Institution: University of Cambridge		
Unit of Assessment: UOA1		
Title of case study: Innovative diagnostics and therapeutic advances in the global management of lysosomal diseases.		
Period when the underpinning research was undertaken: January 2000 – December 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:**
Timothy M Cox	Professor of Medicine Director of Research	October 1989–September 2015 October 2015–September 2020
Period when the claimed impact occurred: August 2013 – July 2020		
Is this case study continued from a case study submitted in 2014? No		

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

Lysosomal diseases are a group of rare, and incurable, genetic disorders that cause progressive tissue injury and premature death. Cox's research has unravelled pathophysiological mechanisms underlying these diseases, directly informing international treatment guidelines, and collaborating on the development of new diagnostic tests and innovative treatments – miglustat, eliglustat and currently venglustat. These treatments (substrate reduction therapy) have been approved internationally for the treatment of Gaucher and Niemann-Pick C diseases, dramatically improving patient survival and quality of life. Cox has also spun-out Cambridge Gene Therapy, a biotech company that has obtained regulatory approval and orphan drug designations for a clinical programme to treat Tay-Sachs and Sandhoff diseases by gene therapy.

2. Underpinning research (indicative maximum 500 words)

Lysosomes are intracellular compartments that are responsible for breaking down and recycling cellular macromolecules. This critical cell function is disrupted in >80 genetic diseases – collectively termed lysosomal diseases – that affect 1 in every 5,000 live births. Lysosomal diseases are characterized by an abnormal accumulation of incompletely degraded but biologically active substrates in lysosomes. Lysosomal diseases have widespread effects on organ function including the brain, liver, spleen, bone marrow, lungs and skeleton; those presenting in infancy or childhood are rapidly fatal. Cox's research seeks to develop innovative treatments for the sphingolipidoses that represent 15 of the lysosomal diseases. Sphingolipids are abundant in nerve cells, and their impaired recycling accounts for progressive neurodegeneration in Gaucher, Niemann-Pick type C and Tay-Sachs diseases.

New orally bioavailable treatments of sphingolipidoses: Before 2000, only a small fraction of the 20,000–30,000 patients with Gaucher disease worldwide had access to treatment. This involved life-long, repeat infusions of enzyme replacement therapy; patients using indwelling catheters have a risk of infection. Although effective, parenteral enzyme treatment was suboptimal due to limited enzyme penetration of affected tissue, especially the skeleton and nervous system. In collaboration with Oxford Glycosciences, Cox's research brought about a sea change in treatment of these devastating diseases, by pioneering oral substrate reduction therapy, which rebalances the turnover of sphingolipids in the lysosome. Cox and colleagues repurposed a novel iminosugar (miglustat, approved as Zavesca™) which reversibly inhibits UDP-glucosylceramide synthase and has been shown to reduce the toxic sphingolipid in Gaucher disease and related disorders. A series of Cambridge-led clinical trials enrolling 70 patients across six national centres, showed miglustat improves clinical features of non-neuronopathic Gaucher's disease and reverses the key blood and organ manifestations of the disease [1,2]. Consequently, Zavesca™ (Actelion) became an internationally approved drug for non-neuronopathic Gaucher disease. Based on these clinical benefits, Cox and colleagues conducted additional research to test miglustat as a potential treatment of other neuronopathic lysosomal diseases including Sandhoff and Niemann-Pick disease type C [3].

After successfully introducing miglustat, Cox worked with Genzyme-Sanofi to develop eliglustat (Cerdelga™), a second, more potent and better tolerated inhibitor of UDP-glucosylceramide synthase. In the pivotal Phase III, randomised, multinational trial (ENCORE) of eliglustat among 106 patients with Gaucher's disease, Cox and colleagues demonstrated Cerdelga™ is effective

at maintaining haematological and organ stability in patients [4]. In a further study of 157 patients, the safety and long-term efficacy of the drug was shown [5]. Consequently, Cerdelga™ is now a first-line oral therapy for naïve and previously treated patients with Gaucher disease without neurological features and is undergoing clinical trials for affected children. Experimental studies by Cox suggest that its therapeutic benefit extends to B-cell lymphoma and multiple myeloma - sphingolipid-related cancers that commonly occur in patients with Gaucher disease [6].

To develop this new therapeutic paradigm of substrate reduction therapy for intractable neurological disease, Cox is now Principal Investigator of several ongoing clinical trials of the highly potent derivative, venglustat [7]. This orally active drug also inhibits UDP-glucosylceramide synthase but crosses the blood-brain barrier. Hence severe forms of Gaucher disease, Fabry, late-onset Tay-Sachs and Sandhoff diseases – neurodegenerative sphingolipid disorders otherwise incurable – are predicted to be ideal candidates for venglustat treatment.

Novel biomarker discovery: Determining the efficacy of new treatments in small trials in rare diseases is challenging. To address this, Cox and colleagues generated an enriched human Gaucher spleen cDNA library in which the chemokine CCL-18 (or PARC) was identified - serum levels of CCL-18 are now used in therapeutic monitoring and to diagnose Gaucher disease [8].

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] ***Cox T**, … Zimran A. Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis; Lancet. 2000; 355(9214):1481-1485. doi: 10.1016/S0140-6736(00)02161-9

[2] ***Cox TM**…Steiner RD. Miglustat as maintenance therapy after enzyme therapy in adults with stable type 1 Gaucher disease. Orphanet Journal of Rare Diseases; 2012 Dec 27;7:102. doi: 10.1186/1750-1172-7-102.

[3] *Lachmann RH,… **Cox TM**. Substrate reduction therapy in Sandhoff disease: Evidence for improvement in nervous function in patients treated with miglustat. J Inherit Met Dis, 2006; 29:130 *; Patterson MC, Garver WS, Giugliani R, Imrie J, Jahnova H, Meaney FJ, Nadjar Y, Vanier MT, Moneuse P, Morand O, Rosenberg D, Schwierin B, Héron B. Long-term survival outcomes of patients with Niemann-Pick disease type C receiving miglustat treatment: A large retrospective observational study. J Inherit Metab Dis. 2020 Apr 23. doi: 10.1002/jimd.12245

[4] ***Cox TM**, … Puga AC. Eliglustat compared with imiglucerase in patients with Gaucher's disease type 1 stabilised on enzyme replacement therapy: a phase 3, randomised, open-label, non-inferiority trial; Lancet. 2015; 385(9985):2355-62 doi: 10.1016/S0140-6736(14)61841-9 *

[5] ***Cox TM**, …,Peterschmitt MJ. Eliglustat Maintains Long-term Clinical Stability in Patients with Gaucher Disease. Type 1 Stabilized on Enzyme Therapy; Blood. 2017; 129: 2375-2383 doi: 10.1182/blood-2016-12-758409.

[6] *Pavlova EV, …, **Cox TM**. Inhibition of UDP-glucosylceramide synthase in mice prevents Gaucher disease-associated B cell malignancy. Journal of Pathology. 2015; 235:113-124. DOI: 10.1002/path.4452.

[7] *Schiffmann R, **Cox TM**, …Fischer, T. Venglustat combined with imiglucerase positively affects neurological features and brain connectivity in adults with Gaucher disease type 3; Molecular Genetics and Metabolism. 2020; 129: S144-S145. DOI: 10.1016/j.ymgme.2019.11.382

[8] *Moran MT, … **Cox TM** Pathologic gene expression in Gaucher's disease with upregulation of cysteine proteinases including osteoclastic cathepsin K; Blood. 2000; 96 (5): 1969-1978.

Funding relevant to the work in this case study:

- Medical Research Council: Predictive measures to stratify clinical outcomes in children and adults with Gaucher disease and responses to specific therapies (MR/K015338/1) GBP3,740,000 Chief Investigator (Prof Cox) 2013-2019 (supported by NIHR BRC metabolic theme 2018).

- Medical Research Council MR/K025570/1 Biomedical catalyst - Developmental Pathway Funding Scheme/Developmental Clinical Studies: Gene Therapy for Tay-Sachs and Sandhoff diseases. GBP3,190,000. Principal Investigator (Prof Cox) 2013-2020.

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

Impact on the health and wellbeing of people

Innovative Treatments: Cox and colleagues drove the successful clinical trials of the first compound, miglustat, for the treatment of sphingolipid diseases: this led directly to clinical approval in Europe in 2009 and subsequently in 44 additional countries, including the USA in August 2014 [A]. In 2018, the FDA approved a miglustat generic for the treatment of sphingolipid-driven diseases [A]. The effectiveness of oral miglustat treatment for Gaucher disease motivated the development of eliglustat as a second generation, potent oral treatment (Genzyme Corp, later Sanofi Genzyme). Cox was involved as an advisor, a member of the safety monitoring committee and then Chief Investigator of the pivotal, large Phase III that showed the efficacy of eliglustat [5] and ultimately led to its European Medicines Agency recommendation in 2018 [A].

As a direct result of Cox's research, Sanofi Genzyme has supplied eliglustat (approved as Cerdelga™) for clinical use since 2014 and was approved for prescription by The National Institute for Health and Care Excellence (NICE) (HST5) [B] and the Scottish Medicines Consortium (1277/17) in 2017. Eliglustat was made available in NHS England (September 2017) and NHS Scotland (February 2018) [C]. Of the 250 Gaucher patients in the UK national cohort study, within the first two years since UK authorization, 70 patients are taking the oral substrate-reduction therapy. Worldwide, of 7,000 patients in the international registry, more than 1,200 are now taking eliglustat and it has been approved in more than 55 countries, demonstrably improving the quality of life of these patients [D] and [4,5]; following one year of eliglustat, 98% of patients expressed a preference for oral therapy and the main reason cited was convenience [5]. Patient testimony has demonstrated the improved quality of life for patients, as Adele, a Gauchers Type I patient describes her experience in the Gaucher's Association April 2017 Newsletter: "*Presently I am still taking Eliglustat and […] I can honestly say that I have never felt better, which allows me to do all the things I have always wanted to do. Mostly this involves daily long walks with my dog."* [G].

Novel Diagnostics: The PARC-CCL-18 biomarker discovered by Cox is now used widely within standardised assays for clinical monitoring of Gaucher disease. This Gaucher biomarker has positively affected clinical practice, as clinicians have been able to use these proteins as biomarkers in diagnosing disease and importantly, in following treatment response in Gaucher disease and other lysosomal diseases. This has had a global impact on treatment and patient benefit for those suffering from these lysosomal diseases, because it provides clinicians with the means to compare and monitor dynamic therapeutic responses to a range of treatments with distinct modes of action [E and F]. Indeed, Jeremy Manuel OBE LLB, Founder of the UK Gaucher's Association and Honorary President and co-Founder of the International Gaucher Alliance, notes that "*It was Prof Cox who initiated the national strategy of centres for the treatment Gaucher patients which subsequently expanded to cover all Lysosomal diseases patients and he continues to be a clear and guiding voice on the ongoing advisory groups responsible for developing and delivering National Protocols and the best possible for treatment for patients (where this a treatment and management of conditions) where there is none*." [F]

Patient education and empowerment: Building on decades of support for the UK Gaucher's Association since its inception, Cox helped generate a forum and advocacy group for families and patients suffering from Tay-Sachs and Sandhoff diseases. As a Patron, Cox supported establishment of the UK Cure Tay-Sachs Foundation in 2011 and subsequently in 2014 the formation of the European Tay-Sachs and Sandhoff disease Charity Consortium. He now serves as the Consortium's Medical Advisor [F].

Cox was also instrumental in the establishing the International Gaucher Alliance in 2018. The Alliance is an umbrella group representing the interests of Gaucher patients in 55 countries. Cox has consistently raised public awareness of this disease and supported the formation of EU Charities (Europe and elsewhere) [F], as verified by Jeremy Manuel, who has described Cox's

influence as follows: "*He has always championed the involvement of Patient advocates in all areas of clinical, scientific and public life and inspired the patient community to partner with the clinical and scientific community in their efforts to improve the lot of Gaucher patients, and promoted the involvement of patients to industry, regulators and those responsible for managing the delivery of healthcare and paying for access to treatment. All Doctors promote the cause of the patient before them not all seek to improve and enhance the position of their cohort on a National and Global basis*." Cox remains actively involved with these groups and provides education and updates to patients via their communication channels [G].

Impact on practitioners and the delivery of professional services

Cox's research and policy creation has provided clinicians with new treatments, ways of monitoring these diseases and better guidelines for clinical management. Patients have benefitted from the following impacts on practitioners:

- In 2014 the FDA approved eliglustat.
- In 2018 the FDA approved a miglustat generic from Amerigen Pharmaceuticals for the treatment of Type I Gaucher disease [A].
- In 2018, the European Medicines Agency recommended eliglustat (tartrate) for the treatment of Type I Gaucher disease [A].
- Eliglustat is now a first-line oral treatment of choice for patients for adults with Type I Gaucher disease [B and C].
- Phase I/II Trials are underway with a derivative called venglustat, an oral treatment which is more effective at penetrating the brain in patients with sphingolipid derangements in Fabry disease and neuronopathic Gaucher disease (Cox is PI). In addition, he leads the European initiative with EMA as CI in the Phase I/II trial in late-onset Tay-Sachs and Sandhoff diseases (announced Jan 2020). Phase I and II clinical trials for Venglustat in adults with Late-onset Tay-Sachs and Sandhoff diseases are currently being conducted and Phase III extension studies in Neuronopathic Gaucher disease type 3 are currently being run (AMETHSIST [ClinicalTrials.gov Identifier: NCT04221451] and LEAP [NCT02843035] trials).

Impact on commerce and the economy

Global drug sales: Initial approval of miglustat (Zavesca®) priced at USD26,820 per month, per patient, had 2016 world sales of USD104,000,000 [H]. Actelion (makers of Miglustat) were then bought by Johnson & Johnson for USD30,000,000,000 [H]. In April 2018 the U.S. FDA approved Amerigen Pharmaceuticals' generic form of Miglustat; and its partner Miglustat Dipharma, a generic, is used in 33 countries – the first generic approval for miglustat (Zavesca®) [H].

Commercial impact has also been generated through the global sales of eliglustat (Cerdelga®) as sales over the REF impact assessment period have eclipsed EUR773,000,000 [H]. Following its FDA approval in August 2014, eliglustat sales totalled EUR4,000,000 in Qs 3 and 4 of that year. Sales have continued to rise year on year, and in Q1 of 2020, total sales were EUR53,000,000, of which 53% was in the USA and 41% was in Europe [H].

Biotech spinoff company: Cox established Cambridge Gene Therapy (Companies House No. 11112130) in December 2017, which aims to develop and broaden the clinical programmes targeting lysosomal diseases and in particular using pioneering gene therapy as a treatment for Tay-Sachs disease, which is currently incurable [I]. He has secured seed funds of GBP500,000 from Cambridge Enterprise to support pivotal clinical trials and full translational development of this research [J].

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

[A] Evidence supporting FDA and EMA approval of eliglustat. (i) FDA approval of eliglustat and miglustat generic for the treatment of Gaucher disease (ii) EMA decision for the inclusion of eliglustat (Cerdelga®).

[B] Evidence supporting the NICE recommendation for Eliglustat use in England. NICE recommendation and consultation document (ENCORE drawn up as key evidence throughout and particularly across pp. 8–37)

[C] Evidence supporting availability of eliglustat for use in Scotland

Scottish Medicines Consortium Guideline (ENCORE drawn upon as key evidence throughout and [4] and [8] referred to in References on p.8, alongside other outputs by Cox et al.)

[D] Evidence showing the effectiveness and global use of Eliglustat for the treatment of Gauchers disease and its effects on improved quality of life. Outcomes after 8 years of eliglustat therapy for Gaucher disease type 1: Final results from the Phase 2 trial. Lukina E, Watman N, Dragosky M, Lau H, Avila Arreguin E, Rosenbaum H, Zimran A, Foster MC, Gaemers SJM, Peterschmitt MJ. Am J Hematol. 2019, 94 :29-38; Mistry PK, Balwani M, Charrow J, Kishnani P, Niederau C, Underhill LH, McClain MR. Real-World Effectiveness of Eliglustat in Treatment-Naïve and Switch Patients Enrolled in the International Collaborative Gaucher Group Gaucher Registry. Am J Hematol. 2020 May 21. doi: 10.1002/ajh.25875

[E] Evidence to support the implementation and broad clinical use of the CCL-18 biomarker. (i) Glucosylsphingosine Is a Highly Sensitive and Specific Biomarker for Primary Diagnostic and Follow-Up Monitoring in Gaucher Disease in a non-Jewish, Caucasian Cohort of Gaucher Disease Patients. Rolfs A, Giese A-K, Grittner U, Mascher D, Elstein D, Zimran A, Böttcher T, Lukas J, Hübner R, Gölnitz U, Röhle A, Dudesek A, Meyer W, Wittstock M, Mascher H. 2013; PLoS One, 8(11), e79732; (ii) Gaucher Disease, Pastores GM, Hughes DA. 2000 Jul 27 [updated 2018 Jun 21]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2020; (iii) Validating Glycoprotein Non-Metastatic Melanoma B (gpNMB, osteoactivin), a new biomarker of Gaucher Disease, Murugesan V, Liu J, Yang R, Lin H, Lischuk A, Pastores G, Zhang X, Chuang W-L, and Mistry PK. Blood Cells Mol Dis. 2018; 68: 47–53

[F] Testimonial evidence of the impact Prof Cox's work has had on the UK health system. Testimonial from Jeremy Manuel OBE LLB, Founder of the UK Gauchers Association and Honorary President and co-Founder of the International Gaucher Alliance.

[G] Supporting information about empowering patients of these diseases by Professor Cox.
Gaucher News April 2017 (Type I Gaucher patient discusses her diagnosis and treatment experience on p. 6, and Professor Cox provides an update on the GAUCHERITE study to key stakeholders on p.14).

[H] Evidence supporting the global financial impact of Miglustat and Eliglustat sales. (i) Actelion 2016 sales, (ii) Sale of Actelion to Johnson & Johnson, (iii) 2019 EMA approval of Miglustat Diapharma, (iv) 2014 – 2020 eliglustat sales.

[I] State-of-the-Art account of experimental development of clinical gene therapy programme for Tay-Sachs and Sandhoff disease. Cachon-Gonzalez MB, Zaccariotto E, Cox TM. Genetics and Therapies for GM2 Gangliosidosis. Current Gene Therapy. 2018;18: 68-89 (free open access).

[J] Supporting evidence confirming the Seed funding for a spin-off company to develop gene therapies for Tay-Sachs and Sandhoff diseases (GM2 gangliosidosis).
Cambridge Enterprise Letter of Support from June 2020.