Institution: University College London		
Unit of Assessment: 1 - Clinical Medicine		
Title of case study: Transforming the diagnosis and treatment of ATTR amyloidosis: from a rare untreatable disease to a common remediable disorder		
Period when the underpinning research was undertaken: 2014-2020		
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:**
Julian Gillmore	**Professor of Medicine, Director of UCL Centre for Amyloidosis**	**2005 to present**
Marianna Fontana	**Professor of Medicine**	**2012 to present**
Philip Hawkins	**Principal Clinical Research Fellow**	**1999 to present**
Period when the claimed impact occurred: 2014-2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Research at UCL's National Amyloidosis Centre (NAC) has revolutionised diagnosis and clinical staging of Transthyretin (ATTR) amyloidosis, a fatal cardiomyopathy, previously diagnosed using invasive and risky heart biopsies. The UCL team has repurposed a widely available scintigraphic imaging technique, developed new cardiac MRI technologies and created clinical management algorithms that uniquely allow non-invasive diagnosis, staging and quantitative monitoring of ATTR amyloidosis. These tools have been adopted worldwide in clinical guidelines and practice and have facilitated clinical trials and development of new treatments, including the first licenced gene silencing drug. In the UK alone, approximately 500 people/year are now correctly diagnosed with ATTR amyloidosis using these safe, widely available clinical tests. Of those diagnosed in the UK in 2020, 151 patients are receiving NHS approved gene silencing therapy and a further 255 recruited onto Phase 3 trials.

2. Underpinning research

Transthyretin (ATTR) amyloidosis is a progressive and usually fatal disease resulting from deposition of the serum protein transthyretin in abnormal aggregates known as amyloid fibres. It causes a serious cardiomyopathy in people over 60 years, and rare hereditary forms also cause neuropathy and wasting in younger adults. ATTR cardiomyopathy was previously untreatable and always fatal; it could be diagnosed only through heart muscle biopsy, which was associated with serious complications including death. Research at UCL's NAC has allowed the disease to be accurately diagnosed without biopsy using scintigraphic imaging, characterised and quantified by MRI, and staged by simple blood tests, all of which have expedited participation in and progress of clinical trials leading to development of gene silencing and other new therapies.

Diagnosis using scintigraphic (radiotracer) imaging: eliminating need for cardiac biopsies
In 2012, researchers at UCL realised the potential for repurposing a bone imaging technology, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scintigraphy, as a non-invasive (non-cardiac biopsy) method to diagnose ATTR cardiomyopathy. In 2015-16, they led an international collaborative study of 1217 patients with suspected cardiac amyloidosis referred to

European and US centres, which demonstrated diagnostic radiotracer uptake in the hearts of more than 99% of patients with ATTR amyloidosis. The study confirmed that higher levels (grade 2 or 3) of radiotracer uptake in conjunction with some simple blood and urine tests was specific for ATTR amyloidosis. The team validated a now widely accepted and used diagnostic algorithm enabling diagnosis of cardiac ATTR amyloidosis without the need for cardiac biopsy. This has raised awareness of the condition, with more clinicians referring patients for diagnostic tests (**R1**).

Multiparametric cardiac MRI (CMR): uniquely appraising the distribution, burden and effects of cardiac amyloid

UCL researchers discovered the unique potential of CMR in cardiac amyloidosis in 2005. They subsequently developed CMR technology using late gadolinium enhancement (LGE) and T1 mapping to create a robust technique for characterizing the effects and quantifying the burden of cardiac amyloid, and spearheaded development of international CMR consensus criteria ratifying its clinical value (**R2**). The technique uniquely measures amyloid throughout the heart and reveals new details of the pathology of cardiac amyloidosis, including reduced myocardial perfusion. For the first time, clinicians can quantitatively monitor cardiac amyloid deposits and their effects on heart muscle and perfusion, informing prognosis and gauging response to new treatments (**R3**).

Staging the disease with blood biomarkers: informing prognosis and enabling trials

The UCL team devised a simple but rigorous clinical staging method using two commonly measured blood biomarkers to inform prognosis and to stratify by disease severity patients in clinic and participating in trials. 869 patients with cardiac ATTR amyloidosis attending NAC were stratified into three disease stages based on levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and estimated glomerular filtration rate (eGFR), used as markers of heart and kidney function respectively (**R4**). Stratification was independently validated using a cohort of patients in France and additional utility of the staging method used serially has lately been validated to predict disease progression (**R5**).

Elucidating the dynamic relationship between amyloid formation and clearance: underpinning development of the world's first gene silencing therapy

Seminal clinical studies by the UCL team in two more commonly diagnosed forms of amyloidosis, AA (autoimmune) and AL (light chain) amyloidosis, defined the relationships between amyloid formation and its effects on organ function, and for the first time demonstrated that amyloid may regress when its production was reduced by treatment, and that this led to improvements in symptoms and survival (**R6**). These studies directly informed development of the first ever RNAi gene-silencing medicine patisiran (Alnylam Pharmaceuticals) which inhibits production of transthyretin. Recent CMR studies of UCL's NAC patients taking patisiran have provided the first proof that cardiac ATTR amyloid can regress (**R7**).

3. References to the research

R1 Gillmore JD, Maurer MS, Falk RS, (35 more authors including Fontana M), Hawkins PN. (2016). Non-biopsy Diagnosis of Cardiac Transthyretin Amyloidosis.*Circulation*.2016133:2404-2412. https://doi.org/10.1161/CIRCULATIONAHA.116.021612

R2 Martinez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Zumbo G, Knight DS, Kotecha T, Francis R, Hutt DF, Rezk T, Rosmini S, Quarta CC, Whelan CJ, Kellman P, Gillmore JD, Moon JC, Hawkins PN, Fontana M. (2017). Magnetic Resonance in Transthyretin Cardiac Amyloidosis. *J Am Coll Cardiol*. 70:466-477. DOI: 10.1016/j.jacc.2017.05.053.

R3 Fontana M, Pica S, Reant P, Abdel-Gadir A, Treibel TA, Banypersad SM, Maestrini V, Barcella W, Rosmini S, Bulluck H, Sayed RH, Patel K, Mamhood S, Bucciarelli-Ducci C, Whelan CJ, Herrey AS, Lachmann HJ, Wechalekar AD, Manisty CH, Schelbert EB, Kellman P, Gillmore JD, Hawkins PN,Moon JC (2017). Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. *Circulation*. 2015 Oct 20;132(16):1570-9. DOI: 10.1161/CIRCULATIONAHA.115.016567

R4 Gillmore JD, Damy T, Fontana M, Hutchinson M, Lachmann MJ, Martinez-Naharro A, Quarta CC, Rezk T, Whelan CJ, Gonzalez-Lopez E, Lane T, Gilbertson JA, Rowczenio D, Petrie A, Hawkins PN (2017). A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J*.;39:2799-2806 DOI: 10.1093/eurheartj/ehx589.
R5 Law S, Petrie, A, Chacko L, Ravichandran S, Gilbertson JA, Rowczenio D, Wechalekar A, Martinez-Naharro A, Lachmann HJ, Whelan CJ, Hutt DF, Hawkins PN, Fontana M, Gillmore JD. (2020) Disease progression in cardiac transthyretin amyloidosis is indicated by serial calculation of NAC transthyretin amyloidosis stage. *ESC Heart Fail.* 7(6):3942-3949.Sep 13. doi: 10.1002/ehf2.12989.
R6 Lachmann HJ, Goodman HJB, Glibertson JA, Gallimore JR, Sabin CA, Gillmore JD, Hawkins PN. (2007) Natural history and outcome in systemic AA amyloidosis. *N Engl J Med*. Jun 7;356(23):2361-71. DOI:https://www.nejm.org/doi/full/10.1056/nejmoa070265
R7 Fontana M, Martinez-Naharro A, Chacko L, Rowczenio D, Gilbertson JA, Whelan CJ, Strehina S, Lane T, Moon J, Hutt DF, Kellman P, Petrie A, Hawkins PN, Gillmore JD. (2020) Reduction in CMR Derived Extracellular Volume with Patisiran Indicates Cardiac Amyloid Regression. *JACC Cardiovasc Imaging.* Oct 28:S1936-878X(20)30801-9. doi: 10.1016/j.jcmg.2020.07.043.

4. Details of the impact

Prior to 2013, knowledge and awareness of ATTR amyloidosis were poor and cardiologists diagnosed few patients. Researchers at UCL's NAC have created a diagnostic clinical pathway that eliminates the need for invasive, costly and risky heart biopsies, allowing safe and effective diagnosis. Their methods have been incorporated into best practice clinical guidelines and now thousands of patients have been correctly diagnosed, worldwide. These UCL-led innovations and collaborations with pharmaceutical companies have expedited development of new medicines to treat ATTR amyloidosis, which are transforming thousands of lives.

Advances in NHS treatment services and benefits to patients
Diagnostic methods developed at UCL have revolutionized management of ATTR amyloidosis. The possibility of amyloidosis as a rare cause of heart failure was seldom pursued since it required a highly specialised cardiac biopsy and there was no treatment. Now, the diagnosis of ATTR amyloidosis is readily confirmed with ^{99m}Tc-DPD scintigraphy; staging of disease severity achieved simply using routinely performed blood tests; and cardiac MRI is used in addition to characterise and serially quantify the amyloid burden. MRI can thus track the course of disease, its response to emerging treatments and inform clinical trials.

NHS implementation of these technologies has dramatically increased diagnosis of ATTR amyloidosis, and as a consequence, cardiac biopsies are now only performed in complex cases. In 2013-14, UCL's NAC central records show that 38 UK patients were diagnosed using cardiac biopsies. Since the development of the new non-invasive UCL methods (published in 2016) the numbers of patients diagnosed has steadily increased and in 2019-20, 500 patients were diagnosed without the use of cardiac biopsies (**S1**). Diagnosis by ^{99m}Tc-DPD scintigraphy is currently saving the NHS approximately GBP450,000 per year (NHS tariffs – ^{99m}Tc-DPD scintigraphy GBP200; cardiac biopsy – GBP1,100).

Scintigraphy for ATTR is now performed widely in Europe, Australia and the US. Curium Pharma UK Ltd, which distributes ^{99m}Tc-DPD radiotracer in the UK, supplied 41 NHS hospitals with ^{99m}Tc-DPD kits in 2020, compared to only 7 hospitals in 2015; sufficient to scan several thousand patients (**S2**).

Cardiac MRI (CMR) innovations, developed and validated at UCL are now provided in more than 60 NHS hospitals and allow the underlying quantity of amyloid to be measured for the first time. Changes in amyloid load and other CMR parameters measured over time are now frequently used as efficacy endpoint measures in industry sponsored trials (**S3**). In 2016, NHS Highly Specialised Services commissioned a dedicated GBP3,000,000 CMR facility at UCL's NAC,

which has served more than 4500 patients. Central NHS funding of GBP8,000,000 per year ensures access of all amyloidosis patients to these advances in clinical care.

Identifying ATTR amyloidosis in the wider heart disease population
Cardiologists are increasingly using ^{99m}Tc-DPD scintigraphy in several common cardiac disease populations in which amyloid deposition may be a contributor or even the primary cause of symptoms. These include the 450,000 UK patients with heart failure with preserved ejection fraction (HFpEF), of whom up to 10% may have cardiac amyloid that could be treated. Scintigraphy has also shown co-existing ATTR amyloidosis in more than 10% of patients undergoing surgery for aortic valve stenosis (approximately 5000 patients per year in England), which previously was missed in most cases (**S4**); this allows additional risk assessment before surgery, and consideration of specific amyloid therapy. Crucially, it has been possible to confirm that patients with co-existing ATTR amyloidosis greatly benefit from valve surgery.

Updated clinical guidelines for management of ATTR amyloidosis
The UCL diagnostic methods are now included in UK, European and US guidelines for the clinical management of ATTR amyloidosis (**S5**). Guidelines developed by the Amyloid Research Consortium and specialist medical societies provide best practices for diagnosis and characterisation of ATTR amyloidosis, facilitating rapid and accurate identification without need for cardiac biopsy. They state, “Myocardial scintigraphy with bone avid tracers …. has high sensitivity and specificity for ATTR-CM…. Ease of access, simplicity of imaging, relatively low cost and specificity are some of the advantages of myocardial scintigraphy compared with…. [other methods]” (**S5**).

Role of UCL diagnostic pathway in developing new treatments
Scintigraphy, CMR and staging methods developed at UCL have been adopted in at least 8 major clinical trials of novel therapies (**S6**), involving approximately 2500 patients. President and CMO of Eidos Therapeutics Inc. said, “We enrolled the vast majority of participants in our study based on the UCL NAC algorithm, providing an efficiency in recruitment that we believe is unprecedented... This algorithm has been widely and enthusiastically adopted at major centers throughout the United States and the rest of the developed world and is making an incredible contribution to increasing the numbers of patients being accurately diagnosed earlier in the course of their disease (if at all), which significantly improves their survival” (**S7**).

According to Pfizer, who licenced a treatment (tafamidis) for ATTR cardiomyopathy in the US in May 2019, the number of patients diagnosed increased from approximately 2,000 to more than 17,500 patients since the UCL scintigraphy method was introduced; 7,500 US patients are now being treated with Pfizer’s tafamidis, generating Q3 sales in 2020 of USD351,000,000. Pfizer’s tafamidis franchise has now been estimated to exceed USD2.5 billion in 2020 (**S8**).

The UCL NAC team’s expertise in amyloidosis has, together with its large, well characterised patient population and the new diagnostic tools, underpinned an ongoing collaboration with Alnylam Pharmaceuticals Inc. For over a decade, Professor Hawkins has acted as a consultant to Alnylam to support development of a revolutionary gene silencing RNA interference (RNAi) therapy (patisiran) for ATTR amyloidosis (**S9**). NAC is a core laboratory for international clinical trials and the UCL team’s expertise has contributed to approvals of the new therapies at the European Medicines Agency and in NICE evaluations, leading to approval for use of gene silencing medicines within the NHS. President of R&D at Alnylam said: “Our longstanding work with NAC represents an exemplar of healthcare collaboration that has underpinned a landmark innovation in pharmacology and medical practice” (**S10**).

Treatment with patisiran can reverse clinical symptoms within a year and it is approved for use in the UK, EU and US (**S11**). This remarkable success has heralded a new era in medicine. Alnylam achieved Q3 product sales in 2020 for patisiran of USD82,500,000, with more than 1,150 patients being treated worldwide. British hand surgeon Carlos Heras-Palou, founder and chairperson of the UK’s ATTR Amyloidosis Patients’ Association (UKATPA), who was treated with patisiran described the gene silencing therapy as "ground-breaking….like the proverbial

silver bullet. The treatment has saved my career, and my life". All eligible patients in the UK with hereditary ATTR amyloidosis now gain access to the gene silencing therapy via UCL's NAC, courtesy of the NHS. In 2020, 151 patients in the UK were successfully treated with patisiran.

5. Sources to corroborate the impact

S1. NAC annual audit data, provided to NHS England (Available on Request).
S2. Evidence for radio tracer kit numbers – email from Curium account manager.
S3. Testimonial from CEO, Society for Cardiovascular Magnetic Resonance.
S4. i) Scully P et al. (2020) Prevalence and outcome of dual aortic stenosis and cardiac amyloid pathology in patients referred for transcatheter aortic valve implantation. *Eur Heart J*. Aug 1;41(29):2759-276. doi:10.1093/eurheartj/ehaa170.
ii) Nitsche C et al. (2020) Prevalence and Outcomes of Concomitant Aortic Stenosis and Cardiac Amyloidosis. *JACC* online https://doi.org/10.1016/j.jacc.2020.11.006.
S5. Clinical Guidelines including all major international cardiology associations.
S6. Eight Pharma-led clinical trials of novel treatments for amyloidosis employing NAC non-biopsy imaging diagnosis and/or CMR technology (GSK, Eidos Therapeutics, Alnylam Pharmaceuticals, Ionis Pharmaceuticals).
S7. Testimonial from President and CMO, Eidos Therapeutics Inc.
S8. Evidence from Pfizer re disease awareness and use of non-invasive diagnostic imaging:
i) https://www.fiercepharma.com/marketing/hey-don-t-forget-vyndaqel-pfizer-rare-heart-disease-drug-s-cruising-fast-toward
ii) Pfizer Physician website: Formal diagnosis of Transthyretin Amyloid Cardiomyopathy (ATTR-CM) (using CMR and scintigraphy)
https://www.pfizerpro.co.uk/formal-diagnosis-of-attr-cm
S9. Adams D. et al., (approximately 40 authors including Hawkins PN) (2018) Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. *New Engl J Med*. 2018;79:11-21. doi:10.1056/NEJMoa1716153 *(Included in NEJM 'most notable' collection)*
S10. Testimonial letter from President R&D, Alnylam.
S11. EMA, NICE and FDA approval for use of Patisiran to treat hereditary ATTR amyloidosis:
i) EMA https://www.ema.europa.eu/en/medicines/human/EPAR/onpattro (2018)
ii) NICE https://www.nice.org.uk/guidance/hst10/chapter/1-Recommendations (2019)
iii) FDA https://www.fda.gov/news-events/press-announcements/fda-approves-first-its-kind-targeted-rna-based-therapy-treat-rare-disease (2018)