Preserving Genetic Diversity in Golden Retrievers

"Recognizing that no dog is genetically perfect; that maintaining a rich and diverse gene pool is important for the long-term health of the breed; and that good breeding decisions must balance many factors, it is suggested that breeders give the highest health priority to selection against heritable disorders that significantly decrease quality of life and that have the greatest likelihood for improvement through careful breeding decisions."[1]

In a wise and impressively forward-thinking accomplishment in the summer of 2012, the GRCA Board of Directors amended the Code of Ethics to include the above statement. This wording demonstrates an understanding that canine breeding genetics is far more complex than most have believed in the past, and that a new emphasis on a "big picture" approach is vital to the future welfare of our breed. Real-world experience and scientific studies are converging to teach us that taking steps to actively preserve genetic diversity will be important to protecting our breed's health for future generations. So let's examine in more detail what genetic diversity means to purebred dogs, beginning with an excellent discussion from The Kennel Club (UK), excerpted here.[2]

> ***Genetic Populations***
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> *Some years ago now, the Kennel Club took the decision to try to better understand the genetic population structure of the breeds that it recognises. Initially this work was undertaken in collaboration with research scientists at Imperial College in London. More recently, this work has been continued by Dr Sarah Blott and her colleagues at the newly established Kennel Club Genetics Centre at the Animal Health Trust (AHT). Moving forward we need to look at ways to manage the genetic diversity in the dog population to try and prevent breeds from becoming genetically homogenous. One way of achieving this will be to ensure there is a greater number of individual dogs contributing to the genetic population.*
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> ***Why should breeders worry?***
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> *Why should breeders worry about these trends in their breed's genetic population structure? Increases in a breed's average inbreeding coefficient, and indeed on the average inbreeding coefficient of their own dogs, means that the chances of genes becoming homozygous, i.e. the chances that a puppy will inherit the same copy of a gene from both its dam and sire, will increase. This is of course true for genes that have a beneficial impact, and this has traditionally been the reason for breeders practising what they call 'line breeding'. But sadly it is also equally true for those genes which have a potentially deleterious and sometimes very serious impact if they too become homozygous. There is absolutely no way that we can make precise predictions about the impact that increases in average inbreeding coefficients will have on a breed, but what we do know is that, as the inbreeding coefficients increase, the risk of these having a serious and deleterious impact on the breed will also increase.*
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> *The simple case would be a single recessive mutation that might cause a new inherited disease in the breed. As the level of inbreeding increases, then the risk of a dog inheriting a copy of this recessive mutation from both parents will increase, causing the dog to become clinically affected. More complex is a group of, as yet, anonymous genes which we believe make a contribution to a breed's genetic fitness and vitality. As levels of inbreeding rise, the risk of more and more of these genes becoming homozygous for deleterious recessive mutations increases, resulting in what is known as inbreeding depression. The most commonly seen consequences of inbreeding depression are reductions in the average litter size for a breed and an increasing inability for breeders to get their bitches pregnant. In the future, breeders will undoubtedly have to manage these risks by managing the increases in inbreeding from generation to generation.*

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1 From the GRCA Code of Ethics, available at *http://www.grca.org/thegrca/code.html*

2 Complete statement available at *http://www.the-kennel-club.org.uk/services/public/mateselect/genetic-diversity.aspx*

STUDY DETAILS

The initial study referenced above[3] included detailed population structure analysis of 10 breeds, one of which was Golden Retrievers. This research used UK pedigrees so some of the calculations will not apply precisely to the US Golden population, but the broad conclusions undoubtedly apply to US dogs and certainly should be taken seriously.

The scientific analysis included 317,527 Goldens registered with The Kennel Club from the 1970s thru 2006, which averaged 6-8 generations of dogs. During that period, they found that only 18% of females and 5% of males produced offspring, and that the "popular sire syndrome" was more pronounced in Goldens than in any of the other breeds studied. The authors stated, *"It is striking that seven breeds retain <10% of genetic variants up to generation 6, indicating a severe effect of breeding patterns on total genetic variation."* In Goldens the figure was even lower, because by the end of 2006, the breed had maintained only **6.3% of the genetic variants** contained in the breed in the 1970s. That's essentially like taking 93% of all the Goldens that existed in the 1970s and removing them from the breed, thereby creating an extreme population bottle neck.

The study authors summarized, *"Dog breeds are required to conform to a breed standard, the pursuit of which often involves intensive inbreeding: the inbreeding effective population size of most breeds considered here is orders of magnitude smaller than the census size and exceeds 100 only in the Labrador retriever. This has adverse consequences in terms of loss of genetic variability and high prevalence of recessive genetic disorders."* They concluded, *"Dog registration rules have been rigidly enforced only for ~50 years; prior to that occasional outcrossing [to other breeds] was still possible. Anecdotal evidence suggests that loss of genetic variation and high levels of inbreeding have adverse consequences for canine health and fertility. [snip] On the basis of these results, we [recommend] that remedial action to maintain or increase genetic diversity should now be a high priority in the interests of the health of purebred dogs. Possible remedial action includes limits on the use of popular sires, encouragement of matings across national and continental boundaries, and even the relaxation of breed rules to permit controlled outcrossing [to other breeds]."*

FROM GOOD INTENTIONS TO UNINTENDED CONSEQUENCES

But how did this happen? Well, to start with, simply the creation of the breed and subsequent closing of the stud book caused a population bottleneck and initiated the implementation of inbreeding. From that point, essentially every trait that we collectively select **for** or **against** in our breed whittles away at genetic diversity over time. So, for example, as we select for desired Golden temperament, structure, and aptitude – and away from hip, elbow, eye, and heart disease – we are constantly eliminating some dogs (and all their genetic variation) from breeding and thus decreasing the size of the remaining gene pool. Of course, there is no doubt that these breeding practices certainly can help produce healthier, happier dogs. But because this process has been driven by the extensive use of popular sires in our breed, an unintended consequence is that hidden harmful genes have been widely distributed throughout the gene pool, and previously uncommon diseases have now become more common.

And this is not just scientific theory, because we can see it in action by observing Golden Retriever health history over the last forty to fifty years. As early breed type stabilized and population increased, it became apparent that dogs clinically affected with hip dysplasia were far too common in the breed. Aided by the formation of the Orthopedic Foundation for Animals (OFA) in 1966, fairly rigorous selection against this disease became widespread among serious breeders in the late 1960s and 1970s. The Canine Eye Registry Foundation (CERF) was formed soon afterward, and selection against eye disease also became increasingly common. Clinically significant eye disease such as PRA was rare in the breed at that time, but we screened eyes because a "health certification" was available and because the prevailing belief at the time was that eliminating even minor anomalies would result in a healthier breed. It is worth noting that even though eye abnormalities such as juvenile cataracts very rarely caused clinically significant disease in Goldens, cataracts were the most common reason for failure to "clear" eyes. So even though breeders were doing yearly eye exams, for a number of generations hip dysplasia really was the primary clinically significant disease in the breed of which most breeders were aware.[4]

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Fast forward to today, and many or most of us have had experience with, or know of, too many dogs with clinically significant: subaortic stenosis, elbow dysplasia, pigmentary uveitis, cancer, PRA, ichthyosis, masticatory muscle myositis, food sensitivities, inflammatory bowel disease, allergies, atopy, hypothyroidism, epilepsy, ectopic ureters, liver shunts, juvenile renal dysplasia, bleeding disorders, and more. (**Table 1**) Of course, all of these diseases existed in Goldens 40 years ago too, and some of our current awareness is likely due to informa-

3 Calboli FCF et al **Population Structure and Inbreeding From Pedigree Analysis of Purebred Dogs** Genetics. 2008 May; 179(1): 593–601.

4 Veterinary literature has reported elevated numbers of Goldens with cancer for at least 40 years since the early 1970s, but there are no reliable data that indicate whether this was because of breed popularity (higher numbers of Goldens overall) or whether the actual prevalence was higher in Goldens than in other dogs. In general, cancer incidence was not on most breeders' radar screens until the GRCA/GRF Health Survey in 1998.

5 Summers JF et al. **Inherited defects in pedigree dogs. Part 2: Disorders that are not related to breed standards.** Vet J. 2010 Jan;183(1):39-45. doi: 10.1016/j.tvjl.2009.11.002. Epub 2009 Dec 5.

tion-sharing via the Internet. But it is also undeniable that many of these conditions have become increasingly common in the breed over time, and this is supported by the findings of another study of UK dogs (but certainly relevant to US Goldens), which noted, *"A total of 312 non-conformation linked inherited disorders was identified, with German shepherd dogs and Golden retrievers associated with the greatest number of disorders. The most commonly reported mode of inheritance was autosomal recessive (71%)"*[5] Further, some of these diseases raise concerns about general immune system impairment in the breed, which in itself is a sign of harmful reduction in genetic diversity. Obviously no one intentionally tried to damage the breed by promoting disease genes, but it was nonetheless a consequence of our actions because diseases tend to increase when the extensive use of popular sires and linebreeding widely disseminates some harmful genes and drives genetic diversity too low. Genes that used to be infrequent were hidden (since most follow a recessive MOI) because in a more diverse gene pool they did not pair up very often, so they did not cause disease. But in our ever shrinking gene pool, they now find matches and combinations that cause disease, and previously rare conditions have become more common.

Table 1. Diseases Common in Golden Retrievers

1970	2014
Pre-breeding screening tests used: • Hip dysplasia • Juvenile cataracts • PRA No useful pre-breeding screening **tests available:** • Cancer • Epilepsy	**Pre-breeding screening tests used:** • Hip dysplasia • Juvenile cataracts • Elbow dysplasia • Subaortic stenosis • Pigmentary uveitis* • prcd-PRA, PRA-1, PRA-2 • Ichthyosis * screening is ineffective No useful pre-breeding screening **tests available:** • Cancer • Epilepsy • Masticatory muscle myositis • Food sensitivities • Inflammatory bowel disease • Skin allergies • Atopy • Hypothyroidism • Ectopic ureters • Juvenile renal dysplasia • Liver shunt • Bleeding disorders

CHANGING MINDSET

So now what? Now that some of these conditions are more common, and we are aware of them, we can't stop screening and just ignore them – surely that would be harmful too. It's really quite a conundrum that we find ourselves in. The previously discussed study recommended that *"remedial action to maintain or increase genetic diversity should now be a high priority in the interests of the health of purebred dogs."* Increase genetic diversity? Since genetic diversity can never increase by intent in a closed gene pool (it can increase by random mutation), that would require opening the stud book, which is a topic beyond the scope of this discussion. So what **can** we do to stop digging this hole deeper and at least maintain the genetic diversity we have left?

Well, at its highest level, maintaining genetic diversity means including the most dogs possible in the breeding pool. Not just titled dogs, not just dogs with all their health clearances, not just dogs owned by educated, dedicated breeders – but also backyard-bred dogs, pet dogs, and puppy mill dogs. Okay, we've crossed off introducing other breeds, and we're crossing off puppy mill dogs, too. But we can't keep crossing dogs off the list, or we're right back where we started.

Cutting right to the chase, if we want to expand our traditional pool of breeding dogs, we will have to change our way of thinking. We have to be willing to modify our breeding priorities and modify our standards of breeding exclusivity, and yes, these changes may make us uncomfortable. Very importantly, breeding to maintain genetic diversity means making personal decisions to limit the use of popular sires and popular lines because these breeding methods greatly accelerate gene loss and the dispersal of potentially harmful genes throughout the gene pool. However, those practices are not the immediate topic, and this report has a different focus.

HEALTH TESTING

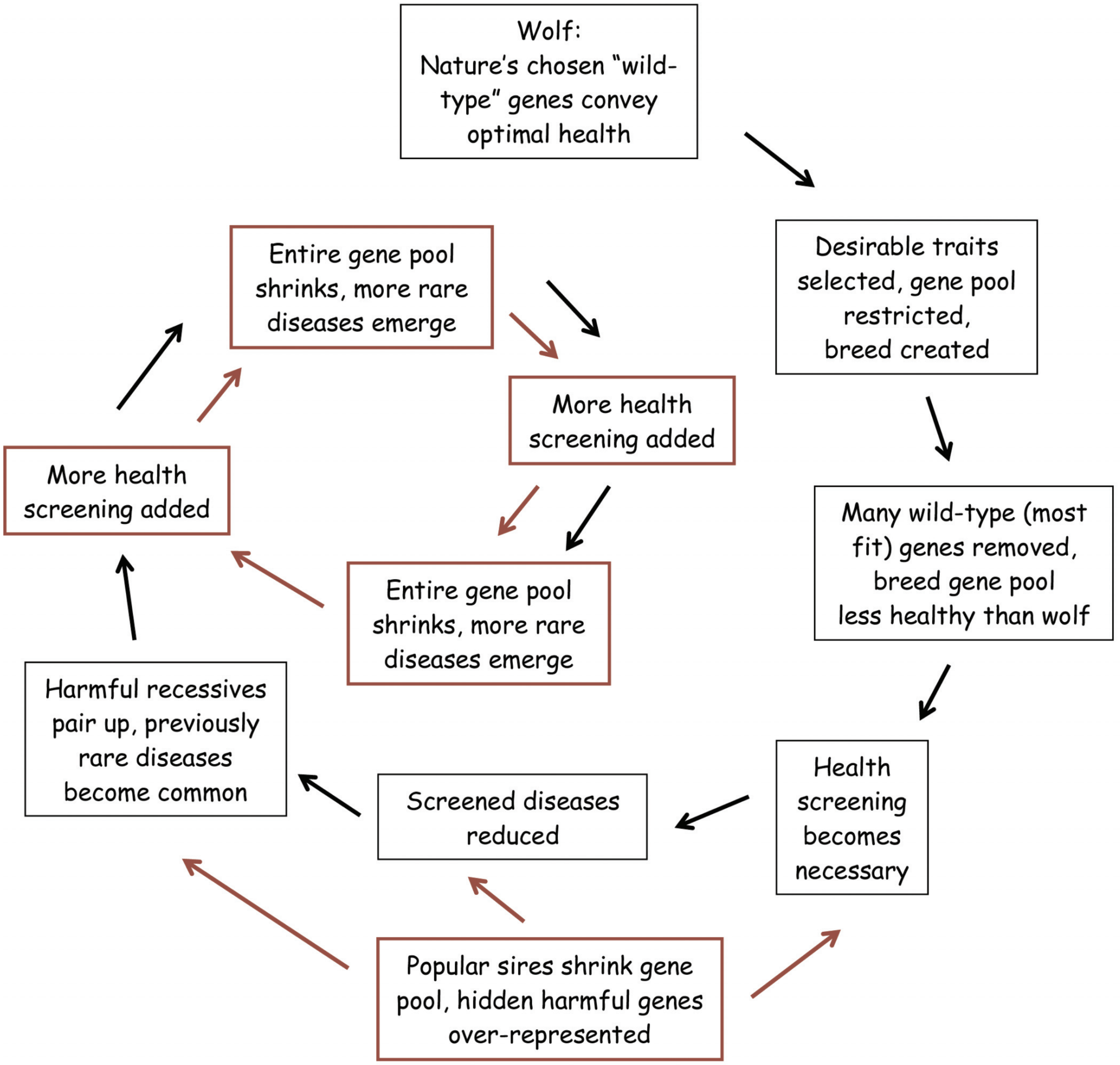
Many long-time breeders have watched the evolution of ever-increasing demands of health testing with concern, and discuss privately that expectations are reaching the breaking point. And they are right, because narrowly selected breeding choices reduce genetic diversity, and diseases can increase if these pressures continue to drive diversity lower in a population that developed with widespread use of popular sires. Keep in mind that when we remove a dog from breeding due to a failed health test or any other reason, we are removing **all** of that dog's genes from the gene pool, not just genes associated with disease or unwanted traits. Likewise, as discussed above, when we create a popular sire, we are widely disseminating **all** of his genes, including any hidden harmful genes. And although driven primarily by popular sires in the beginning, this can reach a tipping point in which there are so many deleterious genes in the breed, that targeting too many health conditions for removal can itself contribute to a spiral: we do health testing so that we can breed for improved health, but the more testing and consequent removal of dogs from breeding that we do, the more health problems we have, so we need to do even more testing.

The common traditional breeding dogma has been to test hips, elbows, eyes, and heart, and generally not breed dogs that have evidence of disease. And while this practice helps reduce the incidence of **those specific** diseases in the offspring, the very basis of that process involves eliminating entire individual genomes from the breed – including potentially many healthy and valuable genes. A recent scientific publication raises con-

6 Wade CM. **Inbreeding and genetic diversity in dogs: results from DNA analysis.** Vet J. 2011 Aug;189(2):183-8. doi: 10.1016/j.tvjl.2011.06.017. Epub 2011 Jul 13.

7 Meyers-Wallen VN. **Ethics and genetic selection in purebred dogs.** Reprod Domest Anim. 2003 Feb;38(1):73-6.

FIGURE 1. GOLDEN RETRIEVER CREATION AND DEVELOPMENT



cerns with widespread use of that approach, stating, *"Requirements that breeding stock must be 'clear' for all genetic disorders may firstly place undue genetic pressure on animals tested as being 'clear' of known genetic disorders, secondly may contribute to loss of diversity and thirdly may result in the dissemination of new recessive disorders for which no genetic tests are available."*[6] This was echoed in another scientific journal article, *"There is not only a great potential to improve overall canine health through genetic selection, but also the potential to do harm if we fail to maintain genetic diversity."*[7] An illustration of this process appears in **Figure 1**.

Thus, despite the very best of intentions, such practices may reflect a short-sighted approach to health testing in Goldens, and we need a more sustainable way to manage disease. An approach to health testing that serves the immediate offspring and also helps to maintain more genetic diversity in the breed, is to "test and disclose" as opposed to strict "test and eliminate." Performing appropriate health screening tests is still a vital part of this process, but with increased emphasis on full disclosure of both normal and abnormal results. Then, instead of rigorous elimination from breeding of dogs that are found to have evidence of disease, breeders would evaluate the "big picture" by prioritizing health considerations just as they do with elements of structure, temperament, and aptitude. In this model, dogs with serious heritable disease would still be removed from breeding because such diagnoses would be of high health priority. But when a thoughtful decision is made to breed a dog with a less severe or less heritable diagnosis, careful selection of a mate that demonstrates strong health history in that area will help to keep quality of life in the offspring high while also moderating shrinkage of the gene pool.

A similar strategy – "test and replace" – can be used for carriers of recessive diseases for which there is a DNA test available. In this case, the genetic variety represented in a line is maintained by breeding carriers to normals for as many generations as necessary until homozygous normal offspring can be selected to replace the carriers. These methods more closely satisfy the age-old medical maxim of, "Above all do no harm" than does the current more common practice of eliminating "imperfect" dogs from breeding. And besides, we know there's no such thing as a "perfect" dog anyway, because a dog with "all clearances" is only a dog whose detrimental genes were not exposed by our testing methods – and such dogs certainly carry detrimental genes just like all dogs do, and just like another dog that may have a detectable hereditary flaw does.

So how do we go about prioritizing health considerations? First, we recognize that this is somewhat of a personal process, and not all of us will arrive at identical conclusions. And this individuality actually contributes to genetic diversity because different priorities will be reflected in varied choices. We should also recognize that health prioritization is a very complex and dynamic process that will keep evolving over time as veterinary science, genetic testing, and even our own breeding programs continue to provide more information.

PRESERVING THE PAST, PROTECTING THE FUTURE

The genetic concepts presented here may not be familiar to everyone, and certainly have not been used to guide our breed's development and many individual breeding decisions. The emphasis on preserving breed viability through increased focus on genetic diversity may seem overblown to some, especially since we've been doing it the way we've been doing it for over forty years, and the sky hasn't fallen yet. (Actually, some breeders and owners might argue that the sky is indeed beginning to fall…)

But if we don't take steps to change…well, the breed's increasing incidence of previously uncommon diseases – and even more worrisome – diseases for which there are no effective screening tests, clearly demonstrate that we are already in the Red Zone of Figure 1. If we ignore the warning signals and wait until more severe signs of trouble reveal themselves, our options may be much more unpleasant than the suggestions presented here, because tougher problems usually require more drastic solutions.

Hopefully, we can at least slow down digging the hole deeper, because the breed may not be able to withstand another 40 years of doing what we've been doing.

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