Institution: University of Nottingham		
Unit of Assessment: UoA1		
Title of case study: Commercialising autoantibody blood tests for the early detection of cancer.		
Period when the underpinning research was undertaken: 2003 - 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:**
Professor John Robertson	Professor of Surgery	1989-present
Period when the claimed impact occurred: 2014 - 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Innovative research on the effectiveness of autoantibodies to detect early cancers by Professor John Robertson led to the development of the successful clinical test, *EarlyCDT-Lung*. Oncimmune, a University of Nottingham spinout company established in 2003, has, since 2014, further developed and commercialised *EarlyCDT-Lung,* and developed and commercialised *EarlyCDT-Liver.* The company made an initial public offering on the London Stock Exchange of approximately GBP66,300,000 in 2016. Following the award of a CE Mark for *EarlyCDT-Lung* in 2017, and the launch of *EarlyCDT-Liver* in May 2018, Oncimmune has secured multiple lucrative contracts for distribution (e.g. Biodesix) and to further exploit the technology underpinning *EarlyCDT* tests (e.g. Roche). Total income from sales in the period is in excess of GBP3,616,000, and the company has attracted further investments of GBP15,000,000. The tests are run on standard laboratory equipment and have been demonstrated to represent savings in healthcare costs, associated with gains in life years and operational savings. *EarlyCDT-Lung* is in clinical use in 24 countries globally, including within the UK NHS, with a total of 200,000 tests completed worldwide. High risk patients screened with *EarlyCDT-Lung* are diagnosed with their cancer on average 87 days earlier, when the cancer is less advanced and more likely to be successfully treated.

2. Underpinning research

The Problem

Cancer is the world's second leading cause of death resulting in an estimated 10 million deaths in 2020 which is expected to rise to 16.3 million deaths by 2040 (World Health Organisation). Lung cancer is the world's leading cause of cancer-related mortality. More than 80% of patients present with advanced disease and less than 10% survive for ten years following diagnosis. Liver cancer is the sixth most common cause of cancer-related death worldwide. Early diagnosis of both lung and liver cancer is paramount to improved survival by enabling surgical resection prior to the cancer spreading from the organ of origin. Research has shown that early detection of solid tumours can significantly increase the chances of survival, however, current screening methods generally depend on access to equipment such as computed tomography (CT) scanners which is limited even in countries such as the United States where less than 10% of eligible patients receive a CT scan. Novel approaches are needed to develop optimal screening tests in terms of sensitivity, specificity, cost effectiveness and high patient compliance.

The Research: Diagnosing Lung Cancer

Tumour-Associated Antigens (TAA) are produced by tumour tissue and trigger an immunological response resulting in the accumulation of autoantibodies (AAbs). Initial research directed by Professor John Robertson showed that the use of panels of AAbs was significantly better than using AAbs to a single TAA, increasing the sensitivity of detection of primary breast cancer compared to controls **[1]**. The early research was patented by the University of Nottingham and on the basis of the commercial and clinical potential of this, the spinout company Oncimmune was established in 2003. In addition to his academic role at the University, Professor Robertson served as the Chief Scientific Officer (CSO) for Oncimmune from 2003-2013 overseeing research and the development of *EarlyCDT-Lung*; this involved collaborations with other University of Nottingham researchers (Herb Sewell, Caroline Chapman). Further research confirmed the technical validation of the *EarlyCDT-Lung* test **[2]** and then the clinical validation, which showed the test could detect early stage lung cancer **[3]**. Professor Robertson also had responsibility for progressing the company's patent

strategy, with the last of a family of seven patents filed in 2007, all with Professor Robertson as lead inventor.

In 2011, Professor Robertson published a further study in collaboration with Professor Lam (British Colombia Cancer Centre), which confirmed reproducibility and was large enough to show *EarlyCDT-Lung* could detect both Small Cell Lung Cancer and Non-small Cell Lung Cancer **[4]**. A further publication in 2014, from a collaboration with Professor James Jett (Mayo Clinic), reported on the use of *EarlyCDT-Lung* test in routine clinical practice in the United States, and confirmed that it performed as predicted and could act as a complementary tool to CT scans for detection of early lung cancer **[5]**.

In 2017, Professor Robertson, working with Professor Sewell (University of Nottingham, Life Sciences), and collaborating with Professor Massion, (Vanderbilt University, Nashville), investigated autoantibody signatures as an adjunctive test to help evaluate the malignancy potential of lung nodules **[6]**. A large number of benign nodules are detected by CT, therefore the ability of *EarlyCDT-Lung* to make this distinction between malignant and benign nodules was evaluated. The study reported that a positive test reflected a significant increased risk for malignancy in lung nodules 4 to 20 mm in diameter. The publication highlighted that *EarlyCDT-Lung* has clinical utility by adding to current lung nodule risk models for malignancy in indeterminate pulmonary nodules (IPN) **[6]**.

Professor Robertson was a co-investigator in the Early Cancer Detection Lung Cancer Scotland (ECLS) study (recruitment 2013-2016, published 2020), and wrote the first draft of the protocol in 2011. The study is thought to be the world's largest randomised clinical trial for the early detection of lung cancer using biomarkers in the blood **[7]**. The study aimed to determine whether using the *EarlyCDT-Lung* test to identify those at high risk of lung cancer and subsequent CT scanning reduced the incidence of patients with late-stage lung cancer (III & IV) or unclassified presentation (U) at diagnosis, compared with standard clinical practice. The ECLS study demonstrated that using the *EarlyCDT-Lung* significantly decreased the incidence of advanced stage disease at diagnosis. Participants in the intervention arm were diagnosed with lung cancer on average 87.3 days earlier than the control arm **[7].**

The Research: Diagnosing Liver and Other Cancers

In 2008, the University of Nottingham and Professor Robertson established the UK's first academic Centre for Excellence for Autoimmunity in Cancer (CEAC). CEAC collaborated with Oncimmune R&D scientists to develop new AAb detection tests for liver cancer. Professor Robertson co-supervised PhD student, Catrin Middleton (2010-13) to investigate AAb detection in hepatocellular carcinoma (HCC), the most common type of primary liver cancer. This demonstrated that a 21-antigen panel achieved a specificity of 92% and sensitivity of 45% for the detection of HCC. This same panel identified 21% of 169 high-risk controls as having elevated autoantibody levels. This minimally invasive blood test showed results comparable to current gold standards in HCC (Ultrasonography) **[8]**.

3. References to the research

[1] Chapman C, Murray A, Chakrabarti J, Thorpe A, Woolston C, Sahin U, Barnes A, **Robertson J**. Autoantibodies in breast cancer: their use as an aid to early diagnosis. *Ann. Oncol*. **2007**. 18(5); 868-873. http://dx.doi.org/10.1093/annonc/mdm007

[2] Murray A, Chapman CJ, Healey G, Peek LJ, Parsons G, Baldwin D, Barnes A, **Sewell HF**, Fritsche HA, **Robertson JFR**. Technical validation of an autoantibody test for lung cancer. *Ann Oncol*. **2010**. 21(8); 1687-1693. http://dx.doi.org/10.1093/annonc/mdp606

[3] Boyle P, Chapman CJ, Holdenrieder S, Murray A, Robertson C, Wood WC, Maddison P, Healey G, Fairley GH, Barnes AC, **Robertson JFR**. Clinical validation of an autoantibody test for lung cancer. *Ann Oncol*. **2011**. 22(2); 383-389. http://dx.doi.org/10.1093%2Fannonc%2Fmdq361

[4] Lam S, Boyle P, Healey GF, Maddison P, Peek L, Murray A, Chapman CJ, Allen J, Wood WC, **Sewell HF**, **Robertson JFR**. EarlyCDT–Lung: An immunobiomarker test as an tid to tarly detection of lung cancer. *Cancer Prev Res*. **2011.** 4(7);1126-34. http://dx.doi.org/10.1158/1940-6207.CAPR-10-0328

[5] Jett JR, Peek LJ, Fredericks L, Jewell W, Pingleton WW, and **Robertson JFR**. Audit of the autoantibody test, EarlyCDT®:-Lung, in 1600 patients: an evaluation of its

performance in routine clinical practice. *Lung Cancer*. **2014**. 83(1); 51-55. http://dx.doi.org/10.1016/j.lungcan.2013.10.008

[6] Massion PP, Healey GF, Peek LJ, Fredericks L, **Sewell HF**, Murray A, **Robertson JFR**. Autoantibody signature enhances the positive predictive power of pomputed tomography and nodule-based risk models for detection of lung cancer. *J Thoracic Oncologyl.* **2017**. 12(3); 578-584. https://doi.org/10.1016/j.jtho.2016.08.143

[7] Sullivan FM, Mair FS, Anderson W, Armory P, Briggs A, Chew C, Dorward A, Haughney J, Hogarth F, Kendrick D, Littleford R, McConnachie A, McCowan C, McMeekin N, Patel M, Rauchhaus P, Ritchie L, Robertson C, **Robertson J**, Robles-Zurita J, Sarvesvaran J, **Sewell H**, Sproule M, Taylor T, Tello A, Treweek S, Vedhara K, Schembri S. Earlier diagnosis of lung cancer in a randomised trial of an autoantibody blood test followed by imaging. *European Respiratory Journal*. **2020** (accepted version published online July 2020) http://dx.doi.org/10.1183/13993003.00670-2020

[8] Middleton CH, Irving W, **Robertson JFR**, Murray A, Parsy-Kowalska CB, Macdonald IK, McElveen J, Allen J, Healey GF, Thomson BJ, Ryder SJ, Holdenrieder S, and Chapman CJ. Serum autoantibody measurement for the detection of hepatocellular carcinoma. *PLoS One.* **2014**. 9(8); e103867. http://dx.doi.org/10.1371/journal.pone.0103867

Grants and investment

[9] Collaborative research investment from Oncimmune: Funding for CEAC to support R & D collaborative work between University of Nottingham and Oncimmune. £2,390,000 (2009-2013)

[10] Tumour Markers Early Detection (2012-2015) – Robertson J.R. PI funded through charitable donations including Whitaker Charitable fund and Candis Totalling £122,000

[11] Early Cancer Detection test – Lung Cancer Study (ECLS) Robertson J.R Co-applicant. Total £1,871,000 (£871K NHS support costs, £250K Scotland's Chief Scientist Office, £750K Oncimmune) (2012–16)

4. Details of the impact

From concept to product

Professor Robertson was the originator of the idea that a panel of autoantibodies (AAbs) could be beneficial in detecting early cancers. He has subsequently overseen the development of a clinical test from initial biological studies all the way through to clinical use. This journey included the founding of Oncimmune as a University of Nottingham spin out in 2003, commercial success for the company, and benefits to patients around the world who have received the test, and had cancers diagnosed earlier, leading to improved outcomes.

Early research by Professor Robertson and his collaborators, together with four associated patent families and the development of the *EarlyCDT-Lung* test, formed the basis of Oncimmune, which is based in Nottingham City Hospital and (since 2006) has also had a site in the United States (De Soto, Kansas). *EarlyCDT-Lung* was marketed for use as a diagnostic test for the early detection of lung cancer in high-risk patients (particularly long-term smokers and ex-smokers). The same technology is now being developed for other solid tumours and an equivalent test for liver cancer *EarlyCDT-Liver* was launched in 2018.

Growth of Oncimmune Holdings PLC

Oncimmune Holdings PLC, floated on the London stock exchange in 2016 making an initial public offering (IPO) of approximately **GBP66,300,000 [A, B[b] p. 79]** which is one of the biggest University of Nottingham IPOs (private to public). In 2017, the company obtained a CE mark for *EarlyCDT-Lung* **[C, p. 4]** in a format that allowed it to be run on 96 Well ELISA Microplate instruments, used as standard equipment in hospital laboratories worldwide, opening new market opportunities for the ELISA kit product.

Oncimmune has secured multiple agreements for the sale of *EarlyCDT-Lung* with major suppliers to healthcare providers around the world, including in North and South America, Asia, Russia, Europe and the Middle East **[D, p. 1 to 18]**. In November 2019, Oncimmune signed an agreement with Biodesix Inc, worth 28,000,000USD (11-2019) over five years, to sell *EarlyCDT-Lung* for use by clinicians in identifying nodules at high risk of lung cancer. This facilitated access to the United States, the world's largest healthcare market, with sales

alongside Biodesix's Nodify XL2 product **[E]** via a national sales force connected directly with pulmonologists and, corporately, into national hospital systems. In May 2018, Oncimmune successfully launched the *EarlyCDT-Liver* test into the US Market **[F]**. In total, income from sales of *EarlyCDT-Lung* and *-Liver* tests between financial year's 2015/6 and 2019/20 has realised revenue of **GBP3,616,000 [B[a, b]].** In financial year 2017/8 investments of **GBP15,000,000** was attracted **[B[b], p. 43]** and **GBP12,200,000** raised by issue of equity in financial year 2015/6 **[B[b] p. 111].**

Since 2014, Oncimmune has signed a significant number of contracts with both clinical groups and pharma companies to expand the company and the uses of the technologies that underpin *EarlyCDT* tests **[D, p. 19 to 36].** In March 2019, Oncimmune acquired Protagen Diagnostics AG, a leader in personalised immune-profiling, for a total sum of up to GBP4,110,000 **[G]**. In May 2020, Oncimmune signed a new contract with Roche Pharmaceuticals for an undisclosed fee to exploit its blood autoantibodies technology for immune-profiling, rather than cancer diagnosis, in order to monitor therapeutic outcomes and disease prognosis. Oncimmune's Chief Executive said *"This contract, the largest we have signed to date, provides further evidence of our ability to convert pipeline opportunities into contracted revenues"* **[H].**

Impact on Patient Health

Early diagnosis of lung cancer more than triples the 5-year survival rate to 56% if the tumour is found to be localised. Unfortunately, only approximately 15% of lung cancers are diagnosed whilst still localised. *EarlyCDT-Lung* is able to detect AAbs to lung cancer up to 4 years before diagnosis by standard clinical pathways, other than low-dose CT screening, and can therefore allow lung cancer to be detected while it is still small and surgically curable. In comparison to invasive tests, *EarlyCDT-Lung* is a simple blood test which can be run in any laboratory using standard equipment, making the test accessible to low and moderate as well as high income countries. By October 2020, over 200,000 of the *EarlyCDT* lung tests have been performed on patients across 24 countries around the world **[B[b], p. 5, 7].**

The Early Cancer Detection Lung Cancer Scotland (ECLS) trial, supported by the Chief Medical Officer & Chief Scientific Officer of Scotland and carried out within NHS Scotland, demonstrated that *EarlyCDT-Lung* was successful in early detection of lung cancer across a high risk population (12,208 participants) **[7]**. Patients who received the *EarlyCDT-Lung* test were diagnosed with lung cancer 87 days earlier compared to those in the control arm, increasing the chance their cancer would be successfully treated. Former Chief Medical Officer for Scotland states *"There can be no doubt that late stage lung cancers kill patients and so the reduction in late stage diagnosis demonstrated by the ECLS study is a clinically significant result, promising substantial healthcare advantages if the test were to be widely implemented… Importantly, the ECLS study has brought in immediate benefits to the patients randomised to have the EarlyCDT-Lung test. Those patients diagnosed with early stage disease, who may otherwise have not presented until late stage, will now have significantly improved outcomes and greater chance of cure*" **[I].**

In April 2020, NICE (National Institute for Health and Care Excellence, UK) completed a review of *EarlyCDT-Lung*, which included studies reported in four of Professor Robertson's publications **[4, 5, 6, 7].** This was published as a Medtech Innovation Briefing ("MIB") providing advice that will be available to all NHS England clinicians, and those supporting staff who are considering using new medical or diagnostic technologies. It concluded that the test "*enables earlier and accurate diagnosis in people at high risk of lung cancer*", which "*could mean treatment is offered early, giving improved outcomes*" **[C, p.2]**. In addition, on the strength of the ECLS trial, Former Chief Scientific Officer for Scotland said "*the use of the test for assessing the risk of IPNs will, I believe, be taken up and integrated into NHS care without further large scale trial*" **[I].** In December 2020 the first contracts were signed to supply *EarlyCDT-Lung* to the NHS Norfolk and Waveney Clinical Commissioning Group and to NHS Lung Health Check Programmes in Wessex and Yorkshire as part of the iDx-LUNG evaluation programme. **[J]**

Impact on Healthcare Costs

Detecting early stage lung cancers results in significantly lower healthcare costs: curing more patients avoids expensive therapies needed to treat locally advanced and/or metastatic disease. Patients who have IPNs and an estimated intermediate risk (5%- 65%) of lung cancer are frequently accessed via CT surveillance to detect nodule growth. A study, published in 2018, conducted by the health economics consultancy Policy Analysis Inc. used a decision-analytic model to evaluate the cost-effectiveness of *EarlyCDT-Lung* as an aid to the early diagnosis of lung cancer **[K]**. The study found that although expected costs would be higher by USD949,442 (USD949 per person), due to earlier diagnosis life years would be higher by 53 (0.05 per person), resulting in a cost per life-year gained of USD18,029 and a cost per quality-adjusted life year (QALY) gained of USD24,330 **[K, p. 9]**, confirming that *EarlyCDT-Lung* '*is likely to be a cost-effective use of healthcare resources*' **[K, p. 2]**.
Subsequently, a National Institute for Health Research-funded study led by Leeds University Academic Unit of Health Economics further demonstrated the cost-effectiveness of using the *EarlyCDT-Lung* in the cancer risk assessment of IPNs. The study states that '*At £70 per test, EarlyCDT-Lung and CT surveillance was found to be cost-effective compared to CT surveillance alone with an incremental cost-effectiveness ratio (ICER) of less than £2,500 depending on the test accuracy parameters used*' and added that use of *EarlyCDT-Lung* '*will have a positive impact on patient outcomes*' **[L, p. 1]**.Both these studies are referenced by the NICE Medtech Innovation Briefing **[C, p. 4]**, confirming that the adoption of the *EarlyCDT-Lung* test could result in cost savings through the NHS saving resources (operational costs of CT scanning and radiologist time) and through reducing waiting times **[C, p. 2]**.

5. Sources to corroborate the impact

[A] London Stock Exchange announcement Oncimmune Holding IPO, https://www.lseg.com/markets-products-and-services/our-markets/london-stock-exchange/equities-markets/raising-equity-finance/market-open-ceremony/london-stock-exchange-welcomes-oncimmune

[B] [B[a]] Summary of revenue from Oncimmune yearly reports for 2020, 2019, 2018, 2017 and 2016, [B[b]] Oncimmune yearly reports for 2020, 2019, 2018, 2017 and 2016

[C] *EarlyCDT-Lung* for cancer risk classification of indeterminate pulmonary nodules', NICE Medtech Innovation Briefing (17 March 2020), https://www.nice.org.uk/advice/mib209

[D] Oncimmune Press releases between 2017 and 2020

[E] Biodesix Acquisition Announcement (1 November 2019), https://www.londonstockexchange.com/news-article/ONC/oncimmune-and-biodesix-seal-deal/14290418

[F] *EarlyCDT-Liver* Launch (14 May 2018), https://investegate.co.uk/oncimmune-hldngs-plc--onc-/rns/oncimmune-launches-earlycdt--liver-test-in-the-us/20180514070010891 8N/

[G] Oncimmune acquisition of Protagen (19 March 2019), https://www.londonstockexchange.com/news-article/ONC/oncimmune-acquires-protagen-diagnostics-ag/14006613

[H] Oncimmune announcement of immunotherapy deal with Roche (28 May 2020), https://www.londonstockexchange.com/news-article/ONC/contract-with-roche-to-profile-autoantibodies/14555572

[I] Letter of Support from the former Chief Medical Officer for Scotland

[J] Oncimmune announcement of NHS launch (14 December 2020), https://www.londonstockexchange.com/news-article/ONC/earlycdt-lung-blood-test-launch-into-the-nhs/14790898

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