Another Fatal Genetic Disease of Golden Retrievers: *What Should We Expect in the Future?*

GRCA Health and Genetics Committee

A little over a year ago, Golden Retriever owners were shocked to learn that a form of Neuronal Ceroid Lipofuscinosis (NCL) was an inherited fatal disease of Golden Retrievers. For those who do not know about this disease yet, Goldens with NCL are normal at birth but start to show signs of neurologic disease between one and two years of age. NCL is progressive, fatal and some very successful Goldens are carriers of this disease. Additional information on Golden Retriever NCL is available at *www.CanineGeneticDiseases.net/GoldenNCL/*. Our hearts go out to the affected Goldens and their owners. Another fatal genetic disease, **Congenital myasthenic syndrome (CMS) of Golden Retrievers,** was recently described. Like NCL, CMS is an autosomal recessive disease and both diseases can be avoided by following one very basic rule: ***Two carriers for the same recessive disease should not be bred to each other.***

DNA tests are a major tool for preventing breeding of carriers to each other when the DNA variant causing the disease has been described. Genetic diversity within the breed is the major means for preventing the genetic diseases where the genes that cause the disease are not yet described and/or a DNA test is not commercially available. Here is the summary information on the most recently described fatal genetic disease of Golden Retrievers.

Congenital myasthenic syndrome (CMS) of Golden Retrievers was first described in four puppies from California in a paper published early this year (9). All four puppies were related and had the same breeder. At least two of the affected puppies were the result of a dog being bred to his daughter. Three of the four puppies ended up being euthanized and the other was lost to follow-up.

Beginning at weaning age, CMS affected puppies display weakness and exercise intolerance. CMS is a diagnosis for a spectrum of conditions affecting the interaction of peripheral nerves and the muscles. In people, 32 different types of CMS have been described. Golden Retriever CMS is attributed to a recessive mutation in COLQ (collagen-like tail subunit of asymmetric acetylcholinesterase) inherited from each parent. This COLQ mutation has not been found in unrelated Golden Retrievers, dogs of other breeds or wild canids. However, CMS in Labrador Retrievers is caused by a different mutation in the COLQ gene (6). At this time, Golden Retriever CMS appears to be a problem for one breeder and a Google search did not indicate the commercial availability of a DNA test for Golden Retriever CMS. However, the mutation has been described in the Golden Retriever and the disease is predicted to occur in puppies who receive the mutated COLQ gene from each parent. We know that it was not detected in the unrelated Golden Retrievers (<100) tested but it could easily exist in some other bloodlines.

Recessive diseases like NCL and CMS are most common when closely-related dogs are bred to each other. The original description of NCL in Golden Retrievers involved two litters of puppies resulting from the breeding of a sire and dam who each had the same mother (i.e. they were half-siblings) (3). NCL became a problem for the breed as a whole due to the unintended selective use of some highly successful NCL carriers for breeding that increased the chance of two carriers being bred to each other. Similarly, Golden Retriever CMS was identified in puppies produced in inbred Golden Retrievers and the two affected Goldens with pedigrees available were from a father to daughter breeding (8). In short, narrowing the gene pool whether intentional or not, increases the chance for autosomal recessive disease.

CMS and NCL are not alone. There are other fatal genetic diseases lurking out there in the canine genome. A few have been discovered and more will undoubtedly be discovered. More than 150 genetic variants for diseases affecting dogs are known today and two in five dogs have at least one copy of one of those genes (2). The genes causing canine diseases are being described at an increasing rate. Many of the existing tests are for single gene disorders – diseases like NCL and CMS where that genetic change is usually sufficient by itself to cause disease (3). In the future, it is likely that DNA tests will be developed for DNA variants that interact with other genes, environmental factors and/or age to increase the risk for disease. These are multifactorial diseases like hemangiosarcoma where a single gene is not sufficient to cause the disease (8). In addition, there are diseases that are inherited only through direct maternal lineage – the mitochondrial disorders that are carried within the cytoplasm of the dam's eggs. In short, the number of genes associated with diseases of Golden Retrievers and the number of DNA tests will continue to increase. One of the fatal mitochondrial diseases is discussed below as an example.

Golden Retriever sensory ataxic neuropathy (SAN) is a progressive neurodegenerative disease of the nerves that interact with muscles (1; 4). SAN most frequently presents between 2 and 8 months of age. Affected dogs have abnormal movement, particularly in their rear limbs. They may be unsteady on their feet, may "bunny hop," and males may not

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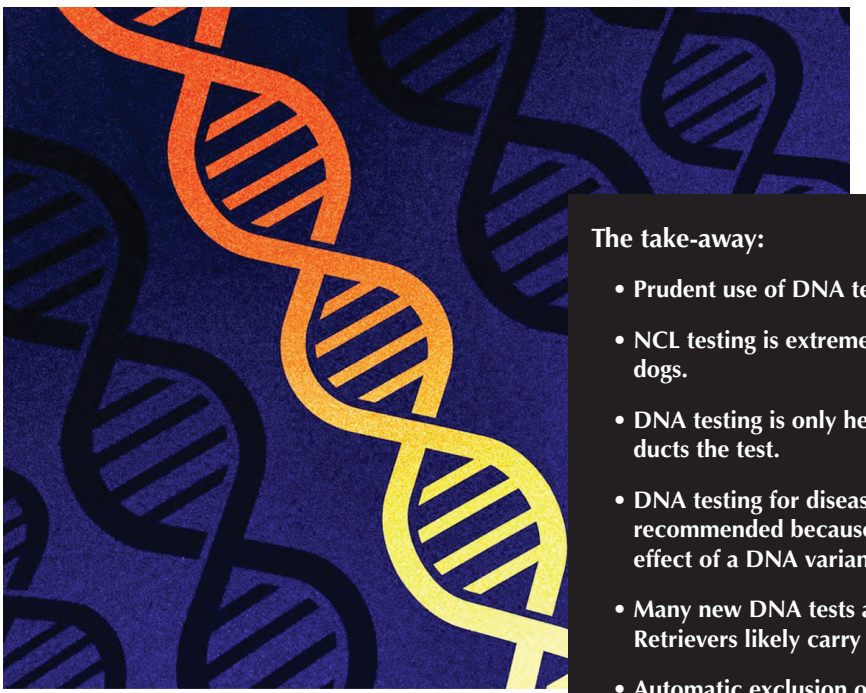
lift their leg when urinating. The gait disturbances are reportedly slowly progressive over months to years and can result in euthanasia (4). Although first reported in the 1990s, all known cases of this disease trace in direct female descent from a Golden Retriever bitch whelped in 1971 (1).

SAN is due to a DNA defect in mitochondria, the powerhouse of the cell. Mitochondria have their own DNA, distinct from the DNA in the nucleus. Affected Golden Retrievers have a mutation in $tRNA^{Tyr}$ in the mitochondrial DNA. The reason that all known Golden Retrievers with SAN have a direct female line of descent from one Golden Retriever bitch is because the mitochondria of a fertilized egg come from the dam, not the sire. The mitochondria in sperm are localized to the midpiece of the sperm. At fertilization of an egg, the midpiece of the sperm does not normally enter the egg. This means that under normal circumstances, males provide genomic (nuclear) DNA but mitochondria and their mitochondrial DNA come from the cytoplasm of the mother's egg. Even an affected father will not normally transmit the disease or carrier status to his offspring (this is very different from X-linked diseases such as Golden Retriever hemophilia A – X-linked diseases are not discussed here). However, there are many mitochondria in every cell and, in most cases, Golden Retrievers with SAN, and some of their apparently normal relatives, have both normal and abnormal mitochondria. The signs of SAN correlate with the percent of the mitochondria that are affected (1). Therefore, the absence of clinical disease is not proof that a bitch will not have affected offspring. That is why the disease persists – if the dam always showed signs, the disease could be controlled by not breeding symptomatic females. Currently, about 5% of the female Golden Retrievers in Sweden are estimated to have mitochondria with this DNA mutation (1). c A DNA test for SAN is commercially available and breeders can prevent the disease by pedigree analysis and/or testing of females directly descending from the affected female line.

A final word of caution – all tests have error rates. A correctly controlled DNA test is very accurate. However, quality control is crucial – an inaccurate DNA test can cause a lot of problems for a breeder. Errors can happen at any stage – collection of the DNA, conduct of the test and reporting of the findings. In humans, direct-to-consumer raw genetic testing is available for a large number of ancestry or health-related conditions. In one recent report, 40% of the health-related positive tests on the raw direct-to-consumer test results were found to be false positive (the test indicated that the mutation was present when it was not) by subsequent more carefully controlled medical DNA testing (7). In short, the quality of DNA testing matters. In addition, DNA mutations that cause disease in one breed will not always cause disease in a different breed (5). As a result, an international effort summarized online by the Harmonization of Genetic Testing in Dogs (HGTD) https://dogwellnet.com/ctp/, was recently established to provide an international database on the testing laboratories, the genetic tests, and each breed's DNA test. These are early days in the process of providing public information, but owners should remember that the quality is more important than the cost of a DNA test.



The take-away:

- **Prudent use of DNA testing can prevent disease in Golden Retrievers.**
- **NCL testing is extremely important for Golden Retriever breeding dogs.**
- **DNA testing is only helpful when a high-quality testing laboratory conducts the test.**
- **DNA testing for diseases that do not 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.**
- **Two carriers for the same fatal recessive disease should not be bred to each other.**