Institution: The University of Liverpool		
Unit of Assessment: UoA12 Engineering		
Title of case study: Non-invasive diagnosis and treatment of vision threatening conditions		
Period when the underpinning research was undertaken: 2010 – 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Names(s):	**Roles(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
A Elsheikh	Professor	2010 – present
A Eliasy	Research Assistant	2015 – present
BT Lopes	Research Assistant	2017 – present
R Vinciguerra	Honorary Research Assistant	2016 – 2019
A Joda	Research Assistant	2012 – 2014
A Abass	Lecturer	2017 – present
Period when the claimed impact occurred: 2016 – 31st July 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Healthcare technologies developed in Liverpool and incorporated into commercially-available instruments have made an impact on the diagnosis and treatment of two vision threatening conditions, glaucoma and keratoconus. Innovative research on ocular deformation under an air jet has allowed simultaneous characterisation of eye pressure and corneal biomechanical behaviour, in two novel biomechanical parameters: biomechanically corrected intraocular pressure (bIOP) and stress-strain index (SSI) for the material of the cornea. The accurate determination of bIOP and SSI is now possible using the non-contact instrument, CorVis ST produced by Oculus and sold worldwide since 2016. The sensitivity of the instrument supports early detection while its accuracy improves the quality of diagnoses. The technology is benefitting hundreds of thousands of patients per year including 30,000 in China alone.

2. Underpinning research

2.1 Background and context

The research at the University of Liverpool addressed two long-standing problems with significant ocular health implications, namely the measurement of the eye's internal pressure and the estimation of the cornea's biomechanical behaviour. The inability to measure eye pressure accurately resulted in poor outcomes of glaucoma management, a prevalent, severe and asymptomatic disease, where eye pressure is the main modifiable risk factor. Ineffective management meant that 15% of glaucoma patients lose their eyesight despite treatment. The further inability to estimate the cornea's biomechanical behaviour, made it difficult to diagnose keratoconus (a genetic disease, causing loss of corneal stiffness and progressive ocular distortion) at an early stage, before serious loss of clear sight takes place.

Collaboration with Oculus Optikgeraete GmbH started in 2013 to address these two needs. The development in Liverpool of two new biomechanical parameters, namely biomechanically corrected intraocular pressure (bIOP) and corneal material stiffness estimates using a Stress-Strain Index (SSI), presented the opportunity to use non-contact technology to produce a more

accurate and sensitive instrument and therefore to turn the CorVis ST into a powerful diagnostic and management tool for serious vision-threatening conditions.

2.2 Underpinning research

The research was led by Professor Ahmed Elsheikh, and carried out by Liverpool's Biomechanical Engineering Group, from 2010, and benefitted from funding by the National Institute of Health Research, the EPSRC and, from 2013, Oculus. It was based on a combination of representative numerical simulations, experimental validation (using ex-vivo human donor eyes) and clinical validation. The main outcomes were innovative methods that use the profile of ocular deformation under the action of an external air jet to produce estimations of both eye pressure [3.1, 3.2] and corneal biomechanical behaviour [3.3]. The methods developed in Liverpool were validated comprehensively by a group of clinicians from the USA, Italy, Brazil, South Korea and China (in 2015-2016), and later implemented in the CorVis ST operating software in August 2016 by Oculus, Figure 1 [3.3 – 3.5].

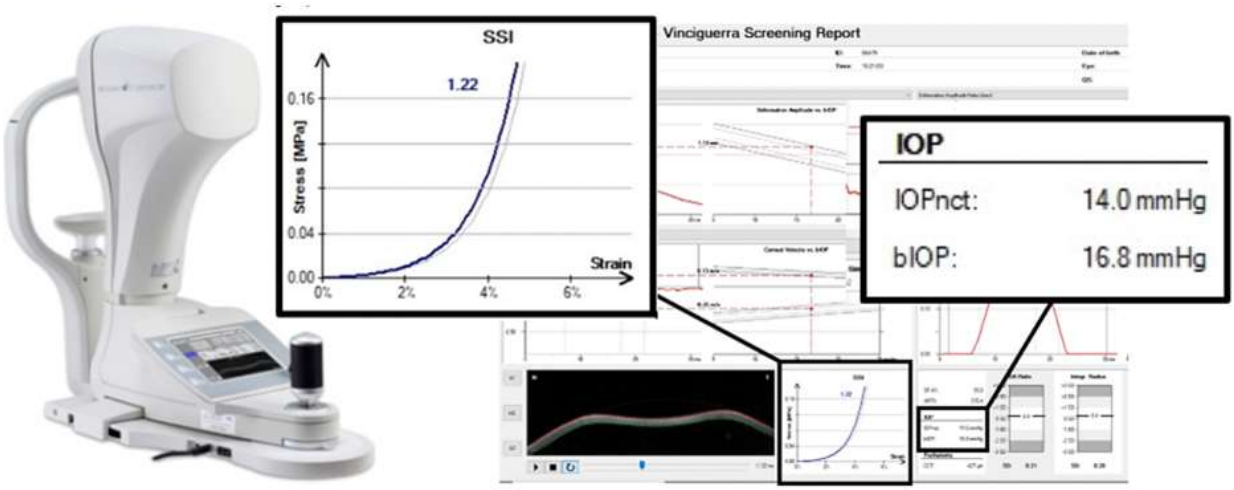

Figure 1 A CorVis ST instrument (left) sold worldwide by Oculus and a typical set of results from the instrument (right) showing non-contact estimations of biomechanically-corrected IntraOcular Pressure (bIOP) and a Stress-Strain Index (SSI) describing the material behaviour of the cornea

The success of these methods allowed the Liverpool group in 2017, with collaborators in Brazil, Italy and the USA, to develop, using statistical analyses, two new clinical parameters (Corneal Biomechanical Index, CBI [3.4], and Topography-Biomechanics Index, TBI [3.5, 3.6]) for detection and risk profiling of keratoconus in its early stages. With these parameters, it has been possible to detect and treat the disease (by cross-linking the cornea) to prevent its progression and most subsequent corneal distortion and loss of clear vision.

3. References to the research

3.1 Joda AA, Shervin MMS, Kook D, Elsheikh A, *Development and Validation of a Correction Equation for CorVis Tonometry*, Computer Methods in Biomechanics and Biomedical Engineering, 2015; 19(9): 943-953, https://doi.org/10.1080/10255842.2015.1077515

3.2 Chen K-J, Eliasy A, Vinciguerra R, Abass A, Lopes BT, Vinciguerra P, Ambrósio Jr. R, Roberts CJ, Elsheikh A, *Development and Validation of a new Intraocular Pressure Estimate for Patients*

with Soft Corneas, Journal of Cataract and Refractive Surgery, 2019; 45: 1316-1323, doi: 10.1016/j.jcrs.2019.04.004

3.3 Eliasy A, Chen KJ, Vinciguerra R, Lopes BT, Abass A, Vinciguerra P, Ambrósio Jr. R, Roberts CJ, Elsheikh A, *Determination of Corneal Biomechanical Behaviour in-vivo for Healthy Eyes Using CorVis ST Tonometry: Stress-Strain Index*, Frontiers in Bioengineering and Biotechnology, 2019; 7: Article 105, https://doi.org/10.3389/fbioe.2019.00105

3.4 Vinciguerra R, Ambrósio Jr. R, Elsheikh A, Roberts CJ, Lopes B, Morenghi E, Azzolini C, Vinciguerra P, *Detection of Keratoconus with a new CorVis ST Biomechanical Index*, Journal of Refractive Surgery, 2016; 32(12): 803-810, https://doi.org/10.3928/1081597X-20160629-01

3.5 Roberts CJ, Mahmoud AM, Bons JP, Hossain A, Elsheikh A, Vinciguerra R, Vinciguerra P, Ambrósio Jr. R, *Introduction of Two Novel Stiffness Parameters and Interpretation of Air Puff Induced Biomechanical Deformation Parameters with a Dynamic Scheimpflug Analyzer*, Journal of Refractive Surgery, 2017; 33(4): 266-273, https://doi.org/10.3928/1081597X-20161221-03

3.6 Ambrósio Jr, R, Lopes B, Faria-Correia F, Salomão MQ, Bühren J, Roberts CJ, Elsheikh A, Vinciguerra R, Vinciguerra P, *Integration of Scheimpflug-based Corneal Tomographic and Biomechanical Assessments for Enhancing Ectasia Detection*, Journal of Refractive Surgery, 2017; 33(7):434-443, https://doi.org/10.3928/1081597X-20170426-02

Awards

The paper on the development of the CBI [3.4] was recognised by the International Society of Refractive Surgery in 2017 with the award to one of the authors, Dr Ricardo Vinciguerro, of the Troutman Prize. This 'recognizes the scientific merit of a young author publishing in the Journal of Refractive Surgery'; https://www.isrs.org/about-isrs/awards

Funding

- PI: Elsheikh A, H2020, Project: Imaging-based Customised Eye diagnostics (IMCUSTOMEYE), 2017-2020, €812,000
- PI: Elsheikh A, "Further development of the CorVis ST non-contact tonometer", Oculus Optikgeraete GMBH, 2013-2016, GBP138,860
- PI: Elsheikh A, "Development of an intraocular pressure measurement device for glaucoma management", National Institute for Health Research (Health Technology Development Programme - HTD539), 2010-2014, GBP836,062.

4. Details of the impact

The new technologies developed in Liverpool and incorporated into the CorVis ST non-contact tonometer have made impact on the diagnosis and treatment of two vision-threatening conditions; glaucoma and keratoconus.

Greater accuracy of glaucoma treatment

Glaucoma affects 79m people worldwide (480,000 in England) and if not treated, can lead to irreversible blindness. The disease is associated with elevated intraocular pressure (IOP), causing pressure on the optic nerve head and damaging the nerves linking the light-sensitive cells of the retina to the brain. The main modifiable risk factor for glaucoma is IOP and therefore the accurate measurement of IOP is essential for adequate treatment of the disease. Until recently, all IOP measurement techniques were influenced by the stiffness of the cornea, and the resulting inaccuracies have led to both false negatives and false positives in glaucoma risk profiling. Poor measurement has also meant that 15% of glaucoma patients eventually lose their eyesight within

15 years whilst under treatment. The new bIOP measurement developed in Liverpool [3.2] became available with the CorVis ST produced by Oculus in 2016 and is being used in clinical centres in many countries including Brazil, China, Germany, Iran, Italy and South Korea. Follow-up studies have confirmed the stability and repeatability of the bIOP readings and encouraged more clinicians to rely on them in glaucoma management instead of the reference standard – the Goldmann Applanation Tonometer [5.1, 5.2].

Earlier diagnosis of keratoconus

Keratoconus is a genetic disease associated with deterioration of corneal stiffness. It affects more than 1% of the population – mainly adults within the 18-25 age group, and therefore has serious long-term effects on their quality of life. The disease is known to start with tissue softening long before corneal distortion takes place, and if it was to be diagnosed during this period, the cornea can be stiffened artificially (through various cross-linking techniques) to prevent distortion and loss of clear vision. The new biomechanical parameter, the stress-strain index (SSI) was developed in Liverpool specifically for the diagnosis and treatment of keratoconus and incorporated into the CorVis ST instrument sold world-wide by Oculus. It has been validated in several large multi-centre studies, where the high accuracy of the parameters to identify eyes with keratoconus (in clinical and sub-clinical stages) was proven in 98% of cases [5.3 – 5.5]. Through availability in the CorVis software, several clinical centres (including centres in Brazil, India, Italy, China and Germany) have been using these parameters to diagnose sub-clinical keratoconus and in taking decisions on when to intervene with a cross-linking treatment.

Clinical impact

With the new methods from Liverpool incorporated in the operating software of the CorVis ST from August 2016, clinical application of the methods is widespread, benefiting "*hundreds of thousands of patients per year globally, including approximately 30,000 in China alone*" [5.6]. The subsequent growth in clinical publications on the effectiveness of the methods (from 3 in 2013, to 40 in 2017, and 70 in 2019 on PubMed) indicates an increase in implementation in clinical practice. The parallel growth in the use of the CorVis ST, especially in China and the EU, as confirmed by senior clinicians in major hospitals in Wenzhou and Milan, presents further evidence of the increase in implementation.

A senior consultant at Wenzhou Eye Hospital noted [5.7]:

"*we have used the biomechanically-corrected intraocular pressure* (*bIOP) measurements provided by the CorVis ST and found it to be the least affected estimates of IOP (among outputs of all tonometry devices) by refractive surgeries, and as a result CorVis became a successful tonometer with clinical centres in China using it in glaucoma management. The Stress-Strain Index (SSI) was also less influenced by the central corneal thickness (CCT) and IOP, and provides much needed information on corneal stiffness that can help following up progression of keratoconus and could enable optimisation of CXL (Collagen Cross Linking) in the future*."

While, a senior consultant in Milan's Humanitas San PioX Hospital wrote [5.8]:

"*bIOP has dramatically improved the management of my glaucoma patients*" and "*SSI can surely improve our understanding of normal corneas and diseased ones such as keratoconus which have a decrease in corneal stiffness; hence can be very useful in customizing treatments*".

Further, in India where the new technologies are being increasingly used, a senior consultant at Sankara Nethralaya Hospital (with 1500 patients per day), commented [5.9]:

"*A clinical study done in our centre confirmed that bIOP did not correlate with corneal thickness, making it a reliable measure of IOP, suitable for all eyes irrespective of corneal geometry*." And *SSI was "… a reliable indicator of corneal stiffness."* She added*:" We have found numerous clinical*

applications of the SSI: early detection of keratoconus, assessment of success of collagen crosslinking in arresting the progression of keratoconus, monitoring patients after refractive surgery to detect any biomechanical destabilization."

5. Sources to corroborate the impact

5.1 Lopes BT, Roberts CJ, Elsheikh A, Vinciguerra R, Vinciguerra P, Reisdorf S, Berger S, Koprowski R, Ambrósio R, Repeatability and Reproducibility of Intraocular Pressure and Dynamic Corneal Response Parameters Assessed by the CorVis ST, Journal of Ophthalmology, 2017, Article ID 8515742. doi.org/10.1155/2017/8515742

5.2 Matsuura M, Murata H, Fujino Y, Yanagisawa M, Nakao Y, Nakakura S, Kiuchi Y, Asaoka R, Repeatability of the Novel Intraocular Pressure Measurement From CorVis ST, Translational Vision Science & Technology, 2019, 8(3):48. doi: 10.1167/tvst.8.3.48.

5.3 Salomão MQ, Hofling-Lima AL, Faria-Correia F, Lopes BT, Rodrigues-Barros S, Roberts CJ, Ambrósio R, Dynamic corneal deformation response and integrated corneal tomography, Indian Journal of Ophthalmology, 2018, 66: 373-382. doi: 10.4103/ijo.IJO_831_17

5.4 Kataria P, Padmanabhan P, Gopalakrishnan A, Padmanaban V, Mahadik S, Ambrosio R, Accuracy of Scheimpflug-derived corneal biomechanical and tomographic indices for detecting subclinical and mild keratectasia in a South Asian population, J Cataract and Refractive Surgery, 2019, 45(3): 328-336. doi: 10.1016/j.jcrs.2018.10.030

5.5 Ferreira-Mendes J, Lopes BT, Faria-Correia F, Salomao MQ, Rodrigues-Barros S, Ambrosio R, Enhanced Ectasia Detection Using Corneal Tomography and Biomechanics, American J Ophthalmology, 2019, 197: 7-16. doi: 10.1016/j.ajo.2018.08.054

5.6 Letter, 14 11 20, from Oculus Product Manager providing corroboration of contribution of underpinning research to the development of the new instrument and of impact in China for 30,000 patients per annum.

5.7 Letter from senior consultant at Wenzhou Eye Hospital corroborating clinical success of Liverpool's new biomechanical parameters, bIOP and SSI.

5.8 Letter,15 11 20, from senior consultant in Milan's Humanitas San PioX Hospital corroborating success of Liverpool's new biomechanical parameters, bIOP and SSI in management and understanding of glaucoma and keratoconus.

5.9 Letter, 16 11 20, from senior consultant at Sankara Nethralaya Hospital, Chennai corroborating success in early detection of keratoconus of the SSI developed in Liverpool.