Institution: Queen's University Belfast

Unit of Assessment: 1

Title of case study: Successful Commercial Exploitation of Digital Pathology for Cancer Education, Biomarker Discovery and Clinical Diagnosis

1. Summary of the impact

PathXL Ltd is a digital pathology software company, founded by Queen's researchers who successfully commercialised a novel technology for objective evaluation of performance in cancer diagnostics and thereby improved cancer pathology training. The company's products initially revolutionized the professional training of young pathologists in the UK and Australia. Now products extend to software for tissue biomarker development, stratified medicine and biobanking. PathXL Ltd has raised significant venture capital funding to expand its business growing from 2 to 30 people and is now selling a range of world leading digital pathology products for education, biopharmaceutical and diagnostic research and clinical practice across the world.

2. Underpinning research

Research, led by Peter Hamilton who is Professor of Bioimaging & Informatics at Queen's (since 2002) focused on the development of Bayesian Belief Networks – a mathematical method that can be used to represent knowledge - and its use in decision making in medicine. The work aimed to "capture" the expert knowledge and decision making processes used by skilled pathologists in cancer diagnosis, and integrate this with a range of other knowledge management and computer-based representation techniques to establish a computer programme for use in the routine pathological diagnosis of cancer tissue samples. There is a growing trend to use digital image analysis and to capture diagnostic data using algorithms in order to make image interpretation more objective and improve the judgments made by experts. Hamilton and his colleagues established how a simple relational network, the careful representation of diagnostic clues and the definition of the weights associated with these diagnostic clues could be used to represent most diagnostic problems in pathology[1,2,3]. In addition, they developed a completely novel means by which to objectively map the diagnostic process using cumulative probability calculations, which the team called diagnostic decision maps. This had never before been used in cancer pathology decision making. These new technologies provided the basis for comparing performance and diagnostic precision between different pathologists and allowed subsequent research on performance variation, training modalities and skill acquisition in cancer pathology[4,5]. This unique approach to studying diagnostic decision making was subsequently enhanced by integrating it with representative digital image libraries and using "fuzzy logic" (at that time a novel mathematical approach to representing human language) to transfer the skills used in cancer diagnosis to a computer program[3,5]. Together with digital whole slide scans of cancer samples, it was used to create a comprehensive virtual computer training environment for pathologists. The management and viewing of whole slide images is common today – but in early 2000 the Queen's team were the first to develop specialist software for viewing virtual slides and integrate them within bespoke educational software to construct comprehensive digital slide sets across a range of diagnostic problems and deliver these as part of a web-based virtual learning environment for training, quality assurance and skill acquisition in cancer pathology[5]. The virtual learning software was developed and tested across a range of diagnostic problems including breast cytopathology, endometrial hyperplasia and cervical intraepithelial neoplasia, demonstrating distinct benefits and enhancement to decision making and training. This work was published extensively in higher impact pathology-focussed journals [1-5] where the greatest impact would be achieved and was extended to other advanced areas of tissue imaging[6]. Various aspects of the research were carried out in collaboration with colleagues at Queen's and with Peter Bartels (University of Arizona, USA) and Rodolfo Montironi (University of Ancona, Italy).

This research led to the development of a commercial spin-out company from Queen's called originally i-Path Diagnostics Ltd and later after a relaunch and expansion in 2012 named PathXL

Ltd. The company quickly generated revenue, seed funding followed by venture capital and now has a team of over 30 people working in non-university purpose-built offices and labs.

3. References to the research

1. **Hamilton PW**, Anderson N, Bartels PH, Thompson D. Expert system support using Bayesian belief networks in the diagnosis of breast fine needle aspiration biopsy specimens of the breast. J Clinical Pathology 1994;47:329-336. doi: 10.1136/jcp.47.4.329
   This paper showed for the first time how mathematical algorithms could be used to represent breast cancer diagnosis and how software could be developed to support diagnostic decision making in breast cytology
2. **Hamilton PW**, Bartels PH, Montironi R, Anderson N, Thompson D. Improved diagnostic decision making in pathology. Do inference networks hold the key? J Pathology 1995;175:1-5. doi: 10.1002/path.1711750102
   This paper laid down the principles for developing and adopting the technology in pathology – aimed at demonstrating to practicing pathologists through a mainstream high impact pathology journal the benefits of computer-based systems in pathology
3. Montironi R, Bartels PH, Thompson D, Scarpelli M, **Hamilton PW.** Prostatic intraepithelial neoplasia (PIN). Performance of Bayesian belief network for diagnosis and grading. J Pathology 1995;177:153-162. doi: 10.1002/path.1711770209
   This paper developed previous ideas but applying the technology to tissue histology to support diagnosis and grading of early neoplasia in the prostate.
4. **ML Morrison**, **WG McCluggage**, **G Price**, **J Diamond**, MRM. Sheeran, KM Mulholland, MY Walsh, R Montironi, PH Bartels, D Thompson, **PW Hamilton**. Expert System Support Using A Bayesian Belief Network For The Classification Of Endometrial Hyperplasia. J Pathology 2002;197:403-414. doi: 10.1002/path.1135
   This paper further extended our work, showing clear advantages of our technology in difficult diagnostic areas such as endometrial pathology. This paper was awarded the best bioinformatics paper of the year and republished in Int J Medical Informatics
5. **Diamond J**, Anderson NH, Thompson D, Bartels PH, **Hamilton PW**. A computer-based training system for breast fine needle aspiration cytology. J Pathology 2002;196:113-121. doi: 10.1002/path.1012
   This paper was the first to integrate the novel technology into a virtual training environment for breast cancer cytology
6. Yinhai Wang, David McCleary, Ching-Wei Wang, Paul Kelly, **Jackie James, Dean A. Fennell and Peter Hamilton**. Ultra-fast Processing of Gigapixel Tissue MicroArray Images using High Performance Computing. Cellular oncology 2010; 32: 181-181.
   Example of one paper estending digital pathology technology development for high throughput tissue microarray image analysis for biomarker discovery and translational research

Grants supporting the initial research:

Ulster Cancer Foundation Research Grant 1993-1996 £80,000
Development of Bayesian belief network for decision support in breast fine needle aspiration cytology

DENI Smart Award 1998 £40,000
Development of decision support system for breast cancer

Medical Research Council 1998 £170,000
Automated machine vision for the histopathological diagnosis and grading of prostate neoplasia

UK Broadband Fund 2004 £60,000
e-Learning and decision support for Diagnostic Pathology

More recent grants supporting academic development of theme:

DEL All Ireland Strengthening Award 2011 £1.2m

Cancer Bioinformatics
Marie Curie FP7 Grant 2012 £1.9m
Fast-Path: Fast-Tracking Pathology via Automated Image Analysis and High-Performance Computing: Application to Prostate Cancer Diagnostics
Invest Northern Ireland R&D Collaborative grant (Queen's, PathXL, Almac Diagnostics) £2.1m
Cancer Predictive Biomarker Discovery and Development Program

4. Details of the impact

This research has had major commercial impact realised through the establishment of PathXL Ltd., a highly successful company that has translated the initial technology and its subsequent developments into products with international appeal that impacts significantly on pathology education, research and diagnostic practice. This is a genuine example of technology transfer from an initial impact in cancer education subsequently extending, through continued collaboration with university researchers, to impact in pharmaceutical research and clinical practice. The company's growth and operations have an important economic impact in the UK. Impacts are therefore evidenced in each of these areas:

Successful commercialisation of IP and impact on pathology education

PathXL sold its technology to high profile customers such as Royal College of Pathologists of Australasia (RCPA) to support digital educational requirements and so generated significant revenue[1]. The educational products InView™/Simulator™ were so unique in their approach that accreditation was granted by both RCPA (2004) for training resident pathologists and the Royal College of Pathologists UK (2006) for continual professional development. The RCPA[2] said "*InView has proven to be a cutting edge training tool that can be utilised within large and small training laboratories*". Installation into private and publically funded research laboratories in Australia (2004-5) was to follow. In the UK, a number of pathology training schools adopted the novel approach to pathology training including the Thames Histopathology Training School (2006). Professor Simon Herrington, Secretary of the Pathological Society[3] said "*PathXL Simulator is an excellent additional learning resource which complements the traditional methods of teaching". "PathXL is an excellent development and provides a very useful educational resource, particularly for pathologists in training"*. Professor Hazan Rizvi[4] said *"Our main problem was being able to share this programme with collaborators and users. Having a web-based, easy to use interface makes this possible – PathXL Tutor is the perfect solution"* giving the company credibility in a professional marketplace.

Queen's developed technology for web-based viewing of large gigapixel medical images transferred across to the company and resulted in subsequent development of a sophisticated web-based image management system for digital pathology – now called PathXL Tutor™. PathXL Tutor™, became a general purpose platform for web based delivery, viewing and reporting of digital slides for educational and research purposes and was subsequently used to underpin undergraduate courses in several UK and European Universities and to support professional organisations such as the RCPA and Pathological Society of Great Britain and Ireland (2006-2007). In addition, since 2008, the company supports the largest pan-European competency test system for pathologists (2008-11) via the European Association of Pathology Chairs. In total, over 6,000 trainee pathologists have used and benefitted from PathXL software over the last five years. Olympus are now distributing the PathXL educational solutions.

Expansion of market impact into pharmaceutical research, biomarker imaging and clinical practice

In 2011, PathXL focussed increasingly on developing digital pathology software for the R&D Biobank sector. Together with the Queen's Northern Ireland Biobank, a new information management system was developed to support donor recruitment, sample tracking, clinical information handling and digital imaging to support high quality biosample collections. PathXL Biobank software now supports other national biobanking initiatives such as the Mesobank - a UK national multicentre collection of mesothelioma samples. PathXL is also establishing a contract for digital pathology services with a multinational contract research organisation servicing some of the largest biopharmaceutical organisations in the world.

Most excitingly during 2008-10, the Queen's group developed new methods for the automated identification of cancer tissue from digital microscope slides, using novel computer vision and image analysis techniques. This IP was subsequently transferred to PathXL in 2011. Now in 2013, PathXL has established a revolutionary new product called TissueMark™ aimed at supporting modern tissue research and molecular pathology laboratories. The methodology involves the automated identification of tumour based on patent pending pattern recognition algorithms for macro-dissection and tumour cell enrichment. This technology underpins the identification of new molecular markers in cancer and can alleviate the current bottleneck that inhibits high throughput molecular analysis of cancer tissue samples. TissueMark™ is now being used by AstraZenica (UK) and Novataris (Boston, USA).
Finally, PathXL has developed a Digital Pathology Management System for small hospital laboratories to support increased adoption of digital pathology for frozen section analysis, remote consultations and primary diagnostics. This is now being used pathology laboratories in USA, UK and Ireland. Digital pathology adoption is following the same trend as digital radiology, but is about 10 years behind. They are implementing solutions for a number of clinical laboratories and also partnering with CSC (major provider of IT systems to hospitals) to provide digital pathology software solutions for diagnostic pathology networks in UK. PathXL continues to deliver new solutions to this expanding market.

Impact on local economy and international markets

PathXL Ltd is now seen as a leader in digital pathology solutions by providing sophisticated web-based digital pathology solutions and Biobank software that support workflows in research and diagnostic laboratories. Unlike other vendors it is independent of scanner and image format and can integrate easily with other third party platforms. PathXL has raised in excess of £1.7m venture capital to grow its business and now employs a strong team of 30 people, a majority of which are based in PathXL's head office in Belfast. It is currently raising further capital to expand its operations globally. The company has just appointed distributors on Australia, Germany and Italy. In 2013, it opened an office in USA and appointed a Head of Sales and Business development for North America. It is selling its digital pathology solutions globally with over 30 key account customers worldwide. Since venture-backed funding, its sales have doubled year on year with expected turn-over in 2015 in excess of £4 million.

5. Sources to corroborate the impact

1. *http://www.rcpa.edu.au/static/File/Asset%20library/PathWay/Other/13a.pdf*
2. http://www.pathxl.com/files/casestudies/cs_PathXLsimulator.pdf
3. http://www.pathxl.com/files/casestudies/cs_PathXLtutor.pdf
4. http://www.pathxl.com/files/casestudies/cs_tma02.pdf
5. PathXL Website: www.pathxl.com
6. PathXL investment deal of the month: http://www.crescentcapital.co.uk/2013/01/03/pathxl-investment-clinches-deal-of-the-month/
7. Seven figure sum investment in PathXL: http://www.insidermedia.com/insider/ireland/82196-seven-figure-sum-investment-pathxl
8. Frost & Sullivan Award Enabling Technology Award http://www.frost.com/prod/servlet/press-release.pag?docid=258395100
9. PathXL winner in Deloitte Fast50 Companies http://www.newswiretoday.com/news/120815/PathXL_Shortlisted_for_The_Deloitte_Technology_Fast_50/
10. PathXL and Olympus work together http://www.newswiretoday.com/news/113467/