Institution: University College London

Unit of Assessment: 1 Clinical Medicine

Title of case study: Transforming the diagnostic pathway for men at risk of prostate cancer by the introduction of magnetic resonance imaging (MRI)

Period when the underpinning research was undertaken: 2010 to 2018

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:
Mark Emberton	**Professor**	**1998 to present**

Period when the claimed impact occurred: 2015 to present

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Research at UCL has led to the introduction of magnetic resonance imaging (MRI) into the prostate cancer detection pathway which has transformed the diagnosis and risk-stratification of one of the world's most common cancers. MRI is now recommended as standard-of-care in national and international clinical guidelines, resulting in 1-in-4 men (250,000 men in Europe alone) avoiding an unnecessary biopsy. Since its roll-out, detection rates of important prostate cancers have doubled (48% to 93%) and over-diagnosis has been halved (10% to 5%). These two improvements have been achieved with less harm to the patient and reduced costs to healthcare systems.

2. Underpinning research

For the last 50 years, men at risk of prostate cancer have been assessed using prostate specific antigen (PSA) as a trigger for biopsy of the prostate. The random deployment of needles through the rectum into the prostate was inaccurate (both missed and misclassified cancers) and resulted in harm (bleeding and sepsis). The UCL research group was first to identify and publish on a method of improving healthcare outcome by incorporating MRI into the diagnostic pathway (**R1**). Since then, UCL researchers have undertaken a comprehensive health technology development programme to demonstrate the value of MRI in men suspected of having prostate cancer. They built consensus among clinicians (**R2**) and provided evidence to support its use (**R3**). This body of work has culminated in two multi-centre studies: PROMIS (**R4**) and PRECISION (**R5**). These two pivotal studies created the level-one evidence that was required to change practice globally.

The PROMIS trial was a multicentre, paired-cohort study to test diagnostic accuracy of multiparametric-MRI (MP-MRI) against the practice standard (trans-rectal ultrasound guided [TRUS] biopsy) by invoking a reference test (template prostate mapping biopsy [TPM-biopsy]). In total, 576 men were recruited from 11 UK hospitals. The results changed our understanding of prostate cancer diagnosis by revealing that the existing practice standard performed poorly and could be replaced by MRI. In PROMIS, MRI was found to be twice as good at detecting clinically significant disease compared to the practice standard: 93% (95% CI 88-96%) versus 48% (42-55%; p<0·0001). In addition, MRI was shown to have a role in safely reassuring men that they did not have clinically significant prostate cancer by virtue of the high negative predictive value of 97%. This single attribute would permit just over one quarter of men to avoid a biopsy.

The study showed that using MP-MRI to triage men should allow 27% of patients to avoid a primary biopsy and diagnosis of 5% fewer clinically insignificant cancers. If subsequent TRUS-biopsies were directed by MP-MRI findings, up to 18% more cases of clinically significant cancer might be detected compared with the standard pathway of TRUS-biopsy for all. MP-MRI, used

as a triage test before first prostate biopsy, could reduce unnecessary biopsies by a quarter (**R4**). **The PRECISION trial** randomised 500 men into two groups: an MRI-targeted biopsy group and a TRUS biopsy group. Clinically significant cancer was detected in 38% of men in the MRI-targeted biopsy group, compared with 26% in the TRUS biopsy group. Fewer men in the MRI-targeted biopsy group received a diagnosis of clinically insignificant cancer indicating that MRI would be helpful in reducing over-diagnosis. PRECISION showed that the MRI group had fewer missed diagnoses, despite fewer men biopsied overall. This improved detection efficiency was associated with more representative pathology and less harm to the patient (**R5**). Having demonstrated the effectiveness of MRI in the diagnostic pathway for prostate cancer, the UCL group developed a standardised methodology for image acquisition and high-quality image interpretation (**R6**), identifying specific sequences that form the basis for standardised MRI-guided stratification of prostate cancer (**R7**).

3. References to the research

R1 Ahmed HU, Kirkham A, Arya M, Illing R, Freeman A, Allen C, Emberton M. (2009). Is it time to consider a role for MRI before prostate biopsy? *Nat Rev Clin Oncol* Apr;6(4):197-206. doi: 10.1038/nrclinonc.2009.18

R2 Dickinson L, Ahmed HU, Allen C, Barentsz JO, Carey B, Futterer JJ, Heijmink SW, Hoskin PJ, Kirkham A, Padhani AR, Persad R, Puech P, Punwani S, Sohaib AS, Tombal B, Villers A, van der Meulen J, Emberton M (2011). Magnetic resonance imaging for the detection, localisation, and characterisation of prostate cancer: recommendations from a European consensus meeting. *Eur Urol.* Apr;59(4):477-94. doi: 10.1016/j.eururo.2010.12.009.

R3 Valerio M, Donaldson I, Emberton M, Ehdaie B, Hadaschik BA, Marks LS, Mozer P, Rastinehad AR, Ahmed HU. (2015). Detection of Clinically Significant Prostate Cancer Using Magnetic Resonance Imaging-Ultrasound Fusion Targeted Biopsy: A Systematic Review *Eur Urol* Jul;68(1):8-19. doi: 10.1016/j.eururo.2014.10.026 .

R4 Ahmed HU, Ahmed HUU, Bosaily AE, Brown LC, Gabe R, Kaplan R, Parmar MK, Collaco-Moraes Y, Ward K, Hindley RG, Freeman A, Kirkham AP, Oldroyd R, Parker C, Emberton M, and the PROMIS study group (2017). Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet*. 25;389(10071):815-822. doi: 10.1016/S0140-6736(16)32401-1.

R5 Kasivisvanathan V, Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MA, Briganti A, Budäus L, Hellawell G, Hindley RG, Roobol MJ, Eggener S, Ghei MSG, Villers A, Bladou F, Villeirs GM, Virdi J, Boxler S, Robert G, Singh PB, Venderink W, Hadaschik BA, Ruffion A, Hu JC, Margolis D, Crouzet S, Klotz L, Samir TS, Pinto P, Gill I, Allen C, Giganti F, Freeman A, Morris S, Punwani S, Williams NR,Brew-Graves C, Deeks J, Takwoingi Y, Emberton M, Moore CM on behlaf of PRECISION Study Group Collaborators. (2018). MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med*. May 10;378(19):1767-1777. doi: 10.1056/NEJMoa1801993.

R6 Giganti F, Stabile A, Stavrinides V, Osinibi E, Retter A, Orczyk C, Panebianco V, Trock BJ, Freeman A, Haider A, Punwani S, Allen C, Kirkham A, Emberton M, Moore CM (2020). Natural history of prostate cancer on active surveillance: stratification by MRI using the PRECISE recommendations in a UK cohort. *Eur Radiol* 31, 1644–1655. doi: 10.1007/s00330-020-07256-z.

R7 Hamid S, Donaldson IA, Hu Y, Rodell R, Villarini B, Bonmati E, Tranter P, Punwani S, Sidhu HS, Willis S, der Meulen J, Hawkes D, McCartan N, Potyka I, Williams NR, Brew-Graves C, Freeman[i] A, Moore CM, Ahmed HU. (2018). The SmartTarget Biopsy Trial: A Prospective, Within-person Randomised, Blinded Trial Comparing the Accuracy of Visual-registration and Magnetic Resonance Imaging/Ultrasound Image-fusion Targeted Biopsies for Prostate Cancer Risk Stratification. *Eur Urol.* May;75(5):733-740. doi: 10.1016/j.eururo.2018.08.007.

4. Details of the impact

The use of MRI has transformed diagnosis of prostate cancer allowing specialists to identify tumours in the prostate without the need for invasive, risky and sometimes unnecessary procedures. Millions of men every year are benefitting from having MRI incorporated into the diagnostic pathway now that clinical guidelines both in the UK and internationally recommend its use. The benefits include: fewer men biopsied, fewer needle deployments, fewer missed important cancers, a reduction in the risk of over-diagnosis, less harm and less cost. In Europe alone, one million men per year are able to derive these benefits.

National and international guidelines for prostate cancer diagnosis

Following the UCL led research, in May 2019, the National Institute of Clinical and Care Excellence (NICE) amended their recommendation for the diagnosis of prostate cancer and identified MRI as a cost-effective intervention in the diagnostic pathway for a man at risk. The following specific recommendations were made, "1.2.2 Offer multiparametric MRI as the first-line investigation for people with suspected clinically localised prostate cancer. 1.2.3 Offer multiparametric MRI-influenced prostate biopsy to people whose Likert score is 3 or more. [2019]. 1.2.4 Consider omitting a prostate biopsy for people whose multiparametric MRI Likert score is 1 or 2 (normal scan)." (**S1**). The European Association of Urology, representing 15,000 members from over 130 countries, amended their guidance on MRI to match the NICE recommendations almost word for word and said in a statement: "As a result of the PRECISION trial and a number of other high-profile studies, the 2019 European Association of Urology and 2019 UK National Institute for Health and Care Excellence Guidelines in Prostate Cancer now recommend performing an MRI before prostate biopsy in biopsy-naive men" (**S2**). A panel from the American Urological Association and Society of Abdominal Radiology states: "Data support its use in men with a previous negative biopsy and ongoing concerns about increased risk of prostate cancer. Sufficient data now exist to support the recommendation of magnetic resonance imaging before prostate biopsy in all men who have no history of biopsy." (**S3**).

Benefits to patients and healthcare services

All men at risk of prostate cancer living in UK, Europe and the US are benefiting from this innovation. The PROMIS study (**R4**) demonstrated that a quarter of men could avoid an unnecessary biopsy. This translates to 1-2 million men globally year-on-year avoiding the unnecessary puncture of their prostate. This represents a significant reduction in the costs and harms associated with the procedure.

Reducing unnecessary pathology tests: Each of the 12-24 million biopsy needle deployments that are no longer necessary would generate tissue that requires processing, reporting on, and storage. Where biopsy is necessary, MRI allows targeted sampling, which means 4 needles suffice rather than the standard 12 (**R4**), reducing needle deployments by a further 24-32 million. This is a huge reduction in unnecessary tissue retrieval and processing, equating worldwide to approximately 35-50 million biopsy cores each year. Savings to the NHS are approximately GBP10,000,000-15,000,000 year on year, based on 200,000 MRI exposures per year conferring a 25% reduction in biopsy rates and a reduced needle deployment rate in those biopsied (assuming cost of biopsy GBP10 per core). In the USA, with predicted MRI exposures of 1 million, the cost savings are approximately USD600,000,000 year on year based on the same assumptions and a cost of USD100 per core. This reduction in pathology tests also represents a significant reduction in waste (these are unnecessary biopsies) in a specialty that is already under strain due to staff shortages.

Reducing harm for the patients: The MRI diagnostic approach provides a better patient experience and reduces side-effects associated with biopsy, reducing the need for further engagement with the healthcare system and associated potential loss in earnings. The results from the PRECISION study (**R5**) give a comparison of the harm profile for MRI-based diagnosis versus systematic TRUS biopsy. Side-effects were reduced significantly: blood in urine (63% reduced to 30%); blood in semen (60% reduced to 32%); blood in faeces (22% reduced to 14%); sexual problems (16% reduced to 11%) and pain (23% reduced to 13%) (**R5**). Given that approximately 5 million men are assessed each year, these data translate to millions of men avoiding a biopsy-related harm.

Reducing risk of under-diagnosis: Because MRI detection is positively associated with tumour grade, tumour stage and tumour volume it detects all truly important cancers. In the PROMIS study all Gleason dominant pattern 4 tumours or worse were identified. These are the very tumours that have been shown to be associated with premature death in the recent 29-year update of the Swedish SPCG-4 study (**S4**) which shows that prior to MRI, about half the men being assessed were given the 'all clear' incorrectly. The results of the PROMIS (**R4**) study demonstrate that such mis-diagnoses are now a thing of the past.
Surgery tailored to the individual: MRI scanning of the prostate means prostate surgery is now tailored to the individual rather than inevitably resulting in total removal of the prostate. Surgical MRI pre-planning alerts the surgeon to the exact location of the tumour. Surgery is targeted to the tumour itself and a wide margin around it (**S5**), reducing the need for further treatments in many cases, whilst at the same time preserving more of the prostate, thereby reducing the chance of side-effects (**S6**). Radiotherapists have also been able to exploit the information from MRI to better control the dose of radiotherapy to the tumour and decrease the dose to the normal tissue, thereby reducing toxicity (**S7**). Regular MRI scanning has also replaced the need for follow up biopsies in men identified at low risk. Moreover, the UCL team has recently shown that the grading and stratification data the MRI scan provides can help predict the likelihood of disease progression, providing a novel and powerful prognostic biomarker (**S8**).
Tissue preservation therapies: By exploiting the information provided by MRI, the UCL team has taken tissue preserving therapies with a number of energy sources, including Padeliporfin vascular-targeted photodynamic therapy, from Phase I through to Phase III studies (**S9, S10**). Many are now in widespread use as a safer and better-tolerated alternative to standard whole gland treatments. The benefits to patients of tissue-preserving therapy include less urinary incontinence and sexual dysfunction, reduced from 3 in 5 men to 1 in 20 men (**S5**).

MP-MRI for prostate cancer underpins new era for treatment and therapeutic platforms
The MRI diagnostic technology developed at UCL underpins an ecosystem of new technology and pharma companies that have been set up to exploit the new phenotypic information arising from the images. These new companies cover several domains and include many new SMEs (university spin out companies as well as some of the largest commercial entities in healthcare, such as Watson Elementary Ltd; Philips Dynacad; Siemens Healthineers [FDA approved Aug 2020]); over 10 image-registration companies (MIMM-Soft; Koelis; Philips Uronav); therapy companies (Sonacare Medical; Angiodynamics; artificial intelligence companies (Enlitic Inc.); biotech (Nanospectra); and pharma (STEBA Bio).

The Chief Commercialization Officer at Sonacare Medical said: "The work Professor Mark Emberton, of University College Hospital, has spearheaded and championed throughout the years incorporating mpMRI into the diagnostic pathway and its continued reported clinical outcomes (through the PROMIS and PRECISION trials) has resulted in an entire new eco-system of companies seeking to fully explore the new information on tumor location, disease progression focalized precision-based treatment and post-operative monitoring. ... PROMIS and PRECISION have supported, with strong clinical data and advocacy of proper technique, the birth and steady growth of companies like Sonacare Medical and have brought to urology a whole new class of diagnosis and precision guided treatment of prostate cancer." (**S11**).

5. Sources to corroborate the impact

S1 NICE Guidelines NG131 (2019)
https://www.nice.org.uk/guidance/ng131/chapter/Recommendations#assessment-and-diagnosis

S2 European Association of Urology guidelines
https://uroweb.org/guideline/prostate-cancer/?type=summary-of-changes. EAU press statement 10 October 2019 Results of EAU RF PRECISION study lead to changes in international prostate cancer diagnosis guidelines https://uroweb.org/results-of-eau-rf-precision-study-lead-to-changes-in-international-prostate-cancer-diagnosis-guidelines/.

S3 Bjurlin MA, Carroll PR, Eggener S, Fulgham PF, Margolis DJ, Pinto PA, Rosenkrantz AB, Rubenstein JN, Rukstalis DB, Taneja SS, Turkbey B (2020) Update of the Standard Operating Procedure on the Use of Multiparametric Magnetic Resonance Imaging for the Diagnosis, Staging and Management of Prostate Cancer. *J Urol.* Apr;203(4):706-712. doi: 10.1097/JU.0000000000000617.

S4 Bill-Axelson A, Holmberg L, Garmo H, Taari K, Busch C, Nordling S, Häggman M, Andersson SO, Andrén O, Steineck G, Adami HO, Johansson JE (2018) Radical Prostatectomy or Watchful Waiting in Prostate Cancer — 29-Year Follow-up *N Engl J Med* 379:2319- 2329.

S5 Jäderling F,Akre O, Aly M, Björklund J, Olsson M, Adding C, Öberg M, Blomqvist L, Nyberg T, Wiklund P, Carlsson S. (2018) Preoperative staging using magnetic resonance imaging and risk of positive surgical margins after prostate-cancer surgery. *Prostate Cancer Prostatic Dis*. Nov 30. doi: 10.1038/s41391-018-0116-z.

S6 Yap T, Ahmed HU, Hindley RG, Guillaumier S, McCartan N, Dickinson L, Emberton M, Minhas S. (2016). The Effects of Focal Therapy for Prostate Cancer on Sexual Function: A Combined Analysis of Three Prospective Trials. *Eur Urol*. May;69(5):844-51. doi: 10.1016/j.eururo.2015.10.030.

S7 J Uzan, A E Nahum , I Syndikus (2016). Prostate Dose-painting Radiotherapy and Radiobiological Guided Optimisation Enhances the Therapeutic Ratio. *Clin Oncol (R Coll Radiol)* Mar;28(3):165-70. DOI: 10.1016/j.clon.2015.09.006

S8 Stavrinides V, Giganti F, Trock B, Punwani S, Allen C, Kirkham A, Freeman A, Haider A, Ball R, McCartan N, Whitaker H, Orczyk C, Emberton M, Moore CM. (2020). Five-year Outcomes of Magnetic Resonance Imaging-based Active Surveillance for Prostate Cancer: A Large Cohort Study. *Eur Urol*. Sep;78(3):443-451. doi: 10.1016/j.eururo.2020.03.035.

S9 Giganti F, Moore CM, Robertson NL, McCartan N, Jameson C, Bott SRJ, Winkler M, Gambarota G, Whitcher B, Castro R, Emberton M, Allen C, Kirkham A. (2017). MRI findings in men on active surveillance for prostate cancer: does dutasteride make MRI visible lesions less conspicuous? Results from a placebo-controlled, randomised clinical trial. *Eur Radiol*. Nov;27(11):4767-4774. doi: 10.1007/s00330-017-4858-0.

S10 Azzouzi AR, Vincendeau S, Barret E, Cicco A, Kleinclauss F, van der Poel HG, Stief CG, Rassweiler J, Salomon G, Solsona E, Alcaraz A, Tammela TT, Rosario DJ, Gomez-Veiga F, Ahlgren G, Benzaghou F, Gaillac B, Amzal B, Debruyne FMJ, Fromont G, Gratzke C, Emberton M, on behalf of the PCM301 Study Group (2017) Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial. *Lancet Oncol.* Feb;18(2):181-191. doi: 10.1016/S1470-2045(16)30661-1.

S11 Testimonial letter from Chief Commercialization Officer, Sonacare Medical, Charlotte, NC 28216, USA