Institution: The University of Manchester		
Unit of Assessment: 2 (Public Health, Health Services and Primary Care)		
Title of case study: ASPIRE™: Using machine learning to detect undiagnosed fractures in patients with osteoporosis		
Period when the underpinning research was undertaken: 2009 - 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:**
Paul A. Bromiley	Lecturer in Health Data Sciences Research Fellow Research Associate	2018 - present 2016 - 2018 2000 - 2016
Timothy F. Cootes	Professor of Computer Vision	2006 - present
Eleni P. Kariki	Honorary Academic Clinical Fellow	2015 - present
Judith E. Adams	Honorary Professor Honorary Chair	2012 - 2017 2007 - 2012
Period when the claimed impact occurred: 2018 - 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

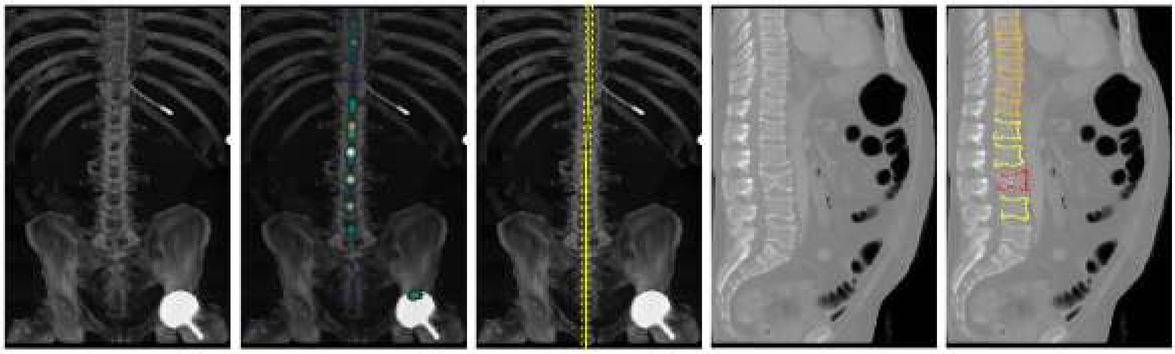
Osteoporosis weakens bones, increases risk of fractures and affects half of all people aged over 50. Vertebral fragility fractures (VFFs) are a common early manifestation, but those seen opportunistically on computed tomography (CT) images are often not reported by radiologists. At the University of Manchester (UoM) we have developed software to identify VFFs in CT images, combining it with oversight from radiologists to create ASPIRE™, a service that improves VFF identification. Implementation at NHS sites (2018-2019) analysed 9,797 patients and identified VFFs in 2,018 of them. Only 74 patients had been referred by hospital radiologists; ASPIRE™ referred 1,945, ensuring better management.

2. Underpinning research

An audit conducted at the Manchester Royal Infirmary in 2007 [1] revealed that VFFs seen on CT images were described in only 13% of radiology reports, indicating numerous missed opportunities for early diagnosis and treatment. Remedial measures were implemented to visualise VFFs more clearly, but a repeat audit in 2015 [2] revealed a still unacceptably low reporting rate of 36%. A vacancy rate of 30% placed pressure on the radiology workforce, and these busy professionals therefore needed innovative methods of support. The low reporting rate led to an interest in developing computer-aided diagnostic (CAD) software to assist radiologists to better identify and refer people at risk of developing more severe problems.

At the UoM we pioneered the development of a particular class of machine learning models (‘appearance models’) that could accurately identify the outlines of structures in images. They combined models of shape with those of the patterns of image data. The latest variant, the Random Forest Regression Voting Constrained Local Model (RFRV-CLM) [3], used an extremely powerful model of the local patches of image data that allowed accurate fitting of uncommon shapes [4]. This is essential for clinical images, where diagnosis is the aim and pathological shapes are of most interest. From 2012, an ongoing research programme has been conducted at the UoM to apply innovative RFRV-CLM models to measure the shapes of vertebrae in clinical images and detect VFFs. Dual X-ray absorptiometry (DXA) images are used clinically to confirm suspected osteoporosis. Initial work on these images demonstrated a 68% reduction in the proportion of incorrectly identified vertebrae compared to previous appearance models [4]. However, the NHS acquires large numbers of CT images in clinical practice (5,959,860 in 2019-2020). Detecting VFFs incidentally from this much larger number of images provided an opportunity to identify and treat osteoporosis early, prior to significant morbidity developing. CT images are 3D but, due to the time required (~30 minutes in 2D vs. ~5 hours in 3D), it was infeasible to perform sufficient 3D annotation to train RFRV-CLMs. Our team therefore developed methods to allow application in a series of 2D steps [5], as described in Fig. 1. In fully automatic operation, this system achieved 67% precision at 72% recall [5]; i.e. double the level of recall observed in clinical practice [2].

Cootes invented the RFRV-CLM [3]; he and Adams originated and directed the project. Bromiley's investigations developed and validated RFRV-CLMs [3], applied them to vertebrae visualised in images [4], and fitted such models to 3D CT images [5]. Kariki provided clinical expertise in the annotation and diagnosis of images [6,2,5]. The project also involved close collaboration with patients and advocacy groups through the Royal Osteoporosis Society (ROS) and the UoM Research User Group, which informed the direction of the research. Optasia Medical has a strategic alliance agreement with the ROS, which was a co-applicant on the grants that funded development of the software.



(a) (b) (c) (d) (e)

Figure 1: Processing 3D CT image volumes in a series of 2D steps. The original volume is summed in the anteroposterior direction (a) and an initialisation model finds the spinal mid-line (b, c). A lateral image is produced from a thick slice around the mid-line (d), then vertebrae are identified by an RFRV-CLM (e) and classified as normal (yellow) or fractured (orange=mild, red=severe) based on height reduction.

3. References to the research

1. A.L. Williams, A. Al-Busaidi, P.J. Sparrow, **J.E. Adams** and R.W. Whitehouse. Under-reporting of osteoporotic vertebral fractures on computed tomography. *European Journal of Radiology* 2009; 69(1) p 179-183. doi: 10.1016/j.ejrad.2007.08.028 (65 citations, Web of Science (WoS), 12 January 2021).
2. **E.P. Kariki**, **P.A. Bromiley**, **T.F. Cootes** and **J.E. Adams.** Opportunistic identification of vertebral fractures on computed radiography: need for improvement. *Osteoporosis International* 2016; 27(S2) p. 621. doi: 10.1007/s00198-016-3743-z.
3. C. Lindner, **P.A. Bromiley**, M.C. Ionita and **T.F. Cootes**. Robust and accurate shape model matching using random forest regression voting. *IEEE Transactions on Pattern Analysis and Machine Intelligence* 2015; 37(9) p. 1862-1874. doi: 10.1109/TPAMI.2014.2382106 (82 citations, WoS, 12 January 2021). **This the leading journal for computer vision**.
4. **P.A. Bromiley**, **J.E. Adams** and **T.F. Cootes**. Localisation of vertebrae on DXA images using constrained local models with random forest regression voting. Proc. MICCAI Workshop on Computational Methods and Clinical Applications for Spine Imaging (CSI 2014). Boston USA, 14th September 2014. In: *Lecture Notes in Computational Vision and Biomechanics* 2015; vol. 20, Springer International

Publishing, p. 159-171. doi: 10.1007/978-3-319-14148-0_14. **This paper won an honourable mention in the best paper award at CSI 2014.**

5. **P.A. Bromiley, E.P. Kariki**, **J.E. Adams** and **T.F. Cootes**. Fully automatic localisation of vertebrae in CT images using random forest regression voting. Proc. MICCAI Workshop on Computational Methods and Clinical Applications for Spine Imaging (CSI 2016), Athens, Greece, 17 October, 2016. In: *Lecture Notes in Computer Science* 2017; vol. 10182, Springer International Publishing, p. 51-63. doi: 10.1007/978-3-319-55050-3_5. **This paper was runner-up in the best paper award at CSI 2016**.
6. **P.A. Bromiley**, **E.P. Kariki** and **T.F. Cootes**. Computer-aided opportunistic identification of vertebral fractures in computed tomography images. Osteoporosis Online Conference 2020, 1st Dec 2020. In: *Therapeutic Advances in Musculoskeletal Disease* 2020; 12 p. 61, 2020. doi:10.1177/1759720X20969289.

Grants funding the research:

T.F. Cootes, A.J. Lacey, J.E. Adams and R. Stephen. 'An Automated Tool to Identify Vertebral Fractures in Various Imaging Modalities' funded by Department of Health/Wellcome Trust Health Innovation Challenge Fund. July 2013-July 2019. GBP805,740.

T.F. Cootes, J.E. Adams, K Payne and A. Holmes. 'STOpFrac: A Software Tool for Opportunistic Diagnosis of Vertebral Fractures'. NIHR i4i Product Development Award. November 2016-November 2019. GBP867,143.

4. Details of the impact

Context

Previously, VFFs were underreported by radiologists, and few patients were referred to appropriate services for follow-up. Our software and the associated ASPIRE™ service has enabled radiologists to better detect and refer patients with VFFs for further effective management safely and efficiently.

Pathways to impact

Having developed the technology for routine assessment of VFFs, there were two important pathways to impact:

1. Ensuring acceptance amongst patients and professionals.
2. Developing systems to deliver the technology in routine healthcare settings.

Acceptance among patients and professionals

The ROS formed the Osteoporosis and Bone Research Academy to generate a priority-setting national research agenda for the charity. Due to the success of the ASPIRE™ project, two of the named researchers (Bromiley and Kariki) were recruited to the Academy. The Research Roadmap produced by the academy highlights identification of VFFs on routine imaging as a research priority. The ROS Clinical Lead for Quality Improvement stated in a presentation describing ASPIRE™ at the British Institute of Radiology Artificial Intelligence (AI) in Radiology meeting, London, 24th Jan 2020 that "*AI is a promising application to support access to secondary fracture prevention in those with previously undiagnosed vertebral fragility fractures"* and that it *"could be a useful safety net for services in routine identification of these people*". The project also received extensive attention in the radiology press [A-E], including a front-page lead article in *Rad Magazine* [F].

Developing systems to deliver the technology

Starting in 2014, the software has been transferred to the commercial end user, Optasia Medical Ltd., as the basis of ASPIRE™, the world's first machine-learning based teleradiology service specifically targeting VFFs [G, H]. Optasia has received GBP706,000 in funding from investors during the project and employs eight people in Greater Manchester [H]. ASPIRE™

works as follows: CT images are routinely acquired during clinical practice and the primary indication (the reason for requesting the procedure) is reported by radiologists within the radiology department. Simultaneously, the image is submitted to the ASPIRE™ service, which uses our software to semi-automatically produce a report on VFFs. A GMC-registered radiologist employed at Optasia reviews the diagnoses. Finally, a report is automatically generated. If VFFs are found, the patient's local fracture liaison service is informed. Through high levels of automation achieved using UoM technology, and a focus on providing detailed and standardised reports, ASPIRE™ improves the accuracy of VFF identification compared to reporting within radiology departments, as indicated below, without adding to hospital workloads.

ASPIRE™ was registered with the Care Quality Commission on 25 November 2016. The CQC is the independent regulator of health and social care in England and assesses services "to check they are likely to be safe, effective, caring, responsive and well-led" . ASPIRE™ was last inspected on 9 November 2019 and rated “good” [G, H]. It also achieved CE marking as a Type-II medical device [H].

Reach and significance of the impact

Five retrospective studies were performed at NHS sites within the UK, studying historic data to measure rates of under-reporting of VFFs within radiology departments. The results generated from the study at Croydon Health Services NHS Trust, which serves 386,000 residents, led to the implementation in 2017 of a new reporting system to ensure that all patients with VFFs identified on CT are referred for a bone health review to ensure timely assessment and commencement of osteoporosis treatment [I].

In 2018 and 2019, ASPIRE™ was implemented prospectively for periods of three months at each of three NHS sites, serving an aggregate catchment population of 1,630,000 persons: the Nottingham University Hospitals NHS Trust, Bradford Teaching Hospitals NHS Foundation Trust and Royal Surrey County Hospital [H]. These initial deployments were funded by the NIHR product development award described above and funding provided to Optasia by Amgen Inc. (Thousand Oaks, California), an American multinational biopharmaceutical company, and Saffron Hill Ventures, a UK venture capital company. These companies were not funded by the hospitals involved or by the NHS.

The deployments ran in parallel with in-hospital reporting and included CT images from 9,797 patients (50% female). ASPIRE™ identified VFFs in 2,019 patients (21%). Only 665 (33%) of these were identified by reporting radiologists at the hospitals involved, in line with detection levels reported previously [2]. Furthermore, only 74 patients had been referred to their local fracture liaison service (FLS). Thus, ASPIRE™ referred 1,945 extra patients who would not otherwise have been referred to their local FLS for follow-up [G-H].

Detailed short-term follow-up was performed for patients in the Nottingham study [J]. ASPIRE™ reviewed CT scans from 4,416 patients, identifying VFFs in 850 (19%). Hospital-based radiologists had identified only 416 of these patients (48%). Of the patients identified by ASPIRE™, 309 (36%) received further diagnosis or treatment. The remainder were excluded due to being on the cancer pathway (31%), already being known as VFF or osteoporosis patients (18%), or other reasons. Long-term follow-up data are not yet available. However, other research suggests a VFF results in a mean quality-adjusted life year (QALY) loss of 0.16 per year for at least 18 months (Abimanyi-Ochom et al., *Osteoporos Int*. 2015;26(6):1781-1790). Women with a prevalent VFF have a 25% likelihood of experiencing a further VFF over the next five years; effective drug treatments halve this risk. Figures for men are less well established, but fracture prevalence is known to be at least as high as in women. Therefore, ASPIRE™ has already yielded an estimated 21 QALYs gained through VFF prevention alone (ignoring hip and other fractures) over a five-year period among the 1,945 patients referred during the three studies.

5. Sources to corroborate the impact

The significance of the project within the radiological community is supported by the industry prize received by Optasia Medical Ltd. and by the national and international press attention it has received, including:

A. *The Daily Mail*. 'Muscle twitcher that strengthens crumbly bones: Tiny implant could revolutionise the treatment of osteoporosis.' 19 August 2014. www.dailymail.co.uk/health/article-2728291/Muscle-twitcher-strengthens-crumbly-bones.html.

B. Optasia Medical won the Bionow Healthcare Project of the Year 2015 for the ASPIRE™ service. www.optasiamedical.com/winners-bionow-healthcare-project-of-the-year-2015/

C. *The Times* 'Super North' Supplement. 'Dr Holmes leads early detection of osteoporosis' http://www.neotherix.com/news/2016-02-23_Super_North_supplement.pdf 23 February 2016. (Front page article.)

D. AuntMinnie Europe, 'Optasia deploys CT AI algorithm at U.K. hospitals.' 24 July 2019. www.auntminnieeurope.com/index.aspx?sec=sup&sub=cto&pag=dis&ItemID=617635.

E. AuntMinnie Europe, 'Optasia reports vertebral fracture detection milestone.' 09 December 2019. www.auntminnieeurope.com/index.aspx?sec=sup&sub=aic&pag=dis&ItemID=618164.

F. RAD Magazine, 'AI detects previously undiagnosed vertebral fractures.' 11 December 2019. https://twitter.com/RADMagazine/status/1204750239753809920 (Front page lead article).

G. www.optasiamedical.com The Optasia Medical Ltd. company website describes the ASPIRE™ service, focusing on the clinical and commercial aspects, and provides contact details for Clinical Commissioning Groups interested in purchasing the service.

H. Letter from the CEO of Optasia Medical Ltd., dated 4 October 2020, describing the collaboration between the University and Optasia Medical Ltd. in the development of ASPIRE™, the regulatory status of the service, and the results of the clinical implementations at various NHS sites.

I. R. Rajak, K. Patel, R. Lawless, J. Staal and A. Holmes. Incidental capture of vertebral fragility fractures (VFFs) from CT imaging in a large district general hospital in London. *Rheumatology* 2019;58(S3): kez108.073. doi: 10.1093/rheumatology/kez108.073 . This publication describes the retrospective study at the Croydon Health Services NHS Trust, and the new VFF reporting service implemented across the Trust in response to the low referral rates discovered by the study.

J. T. Ong, R. Copeland, C.N. Thiam, G. Cerda Mas, L. Marshall and O. Sahota. Integration of a vertebral fracture identification service into a fracture liaison service: a quality improvement project. *Osteoporos Int* 2020. doi: 10.1007/s00198-020-05710-8 . This publication describes the clinical implementation at Nottingham, including detailed short-term follow-up data on the patients identified by the ASPIRE™ service.