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Chapter

Diagnosis, Prognosis, Management, Treatment, Research and Advances in Canine Dilated Cardiomyopathy

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Abstract

Dilated cardiomyopathy involves enlargement of the ventricular chamber and systolic dysfunction. The reduction in quality of life and increased levels of congestive heart failure, combined with the high diagnosis rate within the canine population, highlights the need for research into this disorder. This chapter looks at prevention, diagnosis, prognosis, and treatment of dilated cardiomyopathy. It details the disease pathology and physiology through to present clinical practices and studies to support prevention and treatment. This chapter also looks at the research being undertaken to further understand cardiomyopathies in dogs and develop new interventions. This ranges from fatty acids profiles to genetics and even personalized medicine and comparisons with human cardiomyopathy.

Keywords: Dilated cardiomyopathy (DCM), Canine, Echocardiography, Holter Monitoring

1. Introduction

DCM is characterised by ventricular chamber enlargement and systolic dysfunction which often leads to congestive heart failure [1]. The aetiology of DCM is complex. Genetic factors, myocardial ischemia, hypertension, toxins, infections and metabolic defects have been implicated [2]. DCM is the most common specific heart disease diagnosis within the Swedish insured canine population, following the more general diagnosis of cardiomyopathy, accounting for 10% of the cardiac diagnoses [1]. Prevention of disease requires a thorough understanding of the underlying causes of disease. Where the causes of disease are understood it can allow for modifications in diet, behaviour, and/or preventative medicine to be prescribed, or risk-reducing surgery to be undertaken where appropriate [3–5]. The underlying causes of non-communicable diseases are varied, with a wide range of environmental and genetic factors contributing to disease [6–11]. In most cases a combination of interacting factors contribute to disease risk, initiation, and progression [12–15].

2. Diagnosis and prognosis of canine cardiomyopathy

Dilated cardiomyopathy (DCM) is a significant cause of congestive heart failure in dogs, characterised by the enlargement and impaired contraction of the left or both ventricles [1–3]. The development of DCM can be classified into three main stages [4, 5]. In Stage 1, the heart appears normal, with no clinical evidence of heart disease and often includes dogs that are genetically predisposed to DCM [6]. Stage 2 (the preclinical or occult phase) is characterised by morphological and electrical cardiac changes with a prolonged period without overt clinical symptoms. Stage 3 (the overt phase) includes clinical signs of congestive heart failure [1–3, 7]. It should also be noted that adult DCM clinical signs can vary between breeds.

The gold standard approach to DCM diagnosis relies on echocardiographic and 24-hour electrocardiographic (ECG) assessments (**Figure 1**), in conjunction with monitoring clinical presentation and signalment [7–9]. The most common early clinical signs include exercise intolerance and heart murmurs/irregular heart rhythms. As the condition develops pulmonary congestion edema may develop and abdominal fluid accumulation and/or pleural effusion may be present. Notable other signs including weakness, inappetence, weight loss, breathlessness, coughing, increased breathing rate, collapse and lethargy are more frequent in dogs with heart failure caused by DCM, as is sudden death [3]. Congenital or acquired cardiac diseases with similar presentations to DCM must be also be excluded [10, 11].

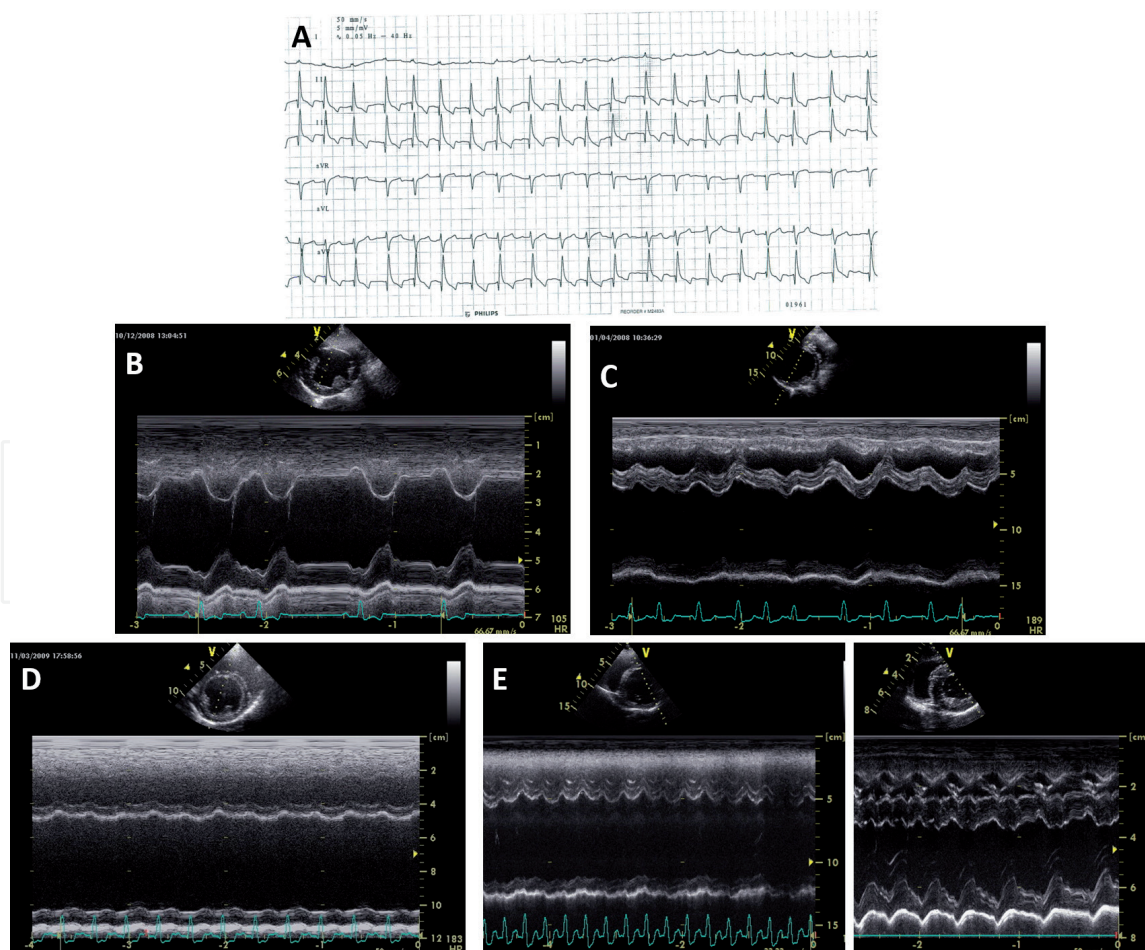


Figure 1.
A) Six lead ECG showing fast atrial fibrillation in a dog with dilated cardiomyopathy (DCM). Motion-mode echocardiogram from dogs that were classified as B) clinically normal, C) DCM showing dilation of the left ventricle and irregular filling associated with atrial fibrillation, D) DCM showing dilation of the left ventricle and a sinus tachycardia, and E) DCM (Left) alongside a motion-mode echocardiogram from a normal dog (Right), note the difference in the size of the ventricles and the amount of movement in the walls.

Echocardiography is used to assess left ventricular (LV) dimensions and function, where a dilated ventricle, based on M-mode or 2D measurements, with reduced contractility is indicative of DCM [9, 12]. M-mode is a time motion technique displaying the movement of structures over several cardiac cycles along a specific plane [13, 14]. The use of M-mode in conjunction with ECG allows LV measurements to be made more reliably (see **Figure 1** for examples). The LV end-diastolic internal diameter (LVIDd) should be measured during the onset of the QRS complex and near the end of the T wave for LV internal dimension during systole (LVIDs) [15]. Comparisons are ideally made against breed-specific LV measurements, but where this is not possible values should be compared to breeds of a similar size and weight [9].

Fractional shortening is a major indicator of systolic function, where values less than 20–25% suggest impaired contractility. This is calculated as follows:

$$FS = [(LVIDd - LVIDs) / LVIDd] \times 100 \quad (1)$$

In some cases, fractional shortening may be misleading, for example in athletic breeds values may appear to be lower, and in dogs with severe mitral regurgitation they can be higher [2, 15, 16], therefore caution is recommended when making a diagnosis. End point to septal separation (EPSS) is the minimum distance between the anterior mitral leaflet (E point) to the LV septal wall, during the rapid filling phase of diastole [17, 18]. An EPSS measurement of >10 mm in any breed is considered abnormal. Increased values can occur in volume overload or reduced fractional shortening resulting in LV dilation [11, 13].

A characteristic feature of DCM is the ventricular chamber becoming more spherical as the ventricle dilates [19]. The index of sphericity (SI) is calculated during diastole by dividing the LV length with the LV width, where a value <1.65 is indicative of an abnormally rounder chamber [10].

Although M-mode echocardiography is commonly used (**Figure 1**), its one-dimensional nature restricts the spatial information provided and the technique is reliant on geometrical assumptions that may be altered during pathological states [8, 14, 20, 21]. The American Society of Echocardiography recommends that linear measurements should not be used to calculate LV volume, and suggest that the biplanar Simpson's methods of discs (SMOD) is more suitable [22]. A study in Dobermans concluded that SMOD is more sensitive than M-mode in detecting early echocardiographic changes observed in DCM. Thus, it is recommended that where possible, SMOD reference values should be used [8, 10].

The SMOD volume formula is based on tracing the endocardial border across the mitral annulus and measuring the long axis of the left ventricle. The LV cavity is divided into 20 discs of equal height, where the cross-sectional area of each disc is based on the diameters obtained from two orthogonal LV views. End-diastolic (EDV) and end-systolic (ESV) volumes are calculated from the summation of the stacked discs, often utilising the software available on many ultrasound machines. These volumes can be normalised to body surface area to give volume indices (EDV-I and ESV-I). The current recommendations are that an ESV-I > 80 ml/m² is a strong indication of systolic dysfunction [2, 8, 22]. Ejection fraction (EF) is calculated in a similar way to fractional shortening, but volume measurements are used as follows:

$$EF = (EDV - ESV) / EDV \quad (2)$$

Thus, EF takes into account both radial and longitudinal cardiac changes, where dogs with EF <40% are reflective of reduced inotropy [2, 22].

ECG is used for the detection of arrhythmias but, as arrhythmias are often intermittent, they may be missed by an in-house 5-minute ECG commonly used in first opinion practice. 24-hour ambulatory ECG (Holter) monitoring provides a more representative assessment, where the patient is not restricted to a clinical setting, yet continuous monitoring is enabled [11, 23]. Holter monitoring for 24 hours is often used to identify individuals that have arrhythmias, with ventricular arrhythmias being common in animals [88]. Owners additionally record activities such as sleeping or running to enable changes in heart rate or rhythm to be correlated with patient activity [24]. Most dogs with DCM show evidence of arrhythmias and in certain breeds these may precede echocardiographic abnormalities [25, 26].

Atrial fibrillation (AF) is a common supraventricular tachyarrhythmia in large and giant breeds [3, 27]. Despite the presence of AF in a large percentage of dogs with DCM, the mechanistic and clinical relationship between DCM and AF has not been clarified [16–19]. **Figure 1A** shows an example of a six lead ECG showing fast atrial fibrillation in a dog with DCM. One canine study showed that 80.5% of individuals with DCM also had a diagnosis of AF [20], with another study showing occurrence in 87.6% of the patients [19]. Most individuals were diagnosed with AF at the same time as DCM or in the 2 years prior to the diagnosis of DCM, which indicates that AF may be a precursor to a clinical diagnosis of DCM [20]. Therefore, individuals diagnosed with AF should be carefully monitored and regularly presented for heart testing to check for DCM. There is the potential to improve the survival of individuals diagnosed with AF by treating them with drugs such as pimobendan prior to the development of DCM or heart failure [21].

Ventricular premature complexes (VPC) appear to be more common in the Doberman and Boxer breeds than other breeds. In Dobermans, >300 VPCs/24 hours, or two successive Holter recordings within one year showing between 50 and 300 VPCs/24 hours is considered diagnostic for preclinical DCM, even if echocardiographic findings appear normal [10]. Thus, Holter monitoring is useful in identifying Dobermans that are destined to develop DCM. Similar diagnostic reference ranges are lacking in the Boxer but >50 VPCs/24 hours would be considered to be abnormal [2].

The European Society of Veterinary Cardiology (ESVC) has proposed a scoring system to aid in the diagnosis of DCM, especially for dogs that present with equivocal findings. The following cardiac changes fall into the major criteria and are allocated 3 points each: (i) LV enlargement, (ii) reduced systolic function, and (iii) increased LV sphericity. The remaining findings are considered minor (1 point each): (a) arrhythmias in specific breeds; (b) AF; (c) increased EPSS; (d) increased pre-ejection period: ejection time ratio; (e) LV fractional shortening in equivocal range; (f) left or biatrial enlargement. A total of ≥ 6 points is indicative of DCM and a score of 1–5 should encourage repeated examination for evidence of disease progression [2].

Annual screening using echocardiography and Holter monitoring, has been recommended for breeds genetically predisposed to DCM, including Dobermans, Boxers, Newfoundlands, Great Danes and Irish Wolfhounds (IWH). Detection of the pre-clinical phase allows earlier therapeutic intervention, can improve prognosis, and enables the removal of affected dogs from breeding programmes if appropriate [10, 28, 29]. This is particularly important in Dobermans as 30% die suddenly prior to the onset of congestive heart failure [30, 31]. However, yearly testing can be expensive as it often requires referral to specialists thus restricting accessibility. In some countries, breed groups/welfare groups have set up testing programmes,

and some even support these financially or fundraise, due to the concern about the numbers of animals developing cardiovascular problems.

Given the complex nature of diagnosis, that gold standard tests may not always be available for every client, and the financial restraints faced by some owners, development of further and/or potentially cost effective diagnosis tools are always needed [5, 7]. Biomarkers such as N-Terminal pro B-type natriuretic peptide (NT-proBNP) have been used in humans to identify patients with occult LV dysfunction. The NT-proBNP assay is useful to differentiate between cardiac and non-cardiac causes of respiratory distress, where conventional testing alone could lead to ambiguous results [28, 32]. In a study of 328 Dobermans, those that had plasma concentrations of NT-proBNP >400 pmol/L, in the absence of renal dysfunction, were more likely to have echocardiographic abnormalities. However, the results cannot be considered diagnostic as NT-proBNP concentrations overlapped in groups of dogs with and without preclinical DCM [7, 33]. The use of in-house 5-minute ECG has reasonable specificity and in Dobermans the detection of 1 VPC strongly suggests that >100 VPC would be recorded via Holter. However, due to poor sensitivity, absence of VPC should not rule out the possibility of DCM [6, 23]. The emphasis is that the results from these tests should not be used to establish a diagnosis, but rather to identify dogs that would benefit further from more costly diagnostic tests [34].

Two histopathological variations of canine DCM have been identified: “attenuated wavy fibre type” and “fatty infiltration type” [22] indicating that differing types of canine DCM exist. The fatty infiltration type has only been reported in Doberman Pinschers, Estrela mountain dogs, Great Danes, and Boxers [22–25]; whereas the wavy fibre type can occur in all breeds [22, 23]. As the wavy fibre type is found across breeds, and in many individuals, it could be the tissue’s response to the other processes of DCM. In general, atrophy, or attenuation, of muscle fibres is often a result of processes that prevent normal contractile ability: contractile ability is consistently compromised in DCM [26]. The clinical relevance and prevalence of these two histopathological variants remain to be established, and as post mortem tissue is required presently for phenotypic analysis this may not be useful in a clinical setting but could provide valuable research insights into the disorder [27].

The long-term prognosis of canine DCM can be highly variable, with well managed dogs maintaining a good quality of life for many years and others dying within weeks of diagnosis despite careful clinical management [19, 28, 29]. There are some breed specific prognosis trends such as Doberman Pinschers which generally have a poor prognosis. Their mean time to death (from diagnosis) is in the range of 7.4 to 9.7 weeks [29, 30], which is low in comparison to other breeds reported to be about four times that at 34 weeks [29]. Doberman Pinschers also had the lowest upper quartile range for survival time in a study, but analysis carried out by the same research showed that Great Danes also suffer from a poor prognosis, with the lowest median survival time of any breed [17, 28].

Age of onset can also affect prognosis and may be a useful indicator that differing types of canine DCM exist. Portuguese water dogs have a specific juvenile form of DCM, where age of onset is measured in weeks from birth [31, 32], while in most other cases age of onset is measured in years [17]. Great Danes have a mean age of onset of 4.8 (SD \pm 2.3) years [33], comparable to Irish Wolfhound mean age of onset of 4.40 (SD \pm 2.03) years [34]; but lower than Doberman Pinscher’s at 7.3 years in males and 8.6 years in females [30]. Once identified, knowledge about the differing canine DCM types could benefit current and future potential treatments in addition to elucidating other clinically important factors in canine DCM, such as longevity and prognosis.

3. Treatment and management options

The ultimate aim of treatment is to cure disease, but this is currently not always possible. When a cure is not available, treatment of disease is aimed at reducing the impact of the disease, extending lifespan, and maintaining quality of life. Treatment of DCM in people is focused primarily on managing symptoms if at the overt stage of disease or, if presented with a preclinical case, prolonging the time between diagnosis and congestive heart failure [35]. Due to the predisposition of certain canine breeds, preclinical cardiac screening can help diagnose early abnormal findings, leading to a more successful diagnosis and potentially a management and treatment regime [36], in addition to possibly altering breeding programmes and preferences for some owners/breeders.

As with human DCM, in veterinary cases the ultimate aim is to minimise the effect of heart failure with attempts to delay disease progression depending on the stage of diagnosis [37]. Strategic treatments presently include vasodilators, angiotensin-converting enzyme (ACE) inhibitors, diuretics and positive inotropes. With atypical breeds or American cocker spaniels and Golden retrievers, dietary supplementation of taurine and L-carnitine is usually recommended if the suspected aetiology of DCM is diet-related [38–40].

In regards to treating earlier stages of DCM, there is often a focus on the prevention of further myocardial dysfunction by using the cardioprotective effect of ACE inhibitors [41]. These interventions focus on the vasodilation of blood vessels by reducing angiotensin II effects within the renin-angiotensin-aldosterone system (RAAS), a system heavily associated with severe heart disease through aldosterone release [42]. ACE inhibitors currently approved for veterinary purposes include benazepril, enalapril, imidapril and Ramipril, with the former being used to treat initial stages of heart failure and the latter three for more progressive stages [43].

Furosemide and spironolactone are both recommended diuretics, with the former inhibiting the re-absorption of sodium and chloride in the thick ascending loop of Henle to promote natriuresis. The latter is a weak potassium-sparing diuretic which works as an aldosterone antagonist. Monotherapy of these diuretics are not recommended [44] as they reduce plasma volume, further stimulating RAAS activity [42]. Therefore, diuretics are often used in combination with ACE inhibitors.

In Ref. to the undetermined link between canine DCM and atrial fibrillation (AF), for these patients, positive inotropes such as digoxin are particularly effective by increasing vagal tone, hence, decreasing heart rate [45]. Another drug often used is diltiazem, a calcium channel blocker also slowing conduction through the atrio-ventricular node. Although it is in fact a negative inotrope, it is particularly effective in dogs with AF by increasing diastolic filling time and therefore improving cardiac output [46]. Even though both of these drugs can be used individually, research indicates that using these drugs in combination can prove to be more effective [47]. With digoxin having a narrow therapeutic index, digoxin toxicity can occur and gradual withdrawal should take place if clinical signs such as depression, anorexia and vomiting are seen [45]. In addition, pimobendan has been investigated in relation to prolonging the onset of coronary heart failure due to DCM by having similar effects to digoxin whilst advantageously keeping myocardial oxygen demand to a minimum [42]. Pimobendan has also been shown to increase the survival rate in Dobermans [36] and we can assume it offers similar benefits to other breeds.

Although the majority of canine DCM treatments focus on managing the condition whilst optimising quality of life, diet-associated DCM can be potentially reversible with certain supplements such as taurine and L-carnitine [40]. Taurine deficiency is a prime cause of DCM in cats, evidence suggests micronutrient

shortages (e.g. selenium, iron) are linked to human DCM, and there are some trials suggesting there may be a link in certain canine breeds, including American cocker spaniels, Golden retrievers [38, 40]. Accumulating research indicates that nutrient imbalances may cause or exacerbate DCM due to reduced myocardial expenditure [48]. There are minimal to no side-effects of taurine supplementation in dogs [49], therefore treating American cocker spaniels, Golden retrievers and atypical breeds presenting with DCM with taurine pending the results of blood testing may be prudent. Furthermore, alongside nutraceuticals such as taurine and L-carnitine, omega-3 fatty acids have been shown to significantly reduce muscle loss and prostaglandin E2 production, and these results also correlate with increased survival rate [50]. However, these supplementary products are very expensive, especially when prescribed for larger breed dogs, so finding the possible aetiology for the disease is vital to determine the efficacy of these products [49].

Beta-blockers such as carvedilol have shown to have positive impacts for people with DCM [51–53]. Although carvedilol is a popular choice in humans with DCM and congestive heart failure [54, 55], there is limited evidence to date that these are beneficial in canine breeds with DCM [56]. Where used, careful monitoring should be ensured and treatment is best tolerated in dogs during the early stages of DCM [42].

In latter stages of DCM, the last resort for treating human heart disease includes transplants or inserting cardiac assist devices such as pacemakers [37], but these are far less realistic for canine patients due to cost, disease prognosis and surgical risk for the animal. Therefore, medical management based on symptomatic relief is the only current option for these patients [37].

Given that identifying, preventing, managing, and treating canine DCM is still a clinical challenge, new approaches are still needed. One new approach focusses on therapeutic gene transfer to target underlying molecular defects of ventricular dysfunction. Gene therapy could replace a defective gene, or part of a gene, with a functional one, resulting in effective amounts of a certain protein being produced that was once deficient [57, 58]. Evidence suggests Ca^{2+} handling is damaged in a heart with cardiac failure, and experiments involving altering calcium-handling protein levels in rodents through cardiac gene therapy have been successful [59]. Although achieving myocardial transduction in larger animal models presents many difficulties, therapeutic gene transfer may be a viable option in the future to treat canine DCM regardless of underlying cause. Another example of gene therapy is the use of vascular endothelial growth factor-B167 (VEGF-B167), which was administered via an intracoronary route in a study of 10 dogs with DCM [60]. The method was well tolerated by the canine patients. VEGF-B has anti-apoptotic and cardioprotective effects, so could be used to mitigate progression of DCM. Naturally many genes are associated with cardiomyopathy or in the drug and gene pathways [27, 61, 62], and additionally multiple genetic associations have been associated with the disorder [20] which potentially increases the complexity of gene therapy interventions.

Another of the requirements of gene therapy is understanding which mutations cause DCM in which species/breeds, therefore large trials are necessary in order to understand the basics, in addition to understanding the best methods of introducing gene therapy itself. For example gene therapy trials into dystrophin delivery via viral vectors has been promising but cardiovascular tissue is more complex than skeletal muscle, even when delivered via intravenous injection in dogs [63, 64]. Therefore gene therapy may be a very promising avenue of research, but the impact of gene associations and delivery methods may need to be taken into account for differing individuals and/or breeds.

Other new approaches being researched currently include myocardial regeneration therapies such as the use of resident cardiac stem cells, bone marrow stem cells, and skeletal myoblasts via transplantation therapies [65]. Cellular cardiomyoplasty has been explored via transplants of skeletal muscle cells into myocardium of canine DCM hearts. In early trials three of five dogs died early of tachyarrhythmias and pulmonary embolism, however two dogs survived and showed improved function of the heart [66]. Further investigation into this method is needed to understand the mechanisms and to prove if it can be successfully used in the clinic. Previous research on hamsters using smooth muscle cell transplants also showed clinical improvement in heart function [67], therefore this method could be developed for dogs and other species.

The use of cardiosphere-derived stem cells (CDCs) from adult dog hearts has also been trialled [68]. These cells can differentiate into cardiomyocytes *in vitro* and a study in Doberman pinschers diagnosed with DCM detailed patients given an infusion of canine CDCs via the coronary vessels [68, 69]. There was no rejection of the cells, and no adverse reactions were reported [69]. It has been suggested that therapy using CDCs can slow down ventricular enlargement and the effects of DCM such as systolic dysfunction. Studies on larger sample sizes need to be undertaken.

2-deoxyadenosine triphosphate (dATP) is an energy substrate that can be used by myosin instead of ATP during formation of cross-bridges in myocardial contraction. A study discovered that substituting ATP with dATP in both normal and DCM hearts leads to increased activity of myofilaments and increased systolic function [70]. Another potential pharmaceutical method is active myosin using drugs such as danicamtiv, which has undergone *in vitro* and *in vivo* trials in dogs, people and other mammals [71].

Transvenous electrical cardioversion of AF involves the placement of electrode coils in the vasculature of the heart, with the right atrium acting as the anode, and the left pulmonary artery acting as the cathode. A connection with a defibrillator is made and electrical shocks are given in time with the R wave. In a study of two canine cases affected by DCM, treatment resulted in the heartbeat returned to a normal sinus rhythm [72]. There is therefore potential for this therapy to be used to reduce the risk of AF leading to DCM development.

4. Genetics of cardiomyopathy and association with other conditions

Despite known pre-dispositions to diseases in the majority of UK kennel club registered breeds, there are currently only 93 disease associated variants identified and only 61 genetic tests commercially available across all breeds [73–75]. In human genetic testing there are tests available for 10485 conditions [76, 77]. This is a large difference despite close similarity between many diseases affecting dogs and humans [78–80]. Many tools have been utilised when identifying genetic variants associated with human diseases, these include genome wide association studies, candidate gene studies, whole exome sequencing, and whole genome sequencing [81–84]. These tools have also been utilised to some extent in some canine studies, but these approaches are often restrictively expensive for companion animal studies with limited funding available [85, 86]. The cost of these methods is delaying their clinical and research application in evaluating the genetic basis of canine diseases. Identification of susceptibility loci for these diseases has the potential to bring improvements in diagnosis and may lead to improved treatments in line with diseases which already have genetic loci associated with them [87–92].

The development and progression of common non-communicable diseases such as heart disease are influenced by a combination of risk factors. It has

been shown in several diseases that interactions between environmental and genetic risk factors are important in the development and progression of disease [13, 15]. Environmental risk factors for people with DCM are often modifiable as individuals can make informed choices with regards to lifestyle changes to reduce their risk of developing disease [7, 10, 93], likewise dog owners may be able to modify environmental risk factors for their animals. Currently genetic risk factors are not modifiable, although genome editing technologies may allow this in the future [94]. Despite this, individuals identified as having a high genetic risk of developing a disease are currently able to reduce their risk of developing disease. Options available include making lifestyle changes to reduce other risk factors, increased disease surveillance, and prophylactic medicine and surgery [4, 7, 10, 92, 93, 95, 96]. Increased disease surveillance can allow for early disease detection and therefore early treatment, which is associated with improved prognosis [87, 92]. An additional benefit of knowledge of the underlying genetic cause of disease is that it could lead to targeted treatments such as rectifying the defective gene or drugs targeting affected pathways [88, 89].

There are over 50 genes associated with DCM in people, some with multiple mutations, whereas there have only been 10 loci associated with canine DCM [85, 86, 97–100]. We have recently reviewed the genetics of canine and human DCM [27]. There has also been a RNAseq study examining the difference in expression of genes between canine DCM hearts and non-DCM hearts [101]. In the RNAseq study, genes involved in cellular energy metabolism were expressed less in the DCM hearts than the non-DCM hearts [101]. In several breeds canine DCM has been shown to be heritable [29, 31, 34]. To date mutations in only two genes (*PDK4* and *STRN*) and a single nucleotide polymorphism (SNP) on chromosome 5 have been associated with canine DCM [85, 97, 98, 102], and these are limited to a few breeds, suggesting additional genetic causes remain unknown. Of note are also cardiac troponin T and dystrophin which have both been highlighted in people, dogs and other species in relation to dilated cardiomyopathy [103–105], as mentioned in relation to gene therapy trials.

Genetic models and studies have also shown sex-linked genetic influences in relation to pathogenesis and a multigenic contribution to canine DCM [102]. The work showed that by combining three factors (*PDK4*, Chr5 TIGRP2P73097 SNP and an X-linked locus) DCM incidence could be more accurately predicted in a canine population. Overall this data showed that models incorporating multiple factors were more effective than those incorporating a single factor [102]. This has implications for future studies of the genetics and management of DCM, including monitoring which could enable earlier clinical intervention of individuals who are high risk.

In addition to commonly being diagnosed with DCM, IWHs are frequently diagnosed with atrial fibrillation (AF) [16, 19]. Despite the presence of AF in a large percentage of dogs with DCM, the mechanistic and clinical relationship between DCM and AF has not been clarified [16–19]. IWHs can develop DCM without AF, though it seems that <2% of IWHs with AF do not go on to develop DCM [16, 19]. If AF is a potential precursor to DCM, the time from diagnosis of AF to DCM is important, as if it is several years than the presence of AF could be less of a concern than if it is merely a few months. Also, if AF is a precursor to DCM, there is the potential to give individuals diagnosed with AF drugs such as the phosphodiesterase III/calcium sensitizing drug, pimobendan, to improve survival [21]. In addition to the potential clinical implications of AF diagnosis, if AF can be shown to be related to DCM, both diagnoses can be used for genetic association testing. This also has implications for individuals included in the unaffected group for genetic association testing, as individuals included in the unaffected group must be free of both DCM

and AF. There is some evidence that males are affected by DCM more often, or earlier in life than females [16, 18, 20, 30, 106].

Hypothyroidism has also been linked to increased DCM rates in some studies. For example Doberman Pinschers with DCM were 2.26 times more likely to have or develop hypothyroidism [107], and suggestions to links between the two conditions was also proposed in two Great Dane individuals [108]. Some research has not necessarily shown a link between the two disorders [109–111], therefore there are still questions around links, especially causal ones. Although exact mechanisms, or indeed associations have yet to be determined, evidence does support that the thyroid hormones can have positive inotropic and chronotropic effects, and that under both experimental and in patients these may have important influences over cardiovascular health and functions [112].

5. Canines as a model for human cardiomyopathy

Current understanding of disease processes and treatments is based on studying affected individuals compared to unaffected individuals, along with the use of animal models of disease, cell lines, and computer simulations [113–119]. Natural models of disease allow researchers access to additional cases of disease without inducing disease and causing additional suffering, because the animals involved develop disease irrespective of involvement in a study. Therefore, a relevant resource for investigating health and disease is the companion animal population, within which dogs in particular are useful as natural models of the equivalent human disease [1, 120–123].

The canine population overall is genetically heterogeneous, yet breeds are comparatively homogeneous which enhances their value as genetic models of disease [124]. Each breed of dog is a closed population and ancestry can typically be traced for many generations, often to the founding members of the breed [124–126]. This facilitates understanding the mode of inheritance of traits and diseases, and also restricts the amount of genetic diversity within a breed [34, 121, 125, 127]. Founder effects and subsequent inbreeding within pedigree dog breeds have led to differing allele frequencies between breeds, and some breeds are more prone to developing particular conditions than others [124, 128, 129]. This makes breeds with homologs of human conditions ideal for identifying potential genetic loci associated with disease for both canine and human benefit [123, 130].

Many canine disease phenotypes can be closely matched to human disease phenotypes with similar disease progression, pathology, treatment options, and prognosis [78–80]. Indeed there are currently 383 potential canine models for human disease listed in OMIA (Online Mendelian Inheritance in Animals), greater than any other species [78, 79]. Dogs are typically treated as family members and so inhabit the same environment as their owners with the associated exposure to the same potential environmental toxins, including, for example, air pollution [131]. Pet dogs also frequently benefit from high quality medical care, such that illnesses are detected and treated promptly, similar to the human population [132]. These characteristics of the canine population make it a valuable resource as a model of human disease. Examples of diseases with homologies in humans and dogs include diabetes, cardiomyopathies, cancers, and eye diseases [79, 120, 123, 133, 134].

6. Conclusions

Diagnosis of disease is informed by patient symptoms, family history, medical testing, and in some cases genetic testing [135–137]. With greater understanding

of disease progression, these aspects can be more accurately assessed and give earlier accurate diagnoses [87]. Early diagnosis can enable early treatment, which can result in improved outcomes compared to patients diagnosed later in the disease course [87, 92, 138]. Screening for disease prior to the onset of symptoms can catch diseases at an early stage, but may not be useful or affordable for an entire population. Screening asymptomatic individuals can be recommended when there is an additional reason to suspect that an individual may develop disease, such as family/breed history of the disease or a genetic test result indicating susceptibility to disease [95, 96]. A positive genetic test result often does not fully predict disease development, but merely indicates that the individual has a genetic pre-disposition to developing the disease [139]. Thus, a positive genetic test result does not always result in direct medical intervention, yet it can lead to increased awareness of the disease and enrolment of the individual on a health monitoring programme [92, 96]. Not only can the dog be an excellent model, but lessons can also be learned from other species with DCM [61].

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Conflict of interest

The authors declare no conflict of interest.

Abbreviations

ACE	Angiotensin-converting enzyme
AF	Atrial fibrillation
CDCs	Cardiosphere-derived stem cells
dATP	Deoxyadenosine triphosphate
DCM	Dilated cardiomyopathy
EF	Ejection fraction
ECG	Electrocardiograph
EDV	End-diastolic volume
EDV-I	End-diastolic volume indices
ESV	End-systolic volume
ESV-I)	End-systolic volumes indices
EPSS	End point to septal separation
ESVC	European Society of Veterinary Cardiology
SI	Index of sphericity
IWH	Irish Wolfhounds
LV	Left ventricular
LVIDd	Left ventricular end-diastolic internal diameter
LVIDs	Left ventricular internal dimension during systole
NT-proBNP	N-Terminal pro B-type natriuretic peptide
OMIA	Online Mendelian Inheritance in Animals

RAAS	Renin-angiotensin-aldosterone system
SMOD	Simpson's methods of discs
VEGF-B167	Vascular endothelial growth factor-B167
VPC	Ventricular premature complexes

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References

- [1] Egenvall A, Bonnett BN, Häggström J. Heart Disease as a Cause of Death in Insured Swedish Dogs Younger Than 10 Years of Age. *Journal of Veterinary Internal Medicine*. 2006;20(4):894-903.
- [2] McNally EM, Golbus JR, Puckelwartz MJ. Genetic mutations and mechanisms in dilated cardiomyopathy. *The Journal of Clinical Investigation*. 2013;123(1):19-26.
- [3] Banks E, Joshy G, Weber M, Liu B, Grenfell R, Egger S, et al. Tobacco smoking and all-cause mortality in a large Australian cohort study: findings from a mature epidemic with current low smoking prevalence. *BMC Medicine*. 2015;13(1):38.
- [4] Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in *brca1* or *brca2* mutation carriers with cancer risk and mortality. *The Journal of the American Medical Association*. 2010;304(9):967-75.
- [5] McFadden E, Stevens R, Glasziou P, Perera R. Implications of lower risk thresholds for statin treatment in primary prevention: Analysis of CPRD and simulation modelling of annual cholesterol monitoring. *Preventive Medicine*. 2015;70:14-6.
- [6] Hall JM, Lee MK, Newman B, Morrow JE, Anderson LA, Huey B, et al. Linkage of early-onset familial breast cancer to chromosome 17q21. *Science*. 1990;250(4988):1684-9.
- [7] Parkin DM. 3. Cancers attributable to consumption of alcohol in the UK in 2010. *British Journal of Cancer*. 2011;105(S2):S14-S8.
- [8] Parkin DM. 2. Tobacco-attributable cancer burden in the UK in 2010. *British Journal of Cancer*. 2011;105(S2):S6-S13.
- [9] Parkin DM. 5. Cancers attributable to dietary factors in the UK in 2010. *British Journal of Cancer*. 2011;105(s2):s24-S6.
- [10] Parkin DM. 9. Cancers attributable to inadequate physical exercise in the UK in 2010. *British Journal of Cancer*. 2011;105(S2):S38-S41.
- [11] Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, et al. Identification of the breast cancer susceptibility gene *BRCA2*. *Nature*. 1995;378(6559):789-92.
- [12] Chu Y-H, Tzeng S-L, Lin C-W, Chien M-H, Chen M-K, Yang S-F. Impacts of MicroRNA Gene Polymorphisms on the Susceptibility of Environmental Factors Leading to Carcinogenesis in Oral Cancer. *PLoS ONE*. 2012;7(6):e39777.
- [13] Nickels S, Truong T, Hein R, Stevens K, Buck K, Behrens S, et al. Evidence of Gene-Environment Interactions between Common Breast Cancer Susceptibility Loci and Established Environmental Risk Factors. *PLoS Genetics*. 2013;9(3):e1003284.
- [14] Sharafeldin N, Slattery ML, Liu Q, Franco-Villalobos C, Caan BJ, Potter JD, et al. A Candidate-Pathway Approach to Identify Gene-Environment Interactions: Analyses of Colon Cancer Risk and Survival. *Journal of the National Cancer Institute*. 2015;107(9):djv160.
- [15] Song C, Chang Z, Magnusson PKE, Ingelsson E, Pedersen NL. Genetic factors may play a prominent role in the development of coronary heart disease dependent on important environmental factors. *Journal of Internal Medicine*. 2014;275(6):631-9.
- [16] Brownlie SE, Cobb MA. Observations on the development of congestive heart failure in Irish

wolfhounds with dilated cardiomyopathy. *Journal of Small Animal Practice*. 1999;40(8):371-7.

[17] Martin MW, Stafford Johnson MJ, Celona B. Canine dilated cardiomyopathy: a retrospective study of signalment, presentation and clinical findings in 369 cases. *Journal of Small Animal Practice*. 2009;50(1):23-9.

[18] Tidholm A, Jonsson L. A retrospective study of canine dilated cardiomyopathy (189 cases). *Journal of American Animal Hospital Association*. 1997;33(6):544-50.

[19] Vollmar AC. The prevalence of cardiomyopathy in the Irish wolfhound: a clinical study of 500 dogs. *Journal of the American Animal Hospital Association*. 2000;36(2):125-32.

[20] Simpson S, Dunning MD, Brownlie S, Patel J, Godden M, Cobb M, et al. Multiple Genetic Associations with Irish Wolfhound Dilated Cardiomyopathy. *Biomed Res Int*. 2016;2016:6374082.

[21] Vollmar AC, Fox PR. Long-term Outcome of Irish Wolfhound Dogs with Preclinical Cardiomyopathy, Atrial Fibrillation, or Both Treated with Pimobendan, Benazepril Hydrochloride, or Methyl Digoxin Monotherapy. *Journal of Veterinary Internal Medicine*. 2016;30(2):553-9.

[22] Tidholm A, Jonsson L. Histologic characterization of canine dilated cardiomyopathy. *Veterinary Pathology*. 2005;42(1):1-8.

[23] Aupperle H, Marz I, Baldauf K, Roggon N, Kresken JG. Pathology of DCM in Great Danes. *Journal of Veterinary Internal Medicine*. 2014;28(2):730-.

[24] Lobo L, Carvalheira J, Canada N, Bussadori C, Gomes JL, Faustino AM. Histologic characterization of dilated

cardiomyopathy in Estrela mountain dogs. *Veterinary Pathology*. 2010;47(4):637-42.

[25] Stephenson HM, Fonfara S, López-Alvarez J, Cripps P, Dukes-McEwan J. Screening for dilated cardiomyopathy in Great Danes in the United Kingdom. *Journal of veterinary internal medicine / American College of Veterinary Internal Medicine*. 2012;26(5):1140-7.

[26] Tidholm A, Haggstrom J, Borgarelli M, Tarducci A. Canine idiopathic dilated cardiomyopathy. Part I: Aetiology, clinical characteristics, epidemiology and pathology. *The Veterinary Journal*. 2001;162(2):92-107.

[27] Simpson S, Edwards J, Ferguson-Mignan TFN, Cobb M, Mongan NP, Rutland CS. Genetics of Human and Canine Dilated Cardiomyopathy. *International Journal of Genomics*. 2015;2015:13.

[28] Martin MWS, Stafford Johnson MJ, Strehlau G, King JN. Canine dilated cardiomyopathy: a retrospective study of prognostic findings in 367 clinical cases. *Journal of Small Animal Practice*. 2010;51(8):428-36.

[29] Petric AD, Stabej P, Zemva A. Dilated cardiomyopathy in Doberman Pinschers: Survival, Causes of Death and a Pedigree Review in a Related Line. *Journal of Veterinary Cardiology*. 2002;4(1):17-24.

[30] Calvert CA, Pickus CW, Jacobs GJ, Brown J. Signalment, Survival, and Prognostic Factors in Doberman Pinschers With End-Stage Cardiomyopathy. *Journal of Veterinary Internal Medicine*. 1997;11(6):323-6.

[31] Dambach DM, Lannon A, Sleeper MM, Buchanan J. Familial dilated cardiomyopathy of young Portuguese water dogs. *Journal of veterinary internal medicine / American*

- College of Veterinary Internal Medicine. 1999;13(1):65-71.
- [32] Werner P, Raducha MG, Prociuk U, Sleeper MM, Van Winkle TJ, Henthorn PS. A novel locus for dilated cardiomyopathy maps to canine chromosome 8. *Genomics*. 2008;91(6):517-21.
- [33] Meurs KM, Miller MW, Wright NA. Clinical features of dilated cardiomyopathy in Great Danes and results of a pedigree analysis: 17 cases (1990-2000). *Journal of the American Veterinary Medical Association*. 2001;218(5):729-32.
- [34] Distl O, Vollmar AC, Broschk C, Hamann H, Fox PR. Complex segregation analysis of dilated cardiomyopathy (DCM) in Irish wolfhounds. *Heredity*. 2007;99(4):460-5.
- [35] Guttmann OP, Mohiddin SA, Elliott PM. Almanac 2014: cardiomyopathies. *Heart*. 2014;100(10):756-64.
- [36] Summerfield NJ, Boswood A, O'Grady MR, Gordon SG, Dukes-McEwan J, Oyama MA, et al. Efficacy of pimobendan in the prevention of congestive heart failure or sudden death in Doberman Pinschers with preclinical dilated cardiomyopathy (the PROTECT Study). *J Vet Intern Med*. 2012;26(6):1337-49.
- [37] Sleeper MM, Bish LT, Sweeney HL. Status of therapeutic gene transfer to treat canine dilated cardiomyopathy in dogs. *Vet Clin North Am Small Anim Pract*. 2010;40(4):717-24.
- [38] Kaplan JL, Stern JA, Fascetti AJ, Larsen JA, Skolnik H, Peddle GD, et al. Correction: Taurine deficiency and dilated cardiomyopathy in golden retrievers fed commercial diets. *PLoS One*. 2018;13(12):e0210233.
- [39] Kramer GA, Kittleson MD, Fox PR, Lewis J, Pion PD. Plasma taurine concentrations in normal dogs and in dogs with heart disease. *J Vet Intern Med*. 1995;9(4):253-8.
- [40] Kittleson MD, Keene B, Pion PD, Loyer CG. Results of the multicenter spaniel trial (MUST): taurine- and carnitine-responsive dilated cardiomyopathy in American cocker spaniels with decreased plasma taurine concentration. *J Vet Intern Med*. 1997;11(4):204-11.
- [41] O'Grady MR, O'Sullivan ML, Minors SL, Horne R. Efficacy of benazepril hydrochloride to delay the progression of occult dilated cardiomyopathy in Doberman Pinschers. *J Vet Intern Med*. 2009;23(5):977-83.
- [42] Oyama MA. Cardiac Drugs for Treatment of Canine Heart Failure. *NAVCClinician's Brief*. 2009;7:56-9.
- [43] Lefebvre HP, Brown SA, Chetboul V, King JN, Pouchelon JL, Toutain PL. Angiotensin-converting enzyme inhibitors in veterinary medicine. *Curr Pharm Des*. 2007;13(13):1347-61.
- [44] O'Grady MR, O'Sullivan ML. Dilated cardiomyopathy: an update. *Vet Clin North Am Small Anim Pract*. 2004;34(5):1187-207.
- [45] Merrett D. Digoxin therapy. *Aust Vet J*. 2000;78(9):612-5.
- [46] Stephenson H. Dilated cardiomyopathy therapy. *Vet Times*. 2011.
- [47] Gelzer AR, Kraus MS, Rishniw M, Moise NS, Pariaut R, Jesty SA, et al. Combination therapy with digoxin and diltiazem controls ventricular rate in chronic atrial fibrillation in dogs better than digoxin or diltiazem monotherapy: a randomized crossover study in 18

dogs. *J Vet Intern Med.* 2009;23(3):499-508.

[48] Adin D, DeFrancesco TC, Keene B, Tou S, Meurs K, Atkins C, et al. Echocardiographic phenotype of canine dilated cardiomyopathy differs based on diet type. *J Vet Cardiol.* 2019;21:1-9.

[49] Sanderson SL. Taurine and carnitine in canine cardiomyopathy. *Vet Clin North Am Small Anim Pract.* 2006;36(6):1325-43, vii-viii.

[50] Freeman LM, Rush JE, Kehayias JJ, Ross JN, Jr., Meydani SN, Brown DJ, et al. Nutritional alterations and the effect of fish oil supplementation in dogs with heart failure. *J Vet Intern Med.* 1998;12(6):440-8.

[51] Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med.* 1996;334(21):1349-55.

[52] Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med.* 2001;344(22):1651-8.

[53] Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet.* 2003;362(9377):7-13.

[54] Kveiborg B, Major-Petersen A, Christiansen B, Torp-Pedersen C. Carvedilol in the treatment of chronic heart failure: lessons from the Carvedilol Or Metoprolol European Trial. *Vasc Health Risk Manag.* 2007;3(1):31-7.

[55] Watanabe K, Arozal W, Sari FR, Arumugam S, Thandavarayan RA, Suzuki K, et al. The Role of Carvedilol in the Treatment of Dilated and Anthracyclines-Induced Cardiomyopathy. *Pharmaceuticals.* 2011;4(5):7700-781.

[56] Oyama MA, Sisson DD, Prosek R, Bulmer BJ, Luethy MW, Fuentes VL. Carvedilol in dogs with dilated cardiomyopathy. *J Vet Intern Med.* 2007;21(6):1272-9.

[57] Lyon AR, Sato M, Hajjar RJ, Samulski RJ, Harding SE. Gene therapy: targeting the myocardium. *Heart.* 2008;94(1):89-99.

[58] Vinge LE, Raake PW, Koch WJ. Gene therapy in heart failure. *Circ Res.* 2008;102(12):1458-70.

[59] Dieterle T, Meyer M, Gu Y, Belke DD, Swanson E, Iwatate M, et al. Gene transfer of a phospholamban-targeted antibody improves calcium handling and cardiac function in heart failure. *Cardiovasc Res.* 2005;67(4):678-88.

[60] Paradies P, Carlucci L, Woitek F, Staffieri F, Lacitignola L, Ceci L, et al. Intracoronary Gene Delivery of the Cytoprotective Factor Vascular Endothelial Growth Factor-B167 in Canine Patients with Dilated Cardiomyopathy: A Short-Term Feasibility Study. *Vet Sci.* 2019;6(1).

[61] Simpson S, Rutland P, Rutland CS. Genomic Insights into Cardiomyopathies: A Comparative Cross-Species Review. *Vet Sci.* 2017;4(1).

[62] Kubale V, Prozorowska E, Glocová K, Slater L, Rutland CS. The Function of Seven Transmembrane Receptors in the Cardiovascular System and Their Role in the Development of Cardiomyopathy. *Cardiac Diseases.* London: IntechOpen; 2020.

- [63] Yue Y, Ghosh A, Long C, Bostick B, Smith BF, Kornegay JN, et al. A single intravenous injection of adeno-associated virus serotype-9 leads to whole body skeletal muscle transduction in dogs. *Mol Ther*. 2008;16(12):1944-52.
- [64] Wang Z, Storb R, Halbert CL, Banks GB, Butts TM, Finn EE, et al. Successful regional delivery and long-term expression of a dystrophin gene in canine muscular dystrophy: a preclinical model for human therapies. *Mol Ther*. 2012;20(8):1501-7.
- [65] Sawa Y. Current status of myocardial regeneration therapy. *Gen Thorac Cardiovasc Surg*. 2013;61(1):17-23.
- [66] Borenstein N, Chetboul V, Rajnoch C, Bruneval P, Carpentier A. Successful cellular cardiomyoplasty in canine idiopathic dilated cardiomyopathy. *Ann Thorac Surg*. 2002;74(1):298-9; author reply 9.
- [67] Yoo KJ, Li RK, Weisel RD, Mickle DA, Li G, Yau TM. Autologous smooth muscle cell transplantation improved heart function in dilated cardiomyopathy. *Ann Thorac Surg*. 2000;70(3):859-65.
- [68] Hensley MT, de Andrade J, Keene B, Meurs K, Tang J, Wang Z, et al. Cardiac regenerative potential of cardiosphere-derived cells from adult dog hearts. *J Cell Mol Med*. 2015;19(8):1805-13.
- [69] Hensley MT, Tang J, Woodruff K, Defrancesco T, Tou S, Williams CM, et al. Intracoronary allogeneic cardiosphere-derived stem cells are safe for use in dogs with dilated cardiomyopathy. *J Cell Mol Med*. 2017;21(8):1503-12.
- [70] Cheng Y, Hogarth KA, O'Sullivan ML, Regnier M, Pyle WG. 2-Deoxyadenosine triphosphate restores the contractile function of cardiac myofibril from adult dogs with naturally occurring dilated cardiomyopathy. *Am J Physiol Heart Circ Physiol*. 2016;310(1):H80-91.
- [71] Grillo MP, Markova S, Evanchik M, Trelu M, Moliner P, Brun P, et al. Preclinical in vitro and in vivo pharmacokinetic properties of danicamtiv, a new targeted myosin activator for the treatment of dilated cardiomyopathy. *Xenobiotica*. 2021;51(2):222-38.
- [72] Jung SW, Newhard DK, Harrelson K. Transvenous electrical cardioversion of atrial fibrillation in two dogs. *J Vet Cardiol*. 2017;19(2):175-81.
- [73] Donner J, Kaukonen M, Anderson H, Möller F, Kyöstilä K, Sankari S, et al. Genetic Panel Screening of Nearly 100 Mutations Reveals New Insights into the Breed Distribution of Risk Variants for Canine Hereditary Disorders. *PLoS ONE*. 2016;11(8):e0161005.
- [74] Farrell LL, Schoenebeck JJ, Wiener P, Clements DN, Summers KM. The challenges of pedigree dog health: approaches to combating inherited disease. *Canine Genetics and Epidemiology*. 2015;2(1):1-14.
- [75] The Kennel Club UK. DNA screening schemes and results 2016 [Available from: <http://www.thekennelclub.org.uk/health/breeding-for-health/dna-screening-schemes-and-results/>].
- [76] GTR®. The NIH genetic testing registry 2016 [Available from: <http://www.ncbi.nlm.nih.gov/gtr/>].
- [77] Rubinstein WS, Maglott DR, Lee JM, Kattman BL, Malheiro AJ, Ovetsky M, et al. The NIH genetic testing registry: a new, centralized database of genetic tests to enable access to comprehensive information and improve transparency. *Nucleic Acids Research*. 2013;41:D925-35.

- [78] Lenffer J, Nicholas FW, Castle K, Rao A, Gregory S, Poidinger M, et al. OMIA (Online Mendelian Inheritance in Animals): an enhanced platform and integration into the Entrez search interface at NCBI. *Nucleic Acids Research*. 2006;34(Database issue):D599-D601.
- [79] OMIA. Online Mendelian Inheritance in Animals, OMIA. Faculty of Veterinary Science, University of Sydney 2016 [Available from: <http://omia.angis.org.au/>].
- [80] Tsai KL, Clark LA, Murphy KE. Understanding hereditary diseases using the dog and human as companion model systems. *Mammalian Genome*. 2007;18(6-7):444-51.
- [81] Butler MW, Burt A, Edwards TL, Zuchner S, Scott WK, Martin ER, et al. Vitamin D Receptor Gene as a Candidate Gene for Parkinson Disease. *Annals of Human Genetics*. 2011;75(2):201-10.
- [82] Rivas MA, Beaudoin M, Gardet A, Stevens C, Sharma Y, Zhang CK, et al. Deep resequencing of GWAS loci identifies independent rare variants associated with inflammatory bowel disease. *Nature Genetics*. 2011;43(11):1066-73.
- [83] Saunders CJ, Miller NA, Soden SE, Dinwiddie DL, Noll A, Alnadi NA, et al. Rapid Whole-Genome Sequencing for Genetic Disease Diagnosis in Neonatal Intensive Care Units. *Science Translational Medicine*. 2012;4(154):154ra35.
- [84] Yang Y, Muzny DM, Reid JG, Bainbridge MN, Willis A, Ward PA, et al. Clinical Whole-Exome Sequencing for the Diagnosis of Mendelian Disorders. *The New England journal of medicine*. 2013;369(16):1502-11.
- [85] Mausberg T-B, Wess G, Simak J, Keller L, Drögemüller M, Drögemüller C, et al. A Locus on Chromosome 5 Is Associated with Dilated Cardiomyopathy in Doberman Pinschers. *PLoS ONE*. 2011;6(5):e20042-e.
- [86] Philipp U, Vollmar A, Häggström J, Thomas A, Distl O. Multiple Loci Are Associated with Dilated Cardiomyopathy in Irish Wolfhounds. *PLoS ONE*. 2012;7(6):e36691-e.
- [87] Andrae B, Andersson TML, Lambert PC, Kemetli L, Silfverdal L, Strander B, et al. Screening and cervical cancer cure: population based cohort study. *British Medical Journal*. 2012;344:e900.
- [88] Greenberg B, Butler J, Felker GM, Ponikowski P, Voors AA, Desai AS, et al. Calcium upregulation by percutaneous administration of gene therapy in patients with cardiac disease (CUPID 2): a randomised, multinational, double-blind, placebo-controlled, phase 2b trial. *The Lancet*. 2016;387(10024):1178-86.
- [89] Ho CY, Lakdawala NK, Cirino AL, Lipshultz SE, Sparks E, Abbasi SA, et al. Diltiazem Treatment for Pre-Clinical Hypertrophic Cardiomyopathy Sarcomere Mutation Carriers A Pilot Randomized Trial to Modify Disease Expression. *JACC: Heart Failure*. 2015;3(2):180-8.
- [90] Kaback MM. Population-based genetic screening for reproductive counseling: the Tay-Sachs disease model. *Eur J Pediatr*. 2000;159(3):S192-S5.
- [91] Li X, You R, Wang X, Liu C, Xu Z, Zhou J, et al. Effectiveness of prophylactic surgeries in BRCA1 or BRCA2 mutation carriers: a meta-analysis and systematic review. *Clinical Cancer Research*. 2016;22(15):3971-81.
- [92] Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is

underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. *European Heart Journal*. 2013;34(45):3478-90.

[93] Blair SN, Kohl HW, 3rd, Barlow CE, Paffenbarger RS, Jr., Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. *The Journal of the American Medical Association*. 1995;273(14):1093-8.

[94] Maeder ML, Gersbach CA. Genome-editing Technologies for Gene and Cell Therapy. *Mol Ther*. 2016;24(3):430-46.

[95] George R, Kovak K, Cox SL. Aligning Policy to Promote Cascade Genetic Screening for Prevention and Early Diagnosis of Heritable Diseases. *Journal of Genetic Counseling*. 2015;24(3):388-99.

[96] Ranthe MF, Carstensen L, Øyen N, Jensen MK, Axelsson A, Wohlfahrt J, et al. Risk of Cardiomyopathy in Younger Persons With a Family History of Death from Cardiomyopathy: A Nationwide Family Study in a Cohort of 3.9 Million Persons. *Circulation*. 2015;132(11):1013-9.

[97] Meurs KM, Lahmers S, Keene BW, White SN, Oyama MA, Mauceli E, et al. A splice site mutation in a gene encoding for PDK4, a mitochondrial protein, is associated with the development of dilated cardiomyopathy in the Doberman pinscher. *Human Genetics*. 2012;131(8):1319-25.

[98] Meurs KM, Stern JA, Sisson DD, Kittleson MD, Cunningham SM, Ames MK, et al. Association of dilated cardiomyopathy with the striatin mutation genotype in boxer dogs. *Journal of veterinary internal medicine / American College of Veterinary Internal Medicine*. 2013;27(6):1437-40.

[99] Posafalvi A, Herkert JC, Sinke RJ, van den Berg MP, Mogensen J, Jongbloed JDH, et al. Clinical utility gene card for: dilated cardiomyopathy (CMD). *European Journal of Human Genetics*. 2012;21(10).

[100] Schatzberg SJ, Olby NJ, Breen M, Anderson LV, Langford CF, Dickens HF, et al. Molecular analysis of a spontaneous dystrophin 'knockout' dog. *Neuromuscular Disorders*. 1999;9(5):289-95.

[101] Friedenbergs SG, Chdid L, Keene B, Sherry B, Motsinger-Reif A, Meurs KM. Use of RNA-seq to identify cardiac genes and gene pathways differentially expressed between dogs with and without dilated cardiomyopathy. *American Journal of Veterinary Research*. 2016;77(7):693-9.

[102] Simpson S, Edwards J, Emes RD, Cobb MA, Mongan NP, Rutland CS. A predictive model for canine dilated cardiomyopathy-a meta-analysis of Doberman Pinscher data. *PeerJ*. 2015;3:e842.

[103] Schatzberg SJ, Olby NJ, Breen M, Anderson LV, Langford CF, Dickens HF, et al. Molecular analysis of a spontaneous dystrophin 'knockout' dog. *Neuromuscul Disord*. 1999;9(5):289-95.

[104] England J, Loughna S, Rutland CS. Multiple Species Comparison of Cardiac Troponin T and Dystrophin: Unravelling the DNA behind Dilated Cardiomyopathy. *J Cardiovasc Dev Dis*. 2017;4(3).

[105] Biesiadecki BJ, Elder BD, Yu ZB, Jin JP. Cardiac troponin T variants produced by aberrant splicing of multiple exons in animals with high instances of dilated cardiomyopathy. *J Biol Chem*. 2002;277(52):50275-85.

[106] Wess G, Schulze A, Butz V, Simak J, Killich M, Keller LJM, et al. Prevalence of dilated cardiomyopathy in

Doberman Pinschers in various age groups. *Journal of Veterinary Internal Medicine*. 2010;24(3):533-8.

[107] Beier P, Reese S, Holler PJ, Simak J, Tater G, Wess G. The role of hypothyroidism in the etiology and progression of dilated cardiomyopathy in Doberman Pinschers. *J Vet Intern Med*. 2015;29(1):141-9.

[108] Phillips DE, Harkin KR. Hypothyroidism and myocardial failure in two Great Danes. *J Am Anim Hosp Assoc*. 2003;39(2):133-7.

[109] Calvert CA, Jacobs GJ, Medleau L, Pickus CW, Brown J, McDermott M. Thyroid-stimulating hormone stimulation tests in cardiomyopathic Doberman pinschers: a retrospective study. *J Vet Intern Med*. 1998;12(5):343-8.

[110] Tidholm A, Jonsson L. A retrospective study of canine dilated cardiomyopathy (189 cases). *J Am Anim Hosp Assoc*. 1997;33(6):544-50.

[111] Tidholm A, Haggstrom J, Hansson K. Effects of dilated cardiomyopathy on the renin-angiotensin-aldosterone system, atrial natriuretic peptide activity, and thyroid hormone concentrations in dogs. *Am J Vet Res*. 2001;62(6):961-7.

[112] Taylor RR, Covell JW, Ross J, Jr. Influence of the thyroid state on left ventricular tension-velocity relations in the intact, sedated dog. *J Clin Invest*. 1969;48(4):775-84.

[113] Al-Mamun MA, Farid DM, Ravenhil L, Hossain MA, Fall C, Bass R. An in silico model to demonstrate the effects of Maspin on cancer cell dynamics. *Journal of Theoretical Biology*. 2016;388:37-49.

[114] Betz RC, Petukhova L, Ripke S, Huang H, Menelaou A, Redler S, et al. Genome-wide meta-analysis in alopecia

areata resolves HLA associations and reveals two new susceptibility loci. *Nature Communications*. 2015;6.

[115] Brown DC, Agnello K, Iadarola MJ. Intrathecal resiniferatoxin in a dog model: efficacy in bone cancer pain. *Pain*. 2015;156(6):1018-24.

[116] Eckstein F, Kwok CK, Boudreau RM, Wang Z, Hannon MJ, Cotofana S, et al. Quantitative MRI measures of cartilage predict knee replacement: a case-control study from the Osteoarthritis Initiative. *Annals of the Rheumatic Diseases*. 2013;72(5):707-14.

[117] Lee D-F, Su J, Kim Huen S, Chang B, Papatsenko D, Zhao R, et al. Modeling Familial Cancer with Induced Pluripotent Stem Cells. *Cell*. 2015;161(2):240-54.

[118] Mariani P, Servois V, De Rycke Y, Bennett SP, Feron JG, Almubarak MM, et al. Liver metastases from breast cancer: Surgical resection or not? A case-matched control study in highly selected patients. *European Journal of Surgical Oncology*. 2013;39(12):1377-83.

[119] Simoni RD, Hill RL, Vaughan M. The Discovery of Insulin: the Work of Frederick Banting and Charles Best. *Journal of Biological Chemistry*. 2002;277(26):e15.

[120] Basso C, Fox PR, Meurs KM, Towbin JA, Spier AW, Calabrese F, et al. Arrhythmogenic Right Ventricular Cardiomyopathy Causing Sudden Cardiac Death in Boxer Dogs: A New Animal Model of Human Disease. *Circulation*. 2004;109(9):1180-5.

[121] Davidson AG, Bell RJ, Lees GE, Kashtan CE, Davidson GS, Murphy KE. Genetic cause of autosomal recessive hereditary nephropathy in the English Cocker Spaniel. *Journal of veterinary internal medicine / American College of*

Veterinary Internal Medicine.
2007;21(3):394-401.

[122] Egenvall A, Nødtvedt A, von Euler H. Bone tumors in a population of 400 000 insured Swedish dogs up to 10 y of age: incidence and survival. *Canadian Journal of Veterinary Research*. 2007;71(4):292-9.

[123] Zangerl B, Goldstein O, Philp AR, Lindauer SJP, Pearce-Kelling SE, Mullins RF, et al. Identical Mutation in a Novel Retinal Gene Causes Progressive Rod-Cone Degeneration (prcd) in Dogs and Retinitis Pigmentosa in Man. *Genomics*. 2006;88(5):551-63.

[124] Parker HG, Kim LV, Sutter NB, Carlson S, Lorentzen TD, Malek TB, et al. Genetic structure of the purebred domestic dog. *Science*. 2004;304(5674):1160-4.

[125] Calboli FCF, Sampson J, Fretwell N, Balding DJ. Population Structure and Inbreeding From Pedigree Analysis of Purebred Dogs. *Genetics*. 2008;179(1):593-601.

[126] Jansson M, Laikre L. Recent breeding history of dog breeds in Sweden: modest rates of inbreeding, extensive loss of genetic diversity and lack of correlation between inbreeding and health. *Journal of Animal Breeding and Genetics*. 2014;131(2):153-62.

[127] Willet CE, Makara M, Reppas G, Tsoukalas G, Malik R, Haase B, et al. Canine Disorder Mirrors Human Disease: Exonic Deletion in HES7 Causes Autosomal Recessive Spondylocostal Dysostosis in Miniature Schnauzer Dogs. *PLoS ONE*. 2015;10(2):e0117055.

[128] Marsden CD, Ortega-Del Vecchyo D, O'Brien DP, Taylor JF, Ramirez O, Vilà C, et al. Bottlenecks and selective sweeps during domestication have increased deleterious genetic variation in dogs. *Proceedings of the*

National Academy of Sciences.
2016;113(1):152-7.

[129] Olsson M, Frankowiack M, Tengvall K, Roosje P, Fall T, Ivansson E, et al. The dog as a genetic model for immunoglobulin A (IgA) deficiency: Identification of several breeds with low serum IgA concentrations. *Veterinary Immunology and Immunopathology*. 2014;160(3-4):255-9.

[130] Decker B, Parker HG, Dhawan D, Kwon EM, Karlins E, Davis BW, et al. Homologous Mutation to Human BRAF V600E Is Common in Naturally Occurring Canine Bladder Cancer—Evidence for a Relevant Model System and Urine-Based Diagnostic Test. *Molecular Cancer Research*. 2015;13(6):993-1002.

[131] Calderón-Garcidueñas L, Mora-Tiscareño A, Ontiveros E, Gómez-Garza G, Barragán-Mejía G, Broadway J, et al. Air pollution, cognitive deficits and brain abnormalities: A pilot study with children and dogs. *Brain and Cognition*. 2008;68(2):117-27.

[132] Ostrander EA, Galibert F, Patterson DF. Canine genetics comes of age. *Trends in Genetics*. 2000;16(3):117-24.

[133] Fosmire SP, Thomas R, Jubala CM, Wojcieszyn JW, Valli VEO, Getzy DM, et al. Inactivation of the p16 Cyclin-Dependent Kinase Inhibitor in High-Grade Canine Non-Hodgkin's T-Cell Lymphoma. *Veterinary Pathology*. 2007;44(4):467-78.

[134] Lakey JRT, Cavanagh TJ, Zieger MAJ, Wright M. Evaluation of a Purified Enzyme Blend for the Recovery and Function of Canine Pancreatic Islets. *Cell Transplantation*. 1998;7(4):365-72.

[135] Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American

Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2009;19(11):1167-214.

[136] Mant J, Fitzmaurice DA, Hobbs FDR, Jowett S, Murray ET, Holder R, et al. Accuracy of diagnosing atrial fibrillation on electrocardiogram by primary care practitioners and interpretative diagnostic software: analysis of data from screening for atrial fibrillation in the elderly (SAFE) trial. *British Medical Journal*. 2007;335(7616):380-2.

[137] Porto G, Brissot P, Swinkels DW, Zoller H, Kamarainen O, Patton S, et al. EMQN best practice guidelines for the molecular genetic diagnosis of hereditary hemochromatosis (HH). *European Journal of Human Genetics*. 2015;24(4):479-95.

[138] Rebbeck TR, Friebel T, Lynch HT, Neuhausen SL, van 't Veer L, Garber JE, et al. Bilateral Prophylactic Mastectomy Reduces Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers: The PROSE Study Group. *Journal of Clinical Oncology*. 2004;22(6):1055-62.

[139] Antoniou A, Pharoah PDP, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average Risks of Breast and Ovarian Cancer Associated with BRCA1 or BRCA2 Mutations Detected in Case Series Unselected for Family History: A Combined Analysis of 22 Studies. *The American Journal of Human Genetics*. 2003;72(5):1117-30.