Institution: University College London

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Fundus autofluorescence imaging transforms understanding of retinal disease

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

Fundus autofluorescence imaging has transformed understanding of retinal disease and brought enormous benefit to millions of patients world-wide. By visualising what is predominantly a lipofuscin signal from the retinal pigment epithelium, retinal diagnosis is now much more sophisticated, therapy can be better targeted to an individual patient's needs and clinical trials can use area of loss of autofluorescence as an outcome measure. Certain inherited retinal disorders have distinctive patterns of altered fluorescence and ageing changes can be followed with much greater precision. A global industry has built up around the devices required to image retinal autofluorescence safely.

2. Underpinning research (indicative maximum 500 words)

Age-related macular degeneration (AMD) is the leading cause of visual impairment in the UK, affecting 462,000 people to some degree. For many years it was known that the so-called "age pigment", lipofuscin, accumulates in the cells of the eye and is critically implicated in the pathogenesis of AMD and other forms of retinal disease. However until the early 1990s, all that was known about the accumulation of lipofuscin in AMD was obtained from post-mortem studies; it was not possible to view it in the living eye. Research at the UCL Institute of Ophthalmology, led by Fred Fitzke and Alan Bird, pioneered the technique of Fundus Autofluorescence (FAF) Imaging to allow visualisation of lipofuscin. Our work in optics and imaging of the eye led to the first images of Fundus Autofluorescence using the Scanning Laser Ophthalmoscope (SLO), which were published in 1995 **[1]**. These provided high resolution imaging of the distribution and levels of FAF attributable to specific molecular species which are fundamentally involved in the pathogenic mechanisms of AMD, hereditary retinal degenerations such as retinitis pigmentosa and other blinding diseases **[2]**.

Over the following years, we, with colleagues at Moorfields Eye Hospital, pioneered use of the technique, remaining from some time the only centre publishing in this area. Our research efforts measuring visual function in spatially contiguous locations of the retina in the same eyes of patients showed that FAF is of great value in the diagnosis of many retinal disorders including inherited macular dystrophies **[3]**. We showed that it provides insights into the distribution of macular pigment **[4]** and importantly demonstrated key linkages between FAF and retinal function in inherited retinal degenerations **[5]** and age-related macular degeneration **[6]**.

Since then a world-wide intensive research effort has been underway to study FAF and understand the fundamental pathophysiological processes leading to loss of vision. Building on our research, it is now understood that a key molecule (A2E) contributes to the FAF. This molecule accumulates in the cell layer underlying the photoreceptor layer (the Retinal Pigment Epithelial cells), on which the photoreceptors depend for their metabolic support and which is centrally implicated in the abnormalities of AMD. With the advent of "molecular imaging" it has been recognised that FAF allows characterisation of the role of key molecules by imaging the living eyes of patients using these non-invasive techniques based on confocal scanning laser ophthalmoscopy. The optical properties of the eye allow unprecedented resolution using this form of molecular imaging and enables measurement of the effects on visual function during the course of the abnormality. FAF provides a measure of the abnormal processes which would otherwise not be detectable nor visible using previous methods.

Our investigations have shown that photoreceptors can retain their function in the early stages of disease, diagnosed by an abnormal increase of FAF. This provides a window of opportunity for novel interventions before the patient experiences loss of vision. By providing earlier indications of

abnormality in cellular function, FAF provides novel measures of clinical endpoints which are closely linked to visual function and reflect fundamentally important aspects of metabolic function.

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

[1] von Rückmann A, Fitzke FW, Bird AC. Distribution of fundus autofluorescence with a scanning laser ophthalmoscope. Br J Ophthalmol. 1995 May;79(5):407-12. http://doi.org/bmc975

[2] von Rückmann A, Fitzke FW, Bird AC. Fundus autofluorescence in age-related macular disease imaged with a laser scanning ophthalmoscope. Invest Ophthalmol Vis Sci. 1997 Feb;38(2):478-86. http://www.iovs.org/content/38/2/478.long

[3] von Rückmann A, Fitzke FW, Bird AC. In vivo fundus autofluorescence in macular dystrophies. Arch Ophthalmol. 1997 May;115(5):609-15. http://doi.org/c2h4j2

[4] Robson AG, Moreland JD, Pauleikhoff D, Morrissey T, Holder GE, Fitzke FW, Bird AC, van Kuijk FJ. Macular pigment density and distribution: comparison of fundus autofluorescence with minimum motion photometry. Vision Res. 2003 Jul;43(16):1765-75. http://doi.org/b2m932

[5] Robson AG, Egan CA, Luong VA, Bird AC, Holder GE, Fitzke FW. Comparison of fundus autofluorescence with photopic and scotopic fine-matrix mapping in patients with retinitis pigmentosa and normal visual acuity. Invest Ophthalmol Vis Sci. 2004 Nov;45(11):4119-25. http://dx.doi.org/10.1167/iovs.04-0211

[6] Scholl HP, Bellmann C, Dandekar SS, Bird AC, Fitzke FW. Photopic and scotopic fine matrix mapping of retinal areas of increased fundus autofluorescence in patients with age-related maculopathy. Invest Ophthalmol Vis Sci. 2004 Feb;45(2):574-83. http://doi.org/fh9qxv

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

Our research into FAF imaging has transformed clinical practice in retinal disease. The 2010 text book *Medical Retina: Focus on Retinal Imaging* describes how "*the era of FAF imaging as applied today has begun in 1995. Von Ruckmann, Fitzke and Bird described in their landmark paper the use of a confocal scanning laser ophthalmoscope for FAF imaging in a large number of patients*" **[a]**. The subsequent widespread adoption of this technique has led to patient benefits in terms of earlier detection and monitoring of disease. The technique has also impacted on the development of new therapies, as efficacy can be better assessed. The economic impacts on commercial companies who produce equipment have also been substantial.

FAF imaging is now a widely used technique in the assessment of retinal disease, and is available nationwide as part of NHS services. At Moorfields Eye Hospital alone, between 300 and 500 patients per week are imaged by FAF (c.20,000 per year) **[b]**. In the Department of Health's 2007 document, *What is Physiological Measurement? A guide to the tests and procedures conducted by Physiological Measurement diagnostic services*, FAF is listed as a standard technique, as follows:

> "*Test: Fundus autofluorescence (AF) with confocal scanning laser ophthalmoscope (Heidelberg Retina Angiograph HRA). Function: To image the lipofuscin pigment in the retinal pigment epithelium for diagnosis and monitoring of retinal dystrophies and degenerations. Indication: Retinal dystrophies; Age-related macular degeneration*" **[c]**

2009 guidelines from the Royal College of Ophthalmologists described FAF as a "*commonly used retinal imaging technique*" and recommended it in the diagnosis of Age Related Macular Degeneration as follows: "*The use of scanning laser ophthalmoscopy to generate fundus autofluorescence images and the use of en-face imaging using spectral domain OCT have made it easier to diagnose GA [geography atrophy] as these can reveal areas of GA which may not be clinically visible on biomicroscopy*" and "*[Autofluorescence] can give an indication of the health of the RPE*." The 2013 update to these guidelines further emphasised the utility of FAF, saying: "*Several imaging modalities may be useful, in particular fundus autofluorescence, in the evaluation of GA*" (emphasis added) and "*Fundus autofluorescence imaging especially when combined with optical coherence tomography is helpful in distinguishing PD from AMD*" **[d]**.

That the impact of this technique on clinical practice has spread beyond the UK is demonstrated by a 2010 review article in Eye Net magazine (produced by the American Academy of Ophthalmology) which described how "*Fundus autofluorescence (FAF) has recently pole-vaulted from a research tool to a real clinical application*" **[e]**.

The application of FAF imaging in the clinic has considerable benefits for patients. As described in a recent review, which described FAF imaging as "*a valuable asset in diagnosing retinal disease*", the technique may allow for earlier identification of retinal diseases which are not otherwise evident **[f]**. This allows earlier treatment, and better monitoring of the efficacy of this treatment.

Development of new therapies

New forms of interventions such as gene therapy and stem cell therapy increasingly rely on FAF and related novel forms of imaging to determine potentially beneficial effects of treatment. Clinical trials use FAF and other new forms of imaging in addition to conventional endpoints such as visual function (visual acuity or visual fields) and electrophysiological measures. For example, a recent trial of intravitreal injections of ranibizumab for pigment epithelial detachment (PED) secondary to AMD used FAF as one of its methods of assessment, as did another study of subconjunctival sirolimus for the treatment of geographic atrophy **[g]**. One trial investigator reported that "*In designing clinical trials that test new pharmacologic interventions, [fundus autofluorescence] is helpful in distinguishing progressers from slow progressers*" **[h]**.

In the US, the FDA recently advised that: "*FDA's Center for Drug Evaluation and Research (CDER) has accepted as an anatomic endpoint a decrease in the rate of growth of an area of retina that no longer has any photoreceptors. This can be measured in one of several ways… The hallmark of dry AMD is geographic atrophy in the macula. Geographic atrophy is a breakdown in the retinal pigment epithelium (RPE) and subsequent overlying retinal tissue. There is not a uniform destruction of the retina, and photoreceptors are often spared at the periphery of the lesions. These "fuzzy borders," when viewed by fundus photography or autofluorescence, often surround an area where there is complete destruction of the photoreceptors. Reduction in the rate of progression of these areas of complete destruction of the photoreceptors can sometimes be measured indirectly by fundus photography or autofluorescence. When the area of complete destruction of the photoreceptors in dry AMD can be measured, it is an acceptable endpoint. A change in the area of non-seeing retina has been used as a clinical endpoint to support New Drug Applications (NDAs) such as ganciclovir and foscarnet in the treatment of cytomegalovirus (CMV) retinitis"* **[i]**.

Economic impacts

Since our first demonstration of FAF in the eyes of patients using the SLO, numerous other research centres throughout the world have taken up the technique and many thousands of instruments have been deployed clinically worldwide. Several major companies now manufacture these devices, including Canon, Heidelberg Engineering and Optos **[j]**. Large numbers are sold every year. *[Text removed for publication]* **[k]**. Globally, it has been estimated that c.10,000 of these instruments have been sold. Thus the economic impacts of this industry are considerable: with instruments costing about $200,000, this implies spending of c.$2bn for the instruments alone. In addition to this sum, there has been worldwide investment in clinical staff, infrastructure and medical resources to provide FAF imaging for patients. This is a clear indicator of the impact FAF has on clinical practice and perceived benefit to patients.

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

[a] Holz FG, Spaide RF. (Eds.) Medical Retina: Focus on Retinal Imaging. New York: Springer; 2010. (Essentials in Ophthalmology). ISBN 978-3-540-85540-8. Chapter 5 is on FAF and references the underpinning research. Copy of relevant section available on request.

[b] Patient numbers can be corroborated by Moorfields Eye Hospital. Contact details provided. As

well as Moorfields, examples include:

- Gloucestershire Eye Unit (http://www.ophthalmology.severndeanery.nhs.uk/about-us/hospitals/gloucestershire-eye-unit/)
- Southampton Eye Unit http://jobs.uhs.nhs.uk/job/UK/Hampshire/Southampton/University_Hospital_Southampton_NHS_Foundation_Trust/The_Eye_Unit/The_Eye_Unit-v289350?ss=2&nc=80841382794467 (Copy available on request)
- Great Ormond Street: http://www.gosh.nhs.uk/health-professionals/clinical-specialties/ophthalmology-information-for-health-professionals/refer-a-patient/

[c] Department of Health. What is Physiological Measurement? A guide to the tests and procedures conducted by Physiological Measurement diagnostic services. May 2007. (Copy available upon request.)

[d] 2009 guidelines are available here: http://www.heartofengland.nhs.uk/wp-content/uploads/FOI1808Attachment1.pdf (And copy available on request.) The current (2013) guidelines are available from the RCOpth website: http://www.rcophth.ac.uk/core/core_picker/download.asp?id=1851&filetitle=Age%2DRelated+Macular+Degeneration%3A+Guidelines+for+Management+2013

[e] http://www.aao.org/publications/eyenet/201006/feature.cfm

[f] http://www.revophth.com/content/d/imaging_and_diagnostic_instruments/c/22655/

[g] Examples include:

- Clemens CR, Alten F, Milojcic C, Nicole E. Morphologic Changes In Pigment Epithelial Detachment After Ranibizumab Treatment Assessed By Spectral Domain Oct, Fundus Autofluorescence, Fluorescein And Icg Angiography: Six-month Results Of A Prospective Randomized Study. ARVO 2011 Abstract no 1658/A53 http://tinyurl.com/ox2bbh3
- Wong WT, Dresner S, Forooghian F, Glaser T, Doss L, Zhou M, Cunningham D, Shimel K, Harrington M, Hammel K, Cukras CA, Ferris FL, Chew EY. Treatment of geographic atrophy with subconjunctival sirolimus: results of a phase I/II clinical trial. Invest Ophthalmol Vis Sci. 2013 Apr 26;54(4):2941-50. http://dx.doi.org/10.1167/iovs.13-11650.

[h] Frank Holz, University of Bonn, quoted in a 2008 article in Healio, Ocular Surgery News: http://www.healio.com/ophthalmology/retina-vitreous/news/print/ocular-surgery-news/%7B1a16733d-8f99-4f6b-bfec-2da309dc675f%7D/fundus-autofluorescence-imaging-may-help-predict-amd-progression

[i] Briefing Document FDA Cellular, Tissue, and Gene Therapies Advisory Committee CTGTAC Meeting #52 Cellular and Gene Therapies for Retinal Disorders June 29, 2011. http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/bloodvaccinesandotherbiologics/cellulartissueandgenetherapiesadvisorycommittee/ucm259087.pdf

[j] At least 5 companies, selling 14 different products reported here: http://www.medicalexpo.com/medical-manufacturer/slo-ophthalmoscope-887.html . These include:
Canon http://www.canon-europe.com/Medical/Eye_Care/FAF/Index.aspx
Heidelberg Engineering http://www.heidelbergengineering.com/us/products/spectralis-models/imaging-modes/autofluorescence/
Optos http://www.optos.com/en/Products/Retinal-imaging-products/Ultra-widefield-imaging/Fundus-Autofluorescence/

[k] Correspondence from Vice President of Medical Affairs & Quality, Optos. Copy available on request and contact details provided.

Contact details