Institution: University of York		
Unit of Assessment: 12 - Engineering		
Title of case study: Intelligent medical devices for reducing healthcare costs and improving the quality of life of people with Parkinson's		
Period when the underpinning research was undertaken: Oct 2005 – Sep 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:**
Prof. Stephen L. Smith	Professor	Jan 1994 – present
Dr. Michael A. Lones	Research Associate	Jan 2005 – Oct 2013
Prof. A. M. Tyrrell	Professor	Apr 1990 – present
Period when the claimed impact occurred: Aug 2013-Dec 2020		
Is this case study continued from a case study submitted in 2014? N		

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

ClearSky Medical Diagnostics Ltd., University of York spinout (2013), markets clinically validated, regulatory compliant (CE Marked) medical devices to reduce healthcare costs and improve the quality of life of people with Parkinson's. These have been used to assess over 600 patients in the UK and China where a saving of 24 hours of nursing time per patient consultation has been achieved. The devices, that combine novel machine learning algorithms (developed by Prof. Smith, University of York) with commercially available hardware, have also been used in clinical trials to provide an objective assessment of repurposed drugs for delaying and even halting neurodegeneration.

2. Underpinning research (indicative maximum 500 words)

Conventional diagnosis and monitoring of neurodegenerative disorders, such as Parkinson's, is highly subjective, relying solely on a clinician's observations against a rating scale, and occasionally, expensive brain scans. Research undertaken by Prof. Smith's group since 2005 at York, has overcome these limitations by employing a non-invasive and objective assessment using novel machine learning.

The underpinning research comprises two biologically inspired algorithms: Implicit Context Representation Cartesian Genetic Program (IRCGP) and Artificial Biochemical Networks (ABNs).

IRCGP is an evolutionary algorithm developed in 2005 by Smith. Its advantages over traditional forms of evolutionary algorithms, based around its implicit context representation, have been reported in a series of investigations conducted by Smith's group [3.1]. The use of these algorithms to reliably diagnose Parkinson's disease patients demonstrated by Smith in clinical studies undertaken at the Royal Liverpool and Broadgreen Hospitals in 2007 [3.2], Leeds General Infirmary in 2011 [3.3] and Ruijin Hospital, China in 2017 [3.4], has transformed the conventional clinical "finger-tapping test", revealing microscopic movements in Parkinson's patients that are invisible to the naked eye.

ABNs are a class of computational architectures inspired by the function and organisation of biochemical networks. ABNs were developed at York by Lones and Tyrrell from 2008-13 as part of the EPSRC AlBiNo project [3.5] and can be coupled to complex dynamical systems, performing difficult computational behaviours such as control and classification. When combined with IRCGP these algorithms can discriminate between Parkinson's disease patients and age-matched controls with accuracies exceeding 90% - a significant improvement on existing diagnostic accuracy of 75% [3.6].

These biologically inspired machine learning algorithms have been integrated with commercially available hardware such as electromagnetic tracking sensors and accelerometers to record, worldwide, over 700 patients' movements in detail as they perform a variety of conventional clinical tasks. The result is a technology that facilitates measurement of a host of patient groups,

including Parkinson's disease, Alzheimer's disease, Progressive Supranuclear Palsy, Multiple System Atrophy, Essential Tremor and Dystonia.

This research improves on previous technologies in two important ways:
(i) The biologically inspired machine learning algorithms have been trained to differentiate between neurodegenerative conditions with a higher degree of accuracy than can be achieved using traditional signal processing algorithms or conventional clinical evaluation and are less susceptible to variations in patients' motor function ability.
(ii) Integrating low cost, commercially available wireless sensors, permits diagnosis and monitoring to be taken out of the laboratory and into conventional clinical settings such as hospital day clinics and the patient's home, to facilitate reliable and immediate assessment [3.4].
These advancements have made the technology particularly suitable for use in routine diagnosis and monitoring of patients, the evaluation of new drugs and therapies. It has led to repeated funding from the Royal Academy of Engineering including an Enterprise Fellowship to Smith in 2013 to launch ClearSky Medical Diagnostics Ltd. making the technology commercially available.

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

3.1. Smith SL, Lones MA. Implicit context representation Cartesian genetic programming for the assessment of visuo-spatial ability. In 2009 IEEE Congress on Evolutionary Computation. May 2009; 18;1072-1078. DOI: 10.1109/CEC.2009.4983065.

3.2. Smith SL, Gaughan P, Halliday DM, Ju Q, Aly NM, Playfer JR. Diagnosis of Parkinson's disease using evolutionary algorithms. Genetic Programming and Evolvable Machines. Dec 2007. 8(4):433-47. DOI: doi.org/10.1007/s10710-007-9043-9

3.3. Lones MA, Alty JE, Cosgrove J, Duggan-Carter P, Jamieson S, Naylor RF, Turner AJ, **Smith SL**. A new evolutionary algorithm-based home monitoring device for Parkinson's Dyskinesia. Journal of medical systems. Sep 2017. 41(11):176. doi.org/10.1007/s10916-017-0811-7

3.4. Gao C, **Smith S**, **Lones M**, Jamieson S, Alty J, Cosgrove J, Zhang P, Liu J, Chen Y, Du J, Cui S. Objective assessment of bradykinesia in Parkinson's disease using evolutionary algorithms: clinical validation. Translational neurodegeneration. Aug 2018; 7(1):18. doi.org/10.1186/s40035-018-0124-x

3.5. Lones MA, Fuente LA, Turner AP, Caves LS, Stepney S, **Smith SL**, **Tyrrell AM**. Artificial biochemical networks: Evolving dynamical systems to control dynamical systems. IEEE Transactions on Evolutionary Computation. Apr 2014;18(2):145-66. DOI: 10.1109/tevc.2013.2243732

3.6. Lones MA, **Smith SL**, Alty JE, Lacy SE, Possin KL, Jamieson DS, **Tyrrell AM**. Evolving classifiers to recognize the movement characteristics of Parkinson's disease patients. IEEE Transactions on Evolutionary Computation. Aug 2014; 18(4):559-76. DOI: 10.1109/TEVC.2013.2281532

[3.1 - 3.6] Peer reviewed publication; [3.5] [3.6] Returned to REF2014; [3.3] [3.4] Returned to REF2021; [3.3] Won the ACM 2018 Gold Award for Human-Competitive Results (https://arxiv.org/pdf/1810.09416.pdf)

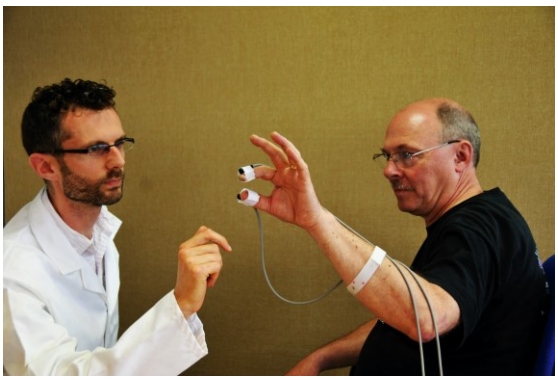
4. Details of the impact (indicative maximum 750 words)

The biologically inspired computer algorithms developed by Smith and colleagues at the University of York, have led to the creation of two clinically validated and regulatory compliant (CE Marked) products marketed by ClearSky Medical Diagnostics [5.1].

LID-Monitor- Recognition and Monitoring of Levodopa-induced Dyskinesia
Protected by patent WO2014009757A1. Granted in Europe (2019) EP2872041B1.

This CE-Marked system has been used by Leeds General Infirmary, Harrogate and Scarborough hospitals in the UK [5.2] and Ruijin Hospital, Shanghai [5.3] to monitor Parkinson's disease patients in their own homes and inform the management of their medication. The most effective form of treatment for Parkinson's disease symptoms is a drug called levodopa, but approximately 90% of patients who take it for ten years or more develop severe side effects including involuntary movements called dyskinesia, a major source of disability severely affecting the patient's quality of life. In conventional practice, physicians rely on patients' own descriptions or, in severe cases, patients are admitted to hospital for several days, to monitor symptoms and adjust their medication accordingly. This system provides an objective measure of dyskinesia over extended time periods permitting a better-informed course of medication, thereby reducing unplanned hospital admissions, consultations and greatly improving the patient's quality of life.

PD-Monitor - Objective Assessment and Monitoring of Parkinson's Disease
Protected by patent WO2012098388A1. Granted in Europe (2020) EP2666120B1, United States (2017) US9615776B2, China (2018) CN103430192B, Canada (2019) CA2825082C, and Australia (2017) AU2012208360B2.



This novel non-invasive CE-Marked device, used in 12 hospitals in the UK [5.2, 5.8, 5.9, 5.10], USA [5.4, 5.5], Australia [5.6] and China [5.3], confirms diagnosis of Parkinson's disease by digitally measuring patients performing a simple finger tapping test used in conventional clinical evaluation. This allows microscopic movements, invisible to the human eye, to be identified that characterise the symptoms of Parkinson's disease in a way that has not previously been possible.

These products have had significant impacts in the following areas:

i) Monitoring the effectiveness and side effects of prescribed medication.
LID-Monitor has been introduced to assess the clinically most challenging Parkinson's disease patients in their own homes [5.2]. By undertaking objective measurements which can be instantly relayed to consultants, freeing up their time whilst maintaining close monitoring of their patients' condition. "This technology provides objective, reliable measurements that can be easily assessed by health professionals to inform management of patients with Parkinson's disease. Real benefits, such as reducing specialist consultations, hospital admissions and time spent in hospital have now been realised" says consultant neurologist at Leeds Nuffield Hospital and recently of Leeds General Infirmary (retired 31st May 2020) [5.2]. A health economic assessment undertaken by the York Health Economic Consortium (YHEC) Ltd. in 2015 found that implementing LID-Monitor countrywide will result in a dominant incremental cost-effectiveness ratio (ICER) and an annual net monetary benefit (NMB) of over GBP84,000,000 for the whole of England [5.7].
In China, it is common for Parkinson's disease patients to be under-medicated to reduce the disruptive effect of dyskinesia, making management in the home easier. However, this comes at the expense of a patient's quality of life, since under-medication leads to 'off' periods where a

person will hardly be able to move at all, making everyday tasks impossible [Parkinson's UK]. The use of LID-Monitor in China has allowed higher doses of medication to be prescribed, improving the quality of life of patients, without the disruptive side-effects affecting care in the home. "With the remote technology of LID-Monitor, we can, from the hospital in Shanghai, acquire detailed information about the responses of patients to medication within their own homes instead of patients and their carers often with children who have to ask for a day's leave from work traveling to us. The use of LID-monitor has also saved 24 hours of nursing per user. So not only is there cost saving directly on the healthcare system, there is indirect saving on productivity when family members, the carers' time is considered." – Consultant Neurologist and Director of Neurology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine [5.3].

ii) Improving access to specialist care in remote and rural China

In China 4,900,000 people are expected to have Parkinson's by 2030, many of whom live in remote and rural areas with little access to specialist care – this also includes areas in the metropolis of Shanghai (population 24,280,000). Introduction of PD-Monitor has made a significant impact on the care these patients now receive. "The use of the devices has made a significant change in our medical practice and care of PD patients, especially those that are living far away from my center including those who have to travel from another city to seek specialist care. We have now used the devices on over 300 patients through a number of programs and research initiatives including a recent screening program carried out in partnership with a community in Shanghai this year where we used PD-Monitor to screen 170 senior residents in that community." – Consultant Neurologist and Director of Neurology Ruijin Hospital, Shanghai Jiao Tong University School of Medicine [5.3].

iii) Determining the efficacy of repurposed drugs for slowing the progression of Parkinson's

Studies across the UK are investigating the potential of repurposed drugs to slow down or even halt the progression of Parkinson's disease. One of the greatest challenges in undertaking these studies is assessing the efficacy of the respective drug on the progression of Parkinson's as conventional clinical assessment is imprecise and unreliable as it based upon subjective observation. PD-Monitor has demonstrated the ability to provide an objective assessment with higher precision and is therefore critical in determining the true benefits of these repurposed drugs.

From July 2017- March 2020 PD-Monitor was used throughout the UK as part of a national study (PD-STAT) to determine the effectiveness of simvastatin (a drug conventionally used to reduce cholesterol) as a neuroprotector in seven NHS Trusts (Derriford Hospital, Plymouth; Royal Cornwall Hospital, Truro; St Peter's Hospital, Chertsey; Royal Free Hospital, London; John Radcliffe Hospital, Oxford; Addenbrookes Hospital, Cambridge; Clinical Ageing Research Unit, Newcastle) [5.8]. Since January 2020, PD-Monitor has also been used in two further clinical trials: AZA-PD - investigating the beneficial effects of azathioprine as an immunosuppressor for people with Parkinson's at Addenbrookes Hospital and the University of Cambridge [5.9]; and Exenatide-PD, a glucagon-like peptide-1 receptor agonist, at King's College Hospital NHS Foundation Trust, University College London Hospitals NHS Foundation Trust (UK) and UCL [5.10].

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1. ClearSky Medical Diagnostics Ltd. Web Site - www.clearskymd.com
5.2. Corroboration Letter: Consultant Neurologist, Leeds Nuffield Hospital and recently of Leeds General Infirmary, UK.
5.3. Corroboration Letter: Consultant Neurologist and Director of Neurology, Ruijin Hospital, Jiao Tong University School of Medicine, Shanghai, China.
5.4. Alty JE, Cosgrove J, Lones MA, Smith SL, Possin K, Schuff N, Jamieson S. Clinically 'slight' bradykinesia in Parkinson's disease is accurately detected using evolutionary computation analysis of finger tapping. Mov Disord. 2016, Jun 1; 31.

5.5. Lacy SE, Lones MA, Smith SL, Alty JE, Jamieson DS, Possin KL, Schuff N. Characterisation of movement disorder in Parkinson's disease using evolutionary algorithms. In Proceedings of the 15th annual conference companion on Genetic and evolutionary computation 2013, Jul 6 (pp. 1479-1486).
5.6. Muhamed SA, Newby R, Smith SL, Alty JE, Jamieson S, Kempster P. Objective Evaluation of Bradykinesia in Parkinson's Disease using Evolutionary Algorithms. In BIOSIGNALS 2018 (pp. 63-69).
5.7. Filby A, Lewis L, Taylor M, Smith SL, Dettmar PW, Jamieson SD, Alty JE. Cost Effectiveness Analysis of a Device to Monitor Levodopa-Induced Dyskinesia in Parkinson's Patients. Value in Health. 2015 Nov 1;18(7):A358
5.8. Chief Investigator, PD-STAT Clinical Trial, Peninsula Medical School, University of Plymouth. https://www.plymouth.ac.uk/research/parkinsons/applied-parkinsons-research/pd-stat-simvastatin-as-a-neuroprotective-treatment-for-parkinsons-disease
5.9. Chief Investigator, AZA-PD Clinical Trial, Department of Clinical Neurosciences, University of Cambridge. https://ccpp.cam.ac.uk/ClinicalTrials/clinical-trial-b-azathioprine
5.10. Chief Investigator, Exenatide-PD Clinical Trial, Queen Square Institute of Neurology, University College London. https://www.ucl.ac.uk/comprehensive-clinical-trials-unit/research-projects/2021/jan/exenatide-parkinsons-disease