

# The Genetics of Canine Cancer: A Practical Summary of the Peer-Reviewed Literature

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## Introduction

Cancer is now the leading cause of death in many purebred dogs, and its incidence varies enormously by breed. Some cancers affect a large share of dogs in one breed while remaining rare in others. This wide variation between breeds is itself evidence of a genetic component. If cancer risk were purely a matter of chance or environment, breed would not matter nearly as much as it does.

Over the past two decades, genome-wide association studies (GWAS) have begun to identify the specific chromosomal regions responsible for this inherited risk across several canine cancers. This document summarizes what the peer-reviewed literature currently shows about the genetics of five of the most consequential canine cancers: hemangiosarcoma, mast cell tumors, lymphoma, osteosarcoma, and histiocytic sarcoma. It also describes a practical, already-proven method, estimated breeding values (EBVs), for using this genetic information to reduce cancer incidence through selection.

## How Cancer Risk Is Inherited

For more than three decades, veterinary research has focused on finding associations between genes in the canine genome and the development of cancer, in the hope that a DNA test could identify at-risk puppies at birth. Research across the cancers summarized in this document has consistently pointed to the same underlying architecture: cancer risk is influenced by many genes acting together, not by any single gene. When a trait works this way, it is called polygenic, or oligogenic when only a handful of genes are involved.

When a polygenic mode of inheritance is at play, a long-proven method for altering gene frequency in future generations is to use statistical modeling to assess each individual's genetic risk. This approach is based on the genetic relationships among individuals in a population and on which of those individuals have developed the disease. These statistical estimates of relative genetic merit are called estimated breeding values (EBVs). In humans, a similar health measure is known as a polygenic risk score, calculated from a person's family history of disease and, increasingly, from genetic differences found in their DNA.

Genomically enhanced EBVs, or gEBVs, incorporate DNA information directly and are more accurate than EBVs based on pedigree alone. Without DNA on a puppy, all puppies from the same two parents share an identical EBV. With DNA information, each puppy's own genetic makeup can be assessed individually, as soon as it is feasible to obtain a DNA sample.

The individual genes that act as modifiers or enhancers within this polygenic architecture can, to some extent, be identified using standard linear modeling techniques applied to SNP array data. This is the statistical basis for a gEBV. Building an accurate gEBV requires genotyping many dogs with a modern SNP array and tracking their health outcomes over their lifetimes. One increasingly practical way to gather this genomic data is low-pass sequencing followed by imputation to a full genome sequence, an approach that both surveys where a breed's genome varies most and supplies the raw material needed to discover new genome locations linked to specific cancers. Realistically, this kind of work requires data from at least several tens of thousands of dogs within a breed before a single dog's DNA sample could reliably predict its cancer risk as it ages.

## Hemangiosarcoma

Hemangiosarcoma is one of the most dreaded and deadly of all canine cancers, and Golden Retrievers are especially prone to it. Cornell University's Baker Institute estimates that 1 in 5 Golden Retrievers will be diagnosed with hemangiosarcoma in their lifetime<sup>1</sup>. It is often a silent killer, undetected until just days before death.

In 2015, a genome-wide association study of Golden Retrievers identified two loci on chromosome 5 shared between hemangiosarcoma and B-cell lymphoma<sup>2</sup>. Dogs affected by either cancer were analyzed together as a single combined phenotype, since both cancers appear to share much of their genetic risk. The two loci together account for about 20% of the risk of developing these cancers, and all chromosomes combined account for about 43% of the phenotype's variance<sup>2</sup>, indicating that many additional, still-unidentified loci also contribute to risk.

In November 2023, the Morris Animal Foundation funded a follow-on study, still underway, that aims to calculate EBVs describing hemangiosarcoma risk for each of the 3,044 dogs enrolled in the Golden Retriever Lifetime Study (GRLS) and their ancestors. The research team is a collaboration of scientists from the University of Massachusetts Chan School of Medicine, the University of Connecticut, and the International Working Dog Registry (IWDR). Younger dogs related by pedigree to the GRLS dogs are also being included, using relationships obtained from the k9data.com database, and the resulting statistical model will account for pedigree relationships, DNA information, and other contributing factors such as gender and year of birth.

## Mast Cell Tumors

While a validated DNA test for hemangiosarcoma risk does not yet exist, a comparable approach has already succeeded for a different cancer, mast cell tumors. This was demonstrated in a Labrador Retriever guide dog breeding colony, where the age of onset of mast cell tumors was found to be 28% heritable<sup>3</sup>. 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 2019, with some fluctuation in between<sup>3</sup>. This progress was made using pedigree-based EBVs alone. No DNA test for mast cell tumor risk was available at the time. This example demonstrates that EBV-based selection can be used to actively manage a polygenic cancer's priority within a real breeding program, not just in theory. It also shows that genetic progress against a cancer does not have to wait for a DNA test to become available.

## Lymphoma

Lymphoma is another cancer with a well-documented but complex genetic basis. The same 2015 Golden Retriever GWAS that identified hemangiosarcoma risk loci found those loci shared with B-cell lymphoma<sup>2</sup>. A larger four-breed study of Bernese Mountain Dogs, Golden Retrievers, Flat-Coated Retrievers, and Rottweilers found that these hematopoietic cancer risks are driven by the additive effect of several risk haplotypes, rather than any single gene<sup>4</sup>. In Bullmastiffs, a separate GWAS identified two additional risk regions, on chromosomes 13 and 33, reflecting a comparably polygenic background that appears distinct from the loci found in other breeds<sup>5</sup>.

Breed predisposition to lymphoma also varies across countries. A multi-country European study found that Golden Retrievers showed elevated lymphoma risk in the United Kingdom, but not across the wider European population studied. Boxers, in contrast, showed consistently elevated risk across France, Italy, and the UK<sup>6</sup>. These findings suggest that genetic risk factors for lymphoma may differ between regional or national breeding populations of the same breed. This underscores the importance of collecting data from

the specific population a breeder is working within, rather than assuming a risk estimate from one country or lineage automatically applies to another.

No published study isolates a heritability estimate for lymphoma cleanly from the other hematopoietic cancers with which it shares genetic risk<sup>2,4</sup>. This is a genuine gap in the current literature, not a reflection of lymphoma being any less genetic than the other cancers discussed here.

## Osteosarcoma

Osteosarcoma, the most common bone cancer in dogs, disproportionately affects large and giant breeds. A landmark 2013 GWAS across Greyhounds, Rottweilers, and Irish Wolfhounds identified 33 inherited risk loci that together explain 55% to 85% of the phenotype's variance. As with other cancers discussed here, wide variation among breeds was identified: 57% in Greyhounds, 85% in Rottweilers, and 53% in Irish Wolfhounds<sup>7</sup>. The strongest single association, in Greyhounds, lies just upstream of the CDKN2A/B gene region, a region also implicated in canine osteosarcoma tumor tissue itself and as discussed below, in histiocytic sarcoma risk in an entirely different set of breeds.

Pedigree-based heritability estimates for osteosarcoma risk in two additional breeds are similarly high: 0.65 in Irish Wolfhounds<sup>8</sup> and 0.69 in Scottish Deerhounds<sup>9</sup>. A detailed segregation analysis of a large Scottish Deerhound pedigree, comprising 1,057 dogs and roughly 21% of the breed's AKC registrations over the preceding 20 years, found strong statistical support for a single dominant-acting major gene that raises lifetime risk roughly 15-fold, from a baseline of about 5% to about 75%<sup>9</sup>. No molecular variant has been identified; this is a statistical inference from pedigree and segregation data, not a validated DNA marker. The study estimated the risk allele's frequency in this sample at about 12% to 13%, but the authors caution that this figure is likely higher than the allele's true frequency in the wider Deerhound population, since the dogs studied were deliberately sampled by extending pedigrees outward from five affected dogs, a design that enriches for carriers<sup>9</sup>. The same analysis found that gender significantly modifies penetrance, with estimated lifetime risk substantially higher in females, 90% to 99%, than in males, 72% to 77%, though the authors note this gap could also reflect higher early mortality among male carriers from unrelated causes rather than a true biological effect<sup>9</sup>. A smaller 2017 follow-up study, examining two more recent Deerhound family cohorts of 56 and 57 dogs, reported findings that, despite considerably less statistical power than the original analysis, largely confirm its conclusions<sup>18</sup>. This remains a notably simpler genetic picture than the many-gene architecture found in most other breeds and cancers discussed in this document, though a contributing role for additional modifying genes cannot be ruled out.

A more recent GWAS in Leonbergers found a genome-wide SNP heritability of 20.6%, and independently confirmed the CDKN2A/B locus as a major risk factor in that breed as well<sup>10</sup>. A 2019 reanalysis of the original three-breed data concluded that polygenic osteosarcoma risk can, in some dogs who inherit many risk alleles at once, reach a magnitude comparable to a single-gene, or Mendelian, disorder<sup>11</sup>.

A large UK veterinary-record study found that Scottish Deerhounds, Leonbergers, Great Danes, and Rottweilers all carry substantially elevated odds of osteosarcoma compared to crossbred dogs, with odds ratios ranging from about 27-fold in Rottweilers to as high as 118-fold in Scottish Deerhounds<sup>12</sup>.

## Histiocytic Sarcoma

Histiocytic sarcoma is most strongly associated with Bernese Mountain Dogs and Flat-Coated Retrievers, and it is unusually lethal. Peer-reviewed studies estimate it accounts for about 15% of all Bernese Mountain Dog deaths and about 14% of Flat-Coated Retriever deaths<sup>13</sup>, with lifetime risk in Bernese Mountain Dogs reported as high as 25%<sup>14</sup>.

A detailed 2009 segregation analysis of Bernese Mountain Dog families tested, and ruled out, a fully recessive single-gene model, instead favoring an oligogenic model involving a small number of genes acting together, building on earlier work that had already pointed toward a polygenic mode of inheritance for the disease<sup>15</sup>. Consistent with that conclusion, a 2021 GWAS of four breeds found that a handful of loci, including a region overlapping CDKN2A on chromosome 11 already implicated in osteosarcoma, together explain at least 61.8% of the phenotype's variance in Bernese Mountain Dogs, Rottweilers, and Flat-Coated Retrievers, and dogs carrying most of the risk alleles at these loci face more than five times the odds of developing the disease<sup>4</sup>. A separate study of Flat-Coated Retrievers, in which 20% of the breed develops histiocytic sarcoma, found two different risk loci together explaining 35% to 37% of the phenotype's variance<sup>16</sup>. An earlier, more targeted study had already found a single haplotype near the MTAP-CDKN2A region present in 96% of affected Bernese Mountain Dogs studied, a striking concentration of risk around one genomic neighborhood<sup>17</sup>.

### What These Findings Have in Common

Taken together, these five cancers illustrate a consistent pattern in canine cancer genetics. First, polygenic or oligogenic inheritance, risk shaped by several to many genes acting together, is the norm rather than the exception. The Scottish Deerhound's single dominant-acting osteosarcoma major gene is a notable exception, not the rule. Second, the same genomic neighborhoods keep recurring across unrelated cancers and unrelated breeds. The CDKN2A/B region on chromosome 11 has been implicated in both osteosarcoma and histiocytic sarcoma, and the chromosome 5 loci shared by hemangiosarcoma and lymphoma in Golden Retrievers overlap with a locus also found in histiocytic sarcoma in Flat-Coated Retrievers and Bernese Mountain Dogs. This overlap suggests that a relatively small number of biological pathways may govern cancer susceptibility across many different canine cancers and breeds. Third, no validated DNA test yet exists that can, by itself, reliably identify at-risk puppies for any of these cancers at birth. What does exist, and has already worked, is statistical selection using EBVs built from pedigree and diagnosis data, as demonstrated by the mast cell tumor result described above.

The Deerhound case raises a further question. Why would a single major gene be statistically detectable in this breed but not in Greyhounds, Rottweilers, Irish Wolfhounds, or Leonbergers, where osteosarcoma risk instead appears highly polygenic? Effective population size may be part of the answer. The Deerhound population studied showed a measurable degree of inbreeding, consistent with the breed's small numbers and descent from a limited group of founding imports. The original researchers noted that inbreeding tends to concentrate genetic variance onto fewer loci, a process they called trait "Mendelization."<sup>9</sup> This can make a major gene easier to detect statistically, even when it is not biologically unique to the breed. A similar risk variant, potentially acting through the same CDKN2A/B pathway already implicated in several other breeds, could exist much more broadly across the species. In a breed with a larger, more genetically diverse population, that same variant would likely remain at low frequency and blend into the polygenic background already described above, rather than standing out as a single dominant gene. This is an interpretation, not a proven fact. No molecular variant was ever identified in the Deerhound study, so the underlying gene cannot yet be directly compared across breeds.

### A Practical Path Forward: EBVs and IWDR

Because most of these cancers are late-onset diseases, there has been no tool available for well-intentioned dog breeders to apply meaningful selection pressure against them. Most canine parents will have produced one to three litters by their sixth year of age, so parents who go on to develop cancer later in life will often already have progeny that have themselves become parents, perpetuating elevated risk across generations before anyone notices a problem.

EBVs, and gEBVs where DNA information is available, are tools that can be implemented now, without waiting for a single-gene DNA test that may never arrive for most of these polygenic cancers. Calculating them requires that breeders cooperate by contributing pedigree records and diagnosis information to one centralized database. For dog breeders world-wide, the [International Working Dog Registry](#) (IWDR) is now a viable option.

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, IWDR is a comprehensive record-keeping system for canine breeding, which also includes the routine weekly updating of EBVs. As genomic data becomes available on hundreds or thousands of individual dogs, gEBVs will also begin to appear.

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. The medical diagnoses and behavioral data are summarized weekly into EBVs for multiple health and behavior traits. Individual trait EBVs are then summarized into an overall index that ranks each dog on relative genetic merit. As data on more cancer diagnoses and pedigrees accumulate in centralized systems like IWDR, the same statistical approach that has already reduced mast cell tumor risk in one breeding colony can be extended to hemangiosarcoma, lymphoma, osteosarcoma, and histiocytic sarcoma as well.

### Heritability and Genetic Findings at a Glance

| Cancer              | Breed(s) Studied                                                                  | Heritability / Variance Explained                                                                                | Key Loci                                          | Ref             |
|---------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|-----------------|
| Hemangiosarcoma     | Golden Retriever                                                                  | ~20% (2 loci); ~43% all autosomes (combined with lymphoma)                                                       | Chromosome 5 (~29, ~33 Mb)                        | 2               |
| Mast Cell Tumors    | Labrador Retriever (guide dog colony)                                             | 28% heritable (age of onset)                                                                                     | Not locus-mapped in this study                    | 3               |
| Lymphoma            | Golden Retriever, Bernese Mtn Dog, Rottweiler, Flat-Coated Retriever, Bullmastiff | Shares loci with hemangiosarcoma/histiocytic sarcoma; no isolated estimate published                             | Chromosome 5 (shared); CFA13, CFA33 (Bullmastiff) | 2, 4, 5         |
| Osteosarcoma        | Greyhound, Rottweiler, Irish Wolfhound, Scottish Deerhound, Leonberger            | 53–85% (3-breed GWAS); $h^2=0.65$ (Irish Wolfhound); $h^2=0.69$ (Deerhound); $h^2\text{SNP}=20.6\%$ (Leonberger) | CDKN2A/B region (chromosome 11)                   | 7, 8, 9, 10, 18 |
| Histiocytic Sarcoma | Bernese Mountain Dog, Flat-Coated Retriever, Rottweiler                           | $\geq 61.8\%$ (4-breed GWAS); 35–37% (Flat-Coated Retriever only)                                                | CDKN2A region (Chr 11); Chr 5, 14, 19             | 4, 15, 16, 17   |

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