**Institution:** University of Kent

**Unit of Assessment:** 9: Physics

**Title of case study:** Improving Medical Diagnostics and Enabling Stakeholders to Access the OCT Market

**Period when the underpinning research was undertaken:** 2000-2019

**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. Adrian Podoleanu | Professor, Head of the Applied Optics Group (AOG) | 1993 onwards |
| Dr Adrian Bradu | RA, then Lecturer | 2001 onwards |
| Dr George Dobre | Lecturer, then Senior Lecturer | 1997 onwards |

**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** (indicative maximum)

Research undertaken by the Applied Optics Group (AOG) in the School of Physical Sciences (SPS) at the University of Kent has provided the impetus for new commercial developments in Optical Coherence Tomography (OCT) and enabled the exploitation of broadband lasers for medical diagnostics. In both cases, novel diagnostic instruments were developed, which are now routinely used in clinics. Instruments building on *en-face* OCT technology (in particular the AngioVue and the Solix developed by Optovue) enable better management of conditions such as diabetic retinopathy, age-related macular degeneration, and glaucoma. This now benefits millions of people across the world. Laser technology, in turn, has improved skin cancer diagnostics for thousands at Bispebjerg Hospital (Denmark). Through knowledge transfer and collaborations with the AOG, four different companies that are involved in developing medical diagnostic instruments have directly benefited. NKT (a world-leading niche market company for supercontinuum lasers), for example, has gained improved access to the OCT market (worth $1bn USD).

**2. Underpinning research** (indicative maximum 500 words)

The diagnosis and treatment of various medical conditions ranging from glaucoma to skin cancer relies on accurate imaging technologies. The University of Kent's Applied Optics Group (AOG) is generating and advancing the knowledge behind such technologies. AOG research is twofold, focusing on the development of *en-face* OCT on the one hand, and the exploitation of laser technology for the advancement of OCT on the other.

**Strand 1: *en-face* OCT**

The AOG is at the forefront of fundamental research into Optical Coherence Tomography (OCT). By the early 2000s, OCT was widely accepted as a paradigm-changing methodology in ophthalmology, but could not yet be fully exploited. To address this issue, work at Kent since 2000 developed platforms for multiple parallel imaging channels, which made the new OCT method easier to understand, provided *en-face* high-resolution imaging in real time, and led to the development of OCT/SLO (*en-face* confocal scanning ophthalmoscopy). Pioneering Kent instrumentation **[P1]** provided a new method for detecting the appearance of eye lesions, which changed the paradigm and methodology of image-based diagnostics. Features from OCT and conventional confocal images could now be matched to assess the lateral extent of various retinal lesions crucial to sight, which led to simpler and more effective diagnosis.

Commercial versions of the OCT/SLO *en-face* instrument were being developed by all major OCT manufacturers from 2008 onwards.

Research by AOG since 2003 further demonstrated that clinical OCT and angiography data from patients can be acquired and viewed simultaneously in the *en-face* mode **[R1]**. This paved the way for the development of OCT Angiography (OCTA). Clinicians currently regard OCTA as the method of choice alongside OCT reflectance imaging. OCTA enables non-invasive examinations of the structural, vascular, and functional features of the retina by using the *en-face* OCT orientation to demonstrate correlations between structural and functional information.

**Strand 2: OCT and laser technology**

Two key challenges of OCT imaging were the pursuit of better depth resolution and imaging in different spectral bands, both of which could ultimately be overcome through utilising supercontinuum lasers. Supercontinuum lasers emit broadband radiation, which improves resolution but generates noise. The AOG's research since 2009 improved noise performance of supercontinuum lasers, known for their broadband spectral emission **[R2, R3]**, thus making them a contender for the more established swept lasers to power OCT instrumentation in clinical dermatology **[R4]**. Since 2013, the AOG has been collaborating with NKT Photonics Ltd (a world leader in high-performance fibre lasers and photonic crystal fibres) to advance knowledge and to enable NKT to progress supercontinuum technology to ultra-high-resolution OCT and photoacoustics. The latter complements the multimodal aspects that can be addressed with supercontinuum sources. Through the collaboration with NKT, supercontinuum lasers, which are required by the OCT community for low-noise, high-axial resolution, as well as to build the next generation of versatile multi-modality imagers with high-power broadband emission, were developed **[R2, R3, R4]**.

Since 2015, and in collaboration with the Danish Technical University (DTU) and NKT, Professor Podoleanu, a co-investigator for ShapeOCT, further helped to drive gains in the OCT performance of supercontinuum sources, demonstrating the fastest OCT at new spectral limits in the mid-infrared (4 μm) **[R5]**.

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

**[R1]**: Rosen, R. B, M., Hathaway, J., Rogers, J., Pedro, G., Laissue, Patricia P., **Dobre**, **G. M.**, and **Podoleanu, A.** (2009). Multidimensional *en-face* OCT imaging of the retina. *Optics Express*, 17: 5, pp. 4112-4133. doi: http://dx.doi.org/10.1364/OE.17.004112

**[R2]**: Bondu, M., Lall, G. S., Marques, M. J., Moselund, P. M., **Bradu, A.**, and **Podoleanu, A.** (2017). Multispectral photoacoustic microscopy and optical coherence tomography using a single supercontinuum source. *Photoacoustics,* 9, pp. 21-30. doi: https://doi.org/10.1016/j.pacs.2017.11.002

**[R3]**: Jensen, M., Gonzalo, I. B., Engelsholm, R. D., Maria, M., Israelsen, N. M., **Podoleanu, A.**, and Bang, O. (2018). Noise of supercontinuum sources in spectral domain optical coherence tomography. *Journal of the Optical Society of America,* 36:2, pp. 154-160. doi: https://doi.org/10.1364/JOSAB.36.00A154

**[R4]**: Israelsen, N. M., Maria, M., Mogensen, M., Bojesen, S., Jensen, M., Haedersdal, M., **Podoleanu, A.**, and Bang, O. (2018). The value of ultrahigh resolution OCT in dermatology: delineating the dermo-epidermal junction, capillaries in the dermal papillae and vellus hairs. *Biomedical Express,* 9, pp. 2240-2265. doi: https://doi.org/10.1364/BOE.9.002240

**[R5]**: Israelsen, N. M., Petersen, C. R., Barh, A., Jain, D., Jensen, M., Hannesschläger, G., Tidemand-Lichtenberg, P., Pedersen, C., **Podoleanu**, **A.**, and Bang, O. (2019). Real-time High-Resolution Mid-infrared Optical Coherence Tomography. *Light Science and Applications*, 8:1. doi: https://doi.org/10.1038/s41377-019-0122-5

**Patents**

**[P1]**: 'Optical mapping apparatus with adjustable depth resolution and multiple functionality', WO2004002298A1, Pub. date: 08/01/2004. Inventors: **A. Podoleanu, D. A. Jackson, J. A. Rogers, G. Dobre,** and **R. Cucu**. Link: https://kar.kent.ac.uk/85748/

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

The advancement of *en-face* and laser technology by the University of Kent's AOG has led to: (1) impact on commerce and the economy (for OPTOS, NKT, Optovue, DTU/Norblis); (2) impact on health and wellbeing, with millions of people benefiting from advancements in *en-face* OCT and several thousand people benefiting from enhanced laser technology.

**Advancing *en-face* OCT: Development of new medical devices, driving diagnostic standards and improving identification and treatment of occult diseases**

In 2011, OPTOS bought OPKO and thus acquired Kent's OCT/SLO, the first combined Scanning Laser Ophthalmoscopes (SLO) and OCT instruments designed to provide retinal images in the *en-face* orientation for the diagnosis of eye diseases **[P1]**. *En-face* gradually became the standard imaging modality in hospitals (with competitors such as Zeiss and Optovue also having started to develop *en-face* orientation technology). OPTOS continued to sell the original OCT/SLO device to clinics around the world until 2016 **[a]**. As part of its R&D plan, OPTOS continues to maintain many of the 'two dozen patents and patent applications [protecting the original OCT/SLO technology, which name Kent inventors]' **[a]**.

The collaboration between the University of Kent's AOG and Rosen **[R1]**, Vice-Chair of Ophthalmology Research, Surgeon Director at the New York Eye and Ear Infirmary (NYEEI), advanced *en-face* OCT technology further still, and led to OCTA being implemented in the clinical context. OCTA offers additional benefits because it is the first non-invasive imaging technique that enables visualisation of vascular networks in the human retina, choroid, skin, etc. Since 2015, this 'landmark discovery' **[b, c]** has enabled an even 'more accurate identification of occult diseases' **[b]**. OCTA has 'revolutionized the clinician's access to non-invasive 3-dimensional vascular beds as a quantitative tool for management of diabetic retinopathy, age-related macular degeneration, and glaucoma' **[b]**. This is significant, given how widespread these diseases are. The projected number of people with age-related macular degeneration alone is 196 million in 2020, increasing to 288 million in 2040.

OCTA has inspired other groups across the globe to develop similar instruments, thus making multimodal images a new standard in the field **[b]**. Rosen further states that Prof. Podoleanu's work 'has inspired a whole new generation of young clinicians' **[b]**, and that it 'has been a crucial stimulus for our own research and clinical missions at NYEEI_MS as well as our partner organizations' **[b]**. The joint work between the University of Kent's AOG and the NYEEI 'has helped to improve the diagnosis prospects for millions of patients since we began in 2000 to the current day' **[b]**.

The CEO at Optovue, an industry-leading ophthalmic company based in California, has also testified to the importance of the AOG's work. With regards to product development and determining a business strategy, the company has been 'guided by the enface OCT images and the combined display of enface OCT with angiography images initially demonstrated by Podoleanu and Rosen' **[c]**. Optovue became the first company to launch and commercialise OCTA instruments, and started to sell their AngioVue instrument in 2014. 'This was a major change in our market strategy that paid off, with the AngioVue installed in more than 1600 ophthalmic practices worldwide' **[c]**. It is estimated that one machine can diagnose 1,000 patients per year, meaning that 1.6 million people were benefiting from the AngioVue on an annual basis by 2020. By 2020, Optovue had in addition to this launched Solix, another new OCTA machine that comes with increased scanning speed. 'Solix is the latest in a range of OCTA instruments which we have been commercialising since 2014, and which owe their existence to the original discovery work of the en-face imaging collaboration of Prof. Adrian Podoleanu and Dr Richard Rosen since 2000.' **[c]**

Furthermore, Centervue has 'contributed to the costs for prosecution of the patents protecting Kent's Master Slave OCT', a powerful and paradigm-changing technology that enables direct *en-face* real-time displays **[d]**, showing that significant interest in the exploitation of AOG-developed technology is continuing.

**OCT and laser technology: improving skin cancer diagnostics**

Sustained and increasing collaboration between the AOG and NKT Photonics has increased NKT's understanding of the OCT market, and since 2014 helped to steer research at NKT **[e]**. Senior Research Scientist Patrick Bowman stated that joint research programs are important not only because they 'drive state-of-the-art research into next-gen lasers for OCT' **[e]**, but also because they enable the company to receive knowledge with regards to how to improve products and indications as to which technical improvements to lasers will be important to OCT in the future. 'As a niche laser supplier, with a small revenue compared to the overall size of the OCT market, the latter is critical for NKT to decide whether or not to compete in certain areas' **[e]**.

Joint work between the AOG and NKT provided NKT with a unique commercial advantage, enabling them 'to progress the supercontinuum technology to ultra-high resolution optical coherence tomography' **[e]**. As a consequence, NKT could enhance their lasers and improve their access to the OCT market valued at $1bn USD **[e]**. In parallel, AOG, NKT, and the Danish Technical University (DTU) advanced the technology of photo-acoustics **[e]**. This is another significant, growing market. 'To give estimates, the value of photo-acoustic imaging in its pre-clinical stage in 2018 was $35M USD. Now on the cusp of wide- spread clinical testing, it is estimated to reach a market value of $240M USD by 2022' **[e]**.

Collaborations between the AOG, DTU, and NKT have led to the training of 5 PhD students (2014-18) in an industrial setting, and enabled NKT 'to extend our collaborators to OPTOS and G&H, and clinical practitioners such as Northwick Park Hospital, London and Moorfields Eye Hospital (Institute of Ophthalmology), London', as well as various hospitals in Denmark **[e]**. Ear, Nose, and Throat surgeons at Northwick Park have benefited from 'having the opportunity to directly guide the development of new technology to suit requirements for some of our surgical interventions', while 'Post-doctorate and PhD students have been hosted both from The University of Kent and Imperial College London as part of our Trust's applied optical imaging programme' **[h]**. It also led DTU 'to pay more attention to the OCT field' **[g]**, to continue collaborating with Podoleanu and the AOG, to diversify their involvement with OCT, and to create their spin-out company Norblis (2018), which makes imaging equipment using broadband lasers in mid-IR **[g]**.

The most significant clinical impact resulting from the various collaborations between AOG and DTU was achieved with Bispebjerg Hospital in Copenhagen. This collaboration **[R2-R4]** enabled Bispebjerg Hospital to obtain images of skin cancer with 'unprecedented resolution' **[f]**. As Mette Mogensen's (Chief Physician at Bispebjerg) letter proves, medical practitioners are now embracing high-resolution OCT as 'novel systems with improved imaging performance' **[f]**. Mogensen stated that the collaboration with DTU and Kent 'improved the diagnostic prospects for thousands of patients' **[f]**, and that discussions with Professor Podoleanu 'have had a significant impact on our understanding of diagnostic imaging and technical limitations and benefits' **[f]**.

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

**[a]** Letter from the research director at Optos demonstrating that sales of OCT/SLO continued until 2016, and that patents are continuing to be maintained beyond this for R&D.

**[b]** Letter from the Vice-Chair of ophthalmology research and surgeon director at New York Eye and Ear Infirmary Mount Sinai, testifying that OCTA has improved diagnostics of occult

diseases since 2015, and that it inspired groups around the world to develop medical instruments.

**[c]** Letter from the founder of Optovue testifying that Optovue has commercialised OCTA instruments since 2014, in particular the AngioVue and the Solix.

**[d]** Letter from the General Manager at Centervue showing that interest in exploitation of Kent's AOG research continues.

**[e]** Letter from the senior research scientist at NKT, evidencing that the collaboration between AOG and NKT helped to steer research at NKT, improving NKT's access to the OCT market.

**[f]** Letter from a consultant at Bispebjerg Hospital, Copenhagen, testifying that the collaboration between AOG, DTU, and Bispebjerg Hospital led to improved imaging of skin, which improves skin cancer diagnostics at Bispebjerg Hospital.

**[g]** Letter from a Professor at DTU evidencing that DTU gained an improved understanding of the OCT market because of collaboration with AOG, which fed into the establishing of their spin-out company Nobrilis.

**[h]** Letter from Northwick Park Hospital evidencing that Northwick Park Hospital has been an associate partner of the European Industrial Doctorate (2014-18) and the NETLAS Training Network, and that these programmes provided opportunities to guide the development of the technology.