Discussion paper

“Options to improve the welfare of flat coated retrievers against inherited diseases”

(1) Context.

This discussion paper has been written following (i) the comments in recent editions of the Independent Flat Coated Retriever Rehoming (IFRR) magazine about the perception that cancers are more common in the flat coated retriever (FCRs) pedigree breed than in other pedigree breeds of dogs and (ii) concerns in the literature about FCRs and inherited diseases e.g. pectinate ligament dysplasia/goniodysgenesis (Pearl, 2015); hip dysplasia (Lewis, 2013; Wood, 2000); patella luxation (Lavrijsen, 2014).

FCRs have been reported in the veterinary literature as a breed that is more prone to develop cancers than other breeds (Seim-Wikse, 2013) particularly in case studies of histiocytic sarcoma (Dobson, 2009, 2013; Quignon, 2007). However such case studies and data from insurance databases (Egenvall, 2000; Jansson, 2014) contain weaknesses in defining the base population, the disease classification, and the reporting of cases and they contain too few cases to provide meaningful comparisons over time or between breeds.

Overall, there is a lack of large, rigorous population based studies on cancers (Nødtvedt, 2012; Rooney, 2009) so there is no valid and reliable information to confirm or deny the suggestions that some cancers are commoner in FCRs than in other pedigree breeds.

Furthermore the potential for DNA studies to identify genetic abnormalities with a high likelihood of causing a specific cancer has not been realised (Greer, 2003; Karlsson, 2007; Linblad-Toh, 2005; Ostrander, 2005; Thomas, 2003a, 2003b) although research is continuing (Farrell, 2015).

There is a danger of mislabelling FCRs as being a breed at high risk of cancers because many of their human companions care so much for their FCR that they take extra steps to diagnose and report cancers compared to the human companions of other breeds.

It would be more appropriate to recognise that the welfare of our current FCRs and future generations would benefit from valid and reliable population based research into cancers and that other concerns about FCR welfare need to be investigated particularly the topic of genetic diversity and inherited diseases.

All pedigree breeds have limited genetic diversity due to population bottlenecks particularly domestication and the formation of the breed (Karlsson, 2007). Two measures of genetic diversity are widely regarded as important when assessing the welfare of pedigree breeds: (a) the coefficient of inbreeding and (b) the effective population size (Woolliams, 2015).

The United Kingdom’s (UK) Kennel Club and their associated researchers use the electronic data of the registrations of FCRs and other pedigree breeds to calculate the coefficient of inbreeding and the effective population size based on the number of registered animals born each year, the variation in sire usage, and the generation interval between the age of parents and the age of their progeny when they themselves reproduce (Kennel Club, 2015a; Lewis, 2015).

The average number of annual registrations recorded by the Kennel Club for the period 2010-2014 for FCRs was 1200 and for comparison purposes with other breeds the average number of annual registrations for the same period was –
Irish Setter 900
Standard Poodle 1000
Weimaraner 1100
Dobermann 1200.
The largest number of registrations was 35,000 for Labrador Retriever puppies (Kennel Club, 2015a).

(a) The coefficient of inbreeding.

The coefficient of inbreeding for an individual FCR is the probability expressed as a percentage that any two genes are copies of a single gene from a common ancestor. The coefficient of inbreeding for the FCR breed is the average of the individual coefficients that have been recorded by the Kennel Club in a time period (Woolliams, 2015).

The coefficient of inbreeding ranges from zero per cent, which indicates there is no risk of two genes being identical because there is no common ancestor, to 25% for a puppy of a brother-sister (full sibling) mating (Alvarez, 2009). For a puppy from 1st cousins, the coefficient of inbreeding is 6.25%.

The average coefficient of inbreeding for the period 1980-2014 was –
Flat Coated Retrievers 7%
Standard Poodle 4%
Dobermann 6%
Weimaraner 8%
Irish Setter 15%
(Kennel Club, 2015a).

(b) The effective population size.

The effective population size is a measure of the gene pool and it should be above 100 for a healthy population (Calboli, 2008; Lewis, 2015). The Kennel Club data (Kennel Club, 2015a) for the period 1980-2014 show an effective population size above 100 for the Standard Poodle breed without giving a precise value and 133.4 for the Dobermann breed indicating for both breeds an overall increase in genetic diversity.

An effective population size between 50 and 99 indicates a loss of genetic diversity and the size for the FCR breed was 67.9 compared to 75.4 for the Weimaraner breed for the period 1980-2014 (Kennel Club, 2015a).

An effective population size below 50 means that a breed is at high risk of detrimental effects from inbreeding (Leroy, 2009) and the Irish Setter breed had an effective population size of 27.3 for the period 1980-2014 (Kennel Club, 2015a).

There are two critical influences on the coefficient of inbreeding and the effective population size (Woolliams, 2015). Firstly, there is the number of generations that are measured, for example, using five generations can yield a coefficient of inbreeding of 17% whereas using only three generations of pedigree can yield a coefficient of inbreeding below 1% (Lewis, 2015) because a pedigree of fewer generations omits potential common ancestors further back in the pedigree (Alvarez, 2009; Pedersen, 2016).

Secondly, the other critical influence is the rate of breeding because natural selection needs time to act against the harmful effects of a high rate of breeding (Maki, 2009).

In common with many other breeds the FCRs breeding trend showed a steep rise in the 1980's and 1990's with some levelling since the year 2000 (Lewis, 2015). This trend indicates reduced genetic diversity in the 1980's and 1990's with some improvement since the year 2000 possibly due to more FCRs coming to the UK to breed before returning home or migrating to live here and to breed, reductions in the rate of breeding, and more extended pedigree generation data.

The values for the coefficient of inbreeding and the effective population size will have different meanings to individuals and organisations with an interest in the welfare of FCRs. There are no absolutely safe values for the coefficient of inbreeding and for the effective population size (Woolliams, 2015) but taking actions to keep the values as low as possible would reduce the risk of genetic factors contributing to the causes of cancers and other complex diseases particularly through allowing natural selection to promote good health.

In summary, there is a lack of population based research into the genetic basis for complex inherited diseases in FCRs including cancers. The genetic diversity is not high in the FCR breed as shown by the coefficient of inbreeding and effective population size and verified by genetic analyses (Quignon, 2007). There are therefore significant threats to the welfare of FCRs and there should be more discussion about the options to improve their welfare.

(2) Options.

The next section considers four options and they are not mutually exclusive so they could be combined and other options could be developed.

When considering these options it seemed appropriate to bear in mind the multiple groups internationally with interests in FCR welfare in this context:
- Animal welfare organisations
- Breed societies
- Kennel clubs: founded to govern dog showing and breeding, to set breed standards, to establish a voluntary register of pedigree and crossbreed dogs, and to publish stud books (https://janedogs.com/kennel-clubs-and-stud-books/)
- Media
- Owners with companion FCRs who also breed FCRs (breeders)
- Owners with companion FCRs who do not breed ("companioners")
- Public in general
- Scientists: geneticists, histologists, cytologists, epidemiologists
- Veterinarians: primary referral
- Veterinarians: secondary/tertiary referral (modified from Rooney, 2009).

(a) Population based FCR breed cancer registry.

Description: as previously described in the IFRR summer 2017 magazine, a cancer registry (Nødtvedt, 2012) could be set up to collect data systematically on FCRs who develop cancer. In parallel, initiatives could be taken to persuade people with an interest in other pedigree breeds to set up a register for their breed.

Opportunities: accurate information instead of data that is unrepresentative of the FCR population.

Challenges:
- willingness of companioners and breeders to participate;
- involvement of veterinarians;
- funding for staff in the registry and for the information technology;
- persuading other breed societies, breeders and companioners to set up their breed's cancer register.

Practical implications: the average length of life of a FCR in the UK is not known but the average of about 1200 registrations of FCR puppies annually is a relatively small number placing the breed outside the top 20 most popular pedigree breeds (Farrell, 2015). Hence a registry would need to collect data from all of the UK to provide valid and reliable information on new cases, deaths, treatments, potential genetic abnormalities, et alia, with a ten year lag time.

The other breeds where parallel research could be promoted are Irish Setter, Standard Poodle, Weimaraner and Dobermann.

(b) Add DNA testing to current screening programmes.

Description: the current screening programmes for FCRs that are required by the Kennel Club Assured Breeder Scheme are the programmes for hip dysplasia screening and the gonioscopy screening (Kennel Club, 2017).

DNA tests could be added to the requirements of the Kennel Club for assured breeders and for puppies to be registered. However the mode of inheritance of most cancers is complex meaning that they are based on multiple factors (Rooney, 2009). Those factors are likely to include several abnormalities in the DNA and several environmental factors all contributing to the development of each cancer. A similar situation is recognised in hip dysplasia (Fels, 2014; Wilson, 2013).

There are no cancer DNA tests on the Kennel Club's list of breed specific DNA tests for any breed (Kennel Club, 2015b).

Opportunities:
- highly accurate if a single abnormality in the genetic DNA can be identified;
- cells can easily be obtained by swabbing the gums and palate.

Challenges:
- high cost of developing the DNA test;
- open to abuse by breeders if swabbing is not supervised by a veterinarian;
- reduction in the breeding population and thereby in genetic diversity (Farrell, 2015) unless other measures are taken.

Practice implications: DNA tests have been successfully added to screening programmes and recorded by the Kennel Club for Dobermanns, Irish Setters and Standard Poodles for diseases other than cancers (Kennel Club, 2015; Rooney, 2009). There is evidence for several genes that need to be present to contribute to a high risk of hip dysplasia in German Shepherds (Fels, 2014) and if similar genes could be identified in FCRs then a DNA test could be a requirement for registration with the Kennel Club.

However it is important to recognise that even if the genes are present each dog will vary in how much she exhibits the disease depending on other genes and factors in the environment particularly in the case of late-onset diseases (Farrell, 2015; Greer, 2003).

(c) Increase genetic diversity.

Description: it is inevitable that the diversity of the genes in the FCR breed is lower than it could be because of the breed's formation and because of domestication which stops free breeding in the wild. Breed formation involves selecting the breeding to meet the breed standards, developing breeding lines and the use of popular sires who make the largest contribution to the rate of inbreeding (Calboli, 2008; Farrell, 2015; Leroy, 2011; Lewis, 2015; Ostrander, 2005).

However, despite the controversies about the origins of the FCR breed, international genetic studies have found wide genetic divergence between pedigree breed populations in different countries (Björnerfeldt, 2008; Larson, 2012). Specifically, as much genetic divergence was identified between golden retrievers in the European and American continents as between human populations in those continents (Karlsson, 2007). A shared common ancestry more than 100 years ago as suggested by the historical records of FCRs does not necessarily translate into common diseases (Ostrander, 2005) hence there is scope to widen the genetic diversity of FCRs.

A number of strategies have been identified each with their own opportunities and challenges. These strategies include:
- increased the importation of FCRs from other countries and increased intercountry mating;
- prevent the registration of offspring from a mating between first degree or second degree relatives;
- preventing the registration of puppies from a sire of more than a specific number of litters as has happened in German Shepherds in Germany (Leroy, 2006) and restricting the number of offspring from a single sire as required by the Finnish Kennel Club for some breeds (Maki, 2009);
- outcrossing which is the mating of a FCR with another breed which could then be followed by back crossing to a FCR and repeated to the 4th generation (3rd back cross) who would be 93% pure FCR.

Opportunities:
- much easier to import and export FCRs in Europe and beyond aided by electronic data on identity, vaccinations and pedigree;
- frozen semen can be used to reduce travelling which is only for mating;
- the Kennel Club as the governing authority can change the rules about registration regarding mating with relatives, regarding outcrossing and 3rd or later back crossing and regarding the number of litter from the same sire.

Challenges:
- resistance from breeders and from breed societies;
- Kennel Club willingness to change the registration rules and to revise breed standards based on appearance and not on genetic purity;
- negative comments by the media about “designer” dogs and the effects of those comments on the general public.

Practice implications: increasing the genetic diversity in the FCR breed through these strategies would improve vigour which includes resistance to infections, metabolic diseases, cancers, hip and other dysplasias (Farrell, 2015; Rooney, 2009). It is increasingly recognised that there has been genetic divergence within the same breed in different countries (Björnerfeldt, 2008) hence the merits of increased intercountry mating.

Outcrossing with back crossing has occurred successfully with Dalmatians who suffer from high uric acid levels and thereby kidney stones (Farrell, 2015), with Boxers who have subsequently won at dog shows ((Rooney, 2009), and with English Bulldogs and Olde English Bulldogs (Pedersen, 2016).

There is no evidence that widening genetic diversity would introduce more new diseases than would be expected by chance (Woolliams, 2015) and there is less likelihood of introducing new diseases than if artificial selection continues unabated particularly through the use of popular sires (Ostrander, 2005).

(d) Further development of estimated breeding values.

Description: an estimated breeding value is a calculation that estimates the likely risk that a male or female parent will pass on a complex inherited disease to their puppy (Farrell, 2015; Lewis, 2013) in order to enable the better selection of the parents (Rooney, 2009). The estimated breeding value is not a value based on money but a value based on risk between the highest risk through to the lowest risk

The Kennel Club estimated breeding value calculation for the hip dysplasia trait in a FCR bitch is derived from:
- the hip score for the bitch and all her relatives whose data are recorded;
- pedigree information that is used to weight the relationships between the relatives and the bitch.

Adding all the data enable the genetic risk of that FCR bitch passing on hip dysplasia to be placed on a scale between the highest risk through to the lowest risk (https://www.thekennelclub.org.uk/about-ebvs/).

At birth, a puppy's estimated breeding value is the average of her parents' estimated breeding values and her estimated breeding value will change during her lifetime to a lower risk or a higher risk as more information becomes available about her and her relatives.

Opportunities:
- useful for a complex inherited diseases;
- clearly visible results within three to five generations (Woolliams, 2015);
- when they become available, adding the results from reliable new screening tests and from DNA tests to the calculation would be a significant advance in animal welfare (Rooney, 2009; Wilson, 2013).

Challenges:
- development costs to the Kennel Club involving particularly geneticists and breed societies to produce the estimated breeding value calculations;
- co-ordination between the breeders and veterinary practices to submit the data to the Kennel Club;

- understanding by the breeders about relative risk.

-Practice implications: even in the absence of a DNA test for hip dysplasia there has been a small sustained improvement in the estimated breeding value for FCRs (Oberbauer, 2017) equivalent to excluding 2% of the highest risk FCRs from breeding during the period 1990 – 2011 (Lewis, 2013).

However there is scope to develop the calculation to include the scores from the related trait of elbow dysplasia which may be due to the action of some of the same genes (Lewis, 2013) and for information on DNA tests to be included (Farrell, 2015; Leroy, 2009) once the development research has been carried out.

(3) Conclusions.

There are justifiable concerns about the welfare of our current FCRs and future generations of FCRs. The four options identified in this discussion paper could all be taken forward for the benefit of our FCRs and there are multiple groups internationally with interests in FCR welfare who could usefully be involved.

The options would require the active participation of breeders and companioners in submitting information with the help of their veterinarians to a central organisation such as a breed cancer registry or a breed disease registry.

Also, information would need to be submitted to the UK Kennel Club and ideally to the Kennel Clubs in other countries regarding the actions by breeders to implement the strategies to increase genetic diversity and to develop the database for estimated breeding values.

The UK's Flat Coated Retriever Society would need to be actively involved in delivering all the options including the promotion of research into DNA tests by scientists, and communications with the media and the general public. Collaborations could be developed with FCR breed societies in other countries.

It would also be important to involve animal welfare organisations, for example, the RSPCA, and rehoming groups.

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Editor's Footnote:

Please respond to this Discussion paper, as the more feedback we get the better we can see the way forward to tackle this growing problem.
Please send your responses to:-
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All to be marked: Cancer in F/Cs.

Thank you very much.