Institution: King's College London

Unit of Assessment: 12 Engineering

Title of case study: Cydar, an AI driven image guidance system for minimally invasive endovascular aortic surgery that reduces radiation exposure

Period when the underpinning research was undertaken: January 2000 – December 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:
Rachel Clough	Clinical Senior Lecturer, Biomedical Engineering	From 01/08/2010
Graeme Penney	Senior Lecturer, Biomedical Engineering	01/04/2007 - 30/04/2019
Thomas Carrell	Honorary Lecturer, Endovascular Surgery	1/04/2004 - 6/12/2004
Derek Hill	Professor of Medical Imaging Sciences	01/10/1989 - 31/12/2004 and 04/07/2005 - 31/03/2007
David Hawkes	Professor of Computational Imaging	01/02/1988 - 31/12/2004
Andreas Varnavas	Research Fellow, Imaging and Biomedical Engineering	01/09/2010 - 31/12/2018
Bijan Modarai	Professor of Vascular Surgery	From 02/01/2008

Period when the claimed impact occurred: August 2013 – July 2020

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

1. Summary of the impact (indicative maximum 100 words)

Minimally invasive endovascular surgery is quicker and safer for patients; however, it comes at the cost of exposing the patient to high doses of harmful ionising radiation and kidney-toxic contrast agents. Researchers at King's College London (King's) have developed a cloud-based, artificial intelligence-driven image guidance system (Cydar-EV) for endovascular surgery, which minimises exposure to radiation and kidney-toxic contrast by shortening the duration of surgery.

Cydar-EV has the European Union (EU) certification mark for health and safety standards, is Food and Drug Association (FDA) cleared, and has been commercialised in the UK, Europe, and the USA by Cydar Medical, a spin-out company of King's College London. Cydar Medical has benefitted approximately 2,000 patients [Text removed for publication] by December 2020. Since 2014, the company has raised approximately [Text removed for publication] and in July 2020 it had 39 employees across the UK, Europe, and the USA.

2. Underpinning research (indicative maximum 500 words)

Minimally invasive procedures are revolutionising the management of cardiovascular diseases, which has previously been dominated by open surgery. Endovascular aortic repair (EVAR) is a successful example of this, and it has replaced open aortic surgery owing to advantages in patient survival, reduced postoperative complications, and shorter length of hospital stay.

EVAR planning is done using high-resolution 3D images from pre-operative CT scans; however, the surgery itself is performed under image-guidance using 2D X-ray fluoroscopy. This loss of dimensional spatial information between 3D pre-operative images and a 2D operating field makes

the operation more complex to perform as the surgeon must try to visualise the 3D anatomy to accurately position the device. This slows down the procedure and leads to three challenges:

(a) Concern regarding the amount of ionising radiation, which is associated with the duration of the procedure
(b) Concern regarding the amount of kidney-toxic contrast used during the procedure to delineate the blood vessels
(c) Imprecise visualisation of the anatomy and positioning of the device leading to high rates of re-intervention (≥20%), requiring further patient hospital admissions and cost to the health service

The School of Biomedical Engineering and Imaging Science at King's has devised methods to align 3D computed tomography (CT) images and 2D X-ray images. Previous solutions to improve visualisation during EVAR include manually aligned, operating table-tracked 3D-2D image overlay; however, this is costly, disrupts the clinical workflow, and has clinically significant image positioning errors.

The King's-developed image guided surgery system matches CT and X-ray images based on their similarity and automatically links the images using a process called image registration. The technology has been proven to be fast, accurate, and robust. The technology has been developed in a step-wise fashion based on advancement in image processing and matching (R1) to automation in the endovascular clinical environment (R2), thereby increasing the speed of registration (R3) and improving the accuracy of the matching algorithm (R4), with full automation and verification of accuracy in the specific use case (R5).The system is now cloud based to take advantage of the high compute power infrastructure available, allowing the technology to run quickly and smoothly at multiple hospital sites simultaneously, with 2,000 patients treated to date. Machine learning algorithms have been developed in-house and are used for increasing the speed of 3D image segmentation, contour generation for intra-operative guidance, and image matching.

The system has been tested in interdisciplinary clinical studies involving engineers, mathematicians, and clinicians. This work has shown patient benefit by a significant reduction in the amount of X-rays used, with a mean reduction in X-ray fluoroscopy screening time of 35% ($p = 0.013$), a 41% reduction in the amount of iodinated contrast used ($p = 0.008$), and a nearly one-hour reduction in mean operating time (17%, $p = 0.06$) (data submitted for EU certification mark (MHRA ref: 5334)[S7]). Superiority to commercial competitors (Siemens Artis Zeego) was demonstrated, with a significant reduction in radiation exposure [S1a], with significant clinical and technical improvements shown compared to standard practice in studies in both the UK and US [S1b, S1c, S1d].

The development and automation of the image registration technology was funded by Guy's and St Thomas' Charity (GBP183,500, 2010–2013), with subsequent funding from Innovate UK (GBP250,000, 2014, 2018) and approximately GBP18,000,000 in equity funding tranches (2014–2020) to develop the product, collect clinical data in a pivotal trial, gain regulatory clearances (CE, FDA, TGA), and build the platform, along with operational and support capabilities.

The National Institute for Health Research have awarded GBP1,740,000 (NIHR201004) this year to fund a trial to investigate the clinical and cost effectiveness of **Cydar-EV** (the name of the product from Cydar Medical) compared to the current reference standard: 2D X-ray fluoroscopy. The trial will run for 3 years and the data will be used for an application to The National Institute for Health and Care Excellence (NICE) for appraisal. A positive report from NICE would support national adoption of the technology.

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

R1. Penney GP, Batchelor PG, Hill DL, Hawkes DJ, Weese J (2001). Validation of a two- to three-dimensional registration algorithm for aligning preoperative CT images and intraoperative fluoroscopy images. Med Phys, 28(6):1024–32. DOI: 10.1118/1.1373400

R2. Carrell TW, Modarai B, Brown JR, Penney GP (2010). Feasibility and limitations of an automated 2D-3D rigid image registration system for complex endovascular aortic procedures. J Endovasc Ther, 17:527–33. DOI: 10.1583/09-2987MR.1

R3. Varnavas A, Carrell T, Penney G (2013). Increasing the automation of a 2D-3D registration system. IEEE Trans Med Imaging, 32:387–99. DOI: 10.1109/TMI.2012.2227337.

R4. Guyot A, Varnavas A, Carrell T, Penney G (2013). Non-rigid 2D-3D registration using anisotropic error ellipsoids to account for projection uncertainties during aortic surgery. Med Image Comput Comput Assist Interv, 16(Pt 3):179–86. DOI: 10.1007/978-3-642-40760-4_23

R5. Varnavas A, Carrell T, Penney G (2015). Fully automated 2D-3D registration and verification. Med Image Anal, 26:108–19. DOI: https://doi.org/10.1016/j.media.2015.08.005

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

Image-guided, minimally invasive surgery is growing rapidly. The global market for EVAR is approximately GBP2,000,000,000 [S10], with a compound annual growth rate of 6.2% and is an increasing burden on health spending. 4,396 EVAR procedures were performed in UK alone between 2017-2019 [S11a, S11b], with an average cost of approximately GBP19,000. EVAR is under an existing NHS care pathway and reduces mortality from 4.7% to 1.7% compared to open surgery [S13], with faster return to normal activities on discharge.

Enterprise: The demonstrated success of the technology led to the development of the King's spin-out company Cydar Medical in 2012. Since 2014, Cydar Medical has raised [Text removed for publication] and by July 2020 had 39 employees across the UK, Europe and the US, in science, development, sales & implementation and central, with approximately 2,000 patients having benefitted in the current REF period [S5]. The system has been installed and is in regular clinical use [Text removed for publication] across the UK (8), France (5), US (5), Germany (2), Netherlands (1) and Spain (1). The product has undergone safety and performance testing under an ISO13485 certified Quality Management System and is CE marked (MHRA ref: 5334, CE conformity application dated November 20, 2015) and FDA 510(k) cleared (dated: July 7, 2016).

Cost and efficiency improvement for NHS: Cydar-EV can be easily implemented without the need for linked capital expenditure on a new fixed imaging or hybrid operating room, which is associated with cost-saving across 6 NHS centres of approximately GBP21,000,000 (GBP2,000,000–GBP5,000,000 per centre [S12]) and in the 12 centres worldwide, approximately GBP42,000,000. Use of Cydar-EV is associated with a reduction in procedure time that has health economic benefit by improving productivity, allowing one additional aneurysm repair per day, valued at GBP8,157 per procedure [S4].

Benefit to patients: Over 2,000 patients have been treated by 2020 using Cydar-EV. In sites where Cydar-EV is installed, the surgeons have real-time, fully integrated 3D visualisation throughout the EVAR procedure, with much greater spatial accuracy than was achieved by previous technology (median error 3.9 mm versus 8.64 mm [p = .001]). This means less kidney-toxic contrast is used during the procedure (41% reduction with Cydar-EV [p = 0.008]) to position the device accurately (data submitted for EU certification mark (MHRA ref: 5334) [S7b]).

Benefit to medical staff: Many of the early pioneers of X-ray guided endovascular surgery died due to cancer-related causes. Operators today may perform thousands of these procedures during the course of their career. In our installations there has been a reduction of 31% in the number of X-rays used, hence reducing the chance of radiation-induced disease [S1]. In words of some users: Cynthia K. Shortell of Duke University Medical Center in the US said: *"It has been an instant, blockbuster hit with everyone involved in these procedures. Every operating room participant has a story about the way Cydar technology benefits our team-shorter procedures, lower radiation, less contrast agent, and much greater accuracy."* Dr Peter Goverde, ZNA Stuivenberg Hospital, Belgium said: *"This will expand extensively the possibilities of our mobile C-arms and reduce contrast and radiation exposure!"* [S9].

Intellectual property: The computer vision is a form of artificial intelligence, which uses NHS Digital-approved, GDPR compliant, high-performance cloud computing. Patents have been granted protecting the 2D-3D image registration (China, EPO, Japan, the USA) and tomosynthesis imaging (the UK, France, Germany, Netherlands, the USA) [S2]. In the period between August 2013 to December 2020, King's has received reimbursement of patenting expenses incurred, amounting to GBP14,548.67 [S6]

In summary, Cydar is the first company in the world with a CE marked, FDA-cleared product using cloud and AI technology to inform and influence surgery in real-time [S8][S7a,S7b,S7c]. There are traditional imaging companies that use hardware to achieve less accurate and reliable image fusion, but these are not considered competitors as they do not aggregate data, and therefore, cannot develop the same intelligent insights and channel for new products. In recognition of its pioneering work, Cydar was the winner of the Cambridge Business Innovation Award and runner-up for Cambridge AI Company of the Year in 2018 [S3].

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

S1. Peer-reviewed, published evidence demonstrating superiority over existing (hardware) systems and user acceptance:

a. Rolls AE, Maurel B, David M, Constantinou J, Hamilton G, Mastracci TM (2016). A Comparison of Accuracy of Image- versus Hardware-based Tracking Technologies in 3D Fusion in Aortic Endografting. Eur J Vasc Endovasc Surg, 52(3):323–31. DOI: 10.1016/j.ejvs.2016.05.001

b. Maurel B, Martin-Gonzalez T, Chong D, Irwin A, Guimbretiere G, Davis M, Mastracci TM (2018). A prospective observational trial of fusion imaging in infrarenal aneurysms. J Vasc Surg, 68(6):1706-13.e1. DOI: 10.1016/j.jvs.2018.04.015

c. Southerland KW, Nag U, Turner M, Gilmore B, McCann R, Long C, Cox M, Shortell C (2018). IF09. Image-Based Three-Dimensional Fusion Computed Tomography Decreases Radiation Exposure, Fluoroscopy Time, and Procedure Time During Endovascular Aortic Aneurysm Repair. J Vasc Surg, 67(6):e61. DOI: 10.1016/j.jvs.2018.03.037

d. Martin-Gonzalez T, Penney G, Chong D, Davis M, Mastracci TM (2018). Accuracy of implementing principles of fusion imaging in the follow up and surveillance of complex aneurysm repair. Vasc Med,18;23:461-466. DOI: 10.1177/1358863X18768885

S2. Patent details: Cydar IP portfolio status summary

S3. Awards:

a. Cydar recognised at 2018 Cambridge AI company awards

b. Cydar medical winners of the business innovation award 2018

S4. NHS National Tariff Workbook: procedure reference YR04Z – Tab APC & OPROC

S5. Testimonial from Paul Mussenden, CEO of Cydar, 24th February 2021

S6. Letter from Kings IP and Licencing,

S7. Regulatory documentation for Cydar

a. US FDA 510(k) cleared letter

b. MHRA notification

c. Cydar's declaration of conformity

S8. Press release, CISION PR Newswire with news of being the first company to have a CE marked, FDA-cleared product using cloud and AI technology to inform and influence surgery in real-time.

S9. Praise from users of Cydar.- Business Weekly 13 February, 2018.

S10. Market research report on endovascular aneurysm repair market

S11. Illustrations from Vascular Services Improvement Program (VSQUIP) for 2017-19 (Total 4396 procedures)

a. Repair of elective complex aortic aneurysms to prevent rupture 2306 procedures

b. Repair of abdominal aortic aneurysm (AAA) to prevent rupture 2090 procedures

S12. News Article reporting costs

S13. Greenhalgh R M, Brown L C, Kwong G P S, Powell J T, Thompson S G, EVAR trial participants, (2004), Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial Lancet, 364(9437):843-8 DOI: 10.1016/S0140-6736(04)16979-1