Research Assessment Exercise 2020
Impact Case Study

University: The Chinese University of Hong Kong
Unit of Assessment (UoA): 3 (Clinical Medicine)

Title of case study: Improving the detection of glaucoma and its progression with topographic analysis of retinal nerve fiber layer (RNFL) thickness

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

Early detection of optic nerve degeneration for timely therapeutic intervention is critical to prevent vision loss in glaucoma, a leading cause of global blindness. We pioneered topographic RNFL evaluation using optical coherence tomography (OCT) for early detection of glaucoma and its progression. Our research has permeated different strata of the society outside the academia, impacting glaucoma care worldwide. This includes contributing to the formulation of regional/international glaucoma management guidelines, devising Trend-based Progression Analysis (TPA), which has been licensed to Carl Zeiss Meditec, a global OCT manufacturer, to detect glaucoma progression in the clinics, and improving study design in glaucoma trials.

(2) Underpinning research (indicative maximum 500 words)

Early diagnosis of glaucoma and detection of its deterioration is key to prevention of glaucoma blindness. Since 2006, the research team led by Prof. Christopher Leung at the Department of Ophthalmology and Visual Sciences, CUHK has been playing a leading role in introducing key concepts and new techniques of RNFL analysis with OCT to improve the diagnostic evaluation of glaucoma.

Topographic evaluation of RNFL thickness for detection and monitoring glaucoma
Whereas clinicians and eye care professionals had been relying on the circumpapillary RNFL thickness to detect and monitor glaucoma, our team was the first to demonstrate topographic analysis of the RNFL thickness over the 6x6mm^2 optic nerve head region to be more sensitive than the circumpapillary RNFL thickness at similar specificities for detection of glaucoma in 2010,[3.1] and detection of glaucoma progression in 2012.[3.2] In the companion studies conducted between 2009 and 2013, we further illustrated the impact of test-retest variabilities of RNFL thickness on the diagnostic performance of glaucoma detection,[3.3] and the relevance of age-related RNFL thinning in the discrimination of disease-related RNFL thinning in the evaluation of glaucoma progression.[3.4] These concepts have been adopted and embedded in the formulation of regional and international guidelines, consensus, and preferred practice pattern of glaucoma management.

Trend-based Progression Analysis (TPA) for analysis of progressive RNFL thinning
In 2016, we completed a landmark 5-year prospective study, demonstrating that progressive RNFL thinning predicts visual field progression.[3.5] This study was performed in response to the discussion with the United States National Eye Institute and Food and Drug Administration (FDA) in the 2010 Glaucoma Clinical Trial Design and Endpoints Symposium, at which the FDA expressed its view to consider structural endpoints, such as RNFL thickness, in clinical trials of new glaucoma drugs if there is evidence to support structural measures to be predictive of clinically relevant functional change. In a follow-up study in 2017, we further demonstrated a faster rate of RNFL thinning to be associated with a higher risk of visual field progression.[3.6] These studies examined and validated the clinical application of TPA – a novel algorithm we devised for topographic analysis of the rates of RNFL thinning with a false discovery rate

controlled at <5%. TPA is able to detect glaucoma progression earlier than the conventional method – Guided Progression Analysis – for change analysis of the RNFL thickness at similar specificities.[3,5] These studies provided the first account illustrating the application of topographic analysis of the rates of RNFL thinning for prediction of visual field progression, which has important implications to expedite clinical trials for evaluation of new glaucoma treatments. We had filed patents for TPA, which has been licensed to Carl Zeiss Meditec (Dublin, CA, USA), a global OCT manufacturer. Recently, a license agreement has also been reached with another OCT manufacturer, Topcon Cooperation (Tokyo, Japan).

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

3.1 ***Leung CK**, Lam S, Weinreb RN, Liu S, Ye C, Liu L, He J, Lai G, Li T, Lam DS. Retinal Nerve Fiber Layer Imaging with Spectral-Domain Optical Coherence Tomography: Analysis of the Retinal Nerve Fiber Layer Map for Glaucoma Detection. *Ophthalmology*. 2010; 117(9):1684-1691. **(no. of citations: 115)**

3.2 ***Leung CK**, Yu M, Weinreb RN, Lai G, Xu G, Lam DS. Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography: patterns of retinal nerve fiber layer progression. *Ophthalmology*. 2012;119(9):1858-1866. **(no. of citations: 90)**

3.3 ***Leung CK**, Cheung CY, Weinreb RN, Qiu Q, Liu S, Li H, Xu G, Fan N, Huang L, Pang CP, Lam DS. Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography: a variability and diagnostic performance study. *Ophthalmology*. 2009;116(7):1257-1263. **(no. of citations: 299)**

3.4 ***Leung CK**, Ye C, Weinreb RN, Yu M, Lai G, Lam DS. Impact of Age-related Change of Retinal Nerve Fiber Layer and Macular Thicknesses on Evaluation of Glaucoma Progression. *Ophthalmology*. 2013;120(12):2485-2492. **(no. of citations: 67)**

3.5 Yu M, Lin C, Weinreb RN, Lai G, Chiu V, ***Leung CK**. Risk of Visual Field Progression in Glaucoma Patients with Progressive Retinal Nerve Fiber Layer Thinning: A 5-Year Prospective Study. *Ophthalmology*. 2016;123(6):1201-1210. **(no. of citations: 40)**

3.6 Lin C, Mak H, Yu M, ***Leung CK**. Trend-Based Progression Analysis for Examination of the Topography of Rates of Retinal Nerve Fiber Layer Thinning in Glaucoma. *JAMA Ophthalmol*. 2017;135(3):189-195. **(no. of citations: 9)**

* denotes corresponding author.
No. of citations as reported from Scopus (www.scopus.com) on 30 September 2019

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

The importance of early detection of glaucoma and its progression is underscored by the irreversible nature of optic nerve degeneration in glaucoma, the poor inter-observer agreement in clinical evaluation of the optic disc even among glaucoma specialists, and the staggering load of 70 million glaucoma population worldwide. Our research on OCT evaluation of RNFL abnormalities, and development of TPA for assessment of glaucoma progression, directed by Christopher Leung, has transformed the clinical practice. This is supported by (1) regional as well as international adoption of our research findings in formulating guidelines and consensus in glaucoma management; (2) the licensing of TPA to global OCT industries, and (3) the serving as consultant to multinational pharmaceutical companies, advising on the application of topographic RNFL thickness evaluation and TPA in clinical trials for testing of new glaucoma treatment.

(1) Adoption of research findings in formulating guidelines and consensus

The concept of applying topographic evaluation of RNFL thickness to facilitate early detection of RNFL abnormalities and progressive RNFL thinning in glaucoma patients (i.e. research findings from references 3.1-3.6) were adopted in the World Glaucoma Association Consensus Series on Glaucoma Progression in 2011[5.1(a)] and Consensus Series on Diagnosis of Primary Open Angle Glaucoma in 2017,[5.1(b)] which were published by Kugler Publications and distributed worldwide. Between 1-10-2013 and 30-9-2019, 3576 print copies and 1632 e-copies were delivered to 87 countries; at least 10350 visitors had accessed the online consensus statements (data provided by Kugler Publications).[5.2] Our research studies on RNFL imaging were referenced 23 times in Consensus Series 8, and 14 times in Consensus Series 10. The consensus statements were also distributed through International Glaucoma Review (www.e-igr.com) which had an annual readership of 10,000-12,000 between 1-10-2013 and 30-9-2019. Christopher Leung was a session leader and co-editor of these consensus series. In addition, our research studies on OCT RNFL imaging were also referenced in the Asia Pacific Glaucoma Guidelines published by the Asia-Pacific Glaucoma Society in 2016 (Christopher Leung is a member of the review committee),[5.3] and the Terminology and Guidelines for Glaucoma published by the European Glaucoma Society in 2014.[5.4] Taken together, our research has generated a new worldwide standard for diagnostic evaluation of glaucoma in clinical care. This is further elaborated by Professor Robert Weinreb, former president of World Glaucoma Association – "not only have his seminal studies contributed to the international consensus on glaucoma care, as documented in the Glaucoma Consensus Reports, but they provide a sustained and enduring foundation for investigators throughout the world who work in these areas".[5.5]

(2) Licensing of TPA to global OCT industries

TPA is an algorithm we developed for topographic evaluation of progressive RNFL thinning. A patent for TPA entitled "Detection of disease-related retinal nerve fiber layer thinning" has been filed in the United States (U.S. Application No. 13/898,176), the European Union (EP Appln No. 13793329.7), and China (CN Appln No. 201380036133.8). The patent was non-exclusively licensed to Carl Zeiss Meditec in 2016 for implementation in the Cirrus HD-OCT. In Hong Kong Eye Hospital, TPA had been applied to more than 600 patients since 2016, among which more than 100 patients were identified to have glaucoma progression with TPA. With TPA, ophthalmologists have identified progressing patients for therapeutic intervention to prevent glaucoma blindness. "With more than 20,000 Cirrus HD-OCT instruments worldwide, the application of TPA would have a global impact on early detection of glaucoma progression", as denoted by Mr. Jeffrey Schmidt, Vice President of Carl Zeiss Meditec.[5.6] Another license agreement was reached with Topcon for implementation of TPA in their OCT models.[5.7]

(3) Consulting to pharmaceutical companies on using topographic analysis of RNFL in clinical trials

Our research has impacted the design of clinical trials for testing new glaucoma treatment. Christopher Leung had been invited by multinational pharmaceutical companies including Novartis, Allergan, Santen, Quark Pharmaceuticals, and Galimedix Therapeutics to advise on using topographic RNFL thickness analysis as an outcome measure in clinical trials of glaucoma treatment in multiple advisory board meetings between 2017 and 2019.[5.8] Progressive RNFL thinning has then been adopted as an outcome measure in clinical trials to investigate novel neuroprotective agents developed by Quark Pharmaceuticals[5.9] and in the development of a glaucoma registry by Santen.[5.10]

Collectively, our research has led to changes permeating different strata of the society outside

the academia; from transforming clinical practice via impacting the formulation of regional and international guidelines and consensus, and improving the design of clinical trials in the testing of new glaucoma treatments, to benefiting patients directly via early detection of glaucoma progression with TPA in the clinics.

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

5.1 (a) Weinreb RN, Garway-Heath DF, **Leung CK**, Crowston JG, Medeiros FA. Ed. Progression of Glaucoma, Consensus Series – 8. Hague, Netherlands: Kugler Publications, 2011. (b) Weinreb RN, Garway-Heath DF, **Leung CK**, Medeiros FA, Liebmann J. Ed. Diagnosis of Primary Open Angle Glaucoma, Consensus Series – 10. Hague, Netherlands: Kugler Publications, 2017.

5.2 Support letter from Kugler Publications

5.3 http://www.icoph.org/resources/334/Asia-Pacific-Glaucoma-Guidelines-.html

5.4 https://www.eugs.org/eng/guidelines.asp

5.5 Support letter from Robert Weinreb, former president of World Glaucoma Association

5.6 Support letter from Carl Zeiss Meditec

5.7 Support letter from Topcon Cooperation

5.8 Copies of consultant agreement from Novartis, Allergan, Santen, Quark Pharmaceuticals, and Galimedix Therapeutics

5.9 Support letter from Quark Pharmaceuticals

5.10 Support letter from Santen