Institution: The University of Leeds

Unit of Assessment: 11 Computer Science and Informatics

Title of case study: Leeds Virtual Microscope: A new tool for pathologists diagnosing cancer

Period when the underpinning research was undertaken: 2006-2016

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:
Roy Ruddle	Senior Lecturer, Reader, Professor	15/01/2000 - date
Rhys Thomas	Research Fellow, Software Engineer	13/07/2009 – 28/02/2016

Period when the claimed impact occurred: 2012 to date

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

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

With digital pathology, doctors can diagnose cancer from high-resolution scans of biopsies. The Leeds Virtual Microscope (LVM) enables pathologists to diagnose patient cases more quickly than from glass slides and was the first digital pathology software capable of running on the ultra-high definition displays that pathologists need for such gigantic images (biopsy 'slides' are typically 10 billion pixels). The LVM research has changed pathology practice in one of the UK's largest hospitals, shaped several companies' R&D programmes, and led to new products that have changed the way pathologists diagnose cancer in the Americas, Europe, Middle East, Africa and Asia-Pacific.

2. Underpinning research (indicative maximum 500 words)

The underpinning research is in three areas.

A. Identifying the need for a better digital pathology viewer

Historically, pathologists viewed digital pathology slides on low-resolution monitors (e.g., 1024x768 pixels), and took 60% longer to diagnose cancer from a digital slide compared to viewing glass slides through a conventional microscope. Key reasons were: (a) the monitors had too few pixels, so pathologists only saw a fraction (21% or less) of the tissue visible with a microscope in each view, and (b) the user interface was very inefficient [1].

Our research to address those reasons began by designing software to display digital slides on a 54 megapixel 'Powerwall' display. An evaluation demonstrated a major improvement over commercial digital slide systems, because pathologists made diagnoses as quickly with the LVM as with a conventional (glass slide) microscope [1].

B. Design of novel software to make clinical diagnoses from digital slides

Major funding from the National Institute for Health Research (NIHR; £690k; 2009-2012) allowed us to design, implement and evaluate two further versions of the LVM providing a similar performance benefit running on a desktop PC with a multi-monitor ultra-high definition display. After some fundamental research [4], the LVM Version 2 [2] allowed the diagnosis of single-slide cases (gastro-intestinal biopsies and skin cancer), which together makes up half of the slide workload in major cancer units.

Version 3 [3] was enhanced with a patented "case world" layout [6] to diagnose complex cancer cases (12 – 25 slides; 25% of pathologists' workload), and won the 2014 Yorkshire & Humber NHS Innovation Award for Medical Devices and Diagnostics.

C. Evaluation of the LVM in a clinical setting

The LVM was evaluated in a series of controlled user experiments with consultant pathologists. While they made diagnoses more slowly with Version 2 of the LVM than with a conventional microscope, the difference was not statistically significant [2]. Version 3 allowed pathologists to make diagnoses as quickly as with a conventional microscope [3].

The LVM's user interfaces [5] won the 2016 Best Paper Award in the ACM Transactions on Computer-Human Interaction, with the journal's editor stating that this "article stands out because it puts into practice—and challenges—accepted design principles for the navigation of such gigapixel images, against the backdrop of real work by medical experts".

Follow-on funding

The evaluations led to commercial interest and the award of further grants from the EPSRC-funded Medical Technologies Innovation and Knowledge Centre (2012-14; £130k; EP/J017620/1), an EPSRC Impact Accelerator Award (2014-2015; £40k; EP/K503836/1), and the Yorkshire & Humber NHS Deanery (2015-2016; £110k). These grants allowed the development of essential extra functionality for the Leeds Teaching Hospitals NHS Trust (LTHT) adoption and Roche commercialisation.

The original multidisciplinary research was carried out jointly with Drs Darren Treanor and Rebecca Randell at the University of Leeds.

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

1. Treanor, D., Jordan Owers, N, Hodrien, J., Quirke, P., & Ruddle, R. A. (2009). Virtual reality Powerwall versus conventional microscope for viewing pathology slides: an experimental comparison. Histopathology, 5, 294-300. DOI

Evaluation with pathologists of LVM version 1, on a 54 megapixel Powerwall display. The results led to major (£690k) research funding from NIHR.

2. Randell, R., Ruddle, R. A., Mello-Thoms, C., Thomas, R., Quirke, P., & Treanor, D. (2013). Virtual reality microscope versus conventional microscope on time to diagnosis: An experimental study. Histopathology, 62, 351-358. DOI

Evaluation with pathologists of LVM version 2 with single-slide patient cases, on high-resolution (11 megapixel) desktop displays.

3. Randell, R., Ruddle, R. A., Thomas, R. G., Mello-Thoms, C., & Treanor, D. (2014). Diagnosis of major cancer resection specimens with virtual slides: Impact of a novel digital pathology workstation. Human Pathology, 45, 2101-2106. DOI

Evaluation with pathologists of LVM version 3 with large (12 – 18 slide) patient cases, on high-resolution medical-grade displays from Barco. The results led to three further grants (from EPSRC and NHS) and paved the way for commercialisation with Roche.

4. Ruddle, R. A., Thomas, R. G., Randell, R. S., Quirke, P., & Treanor, D. (2015). Performance and interaction behaviour during visual search on large, high-resolution displays. Information Visualization, 14, 137-147. DOI

Research with ordinary participants (students, not doctors) which informed the LVM's design.

5. Ruddle, R. A., Thomas, R. G., Randell, R., Quirke, P., & Treanor, D. (2016). The design and evaluation of interfaces for navigating gigapixel images in digital pathology. ACM Transactions on Computer-Human Interaction, 23(1), Article No. 5. DOI

This won the ACM ToCHI 2016 Best Paper Award, redefining design principles for overview-and-detail navigation interfaces, and describing details of the design of LVM version 3.

6. Ruddle, R. A. & Treanor. D. (2015). Patent for virtual microscopy (USA US8970618).

Protects the LVM's main intellectual property and, therefore, Roche's uPath digital pathology *software as well.*

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

The LVM has produced three impact in three areas.

A. New digital pathology products

Software: The LVM research produced intellectual property spanning novel software [1-5], know-how and patents (US8970618 [6]; EP3489733). That intellectual property was assigned in 2016 to Roche-Ventana [A] for a value that cannot be disclosed. Roche is a top 3 laboratory vendor (turnover £45 billion, 94,000 employees), with commercial distribution in over 100 countries and established relationships with anatomic pathology laboratories with over 50% market share worldwide[B].

The LVM was the basis of a fundamental redesign of the entire Roche digital pathology system in 2016-18 to provide users with "an innovative and intuitive way of interacting with their digital pathology cases" [B]. Treanor and Ruddle as consultants during the prototyping and detailed design phases for the new software (2016 – 2017), and were part of its beta-testing team (2018). Since the software's commercial launch as the uPath digital pathology enterprise software in 2019 [C], Roche have issued over 100 active uPath licences in Australia, Europe, the USA and other countries [B].

Scanner hardware: FFEI (a British SME) are the OEM developer and manufacturer of the Roche DP 200 scanner, which is an integral part of the Roche's uPath system and compatible with the LVM. In 2012 FFEI started discussions with Leeds about the LVM, under

a non-disclosure agreement. The "market established by LVM//uPath" helped FFEI secure internal and external investment to fund new imaging technology developments, upgrade R&D and production facilities, and retraining staff, driving their future business strategy [E].

FFEI have supplied WSI devices to over 27 countries in North and South America, Europe, the Middle East and Africa, and the Asia-Pacific region. From 2016 – 2019 their revenues from medical imaging grew from 20% to 50% of total revenue (£12m p.a.), and FFEI expect this trend to continue and include "direct-to-market products as a diversification of FFEI's current OEM business model" [E].

B. Influence pathology practice

The LVM underpinned pathology going fully digital in 2018 at the Leeds Teaching Hospitals NHS Trust (LTHT). LTHT is a major cancer centre and tertiary referral pathology laboratory serving a population of 3 million people, and England's second largest acute hospital trust.

After pilot evaluations during the LVM development [2,3], LTHT chose the LVM as the digital pathology platform for a ground-breaking 15,000-slide safety and validation study (https://doi.org/10.1111/his.13403) that directly led to national Royal College Guidelines for the pathology profession (Jan 2018; https://www.rcpath.org/resourceLibrary/best-practice-recommendations-for-implementing-digital-pathology-pdf.html) [D].

When LTHT pathology went digital, the LVM was rolled-out to the entire department. Benefits include efficiency ("really speeded up interpretation and therefore turnaround times of some of the most complex cases"), understanding of disease ("much clearer appreciation of low power distribution of the interstitial abnormalities"), reducing delays for patients ("more timely delivery of second opinions between hospital sites"), and organisational change ("allowed us to reframe our thinking around future Cellular Pathology strategy for the region") [D].

C. Shaping research & development programmes

As well as Roche and FFEI, the LVM also shaped the R&D programmes of two other companies under non-disclosure agreements.

Display hardware: Barco dominates the global medical display market (https://www.marketsandmarkets.com/ResearchInsight/medical-display-market.asp). From 2012, the LVM team worked with Barco and gave privileged access to research results. Barco gained confidence that "ultra-high definition medical displays made sense commercially" [F], invested in developing a new product to double display resolution (to the 12 megapixel Coronis Uniti) that thousands of doctors now benefit from, and in 2017 started a four-year project to develop a new collection of high-resolution of pathology displays. Barco draws parallels between the MIT Media Lab and the way the LVM team "had a visionary idea … quickly assembled a real working example, and sat people in front of it to see what it looked like" before "deploy[ing] it in a hospital to see how it should be improved" [F].

Pathology software: The LVM influenced the Swedish multinational Sectra Ltd, whose products are used in 2000 hospitals and clinics around the world. The LVM provided Sectra with "two foundational insights": (i) "it was possible to develop a digital viewer with

performance matching diagnosis with a conventional microscope, which was under much debate at the time", and (ii) there was "great potential" for digital diagnosis to go "beyond what was possible in the traditional microscope". This "had a great positive influence on the Sectra business decision to invest and start a branch in pathology" [G].

The LVM's success cemented Leeds as the go-to place for digital pathology R&D, evidenced by the Leeds-led National Pathology Imaging Collaborative (£30m Innovate UK/£11m industry funding)) [H] and Leeds Centre for Doctoral Training (£6m UKRI funding) in AI for Medical Diagnosis and Care [I]. They include Roche, FFEI, Sectra and NHS England as partners.

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

A. Press release about the sale of the of LVM technology to Roche (https://www.leeds.ac.uk/news/article/3828/sale_of_virtual_microscope_technology; 23rd Feb 2016).
B. Letter about LVM acquisition, and design and licencing of the new Roche uPath about digital pathology enterprise software, from the Digital Pathology Life Cycle Leader, Ventana Medical Systems (23rd Oct 2020). Ventana is a member of the Roche Group of companies, and part of Roche's Diagnostics Division.
C. Roche press release about the launch of uPath, incorporating the LVM technology (https://diagnostics.roche.com/global/en/news-listing/2019/roche-launches-uPath-enterprise-software.html; 15th Jan 2019).
D. Letter about the ways the LVM influenced pathology practice and helped a major cancer centre to go digital, from the Clinical Director of Pathology, Leeds Teaching Hospitals NHS Trust.
E. Letter about the LVM's influence on investment, development and sales of a new scanner for digital pathology, from the Chief Executive Officer, FFEI Ltd (2nd Apr 2020).
F. Letter about the LVM's influence on investment in new display products, from Barco's Strategic Product Manager (12th May 2017).
G. Letter about the LVM's influence on investment in new digital pathology software products, from Global Product Manager, Digital Pathology, Sectra Imaging IT Solutions, Sweden (19th Feb 2020).
H. Press release about the Leeds-led National (originally called 'Northern') Pathology Imaging Collaborative and other new centres, from the UK Government *Department for Business, Energy & Industrial Strategy*: "Artificial Intelligence to help save lives at five new technology centres" (https://www.gov.uk/government/news/artificial-intelligence-to-help-save-lives-at-five-new-technology-centres; 6th Nov 2018).
I. Grant announcement for Leeds' UKRI Centre for Doctoral Training in Artificial Intelligence for Medical Diagnosis and Care (2019 – 2027) (https://gtr.ukri.org/projects?ref=EP%2FS024336%2F1).