Institution: The University of Nottingham

Unit of Assessment: UoA5

Title of case study: Development and commercialisation of the *EarlyCDT®-Lung* cancer test delivers early lung cancer detection, company growth and healthcare cost savings.

Period when the underpinning research was undertaken: 2000-present

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:
Herbert Sewell	Professor of Immunology Emeritus Professor	1990-2018 2018-present

Period when the claimed impact occurred: Aug 2014-present

Is this case study continued from a case study submitted in 2014? No.

1. Summary of the impact

Research by Professor Sewell at the University of Nottingham (UoN) led to the development and clinical validation of a blood autoantibody test for early detection of cancer in high risk patients: the *EarlyCDT®-Lung* test. Oncimmune Holdings Plc has benefited from the commercialisation of the test, raising over GBP3,600,000 in sales and GBP15,000,000 by investment since 2014, and over GBP12,000,000 by issue of equity, with an initial public offering on the London Stock Exchange of GBP66,300,000 in 2016. In 2017 the test was awarded CE Mark certification and, as of December 2020, the test has been delivered to over 200,000 patients worldwide. High risk cancer patients screened with *EarlyCDT®-Lung* are diagnosed on average 87 days earlier, when the cancer is less advanced and has a better prognosis. The roll out of the test has also benefited healthcare providers, as the test is cost-effective. The National Institute for Health and Care Excellence (NICE) advised NHS clinicians on the health and cost benefits of implementing the *EarlyCDT®-Lung* test, stimulating Oncimmune' s first contracts with the NHS in December 2020.

2. Underpinning research

Tumour-associated antigens (TAA) produced by a tumorous tissue trigger an immunological response that results in the accumulation of autoantibodies (AAbs). AAbs are found in serum samples of cancer patients, including those with lung cancer and importantly in individuals who show no symptoms of disease and no visible growths as observed in chest x-rays or computed tomography (CT) scans, but who crucially go on to develop lung cancer at a later stage. Circulating AAbs are therefore early indicators of the presence of a tumour and their measurement in at-risk individuals could potentially enable an early cancer diagnosis, prompt and less aggressive treatment for early-stage disease, targeted chemoprevention and consequently better prognosis and improved survival.

In 2003, when the UoN spun out Oncimmune for the development of diagnostics tests using AAbs, Professor Sewell joined Professor John Robertson's team (Professor of Surgery, School of Medicine, UoN). Professor Sewell brought his research expertise on human immune responses in cancer to collaborate in the development of a diagnostic test for lung cancer and more specifically contributing to the technical validation and clinical development of tests. This involved selecting appropriate TAAs for the ELISA assay **[1]**, trouble-shooting false positive tests caused by cross-reactive immune responses and exploring *E. coli* gene expression systems. Together with Professor Robertson, Professor Sewell played a key role in the planning of retrospective studies and producing quality controls to ascertain the integrity of long stored blood samples **[2, 5]**. Professor Sewell was a member of the Scientific Advisory Board of Oncimmune from 2005 to 2014.

In 2010 and 2011 and after seven years of research, Professor Sewell and colleagues published the first ever assay that successfully detected AAbs from a blood sample to a standard sufficient to be used in the clinical setting. These experiments demonstrated linearity, precision and reproducibility, all crucial characteristics for a test to be used as a diagnostic tool. The test, *EarlyCDT®-Lung*, used a panel of AAbs, as opposed to a single one, and was able to identify almost 40% of primary lung cancers using serum of patients

that had been diagnosed with lung cancer or smokers at high risk of developing lung cancer **[1, 2].**

Professor Sewell subsequently played an influential role in the development of a high-throughput and effective method of biomarker discovery that improved the *EarlyCDT®-Lung* test. The aim was to define a cost-effective and fast screening method to find novel antigens for the development of tests to diagnose not only lung cancer, but also other cancer types. The sensitivity and specificity of the *EarlyCDT®-Lung* test were improved from 38% and 86% to 49% and 93% respectively. This improved the positive predictive value (PPV) from 1 in 16 to 1 in 7, meaning a recall of 7 patients instead of 16 for further testing in order to detect one patient with lung cancer **[3, 4]**. For comparison, a CT scan has a PPV of 1 in 36, as it has low specificity in distinguishing malignant from non-malignant growths.

Since the initial work, numerous significant retrospective clinical studies to validate the use of the *EarlyCDT®-Lung* test in clinic and to demonstrate how the test can assess the malignancy of pre-symptomatic lung growths have been designed and performed by Professors Sewell and Robertson with their worldwide collaborators. In particular, these studies have confirmed that the *EarlyCDT®-Lung* test detects lung cancer four years or more, on average, before diagnosis via standard care pathways. This is due to the high specificity and high PPV of the *EarlyCDT®-Lung* test **[5, 6, 7]**. These features make the test a complementary tool to be used for population screening in conjunction with the existing CT scans.

3. References to the research

Key Publications (UoN UoA5 researchers, at the time of publication, are highlighted in bold)

1 Murray A, Chapman CJ, Healey G, Peek LJ, Parsons G, Baldwin D, Barnes A, **Sewell HF**, Fritsche HA, Robertson JF (2010). Technical validation of an autoantibody test for lung cancer. *Ann Oncol.; 21(8):1687-93.* doi: 10.1093/annonc/mdp606

2 Lam S, Boyle P, Healey G, Maddison P, Peek L, Murray A, Chapman CJ, Allen J, Wood WC, **Sewell HF**, Robertson JFR (2011). *Early*CDT–Lung: An immunobiomarker test as an aid to early detection of lung cancer. *Cancer Prev Res.; 4(7):1126-34.* doi: 10.1158/1940-6207.CAPR-10-0328

3 Macdonald IK, Murray A, Healey G, Parsy-Kowalska C, Allen J, Chapman CJ, **Sewell HF**, Robertson JFR (2012). Application of a High Throughput Method of Biomarker Discovery to Improvement of the EarlyCDT®-Lung Test. Plos One 7(12):e51002. doi:10.1371/journal.pone.0051002

4 Macdonald IK, Allen J, Murray A, Parsy-Kowalska C, Healey G, Chapman CJ, **Sewell HF**, Robertson JFR (2012). Development and validation of a High Throughput System for Discovery of Antigens for Autoantibody detection. *PLoS One; 7(7): e40759.* doi:10.1371/journal.pone.0040759

5 Massion P, Healey GF, Peek LJ, Fredericks L, **Sewell HF,** Murray A, Robertson JFR (2016). Autoantibody Signature Enhances the Positive Predictive Power of Computed Tomography and Nodule-Based Risk Models for Detection of Lung Cancer. *J Thorac Oncol.; 12(3):578-84.* doi: 10.1016/j.jtho.2016.08.143

6 Sullivan FM, Farmer E, Mair FS, Treweek S, Kendrick D, Jackson C, Robertson C, Briggs A, McCowan C, Bedford L, Young B, Vedhara K, Gallant S, Littleford R, Robertson JFR, **Sewell HF**, Dorward A, Sarvesvaran J and Schembri S (2017). Detection in blood of autoantibodies to tumour antigens as a case-finding method in lung cancer using the EarlyCDT®-Lung Test (ECLS): study protocol for a randomized controlled trial. *BMC Cancer; 17(1):187.* doi 10.1186/s12885-017-3175-y

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, Raucchaus 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 (2020). Earlier diagnosis of lung cancer in a randomised trial of an autoantibody blood test followed by imaging. *European Respiratory Journal 14;57(1):2000670.* doi: 10.1183/13993003.00670-2020

Grants & Investment

8 2009-13 , Oncimmune, “Funding for CEAC to support R & D collaborative work between UoN and Oncimmune, **Sewell** CoI ,GBP2,390,000

9 2012-15, charitable donations from Whitaker Charitable fund and Candis, "TM Early Detection", **Sewell** CoI, GBP122,000

10 2012–16, "Early Cancer Detection test – Lung Cancer Study (ECLS)", **Sewell** CoI, GBP1,871,000 (GBP871,000 NHS support costs, GBP250,000 Scotland's Chief Scientist Office, GBP750,000 Oncimmune)

4. Details of the impact

Lung cancer is the most common cause of cancer-related death worldwide. Methods that detect lung cancer at an earlier stage when the tumour is still small, often asymptomatic and easier to treat and cure would improve survival rates. Detecting a tumour at an early stage could also significantly lower the cost of treatment, as early stage tumours do not need extensive, invasive and more costly therapies or treatment options. The *EarlyCDT®-Lung* test has benefited patients with early detection of lung tumours, a company with significant commercial activity and healthcare providers with associated cost savings.

Pre-2014 *EarlyCDT®-Lung* commercialisation: The development of the *EarlyCDT®-Lung* test formed the basis for the establishment of the UoN spin-out company Oncimmune Ltd, founded in 2003. Oncimmune is headquartered in Nottingham, and has a discovery research centre in Dortmund (Germany) and a representative office in Shanghai (China). The *EarlyCDT®-Lung* test is underpinned by the blood test development patented by the UoN, which has been exclusively licensed to OncImmune Ltd since 2009 and subsequently assigned to the company by the UoN in 2016.

Building on previous research **[1-4]**, new clinical studies that validate the technology have been published since 2014 **[5-7]**. The presentation of interim results in international conferences during the progression of clinical studies and trials and before their publication in peer-reviewed journals **[5-7]** aided the early dissemination of results, raising confidence in the test and encouraging the early adoption of the test by clinicians.

This new research has generated **new impact** in the following areas:

i. Growth of Oncimmune Holdings Plc:

Sales of *EarlyCDT®-Lung* test

Oncimmune currently markets two products, *EarlyCDT®-Lung and EarlyCDT®-Liver*, with most of its revenue generated from the sale of the former. An income from sales of *EarlyCDT®-Lung* and *-Liver* tests of GBP3,616,000 has been raised in the period from May 2014 to July 2020 **[S1]**. Additionally, GBP15,000,000 was raised by investment for the same period and GBP12,200,000 was raised by the issue of equity in 2016 **[S1]**.

As of December 2020, Oncimmune has 19 commercial distribution and partnership agreements for the sale of *EarlyCDT®-Lung* with major healthcare providers in 24 countries around the world, including in North and South America, Asia, Europe and the Middle East. For example, in June 2019, Oncimmune signed a five-year USD28,000,000 partnership with Biodesix Inc to commercialise the *EarlyCDT®-Lung* test as Nodify Lung™. In March 2020, Biodesix launched the test in the USA, the world's largest healthcare market **[S1]**. In December 2020 Oncimmune launched the *EarlyCDT®-Lung* test into the NHS, with commercial contracts to supply the Norfolk & Waveney Clinical Commissioning Group and the NHS Lung Health Check Programmes in Wessex and Yorkshire **[S2]**.

Further evidence of company growth

Oncimmune Ltd became a public company, Oncimmune Holdings Plc (oncimmune.com/), on the London Stock Exchange in 2016**.** On admission the company had a market capitalisation of over GBP66,300,000 (at that time approximately USD100,000,000) **[S3]**.

In 2017, the company obtained the CE mark for *EarlyCDT®-Lung* test in an ELISA kit format **[S4]**. This opened new market opportunities, as the kit can be run on already well established ELISA 96-well microplate instruments that hospitals worldwide have as standard equipment in their laboratories.

Oncimmune launched ImmunoINSIGHTS in early 2019, upon acquisition of Protagen Diagnostics AG (now Oncimmune Germany GmbH). ImmunoINSIGHTS is a service-based platform built off the autoantibody profiling technology, which enables pharmaceutical and biotech companies, start-ups and academic laboratories to use Oncimmune's large human antigen library for profiling autoantibodies in patients receiving treatment for multiple

diseases **[S5]**. Since that launch, Oncimmune has secured a contract with Roche Pharmaceuticals to profile autoantibodies in patients undergoing immunotherapy trials. The deal *"includes a substantial but undisclosed upfront fee"*. 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"* **[S6]**. In a separate deal in September 2020, Oncimmune signed a contract with Genentech to characterise the autoantibody profiles of patients with autoimmune diseases undergoing clinical trials **[S7]**.

ii. Impact on cancer patient health

The Early Cancer detection test Lung cancer Scotland study (ECLS, 2013-2018, eclsstudy.org/), a phase IV biomarker evaluation, was designed **[6]** and conducted to test whether the *EarlyCDT®-Lung* test combined with CT scan was able to detect lung cancer at earlier stages compared with the standard clinical practice of CT scan alone. The ECLS was conducted within NHS Scotland and supported by the CMO and CSO of Scotland, who said "*Scotland at the time had one of the highest death rates from lung cancer in the world…and therefore it was a priority health care problem for the Government of Scotland. …I was aware of the scale of …the immense health care value that an early detection blood test could bring…I felt it important that I should support a trial of screening using this test in Scotland. ..The reputation and obvious skill of Professor Sewell's team made me extremely confident that they would be an effective team to do the study and that their technology seemed robust… The Scottish Government Health and Social Care Directorate provided more than half the funding for the ECLS Study"* **[S8]**. The ECLS study went ahead in 2018 and randomised 12,208 patients at risk of developing lung cancer aged 50-75. After a two year follow up, the study confirmed that the *EarlyCDT®-Lung* test was able to detect lung cancer at an early stage. In patients given a lung cancer diagnosis during the study, there was a 14.3% risk reduction in stage III/IV (advanced stage) lung cancer incidence in the intervention arm **[7]**.

EarlyCDT®-Lung test has benefited not only those patients that took part in the ECLS study, but also patients around the world that have used the test. To December 2020, 200,000 lung tests have been delivered to patients worldwide **[S1]**. Former Chief Medical Officer and Chief Scientific Officer for Scotland said *"the ECLS study has resulted in immediate benefits to the group of 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. In addition, the population of Scotland will benefit through the focus that the ECLS study has brought to the early detection of lung cancer and the opportunity to use and/or incorporate EarlyDCT-Lung into its national lung cancer screening programme"* **[S8]**.

In March 2020, the UK's National Institute for Health and Care Excellence (NICE) completed a review of *EarlyCDT®-Lung*, concluding that the test can successfully aid earlier and more accurate diagnosis of lung cancer in high-risk patients, with the potential benefit of early treatment and improved outcomes. Consequently, NICE published a Medtech Innovation Briefing (MIB) providing advice that is available to all NHS England clinicians, managers and procurement professionals, supporting commissioners and staff who are considering using new medical or diagnostic technologies **[S9]**. The MIB also notes that this could have a wider benefit by saving other NHS resources (CT scanning and radiologists) and reducing waiting times. As clinical and technical evidence, the briefing cites four outputs with Professors Sewell and/or Robertson authorship including **[5]** or with results from the ECLS study **[7]**. In December 2020, NICE went a step further and selected the *EarlyCDT®-Lung* test for *Diagnostics Assessment Guidance,* which if successful will support wider adoption of the test within the NHS **[S2]**. Linking the success of negotiations with the NHS to the publication of the ECLS results **[7]**, CEO of Oncimmune said *"The successful publication of our co-funded Early detection of Cancer of the Lung Scotland ("ECLS") study with the NHS, …, has been followed by intense discussions with the NHS, leading to due diligence throughout the last six months. As a result of those discussions, we are delighted to be working with the NHS in three regions"* **[S3]**.

Former CMO and CSO of Scotland said *"The results of these studies considered by NICE and also the NICE review will, I believe, inform the subsequent uptake of Early-CDT-Lung in*

NHS Scotland/NHS… the use of the test for assessing the risk of [indeterminate pulmonary nodules] IPNs will, I believe, be taken up and integrated into NHS care without further large scale trials" **[S8]**.

iii. Impact on healthcare costs

Two separate studies have evaluated the potential cost-effectiveness of the *EarlyCDT®-Lung* as an aid to diagnose lung cancer in high risk individuals, as compared with the current protocol of CT surveillance alone.

A study published in 2018, conducted by the health economics consultancy Policy Analysis Inc. and funded by Oncimmune, concluded that the use of *EarlyCDT®-Lung* is likely to be a cost-effective use of healthcare resources. Analysis of medium-risk individuals showed that the cost-effectiveness of introducing the *EarlyCDT®-Lung* would approximately be USD24,000 per QALY (Quality Adjusted Life Year) gained, with more favourable results for high-risk individuals **[S10]**. Cost-effectiveness ratios lower than USD50,000 per QALY are considered good value by USA healthcare providers. Similarly, the NICE threshold of acceptance is lower than GBP20,000 (equivalent to USD25,400 as of September 2020).

A different study by the Institute of Health Sciences at the University of Leeds and the Institute of Health Economics in Alberta, Canada, funded by NIHR, used an alternative analysis method to compare the long-term cost of using the *EarlyCDT®-Lung* in the cancer risk assessment of indeterminate pulmonary nodules as opposed to CT surveillance alone. The study concluded that *"at GBP70 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 GBP2,500".* **[S11]**.

These two studies are cited in the Medtech Innovation Briefing by NICE. The briefing agrees that the adoption of the *EarlyCDT®-Lung* would result in cost savings for the NHS. It also acknowledges the potential for a positive health impact **[S9]**.

Considering that to December 2020 approximately 200,000 *EarlyCDT®-Lung* test have been delivered worldwide **[S1]**, it is inferred that health cost savings have been achieved. These savings should increase as health providers under current contract with Oncimmune deliver more tests and new health providers adopt the test.

5. Sources to corroborate the impact (websites were last accessed on 18/01/2021)

S1 Oncimmune yearly reports for 2020, 2019, 2018, 2017 and 2016.
S2 Oncimmune announces the launch of *EarlyCDT®-Lung* test into the NHS, web link
S3 Oncimmune becomes a public company, web link
S4 *EarlyCDT®-Lung* kit obtains CE mark, web link
S5 Acquisition of Protagen, web link
S6 Oncimmune secures a contract with Roche Pharmaceuticals, web link
S7 Oncimmune announces deal with Genentech, web link
S8 Letter of support from former CMO and CSO for Scotland.
S9 NICE Medtech Innovation Briefing 'EarlyCDT-Lung for cancer risk classification of indeterminate pulmonary nodules', 17 March 2020, web link
S10 Edelsberg et al., Cost-effectiveness of an autoantibody test (*EarlyCDT®-Lung*) as an aid to early diagnosis of lung cancer in patients with incidentally detected pulmonary nodules. PLoS One, 2018, doi.org/10.1371/journal.pone.0197826
S11 Sutton et al., Cost-effectiveness of a new autoantibody test added to Computed Tomography (CT) compared to CT surveillance alone in the diagnosis of lung cancer amongst patients with indeterminate pulmonary nodules. PLoS One, 2020, doi.org/10.1371/journal.pone.0237492