Institution: Royal Veterinary College (RVC)

Unit of Assessment: A 6 Agriculture, Veterinary and Food Science

Title of case study: Enabling general practitioners to diagnose asymptomatic feline hypertrophic cardiomyopathy and identify cats at high risk of catastrophic outcomes

Period when the underpinning research was undertaken: 2001 - 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:**
Virginia Luis Fuentes	Senior Lecturer in Internal Medicine -> Professor of Veterinary Cardiology	02/02/04 – present
David Connolly	Lecturer in Internal Medicine/Cardiology -> Professor in Cardiology	01/10/99 – present
David Brodbelt	Lecturer in Companion Animal Epidemiology -> Professor of Evidence-Based Veterinary Medicine	01/04/05 – present
Adrian Boswood	Lecturer in Internal Medicine -> Professor of Veterinary Cardiology	01/11/96 – present
Harriet Syme	Senior Lecturer -> Professor of Small Animal Internal Medicine	01/01/03 – present

Period when the claimed impact occurred: 01/08/13 - 31/12/20

Is this case study continued from a case study submitted in 2014? N

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

Cardiomyopathy is a disease of heart muscle that can be fatal in cats, causing congestive heart failure (CHF) and arterial thromboembolism (ATE). RVC clinical researchers have been responsible for changing the current approach to diagnosis of feline cardiomyopathy. New recommendations for focused echocardiography, which can be easily conducted by general practitioners, and the use of plasma biomarker tests have been included in consensus statement guidelines and textbook chapters. The RVC-validated NT-proBNP test has been successfully commercialised globally by IDEXX and is increasingly used by general veterinary practitioners. Together, these measures have facilitated earlier diagnosis and treatment of this condition affecting approximately 15% of cats.

2. Underpinning research (indicative maximum 500 words)

With the appointment of Professor Virginia Luis Fuentes in 2004, RVC increased the number of academic specialist cardiologists to 3, creating a critical mass in this discipline to enable significant focus on clinical research. Luis Fuentes brought expertise in feline cardiology and by engaging with charities (Battersea Dogs and Cats Home and Cats Protection), Industry and breed societies, has developed a sustainable research programme investigating the epidemiological risk factors (including genetics) for clinical progression of feline hypertrophic cardiomyopathy (HCM).

Prior to the appointment of Luis Fuentes, RVC cardiologists were studying diagnostic and prognostic indicators that do not require echocardiography and pioneered the use of biomarkers in identifying cats with HCM, whether asymptomatic or presenting with signs of respiratory distress [1, 2]. Both NT-proBNP and high sensitivity cardiac troponin I (cTnI) were shown to be predictors of survival in cats with HCM, with cTnI predicting reduced survival independent of the presence of heart failure or left atrial size [3]. These findings were corroborated by researchers working in the US who were commissioned to conduct similar studies using the same biomarker assays.

Armed with these biomarker tools, Luis Fuentes began systematic prospective study of the epidemiology of cardiomyopathy in cats in rehoming shelters. Luis Fuentes' group described the

relationship between heart murmurs and HCM, which is the most common heart disease in cats [4]. This study showed that not all affected cats have a heart murmur, and not all cats with a murmur have HCM, highlighting the difficulties faced by general practitioners in identifying cats with cardiomyopathy. A subsequent landmark RVC cross-sectional study of 780 cats in rehoming centres (the CatScan study [5]) provided definitive evidence of the high overall prevalence of HCM in cats in the UK (15%) and expanded knowledge of the complex association between murmurs and HCM; HCM is more common in cats with high-grade murmurs, but some cats with HCM have no murmur. The CatScan study demonstrated the striking increase in prevalence of HCM with age, from 4% in cats under 1 year of age, to 29% in cats aged 9 years or older. Furthermore, this study showed that HCM is the predominant cardiomyopathy in asymptomatic cats.

In parallel, the RVC group explored factors associated with cardiac mortality in cats with HCM and found that while many cats remain asymptomatic for years, independent predictors of cardiac mortality were left atrial enlargement, poor left ventricular contractility and/or extreme left ventricular hypertrophy [6]. While left atrial enlargement had been previously reported as a prognostic marker in cats with HCM, Luis Fuentes' 2013 study (the largest to date) identified 15 additional previously unreported prognostic markers in feline HCM and showed that left atrial enlargement was the most important of all. Luis Fuentes' work has also identified the specific risk factors for the most important complications of HCM adverse events (CHF and ATE) [4]. These risk factors are identified with echocardiography, a technique that requires training and experience but one that is becoming more commonly employed in general practice with the increasing availability of practical echocardiography courses, such as those run by the RVC.

The RVC group have pioneered a diagnostic approach based on identifying cats at high risk of cardiac complications, rather than the traditional but hard-to-use morpho-functional classification that has little value for management decision making. By promoting risk assessment in target populations using simple methods such as measurement of plasma biomarkers and simplified (limited) echocardiographic assessment of left atrial size perfectly possible to undertake with the equipment owned by many small animal practices, cats with 'high-risk' HCM can be diagnosed earlier and can benefit from earlier institution of preventative treatment before clinical signs develop.

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

1. **Connolly DJ**, Soares Magalhaes RJ, **Syme HM**, **Boswood A**, **Luis Fuentes V**, Chu L, & Metcalf M. (2008) Circulating Natriuretic Peptides in Cats with Heart Disease. *Journal of Veterinary Internal Medicine* **22**(1): 96-105. https://doi.org/10.1111/j.1939-1676.2007.0024.x
2. **Connolly DJ**, Soares Magalhaes RJ, **Fuentes VL**, **Boswood A**, Cole G, Boag A, **Syme HM** (2009) Assessment of the diagnostic accuracy of circulating natriuretic peptide concentrations to distinguish between cats with cardiac and non-cardiac causes of respiratory distress. *Journal of Veterinary Cardiology*. 11 Suppl 1: S41-50. https://doi.org/10.1016/j.jvc.2009.03.001
3. ***Borgeat K***, Sherwood K, ***Payne JR***, **Luis Fuentes V**, **Connolly DJ**. (2014) Plasma Cardiac Troponin I Concentration and Cardiac Death in Cats with Hypertrophic Cardiomyopathy. *Journal of Veterinary Internal Medicine* **28**(6): 1731-1737. https://doi.org/10.1111/jvim.12459
4. ***Payne JR***, ***Borgeat K***, **Brodbelt DC,** **Connolly DJ**, **Luis Fuentes V**. (2015) Risk factors associated with sudden death vs. congestive heart failure or arterial thromboembolism in cats with hypertrophic cardiomyopathy. *Journal of Veterinary Cardiology.* **17,** Supplement 1:S318-S328. https://doi.org/10.1016/j.jvc.2015.09.008
5. ***Payne JR***, **Brodbelt DC**, **Luis Fuentes V**. (2015) Cardiomyopathy prevalence in 780 apparently healthy cats in rehoming centres (the CatScan study). *Journal of Veterinary Cardiology* **17,** Supplement 1: S244-S257. https://doi.org/10.1016/j.jvc.2015.03.008
6. ***Payne JR***, ***Borgeat K***, **Connolly DJ**, **Boswood A,** Dennis S, Wagner T, Menaut P, Maerz I, Evans D, Simons VE, **Brodbelt DC**, & **Luis Fuentes V**. (2013) Prognostic Indicators in Cats with Hypertrophic Cardiomyopathy. *Journal of Veterinary Internal Medicine* **27**(6): 1427-1436. https://doi.org/10.1111/jvim.12215

Other Quality Indicators
Virginia Luis Fuentes chairs the American College of Veterinary Internal Medicine (ACVIM) Consensus Statement panel on feline cardiomyopathies, which consists of an international group of feline cardiac specialists addressing classification, diagnosis and management, in production of a consensus statement disseminated via the Journal of Veterinary Internal Medicine. She has been invited to give 43 talks on feline heart disease to veterinarians in 15 different countries over the past 5 years. Luis Fuentes was Chair of the Cardiology Specialty of the European College of Veterinary Internal Medicine from 2012-2018. References 4 and 5 were in the top 1% for their field based on citation indices, and reference 3 was in the top 5%.

Based on the quality of the work presented in reference 5 (funded from private industry and endowment funding for PhD studentship support), Luis Fuentes secured competitive funding from Pet Plan Charitable Trust (2018-2020) to continue the CatScan 2 study and re-examine many of the cats that had been rehomed in the original CatScan study.

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

RVC research suggests that, of the 10,900,000 cats in the UK (PDSA, 2019), >1,630,000 are affected by HCM, many of which may not have heart murmurs or signs of the disease [4, 5]. Diagnosis of feline heart disease has been difficult for general practitioners, with diagnosis of cardiomyopathy in asymptomatic cats being particularly problematic without access to advanced echocardiography skills. Traditionally there has been an emphasis on classifying the type of cardiomyopathy using the human nomenclature for cardiomyopathy subtypes, as described in the only textbook specifically on feline cardiology that has been published to date (Côté et al, 2011). This requires sophisticated echocardiographic techniques and interpretation skills, making diagnosis difficult for non-specialists and even trained specialists find this difficult [a].

As a result, rather than pursuing a diagnosis in cats with suspected cardiomyopathy, many veterinarians in general practice have historically adopted a 'wait and see' approach, so that 'high-risk' cats remained undetected until potentially fatal complications developed. Such complications can occur unexpectedly following a veterinary intervention (such as general anaesthesia for routine surgery) or may be spontaneous such as with the sudden onset of arterial thromboembolism. RVC research has underpinned the development of accessible means of screening cats and enabling practitioners to identify those at high risk of developing life-threatening complications of HCM where treatment is indicated.

RVC research was instrumental in working with Guildhay Ltd. and its sister company Biomedica Ltd. in validating a test for NT-proBNP in cats, which was subsequently sold to IDEXX, who further developed this for commercial use [b, c]. IDEXX Laboratories offer 2 feline assays considered as significant refinements of the Guildhay VetSign™ CardioSCREEN Test assay on a commercial basis: the Feline Cardiopet™ proBNP (exclusive to IDEXX Laboratories and used to measure NT-proBNP concentration in plasma from cats, and the SNAP® Feline proBNP, a patient-side test kit made available in 2014, which uses the same detection system as the Feline Cardiopet proBNP reference laboratory test [c].

After IDEXX started to offer NT-proBNP testing, widespread adoption was hampered by scepticism among specialists in veterinary cardiology who expressed doubt in the test utility and recommended suspected cases to be referred to them for echocardiography. Luis Fuentes' publication in 2015 [5] (first presented at a conference in 2014 [d]), however, demonstrated how common this problem is in cats in the general population and how variable the presence of a murmur is associated with this condition, suggesting screening of cats in general practice has a real value. This work was supported in part by IDEXX funding a PhD studentship and research project to perform an epidemiological study of myocardial disease in asymptomatic cats located in rehoming centres. As a result of Luis Fuentes' work, since 2014, IDEXX have seen a steady increase in the numbers of feline NT-proBNP tests run as education and awareness of this publication has increased, and IDEXX continue to use the RVC publications as the foundation for their educational and commercial activities [c]. [Text redacted for publication]

In addition, collaboration between RVC and IDEXX Laboratories has expanded how the NT-proBNP test is used in cat [c]. In emergency feline cases presenting with dyspnoea, removal of pleural fluid by thoracocentesis is both a therapeutic and diagnostic procedure. These feline patients are unstable and clinical scientists at the RVC suggested that measurement of NT-proBNP in the fluid removed by this therapeutic procedure might distinguish between cardiac and non-cardiac causes of dyspnoea in cats without the need for a blood sample to be collected [c]. RVC researchers proved this to be the case, and this was published in 2013 (Humm et al, 2013) using the laboratory test and in 2016 (Hezzell et al, 2016) using the patient-side test. This work has led to significant advances in emergency and critical care of the dyspnoeic cat removing the need for a second stressful procedure of blood sampling in these unstable feline patients.

Following the discovery of the high prevalence of HCM in the general population, and easily recognisable prognostic markers, the RVC Cardiology group has advocated that the emphasis in diagnosis should move away from the traditional morpho-functional classification of cardiomyopathies in cats, and instead focus on screening for cats with advanced disease that are at high risk of cardiac complications. The RVC Cardiology group has proposed pro-active screening of cats from populations where the prevalence of HCM is high, such as older cats. Initial screening can be done using plasma biomarkers such as NT-proBNP and cTnI. Recommendations for proactive screening using biomarkers or focussed echocardiography of cats citing RVC underpinning research have been included in textbook chapters and review articles since 2013, promoting use of focussed left atrial echocardiography [e]. RVC research comprises >10% of the total references used in the ACVIM consensus statement guidelines for the classification, diagnosis, and management of cardiomyopathies in cats, published in 2020 [f]. These emphasise that it is not necessary to use the traditional morphofunctional classification to treat feline HCM appropriately and recommends simple focussed point of care echocardiographic assessment of left atrial size and use of biomarkers by vets in primary care practice as an initial screening test for advanced subclinical cardiomyopathy [f].

Ultrasound machines are now available in the majority of small animal practices, so an alternative in-house method of screening for 'high-risk' cats with HCM is to use echocardiography to assess left atrial size, which is a key prognostic indicator [6]. RVC clinicians teach final year students rotating through the cardiology service how to assess left atrial size using echocardiography as standard practice. This approach is increasingly adopted in general veterinary practice. A 2017 RVC final year research project surveyed veterinary practices to assess diagnostic approaches to heart disease in cats, and found the median confidence level of performing brief echocardiography was 'comfortable' [g].

Data from the RVC VetCompass™ database, which holds information from >15,000,000 veterinary patients seen in 1800 first opinion practices in the UK also suggests increasing frequency of biomarker and echocardiography use in cats by vets in general practice. VetCompass data showed at least 6-fold increase in owners of feline patients being charged for echocardiography when the years 2013 and 2019 were compared, and a 5-fold increase in NT-proBNP tests between 2013 and 2019 [h]. This suggests that general practitioners are changing their attitudes and practises with regard to diagnosing heart disease in cats and adopting this pro-active approach. Increased screening has benefits for high-risk cats by allowing antithrombotic therapy to be started pre-emptively to reduce the risk of arterial thromboembolism, and benefits for owners, who can monitor the resting respiratory rate of their high-risk cat at home as a means of identifying the early signs of congestive heart failure, without having to take the cat on a stressful visit to the veterinary clinic. There are also benefits to veterinary surgeons, who can make a more informed decision about risk/benefit ratios in cats due to undergo elective surgical procedures or receive high rates of intravenous fluid administration that could precipitate congestive heart failure, in order to provide the best care possible to their patients.

5. Sources to corroborate the impact (indicative maximum of 10 references)
All evidence has been uploaded with the submission, unless otherwise stated as held by RVC.

a. Wilkie LJ, Luis Fuentes V, Rishniw M. (2015) Online survey to asses inter- and intra-observer agreement on echocardiographic classification of cardiomyopathy in cats. ACVIM Forum; 2015; Indianapolis; *Journal of Veterinary Internal Medicine* 29; 1263. https://onlinelibrary.wiley.com/doi/epdf/10.1111/jvim.13002

b. Letter from former principal scientist of Guildhay Ltd. corroborating RVC involvement in development of feline NT-proBNP tests.

c. Letter from IDEXX corroborating increase in the numbers of feline NT-proBNP tests run and use of the RVC publications as the foundation for their educational and commercial activities, plus IDEXX diagnostic update on SNAP Feline proBNP Test citing RVC research.

d. Payne JR, Luis Fuentes V and Brodbelt DC (2014) A Cross-Sectional Study of Cardiomyopathy Prevalence in 780 Cats in Rehoming Centers (The CatScan Study). Research report presented 6 June 2014 at ACVIM Forum, Nashville, Tennessee, USA.

e. Evidence corroborating inclusion of the underpinning research in textbooks and review articles:

- Luis Fuentes V. (2016) *Chapter 46 Ultrasound imaging for diagnosis and staging of feline cardiomyopathy*. In: Little S, ed. August's Consultations in Feline Internal Medicine. Volume 7. W.B. Saunders pp452-456. ISBN 9780323226523 https://doi.org/10.1016/B978-0-323-22652-3.00046-3 (Cites Payne 2010, [6])
- Luis Fuentes V. (2015) Editorial. Heart disease: time to take cats seriously. *Journal of Veterinary Cardiology* 17, Supplement 1: S2-S5. https://doi.org/10.1016/j.jvc.2015.10.002 (Cites Payne 2010, [2, 3, 6])
- Luis Fuentes V, Wilkie LJ. (2017) Asymptomatic Hypertrophic Cardiomyopathy: Diagnosis and Therapy. *Veterinary Clinics of North America Small Animal Practice.* 47 (5):1041-54. https://doi.org/10.1016/j.cvsm.2017.05.002 (Cites Payne 2010 [1, 3, 4, 5, 6]
- Côté E, Edwards NJ, Ettinger SJ, Fuentes VL, MacDonald KA, Scansen BA, Sisson DD, & Abbott JA (2015). Management of incidentally detected heart murmurs in dogs and cats. *Journal of Veterinary Cardiology* 17 (4): 245-261. https://doi.org/10.1016/j.jvc.2015.05.001 (Cites [6])
- Borgeat K, Connolly DJ, Luis Fuentes V. (2015) Cardiac biomarkers in cats. *Journal of Veterinary Cardiology* 17, Supplement 1:S74-S86. https://doi.org/10.1016/j.jvc.2015.08.001 (Cites [1, 2])
- Luis Fuentes V. (2020) *Chapter 27 Feline myocardial disease*. In: Bruyette DS, ed. *Clinical Small Animal Internal Medicine.* Hoboken, NJ, USA: John Wiley & Sons, Inc. pp267-274. https://doi.org/10.1002/9781119501237.ch27 [Held by RVC; Fig 2.3 on page 272 present an algorithm for the approach to the asymptomatic cat]

f. Luis Fuentes V, Abbott J, Chetboul V, Côté E, Fox PR, Häggström J, Kittleson MD, Schober K, & Stern JA (2020). ACVIM consensus statement guidelines for the classification, diagnosis, and management of cardiomyopathies in cats. *Journal of Veterinary Internal Medicine* 34(3) 1062–1077. https://doi.org/10.1111/jvim.15745 recommending simple focussed point of care echocardiographic assessment of left atrial size and use of biomarkers by vets in primary care practice as an initial screening test for advanced subclinical cardiomyopathy.

g. Copy of 2017 RVC final year research project surveying veterinary practices to assess diagnostic approaches to heart disease in cats, corroborating median confidence level of vets performing brief echocardiography as 'comfortable' [Figure 11 on page 10].

h. VetCompass™ data corroborating increase in use of echocardiography ('echocard*') and NT-proBNP ('BNP') tests charged to clients attending VetCompass™ practices (2013 to 2019)