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Optimisation of breeding strategies to reduce the prevalence of inherited disease in pedigree dogs

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Abstract

One option for improving the welfare of purebred dog breeds is to implement health breeding programmes, which allow selection to be directed against known diseases while controlling the rate of inbreeding to a minimal level in order to maintain the long-term health of the breed. The aim of this study is to evaluate the predicted impact of selection against disease in two breeds: the Cavalier King Charles spaniel (CKCS) and the Labrador Retriever. Heritabilities for mitral valve disease, syringomyelia in the CKCS and hip dysplasia in the Labrador were estimated to be 0.64 (± 0.07), 0.32 (± 0.125) and 0.35 (± 0.016), respectively, which suggest encouraging selection responses are feasible based upon the estimation of breeding values (EBVs) if monitoring schemes are maintained for these breeds. Although using data from disease databases can introduce problems due to bias, as a result of individuals and families with disease usually being over-represented, the data presented is a step forward in providing information on risk. EBVs will allow breeders to distinguish between potential parents of high and low risk, after removing the influence of life history events. Analysis of current population structure, including numbers of dogs used for breeding, average kinship and average inbreeding provides a basis from which to compare breeding strategies. Predictions can then be made about the number of generations it will take to eradicate disease, the number of affected individuals that will be born during the course of selective breeding and the benefits that can be obtained by using optimisation to constrain inbreeding to a pre-defined sustainable rate.

Keywords: *animal welfare, dog, hip dysplasia, inherited disease, mitral valve disease, syringomyelia*

Introduction

Purebred dog (*Canis lupus familiaris*) breeds are commonly cited as having a relatively high prevalence of disease (Calboli *et al* 2008; Higgins & Nicholas 2008). Many diseases are breed-specific, which provides clues pointing to a genetic origin. As a result, purebred dog breeding has been under the spotlight recently, attracting media interest (Higgins & Nicholas 2008) which has led to the commission of several reviews on the subject: an independent scientific report for the RSPCA (Rooney & Sargan 2008), The Independent Inquiry into Dog Breeding, chaired by Professor Sir Patrick Bateson FRS, (http://dogbreedinginquiry.com/) and the Associate Parliamentary Group for Animal Welfare (APGAW) Working Group on the welfare of pedigree dogs.

An increased prevalence of disease in purebred dog breeds may arise as the result of different genetic processes. Disease or welfare issues may be a result of direct selection for a desired phenotype that brings with it undesirable characteristics, eg dermoid sinus with the ridge phenotype of the Rhodesian Ridgeback or hemi-vertebrae associated with the 'screw' tail of the Bulldog, Pug and Boston terrier. Indirect selection may also lead to an increase in prevalence of disease, breeders may unwittingly select animals that are disease carriers and the genes are then propagated through the population. In some cases, the introduction of genes from out-crossing can bring disease, eg primary lens luxation (PLL) in the Miniature Bull terrier may have been introduced from Jack Russell terriers crossed with the Bull terrier to reduce breed size. Genetic drift also has a role to play: the limited effective population size of many breeds and the large contributions of some individuals leads to an increase in the rate of inbreeding, which is a high risk factor for the emergence of new inherited disease.

Genetic theory also provides the tools with which to control inherited disease in purebred dog populations. The prevalence of disease could be reduced by: (i) selecting within breed away from existing heritable diseases; (ii) using suitable out-crosses to introgress normal healthy alleles back into the recipient breed, followed by selection to bring the healthy allele to a high frequency; and (iii) the management of genetic drift or inbreeding to maintain long-term breed health. Whichever options are used they all require breeding programmes that are designed and managed appropriately. Successful breeding programmes require

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three main components to be in place: adequate data collection systems that record information on individual animals, proper genetic evaluation and an effective means of implementing and monitoring the breeding programme.

In dog breeding the first of these, data collection, is currently one of the most difficult challenges. Historically, there have been very few means of collecting population-wide data and no centralised data repository of comprehensive health information about individual dogs. The British Veterinary Association (BVA)/Kennel Club (KC) schemes for hip dysplasia, elbow dysplasia and eye diseases provide the best examples in the UK of standardised data collection and a centralised repository of information. They are, at present, limited to the aforementioned conditions although heart disease and syringomyelia are to become new BVA/KC schemes in the not-too-distant future. Even in such schemes, the potential bias in the collection of disease data is an issue that needs to be further explored. Bias in monitoring schemes may result from non-submission of poor results or non-random sampling from the population, eg they are dogs to be used for breeding. Data collected outside monitoring schemes, such as that collected for veterinary research or surveillance, can also be biased as there is a greater probability of including diseased animals as they are more likely to be seen by veterinarians than are healthy animals.

Genetic evaluation for complex diseases can be achieved using techniques that have already been implemented in livestock breeding, through the production of estimated breeding values (EBVs) and the potential use of genomic breeding values based on high density single nucleotide polymorphism (SNP) genotyping. Single gene disorders are usefully tackled by the development of more conventional DNA tests. The final part of the equation is persuading breeders to apply sufficient selection pressure to health traits that significant progress can be made. This presents a potential challenge in dog breeding as, in the past, only minimal amounts of selection pressure appear to have been applied to breeding for health. At the same time it will be important to temper the rate of progress obtainable by selection with the maintenance of sufficient genetic diversity. All individuals carry some defective alleles in their genomes which, in the heterozygous (carrier) state, are harmless but in the homozygous state cause disease. If a carrier is widely used, because they have been selected for other characteristics, then the defective allele will appear at a much higher frequency in future generations. It is, therefore, important to manage the risk of this occurring when carrying out selective breeding.

This paper presents examples of genetic and population analyses for three diseases in two breeds (hip dysplasia in Labrador Retrievers; and syringomyelia [SM] and premature mitral valve disease [MVD] in Cavalier King Charles spaniels) which provide the information necessary for deciding on the level of selection intensity against disease that can be applied, whilst maintaining a sustainable level of genetic diversity, in these breeds. These examples will demonstrate how state-of-the-art breeding programmes for health can be designed and implemented in dog breeds.

Materials and methods

Hip dysplasia in Labradors

Scoring on the severity of signs of hip dysplasia for nine features of hip morphology assessed by radiograph was in accordance with the established BVA/KC scheme (Gibbs 1997). Scores range from 0 (best) to 106 (worst). Data comprised hip scores from 25,243 Labradors scored between 2000 and 2007 at greater than one and less than four years old. A transformation of ln(1 + hip score) was applied to the data to improve normality.

Syringomyelia (SM) in Cavalier King Charles spaniels

Data comprised affected/unaffected (one or zero) scores based on veterinary diagnosis from MRI scans indicating the presence/absence of a syrinx in 384 dogs scanned between 1998 and 2009.

Mitral valve disease (MVD) in Cavalier King Charles spaniels

Data comprised 1,252 records of cardiac auscultation indicating the presence/absence of a caudal, left-sided systolic cardiac murmur (and where present the grade relating to intensity; 0 = absent, 6 = most severe murmur) which is recognised as an adequate diagnostic of the severity of mitral valve disease (Gompf 1988). The data came from dogs examined between 1991 and 2008 as part of the breed club heart-monitoring scheme. Data were restricted to those records from dogs greater than four and less than five years old, defining the disease (where present) as premature MVD, which is known to be characteristic of the breed.

Pedigree information

Labrador and Cavalier King Charles spaniel pedigree information was downloaded from the Kennel Club (KC) registration database.

Statistical analysis

Mixed linear models were fitted to the data using ASREML (Gilmour *et al* 2006) to estimate variance components separately for: ln(1 + hip score), diagnosis of syringomyelia (presence of a syrinx) and grade of cardiac murmur. Univariate linear mixed models fitted to each disease variable were of the following general form:

$$Y = Xb + Za + e$$

Where Y is the vector of observations, X and Z are known incidence matrices, b is the vector of fixed effects, a is the vector of random additive genetic effects with the distribution assumed to be multivariate normal (MVN), with parameters $(0, A\sigma^2_A)$, and e is the vector of residuals distributed MVN with parameters $(0, I\sigma^2_E)$. I is an identity matrix of the appropriate size, A is the additive genetic relationship matrix, and σ^2_A and σ^2_E denote the variance of each of the respective random effects. The phenotypic variance was calculated as:

$$\sigma^2_P = \sigma^2_A + \sigma^2_E$$

where σ^2_P refers to the phenotypic variance , σ^2_A the additive genetic variance and σ^2_E the residual component. The heritability is defined as the proportion of the phenotypic variance that is made up by the additive genetic variance:

$$h^2 = \sigma^2_A/\sigma^2_P$$

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Figure 1

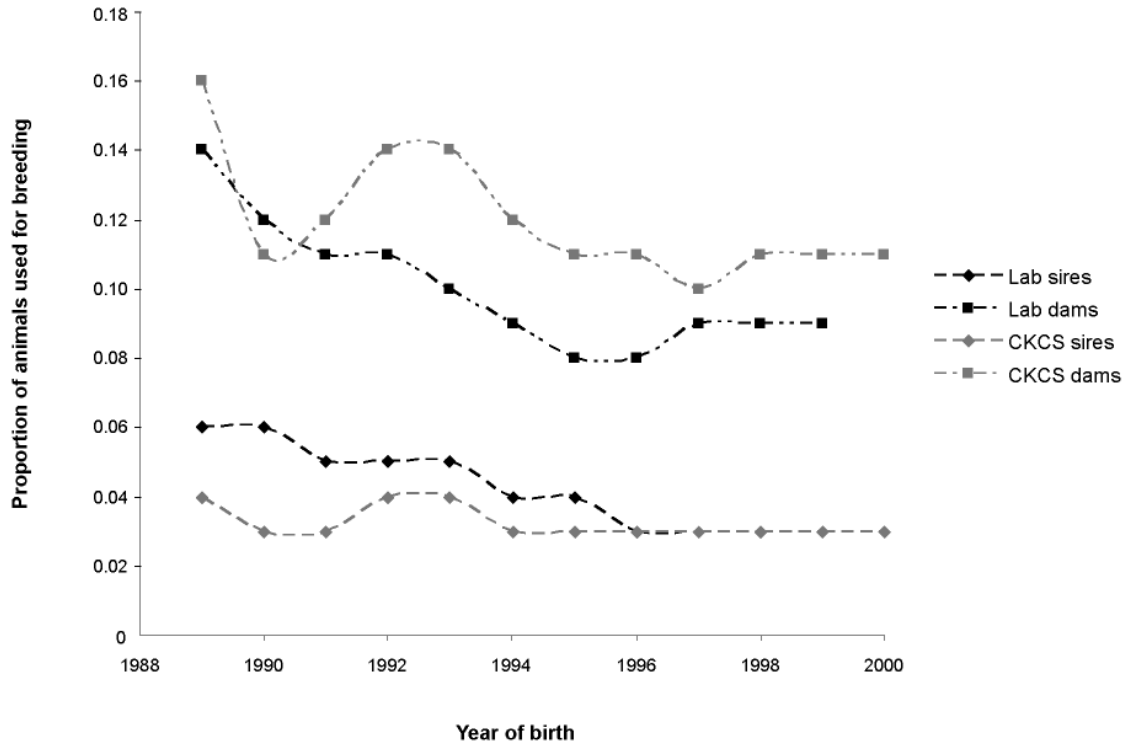

Chart showing the proportion of males and females born each year for Cavalier King Charles spaniels (CKCS) and Labradors (Lab) that were subsequently used for breeding.

EBVs are the vector of predicted genetic effects (a previously) and were calculated for the entire CKCS breed (333,287 animals), and for data with four generations of pedigree (ie to great-great grandparental generation) for Labradors (62,683 animals).

Population analysis

The proportion of males and females born per year that were subsequently used for breeding was calculated from 1989 to 2000 (restricted from 1989 when all registrations were recorded electronically, and to 2000 to ensure complete breeding records). For all sires and dams, the mean and standard deviation of the number of offspring per sire (or dam) was calculated. Generation interval estimates the mean age of individuals when their offspring are born, calculated from the age of the parents at the birth of every offspring, up to animals born in 2007. The inbreeding coefficient (F) for every individual in the entire Kennel Club database (333,287 for CKCS, 800,069 for Labradors) was calculated using the algorithm of Meuwissen and Luo (1992). Mean inbreeding (Ft) per year (t) was calculated between 1989 and 2007 for both breeds, by regression of ln(1 – Ft) on year. This removes any curvi-linearity expected with a constant ΔF (0.0017 in Labradors, 0.002 in CKCS) and, when using natural logarithms (as here) and ΔF is relatively small (as expected here), the slope of the regression estimates –ΔFt where ΔFt is the annual rate of inbreeding. Multiplication by the generation interval yields an estimate of rate of inbreeding per generation, ΔF_g, and $1/(2\Delta F_g)$ gives the estimated effective population size (N_e), an estimate of the effective number of breeding individuals that would give rise to the same ΔF, or rate of loss of genetic diversity, as that observed.

Results

Genetic evaluation of diseases

The heritability estimate of ln(1 + hip score) in Labradors was moderate in magnitude at 0.35 (± 0.016), indicating that 35% of the phenotypic variation in hip score is due to genotypic variation among scored animals aged between one and four years of age. The heritability of SM in the CKCS was estimated at 0.32 (± 0.125) indicating a moderately large transmissible genetic effect on susceptibility to development of SM. The heritability estimate of grade of cardiac murmur in the CKCS was large at 0.64 (± 0.07), indicating that most of the variation in severity of mitral valve prolapse determined via cardiac auscultation at four to five years old is genetic in origin.

Population analysis

The proportion of animals born each year between 1989 and 2000 and subsequently used for breeding has remained broadly steady, with a mean of 22% female CKCS and 19% female Labradors being used for breeding, and a mean of 6% of male CKCS and 7% of male Labradors used as sires (Figure 1).

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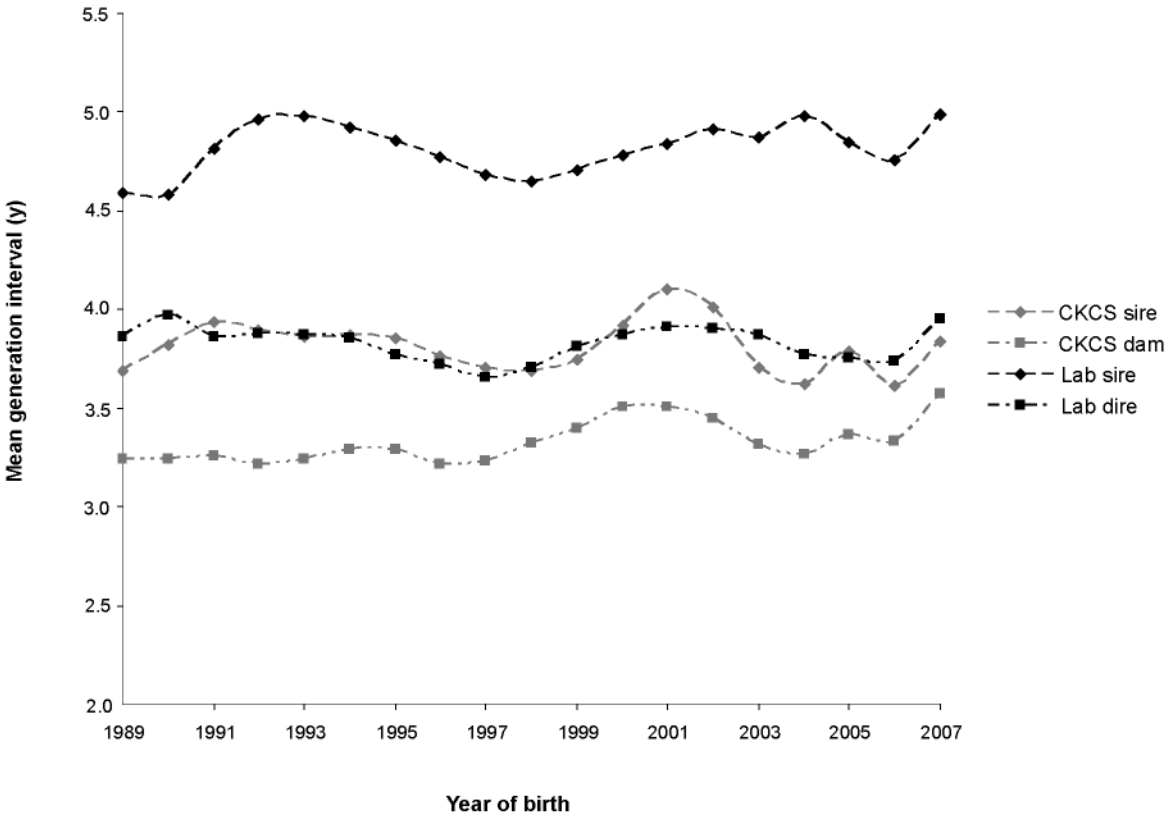
Figure 2



Generation interval for Cavalier King Charles spaniel (CKCS) and Labrador (Lab) sires and dams.

The mean number of offspring of sires and dams themselves born from 1989 to 2000 rose slightly from 29.0 to 32.3 and 11.7 to 12.5, respectively in Labradors but fell from 31.8 to 27.8 for male CKCS and from 8.4 to 8.1 for female CKCS. The standard deviation of the number of offspring per sire and dam ranged from 64.2 (2000 born sires) to 91.9 (1993 born sires) and 8.84 (1989, 1991 and 1998 born dams) to 9.3 (1994 born dams), respectively, in Labradors, and from 33.5 (1999 born sires) to 61.27 (1992 born sires) and 5.7 (2000 born dams) to 6.7 (1991 born dams), respectively in CKCS. The proportion of all offspring sired by dogs born from 1989–2000 that were sired by the most popular dogs is stable, with a mean of 0.49 in the CKCS and 0.60 in Labradors. The most popular dogs were defined as the 10% of sires with the highest number of progeny. This represented, on average, 41 CKCS sires and 108 Labrador sires per annum siring a mean number of litters per sire of 43.9 (CKCS) and 25.8 (Labradors).

Figure 2 shows a chart depicting the trend in generation interval measured from ages of parents of animals born between 1989 and 2007. The generation interval is higher for sires than dams in both breeds, reflecting a greater 'breeding longevity' of sires compared with dams. The generation intervals have consistently been longer in Labradors than the CKCS. Generation intervals for sires and dams of both breeds appear reasonably constant throughout the period shown. Mean generation interval from 1997 to 2007 inclusive is 3.79 and 3.39 years for CKCS sires and dams, and 4.82 and 3.81 years for Labrador sires and dams.

The mean coefficient of inbreeding per year (1989–2007) for both breeds is shown in Figure 3. The average inbreeding climbs steadily over this timeperiod in Labradors, but the rate of inbreeding becomes negative in the CKCS from 2002. The rate of inbreeding per generation was 0.48% for Labradors and 0.41% for CKCS, equivalent to effective population sizes (N_e) of 103 and 123, respectively.

Discussion

The estimates of heritability indicate that selection against hip dysplasia in the Labrador, and syringomyelia and premature MVD in the CKCS should be successful. Furthermore, the calculation of EBVs provides assistance to breeders by providing an objective indicator of genetic predisposition to disease for all registered individuals of the breed. EBVs are a more accurate and sensitive indicator of genetic risk than the phenotype, and will allow breeders to distinguish between unaffected dogs of low and high genetic risk.

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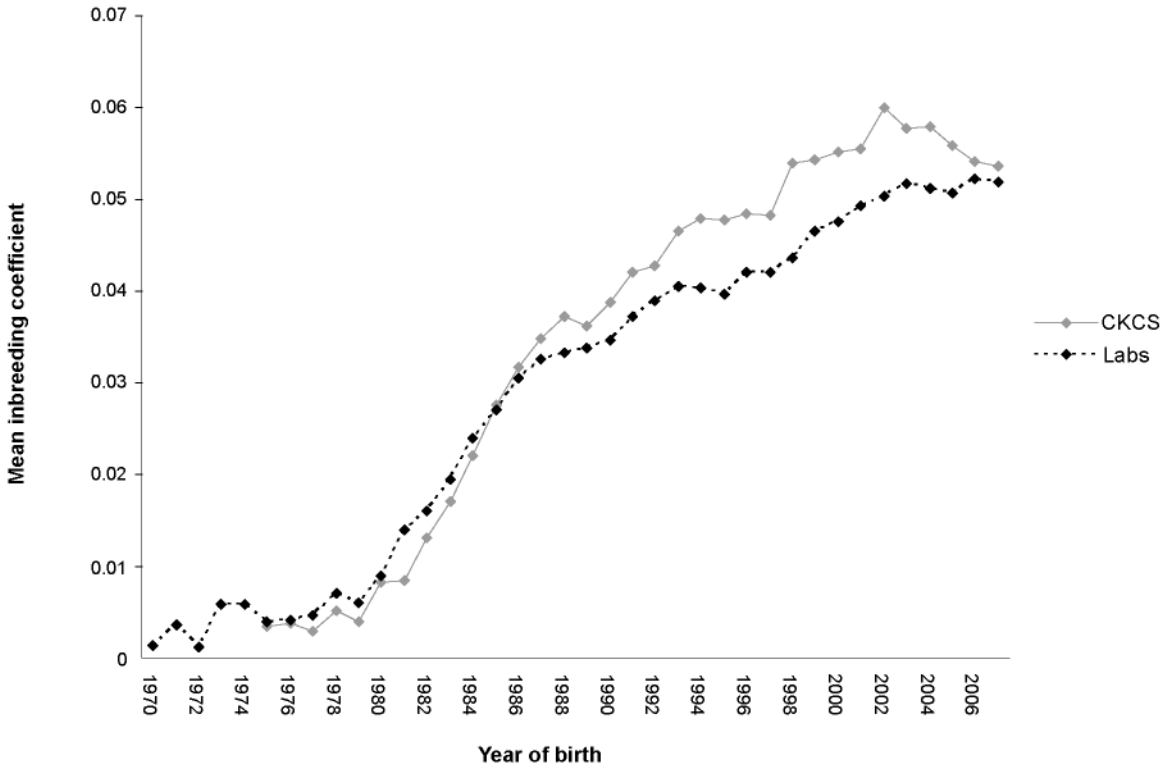
Figure 3



The mean inbreeding coefficient per year of birth for the Labrador and CKCS (calculated from the first year where there were > 100 records in the electronic pedigree).

All the evidence on breeding structure (proportion of males and females being used as sires and dams; mean and standard deviation of number of offspring per sire and dam; and the percentage of animals born that are progeny of the most popular sires) indicates that a small number of individual dogs are making a large contribution to the gene pools of both breeds. The effective population size is a way of quantifying the rate of loss of diversity in a population in terms of the effective number of breeding individuals that would be expected to give rise to the observed rate of inbreeding. Both breeds have moderate effective population sizes which, given the census sizes of these breeds, could probably be improved upon. The estimate of N_e reported for the Labrador (103) is similar to, and not significantly different from, that reported by Calboli *et al* (2008) of 114.

Thus, the components are in place to predict the response to selection against these diseases for a range of selection intensities. However, unconstrained and intense selection can create the conditions conducive to the manifestation of a new genetic disease through the reduction of genetic diversity. It will, therefore, be necessary to incorporate into the breeding programme optimisation techniques that allow maximum genetic gain (against disease) to be achieved while limiting the rate of inbreeding to sustainable levels (Meuwissen & Sonesson 1998; Grundy *et al* 2000). This type of approach has already been successfully applied in livestock breeding, and for small populations of rare breeds where selection is required but the conservation of genetic diversity is of prime importance (Windig *et al* 2007). It is suggested that the rate of increase of inbreeding is set at or below 0.005 (0.5%) per generation ($N_e = 100$) (Gandini *et al* 2004). The current rates of inbreeding in the Labrador and CKCS are just below this guideline value and it will likely prove possible to reduce the rates of inbreeding in these breeds still further, while achieving a satisfactory response to selection away from disease. Therefore, the immediate objectives concerning hip dysplasia in Labradors and syringomyelia and premature MVD in the CKCS are to ascertain, through simulation, the possible timescale for significant reduction in disease prevalence through the optimised use of EBVs, and to begin the process of releasing EBVs to the general public.

For other breeds, our objectives will depend on the amount and quality of disease data available and the numerical size (and therefore likely genetic diversity) of a particular breed. Although aspects of the described optimisation techniques are able to assist in the sustainable preservation of numerically small breeds by minimising inbreeding, our primary aim is to reduce the prevalence of inherited disease through selection. Thus, an increase in the collection of unbiased

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data on inherited canine diseases is of utmost importance to allow accurate EBV calculation for a wide range of diseases. Rigorous recording of canine disease via screening programmes will not only allow clinicians to determine which canine diseases are the most serious, but combined with pedigree resources will provide geneticists with the data needed to start calculating EBVs. Simulation can then be used to provide optimised estimates of the response to selection, and continued disease screening will allow progress to be monitored.

Animal welfare implications

Application of state-of-the-art genetic techniques to breeding schemes for health in purebred dogs will assist breeders in achieving the highest health and welfare standards for their breeds.

Conclusion

Breeding schemes for health provide a viable solution to reducing the prevalence of inherited disease in purebred dogs. This study demonstrates that it is feasible to develop estimated breeding values (EBVs) for known diseases, where there is reasonable data available. The population structures of the Labrador and CKCS provide sufficient scope for selection against disease to be implemented, using optimisation techniques that allow maximum genetic gain to be achieved while keeping inbreeding to a sustainable level.

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