

Identifying Young Puppies At Risk of Developing Hemangiosarcoma Later in Life

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Introduction

Hemangiosarcoma is one of the most dreaded and deadly of all canine cancers. Among Golden Retrievers, Cornell University's Baker Institute estimates that 1 in 5 Golden Retrievers¹ will be diagnosed with hemangiosarcoma in their lifetime. Worse yet, hemangiosarcoma is often a silent killer, undetected until just days before death.

A viable method for preventing this disease is to produce puppies that are genetically predisposed to never develop hemangiosarcoma. While this might sound too good to be true to dog breeders, it has been proven feasible in a Labrador Retriever guide dog breeding colony² where mast cell tumor risk was found to be 28% genetic in origin. Some of that genetic variation will be passed by parents to their offspring, and as the colony selected against this risk over multiple generations, the weight assigned to mast cell cancer risk within its selection index fell from 19% in 2010 to 12% in 2019², a trend consistent with declining incidence of the disease. A similar reduction in incidence of hemangiosarcoma in Golden Retrievers could be realized by working together to identify family lines least likely to pass hemangiosarcoma-causing genes to new puppies.

Background

For more than three decades, veterinary research has focused on finding an association between a specific combination of genes in the canine genome and the development of cancer. Driving this research has been the belief that identifying the root genetic cause of cancer would lead to a DNA test that could identify which newborn puppies are most at risk of developing cancer as they age. Such a simple DNA test would then be used to alter gene frequency in subsequent generations by allowing the least at risk puppies to become parents, thus leading to a reduction in incidence followed by complete elimination of cancer from the population.

While finding a DNA test for cancer risk in young puppies is a laudable goal, it is not clear that it will be achieved in the near future. Research to this point has shown that many cancers, including hemangiosarcoma, likely develop due to a complex interaction between a polygenic mode of inheritance and the local environment in which each dog lives. A polygenic mode of inheritance means that multiple locations in the canine genome determine relative genetic risk of developing cancer.

When a polygenic mode of inheritance is at play in determining a lifetime outcome, like the development of hemangiosarcoma, a long-proven method for altering gene frequency in subsequent generations is to use statistical modeling to assess risk for each member of a population. This is done by taking into account what is known about genetic relationships among individuals in the population and the individuals that have developed hemangiosarcoma. Statistical estimates of relative genetic merit for any physical measurement are known as estimated breeding values (EBVs). In humans, a similar health measure is known as a polygenic risk score, obtained from a person's family history of disease and, in recent years, from genetic differences found in their DNA.

Morris Animal Foundation Funded Study

In November 2023, the Morris Animal Foundation (MAF) funded a research study utilizing the Golden Retriever Lifetime Study (GRLS) dataset, including the DNA information. The proposal packet submitted to MAF included a letter of support for this project from the Golden Retriever Foundation.

The research team conducting the study is a collaboration of scientists with the University of Massachusetts Chan School of Medicine, the University of Connecticut, and the International Working Dog Registry. The aim of the study is to calculate EBVs describing the risk of developing hemangiosarcoma for each of the 3,044 GRLS dogs and their ancestors. Younger dogs related by pedigree to the GRLS dogs will also be included, using relationships obtained from the k9data.com database.

The statistical model used to calculate EBVs will incorporate known pedigree relationships among ancestors, mostly obtained from MAF or from publicly available records from k9data.com. The model will also include DNA information for each of the GRLS dogs, and it will model each dog's risk of developing hemangiosarcoma during its lifetime. The model will also include other factors that might contribute to variation observed across the Golden Retriever study population, like gender and year of birth.

Using Selection to Reduce Hemangiosarcoma

In a genetically reproducing animal population, gene frequency will remain constant across generations until a force operates to change it. There are only four of these forces known to exist: mutation, migration, chance, and selection. Among these, it is the force of selection that breeders use to reshape a population over time. Selection is widely used in livestock (cattle, horses, sheep, and pigs), in a growing number of freshwater and saltwater fish species, in poultry such as chickens and turkeys, and in dogs and cats.

Selection is simple in concept: Allow some young members of a species to become parents of the next generation while preventing all others from reproducing. By using this process, gene frequency in future generations can be altered, and the accuracy with which these selection decisions are made establishes the genetic makeup of the next generation.

When a young puppy is chosen at weaning as a breeder prospect, it will show no outward signs of its genetic predisposition for developing hemangiosarcoma later in life. EBVs are the only available tool for characterizing this inherent risk, preferably including information from a DNA sample obtained on every puppy. Once implemented, such a system can provide EBVs on a host of traits, in addition to an EBV that characterizes hemangiosarcoma risk for every young puppy. Without such a system, there is little hope of reducing the incidence of hemangiosarcoma among dogs of any breed that are prone to develop the disease.

What Can Be Done Now?

Because hemangiosarcoma is a late-onset disease, there has been no tool available for well-intentioned dog breeders to apply any meaningful selection pressure to reduce its incidence in future generations. This is true because most canine parents will have produced one to three litters by their 6th year of age. Those mid-life parents that do develop hemangiosarcoma will almost certainly have progeny that have already become parents, thus perpetuating the cycle over multiple generations. Without a risk assessment tool, people making young breeder selection decisions have been forced to mostly ignore the occurrence of hemangiosarcoma.

A reasonable question that many Golden Retriever breeders must be asking is: Why has the incidence of this disease increased to such an alarming level in the breed? The answer, although impossible to know for

certain, may lie in the canine genome. It is easy to imagine that some trait or traits that are highly desirable in the breed are genetically linked to the genes that predispose to developing hemangiosarcoma, meaning that the genes for both characteristics occur on the same chromosomes and are passed from parents to their offspring as a genetic package. The only tool that will change this picture among future generations of Golden Retriever puppies is to reduce gene frequency of the disease-causing alleles. Selection is the process for accomplishing this goal, but the missing key is a tool for identifying the young puppies that are at risk later in life. EBVs are a tool that can be implemented now and genomically enhanced EBVs (gEBVs) are an even better tool.

A second reasonable question to ask is: Without DNA information on young puppies, is it possible to still calculate a risk EBV? The answer is yes, but with some caveats. First, without DNA on young puppies, all puppies with the same pair of parents will have an identical risk EBV for developing hemangiosarcoma. While this is better than having no information about hemangiosarcoma risk, it is not nearly as good as having a gEBV that incorporates DNA information from each puppy. With DNA information included, the risk can then be assessed for every puppy individually. Furthermore, this risk can be obtained soon after birth, when it is first feasible to obtain a DNA sample from a young puppy.

To implement a process for calculating gEBVs for hemangiosarcoma risk requires that Golden Retriever breeders cooperate by putting data into one centralized database. The data required includes both accurate pedigrees and complete hemangiosarcoma diagnosis information. If the approximate or exact date when the condition was discovered is supplied, then the age at which hemangiosarcoma developed can be included in the statistical model. This will enable searching for genetic differences among dogs that never develop the disease, those that develop the disease at 6-7 years of age, and those that develop the disease after 7 years of age.

So, how can dog breeders gain access to the database tools required to implement EBVs and gEBVs? For Swedish or Finnish dog breeders of many breeds, for German Shepherd breeders in Germany, and for UK dog breeders who belong to the Kennel Club, EBVs on some phenotypes are routinely made available to their members. For most dog breeders based in North America, the only option is the International Working Dog Registry.

International Working Dog Registry (IWDR)

IWDR is a world-accessible database widely used by organizations that breed and train working dogs. With about 120 subscribing organizations, it is used by government agencies that breed and train dogs for scent detection work, for police and military work, and by many guide and service dog organizations.

Drawing on more than five decades of experience developing record-keeping systems for two large US-based guide dog organizations — The Seeing Eye and Guiding Eyes for the Blind — IWDR is a comprehensive record-keeping system for canine breeding. In 2015, IWDR was given to the International Working Dog Association (IWDA). As a 501(c)(3) non-profit organization based in the USA, IWDA's primary mission is "... to support breeding, rearing and training of working dogs and breed clubs through education, facilitating collaboration, and discovery."

Commonly used functionality built into IWDR includes the storage of all medical diagnoses common across working dogs, such as orthopedic, ophthalmic, and cardiac conditions. All medical procedures a dog receives may also be stored. Aspects of behavior are captured using the Behavior Checklist. End users are responsible for entering data on dogs they own, and those data are held private by each breeder or organization that owns the dog, unless they choose to share it with someone else.

The medical diagnoses and the behavior checklist data are summarized weekly into EBVs for 4 health traits (two measures of hip quality, one of elbow quality, and one of skin quality) and 11 aspects of behavior. The 15 EBVs are then summarized each week into an overall index that ranks each dog on relative genetic merit. The weights attached to each trait are determined by how likely the recorded conditions are to prevent a dog from doing the work for which it was bred.

Literature Cited

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