Institution: University of Leicester

Unit of Assessment: UoA4

Title of case study: Diagnosis and treatment of Nystagmus: improving medical effectiveness and patient quality of care

1.Summary of the impact

Infantile nystagmus (IN), previously known as congenital nystagmus, is a condition that impairs vision by causing continual and involuntary oscillatory movements of the eyes. IN begins in infancy and is a lifelong disorder, affecting over 88,000 people in the UK. Leicester is the leading UK centre for research into the underlying mechanisms and treatment of IN: discovering the genetic mutations behind some of the common forms of nystagmus; pioneering early diagnosis of IN; and conducting randomised clinical trials into drug treatments and other therapies. The centre provides advanced scientific and medical knowledge, and support and advice to sufferers of this physically and psychologically debilitating condition. The work has resulted in new methods of diagnosis which are more comfortable and convenient for patients and enable cost-savings for healthcare providers; and has led to the testing and subsequent prescription of pharmacological treatments which offer patients improvements in quality of life.

2. Underpinning research

Researchers in the Ophthalmology Group at the University of Leicester have been focusing on understanding the eye disorder nystagmus for over two decades, spearheading studies into the prevalence, causes and effects of nystagmus, and treatments for these visual disorders.

Discovery of the FRMD7 gene

The cause of infantile IN has long been controversial. There are several types of IN: it can arise from retinal or optic nerve abnormalities, such as albinism (a lack of pigmentation), *PAX6* mutations (which lead to a wide spectrum of ocular defects, including the lack of an iris) or achromatopsia (an inability to perceive colour). Alternatively, it may be 'idiopathic', with no obvious disease cause, and then it is unclear whether the nystagmus is due to abnormalities of the retina or of areas of the brain controlling eye movements.

Between 2003 and 2005 the group conducted numerous field studies observing communities with large families in an effort to find the first gene identified as causing idiopathic IN. The *FRMD7* gene was discovered in 2006 by Professor Irene Gottlob and Dr Shery Thomas in collaboration with the University of Cambridge and the Sanger Institute (**1,2**).Further research has shown that the *FRMD7* gene plays a role in developing nerve cells in the brain by encouraging growth and new connections in the regions controlling eye movement.

The identification of the FRMD7 gene enabled the Leicester group to differentiate subtypes of IN for the first time. The group compared differences in eye movements between, first, idiopathic IN with and without mutations in the *FRMD7* gene (**3**) and, second, *FRMD7*-associated IN and albinism. The group was also the first to systematically characterise retinal abnormalities in idiopathic IN, albinism, achromatopsia, *PAX6* mutations and isolated foveal hypoplasia (underdevelopment of the central part of the retina responsible for high-resolution vision; **4**). These developments have changed the ease and accuracy with which IN is diagnosed, which is important for clinical management of the disease because the various subtypes of IN have different causes, prognoses and treatments.

As a result of this work, the group developed a genetic test for *FRMD7* mutations in collaboration with the Nottingham NHS genetic lab in 2010; this is now available to patients whose IN is believed to be idiopathic (about 14% of IN sufferers) on the NHS in Nottingham and in labs around the world, including the US, Israel, Germany, France and Spain.

Pioneering the use of a new method of diagnosis

In 2011 Leicester was chosen as the UK trial centre for a hand-held UHR SD-OCT (ultra high-resolution spectral-domain optical coherence tomography) scanner, manufactured by the US firm Bioptigen, for research and clinical use in infants and young children. The device creates precise

and highly detailed three dimensional maps of the inside of the eye, including the retina. The group had already developed expertise in diagnosing IN in adults using head-fixed OCT, and recognised the potential of using the technology to diagnose IN and characterise retinal abnormalities in infants and young children, who have difficulty keeping still.

The group has tested hand-held OCT on 315 normal children and 120 children with IN and 75 premature babies born at less than 30 weeks (215 in total) to develop improved diagnostic strategies for young children (**5**). Multiple recordings as children grow allow the charting of eye development in these groups and provides parents with an early diagnosis of retinal abnormalities (for most diseases sensitivity was >85% and specificity >90%). They have also shown OCT measures to be an independent gauge of the level of vision in adults. Currently they are assessing the ability of OCT from infants and children to predict the severity of potential visual deficits on maturation in later life.

Major trials for pharmacological treatment
The success of two medications, memantine (a treatment for Alzheimer's Disease) and gabapentin (a drug to relieve neuropathic pain) for treating acquired nystagmus, has led the group to complete the first randomised controlled trial into pharmacological treatment for IN in 2007 (**6**). The group measured the effect of memantine and gabapentin in an IN group in comparison to a placebo group, showing for the first time that pharmacological intervention can be beneficial in treating IN.

The study has been the springboard for a number of clinical trials, including a large crossover trial for the two medications, which is ongoing (2011 – 2014); a trial into the effects of a new medication Neramexane through collaboration with MERZ Pharma (findings were negative) (2007 – 2010); a randomised controlled trial comparing hard and soft contact lens wear (2010 – 2012); and an evaluation of the effects of the surgical procedure of 'tenotomising' eye muscles for IN, at the request of the National Institute for Health Care and Excellence (NICE; 2009 – 2014).

Other research
The group is developing ways to evaluate the impact of interventions on patient-centred outcome measures, such as quality of life (**7**) and measures of functional vision such as reading performance, in collaboration with Claire Hutchinson and Applied Psychology groups in the College.

Key Contributors: Irene Gottlob, professor and head of group (1999-date); Rebecca J McLean, research associate (1999-date); Frank A. Proudlock, lecturer (2000-date).
Others: Nagini Sarvananthan, clinical research fellow (2002-2004); Shery Thomas, clinical lecturer (2004-2008); Anil Kumar, clinical research fellow (2007-2010); Mervyn Thomas, PhD student (2009-date); Rachel Watkins, human geneticist (2010-2012); Sarim Mohammad, PhD student (2011-date); Helena Lee, clinical research fellow (2012-date).
From other groups: Pierluigi Nicotera, MRC Toxicology Unit; Sue Shackleton, Dept of Biochemistry
From other institutions: Patrick Tarpey, Wellcome Trust Sanger Institute, Cambridge, UK (gene sequencing work); Lucy Raymond, Cambridge Institute for Medical Research, University of Cambridge, UK (gene sequencing work); Elizabeth Engle, Harvard Medical School, Harvard University, USA (studies into *PAX6* mutations); Susanne Kohl, Institute for Ophthalmic Research, Eberhard Karls Universität Tübingen, Germany (achromatopsia studies); MERZ Pharma, Frankfurt, Germany (collaboration on Neramexane study).

3. References to the research

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3. **Thomas S, Proudlock FA, Sarvananthan N, Roberts EO, Awan M, McLean R, Surendran M,**

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6. **McLean R, Proudlock F, Thomas S, Degg C, Gottlob I.** Congenital nystagmus: randomized, controlled, double-masked trial of memantine/gabapentin. *Ann Neurol.* 2007 Feb; 61(2): 130-8.
7. **Rebecca Jane McLean**, Kate C Windridge**, Irene Gottlob.** Living with nystagmus: a qualitative study. *Br J Ophthalmol.* 2012; 96: 981e986. doi:10.1136/bjophthalmol-2011-301183

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Genetic related studies: National Eye Research Institute (2008-2011) £59,000; Ulverscroft Foundation (2007-2010) £205,000.
Optical Coherence Tomography: Medical Research Council (2012-2015) £380,000; Ulverscroft Foundation (2012-1015) £140,000; Nystagmus Network (2012-2015) £8,000; National Eye Research Institute (2009) £50,000; Medisearch (2010-2012) £48,000.
Treatment of nystagmus: MERZ Pharma (2007-2010) £250,000, Fight for Sight (2009-2014) £118,000; Nystagmus Network (2005) £5,000; College of Optometrists (2010-2012) £13,000.
Principal Investigator is Gottlob for all except Medisearch and College of Optometrists (Proudlock)

4. Details of the impact

Infantile Nystagmus (IN) is a condition that has both physiological and psychological effects. It is associated with reduced vision and decreased motion perception. Most sufferers encounter practical difficulties in everyday life: few can drive a car, and some lose out on education and employment opportunities. It has a profound effect on self-esteem and confidence in social situations.

Foremost centre for diagnosis and treatment
Long considered an untreatable condition with only limited options for clinical intervention – and therefore largely ignored, IN is now much better understood by the medical community, sufferers and their families, following 13 years of collaborative clinical research by the group. Leicester has become the foremost centre for the diagnosis and treatment of IN in the UK and has made significant advances in meeting the clinical needs of the UK's estimated 88,000 sufferers. The group sees more than 600 patients a year; some 53% of patients, and 66% of new referrals, come from outside the service area, including private referrals from Europe and further afield.

The Development Manager for the Nystagmus Network, says: "*The Group's strengths come from the experience, breadth of skills and dedication of its members… The combination of clinical and research activities in Leicester is a huge advantage to the tens of thousands of families in the UK affected by nystagmus. Not only is the Group able to provide patients with much needed information about nystagmus (often not routinely available elsewhere), they also offer treatment and the hope of new treatment options in the future*." (**A**)

Widespread use of the gene test
The discovery of the *FRMD7* gene has opened up new avenues for identifying the mechanisms underlying the development of IN, which are currently unknown. The genetic test is used in eight centres in the UK, US, Israel, Germany, France and Spain (**B**). A paper in Nature Genetics about the gene sparked major interest from the research community. There are now a total of 36 publications about mutation of function in the gene. The group was asked to write the gene review about IN in 2009 and updated this in 2011 (**C**).

Genetic counselling
The group discovered that IN caused by *FRMD7* mutations is inherited in an X-linked manner. Women who are carriers have a 50% chance of transmitting the mutation to their sons, and 50% of their daughters will become carriers. Once the disease-causing mutation has been identified in the family, carrier testing for at-risk female relatives and prenatal testing for pregnancies at increased risk are possible. This enables parents and prospective parents to know what to expect from future pregnancies and plan accordingly.

Use of new technology
Optical Coherence Tomography (OCT) is a non-invasive and safe diagnostic method, which has resulted in considerable time-saving for the patient and cost-saving for the NHS. Measurements and collection of genetic material can be performed in 20-30 minutes with minimal discomfort. OCT can be used to visualise the eyes in 3D, in a way that has not been possible previously, even in premature infants. The development has received considerable interest from the media (**D**).

Development of drug treatments
Leicester is the leading centre internationally for testing pharmacological treatments for nystagmus. The 2007 trial has led to the prescription of the drugs memantine and gabapentin for control of the symptoms of IN, and they have been shown to improve visual acuity and dampen movement, leading to improvements in quality of life, including enabling some sufferers to start learning to drive. Gottlob is the only ophthalmologist in the UK with a licence to prescribe these drugs (normally available from a neurologist). She is currently formulating national guidelines on the diagnosis and management of IN for the Royal College of Ophthalmologists, aiming at accreditation by NICE.

Insight and support
Nystagmus sufferers reveal almost universally negative feelings about themselves and their condition. Many feel abandoned by health professionals. "*'Go away and forget about it' …that's basically what I've been told all my life"* and *"I went for 40 years and nobody touched me, nobody discussed it. It's on my medical records and yet nobody was out there for me. So there was no help*." are some of the responses to a quality-of-life survey.

The group works closely with Europe's leading nystagmus charity, the Nystagmus Network, in providing crucial information to sufferers and the general public about how nystagmus affects daily lives. One parent wrote via the Network, letter: "*Through the Nystagmus Network I came into contact with Professor Gottlob and her incredible team at Leicester Hospital. I have never met anyone more inspiring, and knew from that day forward my daughter was being seen by the best person in the world on the subject of Nystagmus.*" (**A**) The group has contributed to a book commissioned by the Network and available on Amazon: The Challenge of Nystagmus (**E**).

5. Sources to corroborate the impact

A. Letter from Information Manager, Nystagmus Network.
B. GeneDx, Gaithersburg, USA; GGA - Galil Genetic Analysis Kazerin, HaZafon, Israel; Medizinisch Genetisches Zentrum München, Munich, Germany; Oregon Health and Science University, Casey Eye Institute Molecular Diagnostic Laboratory, Portland, USA; Pronto Diagnostics Ltd., ProntoLab - MLPA Lab, Tel Aviv, Israel; Nottingham University Hospitals NHS Trust (City Hospital), Nottingham, UK; CHU de Nantes, Institut de Biologie, Nantes, France; Sistemas Genómicos S.L, Sistemas Genómicos S.Lalencia, Spain.
C. **Thomas MG, Thomas S, Kumar A, Proudlock FA, Gottlob I.** *FRMD7*-Related Infantile Nystagmus.In: Pagon RA, Bird TD, Dolan CR, Stephens K, editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-. 2009 Feb 12 [updated 2011 Sep 29].
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E. The Challenge of Nystagmus: Proceedings of the Nystagmus Network Research Workshop, Abingdon, UK, 2-5 September. **Irene Gottlob,** Chris Harris, Larry Abel and Andrea Barreiro. 19 Sep 2012