



## The Golden Retriever Club of America, Inc.

### Advances in Golden Retriever Health Research: 2012 Update

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Wouldn't it be nice if we had a tool to help us improve the odds that our puppies will not get hemangiosarcoma and lymphosarcoma early in life? Could we have new cancer treatments that cause fewer side-effects or are more effective than traditional cancer chemotherapy? How about a genetic test that can identify carriers of subvalvular aortic stenosis (SAS)? This year, the Golden Retriever community has particularly benefited from canine health research. Recent discoveries in the field of canine health research suggest that such tests and treatments may indeed be possible in the next few years.

#### **Increased Cancer Risk Can Be Inherited from the Parent(s)**

A huge milestone was reached this year when a specific region of the canine genome involving the MTAP-CDKN2A locus was identified as a major susceptibility factor for histiocytic sarcoma in the Bernese Mountain Dog.<sup>1</sup> Histiocytic sarcoma is estimated to affect between 15 and 25% of Bernese Mountain Dogs. An inherited change in the MTAP-CDKN2A region is present in 96% of the Bernese Mountain Dogs with histiocytic sarcoma and involves a genetic region that is the canine equivalent of a region of the human genome that has been implicated in the development of cancer.<sup>1</sup> We do not yet know if this same inherited genetic change will be a susceptibility factor in Golden Retrievers who develop histiocytic sarcoma.

In the Golden Retriever, research into inherited factors that increase cancer susceptibility have focused on the two major life-shortening cancers which affect our breed, hemangiosarcoma and lymphosarcoma. With these cancers, current research indicates that inherited susceptibility may involve more than a single gene. Indeed, several inherited genes may increase the risk that a Golden Retriever will develop hemangiosarcoma.<sup>2, 3</sup> Similar discoveries are being made for lymphosarcoma (lymphoma).<sup>4</sup> Once cancer susceptibility genes are identified, it is very possible that we will begin to have tests that can help guide us in making breeding decisions that reduce the risk of cancer in Golden Retrievers. Because several genes appear to be involved, this will not be as simple as not breeding the dogs that have these genes. It is likely that these genetic tests will be a bit like a chemistry blood panel, except this would be a pre-breeding panel that would indicate that a Golden Retriever is at a higher than normal risk of producing puppies with a specific cancer, for example hemangiosarcoma, if bred to a Golden Retriever with certain test results on a genetic panel. Such tests would help breeders select mates that will be the best combinations for producing healthy puppies. Thus, preliminary findings do indeed indicate that some genes and gene combinations

increase the risk for early hemangiosarcoma and that other genes decrease that risk. That means that continued research may give us the tools to produce healthier Golden Retrievers in the future.

### **Genetic Changes that Cause Cancer are Potential Targets for New Therapies**

In addition to inherited changes passed from the sire and dam to their puppies, researchers are identifying genetic changes that occur within the cancer cells themselves to change those cells from normal well-behaved cells into aggressive cancer cells. In some cases, the genetic changes that occur in Golden Retriever hemangiosarcoma and lymphosarcoma cells are different than in those same cancers in different dog breeds.<sup>5, 6</sup> New treatment strategies based upon these findings are currently being investigated and hold the promise of potential new classes of therapies that are less toxic than traditional cancer therapy.<sup>7,8,9</sup> Because these therapies are being developed by researchers who understand the changes in cancers of Golden Retrievers some of these may be particularly effective for the hemangiosarcomas and lymphosarcomas of Golden Retrievers.<sup>7,8</sup> Many of the follow-up studies on new treatments and tests are being conducted as part of the MADGiC project, a project jointly funded by the Morris Animal Foundation and the Golden Retriever Foundation.<sup>9</sup> Additional studies will be conducted as part of a new study that will be funded by the Golden Retriever Foundation and the AKC Canine Health Foundation.<sup>10</sup>

### **The Environment We Provide for Our Dogs Can Influence Their Health**

Several studies have recently identified environment factors that can influence Golden Retriever health. A paper published late last year showed that more than 25% of the spleens from dogs with hemangiosarcoma had evidence of *Bartonella sp* infection, a vector-borne disease.<sup>11</sup> A previous prospective epidemiology study indicated that regular treatment with products that kill ticks, decreased the risk of lymphosarcoma development.<sup>12</sup> These studies certainly suggest that more study is needed into the relationship between vector-borne diseases and cancer in dogs and are a reminder that it is important to keep Golden Retrievers free from parasites.

A major new study will provide a whole lot of additional useful information. The Morris Animal Foundation has initiated a very large epidemiology study that will enroll young Golden Retrievers that will follow Golden Retrievers for a lifetime to identify environmental factors that affect the health of our dogs.<sup>13</sup> GRCA members are encouraged to participate in this study through enrollment of Golden Retrievers who are less than 2 years old.

**Updated health information is available from leading dog health organizations, including the Golden Retriever Foundation, Morris Animal Foundation, AKC Canine Health Foundation, and the Orthopedic Foundation for Animals and GRCA.**

Major dog health websites now contain a wealth of information for dog owners. For example, at <http://www.akcchf.libsyn.com/>, the AKC Canine Health Foundation (CHF) has online podcasts where leading dog disease researchers discuss their studies. Searchable information on dog health studies is available on the Morris Animal Foundation (<http://www.morrisanimalfoundation.org/our-research/studies.html>) and CHF (<http://www.akcchf.org/research/funded-research/>). The Golden Retriever Foundation website has been updated (<http://www.goldenretrieverfoundation.org/>). New health information is continually added to the health section of the GRCA website

<http://www.grca.org/health/index.html>. The Orthopedic Foundation for Animals website includes the Golden Retriever health survey [http://www.offa.org/surveys/survey\\_golden.html](http://www.offa.org/surveys/survey_golden.html) which currently contains owner-reported information on 3475 Golden Retrievers.

## New Tests are Tools that Can Improve the Odds of Healthy Puppies and Maintain a Diverse Gene Pool

The progress in Golden Retriever health involves many conditions in addition to cancer. A recent 2012 paper describes the clinical presentation of Subvalvular Aortic Stenosis (SAS) in the Golden Retriever.<sup>14</sup> This same paper goes on to demonstrate that two clinically normal Golden Retrievers with normal aortic flow rates can produce multiple puppies with SAS and that affected Golden Retrievers can produce affected puppies. This clearly demonstrates the inheritability of SAS in Golden Retrievers and the importance of pre-breeding cardiology exams. Since the research group that conducted this study has been a leader in developing genetic tests for canine heart disease, we are all very hopeful that a genetic test for SAS is not too far away.

In addition, this year full length peer-reviewed scientific papers were published that described the genes that cause Golden Retriever ichthyosis and one form of Golden Retriever progressive retinal atrophy, GR\_PRA1.<sup>15, 16</sup> These two papers describe details of the research that lead to two new tests for genetic diseases in Golden Retrievers. The Health and Genetics Committee has an article on the use of these tests which is available online on the Health section of the GRCA website [www.grca.org](http://www.grca.org). Importantly, ichthyosis and GR-PRA1 are recessive conditions and disease is only seen when an abnormal gene is inherited from both the sire and the dam. That article provides suggestions on how carriers can be bred without producing affected puppies. While it might seem reasonable to just not use carriers as breeding animals, selective use of carriers in conjunction with testing helps to maintain a diverse gene pool. That is important because *all dogs are believed to carry some harmful recessive genes*.

Indeed, recent studies are showing us why we humans and our dogs must each carry these harmful genes. Several recent papers in the human literature indicate a shockingly high rate of functionally important changes in the genes of children that are not inherited from their parents.<sup>17</sup> These changes are due to mutation(s) in one or more genes. The frequency of these mutations goes up with the age of the father. The good news is 1) most of these mutations simply create a small genetic difference in the child that is fully compatible with good health, and 2) the odds of having an important change in any specific gene remains extraordinarily small. However, in people, these new mutations appear to be important in autism as well as in some newly described conditions with multiple birth defects. So, if dogs have a similar rate of change in their genes, we can all imagine that over many generations, important mutations will occur in one or more genes. If the effect is dominant and lethal the situation ends there because the dog dies before offspring are produced. However, dogs with a single copy of a harmful but recessive mutation appear healthy and can pass that gene down to the next generation. Thus, the science is beginning to show us how something happens that we all know must be true – no matter how excellent any individual Golden Retriever may be, he/she carries some deleterious genes. The recessive deleterious genes only cause disease when a dog inherits the same deleterious gene from each parent. As mentioned in the section on cancer, some inherited diseases are polygenic, which means that a combination of two or more different genes interact to cause disease. Recessive and polygenic inherited conditions tend to be seen where the gene pool is limited, because the same dogs appear multiple times in the pedigree. That situation increases the odds that each parent may have inherited the same deleterious gene from a common

ancestor and a puppy can receive that gene from each parent. This is why we see patterns of inherited disease (such as subvalvular aortic stenosis) in purebred dogs where the gene pool is limited. However, as long as we have a large enough gene pool, when genetic tests become available so that we can test our dogs to see which genetic diseases they are carrying, we will be able to avoid those breedings that are likely to produce affected puppies. That is why we need to keep diversity in our gene pool for the health of the breed.

The Health and Genetics Committee is looking forward to major research findings in the next couple of years. We are just beginning to benefit from years of research into canine health conditions. The GRCA Health Committee is looking forward to keeping the membership updated as new research findings unfold and we have new tools that can be used to improve the health of our dogs.

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