

DNA Health Testing Summary Guidance

GRCA members agree to follow the GRCA Code of Ethics (COE) (10). The COE notes that breeding dogs should be tested to determine whether the Golden is, or is not, affected with hip dysplasia, elbow dysplasia, inherited heart disease, or inherited eye disease. In addition, the COE advises members that the "ideal use of DNA tests is to prevent producing affected puppies, while at the same time maintaining genetic diversity and gradually decreasing the prevalence of the disease gene(s) in the breed." The purpose of this article is to briefly summarize differences between DNA tests and the tests for hip, elbow, eye and heart diseases. In addition, this summary notes some current DNA tests that are useful in preventing severe and/or common conditions of Goldens and includes tips from the Health and Genetics Committee.

The established health tests used to determine the presence of hip, elbow, heart and eye conditions in Goldens are tests for the phenotype, which are conditions influenced by genes inherited from the ancestors and often influenced by the environment as well. The genetics of most of these diseases is believed to be complex and involve multiple genes (17). For these phenotypic tests, Goldens are evaluated by veterinary specialists who have completed their veterinary training and then gone on to obtain additional advanced training in a specialized area of veterinary medicine. For orthopedic conditions like hip dysplasia and elbow dysplasia, the x-rays are evaluated by veterinary radiologists. In the U.S., most hip and elbow x-rays are currently evaluated through a

consensus opinion of radiologists associated with the Orthopedic Foundation for Animals (OFA) in Goldens 2 years old or older. In place of, or in addition to, the OFA hip x-ray, some prefer to have hips evaluated by PennHip in Goldens 2 years old or older, which is also acceptable. Hearts are evaluated by veterinary cardiologists at one year of age or older and eyes are evaluated by veterinary ophthalmologists yearly. Yearly eye exams should continue for life in breeding dogs because an important eye disease, pigmentary uveitis (8), most often appears after the prime breeding years. The COE specifies that findings from phenotypic screening examinations of breeding dogs are recorded in an online database meeting specific criteria that include veterinary advisement and/or management. In the U.S. those database requirements are met by the OFA online database. The purpose of the OFA online database is to allow owners to select breeding dogs with ancestors who have had healthy eyes for a lifetime and have relatives with normal hips, elbows and hearts. Doing so improves the odds for healthy offspring.

DNA (genetic) health testing involves assays detecting changes in the actual genes implicated in causing health conditions. There are no current established DNA tests for identifying hip dysplasia, elbow dysplasia and common inherited heart conditions of Goldens. There are also no DNA tests for most of the inherited eye diseases of Goldens, although three different DNA tests can identify genes that can cause three eye diseases that affect the retina of Goldens.

Most of the current DNA tests identify genes



implicated in causing single gene, autosomal recessive diseases, disease that can occur when a Golden receives the implicated gene from each parent. Normally, a Golden receives a copy of each gene from each parent and, for true autosomal recessive diseases, if one copy is normal and the other is abnormal, that Golden will not get the disease. However, they can pass the abnormal gene to their offspring and they are said to be a "carrier" for the disease. If two carriers for the same trait are bred to each other, puppies that receive the abnormal gene from each parent can develop the disease (Figure 1). The goal of DNA testing is to prevent breeding carriers for the same disease to each other. That improves the odds that the puppies will grow up to be healthy

Goldens. Importantly, when a carrier of an autosomal recessive disease is bred to a Golden that is normal/clear, the puppies should not develop the disease (Figure 2).

Years ago, many of us thought that most healthy dogs did not carry genes for genetic disease. Today, we know that all dogs likely are carriers of genetic diseases and numerous geneticists have advised that carriers of genetic disease should not be excluded from breeding programs. A major concern is that today we can only test for a small fraction of the genes important for Golden Retriever health. Eventually, all dogs will likely be identified as carriers of multiple genetic diseases and we can't exclude all dogs from the breeding pool. The data behind that advice includes the fact that dogs have ~20,000 genes organized into their 39 chromosome pairs. Many variants of each of these genes occur and we are just beginning to



recognize some of the variants that cause disease and will undoubtedly identify more harmful variants in the future. Also, because many genetic diseases involve multiple genes, combinations of genes matter also.

Recently identified potentially lethal genetic diseases of Golden Retrievers include forms of neuronal ceroid lipofuscinosis (NCL) and congenital myasthenic syndrome (CMS) (3, 7). Testing for devastating genetic diseases such as NCL, disclosing the results, and assuring that carriers are neutered or in very responsible homes are as much a hallmark of responsible breeders as established tests for normal hips, elbows, hearts and eyes. However, because all dogs likely carry genetic diseases, narrowing the gene pool based upon the DNA tests of today could increase the odds of two carriers of another genetic disease being bred to each other (Figure 3).



That actually happened in Portuguese Water Dogs during the early days of DNA testing when a DNA test was developed for a fatal lysosomal storage disease (GM1 gangliosidosis) and breeders strongly selected against the affected bloodlines, resulting in a narrowing of the gene pool and a striking increase in an eye disease causing blindness more than 30% of Portuguese Water Dogs were at one point reported to be carriers of the blinding eye disease (20).

DNA tests for several autosomal recessive disorders affecting Golden Retrievers are currently available. These include tests for Golden Retriever NCL (7), Golden Retriever CMS (3),

Some Useful Commercial DNA Tests for Simple Recessive Diseases of Golden Retrievers

- Neuronal Ceroid Lipofuscinosis, Golden Retriever form (Golden Retriever NCL) – progressive neurologic disorder – puppies seem normal but develop progressive signs of neurologic disease leading to death as young adults. NCL carrier state is common in some bloodlines. Due to the severity of NCL, testing all Golden Retriever breeding dogs for NCL is recommended.
- Golden Retriever Congenital Myasthenic Syndrome (Golden Retriever CMS) – progressive muscular disease but believed to be rare
- Golden Retriever Ichthyosis 2 (ICH2) Flaking skin disease with frequent secondary infections. Weight loss and lethargy possible. May become unmanageable.
- **Prcd-PRA** typically causes an adult-onset progressive loss of vision leading to blindness
- **GR-PRA1** typically causes an adult-onset progressive loss of vision leading to blindness
- **GR-PRA2** typically causes an adult-onset progressive loss of vision leading to blindness
- Golden Retriever Ichthyosis (ICH1) Very common. Puppies usually have dandruff but adults can be clinically normal or develop significant skin disease
- Golden Retriever Dystrophic Epidermolysis Bullosa skin blisters and erosions at sites of wear and minor trauma believed to be rare

Golden Retriever Ichthyosis 1 (ICH1) (5, 9)), Golden Retriever Ichthyosis 2 (ICH2) (6, 14), prcd-PRA (16), GR-PRA1 (11), GR-PRA2 (12), and Golden Retriever Dystrophic Epidermolysis Bullosa (4). This list and the associated signs of disease are summarized in the blue box inset in the approximate order of their importance. Please note that the list specifies Golden Retriever forms of most of these diseases. That is because the mutation responsible for many genetic diseases (e.g. Golden Retriever NCL) is different from the mutation causing the disease with the same name in a different breed. A test for the NCL or ichthyosis that affects other breeds will not identify the mutation that commonly causes those diseases in Golden Retrievers. The exception to this rule is the mutation that causes prcd-PRA – that mutation is the same in many breeds.

In addition to tests for autosomal recessive disorders, there is a test that is important if a Golden Retriever descends in the direct female line from Goldens born in Sweden. The condition is variably expressed, so some at risk Goldens are clinically normal and some severely affected (18). This condition, Golden Retriever Sensory Ataxic Neuropathy (SAN), is due to abnormal mitochondria and it is inherited in the female line of descent because the egg, but not sperm, provides the mitochondria inherited by a puppy. Therefore, SAN has only been reported in Goldens who descend in their female line from a Golden Retriever bitch whelped in Sweden in 1971 (1).

Breeders frequently ask if they need to post DNA test results online in the OFA database. While that can be helpful

in mate selection if the dog is a breeding dog available to outside Goldens, it is not necessary in most cases. Online databases that require documentation of a health test result, such as the OFA database, help breeders identify pedigrees that may reduce the risk of polygenic diseases, diseases caused by more than one gene. Hip dysplasia, elbow dysplasia, some eye diseases [e.g. pigmentary uveitis (8)] and some heart diseases are believed to be polygenic. In the polygenic diseases, the phenotype of ancestors and siblings helps breeders get a picture of the genetic background. The simple autosomal recessives are different, the DNA test reveals the genetic status for the tested individual. If the dog is normal clear, they should not pass on the disease gene, even if their sibling is a carrier. The goal of the testing is to avoid breeding two carriers to each other. Online posting of the DNA test results is not currently required in the COE, although doing so can encourage those owning dogs related to the carrier to test their dogs.

Some test panels offer a large number of DNA tests of limited value. For example, DNA tests can identify the estimated percentage of Golden Retriever in your Golden. Most of us do not find that helpful. In addition, genetic background can be

Testing Tips from the Health and Genetics Committee

- Autosomal recessive diseases can be prevented if at least one parent (sire or dam) is normal/clear for the gene that causes that disease.
- Prudent use of DNA testing can prevent disease in Golden Retrievers.
- NCL testing is extremely important for Golden Retriever breeding dogs because it is progressive and fatal. Ideally, all Golden Retriever breeding dogs should be tested for Golden Retriever NCL.
 - Please don't let a puppy buyer receive a healthy puppy and watch it slowly die when that can be prevented.
 - Breeders producing NCL carriers are responsible for assuring those carriers are disclosed and neutered or handled responsibly so that no affected puppies are produced.
- DNA testing is only helpful when a high-quality testing laboratory conducts the test.
- Routine DNA testing for diseases that are not known to affect Golden Retrievers is not recommended because genetic background (breed) influences the effect of a DNA variant.
- Many new DNA tests are anticipated in the future and all Golden Retrievers likely carry some potentially harmful recessive mutations.
- Automatic exclusion of carriers from breeding based on carrier status for recessive genes is not recommended; genetic diversity is important for breed preservation.
- DNA tests do **not** replace phenotypic tests for hip dysplasia, elbow dysplasia, inherited heart disease, and inherited eye disease.
- Two carriers for the same fatal recessive disease should not be bred to each other.

DNA Health Testing Summary Guidance, continued

important in the development of genetic diseases, particularly those with incomplete expression. Therefore, it is rarely useful to screen Goldens to see if they carry genetic diseases not known to affect Goldens. In fact, the chance of an error in at least one test will increase with the number of tests conducted. In short, more tests are not necessarily better and increase the risk that at least one test will be inaccurate.

Sometimes we see posting of discounted DNA testing. Please avoid shopping for the lowest price. It is important to remember that DNA test are highly accurate when performed correctly but that correct performance requires rigorous quality control. The two major causes of errors are human errors in sample submission and in the laboratory, including, for example, switched samples and samples contaminated by DNA from the wrong dog. For most breeders, the accuracy of the result is much more important than the price of the test. Dog WellNet has an online listing of canine DNA testing laborato-

References/Resources

- 1. Baranowska et al, 2009. Sensory ataxic neuropathy in golden retriever dogs is caused by a deletion in the mitochondrial tRNATyr gene. PLoS genetics, 5(5), p.e1000499 https://journals.plos.org/plosgenetics/article?id=10.1371/ journal.pgen.1000499
- 2. Canine DNA testing information https://www.akcchf.org/educational-resources/library/ articles/CANINE_GENETIC_TESTING_07-28-2020_ FINAL_with-links.pdf
- 3. Golden Retriever Congenital Myasthenic Syndrome https://vgl.ucdavis.edu/test/cms-gr
- 4. Golden Retriever Dystrophic Epidermolysis Bullosa https://www.vetgen.com/canine-deb.html
- 5. Golden Retriever Ichthyosis-1 https://grca.org/about-thebreed/health-research/ichthyosis/
- 6. Golden Retriever Ichthyosis-2 https://www.vet.upenn.edu/research/academic-departments/clinical-sciences-advanced-medicine/research-labscenters/penngen/penngen-tests/genetic-tests/Detail/67/
- 7. Golden Retriever Neuronal Ceroid Lipofuscinosis http://www.caninegeneticdiseases.net/GoldenNCL/
- Golden Retriever Pigmentary Uveitis https://www.akc.org/expert-advice/dog-breeding/diagnostic-criteria-golden-retriever-pigmentary-uveitis/ and https://www.vetvine.com/list/index/profile/listing_id/101 0/pu-what-s-that-golden-retriever-pigmentary-uveitis
- 9. Grall et al, 2012. PNPLA1 mutations cause autosomal recessive congenital ichthyosis in golden retriever dogs and humans. Nature genetics, 44(2), pp.140-147 *https://www.nature.com/articles/ng.1056*

ries (13). Notably, some, but not most, laboratories list their labs as having some form of accreditation.

Some current summary tips from the Health and Genetics Committee regarding DNA testing are included in the green inset box. Useful DNA tests and new genetic diseases are rapidly increasing. For example, a new lysosomal storage disease, while believed to be rare, was recently described in a family of Golden but no DNA test is yet available (15). We hope the information provided here will be helpful in understanding this exciting area. Please look for updates in the future. Those interested in additional information are encouraged to read the excellent review of canine genetic testing available online from the AKC Canine Health Foundation (2). An excellent illustrated review of the genome and genetic disease oriented toward human disease but helpful in understanding genetic diseases in general is available from the National Human Genome Research Institute (19).

- 10. GRCA Code of Ethics https://grca.org/about-grca/grcacode-of-ethics/
- 11. GR-PRA1 https://vgl.ucdavis.edu/test/golden-retriever-pra
- 12. GR-PRA2 https://vgl.ucdavis.edu/test/golden-retriever-pra
- 13. International Partnership for Dogs list of DNA test providers https://dogwellnet.com/index.php?app= dwlabs&module=search&controller=labs
- 14. Kiener et al, 2021. ABHD5 frameshift deletion in Golden Retrievers with ichthyosis. G3 Genes| Genomes| Genetics https://academic.oup.com/g3journal/advancearticle/doi/10.1093/g3journal/jkab397/6428539
- 15. Mucopolysaccharidosis type 1 description. Faller et al, 2020, A deletion of IDUA exon 10 in a family of Golden Retriever dogs with an attenuated form of mucopolysaccharidosis type I. Journal of veterinary internal medicine, 34(5), pp.1813-1824 https://pubmed.ncbi.nlm.nih.gov/32785987/
- 16. Prcd-Progressive Retinal Atrophy https://www.pnas.org/content/95/6/3048.short
- 17. Refining the Complex Genetics that Influence Canine Hip Dysplasia https://www.akcchf.org/educationalresources/library/articles/refining-the-complexgenetics.html
- 18. Sensory Ataxic Neuropathy https://vgl.ucdavis.edu/test/san-gr
- 19. What's a Genome https://www.genome.gov/About-Genomics/Introduction-to-Genomics
- 20. When Good Dogs Get Bad Genes https://www.akcchf.org/canine-health/your-dogshealth/when-good-dogs-get-bad-genes.html