

# 39 & ME

**"MY DOG TOOK THE DNA TEST AND WAS CLEARED OF EVERY GENETIC DISORDER," BEGAN THE FACEBOOK POST. "BUT NOW MY VET SAYS HE HAS CARDIOMYOPATHY. SHOULD I FIND A DIFFERENT VET? OR COULD THE LAB HAVE MADE A MISTAKE? AND IF SO, SHOULDN'T I BE ABLE TO GET MY MONEY BACK?"**

BY CAROLINE COILE

And herein lies one problem with genetic testing: dog owners, and even dog breeders, too often don't know what it means. And it's not really their fault. Thirty years ago all we had to know was the difference between genotype and phenotype, and dominant and recessive. We thought that if we could identify every carrier through test breedings, and remove them from the gene pool, we could purge our dogs of hereditary illness. We fantasized about DNA tests that might one day allow us to actually "see" a dog's recessive genes. And when that first test happened, and then another, and another, breeders set out to do just that. They removed every carrier they could identify, and in so doing created a genetic bottleneck that reduce their breed's genetic diversity and allowed other heretofore unknown or insignificant diseases to come to the forefront. With more knowledge of our dog's genes came the need for more knowledge on how to use this knowledge.

Now we have hundreds of DNA tests, and predictably, even more misunderstanding when it comes to their use. Which is why the hot-off-the-press AKC Canine Health Foundation's white paper, *Review of the State of Genetic Testing—a Living Resource*, is something everyone who has ever even uttered the phrase "DNA test" should read. And since it's free, and online at [www.akcchf.org/educational-resources/library/articles/CANINE\\_GENETIC\\_TESTING\\_07-28-2020\\_FINAL\\_with\\_links.pdf](http://www.akcchf.org/educational-resources/library/articles/CANINE_GENETIC_TESTING_07-28-2020_FINAL_with_links.pdf), you can read it while you're waiting for groups, or waiting for your next progesterone test results. And it's written so that no matter what your level of expertise, you can start at the basics and work up, or skip around and just check out the newer parts.

As for our friend asking the questions, she could have read several sections concerning genetic tests and breed specificity. Among other things, she would have found out while several companies offer multiplex tests that will test for the presence of alleles associated with as many as somewhere around 175 disorders in certain breeds, they have limitations that far too many dog owners don't understand:

- Far more than 175 (or 200, or 300) genetic diseases exist in dogs. Being clear of 175 of them doesn't mean your dog is "cleared of every genetic disorder." It's just cleared of every disorder on that test panel.
- Many disorders are probably polygenic in nature (that basic was explained earlier in the paper, but basically it means a trait depends on the interaction of alleles at several loci), and some have variable penetrance or expressivity (again,

explained elsewhere, but basically variable penetrance means that the trait doesn't always manifest, and variable expressivity means the trait may manifest to different degrees), and either may depend on alleles at other loci or environmental factors. Despite a vast amount of research on hip dysplasia, for example, we still have no DNA test for it because it's not a simple case of Mendelian inheritance.

- An allele that causes a disease in one breed may not cause it in another. For example, the presence of an allele at a different locus may also be needed for the disease to manifest. That's the case for one of the current witch hunts, the "allele for degenerative myelopathy" (DM). In several breeds, dogs with two mutant copies in the SOD1 gene are at increased risk of DM. Yet in other breeds these mutant copies have no effect on DM susceptibility, probably because another as yet unidentified mutant allele must also be present. The homozygous SOD1 mutation is necessary, but not sufficient, for DM, yet people are having their dogs tested for the SOD1 mutation in breeds in which DM never occurs, and probably can't occur. Then they're either removing dogs from the breeding population or bragging that they are clear, based on a test that is meaningless for their breed. More than 120 breeds carry this alleged DM allele; maybe 30-some actually get DM.
- A disease that looks phenotypically similar may be caused by different mutations. For example, progressive retinal atrophy may appear clinically identical in two different breeds, yet not be genetically related. Testing clear of the gene that causes progressive retinal atrophy (PRA) in Irish Setters doesn't mean your Irish Red and White Setter won't get a form of PRA known only in that breed.
- Not all labs, and not all tests, are created equal. Some are based on only a handful of dogs and await further refinement as more dogs are tested. Some may be rushed to market simply because the company is profit-driven and can't afford to wait and get it right.

Another person wrote in: "My dog tested positive for DM! Now what?" Well...it depends.

- First, consider that the presence of the "DM gene" only matters if your breed is one that gets DM. The same is true for any deleterious gene your dog tests positive for.
- Removing a dog from the gene pool because he has a deleterious allele is like, well, removing you from the gene pool

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because you have one. Because it's estimated that every single person is carrying at least one or two lethal alleles.

- Don't assume because a DNA test says your dog is at risk for a condition that he really is. "A dog that shows the presence of a disease mutation does not necessarily mean the dog will show clinical signs during its life; owners should recognize that the genetic test results are not clinical diagnoses," states the white paper.
- Being "at risk" isn't the same as "gonna get." Understanding the differences between a DNA gene test, which identifies the actual mutation responsible for a disorder, and a DNA linkage test, which identifies a gene that is so close to the actual gene on the chromosome that it acts as a marker for the actual gene, is important here. One has a certainty of being there, whereas the other only a probability, albeit high. And again, understanding that expressivity, penetrance and environmental factors play a role in whether a gene actually manifests as the disease and impacts a dog's quality of life is important.
- Knowing a dog has a risk for a certain disease can be helpful in diagnosing that disease early, or in considering it as a cause for a current condition. However, it can also be detrimental to a diagnosis if the owner or veterinarian assumes it's the cause to the exclusion of other possibilities. "If a dog's test results indicate it has a predisposition for a particular disease, and the clinical signs exhibited are consistent with that disease but those signs actually reflect a different disease in that dog, jumping to the wrong diagnosis may hinder appropriate treatment of the true underlying disease." For example, a dog that loses control of its rear legs and carries two copies of the "DM gene" may just be assumed to have DM, when the real cause might have been disk disease or something else treatable.

And another: "My dog tested positive for PRA. Of course I'm having him neutered, and I'm having every relative I can find tested and, if positive, neutered as well." Whoa! Not every breed, and not every disorder, can be treated the same.

- "If the mutant allele is not abundant in the population, and the disorder is harmful, the goal should be to avoid producing affected offspring or carriers and spreading the disease allele in the population." So yes, if yours is one of the rare dogs in your breed to test positive for PRA (and you know for sure that the DNA test predicts clinical PRA in your breed) you very well should consider neutering affected dogs and possibly carriers. Your goal is to avoid dispersing the allele further into the population. You could, however, breed a carrier to a clear and breed on only from clears. In this way you "nip it in the bud" without giving up the other genes your line possesses. The authors further explain that in some cases, especially in breeds with small populations and a limited gene pool, breeding affecteds may be advisable as long as they are bred to clears. This would produce 100% carriers that could then be used as just described for the next generation.
- If the disorder is widespread in a breed, then eliminating all dogs with the mutant allele might decimate the genetic di-

versity of that breed, resulting in proliferation of other possibly even worse disorders. "Wholesale elimination of dogs from the breeding pool based upon a single test result can irreparably harm the entire breed by decreasing the gene pool or increasing the prevalence of other disease alleles that lack testing schemes."

*"My dog tested positive at Lab A but negative at Lab B... What's going on?"*

Do a Google search for "Dog DNA" and you won't find much actual information about the topic. Instead you'll get page after page of advertisements from company after company pushing genetic tests for dogs. The problem is there's no oversight. Anyone can start a dog DNA testing lab and start collecting samples and sending out results. Each lab has its own proprietary formulas for determining ancestry, for example, just as human ancestry labs do. And as with human labs, analyses of dog ancestry have often yielded similar but somewhat different ancestry estimates. It's possible some differences exist with disease testing as well. *The Harmonization of Genetic Testing for Dogs* ([www.dogwellnet.com/ctp/](http://www.dogwellnet.com/ctp/)) offers a compilation of labs that have voluntarily submitted to meet certain standards.

We've come a very long way in a very short time when it comes to DNA testing, and we're slated to progress at an even more rapid rate in years to come. The paper concludes:

"Genetic testing in dogs will likely follow the steps of human genetic testing protocols. Over the past decade, single-gene tests have given room to multi-gene or panel testing. In humans, panel testing involves the testing of multiple genes associated with a common genetic disorder, such as breast cancer or diabetes. Similarly, panel testing in dogs will likely evolve to the testing of genes behind a specific disorder or breed specific genetic test panels that will assess only breed-relevant disorders. As complex disorders are studied in dogs, and the genetic susceptibility markers are uncovered, genetic panel testing will also include determination of polygenic risk scores for specific conditions, meaning the amount of risk conferred by a group of genetic susceptibility variants underlying specific complex disorders, similar to what is done in humans. Application of statistical network analyses to quantify risk have already been proposed for use in genetic counseling for dogs. Many canine studies have now shown that certain MHC/DLA genes confer risk to autoimmune disease, such as DMS, type 1 diabetes, symmetrical lupoid onychodystrophy, lymphocytic thyroiditis (hypothyroidism) and Addison's disease, among others. Further studies into the MHC/DLA class II haplotypes may clarify their effect on health and disease such that they can be incorporated into some of the multi-gene panels and in selective breeding. Broad-range SNP panels may still be used in the future, but with a different purpose. Specific multiplex panels may use targeted SNPs distributed through the entire genome with a focus on providing genomic estimated breeding values to assess the likelihood of a dog passing on particular complex traits to its puppies. However, this will require a great many dogs with comprehensive phenotyping across varied environments and across breeds to obtain the accuracy in prediction necessary before such tests can be deployed."