Institution: University of Birmingham

Unit of Assessment:UoA1

Title of case study: Improving diagnosis and clinical care for rare inherited diabetes syndromes

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

Although individually infrequent, rare diseases collectively are a major health burden, particularly for individuals who suffer with conditions that are not routinely diagnosed or have no effective care pathways. Through the work of Professor Tim Barrett, the University of Birmingham is internationally recognised for translational research in rare inherited diabetes and obesity syndromes. This has had major impacts on patient care through gene identification for devastating multi-system syndromes; development of a unique international diagnostic testing service combining molecular testing with international clinical expertise; European reference centre status for three NHS highly specialised multidisciplinary services; and leadership of the European Registry for rare diabetes syndromes. Our national and international leadership for these previously poorly-served conditions has enabled sharing of best clinical practice, including development of clinics for Wolfram syndrome across the world.

2. Underpinning research (indicative maximum 500 words)

Rare diseases affect less than 5 people in 10,000. However, there are over 6,000 rare diseases, and although individually of a low frequency, collectively they account for disease in 5-10% of the UK population. The vast majority of these diseases are genetic, i.e. caused by mutations (mistakes) in single genes. We all inherit two copies of all our genes, one from each parent. Rare diseases most often affect people who have inherited mutations in both their copies of a single gene. Their parents are healthy because each is a carrier for one healthy and one mutated copy. This is called autosomal recessive inheritance.

Through the work of Professor Tim Barrett (Professor of Paediatrics, clinical research fellow 1994-1996; honorary member of staff 1996-1998 and full member of staff at UoB since 1998), Professor Eamonn Maher (UoB 1996-April 2013), and Professor Karen Morrison (at UoB since 1999), and a translational research environment built around strong strategic relationships with our local NHS Trusts and outstanding scientific research facilities, the University of Birmingham has developed an international reputation in rare diabetes syndromes.

Wolfram Syndrome is a rare genetic disorder, causing diabetes (usually diagnosed around 6 years of age), optic atrophy (typically diagnosed around 11, and leading to blindness by the age of 20), and deafness. Life expectancy for children born with this disorder is around 30 years. In work dating back to 1994, Professor Barrett has been at the forefront of the understanding of the genetic and cellular mechanisms of Wolfram syndrome in children and adults. This work began with a clinical characterisation study of UK families (1), then a genetic linkage analysis, demonstrating the pattern of inheritance (2). Once the gene was identified, he published a mutation analysis of UK patients (3). Key discoveries include: (i) characterising the progression of the syndrome and timing of complications; (ii) demonstration that the genetic mechanism is autosomal recessive rather than mitochondrial inheritance; (iii) narrowing of the candidate gene to a region on chromosome 4p containing only about 20 genes; (iii) definition of the UK mutational spectrum of the *wfs1* gene in the pathogenesis of Wolfram syndrome, thereby supporting development of NHS diagnostic services.

Alstrom Syndrome is a rare genetic recessive disease which leads to multi-organ dysfunction, characterised by early-onset diabetes, childhood obesity, blindness and deafness. Professor Barrett's work on this disorder was the first to demonstrate the full range of genetic mutations in affected UK families; demonstrating severe insulin resistance in affected children out of all proportion to their degree of obesity (4).

Other rare diabetes syndromes have also been a related research focus. In collaborations with partners in Haifa, Israel and Lyon, France, Professor Barrett played a crucial role in identifying and characterising children with Wolcott-Rallison syndrome and Thiamine Responsive Megaloblastic Anaemia, Diabetes and Deafness (TRMA), respectively (5,6). The characterisation of Birmingham and UK families was crucial to the discoveries of the genes responsible for these diseases.

Subsequent characterisation of these and other families has led to the recognition of the underlying cellular mechanisms responsible for these conditions - endoplasmic reticulum stress in Wolcott-Rallison syndrome and defective thiamine transport underlying TRMA.

The work of this team, associated with their ability to test novel treatments through the paediatric satellite facility of the University's NIHR/Wellcome Trust Clinical Research Facility at Birmingham Children's Hospital, has resulted in Professor Barrett being appointed to lead the NIHR Rare Diseases Translational Research Collaboration Paediatric Cross-cutting Theme. This award was based largely on internationally recognised research expertise and leadership in paediatric rare diseases, evidence of leadership of multi-centre research programmes and evidence of collaboration with industry in rare diseases research.

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

1. **Barrett T**, Bundey S, MaCleod A. Neurodegeneration and Diabetes; UK Nationwide Study of Wolfram (DIDMOAD) Syndrome. Lancet 1995;346:1458-63.*doi:10.1016/S0140-6736(95)92473-6*
2. Collier DA, **Barrett TG**, Curtis D, Macleod A, Arranz MJ, Maassen JA, Bundey S. Linkage of Wolfram syndrome to Chromosome 4p16.1 and Evidence for Heterogeneity. Am J Hum Genet 1996;59:855-863. *PMC1914816*
3. Hardy H, Khanim F, Torres R, Scott-Brown M, Sellar A, Poulton J, Collier D, Kirk J, Polymeropoulos M, Latif F, **Barrett T**. Clinical and Molecular Genetic Analysis of 19 Wolfram Syndrome Kindreds Demonstrating a Wide Spectrum of Mutations of WFS1. Am J Hum Genet 1999;65: 1279-1290. *PMC1288280*
4. Minton J, Owen K, Ricketts C, Crabtree N, Shaikh G, Ehtisham S, Porter J, Carey C, Hodge D, Paisey R, Walker M, **Barrett T**. Syndromic obesity and diabetes; changes in body composition with age and mutation analysis in 12 UK kindreds with Alstrom syndrome. J Clin Endo Metab 2006;91: 3110-6*. DOI 10.1210/jc.2005-2633*
5. Labay V, Raz T, Baron D, Mandel H, Williams H, **Barrett T**, Szargel R, McDonald L, Shalata A, Nosaka K, Gregory S, Cohen N. Mutations in SLC19A2 cause thiamine-responsive megaloblastic anaemia associated with diabetes mellitus and deafness. Nat Genet 1999;22(3):300-4*. PMID10391221*
6. Delepine M, Nicolino M, **Barrett T**, Golomaully M, Lathrop G, Julier C. E1F2AK3, encoding translation initiation factor 2-alpha kinase 3, is mutated in patients with Wolcott-Rallison syndrome. Nature Genetics 2000;25:406-9. PMID10932183

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

Although individually infrequent, collectively rare diseases are common and have a profound effect on patients and their families (as around 80% are inherited, family members may be affected or at risk of having affected children). The need to improve the diagnosis and management of rare diseases is important not only because of the overall numbers of people affected, but also because many common clinical syndromes are now believed to comprise subsets of rare diseases. An investigation by Rare Disease UK found that 46% of patients waited over a year for correct diagnosis following onset of symptoms (with 19% waiting from 5 to over 20 years), 46% were misdiagnosed initially, and "the majority of patients' care is poorly coordinated" [1]. This is because clinical expertise and resources for such patients can be scarce and complex treatments can involve several specialists, who may have little or no experience in identifying optimal care pathways for rare conditions. In 2009, Sir Liam Donaldson (then Chief Medical Officer of England) highlighted diagnosis and management of rare diseases as one of five key areas of public health for the NHS to tackle in his Annual Report.

In Birmingham, Professor Tim Barrett has driven fundamental research into the genetic causes and molecular mechanisms of rare diabetes syndromes: meticulously mapping real patient needs and requirements for optimised multi-disciplinary care in these patients by detailed genotype-phenotype studies. He has successfully translated this work into clinical practice, which has transformed the care for the affected patients and their families. His initiatives to work with patient groups in developing services have just been highlighted in a new Rare Disease UK report on criteria for centres of excellence [2]. Specific impacts include:

1. The development and implementation in routine clinical practice of **a national genetic diagnostic testing service for Wolfram and Alstrom syndromes**, facilitated by the characterisation of the genes for these conditions by Professor Barrett's team. These tests are offered through the West Midlands Regional Genetics Laboratory, which has now become the **national reference centre for genetic testing** for these two diseases, with both tests **adopted by the UK NHS Diagnostic Testing Network (UKGTN)** [3]. The NHS service also undertakes genetic testing for Spain, Malta, India, Brazil, Slovenia and Iran.

2. The **establishment of nationally commissioned, highly specialised multidisciplinary services for Wolfram, Alstrom and Bardet-Biedl syndrome patients**. Molecular and clinical research in Birmingham has transformed healthcare in several inherited versions of diabetes and obesity that are characterised by multi-system involvement; this means that affected patients do not only suffer from diabetes and obesity but also have other complex multisystem problems requiring multi-disciplinary care. Professor Barrett's laboratory work in this respect has tied in closely with his patient care, and through this he has improved quality of life for patients through integrated multi-disciplinary specialist care established as nationally commissioned services. Further work from this group has led to the successful application to deliver highly specialised multidisciplinary services for Wolfram syndrome and Alstrom syndrome (University Hospitals Birmingham (UHB) and Birmingham Children's Hospital (BCH) are the national centres for adults and children respectively delivering both of these services), as well as Bardet-Biedl syndrome (UHB and BCH are two of the four centres delivering this service) [4-6]. These services are commissioned by NHS England and deliver a 'one stop shop' service to patients from all over the UK, Northern Ireland, and abroad. Data from their national audit days shows objective and measurable improvements in quality of life, earlier ages at diagnosis, and children reaching adulthood with reduced morbidities compared to children before the services were established [7]. These highly specialised services are regarded by patients and staff alike as 'the jewel in the crown' of the NHS for their patient-centred care, individualised appointments and coordination of services to maximise efficiency, and their efforts were recognised by an award from Alstrom syndrome UK at their 10th anniversary conference to celebrate the establishment of the world's first Alstrom syndrome paediatric clinic at BCH [8].

Orphanet (www.orpha.net) is the European portal for rare diseases and orphan drugs and the repository for European services, reports and resources in the field. The three services in Birmingham for Wolfram, Alstrom, and Bardet-Biedl syndromes are listed as Designated European centres of expertise for these conditions, and receive referrals from other European states (including Malta, Spain, Republic of Ireland) who do not have designated specialist centres [9].

Professor Barrett also chairs the NHS England Clinical Reference Group for Specialised Diabetes, responsible for advising the NHS on rare disease services. Under Professor Barrett's leadership since April 2013, the impact has been to revise each service specification, setting process and quality standards, and creating quality dashboards with which NHS England will monitor outcomes [10].

3. The **creation of a European network of excellence as a platform for rapid translation of research progress into clinical care**, and influencing international best practice. Under the leadership of Professor Barrett through the EU funded **EURO-WABB** (European Wolfram-Alstrom-Bardet-Biedl) project [11], a European reference network for these rare diseases has been developed, incorporating a network of European genetic testing laboratories, a European registry with over 300 patients registered from 13 different states, and consensus management guidelines for health professionals. The network has just been presented at a dedicated symposium at the European Society for Paediatric Endocrinology international meeting, presented at the International Society for Paediatric and Adolescent Diabetes meeting, and has been selected by the Directorate General for Health as an exemplary European public health project.

This has informed policymakers both within the rare disease community in the UK as well as those developing plans internationally to support rare diseases. For example, Washington University wrote a letter of support [12] stating that *"Professor Barrett presented details of this initiative to the*

International Wolfram Syndrome meeting in Paris in 2010. After hearing Professor Barrett's presentation, Professor Alan Permutt at Washington University began organizing a Wolfram Syndrome Research Clinic in St Louis. This research clinic began with 10 patients in 2010 and now has 23 enrolled patients seen annually. Our research clinic has been supported by the American Diabetes Association, Washington University and the Jack and J.T. Snow Foundation". Similar support was given to colleagues in Almeria, Spain, and their local Hospital "La Inmaculada" wrote to confirm that *"…the meetings on Wolfram's held in Paris within the EUROWABB framework project, specially, the 2010 meeting, provided me with a quite clear idea of how to organise a Clinical Unit on Wolfram's syndrome. Based on these ideas, arisen in these meetings, I organized the clinical unit of Wolfram's syndrome in Almeria, Spain. I discussed with Dr Barrett, the setting up of our Wolfram clinic. This now includes an expanding multidisciplinary team. Children and young adults attend over 2 days for a range of investigations."* [13]

Children with the rare diabetes syndromes Wolcott-Rallison and Thiamine Responsive Megaloblastic Anaemia, Diabetes and Deafness (TRMA) are also seen in the NHS national multidisciplinary rare disease clinics established in Birmingham; and included in the international EURO-WABB rare diabetes syndromes registry, ensuring that the clinical infrastructure established by Professor Barrett and colleagues to translate University of Birmingham research findings into improvements in patient care is used to its full potential.

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

1. Rare Disease UK – Experiences of Rare Diseases: An Insight from Patients and Families (2010) http://www.raredisease.org.uk/documents/RDUK-Family-Report.pdf
2. Rare Disease UK – Centres of Excellence for Rare Diseases (2013). http://www.raredisease.org.uk/documents/Website%20Documents%20/centres-of-excellence-10-a4.pdf
3. List of tests offered by West Midlands Region Genetics Service through UK Genetic Testing Network: http://ukgtn.nhs.uk/fileadmin/uploads/ukgtn/Documents/Resources/Library/Reports_Guidelines/NHS_Directory_of_Genetic_Testing/UKGTN%20Directory%20of%20Genetic%20Testing%20version%20v10%20FINAL.pdf
4. NHS England: Specialised diabetes services http://www.england.nhs.uk/resources/spec-comm-resources/npc-crg/group-a/a17/Alstrom Syndrome service (all ages) each relates to statement about clinical reference group for highly specialised diabetes
5. NHS England: Specialised diabetes services http://www.england.nhs.uk/resources/spec-comm-resources/npc-crg/group-a/a17/Bardet-Biedl Syndrome service (all ages)
6. NHS England: Specialised diabetes services http://www.england.nhs.uk/resources/spec-comm-resources/npc-crg/group-a/a17/ Wolfram Syndrome service (all ages)
7. Paediatric clinic Alstrom audit day presentation March 8th 2013
8. Spring 2008 Alstrom Syndrome UK Support Group newsletter
9. Orphanet directory of specialised services: http://www.orpha.net/consor/cgi-bin/Clinics_Search_Simple.php?lng=EN
10. Revised 2013 service specifications for Alstrom, Bardet-Biedl and Wolfram syndromes
11. EURO-WABB website (www.euro-wabb.org)
12. Letter of support from Washington University in St Louis
13. Letter of support from Hospital "La Inmaculada", Almeria, Spain