Impact case study (REF3)

REF2021

Institution: King's College London

Unit of Assessment: 12 Engineering

Title of case study: IXICO, a King's spin out leveraging medical image data curation and analysis for improving clinical trials in neurology

Period when the underpinning research was undertaken: 2000 – 2004; 2012 – 2013

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:
David Hawkes	Professor of Computational Imaging	01/02/1988 – 31/12/2004
Derek Hill	Professor of Medical Imaging Sciences	01/10/1989 – 31/12/2004; 04/07/2005 – 31/03/2007
Thomas Hartkens	Postdoctoral researcher	02/08/1999 – 31/10/2003
Jo Hajnal	Chair in Imaging Science	From 01/04/2012
Julia Schnabel	Chair in Computational Imaging	01/09/1999 – 31/12/2004; from 01/07/2015

Period when the claimed impact occurred: October 2013 – December 2020

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

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

Research into medical imaging at the School of Biomedical Engineering and Imaging Sciences of King's College London (King's) led to the formation of a spinout company, IXICO, which was listed on the Alternative Investment Market (AIM) of the London Stock Exchange in October 2013. In 2020, the company which employed 78 full time staff members, reported a full year revenue of GBP9,500,000, an order book of GBP21,700,000, and a four-year compound annual growth rate of 33%.

IXICO provides medical imaging solutions for clinical trials and healthcare products that support diagnosis of dementia. Since 2013, IXICO has commercial partnerships with 9 of the top 15 pharmaceutical companies, including Pfizer, Bristol-Myers Squibb, Biogen and Eli Lilly. The company has qualified sites in over 50 countries across the Americas, Europe, and Asia-Pacific, and has analysed over 100,000 brain scans from more than 27,000 patients, by the end of 2020. IXICO's work has provided pivotal imaging results that have impacted trial outcomes, providing more definitive results requiring smaller patient cohorts than other outcome measures.

2. Underpinning research (indicative maximum 500 words)

In 2002 a team led by Derek Hill from the School of Biomedical Engineering and Imaging Sciences at King's, together with collaborators at Imperial College London, designed and engineered a technology demonstrator that explored how to deploy image registration algorithms securely and at scale using an emerging distributed computing infrastructure known as a computational grid [R1], a forerunner for cloud-based computing and secure web services. The demonstrator allowed a user to securely upload a 3D magnetic resonance image (MRI) of a human head to a remote computer server, where the brain was automatically labelled by tissue type (grey matter, white matter and cerebrospinal fluid) and the result returned to the user. This anticipated the distributed computing methods that are commonplace today for analysis of medical images at scale using secure cloud-based services. The modern equivalent can deliver high performance using computationally intensive algorithms yet remain compliant with data protection requirements such as the General Data Protection Regulations (GDPR). In 2002 such a capability did not exist, and this was recognised as a limiting factor for deployment of advanced image analysis algorithms, stopping them from effective deployment at scale for both Neuroscience and medical purposes. On the strength of this novel engineering, the team won funding from the UK e-Science

initiative to explore the potential of grid computing in medical imaging applications (GR/S21533/02). The aim of the project, which was called 'Information extraction from Images (IXI)', was to work out how to use the then emerging grid technology, with its secure protocols, for medical imaging applications with particular emphasis on ensuring full clinical governance standards were maintained at all times. An integrated team working across institutional boundaries, but led by Derek Hill from King's, set about systematically developing the processes and infrastructure needed, first building an image database designed specifically to interface with grid services [R2] and then developing the workflow protocols needed to flexibly perform advanced image analysis using distributed but secure grid services [R3]. The project delivered on all these component parts, achieving a full system capable of protecting personal data while allowing flexible deployment of powerful computer resources in a scalable way. The framework also provided complete provenance information for all outputs, such that any image resulting from IXI grid system processes would be accompanied by a digitally signed record specifying all its antecedent input images, all processes performed including all parameter values used and the software versions of all algorithms deployed. Thus, the system was designed to provide a secure and verifiable data framework for processing of sensitive medical data at scale.

The core technology that has powered the company's business is medical image registration, the spatial alignment of images with one another, to compare images from the same subject or to place information from one subject in the context of others. The team at King's led by Hawkes and Hill pioneered this technology. A particularly challenging problem is aligning images when non-rigid transformations are required, such as when there has been tissue deformation or to align one subject with another. In 2001 they engineered a solution to the problem of non-rigid alignment using a flexible and versatile deformation model built on B-splines [R4]. Achieving accurate results is particularly challenging when corresponding tissues have very different signal properties in the images to be matched. Calculating the change in mutual information between images as one is warped to match the other is a powerful approach but is technically challenging because it relies on analysis of histograms of image intensities that themselves change as the applied deformations change. In 2003 the team presented an elegant means to address this problem [R5]. Jo Hajnal, during his period of engagement with IXICO while at King's (2012-13), continued to work in the area of hippocampal labelling in MRI of the brain for subjects with Alzheimer's Disease, addressing a pivotal need for methods that can form sensitive markers of disease progression [R6].

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

R1. Hill DLG, Hajnal, JV, Rueckert D, Smith, SM, Hartkens T & McLeish K (2002), A Dynamic Brain Atlas. Lecture Notes in Computer Science, vol. 2488, pp. 532–539, Springer-Verlag, Berlin. DOI: 10.1007/3-540-45786-0_66

R2. Rowland A, Hartkens T, Burns M, Hajnal J, Rueckert D & Hill D (2004), A grid enabled medical image database. Proceedings of the UK E-Science All Hands Conference, 1051–1054.

R3. Rowland A, Burns M, Hartkens T, Hajnal JV, Rueckert D & Hill DLG (2004), Information extraction from images (IXI): Image processing workflows using a grid enabled image database. Distributed Databases in Medical Image Computing - MICCAI, (IXI).

R4. Schnabel JA, Rueckert D, Quist M, Blackall JA, Castellano-Smith AD, Hartkens T, Penney GP, Hall WA, Liu H, Truwit CL, Gerritsen FA, Hill DLG, Hawkes DJ (2001), A Generic Framework for Non-rigid Registration Based on Non-uniform Multi-level Free-Form Deformations. MICCAI conference. 573-581. DOI: 10.1007/3-540-45468-3_69

R5. Crum WR, Hill DLG, Hawkes DJ (2003). Information Theoretic Similarity Measures in Non-rigid Registration, IPMI conference 378-387, DOI: 10.1007/978-3-540-45087-0_32

R6. Tong T, Wolz R, Coupe P, Hajnal JV, Rueckert D (2013). Segmentation of MR images via discriminative dictionary learning and sparse coding: Application to hippocampus labelling, 76 (1) DOI: 10.1016/j.neuroimage.2013.02.069

4. Details of the impact

Directly following the successful completion of the IXI project, a university spinout called IXICO Ltd. (literally the Company that came from IXI) was formed in 2004 by Derek Hill and David Hawkes from the School of Biomedical Engineering and Imaging Sciences at King's together with partners at Imperial College [S1]. IXICO's first employee, Thomas Hartkens, transitioned from being a postdoctoral researcher on the IXI project at King's, bringing expertise and software know-how. He was instrumental in importing key elements of the project software, which were rapidly implemented within a bespoke ISO certified quality management system. A critical feature was companywide compliance by construction (i.e. from the ground upwards), with the relevant regulations in place for electronic record-keeping in clinical trials, most notably the USA Food and Drug Administration (FDA) title 21 of the Code of Federal Regulations; Electronic Records (21 CFR, Part 11) [S11]. This technological edge helped launch the company on its path to developing a thriving business offering medical image analysis for clinical trials and healthcare products for diagnosis of dementia. Jo Hajnal, who has been at King's since April 2012, was on IXICO's board, acting as a scientific advisor working with the company 1 day/week until October 2013. He provided expertise on medical image protocol design, data acquisition and image analysis, sustained by his ongoing research activities [R6, S1, S2 p.38].

The table below summarises the key impact metrics for the REF2021 reporting period [S1, S3, S8, S10].

Key impact metrics	2012/13	2020
Turnover	GBP2,500,000	GBP9,500,000
Employees	36	78
Imaging centres	400	2,000+
Brain scans analysed	10,000	100,000+
Safety and eligibility reports	n/a	20,000+

Economic impact

In October 2013, IXICO was listed on AIM, London Stock Exchange's market for small and medium size growth companies, becoming IXICO Plc [S2]. In 2020, the company which employed 78 FTE staff members reported a full year revenue of GBP9,500,000, an order book of GBP21,700,000, and a four-year compound annual growth rate of 33% [S1].

"IXICO Technologies Limited was incorporated in 2004 and spun out of King's (which remains a shareholder), building on the 'IXI' project. … We are very pleased to have achieved [in 2020] GBP1,300,000 [earnings before interest, tax, depreciation, and amortisation] EBITDA profitability, more than doubling our profitability in 2019 (which was GBP500,000) and outperforming the market expectations. GBP1,300,000 EBITDA represents 14% EBITDA margin and further reflects the strengthening of IXICO as a growth medical imaging technology company." – CEO of IXICO [S1]

Impact on the neurological drug development industry and healthcare

A key benefit of IXICO's medical image analysis products is that they provide more definitive results requiring smaller patient cohorts than other outcome measures [S1]. IXICO has worked with 9 of the top 15 pharmaceutical companies (including Pfizer, Bristol-Myers Squibb, Biogen and Eli Lilly) as well as with many speciality biotechnology companies [S1, S7b]. It has completed multiple clinical trials (phases 1–4) and is currently responsible for data acquisition and analysis of primary endpoints on 4 late-phase pivotal clinical trials [S1, *see also patient numbers quoted above*]. During the reporting period, the company has expanded both the neurological conditions that its technology can be applied to and has moved into healthcare, supporting both early diagnosis and disease monitoring.

The company now has active contracts focusing on Huntington's Disease (HD) [S6c, S7a], Parkinson's Disease (PD), Multiple Sclerosis and rare neurological disorders, as well as its historic

strength in Alzheimer's Disease (AD) [S6a, S6b]. For example, IXICO has won 11 clinical trial contracts in HD, including a GBP10,500,000 contract for a late-phase open label study in Huntington's disease with an estimated 1000 subjects in Europe, North America and Asia enrolled during the summer of 2020 [S6d]. An important function that IXICO has provided focuses on the need to enrich clinical trials with carefully profiled subjects. Since 2013, IXICO has provided safety and eligibility reports on over 20,000 subjects [S10].

Impact on health regulatory policy

IXICO's image analysis and data management/curation technologies are playing a key role in a number of public-private consortia, that are gathering the evidence base needed for policy changes in relation to the assessment of key neurological diseases and development of new treatments for them [S9]. For example, IXICO played a leading role in the submission to European regulators to qualify low hippocampal volume as a biomarker that can provide more precise and effective assessment of patients to enrich trials of treatments for AD [S4]. This submission, which was supported by the US Food and Drug Administration (US FDA) [S5], incorporates key data obtained using a core IXICO image analysis technology.

IXICO's role in some of the key consortia is as follows:

- The European Prevention of Alzheimer's Dementia (EPAD) – *"the largest ever public-private partnership in Alzheimer's Disease research"*, which has built an adaptive clinical trials platform to enable pharma companies to efficiently evaluate the safety and effectiveness of their medicines in patients prior to onset of symptoms by utilising adaptive clinical trial approaches. IXICO provided the technology to collect, manage, and analyse magnetic resonance imaging (MRI) scans (pan European register of 0.5m subjects, >1,500 subjects in database in 2020) [S7c].

"IXICO were a pivotal partner in the EPAD programme providing excellent service throughout the 6 years to our sites and central team. Not only did they provide valued operational support they also contributed in a crucial way to design aspects of EPAD in terms of data flows and imaging science. The data from EPAD will make a huge difference to our understanding of Alzheimer's Disease in its early stages and IXICO has been pivotal in providing the best quality and relevant imaging data to that effort." – Professor Craig Ritchie, EPAD Principal Investigator, Chair of the Psychiatry of Ageing and Director of the Centre for Dementia Prevention at the University of Edinburgh [S8 p. 16]

- Critical Path Institute initiatives: Huntington's Disease Regulatory Science Consortium (HD-RSC), a global initiative aiming to improve the regulatory path for new HD therapies, and Critical Path for Parkinson's (CPP) Disease, which brings together the world's largest pharmaceutical companies advancing novel promising treatments for people living with Parkinson's. IXICO is contributing towards FDA clearance of imaging biomarkers to support the development and approval of new medicines to treat HD and PD. Achieving regulatory approval for imaging biomarkers for these diseases is a critical step for conducting more efficient clinical trials using smaller cohorts and is therefore a gatekeeper for maximising societal impact.

In words of Diane Stephenson, Executive Director, Critical Path for Parkinson's Consortium ('CPP'), Critical Path Institute: *"We are delighted to continue our collaboration with the IXICO team in two further Critical Path consortia, the Critical Path for Parkinson's ('CPP') consortium and the HD Regulatory Science Consortium ('HD-RSC'). In these consortia, our aims are to develop new, regulatory-endorsed drug development tools that will improve the clinical trial process and regulatory path for emerging therapies for HD and PD and ultimately de-risk the development of new treatments that are urgently needed. IXICO's expertise in data analysis and regulatory qualification is supporting our efforts to develop the regulatory path to qualify new imaging and digital biomarkers for use in clinical trials."* [S10]

- Amyloid Imaging for Prevention of Alzheimer's Dementia (AMYPAD) – IXICO provided the technology to collect, manage, and analyse MRI and positron emission tomography (PET) scans for evaluating the diagnostic value of amyloid imaging in Alzheimer's Disease [S6e]. The project succeeded in recruiting 844 out of the planned 900 participants

despite the negative impact of COVID-19. These studies are ongoing, but large cohort data is already available, providing a massive community resource [S7d].

The societal impact of IXICO's work is significant. Its technology has been, and continues to be, helping large pharmaceutical companies develop treatments for neurological diseases with major unmet medical needs. IXICO has provided automated analysis of over 100,000 images as part of clinical trials, its technology is now enabling a new generation of clinical trials for neurodegenerative diseases such as Alzheimer's Disease where patients early in their disease pathway can be identified and recruited for better understanding of pharmacological interventions and this has contributed to health policy and regulation.

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

S1. Testimonial from: Giulio Cerroni, the CEO of IXICO, 3rd February 2021

S2. [IXICO AIM Admission Document re: listing on the alternative investment market (AIM)](#)

S3. Testimonial from: Robin Wolz, Senior Vice President, Science and Innovation, IXICO, 4th December 2020.

S4. Hill DLG. et al. (2014), Coalition Against Major Diseases/European Medicines Agency biomarker qualification of hippocampal volume for enrichment of clinical trials in predementia stages of Alzheimer's Disease, Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 10(4):421-429.e3, DOI: [10.1016/j.jalz.2013.07.003](#)

S5. [Letter of support from the FDA to the Critical Paths Institute](#), 10th March 2015

S6. IXICO website references:

    a. [Company information about its technology deployed for commercial contracts](#)

    b. [IXICO's list of active therapeutic areas where it is winning contracts for drug trials](#)

    c. [IXICO is the leading company for Huntington's disease (HD) specialist imaging](#)

    d. [IXICO Press Release: £10.5m contract win and the potential impact of COVID-19](#)

    e. [The AMYPAD prognostic and natural history study](#)

S7. News about IXICO:

    a. [Contract to provide services for a phase III Huntington's disease clinical trial](#)

    b. [Fierce Biotech news: IXICO winning a contract for Imaging clinical trial services](#)

    c. [IXICO selected as imaging analysis partner within EPAD](#)

    d. [AMYPAD announces end of recruitment in its study](#)

S8. [IXICO annual report 2020](#)

S9. [Company information about the national and international collaborations](#)

S10. [IXICO Annual report 2019](#)

S11. [FDA guidance Part 11, Electronic Records; Electronic Signatures - Scope and Application](#)