**Institution:** The University of Manchester

**Unit of Assessment:** 5 (Biological Sciences)

**Title of case study:** Transforming the management of people with inherited eye diseases: a paradigm for the implementation of genomic medicine

**Period when the underpinning research was undertaken:** 2012 - 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: |
|---|---|---|
| Graeme Black | Professor of Genomics & Ophthalmology | 2001 - present |
| Panos Sergouniotis | NIHR Clinical Lecturer in Ophthalmology | 2017 - present |
| | Honorary Research Fellow | 2013 - 2017 |
| Jamie Ellingford | Health Education England Postdoctoral Research Fellow | 2017 - present |
| Rachel Taylor (formerly Gillespie) | MRC/UKRI Innovation Fellow | 2017 - present |
| | MRC Skills Development Fellow | 2016 - 2017 |
| | Research Associate | 2015 - 2016 |

**Period when the claimed impact occurred:** August 2013 - December 2020

**Is this case study continued from a case study submitted in 2014?** No

## 1. Summary of the impact

Inherited eye diseases are a leading cause of blindness in children and working-age adults. Pre-2012, clinical genetic testing for these conditions was non-existent or sporadically undertaken. University of Manchester (UoM) researchers generated the evidence-base to transform the landscape of genetic testing for people with inherited blindness. This has revolutionised clinical practice and enabled more precise diagnoses, better counselling and personalised management for 8,919 patients referred from the UK and internationally. Their impact has also: (i) contributed to national and European guidelines for clinical management, (ii) introduced tools for international, clinical-grade data sharing, (iii) developed an ophthalmic gene therapy centre in the North of England.

## 2. Underpinning research

Basic and translational research from the UoM ophthalmic genetics group has led to a paradigm shift in the clinical care of inherited blindness. This work was mostly funded by medical research charities (such as Fight for Sight, Retina UK) and involved working with patients, for patients. Three key themes include:

### (i) Elucidating disease processes in the human eye

In the past three decades, over 500 genes have been found to be associated with visual impairment. UoM researchers have led the identification of over 30 novel disease-associated genes and contributed towards the discovery of many other genetic disorders.

In one notable example [1], UoM researchers have shown that a specific blinding disorder (coloboma with retinal degeneration) is caused by changes in the microRNA *miR-204*. MicroRNAs are small stretches of RNA that are directly involved in the regulation of gene expression. The study highlighted miR-204 as a new “master regulator” of eye development

and was one of the first to highlight the role of microRNAs as primary pathogenic agents in human disease.

**(ii) Development of next generation sequencing (NGS) genetic testing for mainstream ophthalmology**

UoM researchers were early developers of NGS gene panels (e.g. [2]). Their research has quantified the potential for improvement that could be facilitated by this approach over other testing methodologies. They have demonstrated that NGS techniques offer opportunities to: increase the number and the precision of ophthalmic diagnoses (e.g. [2,3]), alter clinical care pathways [2,4] and enhance economic impact [5] in many blinding conditions.

An example of such a condition is cataract. In a cohort of 36 individuals recruited locally, the researchers identified that NGS can increase the number of people receiving a definitive diagnosis from 3% to 75%. They have followed these studies with quantitative assessments of economic impacts, demonstrating that NGS techniques are 14 times more efficient than standard methodologies for clinical management [5].

In addition, they were the first research group in the UK to develop NGS panel sequencing methods for inherited retinal diseases (IRDs). Using a study group of 50 individuals they demonstrated an increased number of genetic diagnoses from 25% to 50% as a result of NGS testing [3]. Further, through in-depth analysis of a cohort of 201 preschool children, they have shown that NGS testing leads to changes in management for 1 in 3 individuals [4].

**(iii) Catalysing the development and delivery of treatments for inherited retinal diseases**

UoM researchers have contributed to landmark clinical trials assessing the efficacy of gene therapy strategies for inherited blindness. For example, they have developed clinical cohorts of individuals with choroideremia and X-linked retinitis pigmentosa suitable for gene-based therapeutic interventions (e.g. NCT01461213). They have contributed to natural history studies and to the delineation of end-points suitable for clinical trials. In one example, they have shown that people with mutations in the *CHM* gene who received the AAV.REP1 adeno-associated virus have improved visual acuity [6].

**3. References to the research**


1. Conte I, Hadfield KD, Barbato S, Carrella S, Pizzo M, Bhat RS, Carissimo A, Karali M, Porter LF, Urquhart J, Hateley S, O'Sullivan J, Manson FD, Neuhauss SC, Banfi S, **Black GC**. MiR-204 is responsible for inherited retinal dystrophy associated with ocular coloboma. *Proc Natl Acad Sci U S A*. 2015;112:E3236-45. DOI: 10.1073/pnas.1401464112
2. **Gillespie RL**, O'Sullivan J, Ashworth J, Bhaskar S, Williams S, Biswas S, Kehdi E, Ramsden SC, Clayton-Smith J, **Black GC**, Lloyd IC. Personalized diagnosis and management of congenital cataract by next-generation sequencing. *Ophthalmology*. 2014;121:2124-37.e1-2. DOI: 10.1016/j.ophtha.2014.06.006
3. O'Sullivan J, Mullaney BG, Bhaskar SS, Dickerson JE, Hall G, O'Grady A, Webster A, Ramsden S, **Black GC**. A paradigm shift in the delivery of services for diagnosis of inherited retinal disease. *J Med Genet* 2012;49:322-326. DOI: 10.1136/jmedgenet-2012-100847
4. Lenassi E, Clayton-Smith J, Douzgou S, Ramsden SC, Ingram S, Hall G, Hardcastle CL, Fletcher TA, **Taylor RL, Ellingford JM,** Newman WD, Fenerty C, Sharma V, Lloyd IC, Biswas S, Ashworth JL, **Black GC, Sergouniotis PI**. Clinical utility of genetic testing in 202 pre-school children with inherited eye disorders. *Genet Med*. 2020;22(4):745-751. DOI: 10.1038/s41436-019-0722-8
5. Davison N, Payne K, Eden M, McAllister M, Roberts SA, Ingram S, **Black GCM**, Hall G. Exploring the feasibility of delivering standardized genomic care using ophthalmology as an example. *Genet Med.* 2017;19:1032-1039. DOI: 10.1038/gim.2017.9

6. MacLaren RE, Groppe M, Barnard AR, Cottriall CL, Tolmachova T, Seymour L, Clark KR, During MJ, Cremers FP, **Black GC**, Lotery AJ, Downes SM, Webster AR, Seabra MC. Retinal gene therapy in patients with choroideremia: initial findings from a phase 1/2 clinical trial. *Lancet*. 2014 Mar 29;383(9923):1129-37. DOI: 10.1016/S0140-6736(13)62117-0

## 4. Details of the impact

To improve care and outcomes for patients with inherited eye diseases (IEDs), UoM research has led to the development, and widespread introduction, of powerful genomic tests within the healthcare setting, driving the development of novel therapeutics. Impact has been in the following areas:

### (i) Elucidating disease processes in the human eye

UoM researchers have assembled a cohort of individuals with IEDs (>8,000, one of the largest globally). Analysis of this cohort led them to discover >30 novel disease-associated genes. This underpinned development of >100 genetic tests, listed in the NCBI Genetic Testing Registry [A]. Consequently, hundreds of patients globally have benefitted, through access to precise diagnosis and tailored genetic counselling.

### (ii) Implementing genomic medicine for ophthalmology nationally and internationally

Before 2012, comprehensive genetic testing was available to only a small subset of families with IEDs (15% of patients with IRD; 0% with congenital cataract) partly due to low diagnostic rates (<20%). Work between UoM and the NHS led to the development and introduction of new NGS-based tests [B]. The analytical and clinical validity of research testing was demonstrated, initially in IRD [3]. Consequently, healthcare providers in Greater Manchester then throughout the UK funded testing for these patients.

Patients have benefitted significantly. UoM research demonstrated how genetic testing: (i) provides a precise/timely diagnosis, (ii) predicts future complications, (iii) identifies unrecognised systemic features, (iv) confirms eligibility for sight-saving gene-based interventions, (v) informs reproductive and life planning. As a direct result, since August 2013 8,919 patients with IEDs have received genetic testing in Manchester (Figure 1). Clinicians from 47 countries have accessed this service (936 referrals from outside UK). Within the UK, 77% of referrals are from outside the North West. The diagnostic rate for retinal disease, for example, has increased from <15% (pre-2012) to ~80% (2020) [3,4,C]. Since 2018, NHS England has centrally funded genomic testing and established seven genomic laboratory hubs.

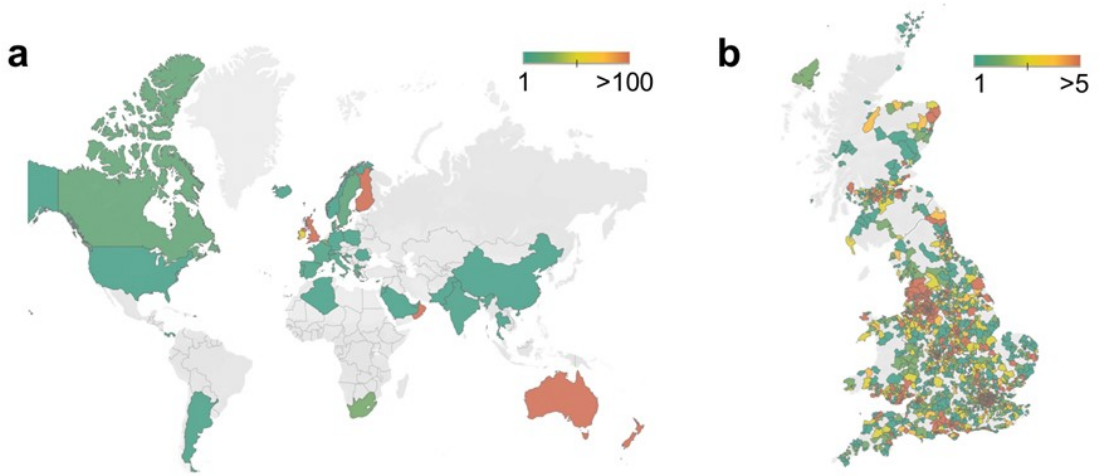


***Figure 1.*** *Referrals to the Manchester laboratory for genetic testing of patients with inherited eye disease. (a) International. NB countries with >100 referrals are: Australia, Finland, New Zealand, Oman and UK. (b) UK (excluding Northern Ireland). The plot illustrates the number of patients referred for testing by the outward postcode of their home address.*

UoM pioneered the use of NGS-based testing for another blinding disorder, congenital cataract. UoM researchers demonstrated the clinical utility (percentage of patients for whom management was changed) and cost-effectiveness (reduced appointments and investigations) of this test, and proposed a novel, more efficient care pathway. This was implemented nationally in the healthcare setting (as per Royal College of Ophthalmologists Genomics Services Guidance (2020) [D]).

*"The University of Manchester … team have, over a number of years, undertaken research that has had an important influence on health policy and delivery of ophthalmic genetic care (…)This is a case par excellence, illustrating the pull through from basic research resulting in beneficial service implementation"* (President Academy Medical Royal Colleges) [E].

Working with patient and professional groups, the UoM team has increased awareness of the broader benefit and issues of genetic testing as a mainstream tool for ophthalmologists. *"The Manchester University team's work has been fundamental in a number of areas. … Over the past 5-7 years we have seen a rapid expansion in the number of community members who have accessed genetic testing…. The work carried out at Manchester has made a significant contribution opening up choices for our community."* (CEO, Retina UK) [C].

The UoM team has also achieved significant international impact, partly via their role as workgroup leader of the European Reference Network on Rare Eye Diseases (ERN-EYE).

*"We have been guided by the work of the Genetics Group at Manchester to assess, develop and implement an integrated pathway. We now have expert centres seeing patients more promptly than ever before … all based on a model born in Manchester. We have seen nearly 1500 patients (…) all part of an integrated care pathway that did not exist in 2015."* (Clinical Professor of Ophthalmology, University College Dublin [F]).

"*The University of Manchester research team has been an outstanding pioneer in the building of the ERN-EYE by leading major interest working groups especially for the genomic testing in the EU, clinical practice guidelines …"* (Coordinator of ERN-EYE) [G(i)].

The UoM team also:

- led on drafting guidelines for genetic testing for rare eye diseases in the EU [G(ii)].
- led efforts to harmonise collection and classification of clinical data, recognised internationally: the relevant terminology was reviewed and ratified at an ERN-EYE workshop (2017) attended by 60 experts from 17 countries [G(iii)]. This resource - the first effort of such scale to provide terminology standards for the rare eye disease community - is used by most patient registries and many electronic healthcare records.
- were the sole ophthalmologists, "*instrumental in the design and structure*" of the DECIPHER eye phenotyping interface [H]. DECIPHER is a widely-used web-based tool that captures clinical data in a standardised way to enable data sharing, and currently openly shares >36,000 rare disease patient records deposited by >250 clinical genetic centres worldwide [H].

**(iii) Catalysing the development and delivery of treatments for inherited retinal diseases**

UoM is at the forefront of developing and delivering gene-based treatments for IEDs. UoM had a prominent role in trials for two blinding conditions, choroideremia and X-linked retinitis pigmentosa. Most UK patients who participated in the gene therapy trials for RPE65-related retinal disease had genetic testing at Manchester. "*By delivering the genetic testing for such programmes, as well as recruiting patients and in some cases undertaking the surgery, the research group at the University of Manchester has also contributed significantly to this body of work*." (President Academy of Medical Royal Colleges) [E]. This work has led to: the first delivery of gene therapy at Manchester Royal Eye Hospital (2017; as research) [I(i)]; NHS England designation of Manchester Royal Eye Hospital as one of the national centres for ophthalmic gene therapy (2019) [E]; the first patient successfully treated with ophthalmic gene therapy in Manchester (2020; as standard NHS care) [I(ii)].

## 5. Sources to corroborate the impact

A. National Center for Biotechnology Information (NCBI) Genetic Testing Registry, listing over 100 tests based on UoM research (examples of genes include *KCNJ13* and *DRAM2*).

B. Examples of publicity for NGS-based genetic tests developed by UoM: BBC News, 16 September 2013, "Child cataract blood test developed". Eyeworld International outlook, October 2015, "New DNA sequencing very personally diagnoses congenital cataracts".

C. Statement from CEO, Retina UK (23 November 2020), confirming the beneficial impact of UoM's research on the inherited retinal disease community; Retina UK news article: "Genetic testing: an essential topic for discussion with the IRD community", 13 February 2020.

D. Royal College of Ophthalmologists Genomics Services Guidance, February 2020 (co-authored by Graeme Black), proposing a novel, more efficient care pathway based on UoM research, which has been implemented nationally.

E. Statement from Chair, Academy of Medical Royal Colleges (20 January 2020), confirming the clinical benefits of UoM's research.

F. Statement from the Professor of Ophthalmology and Retina at the University College Dublin (7 September 2020) confirming the impact and influence of the UoM researchers on the care pathways implemented for patients with inherited eye disease in Ireland. The signatory is also Consultant Ophthalmic Surgeon (Mater University Hospitals) and co-founder of the Irish national registry for inherited retinal degenerations.

G. International impacts via UoM role as workgroup leader of the European Reference Network on Rare Eye Diseases (ERN-EYE):

(i) Statement from the coordinator of the ERN-EYE (14 June 2020), confirming UoM's role in this international network, including on the development of clinical practice guidelines.

(ii) ERN-EYE draft publication on genetic testing in ophthalmology: "The need for widely available genomic testing in rare eye diseases: an ERN-EYE position statement". G.Black, P.Sergouniotis, A.Sodi, F.Cremers, E.De Baere, H.Dollfus, ERN-EYE study group (under review December 2020).

(iii) ERN-EYE publication on terminology standards for the rare eye disease community: "An ontological foundation for ocular phenotypes and rare eye diseases". **Sergouniotis PI**, Maxime E, Leroux D, Olry A, Thompson R, Rath A, Robinson PN, Dollfus H; ERN-EYE Ontology Study Group. Orphanet J Rare Dis. 2019; doi: 10.1186/s13023-018-0980-6.

H. Statement from DECIPHER Project Manager (15 July 2020) confirming the vital role of UoM in its development.

I. Publicity for gene-based treatments for IEDs, underpinned by UoM research:

(i) Invest in Manchester News, 29 August 2017: "Manchester Royal Eye Hospital administers its first gene therapy treatment".

(ii) NHS News, 17 February 2020: "First patients begin gene therapy treatment for blindness as part of NHS Long Term Plan" and Daily Mail, 5 October 2020: "'Doctors saved my sight by injecting a gene into my eye': Experts say this cutting-edge technique could one day also help many with age-related vision loss" (article quoting the first patient to receive gene therapy treatment in Manchester, 8 months after treatment).