

<b>Institution: Royal Veterinary College (RVC)</b>		
<b>Unit of Assessment: A 6 Agriculture, Veterinary and Food Science</b>		
<b>Title of case study: Novel understanding of early stage feline chronic kidney disease allows development of new diagnostic tools, dietary management and drug treatment</b>		
<b>Period when the underpinning research was undertaken: 2004 - 2020</b>		
<b>Details of staff conducting the underpinning research from the submitting unit:</b>		
<b>Name(s):</b>	<b>Role(s) (e.g. job title):</b>	<b>Period(s) employed by submitting HEI:</b>
Jonathan Elliott	Lecturer -> Professor in Veterinary Clinical Pharmacology.	01/07/1990 – present
Harriet Syme	Lecturer -> Professor of Small Animal Internal Medicine.	01/01/2003 – present
Rosanne Jepson	Lecturer -> Associate Professor in Small Animal Internal Medicine.	02/11/2011 – present
Rebecca Geddes	Staff Clinician in Small Animal Internal Medicine -> Clinical Scientist Fellow.	10/09/2018 – present
<b>Period when the claimed impact occurred: 01/08/2013 - 31/12/2020</b>		
<b>Is this case study continued from a case study submitted in 2014? N</b>		
<b>1. Summary of the impact</b> (indicative maximum 100 words)		
<p>Positive impacts on veterinary businesses and on animal health and welfare and, concomitantly, their owners' wellbeing, have resulted directly from RVC's world-leading research into feline chronic kidney disease (CKD), a common condition in older cats. RVC has continued to improve disease management globally through 1) identifying diagnostic markers for earlier detection; 2) determining a role of magnesium in bone mineral disturbance in CKD; and 3) defining a pre-hypertensive stage of hypertension. These advances have led to new commercial diagnostic tests and tools and novel commercial diets for management of early stage disease. In addition, RVC research has facilitated 1) marketing approval for veterinary drugs to treat feline hypertension; 2) investment in clinical trials investigating expanded drug uses and dietary supplementation; and 3) changes to internationally recognised guidelines.</p>		
<b>2. Underpinning research</b> (indicative maximum 500 words)		
<p>Feline CKD is linked to development of other deleterious conditions, such as mineral and bone disorder (MBD) and hypertension. Research into these conditions is hampered without long-term engagement with first opinion practice. In 1994, Professor Jonathan Elliott in partnership with the animal charity, PDSA, set up the RVC Geriatric Cat Clinic, offering free diagnosis and care. More than 4000 cats have been screened and enrolled in longitudinal studies. This case study builds on the previous REF case relating to treatment of established CKD, detailing new impacts since 2014 from work facilitating earlier diagnosis, prior to the onset of persistent azotaemia based on current diagnostic laboratory reference intervals, and instigation of treatment aimed at slowing progression.</p> <p>In 2009, the RVC group published a landmark prospective study of apparently healthy geriatric cats (<math>\geq 9</math> years of age) showing that within 12 months, 30% had evidence of azotaemic CKD [1]. This stimulated interest from diagnostic companies to carry out collaborative work to find more sensitive markers of reduced kidney function to enable earlier recognition of CKD. The RVC team was the first to show plasma symmetric dimethylarginine (SDMA) is closely correlated to plasma creatinine concentration in cats [2], which stimulated further research in collaboration with IDEXX showing how closely SDMA correlated with glomerular filtration rate. Elliott's group continued to characterise the early stage (non-azotaemic) feline CKD patients through</p>		

longitudinal study demonstrating bone and mineral disturbances were evident at this stage. The group validated the measurement of FGF23, a newly discovered phosphaturic hormone, in cats and showed plasma FGF23 concentrations were significantly higher in cats that 12 months later were shown to be azotaemic [3]. (Even though plasma creatinine and phosphate concentrations were no different from those of cats remaining non-azotaemic at 12 months.) This finding provides a rationale for restricting phosphate intake in the non-azotaemic stages of feline CKD. Further work on bone mineral disturbances in azotaemic cats demonstrated that magnesium (hitherto overlooked in small animal veterinary practice) contributes to the bone mineral disturbances in CKD [4]. Hypomagnesemia at diagnosis of azotaemic CKD was associated with a higher risk of death, indicating plasma magnesium concentrations can be useful as a prognostic indicator and should be measured to identify cases requiring more intensive treatment [4].

Hypertension is both a cause and a consequence of CKD and its occurrence negatively impacts on the quality of life of cats, potentially leading to blindness and CNS disturbances. The RVC group demonstrated, for the first time, that blood pressure increases over time in a longitudinal study of aged non-azotaemic and azotaemic cats, the latter being at greater risk of becoming severely hypertensive [5]. These results showed that patients at greater risk of becoming hypertensive often had a blood pressure at initial screen of >140mmHg, thus, newly identifying a 'pre-hypertensive' phase of hypertension.

Through their painstaking longitudinal study of geriatric cats with CKD and/or hypertension, Elliott's group have published 2 further important findings. Firstly, they were able to study CKD progression and showed that 47% of cats diagnosed with stable CKD (IRIS CKD Stages 2 and 3) progressed (defined by a >25% increase in plasma creatinine concentration) within 12 months of first diagnosis, with high plasma phosphate and urine protein-to-creatinine ratio predicting progression in all cats [6]. In addition, through longitudinal study they showed that proteinuria in hypertensive cats is predictive of all-cause mortality, independently of blood pressure control with amlodipine [7], suggesting that amlodipine treatment alone may not provide optimal management of feline hypertension and greater consideration to the proteinuria should be given.

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

1. **Jepson RE, Brodbelt D**, Vallance C, **Syme HM, Elliott J**. (2009) Evaluation of predictors of the development of azotaemia in cats. *Journal of Veterinary Internal Medicine* 23(4): 806-13. <https://doi.org/10.1111/j.1939-1676.2009.0339.x>
2. **Jepson RE, Syme HM**, Vallance C, **Elliott J**. (2008) Plasma asymmetric dimethylarginine, symmetric dimethylarginine, l-arginine, and nitrite/nitrate concentrations in cats with chronic kidney disease and hypertension. *Journal of Veterinary Internal Medicine* 22(2):317-24. <https://doi.org/10.1111/j.1939-1676.2008.0075.x>
3. **Finch NC, Geddes RF, Syme HM, Elliott J**. (2013) Fibroblast growth factor 23 (FGF-23) concentrations in cats with early nonazotemic chronic kidney disease (CKD) and in healthy geriatric cats. *Journal of Veterinary Internal Medicine* 27(2):227-33. <https://doi.org/10.1111/jvim.12036>
4. **van den Broek DHN, Chang YM, Elliott J, Jepson RE** (2018) Prognostic importance of plasma total magnesium in a cohort of cats with azotemic chronic kidney disease. *Journal of Veterinary Internal Medicine* 32(4), 1359–71. <https://doi.org/10.1111/jvim.15141>
5. **Bijsmans ES, Jepson RE, Chang YM, Syme HM, Elliott J**. (2015) Changes in systolic blood pressure over time in healthy cats and cats with chronic kidney disease. *Journal of Veterinary Internal Medicine* 29(3):855-61. <https://doi.org/10.1111/jvim.12600>
6. **Chakrabarti S, Syme HM, Elliott J**. (2012) Clinicopathological variables predicting progression of azotaemia in cats with chronic kidney disease. *Journal of Veterinary Internal Medicine* 26(2):275-81 <https://doi.org/10.1111/j.1939-1676.2011.00874.x>
7. **Jepson R, Elliott J, Brodbelt D, Syme, HM**. (2007) Effect of control of systolic blood pressure on survival in cats with systemic hypertension. *Journal of Veterinary Internal Medicine* 21(3):402-09 [https://doi.org/10.1892/0891-6640\(2007\)21\[402:eocosb\]2.0.co;2](https://doi.org/10.1892/0891-6640(2007)21[402:eocosb]2.0.co;2)

**Other Quality Indicators**

Professor Jonathan Elliott won the 2019 British Small Animal Veterinary Association (BSAVA) Woodrow Award for contributions to the advancement of small animal medicine by a qualified veterinarian. Professor Harriet Syme won the 2015 BSAVA Blaine Award for outstanding contribution to advancement of small animal medicine. Both these awards are indicative of the quality and significance of this body of work. Rosanne Jepson and Natalie Finch (first authors on references 1, 2, 3 and 7) were awarded the International Renal Interest Award in 2011 and 2013 respectively, for the work that underpins this impact case study, and have developed into independent research leaders in the field of kidney disease. The RVC group's research involving their geriatric cat clinic has attracted repeated investment from pet food manufacturers, pharmaceutical companies and diagnostic companies to work with the group to improve their diets, drugs and diagnostics for cats with CKD. In addition, grants from Biotechnology and Biological Sciences Research Council Industrial Case Competition and Petplan Charitable Trust have been won to support the research. Since July 2013, grants and contracts totalling over GBP2,000,000 have been awarded. Based on their contributions to the field, Elliott has been an International Renal Interest Society Board Member since 1998 and Syme since 2018. Jepson has been president of the European Society of Veterinary Nephrology and Urology since 2016, demonstrating her developing leadership credentials in veterinary nephrology. References 4 and 5 were in the top 5% for their field based on field weighted citation indices.

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

Cats are one of the most common companion animals worldwide (approximately 10,900,000 in UK ([PDSA, 2020](#)) and 100,000,000 in US) and CKD has an estimated prevalence of 3.6% in cats of all ages and is the 7th most frequently diagnosed condition in cats in first opinion practice in the UK ([O'Neill et al, 2014](#)).

The development of IDEXX's SDMA assay (launched in 2015) was stimulated by RVC's observation of the relationship between plasma SDMA and creatinine, by collaborative studies which showed the close relationship between SDMA and GFR in the cat ([Braff et al, 2014](#)) and confirmed serum SDMA concentrations were elevated prior to creatinine when testing RVC samples from published prospective longitudinal studies [a]. Since 2015, SDMA has been measured on 7,000,000 feline blood samples submitted to its laboratories worldwide [a]. In 2017, SDMA was added to the Catalyst® Chemistry Analyzer enabling in-house measurement of SDMA, accounting for a further 2,000,000 feline blood samples having SDMA measured [a].

[Text redacted for publication]

The capability of earlier diagnosis has stimulated Purina and Hills each to launch diets to aid management at this disease stage [b], and Royal Canin repurposed and re-launched their CKD diet in September 2020 [c]. [Text redacted for publication]. The RVC's discovery that low serum magnesium also contributes to the pathogenesis of bone and mineral disturbances associated with feline CKD has led to the recommendation that this analyte should be monitored in feline CKD patients. Since publication of these data, Nationwide laboratories and IDEXX have added magnesium to their serum biochemistry profiles aimed at geriatric cats/those with CKD and Pinmoore Animal Laboratory Services and Dick White Diagnostics now offer magnesium measurement as an add-on test [a, d]. In addition, Royal Canin Ltd has filed a patent (US2020/0163363 A1) for supplementing magnesium in the diet of hypomagnesaemic cats with CKD, which cites RVC researchers as joint inventors [Text redacted for publication] [c].

In addition to serum and plasma biomarkers, alternative ways of identifying CKD at an earlier stage have been developed by Waltham Petcare Science Institute in collaboration with RVC scientists. This approach was stimulated by RVC's studies showing clinical laboratory data could predict the onset of azotaemia [1] and led to the RVC collaborating on a machine learning/artificial intelligence approach to health screening data of cats seen in Banfield practices in the US (Bradley et al, 2019; Biourge et al, 2020) [c, e]. This work has led to the commercialisation of Antech's RenalTech tool, launched in 2019, which is made freely available to all veterinary practices that use Antech Diagnostics as a reference laboratory [e]. To October 2020, more than

250,000 results have been provided back to veterinarians [e]. Royal Canin launched their Azopredict tool in September 2020 and have made this tool available to veterinary practices using their diets to support decision making following health screening of geriatric cats [c].

The International Renal Interest Society (IRIS), which works to educate practitioners worldwide, has used RVC's research to inform its diagnostic algorithms and treatment recommendations, which are regularly updated and now incorporate measurement of SDMA [f]. These were also published in the BSAVA Manual of Canine and Feline Nephrology and Urology (3rd ed, 2017), edited by Elliott, Westrop and Grauer (UC Davis and Kansas State University). Between launch and July 2020, 1026 printed copies of the BSAVA Manual 3rd edition sold worldwide, with a further 3,635 full text digital copies accessed [g]. The 3rd edition has also been translated into Spanish with a 500-print run plus e-book produced, with another 1,600 print runs contracted for Chinese and Japanese versions (not yet published) [g]. Elliott, Syme and Jepson have been recognized as Key Opinion Leaders in this field, and have contributed to the dissemination of new best practice through international CPD activities since 2014, including numerous invited presentations to veterinary professional conferences in >20 countries including the UK, Australia, USA, Canada, Russia, Brazil, Italy, Germany, Hungary, Spain, Czech Republic, Sweden, Denmark, Malta, Columbia, Thailand, Israel, France, Portugal, Netherlands and South Korea. During this REF period, RVC feline CKD research underpinning this case has generated 4,260 unique visitors to the RVC website [h]. Mass media coverage (print circulation plus online readership where applicable) exceeded 7,000,000. The research has featured in veterinary professional outlets online and/or print including Vet Times (print circulation 18,000; online readers 528,256), Vet Nurse Online (16,000 members), and Todaysveterinarypractice.com (North American Veterinary Community members 17,800) [h].

The RVC's work on hypertension helped stimulate licensing of amlodipine besylate based product for use in cats by Orion, subsequently sold to Ceva, marketed as Amodip® [i]. [Text redacted for publication] Elliott worked as a consultant for Orion Ltd advising on the clinical trial design, and critically evaluating the data submitted to the European Medicines Agency (EMA). He helped the company publish the data from the pivotal clinical trial and has provided education for practitioners to raise awareness of the importance and prevalence of hypertension in cats associated with the launch of the product.

RVC has also worked closely with Boehringer Ingelheim (BI) regarding extension of the application of their telmisartan product, Semintra®, to management of hypertension in cats, which has provided the market with a new therapeutic approach since 2018 [j]. [Text redacted for publication] Elliott was co-author on the published clinical trial (recognising his role in its design) and provided expert critical evaluation of the data package on efficacy submitted to the EMA. [Text redacted for publication]

The RVC's study showing that blood pressure increases over time in cats stimulated a change in the ACVIM Consensus statement on hypertension to include a pre-hypertensive stage of hypertension (140 to 160mmHg systolic) [k]. This Consensus Statement was accessed online 5,964 times in 2018, and 19,307 times in 2019, where it was in the top 10 downloaded articles [k]. This change is also reflected in the IRIS classification of hypertension, identifying cats with blood pressure in this range for closer monitoring [f]. RVC's research into feline hypertension and reputation in this field has been recognised by the invitation by Springer for Elliott, Jepson and Syme to edit a textbook on Hypertension in the Dog and Cat, which was published in February 2020 [g]. Between February and July 2020, 2,000 chapter downloads have been registered by the publishers [g]. This book has 13 chapters, (7 of which were written by the editors) and provides an evidence-based account of the current state of knowledge in this field.

RVC's research demonstrating a clear link between proteinuria and risk of progression within 12 months of CKD diagnosis was one of the factors in stimulating Boehringer Ingelheim to design a large clinical trial to determine whether telmisartan slows CKD progression [Text redacted for publication] [j].

Since August 2013, >1,000 cats have benefitted from free wellness and monitoring diagnostics and care (beyond the financial capacity of their owners), supported by Mars group's (Waltham and Royal Canin) grants totalling GBP1,641,199, together with GBP72,000 in-kind contributions of clinical renal diets [c], to run RVC clinics. During the REF2021 period, 4 veterinarians have been trained as clinical researchers in feline CKD with a further 5 currently undertaking PhDs.

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

*All corroborating evidence has been uploaded with submission, unless otherwise stated.*

- a. Letter from IDEXX corroborating development and sales of SDMA assay, and inclusion of magnesium in feline biochemistry profiles [Text redacted for publication].
- b. Letter and email from Purina corroborating diet development and sales of NF Early Care diet, plus Hills website information [as accessed 01/05/2019] advising use of early k/d diet on the basis of SDMA testing <https://www.hillspet.com/cat-food/pd-kd-early-support-feline-chicken-dry>
- c. Letter and email from Royal Canin corroborating development and launch of early CKD diet, patent for magnesium dietary supplementation in cats, randomised controlled trial investigating magnesium supplementation in cats with CKD, development of the Azopredict Algorithm and RenalTech Tool, plus Biourge V, Delmotte S, Feugier A, Bradley R, McAllister M, Elliott J. (2020) An artificial neural network-based model to predict chronic kidney disease in aged cats. *Journal of Veterinary Internal Medicine* 34(5) 1920–1931. <https://doi.org/10.1111/jvim.15892>
- d. Emails from Nationwide Labs, Pinmoore Animal Laboratory Services and Dick White Referral Diagnostic Labs corroborating inclusion of magnesium in biochemistry profiles/as an add-on test
- e. Letter from Waltham (Mars Petcare), plus Bradley R et al (2019) Predicting early risk of chronic kidney disease in cats using routine clinical laboratory tests and machine learning. *Journal of Veterinary Internal Medicine*. 33(6), 2644–2656. <https://doi.org/10.1111/jvim.15623>
- f. IRIS Staging of CKD (modified 2017 & 2019) including SDMA and prehypertensive stage [http://www.iris-kidney.com/pdf/IRIS Staging of CKD modified 2019.pdf](http://www.iris-kidney.com/pdf/IRIS_Staging_of_CKD_modified_2019.pdf)
- g. Email from BSAVA corroborating sales of Manual of Canine and Feline Nephrology and Urology (3rd ed, 2017) edited by Elliott, Westrop & Grauer (UC Davis & Kansas State University), plus email from Springer corroborating sales of Hypertension in the Dog and Cat (2020) Elliott J, Syme H, Jepson R (Eds.) Springer. ISBN 978-3-030-33020-0.
- h. RVC web/media statistics from Google Analytics; Meltwater/Signal PR systems; RVC social channels [Held by RVC].
- i. Letter from Orion corroborating role of RVC research in influencing licensing of Amodip® [Text redacted for publication].
- j. Letter from Boehringer Ingelheim corroborating the role of the RVC in extension of claim for Semintra® for treating hypertension, [Text redacted for publication] expert critical evaluation of the data package on efficacy submitted to the EMA and field trial design.
- k. Acierno MJ, Brown S, Coleman AE, Jepson RE, Papich M, Stepien RL, Syme HM. (2018) ACVIM consensus statement: Guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats. *Journal of Veterinary Internal Medicine*. 32(6):1803-1822. <https://doi.org/10.1111/jvim.15331> plus email from ACVIM corroborating download figures.