

Impact case study (REF3)

Institution: Imperial College London		
Unit of Assessment: 11 Computer Science and Informatics		
Title of case study: IXICO: Automated Biomedical Image Analysis for Clinical Trials (pharma) and Healthcare		
Period when the underpinning research was undertaken: 1 Jan 2000 – 1 Dec 2012		
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:
Daniel Rueckert	Professor	Since 1999
Jo Hajnal	Professor	1997 – 2012
Paul Aljabar	PhD student, Post-doc	2003 – 2012
Robin Wolz	PhD student, Post-doc	2008 – 2012
Rolf Heckemann	PhD student, Post-doc	2002 – 2009
Alexander Hammers	Reader	2004 – 2009
Period when the claimed impact occurred: 1 Aug 2013 – 31 Dec 2020		
Is this case study continued from a case study submitted in 2014? Yes		
1. Summary of the impact		
<p>The automated image analysis techniques developed at Imperial College are now widely used for the quantitative interpretation of brain Magnetic Resonance (MR) images as part of clinical trials advancing the development of new drugs and in improving healthcare diagnostics for neurological diseases such as Alzheimer's, Huntington's and Parkinson's. This case study describes the resulting key impacts including:</p> <ol style="list-style-type: none"> 1. the further development of a spin-off company, IXICO, co-founded by researchers from Imperial College, including its admission on AIM and its growth from 36 to 78 employees; 2. the use of automated image analysis techniques and imaging biomarkers in more than 2,000 imaging centres (increased from 400) in 50+ countries; 3. the increase in analysis from 10,000 to over 100,000 brain MR images in clinical trials using the developed image analysis techniques. 		
2. Underpinning research		
<p>The underpinning research has been carried out in the Biomedical Image Analysis (BioMedia) Group at Imperial College between 2000 and 2012.</p> <p>Much of the early work of the group has addressed one of the fundamental problems in computer vision and medical image computing, namely the problem of image registration. The goal of image registration is to find an automatic transformation between points in two or more images. For the transformation to be meaningful, it must map corresponding points across coordinate systems. If the transformation sought is rigid, the problem is relatively straightforward to solve, as the number of unknowns is small (typically 3 in 2D and 6 in 3D). In contrast, if the required transformation is non-rigid, the problem becomes substantially more challenging because the degree of freedom is much higher (typically in the order of hundreds of thousands, or even millions). In practical medical and clinical applications, non-rigid registration, however, is crucial to compensate for intra-subject variation (e.g., tissue deformation, respiratory or cardiac motion) as well as for inter-subject variation.</p>		

In 2001, Rueckert and his colleagues developed a solution to this problem that is based on a flexible and versatile deformation model using B-spline free-form deformations [R1]. This approach is capable of registering mono-modal and multi-modal images, and it was the first to adopt the use of adaptive, hierarchical B-spline free-form deformations that offer the ability to deal with complex deformations. This developed solution has been widely adopted: in a recent comparison study, it has been shown to be amongst the most accurate solutions for this problem [R2]. In 2006, Rueckert's group proposed an improved solution to the registration problem that uses a diffeomorphic deformation to allow the modelling of very large deformations, which occur when registering the images of different subjects [R3].

The ability of these image registration techniques to handle very large deformations has also led Rueckert's group to develop novel solutions to the classical problem of image segmentation, which is based on image registration. As part of the EPSRC-funded IXI [i] and IBIM [ii] projects, they have pioneered the use of non-rigid registration of multiple atlases followed by vote or label fusion for the automatic segmentation of images [R4]. Standard atlas-based segmentation uses image registration to transfer anatomical information from an atlas to new, unseen images. In contrast to this, multi-atlas segmentation [R4] uses multiple atlases and registrations followed by machine learning approaches, such as decision fusion, to provide a consensus estimate of the segmentation. This approach provides a much more robust and accurate segmentation of medical images. It has become the de-facto standard solution for medical image segmentation in many applications (as shown by the large number of citations), in particular for neurological, abdominal, and cardiac images. The name of the research project in [i] ("IXI") has inspired the name of the resulting spin-off company ("IXICO" – see Section 4 for details).

In the EU FP7 PredictAD project [iii], the team further developed the methodology described above to enable the robust and accurate extraction of imaging biomarkers, in particular in the context of neurodegenerative diseases such as dementia. For example, this methodology allows the accurate measurement of hippocampal volume [R5] and volume loss [R6].

3. References to the research

- [R1] J. A. Schnabel, **D. Rueckert**, M. Quist, J. M. Blackall, A. D. Castellano Smith, T. Hartkens, G. P. Penney, W. A. Hall, H. Liu, C. L. Truwit, F. A. Gerritsen, D. L. G. Hill, and D. J. Hawkes. A generic framework for non-rigid registration based on non-uniform multi-level free-form deformations. In Fourth Int. Conf. on Medical Image Computing and Computer-Assisted Intervention (MICCAI), pages 573–581, 2001. (>490 citations, Google Scholar). http://dx.doi.org/10.1007/3-540-45468-3_69
- [R2] A. Klein, J. Andersson, B. A. Ardekani, J. Ashburner, B. Avants, M.-C. Chiang, G. E. Christensen, D. L. Collins, J. Gee, P. Hellier, J. H. Song, M. Jenkinson, C. Lepage, **D. Rueckert**, P. Thompson, T. Vercauteren, R. P. Woods, J. J. Mann, R. V. Parsey. Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. *Neuroimage*, 46(3):786-802, 2009. (>2090 citations, Google Scholar) <http://dx.doi.org/10.1016/j.neuroimage.2008.12.037>
- [R3] **D. Rueckert**, **P. Aljabar**, **R. Heckemann**, **J. Hajnal** and **A. Hammers**. Diffeomorphic Registration using B-Splines. In Ninth Int. Conf. on Medical Image Computing and Computer-Assisted Intervention (MICCAI), pages 702-709, 2006. (>350 citations, Google Scholar). http://dx.doi.org/10.1007/11866763_86
- [R4] **R. A. Heckemann**, **J. V. Hajnal**, **P. Aljabar**, **D. Rueckert** and **A. Hammers**. Automatic anatomical brain MRI segmentation combining label propagation and decision fusion.

NeuroImage, 33(1):115-126, 2006 (>980 citations, Google Scholar).

<http://dx.doi.org/10.1016/j.neuroimage.2006.05.061>

[R5] **R. Wolz, P. Aljabar, J. V. Hajnal, A. Hammers, D. Rueckert** and the Alzheimer's Disease Neuroimaging Initiative. LEAP: Learning embeddings for atlas propagation. NeuroImage, 49(2): 1316-1325, 2010 (>250 citations, Google Scholar).

Patent filed US2012/281900 A1 and exclusively licensed to IXICO.

<http://dx.doi.org/10.1016/j.neuroimage.2009.09.069>

[R6] **R. Wolz, R. A. Heckemann, P. Aljabar, J. V. Hajnal, A. Hammers, J. Lötjönen, D. Rueckert** and The Alzheimer's Disease Neuroimaging Initiative. Measurement of hippocampal atrophy using 4D graph-cut segmentation: Application to ADNI.

NeuroImage, 52(1): 109-118, 2010 (>140 citations, Google Scholar). Patent filed US2012/281900 A1 and exclusively licensed to IXICO.

<http://dx.doi.org/10.1016/j.neuroimage.2010.04.006>

4. Details of the impact

The underpinning research has led to the development of novel imaging biomarkers that are now routinely used in clinical trials to assess the efficacy of new drugs and treatments. The biomarkers are also used in healthcare diagnostics, e.g., for dementias such as Alzheimer's disease (AD).

Economic impact

To maximise the economic impact of the research, a team of Imperial researchers (Rueckert, Hajnal) started IXICO with colleagues from UCL (Hawkes, Hill) in late 2004. In the assessment period for the 2014 REF, IXICO had been established and grown organically. In the current REF assessment period, several new key impacts occurred: in particular, in [October 2013, it became IXICO plc](#) and is now listed on the [Alternative Investment Market \(AIM\) of the London Stock Exchange](#) (date: 15th October 2013). Other impact measures are listed in the table below and compared to the status at the beginning of the assessment period:

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

Since the start of the assessment period, IXICO has grown from 36 to 78 employees. IXICO's revenues have increased from GBP2,500,000 to more than GBP9,500,000. IXICO has become a profitable business and, since 2014, has won more than GBP36,200,000 in business from the global pharmaceutical industry (GSK, Pfizer, Bristol-Myers Squibb, Novartis, Eli Lilly). Its orderbook for 2020 is GBP21,700,000 alone. IXICO's image analysis technology is based on the underpinning research described in Section 2 and has been transferred from Imperial during IXICO's formation and later as part of an IP pipeline agreement with Imperial. It has been, and/or is currently being used to analyse tens of thousands of medical images collected from a total of more than 2,000 imaging centres across North America, Latin America, Europe, Asia and Australasia (in over 50 countries) [I1, I2, I3]. Since 2013, IXICO has been involved in over 50 clinical trials and analysed brain images from more than 100,000 subject visits using its image analysis technology [I2].

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Originally, IXICO had focused on applying its image analysis technology to supporting clinical trials of novel therapies to treat Alzheimer's disease. Since the beginning of the REF assessment period, IXICO has successfully translated the technology to other neurological diseases, including Huntington's disease, Parkinsonian diseases (such as PD, PSP and MSA), Multiple Sclerosis and rare neurological diseases. In particular, IXICO has had much success in the Huntington's disease (HD) clinical trials market, having built the requisite therapeutic expertise and validated the technology specifically for measuring imaging biomarkers that are correlated with disease pathology and progression in HD. Since 2014, IXICO has been selected for 10 clinical trials in HD, 7 of which were started over the past 4 years since 2016 and includes the world's first phase III trial in Huntington's disease for a gene therapy approach that targets the mutant Huntington gene [11].

The developed image analysis techniques also provide an important tool in clinical trials to assess the safety and efficacy of new drugs as well as for enrichment of clinical trials, i.e., as inclusion/exclusion criteria. This enrichment of trials enables the reduction of heterogeneity of the population providing additional power for clinical trials, therefore increasing the sensitivity of trials to detect disease-modifying effects of drugs. Since 2013, IXICO has used the automated image analysis techniques for safety and eligibility reports in over 20,000 cases [12].

Impact on public policy and services

The techniques for automatically computing imaging biomarkers such as low hippocampal volume have had a significant impact on informing the development of new guidelines in regulatory clinical trials. This has been recognised, e.g., by the Coalition Against Major Diseases (CAMD) consortium by submitting to regulators an application to qualify low hippocampal volume as a biomarker [14, 15]. This submission – supported by the US Federal Drug Administration – incorporates key data obtained using the underpinning research described here: the availability of this technology, with the regulatory qualification, is having a global impact on the design of future trials of AD medicines in the pre-dementia population. Furthermore, IXICO is also part of key public/private partnerships that are advancing the scientific and regulatory agenda for clinical trials in neurological diseases. These include:

- EPAD (the European Prevention of Alzheimer's Dementia; <http://ep-ad.org>) – which has built an adaptive clinical trials platform with a readiness cohort of people at risk of Alzheimer's disease and which will enable pharma companies to evaluate efficiently the safety and effectiveness of their medicines in patients prior to onset of symptoms by utilising adaptive clinical trial approaches. IXICO received over EUR600,000 in grant funding to provide the technology to collect, manage and analyse MRI scans.
- AMYPAD (Amyloid Imaging for Prevention of Alzheimer's Dementia, <https://amypad.eu>) – which is evaluating the diagnostic value of amyloid imaging in the diagnosis of Alzheimer's disease. IXICO received over EUR1,000,000 in grant funding to provide the technology to collect, manage and analyse MRI and PET scans.
- HD-RSC (Huntington's Disease Regulatory Science Consortium, <https://c-path.org/programs/hdrsc/>) – which is developing regulatory-endorsed drug development tools to support the development and approval of new medicines to treat HD and involves representatives from the FDA. IXICO is contributing to the regulatory clearance of imaging biomarkers.
- CPP (Critical Path for Parkinson's, <https://c-path.org/programs/cpp/>) – which is developing regulatory-endorsed drug development tools to support the development and approval of new medicines to treat Parkinson's disease and involves representatives from the FDA. IXICO is

contributing to the development of a regulatory-endorsed digital outcome measure for Parkinson's disease.

Beneficiaries of the impact

The beneficiaries are pharmaceutical companies developing new drugs and therapies for neurodegenerative diseases such as Alzheimer's or Huntington's disease through improved efficacy and safety of clinical trials. Furthermore, patients are benefitting from improved imaging-based diagnostics and therapeutics.

Nature of the impact

IXICO's image analysis techniques provide an important tool in clinical trials to assess the safety and efficacy of new drugs as well as for enrichment of trials, enabling the reduction of heterogeneity of the population. The image analysis techniques provide increased sensitivity to detect disease-modifying effects of drugs and trials. This means that fewer patients need to be recruited into trials, leading to significant cost savings for pharma companies. IXICO has also supported clinical trials of novel therapies relating to neurological diseases and contributed to new guidelines for biomarkers in regulated clinical trials.

5. Sources to corroborate the impact

- [I1] Information for investors about IXICO
<https://ixico.com/investors/company-information/rns-news/> Link archived [here](#).
- [I2] IXICO Annual Report and Accounts 2019: pages 2, 8.
<https://ixico.com/assets/IXICO-financial-documents/IXICO-Annual-Report-2019-2.pdf>
Link archived [here](#).
- [I3] IXICO Annual Report and Accounts 2020: pages 1, 10, 14, 15, 29.
<https://ixico.com/assets/IXICO-plc-Annual-Report-2020-v2.pdf> Link archived [here](#).
- [I4] D. L. G. Hill et al. 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, 2014.
<https://doi.org/10.1016/j.jalz.2013.07.003> PDF available [here](#).
- [I5] Letter of Support by the Director, Centre for Drug Evaluation and Research, FDA, USA.
https://c-path.org/wp-content/uploads/2018/03/3.10.2015_letter_of_support.pdf