Institution: University of Manchester

Unit of Assessment: UoA5

Title of case study: Macular pigment measurement in humans: a new instrument, the Macular Pigment Screener (MPS)

1. Summary of the impact

Age Related Macular Degeneration (AMD) is by far the leading cause of blindness in older people in the developed world, affecting 30% of those aged over 65, and is set to increase. The naturally-occurring carotenoids lutein (L) and zeaxanthin (Z) are located in the central retina (macula) and are collectively called the macular pigment (MP). High MP levels confer protection from AMD. Murray and colleagues have developed a new instrument, the Macular Pigment Screener (MPS), which allows regular, non-invasive monitoring of MP in ophthalmic practice. This means that, for the first time, the MPS can show the effect of intervention on the MP, providing a management strategy for AMD patients, and allowing early identification of those at risk of developing AMD. Over 750 instruments have been sold to date, with more than 1M patients in the US alone estimated to be benefiting from routine MP testing.

2. Underpinning research

The impact is based on research that took place in Manchester from 1999 to the present.

The key University of Manchester researchers were:

Dr Ian J. Murray (1987 to present, currently Senior Lecturer)
Mr David Carden (1998 to present, part-time Electronic Engineer)
Dr Hui-Hiang Koh (2001-2005, Research Assistant MSc/PhD student)
Dr James Feather (2003-2005, Post-Doctoral Research Associate)
Dr Maria Makridaki (2007-2010, Research Assistant/PhD student)

Murray provided overall strategic direction, supervision and designed experimental protocols.

The work was carried out in collaboration with ophthalmologist colleagues from Manchester Royal Eye Hospital, Mr Stephen Beatty and Mr Dan Nolan.

The main steps were as follows:

- 1999-2000: Design, development and calibration of a laboratory-based optical system for measuring MP based on LEDs and a monochromator (MSc student H.H. Koh). The instrument was used to show that patients at risk of AMD had lower MP than those with low risk [1]. (D. Carden and I. Murray designed instrument, S. Beatty provided clinical support).
- 2000-2002: New system developed in collaboration with Tinsley Ophthalmic (now part of Elektron Technology). This used a similar technique but with LEDs only, and more sophisticated digital drivers for controlling the measurements [2,3]. (PhD student H.H. Koh, funded by the UK Department of Health via Quotec Ltd.).
- 2000-2002: The above device was used in a pilot clinical trial of early stage AMD patients and age-matched healthy controls, all of whom received lutein supplement tablets [3], in collaboration with Cognis AG. This study established for the first time that patients with early stage AMD were capable of increasing their MP. (Calibration and technical support provided by J. Feather; S. Beatty provided clinical support).
- 2005-2009: Totally novel approach to measurement of MP developed by I. Murray and D. Carden and in collaboration with Tinsley Ophthalmic, who provided funding and an instrument surround. The instrument was subsequently called “MPOD” in UK and Europe and “QuantifEYE®” in the US. Murray established commercial links with US distributors ZeaVision. A patent application was filed in 2005 and published in 2010.
- 2008-2010: New device required improved surround and extensive testing due to its reliance on complex drivers for LED control and to allow introduction to the US market [4,5]. (Main contributors I. Murray and D. Carden).
- 2007-2010: Extensive two-centre clinical trials in collaboration with Dutch colleagues T.

Berendschot and R. van der Veen (Maastricht) who used an alternative lab-based method for determining MP. (PhD student M. Makridaki (MRC funded)). MP data from large healthy populations were published and the new technique compared favourably with the lab-based method [5]. A recent clinical trial in early-stage AMD patients provided clear evidence for the benefit of enhancing MP, and highlights the importance of measuring MP as part of a disease management strategy [6]. (Both trials funded by Cognis AG).

- The instrument was re-launched as "MPS II" for the non-US market in December 2012 [A].

3. References to the research

The research was published in leading international visual science and ophthalmology journals.

1. Beatty S., **Murray I.J.**, Henson D.B., **Koh H.H., Carden D.**, Boulton M.E. (2001). Macular Pigment and Risk for Age-Related Macular Degeneration in Subjects from a Northern European Population. Investigative Ophthalmology and Visual Science. 42 (2), 439-446. (No DOI available) Available on Request
2. Beatty S., **Koh H-H, Carden D., and Murray I.J.** (2000) Macular pigment optical density measurement; a novel compact instrument. Ophthalmic and Physiological Optics. 20(2), 105-111. DOI: 10.1046/j.1475-1313.2000.00483.x
3. **Koh H-H, Murray I.J.**, Nolan, D., **Carden D., Feather J.** and Beatty S. (2004). Plasma and Macular Responses to Lutein Supplement in Subjects With and Without Age-Related Maculopathy: a Pilot Study. Experimental Eye Research. 79, 21-27. DOI:10.1016/j.exer.2004.03.001
4. van der Veen, R. L., Berendschot, T. T., Hendrikse, F., **Carden, D., Makridaki, M. and Murray I.J.** (2009) A new desktop instrument for measuring macular pigment optical density based on a novel technique for setting flicker thresholds. Ophthalmic Physiological Optics. 29, 127-137. DOI: 10.1111/j.1475-1313.2008.00618.x
5. van der Veen R.L., Berendschot T.T., **Makridaki M.**, Hendrikse F., **Carden D.**, **Murray I.J.** (2009). Correspondence between retinal reflectometry and a flicker-based technique in the measurement of macular pigment spatial profiles. Journal of Biomedical Optics, 14(6), 064046-1-064046-6. DOI:10.1117/1.3275481
6. **Murray I.J., Makridaki M.**, van der Veen R.L., **Carden D.**, Parry N.R., Berendschot T.T. (2013). Lutein supplementation over a one-year period in early AMD might have a mild beneficial effect on visual acuity; the CLEAR study. Investigative Ophthalmology and Visual Science, 54(3):1781-8. DOI: 10.1167/iovs.12-10715

4. Details of the impact

Context

In the early 2000s there was much controversy regarding the role of the MP and the possibility that it might prevent macular disease or minimise its effects. Much of the research at the time was based on small numbers of participants and therefore largely speculative. The main impediment to progress was the inability to measure MP in large numbers of participants. The early stages of the research had two primary aims:

i. to establish whether or not MP was linked with AMD, and
ii. to develop a technique to measure MP *in vivo* in large populations which could be used in epidemiological studies and, ultimately, routinely under clinical conditions.

Pathways to impact

- The early work was published in high quality clinically-focussed journals such as Investigative Ophthalmology and Experimental Eye Research [1,3]. The work attracted financial support from the NW Regional Health Authority (1998-1999) and the Department of Health (2000-2002). It was presented at numerous scientific meetings in Europe and, in particular, frequently in the US at a large annual ophthalmic conference (ARVO, Association for Research in Vision and Ophthalmology).
- These activities, concerned with describing and testing the new device and conducting

measurements in patients and age-matched healthy controls, gave rise to interest from industrial partners, notably Tinsley Ophthalmic Instruments (UK), ZeaVision (US) and Cognis AG (Germany). Each of these organisations played a crucial role in the route to market and subsequent impact of the research, as outlined below.

- Tinsley (now Elektron) manufactured a prototype device funded by the DoH (2000-2002, [2,3]) and then funded and manufactured the final instrument (2005-2007) ([4], [A]).
- ZeaVision, who sell dietary supplements ("EyePromise Restore") to increase MP, licence the MPS (called "QuantifEYE®" in the US) to optometrists (see http://www.zeavision.com/quantifeye.html) and have developed a successful marketing route in the US.
- Subsequently (2006-2009) Cognis funded a definitive, placebo-controlled clinical trial to establish that MP has real benefits for AMD patients. The new device was integral to this study and has resulted in the most recent paper [6].
- A European patent application was filed in 2005 and published in October 2010: *Ocular Measurement Apparatus and Method "Macular Pigment Screener";* UK Application number: 0507430.7; Applicants: I. Murray and D. Carden; European Patent Number 1871217.
- The MPS was CE marked by Tinsley in 2006.

The MPS instrument has also had extensive media exposure:

- In 2006 the BBC funded (£11k) a short intervention trial in Murray's laboratory of the effects of a spinach-rich diet on MP in 12 AMD patients. The MPS was used to show substantial increases in MP and the results were reported in a BBC2 series called *The Truth About Food*. Spinach is rich in lutein and, although it is not an optimum way of increasing MP, the main purpose of the programme was to increase awareness of the importance of diet for the health of the eye. The programme was broadcast in 2007.
- In 2007/8 the research was described and discussed in different BBC radio programmes where Murray responded to questions from listeners: BBC Radio Cambridge / Peterborough; KMFM Radio Kent; BBC Radio Gloucestershire; BBC Coventry and Warwick; BBC Radio Kent; MFR Radio Scotland.
- In January 2012 Murray was invited to appear on BBC Radio Manchester to discuss the current research concerned with the links between the health of the normal older eye and diet, thus highlighting the importance of measuring MP in clinics.

Reach and significance of the impact

Specific impacts based on the research can be summarised under the following:

Patient benefits:

- As more than 30% of older people have signs of early stage AMD, it is important for all those aged over 60 to have their MP measured. This enables them to assess their level of risk of developing AMD and take steps to increase their MP levels if these are found to be low. This particularly applies to those at high risk due to family history. The MPS is used in clinical trials (including [6]) to measure the effects of interventions on progression of AMD.
- ZeaVision estimate that currently around 1 million patients are benefitting from routine MP screening in the US alone [B]. In all patients, the device has one major benefit in that it highlights the importance of diet and displays to the patients how improving diet can increase MP and therefore reduce the risk of AMD. ZeaVision state that a report has "estimated US healthcare cost savings of $2.5 billion over 5 years if just 130,000 patients avoided transition to debilitating blindness by being screened and taking MP supplementation" [B].

Practitioner benefits:

- The MPS has allowed practitioners for the first time to assess whether their patients' MP is low and advise on enhancement measures (e.g. eating lutein-rich foods or taking dietary supplements). They combine the MP measurement with an assessment of risk according to heritance and retinal photographs. They can then advise patients on how to minimise risk. The measurement of MP has added an extra dimension to the care offered by optometrists worldwide [C,D,E]. A UK Optometrist states: "With the prevalence of ARMD [AMD] increasing

in most parts of the world the MPS11 allows us to be ready for the very large number of predicted patients who will get ARMD..” [D]. A US Optometrist states that the MPS is “currently the quickest…, most affordable, and most clinically relevant device in the world” that “will revolutionize the practice of eye care” [E].

Benefits to the ophthalmic community:

- The measurement of MP in clinics has not previously been possible. This allows the links between diet, inheritance and structural retinal damage to be meaningfully explored in AMD patients and those at risk of developing the disease. Chairman and Chief Scientific Officer of ZeaVision states: “The ability to screen applicants that are at high risk for AMD and cataracts and introduce the patient to a dietary supplement or counseling that can ultimately reduce the progression of these debilitating eye diseases will forever change Eye Care practices across the healthcare industry” [B].
- As a result the ophthalmic community is now much more aware of the importance of diet and lifestyle in preventing AMD, as described in the Royal College of Ophthalmologists’ guidelines on AMD Management [F]. These guidelines are a direct result of the body of research findings now available on the rationale for controlling diet in the management of MP. The research conducted by Murray’s research group, including the introduction of the MPS, has made a substantial contribution to this opinion.

Commercial impact:

- **Tinsley/Elektron** (UK manufacturer) – Since its introduction in 2005, over 500 units have been sold in the USA and 250 in the rest of the world. The company directly employs 12 staff, 7 in manufacturing and 5 in sales and marketing, and has invested in a new manufacturing facility and new software releases in Nov. 2012 and July 2013. The MPS “is of considerable commercial value” to Elektron and they “expect this to continue as indicated by the future investment figures” [G].
- **ZeaVision** (US distributor) – At present there are more than 500 devices in commercial settings in the US and the majority of US Optometry Schools are introducing MP measurement (using QuantifEYE) to their students. The procedure also generates an income for the practicing optometrist [B].

Industrial investment in research:

- Tinsley Ophthalmic Instruments Ltd.*:* £35k, Nov. 2005-2007, *Development of a Macular Pigment Screener*.
- Cognis Europe: €218k, June 2006-2008, *Macular pigment and lutein (c*ollaborative project with Dr T. Berendschot, The Netherlands).

5. Sources to corroborate the impact

A. Elektron MPSII datasheet http://elektron-technology.com/en-gb/products/ophthalmics/mps-II – cites van der Veen *et a*l., 2009 [4].

B. Letter of support from the Chairman and Chief Scientific Officer of ZeaVision (US distributor), corroborating the sales and commercial value of the QuantifEYE (MPS) in the USA.

C. Article in The Optician, Murray and Carden, Jan. 2008: http://www.opticianonline.net/assets/getAsset.aspx?ItemID=2891

D. Letter of support from a practicing optometrist in the UK, describing the value of the MPS in ophthalmic practice.

E. Letter of support from a practicing optometrist and Associate Professor in the USA, describing the value of the QuantifEYE (MPS) in ophthalmic practice.

F. Royal College of Ophthalmologists’ guidelines: “Age-Related Macular Degeneration 2009 Guidelines for Management” http://www.rcophth.ac.uk/page.asp?section=451&sectionTitle=Clinical+Guidelines

G. Letter of support from the Company Secretary of Elektron Technology plc (UK manufacturer), corroborating the sales and commercial value of the MPS.