Institution: Liverpool John Moores University		
Unit of Assessment: UOA24		
Title of case study: From molecule to mouse to man: transforming the clinical management of all alkaptonuria patients in the UK with molecular and whole-body level approaches		
Period when the underpinning research was undertaken: 2012 - present		
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:**
Jonathan Jarvis	Professor	2012- to date
Gabor Barton	Professor	1993-1996 and 2001- to date
Malcolm Hawken	Research Officer	2006-2015
Mark Robinson	Reader	2011- to date
Period when the claimed impact occurred: August 2013 - present		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Alkaptonuria (AKU) is a rare inherited metabolic disease leading to connective tissue and joint damage, early osteoarthritis and severe pain that impair gait, activities of daily living and quality of life. Research at LJMU since 2012 has contributed to a transformation of the clinical management of this condition through (1) pre-clinical and clinical trials (DevelopAKUre) and eventual licencing of an effective drug therapy for adult patients, for whom no active treatment had previously been available (2) novel clinical gait analysis applied to help reduce joint loading and related pain. Mouse and human studies showed that structural and functional abnormalities develop at a younger age than previously believed, evidenced both in our biochemical research and biomechanical gait analysis in AKU patients. The innovative biomechanical concepts have also transformed how clinical gait analysis is taught in Europe and beyond. The success of the AKU project to repurpose an existing drug for this new application was recognised by the rare disease community with the recent award to our research partner the AKU Society of the EURORDIS Black Pearl 2021 Members Award.

2. Underpinning research

Research on AKU at LJMU is strategically conducted along five research themes that tackle complementary aspects of the condition that leads to severe joint disease affecting movement and gait. Initial biochemical studies in a mouse model of AKU, followed by a clinical trial in human patients confirmed the efficacy of nitisinone in AKU. To complement cellular, biochemical and behavioural approaches to drug development, advanced methods to quantify gait abnormalities were applied to assess how movement changes with age in AKU. For those patients who cannot benefit immediately from nitisinone treatment, conservative gait modification interventions were explored.

Developing drug treatment (UR1): Alkaptonuria (AKU) is a monogenic defect of tyrosine metabolism causing early onset arthritis, severe pain and degeneration of knee, hip and shoulder joints. Professor Jarvis with Gallagher and Ranganath (University of Liverpool) tested the drug nitisinone (Orfadin) in a mouse model of AKU. Nitisinone in the drinking water eliminated the disease process in the knee (Alkaptonuria Society/Big Lottery 'Find AKUre', May 2009-Apr 2012, £363K) [F1] and the results paved the way for a clinical trial. Jarvis was applicant on the successful EU bid for an international trial in human patients (EU 'DevelopAKUre', Mar 2012-Feb 2019, €6M) [F2]. He remained on the Scientific Board, moving to LJMU in 2012. His subsequent behavioural research at LJMU showed that treatment of younger AKU mice did not affect learning or memory. Two further grants underpin the research, these include funding from AKU Society/Childwick Trust "AKU in the young" March 2013 to February 2016, £30k [F3] and funding from Royal Liverpool and Broadgreen University Hospital Trust to LJMU. 2014-2017 £88k [F4].

We argue that AKU represents an extreme osteoarthritis, highly relevant to understanding and treatment of osteoarthritis in the general population.

Jarvis is co-author on a series of peer-reviewed papers presenting the scientific evidence that supports the October 2020 decision from the European Medicines Agency to license the drug for AKU. Research led at LJMU by Professor Jarvis with Dr Sutherland (Research Fellow) and Dr Lewis (PhD student).

Advanced descriptors of human gait (UR2): Clinical gait analysis provides comprehensive data comprising the three-dimensional joint angles, moments and powers in the legs during walking. It is used to plan interventions to manage patients with neuro-musculoskeletal disorders, but the complexity and technical nature of the data limits practical application in clinical settings. We presented a new method to simplify the 50 dynamic angles, moments and powers representing a moving human body in multi-dimensional data space. Our method, the Movement Deviation Profile (MDP) is calculated by a self-organising neural network as the multi-dimensional deviation of a patient's gait from a distribution representing normal gait. This approach improves upon related methods because the asymmetrical response faithfully represents functional asymmetries and is less affected by timing errors. The single number MDP_{mean} is a summary measure of gait deviation that is easy for doctors to use in clinical decision making and assessment of improvement or deterioration over time. Research led by Professor Barton, Reader and now Professor of Clinical Biomechanics at LJMU 2012-2019. His LJMU collaborator was Dr Hawken (Research Officer until 2015).

Age-dependent deterioration of gait (UR3): The MDP was used to quantify how gait deteriorates as a function of age in AKU. After median filtering, a characteristic sigmoid profile emerged superficially resembling the natural progression of clinical symptoms which suggest no abnormalities in younger age then development of symptoms plateauing around 40-50 years. A close examination of the MDP showed important differences from the natural progression derived from standard clinical observation. The objective biomechanical evidence confirmed that AKU affects not only older people as it is commonly believed. Research led by Professor Barton 2015-present, also at LJMU Dr Robinson (Senior Lecturer), Dr King (Associate Lecturer until 2016), and Dr Shepherd (Associate Lecturer since 2016).

AKU affecting the young (UR4): Gait deviations provide objective assessment of movement with AKU, but utility is enhanced with structural or biochemical measures of pathology (imaging, enzyme analysis or plasma homogentisic acid). With the National AKU Centre and joint EU funding (SOFIA), we described natural progression in AKU. Importantly, both gait deviations and the combined questionnaire and structural index (AKUSSI) showed abnormalities in the young, as Professor Jarvis had also shown in mice, highlighting the need to explore interventions in patients under 20. Barton and Jarvis' research suggests that treatment may well be indicated in children affected by this rare metabolic disease to suppress the pathological process. The gait analysis arm of the research was led by Professor Barton since 2013-present. Other LJMU collaborators were Dr Robinson and Dr Shepherd (dates as above).

Gait modifications (UR5): Nitisinone can stop progression of AKU but current evidence shows it cannot reverse the condition and needs further safety testing before use in children. This raises the question of how to supplement or postpone nitisinone treatment with conservative interventions. Gait modifications, e.g. walking with feet pointing out or with sideways trunk sway, reduces loading in the knee and hip joints. We found that trunk sway was achieved in two distinct ways in natural gait: either walking on a wide base, or with a normal narrow base but shifting the pelvis towards the swing side with the trunk sway. The two mechanisms of trunk sway can be matched to the individual biomechanical requirements of AKU patients. Research led by Professor Barton since 2015 with LJMU collaborators Dr King (Associate Lecturer until 2016), Dr Przybyla (Research Officer until 2016) and Dr Anderson (Master's student in 2016).

Our research described above led to innovations that target this disease at a molecular level (based on our biochemical research on the inhibiting effects of nitisinone on enzymes that are central to the mechanism of the disease) and the effects of the disease on whole-body joint

function and gait (based on research that developed novel and clinically useful biomechanical gait analysis and quantification techniques).

3. References to the research

All the publications linked to the original research described above were published in some of the most prestigious peer-reviewed journals in their respective fields. Some papers were included in REF2014 and some of the work conducted was funded following competitive peer-reviewed processes (Alkaptonuria Society/Big Lottery, EU). Continued clinical gait analysis at LJMU is funded by the National Alkaptonuria Centre (Department of Health).

UR 1 linked to developing drug treatment (UR1): Ranganath LR, Psarelli EE, Arnoux JB, Braconi D, Briggs M, Bröijersén A, Loftus N, Bygott H, Cox TF, Davison AS, Dillon JP, Fisher M, FitzGerald R, Genovese F, Glasova H, Hall AK, Hughes AT, Hughes JH, Imrich R, Jarvis JC, Khedr M, Laan D, Le Quan Sang KH, Luangrath E, Lukáčová O, Milan AM, Mistry A, Mlynáriková V, Norman BP, Olsson B, Rhodes NP, Rovenský J, Rudebeck M, Santucci A, Shweihdi E, Scott C, Sedláková J, Sireau N, Stančík R, Szamosi J, Taylor S, van Kan C, Vinjamuri S, Vrtíková E, Webb C, West E, Záňová E, Zatkova A, Gallagher JA (2020) Efficacy and safety of once-daily nitisinone for patients with alkaptonuria (SONIA 2): an international, multicentre, open-label, randomised controlled trial. Lancet Diabetes Endocrinol. 8(9): 762-772. http://dx.doi.org/10.1016/S2213-8587(20)30228-X

UR 2 linked to developing drug treatment (UR1): Preston AJ, Keenan CM, Sutherland H, Wilson PJ, Wlodarski B, Taylor AM, Williams DP, Ranganath LR, Gallagher JA, Jarvis JC. Ochronotic osteoarthropathy in a mouse model of alkaptonuria, and its inhibition by nitisinone. Ann Rheum Dis. 2014 Jan;73(1):284-9. http://dx.doi.org/10.1136/annrheumdis-2012-202878 Epub 2013 Mar 19. PMID: 23511227.

UR 3 linked to advanced descriptors of human gait (UR2): Barton GJ, Hawken MB, Scott M, Schwartz MH (2012) Movement Deviation Profile: A measure of distance from normality using a self-organizing neural network. Invited paper in Special Issue on Network Approaches in Complex Environments, Human Movement Science. 31: 284-294. http://dx.doi.org/10.1016/j.humov.2010.06.003

UR 4 linked to age-dependent deterioration of gait (UR3): Barton GJ, King SL, Robinson MA, Hawken MB, Ranganath LR (2015) Age related deviation of gait from normality in alkaptonuria. Invited paper in Special Issue on Alkaptonuria, Journal of Inherited Metabolic Disease Reports. 24: 39-44. http://dx.doi.org/10.1007/8904_2015_431

UR 5 linked to AKU affecting the young (UR4): Cox TF, Psarelli EE, Taylor S, Barton GJ, Robinson MA, Shepherd H, Mistry A, Genovese F, Braconi D, Giustarini D, Rossi R, Santucci A, Khedr M, Hughes A, Milan AM, Dillon J, Gallagher JA, Ranganath LR. (2019) Subclinical Ochronosis Features In Alkaptonuria: A Cross-Sectional Study. BMJ Innovations. https://doi.org/10.1136/bmjinnov-2018-000324

UR 6 linked to gait modifications (UR5): Anderson J, King S, Przybyla A, Ranganath LR, Barton GJ (2018) Reduction of frontal plane knee load caused by lateral trunk lean depends on step width. Gait and Posture. 61:483-487. http://dx.doi.org/10.1016/j.gaitpost.2018.02.022

Funding:

[F1] Alkaptonuria Society/Big Lottery 'Find AKUre', May 2009-Apr 2012, £363K)
[F2]EU 'DevelopAKUre', Mar 2012-Feb 2019, €6M

[F3] AKU Society/Childwick Trust "AKU in the young" 03-2013 to 02 2016, £30k

[F4] Royal Liverpool and Broadgreen University Hospital Trust to LJMU. 2014-2017 £88k

[F5] National Alkaptonuria Centre (Royal Liverpool Hospital) Clinical gait analysis for all AKU patients (Sept 2013 – present). £130K over the REF period (continues at £26K p/a indefinitely)

[F6] EU SOFIA via NAC (March 2014 - March 2016 £52k.

4. Details of the impact

Building on fundamental research, a large-scale EU funded international clinical trial documented in high quality publications has led to the recent authorisation of nitisinone to treat AKU. The formal approval by the European Medicines Agency makes the treatment available for the first time to all adult AKU patients in Europe and potentially worldwide. Parallel research in gait analysis informs the clinical management of all AKU patients in the UK, translating novel research techniques into clinical practice. A critical finding arising from our research is that AKU affects the young and the findings have triggered new research in this direction. The advanced concepts derived from AKU research are disseminated to practitioners who attend the annual Gait Course of ESMAC followed by secondary dissemination in their home countries.

Developing drug treatment through biochemical research (UR1): Professor Jarvis' work in AKU mice showed that nitisinone prevented pigmentation in the joints, the earliest sign of tissue pathology. The data supported the application (2011) to the EU for the clinical trial of nitisinone in AKU. That trial ran from 2014 to 2019. Nitisinone was effective in humans to reduce circulating homogentisic acid, as it had been in mice (Ranganath et al., 2020). A licence from the European Medicines Agency now authorises use of nitisinone in AKU (**CS1**). Jarvis oversaw the fundamental work in mice and held the statutory permissions required. A series of publications demonstrated a new stain for ochronotic pigment in joints, the time course of pigmentation and the dose-response for nitisinone to reduce pathological change. The research programme also supplied plasma and urine samples for metabolomics and new mass spectrometric assays for key metabolites in AKU.

Advanced descriptors of human gait uncover progressive deterioration of gait (UR2 and UR3): The LJMU team conducted internationally excellent research using mathematical models of artificial neural networks to quantify objectively the deviation of abnormal movements from normality (Barton et al., 2012, 2015). These methods now enable clinicians to integrate the results of complex gait analysis into their clinical decision-making. Prof. Barton and his group at LJMU started collaborating with the clinical research team at the National Alkaptonuria Centre established in 2012 at the Royal Liverpool Hospital. Annual gait analysis for all AKU patients in the UK started at LJMU in 2013 (**CS2**) and a long-term agreement secures gait analysis as part of the NHS specialist commissioned AKU service (£26K per annum indefinitely) [F5]. Clinicians at the NAC use the MDP gait deviation index routinely in their clinical decision-making in patients with alkaptonuria which currently affects a total of 72 known patients in the UK (UR2, UR3: Barton et al., 2012, 2015. The gait deviation profile of patients is presented on the first page of their annual gait report produced after their gait analysis at LJMU (**CS3**) and so directly affects the treatment of all patients in the UK with the condition (**CS4**, **CS5**, **CS6** testimonials). The provision of yearly research-informed gait analysis for all AKU patients in the UK as part of an NHS service is a unique asset and serves as a model for collaborators in Europe and the US (**CS7**).

Gait summary measures showing that AKU affects the young (UR2 and UR4): A paradigm shift in the clinical management of AKU was achieved through our research in AKU gait analysis funded by the EU (as part of SOFIA, £52K) [F6]. Our findings provided new evidence that the condition affects not only adults and older patients but also the younger population (16-20 years). The clinical implications were published (UR4: Cox et al., 2019) *"Impact on clinical practice: This study supports nitisinone therapy from age 16 years in AKU. An AKU paediatric study is needed in those younger than 16 years."* Based on this evidence, an externally funded research project started in 2019 (Childwick Trust) in children with AKU. The results will inform further clinical trials to determine when to start intervention in children with AKU, to minimise cost and potential side effects of early nitisinone treatment.

Gait modifications (UR5): Our research in AKU gait analysis has changed how gait analysis is taught in Europe and beyond. Although the new drug will transform treatment for European patients, many patients across the world will not have immediate access to nitisinone because of international licensing and financial barriers. We have described a gait modification (UR5: Anderson et al., 2018), that could be used to reduce joint loading and pain in AKU as a substitute or in addition to nitisinone treatment. A link to this paper is now included in the 'Moments' smartphone app (**CS8**) which has been used by clinical gait analysts attending the Gait Course of the European Society for Movement Analysis in Adults and Children (ESMAC) every year, confirming impact on teaching and learning of clinical biomechanics (**CS8**). Since 2018 several clinicians and academics have asked permission to use the app in their regional gait courses, clinical work and academic teaching (**CS9**). The total number of downloads is currently 926.

Beneficiaries and scope of reach:

All patients with AKU in Europe will now have access to a new drug and the clinical management of all 72 patients in the UK is enhanced by incorporating the advanced analysis of their gait function in clinical decision-making. Widening the scope of clinical management and research to children will improve their health by preventing irreversible tissue damage and long-term deterioration in later life. New knowledge derived from research informs the training of clinicians as part of the annual instructional gait course by ESMAC at a European level.

5. Sources to corroborate the impact

CS1: (a) First treatment for rare metabolic disorder alkaptonuria (News 18/09/2020): EMA has recommended granting an extension of indication to Orfadin (nitisinone) to include the treatment of alkaptonuria in adult patients. (b) The AKU Society's announcement of the new licence for nitisinone (Orfadin). (c) Lancet paper on the results of the 5-year clinical trial (d) The AKU Society received the Black Pearl Member Award of EURORDIS (Rare Diseases Europe) in 2021

CS2: Gait analysis as part of the NHS specialist commissioned service provided by the National Alkaptonuria Centre in Liverpool: *"For Arash the 3D gait analysis of how he walks is the best part of his visit."*

CS3: The first page of every AKU patient's gait report shows their gait deviation from normality (MDP_{mean}) compared to other AKU patients and a control group, using our published method. This gait report is used by clinicians at the National Alkaptonuria Centre to determine individualised interventions.

CS4: Testimonial from Prof. Ranganath, the founder and previous Clinical Director of the National AKU Centre on how Prof. Barton's research informs care of patients with alkaptonuria and how this work can impact care in osteoarthritis, a very common disease impairing mobility.

CS5: Testimonial from Dr Milad Khedr, the current Clinical Director of the National AKU Centre on how gait analysis conducted at LJMU and using our approaches enhances clinical decision making.

CS6: A mother of two sons with AKU reports practical benefits due to gait analysis.

CS7: The German Speaking Self-Help Group of Alkaptonuria added information about gait analysis to their website, referring to Prof. Barton's publication (in German).

CS8: 'Moments' program on ESMAC web page accessible to students of the annual Gait Course, and download counter at 926. Source: https://esmac.org/download/ (admin access necessary for download metrics can be granted on request)

CS9: Selected examples of requests from clinicians and academics asking for permission to use the 'Moments' program and app with their patients and students indicating its usefulness to the clinical and academic communities utilising gait analysis techniques.