Institution: University of Cambridge		
Unit of Assessment: UOA1		
Title of case study: Resolving the genetic basis**,** diagnosis and treatment of serious disorders of energy balance and metabolism.		
Period when the underpinning research was undertaken: Jan 2000–June 2018		
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:**
Stephen O'Rahilly	Prof of Clinical Biochemistry and Medicine	1991–present
Ismaa Sadaf Farooqi	Prof of Metabolism and Medicine	1997–present
David Savage	Prof of Molecular Metabolism	2001–present
Robert Semple	Reader in Endocrinology and Metabolism	2007–2017
Period when the claimed impact occurred: 1 August 2013–present		
Is this case study continued from a case study submitted in 2014? Y/N: No		

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

Mutations that disrupt pathways controlling how we acquire and dispose of the energy in our food, cause rare but serious diseases that are difficult to treat and lead to premature death. Cambridge University research in the areas of severe childhood-onset obesity and disorders of insulin action has identified the genetic basis for multiple distinct diseases, bringing earlier and improved diagnosis, evaluation and management strategies to these patients around the world. Expertise established as a result of decades of Cambridge research, underpinned the development of a nationally commissioned specialist clinical service improving outcomes for patients with severe insulin resistance. Cambridge research has made critical contributions to the development of licensed therapies for subtypes of severe, early-onset obesity and for the metabolic complications of lipodystrophy.

2. Underpinning research (indicative maximum 500 words)

Discovery of gene mutations that cause disorders of insulin action and childhood-onset obesity: The intake, storage and use of calories by the body is regulated by a complex network of hormones including leptin and insulin, and their associated signalling pathways. Leptin is produced by fat cells and regulates food intake, energy expenditure and body fat. Insulin is produced by the pancreas and acts on cells to control glucose metabolism and growth.

The Cambridge University team identified mutations in leptin (as well as the prohormone convertase 1/3) as the first single gene disorders that cause severe, childhood-onset obesity (Montague *et al* 1997; Jackson *et al* 1997 and [1]). Through comprehensive studies in large cohorts of severely obese children, the team subsequently identified mutations in 15 other genes that cause this condition, seven since 2013, including *MRAP2* [2], the SEMA3A-G/PLXNA1-4/NRP1-2 signalling network [3] and *KSR2* [4].

Since 2000, Cambridge researchers have identified 12 genes that, when mutated, cause severe insulin resistance. Patients with these mutations are at high risk of diabetes, pancreatitis, polycystic ovary syndrome and other serious health issues. Six gene mutations were identified since 2013 (*PCYT1A* [5], *MFN2* [6], *POLD1*, *NSMCE2*, *POC1A*, and *PIK3R1* [7]) that disrupt insulin signalling directly, or prevent the normal development and function of fat tissue. This latter group of disorders, termed lipodystrophies, account for two thirds of cases of severe insulin resistance. Many of these individuals, for example those with mutations in *MFN2* [6], have low blood levels of leptin. Extending their research to disorders where insulin action might be pathologically over-activated, the Cambridge team discovered activating mutations in *PIK3CA* as a cause of severe regional overgrowth syndrome (ROS). ROS is a disfiguring and disabling condition when a part of the body, typically one limb, grows throughout life [8]. The team also showed that *PIK3CA* mutations affecting the liver cause serious hypoglycaemia. These findings were quickly expanded by the research community, leading to the Cambridge University/National Institutes of Health (NIH) team to coin the now widely adopted term "PIK3CA-related Overgrowth Spectrum" (PROS).

Discovery of new interventions: The Cambridge University team have also conducted research to translate their discoveries into effective medical and surgical intervention strategies. In 2002, O'Rahilly and colleagues first reported the beneficial long-term effects of leptin therapy in humans deficient in this hormone [9]. This was a crucial step in the development of recombinant metreleptin for treating a range of conditions associated with leptin deficiency. Savage was then part of the international consortium of clinical experts which demonstrated the long-term efficacy of metreleptin in congenital total lipodystrophy [10]. Farooqi has co-led an international team of researchers to show that the MC4R agonist Setmelanotide produces substantial and durable reductions in excessive appetite and body weight in people with leptin receptor deficiency – a cause of severe childhood obesity [11]. In 2017, the Cambridge team reported for the first time that *Roux-en-Y Gastric Bypass* surgery (RYGB), is highly effective in improving the metabolic status of patients with Familial partial lipodystrophy type 1, the most common form of partial lipodystrophy [12].

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

Evidence of research quality: *Research published in peer-review journals. Research was supported by competitively won grants.

[1] ***Jackson RS…**Farooqi IS*…**O'Rahilly S**. Small-intestinal dysfunction accompanies the complex endocrinopathy of human proprotein convertase 1 deficiency. *J Clin Invest*. 2003 Nov;112(10):1550-60. doi: 10.1172/JCI18784. PMID: 14617756; PMCID: PMC259128

[2] *Asai M…**O'Rahilly S**…**Farooqi IS**, Majzoub JA. Loss of function of the melanocortin 2 receptor accessory protein 2 is associated with mammalian obesity. *Science*. 2013; Jul 19;341(6143):275-8. PMID: 23869016.

[3] *van der Klaauw AA…**O'Rahilly S**…**Farooqi IS**. Human Semaphorin 3 Variants Link Melanocortin Circuit Development and Energy Balance. *Cell*. 2019 Feb 7;176(4):729-742. PMID: 30661757

[4] *Pearce LR…**O'Rahilly S**.**Farooqi IS**. KSR2 mutations are associated with obesity, insulin resistance, and impaired cellular fuel oxidation. *Cell*. 2013 Nov 7;155(4):765-77. PMID: 24209692.

[5] * Payne F…**Semple RK**…**O'Rahilly S**…**Savage DB.** Mutations disrupting the Kennedy phosphatidylcholine pathway in humans with congenital lipodystrophy and fatty liver disease. *Proc Natl Acad Sci* USA. 2014 Jun 17;111(24):8901-6.

[6] * Rocha N…**O'Rahilly S**…**Savage DB**, **Semple RK**. Human biallelic MFN2 mutations induce mitochondrial dysfunction, upper body adipose hyperplasia, and suppression of leptin expression. *Elife*. 2017 Apr 19;6. pii: e23813.

[7] * **Semple RK**. How does insulin resistance arise, and how does it cause disease. Human Genetic Lessons. *European J. Endo*. 2016 May;174(5): R209-R223

[8] *Lindhurst MJ…**O'Rahilly S, Savage DB**…**Semple RK**. Mosaic overgrowth with fibroadipose hyperplasia is caused by somatic activating mutations in PIK3CA. *Nature Genet.* 2012 Jun 24;44(8):928-33

[9] * **Farooqi IS…O'Rahilly S.** Beneficial effects of leptin on obesity, T cell hypo-responsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J Clin Invest.* 2002 Oct;110(8):1093-103.

[10] *Brown RJ…**Savage DB**…Gorden P. Long-term effectiveness and safety of metreleptin in the treatment of patients with generalized lipodystrophy. *Endocrine.* 2018 Jun;60(3):479-489.

[11] *Clément K, Biebermann H, **Farooqi IS** (joint first author)…Kühnen P. MC4R agonism promotes durable weight loss in patients with leptin receptor deficiency. *Nature Med*. 2018 May;24(5):551-555.

[12] * Melvin A…**Semple RK**, **O'Rahilly S**…**Savage DB**. Roux-en-Y gastric bypass surgery in the management of familial partial lipodystrophy type 1. *J Clin Endocrinol Metab*. 2017 Oct 1;102(10):3616-3620.

Major grant funding:

Savage – Continuous Wellcome Trust funding in metabolic research since 2001 Latest Wellcome Trust Senor Fellowship (2020-2025); GBP1,940,000

O'Rahilly – Continuous MRC funding in energy balance research since 1998 Recent MRC Unit Programme funding (with Yeo/Coll) (2018 -2023) GBP2,450,000.
O'Rahilly – Continuous Wellcome Trust funding in metabolic research from 1991. Latest Wellcome Trust Senior Investigator award (2019 - 2024); GBP1,890,000.
Farooqi – Continuous Wellcome Trust funding in obesity research since 1997. Latest Wellcome Trust Principal Research Fellowship (2017-2022); GBP3,580,000.

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

Impact on health and wellbeing of people

An NHS commissioned, national service for patients with severe insulin resistance: Grounded in 20 years of Cambridge University research and based on expertise acquired during their laboratory and clinical investigation, in 2011 Savage, O'Rahilly and colleagues established an NHS commissioned and funded National Severe Insulin Resistance Service (NSIRS) which includes medical, paediatric, specialist nursing and dietetic expertise [A]. Unique in the world, this service provides patients with syndromes of severe insulin resistance, including the lipodystrophies, with accurate diagnoses, optimised therapy and educational support. Between August 2013 and September 2020, the NSIRS provided care to 414 adult and 66 paediatric patients referred from across the UK. Patients received comprehensive genetic diagnostic testing, genetic counselling, specialist nutritional support, optimised drug therapy and, in some cases, bariatric surgery [A]. The NSIRS provided a precise diagnosis to 84% of patients, with around 30% receiving a specific genetic diagnosis [A]; this has brought about a step change in the management of patients with these rare diseases, providing them access to coordinated, expert care, wherever they live. Since its inception, the Cambridge NSIRS has been the only centre in the UK providing metreleptin therapy to patients (n=35) with the metabolic complications of lipodystrophy on a compassionate use basis [A]. Cambridge University researchers support the NSIRS by testing patients for anti-insulin receptor antibodies that can cause Type B insulin resistance; thereby, enabling accurate diagnosis and the use of immunosuppressive therapies which provide dramatic clinical benefits for patients [A].

Improving the patient care pathway for severe obesity and PROS: Genomics England's gene panel for severe early-onset obesity, which is now available to all relevant NHS specialists [B] was based substantially on Cambridge University discoveries and the '45 gene obesity panel' developed by the Cambridge team. The panel was approved by the UK Genetics Testing Network in Feb 2018 and now provides patients with severe obesity and their physicians across the UK with an accurate diagnostic service: in Cambridge University Hospitals Genomic Laboratory alone, the panel has been used to generate clinical reports for over 600 patients [B]. Further, these discoveries underpin the new Endocrine Society Clinical Practice Guidelines for the assessment, treatment and prevention of paediatric obesity (which Farooqi co-authored) that are now used around the world [B].

The Cambridge discovery that mutations in *PIK3CA* cause PROS [8] has been incorporated into NHS diagnostic services for this condition in Cambridge and Manchester [C]. Importantly, this discovery has also enabled the repurposing of Alpelisib – a PI3 kinase inhibitor – by Novartis as the first treatment option for PROS, leading to Alpelisib being designated an orphan drug by the FDA (November 2019) available on a compassionate use basis [D].

Metreleptin therapy for leptin deficiency: The Cambridge University team were the first to demonstrate that recombinant leptin is an effective therapy of congenital leptin deficiency (CLD), reversing the severe obesity, and multiple endocrine and immune deficiencies experienced by these children and restoring them to normal health [8]. These initial observations underpinned the development and licensing of metreleptin as a therapy for this disorder throughout the world. The condition is extremely rare, with only around 30 cases reported worldwide. Currently, more than 20 children with CLD from eight countries receive daily metreleptin injections [E]. In 2018, the NHS England Specialised Commissioning Team commissioned metreleptin for the treatment of NHS patients with CLD in the UK [E]. Currently, all 10 UK children treated with metreleptin for this disorder are well, no longer obese, and have completed their education. Five patients who were treated as children are now young adults in higher education or employment and can expect to

live a normal life. The first CLD patient in the world to receive metreleptin (commenced 20 years ago age 9 years) gave birth to a healthy baby girl in 2016 [E].

Metreleptin therapy for lipodystrophy: The work of O'Rahilly and Farooqi [9] showed for the first time that correction of a state of leptin deficiency by recombinant leptin had a dramatic effect on appetite and metabolism. This work was also a critical step underpinning the development of metreleptin for states of leptin deficiency due to the lack of functional fat tissue that is found in the lipodystrophies. Savage was an expert adviser to Astra Zeneca during the submission to the US Food and Drug Administration (FDA) in 2014, and to Aegerion in 2018 for their submission to the European Medicines Agency (EMA) for evaluation and approval of metreleptin for the treatment of lipodystrophy [F]. Subsequently, also underpinned by Cambridge-led research, in December 2020 the National Institute for Health and Care Excellence (NICE) provisionally approved metreleptin for the treatment of the metabolic complications of lipodystrophy in the NHS [F]. Metreleptin therapy improves the diabetes, hypertriglyceridaemia and fatty liver disease common in lipodystrophy patients, in whom these conditions are otherwise refractory to treatment and often lead to severe complications such as cirrhosis and pancreatitis [10]. Therapy can also greatly improve patients' quality of life: *"It's starvation-level hunger. It consumes your every waking moment…It is impossible to exaggerate my experienced benefit of Metreleptin treatment. It has literally changed my life. Indeed, it has saved my life..The NSIRS has been a beacon in the darkness. Its talented and dedicated team have provided an anchor in a sea of uncertainty. Without them I would never have had access to Metreleptin*" [F]. Of the estimated 200 people in England, who have lipodystrophy complicated by the severe metabolic effects of the resultant relative leptin deficiency, the majority will now be eligible for metreleptin treatment [F].

Setmelanotide, the second licensed targeted therapy for obesity: In November 2020, setmelanotide – an appetite suppressant that acts downstream of the leptin receptor in neurons of the hypothalamus – was licensed by the FDA for the treatment of patients with severe obesity due to mutations in *PCSK1*, *POMC* or *LEPR* [G]. Although difficult to estimate prevalence, it is thought that these mutations affect a few thousand individuals worldwide. The first of these conditions was originally discovered and characterised by the Cambridge team [1] and Farooqi co-led the clinical trials which established the efficacy of setmelanotide in LEPR deficiency [11]. Data from these trials was included in the filing to the FDA [G].

Enabling and strengthening the voice of patients: The NSIRS team worked with patients to establish a new patient-led charity and support group, Lipodystophy-UK. Cambridge hosts its website [H] providing patients with a voice to share their experiences and highlight the issues specific to these conditions. For example: "*After finding myself in hospital with severe diabetes, out-of-control cholesterol, and several other issues my diagnosis of Familial Partial Lipodystrophy left me feeling alone and frightened. Thanks to LDUK I have connected with other patients"*

Impact on commerce and the economy

The commercialisation of the drug metreleptin by Novelion Therapeutics for the treatment of lipodystrophy generated net revenues of USD146,200,000 from sales between 2016-2018 across 10 countries in the US, EU and Asia [I]. This increased to USD85,400,000 sales in 2019 under new owner Amryt Pharma PLC [I].

Impact on practitioners and delivery of professional services

Establishing genetic testing as standard of care: As detailed above, Cambridge research has pioneered the discovery of genetic causes of rare metabolic disorders. As a direct consequence, genetic tests implementing these discoveries are now standard of care around the world. In 2017 the Expert Panel of the American Endocrine Society, of which Farooqi was a member, formally recommended genetic testing in severe early onset obesity for the first time: "*We suggest genetic testing in patients with extreme early onset obesity (before 5 years of age) and that have clinical features of genetic obesity syndromes (in particular extreme hyperphagia) and/or a family history of extreme obesity*" [B]. The 2016 Consensus Document on Diagnosis and Management of the Lipodystrophies produced by the Paediatric Endocrine Society (USA) on behalf of nine endocrine societies from four continents, a document in which Cambridge research represents >10% of all

the cited references, cites [5] and states "*Confirmatory genetic testing is helpful in suspected familial lipodystrophies...Genetic testing should be considered in at-risk family members.*" [F]. In a testimonial from a NSIRS referring clinician: "*The accurate diagnosis and management of these patients would not be possible without the expert services provided by the insulin resistance unit at Cambridge*' [A].

Educating medical practitioners: The European Association for the Study of Obesity (EASO) includes over 20,000 scientists, health care professionals, researchers, students and patients drawn from 36 countries. EASO organises several teaching courses annually with partner stakeholders e.g., Royal College of General Practitioners in the UK: in 2019, over 2,000 professionals participated EASO courses. The Executive Director of EASO noted '*given their seminal contributions to this field, course content on the genetic causes of obesity invariably features the work of Professors Farooqi and O'Rahilly.*' [J]. Each year the NSIRS also delivers 10 or more educational seminars throughout the UK, each attracting an average of ~50 health care professionals. These are aimed at raising awareness of rare genetic metabolic disorders, highlighting diagnostic advances, guiding use of novel therapies (particularly leptin) and offering support via referrals [A]. In 2016, together with EU partners, the Cambridge team established an EU-wide registry of patients with lipodystrophy in an effort to share expertise [K]. The registry has recruited 246 patients from nine centres (Amsterdam, Bologna, Izmir, Leipzig, Münster, Moscow, Pisa, Santiago de Compostela, Ulm) [K]. The Cambridge team have also changed the education and training of healthcare professionals in obesity medicine globally. These include the Blackburn Course in Obesity Medicine at Harvard Medical School which prepares physicians and surgeons for the American Board of Obesity Medicine (ABOM) certification examination that features a core module on the genetics and biology of obesity, richly citing Cambridge research [J].

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

[A] **Severe Insulin Resistance Service:** (i) Annual reports of NHS severe insulin resistance service 2018-2019; (ii) Anonymised list of patient visits and patient data; (iii) Testimonials from satisfied referring clinicians

[B] **Obesity genome panels:** (i) Panel App for Genomics England 'Severe early-onset obesity (Version 2.3)' (ii) Approval of 45 gene obesity panel, NHS England, Feb 2017 (iii) Testimonial from NHS East Genomic Laboratory Hub (iv) Styne DM,.. Farooqi IS… Yanovski JA. Pediatric Obesity-Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017 Mar 1;102(3):709-757.

[C] Manchester genetic diagnostic laboratory offering ROS diagnosis

[D] Alpelisib approval: (i) Alpelisib FDA orphan drug designation (ii) Managed access of Aleplisib: https://clinicaltrials.gov/ct2/show/NCT04085653

[E] **Metreleptin Commissioning for CLD:** (i)Testimonial from Amryt pharma (ii) NHS commissioning of metreleptin for CLD (iii) Patient testimonial of leptin therapy for treatment of CLD

[F] **Metreleptin authorisation for lipodystrophy:** (i) FDA Approves Myalept [metreleptin] to Treat Generalized Lipodystrophy, February 2014 (ii) EMA Approval, July 2018 (iii) NICE approval of metreleptin treatment for lipodystrophy (pub January 2021) (iv) Oral EA, … Savage DB…Brown RJ. Long-term effectiveness and safety of metreleptin in the treatment of patients with partial lipodystrophy. Endocrine. 2019 Jun;64(3):500-511. (v)Testimonials from patients receiving metreleptin therapy (vi)Effectiveness of metreleptin in lipodystrophy: Brown R *et al* The Journal of Clinical Endocrinology & Metabolism. 2016 Dec;101(12),4500–4511

[G] (i) FDA announcement of licensing of setmelanotide, 27th November 2020 (ii) Licensing documents showing trial data from Cambridge.

[H] **Lipodystrophy UK website:** http://lipodystrophyuk.org/

[I] Metreleptin sales revenue: (i) Novelion Therapeutics Reports 2016 -2018 (ii) Amryt Pharma plc Annual Report 2019, page 8

[J] **Training courses for clinicians:** (i) Testimonial from EASO Executive Director (ii) Testimonial from Course Director, Blackburn Course in Obesity Medicine

[K] (i) E-Clip registry (ii) Schnurbein *et al*. European lipodystrophy registry: background and structure Orphanet Journal of Rare Diseases (2020) 15:17, page 1.