Institution: University of Leicester		
Unit of Assessment: 4		
Title of case study: Improving Diagnosis and Patient Outcomes in Developmental Retinal Diseases (DRDs)		
Period when the underpinning research was undertaken: 2006 – 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
1) Prof Irene Gottlob 2) Dr Frank Proudlock 3) Dr Mervyn Thomas	1) Professor of Ophthalmology 2) Associate Professor of Ophthalmology 3) Lecturer in Ophthalmology and Genomic Medicine	1) 1999 – Present 2) 1999 – Present 3) 2018 – Present
Period when the claimed impact occurred: 2013 – 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Building on 20 years of research, the Ulverscroft Eye Unit (UEU) have taken a multidisciplinary approach to improve assessment, diagnosis and patient outcomes of developmental retinal diseases (DRDs). This includes discovery of new genes and improved genetic testing of known genes for DRDs, subsequently influencing national and international genetic testing strategies, resulting in >1400 tests being performed. The UEU have pioneered high-resolution imaging of the eyes in adults and children with DRDs using optical coherence tomography (OCT). They have developed the Leicester Grading System (LGS) for OCT imaging, an internationally used clinical assessment tool for the severity of retinal abnormalities. This has resulted in earlier, less intrusive diagnosis, enabling earlier access to appropriate resources and clinical planning, putting parents' minds at ease and improving outcomes for patients.

2. Underpinning research

DRDs are a group of disorders presenting early in life, characterised by abnormal retinal development and resulting in poor vision. They are often associated with infantile nystagmus (IN), involuntary movements of the eyes.

DRDs arise from mutation of genes expressed in the developing retina (for example *FRMD7*, *PAX6* or genes for albinism) or from environmental factors (such as premature birth). Approximately 1 million babies are born with DRDs per year, and they are the largest cause of moderate visual impairments worldwide.

Genetic studies

In 2006, the UEU discovered the *FRMD7* gene **[R1]**, mutations of which are a common cause of so-called 'idiopathic' nystagmus, since the visual system of sufferers was otherwise considered normal. Using OCT, the UEU demonstrated that *FRMD7* mutations also caused abnormalities in retinal development **[R2, G1-4]**, causing a type of DRD, changing our understanding of infantile nystagmus (IN).

Subsequently the UEU established the first clinically approved test for *FRMD7* mutations **[G5]** thus providing access to clinical testing for >12,000 patients with IN in the UK. Using next generation sequencing, the UEU subsequently developed and clinically validated the first nystagmus gene panel **[R3]**, which tests for all known genes associated with nystagmus (including *FRMD7*).
Thomas and Gottlob together with Genomics England established clinical criteria for genomic testing in patients with infantile nystagmus as part of the 100,000 genomes project. Thus, for the first time, any patient with IN in the NHS has access to whole genome testing, which not only identifies any genetic contribution to their condition but also opens up avenues of genetic research including further novel gene discovery studies.

High-resolution Imaging of the Eyes

The UEU has pioneered high-resolution imaging of the eyes in DRDs using OCT. They have systematically characterised abnormalities of two key structures of the eye in DRDs: (i) the fovea, responsible for detailed vision, and (ii) the optic nerve head, the exit point for information leaving the eye. This includes studies in albinism, *FRMD7*-related nystagmus, achromatopsia, *PAX6* mutations and retinopathy of prematurity **[G1-4]**.

The UEU is a world leader in using hand-held OCT, a technique enabling children's eyes to be imaged from the earliest ages, permitting eye development to be studied while it is taking place. Our underpinning research has provided insight into normal developmental events of the fovea **[R4]** and optic nerve head **[R5]**. These studies have laid the groundwork for ongoing studies generating paediatric normative data to improve the diagnostic potential of hand-held OCT **[G1-4]**. The first studies using hand-held OCT to document the abnormal developmental trajectory of the fovea and optic nerve head in DRDs, such as retinopathy or prematurity, albinism and *FRMD7*-related nystagmus, are either near completion or have been completed.

The Leicester Grading System (LGS) for foveal hypoplasia, developed by the UEU, is an easy-to-use clinical system to grade the severity of foveal abnormalities. The LGS is used worldwide and has been incorporated into other diagnostic schemes. Our studies into foveal development have allowed us to extend application of LGS into infants and young pre-verbal children with DRDs, thus for the first time we are able to predict vision later in life **[R6]**.

Other studies

To understand the societal and holistic impact of DRDs, the UEU have not only performed landmark studies on impact on quality of life and functional vision (for example reading) but also developed disease specific tools to measure quality of life in these patients.

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

R1. Tarpey, P., et al., Mutations in FRMD7, a newly identified member of the FERM family, cause X-linked idiopathic congenital nystagmus. *Nat Genet*, 2006. 38(11): p. 1242-4.
R2. Thomas, M.G., et al., Abnormal retinal development associated with FRMD7 mutations. *Hum Mol Genet*, 2014. 23(15): p. 4086-93.
R3. Thomas, M.G., et al., Development and clinical utility of a novel diagnostic nystagmus gene panel using targeted next-generation sequencing. *Eur J Hum Genet*, 2017. 25(6): p. 725-734.
R4. Lee, H., et al., Potential of handheld optical coherence tomography to determine cause of infantile nystagmus in children by using foveal morphology. *Ophthalmology*, 2013. 120(12): p. 2714-2724.
R5. Patel, A., et al., Optic Nerve Head Development in Healthy Infants and Children Using Handheld Spectral-Domain Optical Coherence Tomography. *Ophthalmology*, 2016. 123(10): p. 2147-57.
R6. Rufai, S.R., et al., Can Structural Grading of Foveal Hypoplasia Predict Future Vision in Infantile Nystagmus? A Longitudinal Study. *Ophthalmology*, 2020. 127(4): p. 492-500.

G1. Title: Ultra high-resolution optical coherence tomography in infants and children: characterisation of normal and abnormal foveal development (Feb 12 - Feb 15)
Principal Investigator: Irene Gottlob
Awarding body: MRC (MR/J004189/1)
Leicester amount: GBP357,055
G2. Title: Optical Coherence Tomography (OCT) in Children (July 2012 – Feb 2023)
Principal Investigator: Irene Gottlob (2012-20), Frank Proudlock (2021-23)
Awarding body: Ulverscroft Foundation Program Grant
Leicester amount: GBP1,041,945
G3. Title: Can handheld optical coherence tomography improve risk prediction of retinopathy of prematurity? (2019)
Principal Investigator: Irene Gottlob
Awarding body: National Eye Research Centre

Leicester amount: GBP69,748
G4. Title: Optical coherence tomography in infants and children: A normative database and assessment of clinical use (Jan 16 - Jan 19)
Principal Investigator: Irene Gottlob
Awarding body: MRC (MR/N004566/1)
Leicester amount: GBP1,159,287
G5. Title: Improving the Genetic Diagnosis in Infantile Nystagmus (Oct 16 – Oct 17)
Principal Investigator: Mervyn Thomas
Awarding body: Fight for Sight
Leicester Amount: GBP14,250.
G6. Title: Predicting future vision in infants and young children with nystagmus using optical coherence tomography and eye movement recordings (Jan 19 – Sept 20)
Principal Investigator: Mervyn Thomas
Awarding body: Fight for Sight
Leicester Amount: GBP14,999

4. Details of the impact

Impact of genetics on diagnosis

Prior to the discovery of the *FRMD7* gene as a major cause of infantile nystagmus, a range of lengthy testing procedures were required to diagnose DRDs, which could be particularly challenging in young children and distressing for parents. Genetic testing provides a more sensitive, cost-effective alternative for diagnosis that is less time-consuming and onerous for the patient and their families **[E2]**. Since uncovering the *FRMD7* gene as a major cause of infantile nystagmus **[R1]**, the UEU have built a strong portfolio of translational research by implementing clinical testing through single gene-based approaches and multigene panels using next generation sequencing.

The UEU developed the world's first "nystagmus gene panel" **[R3, G5]**, which simultaneously tests multiple genes (including the *FRMD7* gene) associated with nystagmus using next generation sequencing. This method of testing now forms the basis of nystagmus genetic testing in the NHS and around the world. Within the UK, this is implemented locally or accessed via genomic laboratory hubs. Data capture from individual clinical genetic labs in the UK and France have shown that testing has been performed in over 1,400 patients with nystagmus. Worldwide testing is performed in multiple centres in over 14 countries **[E1]**.
At a national level, the UEU have been pivotal, not only in disease nomination, but in also devising a virtual gene panel for infantile nystagmus as part of the 100,000 genomes project. The virtual gene panel forms the basis of clinical genetic testing and includes the *FRMD7* gene and crucial genes highlighted in our nystagmus gene panel. This can also be accessed via PanelApp, which is an online open access tool permitting gene panels, such as the nystagmus gene panel, to be shared, downloaded and viewed by the scientific community; >3,000,000 requests have been made by over 17,000 unique visitors **[E1b, G5, R3]**. The use of genetic testing has been captured through questionnaires distributed to international centres for patients with nystagmus and DRDs **[E2]**. These indicate that not only does it result in earlier diagnosis but that in 15-25% of cases, the initial clinical diagnosis was revised because of genetic testing **[E1b, R3]**. The work, led by the University of Leicester, on development and clinical validation of the nystagmus gene panel has formed the basis of guidelines for nystagmus clinical genetic testing in countries such as the USA, Netherlands and South Korea **[E2]**.

Accurate diagnosis of DRDs is challenging with misdiagnosis being a common problem. Other causes of nystagmus such as neurological disorders and syndromes are important to exclude. As outlined in clinical guidelines published by the American Academy of Ophthalmology in February 2020: *"Genetic testing plays an important role in establishing the final diagnosis of infantile nystagmus … FRMD7 infantile nystagmus (FIN) must be confirmed with genetic testing for FRMD7 mutations"* **[E3]**. One paediatric ophthalmologist from the National Eye Institute, USA has stated: *"We use genetic testing as one tool to help differentiate retinal dystrophies from other forms of nystagmus, the genetic testing has been critical"* **[E2]**. Guidance published by the

American Academy of Ophthalmology in February 2020 stated: *"Genetic testing plays an important role in establishing the final diagnosis of infantile nystagmus … FRMD7 infantile nystagmus (FIN) must be confirmed with genetic testing for FRMD7 mutations"* **[E3]**.

Impact of High-resolution imaging studies on diagnosis and patient outcomes

The Leicester Grading System (LGS) was devised to quantify the severity of delay in foveal development based on a series of ground-breaking studies that characterised foveal abnormalities in DRDs for the first-time using OCT **[G1-G4]**. These studies included disorders such as *FRMD7*- **[R3]** and *PAX6*- associated nystagmus, albinism and achromatopsia. The simple-to-use system allows the fovea to be assessed in minutes and is now used widely by ophthalmologists around the world as an extension of their clinical exam **[E2].** A paediatric ophthalmologist from University of Ulsan College of Medicine, South Korea has stated: *"The LGS has enormously helped us classify the severity of foveal hypoplasia and predict the later visual acuity, especially in patients with aniridia, infantile nystagmus, albinism, and prematurity. I am a huge proponent of the grading system".* A paediatric ophthalmologist at the Bartiméus Diagnostic Centre for Complex Visual Disorders, Zeist, Netherlands said: "*Since the publication of the 2011 paper on grading of foveal hypoplasia, we use the grading system routinely in our clinical* practice" **[E2]**.

The LGS is a key element of new clinical schemes for the diagnosis of DRDs **[E4]** including albinism as indicated in the Filière Santé Maladies Rares Dermatologiques National protocol **[E5]**. The LGS determines which genetic panels are used for genetic diagnosis **[E1b]**, and therefore remains central to the diagnostic process in DRDs. Thus, validated approaches and tools provided by UEU in the fields of genetics and OCT have resulted in a paradigm shift in the diagnostic workup and outcomes for DRDs. The LGS and genetic testing are essential parts of the diagnostic workflow that forms the basis of clinical practice across specialist paediatric nystagmus services in the UK **[E3, E6]**.

Using hand-held OCT, researchers at the University of Leicester have been able to demonstrate that the LGS predicts vision later in life for young pre-verbal infants **[R6, G6]**. This can be particularly worrying for parents as these children are not able to communicate the extent of their vision. Knowledge of future vision can allay the anxiety of parents of children with nystagmus. One parent has commented: *"The OCT was essential in helping us to get a better understanding of what our daughter's visual impairment meant for her … I can't imagine how I would be feeling without that assurance and information the OCT was able to yield!"* **[E7]**. This very early diagnosis can make a huge difference to the outcomes for these children, who can be directed towards low vision resources, such as educational support, much earlier. This gives the best chance to support their developmental and educational achievements. Early diagnosis can also aid clinical decision-making and treatment planning.

Raising awareness and impact on clinical practice

Information generated from research into the impact of DRDs on quality of life and vision in daily life, was fed back directly to individuals with DRDs through patient-led conferences. Research from UEU has formed the basis of talks to people with DRDs on vision in daily life and on mental wellbeing. Joe Ambrico, the Vice President and research liaison for the American Nystagmus network has commented: *"The American Nystagmus Network and its members are grateful for the continued support you have provided by sharing the results of your research at ANN events ... your research tends to focus on very practical matters that are of great interest to our members"* **[E8]**.

The expertise developed by the UEU has led to the development of Leicester as a referral point and centre of excellence for the management, diagnosis and treatment of DRDs and the clinic sees >600 patients with nystagmus per year, as well as neuro-ophthalmic and childhood eye diseases **[E9]**.

Leicester is also an important centre for education in DRDs and high-resolution imaging of the retina, running international courses and training clinical staff since 2015. Gottlob and team have

trained >100 clinicians at the Leicester Royal Infirmary Hospital and at Birmingham Children's Hospital in the use of their improved hand-held OCT scanning **methodology** and **LGS [E10]**.

Interest in this approach is extending globally, in September 2020, a live clinical symposium on clinical applications of hand-held OCT was attended by participants from 82 countries from Asia-Pacific, European Union, Latin-American, North East European, Middle East, African and North American regions.

5. Sources to corroborate the impact

E1. NCBI Genetic testing Registry and Panel App Tool.
(a) https://www.ncbi.nlm.nih.gov/gtr/all/labs/?term=90167[geneid]
(b) https://panelapp.genomicsengland.co.uk/panels/246/
E2. Feedback from clinicians at international centres for DRDs disease.
E3. Clinical Guidelines of the American Academy of Ophthalmology (aao.org): Clinical Guidelines: Childhood Nystagmus Workup - American Academy of Ophthalmology (aao.org)
E4. Publications using the Leicester Grading Scheme as the standard for grading foveal hypoplasia (https://www.scopus.com/record/pubmetrics.uri?eid=2-s2.0-79961029653&origin=recordpage)
E5. Filière Santé Maladies Rares Dermatologiques National protocol (p19): pnds_albinisme14juillet_2019-10-11_16-18-32_87.pdf (has-sante.fr)
E6. Diagnostic workflow that forms the basis of clinical practice across specialist paediatric nystagmus services in the UK: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7608566/
E7. Testimonial from parent of child with nystagmus.
E8. Testimonial from the Research Liaison and Vice President of the American Nystagmus Network (ANN).
E9. Referrals to the Leicester Clinic because of expertise developed in DRDs.
E10. International training by the UEU **"***Summary statistics from live international clinical symposium.docx".*