dec 2020		
Is this case study continued from a case study submitted in 2014? <input checked="" type="checkbox"/> /N		
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>Professor E Louise Thomas and Professor Jimmy Bell have worked extensively on developing and applying non-invasive methods for assessment of liver health via Magnetic Resonance Imaging (MRI) and Spectroscopy (MRS). Applying their skills to large cohorts including the UK Biobank, Thomas and Bell vastly expanded the scope and clinical usage of Perspectum Diagnostics's non-invasive analysis package <i>LiverMultiScan</i>TM (LMS). LMS can now determine the extent of liver injury in non-alcoholic fatty liver disease (NAFLD), one of the leading causes of early mortality, and non-alcoholic steatohepatitis (NASH), an advanced form of the disease that causes inflammation and damage. The following impacts have emerged:</p> <ul style="list-style-type: none"> • Clinical benefits: avoidance of painful and risky biopsy surgery for patients, as well as reduced discomfort in the time spent being scanned; significant cost savings for clinicians due to the speed and scope of the scan. • Benefits to the corporate partner: regulatory clearance; growth in employment; upskilling of staff; expansion of portfolio. • Benefits for Large Scale Medical Research Projects: LMS allows for pre-screening in Phase 3 trials that require biopsy and can now be applied to large population data. 		
<p>2. Underpinning research (indicative maximum 500 words)</p> <p>The research of Professor E Louise Thomas and Professor Jimmy Bell at the Research Centre for Optimal Health, University of Westminster, has validated and vastly expanded the use of MR imaging techniques – both whole-body MRI and the more specialised MRS technique that allows for the focused, detailed analysis of a localised region – for characterising ectopic fat in the context of a variety of chronic diseases.</p> <p>Part of this work was undertaken in collaboration with industrial partners including AMRA and Perspectum and has resulted in an ability to analyse, in a matter of seconds, images that would previously have taken hours or days. Thomas and Bell have utilised this technology to extend the application of MR imaging techniques to large-scale human phenotypic studies, through their research in the Imaging Enhancement consortium (UK Biobank) – a £40 million study (2014 to date) that involves the imaging of the brain, heart, bones, carotid arteries, and abdominal fat of 100,000 participants.</p> <p>An early instance of this work occurred in 2016, when Thomas and Bell led a team undertaking a large study of the first 3,000 UK Biobank subjects to be imaged to determine whether a novel MR sequence and its subsequent analysis would be suitable for application to a cohort of this size [1]. The methods they validated were proven to be sufficiently accurate to achieve a very high success-rate of 96% for body composition analysis and, as such, the researchers demonstrated that MR imaging techniques can be used in a way that avoids the conventional, laborious, and time-consuming manual segmentation of individual organs and tissues including the liver, kidneys, pancreas, kidneys spleen, muscles and fat compartments in MR body-images, which usually hinders its use in large cohort studies. This work has subsequently been scaled up and applied to 40,000 subjects.</p> <p>This research led to a Knowledge Transfer Partnership (KTP) with Perspectum Diagnostics in 2016 which involved the development and validation of a new, fast, and accurate MR imaging method – <i>LiverMultiScan</i> (LMS) – for the diagnosis of patients with liver disease. Professor Thomas and Professor Bell undertook rigorous testing of this technique through a study of 4,949 participants (aged 45–73 years) in the UK Biobank imaging enhancement protocol. The researchers found that LMS accurately determined that around 20% of adults in the UK population</p>		

have fatty liver disease, putting them at increased risk of type 2 diabetes mellitus, heart disease, stroke, and cancer [2].

Following initial validation, Thomas and Bell scaled up their MRI research with Perspectum Diagnostics to determine the prevalence of elevated liver iron within 9108 individuals from the UK Biobank cohort [3]. They demonstrated for the first time that measurement of liver iron at a population scale was feasible and can be used to better inform patient stratification and treatment.

Following this success, a further 11 research studies were undertaken in collaboration with Perspectum and the UK Biobank to develop and expand the usage of the LMS product.

For instance, Thomas and Bell undertook a study that involved using LMS to perform a genome-wide association study in 8,289 individuals from UK Biobank whose liver iron level had been quantified by MRI [4]. In doing so, the researchers identified 3 genetic variants that are linked to an increased risk of developing higher liver iron content, and associated liver diseases, and that the same genetic variants are linked to higher risk of many metabolic diseases, such as diabetes, high blood pressure, and heart disease. Further, they used genetic variants associated with waist-to-hip ratio as a tool to show that central obesity is causally associated with increased liver iron content.

Another study examined whether differences in the content and distribution of body fat and ectopic lipids are responsible for ethnic variations in metabolic disease susceptibility [5]. Anthropometry and body composition were assessed in two separate UK cohorts: the Hammersmith (n = 747) cohort and the UK Biobank (n = 9,533), both comprising individuals of South Asian descent, individuals of Afro-Caribbean descent, and individuals of European descent. Regional adipose tissue stores and liver fat were measured by MR techniques. The resultant data, consistent across the two independent UK-based cohorts, presented a limited number of ethnic differences in the distribution of body fat depots associated with metabolic disease. Contrary to conventional thinking, these results suggest that the ethnic variation in susceptibility to features of the metabolic syndrome may not arise from differences in body fat, thus directing researchers to investigate alternative mechanisms for understanding and reducing susceptibility to metabolic disease within minority ethnic communities.

MRI-based cT1 is a biomarker that provides a metric relating to steatohepatitis and liver fibrosis; i.e. a non-invasive method to grade the severity of inflammation and scarring of the liver. In the final study described here, the researchers aimed to identify genetic variants influencing liver cT1 and to use genetics to understand mechanisms underlying liver fibroinflammatory disease and its link with other metabolic traits and diseases [6]. This involved performing a genome-wide association study in 14,440 Europeans from the UK Biobank using the liver cT1 measure by LMS. cT1 has now been shown to be genetically linked to fatty liver disease, insulin resistance, and higher BMI, all of significant clinical importance. Most significantly, the association between zinc transporters and cT1 indicates an important new mechanism in non-alcoholic steatohepatitis (NASH). This creates the opportunity for future studies to determine whether interventions targeting the identified transporters might prevent liver disease in at-risk individuals.

3. References to the research (indicative maximum of six references)

- [1] West J, Dahlqvist Leinhard O, Romu T, Collins R, Garratt S, **Bell JD**, Borga M, **Thomas L** (2016). Feasibility of MR-Based Body Composition Analysis in Large Scale Population Studies. *PLoS One*. 11(9):e0163332.
- [2] Wilman HR, Kelly M, Garratt S, Matthews PM, Milanese M, Herlihy A, Gyngell M, Neubauer S, **Bell JD**, Banerjee R, **Thomas EL**. (2017). Characterisation of liver fat in the UK Biobank cohort. *PLoS One*. 12(2):e0172921
- [3] McKay A, Wilman HR, Dennis A, Kelly M, Gyngell ML, Neubauer S, **Bell JD**, Banerjee R, **Thomas EL** (2018). Measurement of liver iron by magnetic resonance imaging in the UK Biobank population. *PLoS One*. 13(12):e0209340
- [4] Wilman HR, Parisinos CA, Atabaki-Pasdar N, Kelly M, **Thomas EL**, Neubauer S; IMI DIRECT Consortium, Mahajan A, Hingorani AD, Patel RS, Hemingway H, Franks PW, **Bell JD**, Banerjee R, Yaghootkar H. (2019) Genetic studies of abdominal MRI data identify genes regulating hepcidin as major determinants of liver iron concentration. *Journal of Hepatology*. 71(3):594-602.

- [5] Alenaini W, Parkinson JRC, McCarthy JP, Goldstone AP, Wilman HR, Banerjee R, Yaghootkar H, **Bell JD, Thomas EL**. (2020) Ethnic Differences in Body Fat Deposition and Liver Fat Content in Two UK-Based Cohorts. *Obesity*. 28(11):2142-2152
- [6] Parisinos CA, Wilman HR, **Thomas EL**, Kelly M, Nicholls RC, McGonigle J, Neubauer S, Hingorani AD, Patel RS, Hemingway H, **Bell JD**, Banerjee R, Yaghootkar H. (2020) Genome-wide and Mendelian randomisation studies of liver MRI yield insights into the pathogenesis of steatohepatitis. *Journal of Hepatology*. 73(2):241-251.

Grants

- UK Biobank: Enhanced Phenotyping of Participants, **£39,375,709 million** (Wellcome Trust; MRC; BHF) 2014-2023.
- Innovate UK and Perspectum Diagnostics. KTP. **£207,496**, 2016-2019

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

The impacts described here relate to Thomas and Bell's work with Perspectum Diagnostics and their *LiverMultiScan* (LMS) MR imaging method for the diagnosis of patients with liver disease. In collaboration with KTP Associate Dr Henry Wilman, the researchers used their research-based knowledge to test this software at scale (via UK Biobank) and designed a software infrastructure that allowed the product to become commercially viable as a diagnostic tool for use in clinical trials.

Clinical benefits

Thomas and Bell have **made this novel method for diagnosing liver disorders accessible to clinicians** through their collaborative testing, validation, and development of the software infrastructure underpinning the technology. The latter involved creating a pipeline for image analysis and statistical analysis, as well as training Perspectum staff in combining imaging, phenotyping metadata, genetics etc. Due to this work, Perspectum can now deliver LMS as a standardised "service" that does not require any additional hardware, or even software installation in the cases when pre-scanned data is provided to Perspectum. Reflecting its accessibility to clinicians in the NHS, on 26 April 2019 the National Institute for Health and Care Excellence (NICE) issued a "Medtech Innovation Briefing" outlining the use, cost, and clinical care pathways for LMS [a-i]. Such briefings constitute "NICE advice" – involving a critical assessment of evidence – and "are designed to support NHS and social care commissioners and staff who are considering using new medical devices and other medical or diagnostic technologies" [a-ii].

LMS benefits patients as this method of analysis is non-invasive and thus **circumvents the pain and risks associated with invasive liver biopsy**. Such complications include excessive bleeding, infection, the puncturing of nearby tissue or organs and risk of death. An independent study found that the use of LMS in the diagnostic pathway of NAFLD patients can reduce the number of biopsies by almost half (a reduction of 458 per 1,000 patients) [a-iii]. LMS is thus being rolled out by the KTP partners Perspectum Diagnostics at over 240 national and international sites, with the aim of replacing liver-biopsy as the "gold-standard" in the assessment of liver biology.

Study [a-iii] also shows that this use of multiparametric MR imaging **reduces the cost-burden of biopsies**, leading to cost savings of £150,000 per 1000 patients for the NHS. Another independent study points out that, "in clinical practice, liver biopsies are usually repeated every 3–5 years to assess disease progression in patients with known chronic liver disease in order to risk stratify patients and prioritise treatments. This has cost implications both for health service providers and patients" which are thus drastically reduced with the use of LMS, since the method "strongly predicts clinical outcomes in patients with chronic liver disease of mixed aetiologies" [a-iv].

LiverMultiScan also scans quickly and captures data for 4 biomarkers simultaneously: it accurately characterises liver tissue, quantifies its liver fat, and provides T2* and T1 mapping, to analyse the iron and fibro-inflammatory levels, respectively. This means that the excessive time that a patient would ordinarily have to spend undertaking four individual MR scans is drastically cut, resulting in **a better healthcare experience for the patient**. For instance, in the aforementioned study [a-iv] the data inputted into the LMS software was produced using the traditional scanning technique (three separate scans in order to produce multiparametric data) and saw six of their 123 patients being excused from the sample due to suffering claustrophobia

within the MR scanner. Such patient discomfort is minimised when LMS is used to undertake the actual multiparametric MR scan (one scan serving 4 functions simultaneously) as it only takes 15 minutes to complete [a-v].

Benefits to the corporate partner

Perspectum Diagnostics state that “the main revenue stream for the company comes from the pharmaceutical business” and confirm that Thomas and Bell have been “instrumental in supporting this aspect of the business, for example by **supporting regulatory affairs** with their Biomarker Qualification Program (BQP) submission to the FDA” (the U.S. Food and Drug Administration) and “leading the design and analysis of **performance testing studies for regulatory clearance** for multiple products and versions” [b-i, p.5]. This work resulted in Perspectum obtaining 510(k) clearance from the FDA on 27 Nov 2017, allowing this technology to be used in all investigative liver studies. The researchers’ work here has also resulted in the technology being CE marked by notified body BSI 0086 in Europe, meaning it meets the health, safety, and environmental protection standards for products sold within, and from, the European Economic Area (EEA) [b-ii].

In regard to **employment**, Perspectum report that their company has seen “huge company growth, supported by its success in its pharmaceutical business” – the area Thomas and Bell have played an “instrumental” role in – such that they have grown “from 29 FTE (full-time equivalent employees) in July 2016 to 149 FTE at present” [b-i, p.4]. This is due to Perspectum’s products being “used in a large number of clinical trials worldwide” [b-i, p.3], with new teams dedicated to supporting both MR applications and Image Analysis having been “established to meet the considerable demands resulting from the commercial success of the pharma business and expansion of the company portfolio” [b-i, p.4].

Regarding the **expansion of the company portfolio**, Perspectum point out that Thomas and Bell “took the lead on supporting these increased demands on statistical resource to support our pharma customers with study design, powering and analysis of results, and supported the recruitment and development of additional resource in this area” [b-i, p.4]. Thomas and Bell have also beneficially impacted Perspectum by **up-skilling their staff**: “Our knowledge and capabilities in statistical analysis have greatly improved through this KTP [...] includ[ing] new skills in study design, powering and sample size calculation, multiparametric analysis, big data and machine learning” [b-i, p.5].

In March 2019, Beauhurst – a leading source of data for company growth in the UK – ranked Perspectum as the fastest growing Life Sciences company in terms of turnover, with an increase of 935% between 2016 and 2017 [b-iii]. This turnover growth was measured against 23,000 other companies. In a press release regarding this data, Perspectum again highlighted LMS as the key contributor to their **economic growth**: “This rapid growth is driven by the international success of its innovative medical imaging software, including *LiverMultiScan*” [b-iv].

In regard to future growth, Perspectum testify that Thomas and Bell have not only “**developed software infrastructure** for statistical analysis and reporting” for application to “multivariate analysis of new and existing clinical data” [b-i, p.5], but have also “**developed a Biostatistics repository** with shared code for the most common statistical analyses performed within the company. This now enables other team members to perform complex analyses in a standardised manner, using validated code” [b-i, p.6]. Perspectum now have the tools and appropriately trained staff to continue with their growth, as well as their potential **expansion into clinical care pathways**, which they attribute to “research studies [that] have highlight[ed] their utility in the diagnosis of diseases” across the NAFLD spectrum [b-i, p.3]. These are exemplified by outputs [2] to [6] referenced in Sections 2 and 3 above, and Perspectum highlight that the researchers “led the submission of [these] peer-reviewed publications on our imaging biomarkers and their relationship to lifestyle, genetics and outcomes” [b-i, p.5].

Benefits for large scale medical research projects

Diagnosing and treating non-alcoholic steatohepatitis (NASH) – a very severe form of non-alcoholic fatty liver disease (NAFLD) – is of great importance: “Modelling studies predict a steady increase in the incidence of NAFLD at the global level, accompanied by a proportionally larger increase in NASH cases, liver transplantation, HCC [hepatocellular carcinoma] and mortality from liver and non-liver causes” [c-i]. As revealed by *LiverMultiScan*-based research guided by Thomas and Bell, among UK adults NASH could be as high as 12% [c-ii].

Thomas and Bell's successful expansion of the LMS application has made this **an integral tool for the development of novel treatments for NASH, given its ability to analyse large scale data** which opens up a crucial area of medical research that was previously inaccessible – the ability to monitor liver health in the general population without the need for surgical procedures. As biopsy is still mandatory for entry onto the patient arm of NASH phase 3 clinical trials, **using LMS to pre-screen patients reduces the inclusion of people who will fail the biopsy screening**. This reduces the number of patients undertaking unnecessary biopsy and enables them to avoid the associated discomfort and risks described above. As the President and CEO of the Global Liver Institute, states: “As a patient who has experienced liver biopsy and as an advocate representing the interests of liver patients, I cannot overstate the importance of developments in non-invasive testing for NASH and other liver diseases” [c-iii].

The usefulness of LMS in this area, as validated and demonstrated by the research of Thomas and Bell, is such that it is **currently being used in 70 clinical trials across Europe, Asia, and the US**, where, in September 2019, it gained FDA approval for use in such research [c-iii]. Further, LMS now forms part of the imaging aspect of the Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS) study funded by the European Innovative Medicines Initiative 2 Joint Undertaking at €34 million. This study aims at developing, validating, and qualifying non-invasive biomarkers for testing NAFLD. The integration of LMS into this ongoing research project, which includes 47 international research partners based at leading international universities and some of the world's largest pharmaceutical companies, demonstrates its beneficial impact on the development and improvement of diagnostic pathways for patients of NAFLD/NASH [c-iv].

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

- [a] (i) NICE, LiverMultiScan MIB [\[link\]](#) (ii) NICE, Medtech Innovation Briefings [\[link\]](#) (iii) Eddowes PJ, McDonald N, Davies N, et al (2017). Utility and cost evaluation of multiparametric magnetic resonance imaging for the assessment of non-alcoholic fatty liver disease. *Aliment Pharmacol Ther.* 00:1–14. (iv) Pavlides et al. (2016). Multiparametric magnetic resonance imaging predicts clinical outcomes in patients with chronic liver disease. *J Hepatol.* 64:308-315. (v) Perspectum. Fatty liver epidemic affects one fifth of population, shown by UK Biobank MRI Study. *PR Newswire*, 27/2/2017 [\[link\]](#)
- [b] (i) Knowledge Transfer Partnerships, Final Report (inc. testimony from Perspectum Diagnostics) (ii) Perspectum. “LiverMultiScan™ analysis of UK Biobank indicates as many as 1 in 8 adults may have NASH”. 13/4/18 [\[link\]](#) (iii) Beauhurst, 2019, “Top 10 Life Sciences companies” data spreadsheet (iv) BusinessWire, “Perspectum Diagnostics Named Fastest Growing UK-based Life Science Company” 23/2/19 [\[link\]](#)
- [c] (i) Lazarus, Jeffrey V. et al. ‘A cross-sectional study of the public health response to non-alcoholic fatty liver disease in Europe’, *Journal of Hepatology* (72: 1): 14-24 [\[link\]](#) (ii) Harrison, S., Wilman, H.R., Kelly, M. et al. “Prevalence and stratification of NAFLD/NASH in a UK and US cohort using non-invasivemultiparametric MRI” [\[link\]](#) (iii) Perspectum Diagnostics (2019). “FDA Awards Grant for LiverMultiScan to help NASH patients” (iv) Perspectum. “LITMUS Project – LiverMultiScan™ included in ground-breaking €34 million project to develop better test for liver disease”. 24/11/17 [\[link\]](#)