My take on RR IVA

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Introduction

I wrote this review of the Rhodesian Ridgeback Inherited Ventricular Arrhythmia ("RR IVA") research and NCSU DNA test for the benefit of concerned Rhodesian Ridgeback breeders who may not have the background or the time to review and digest what has been published in both the scientific literature and on social media about the subject. My reason for doing this is that I think many in the RR community are making breeding decisions that may not be in the best long-term interests of the breed.

Breeders have flocked to use this test, thinking that the results will provide guidance for future breeding decisions. However, little information has been provided about how the test was devised or what the test results actually mean. Furthermore, comparison of DNA test results with actual arrhythmia as measured by ambulatory electrocardiogram for more than 120 Ridgebacks between 5 and 36 months of age has demonstrated that the DNA test has no predictive value.

Background

"RR IVA" means "Rhodesian Ridgeback Inherited Ventricular Arrhythmia." The name was first applied by Dr. Kathryn Meurs of the College of Veterinary Medicine at North Carolina State University.(1) Dr. Meurs was approached in 2014 by a breeder who reported four instances of sudden death of young Rhodesian Ridgebacks between 7 and 12 months of age, with no apparent cause (hereinafter "Sudden Death Dogs"). The four dogs were closely related, including two littermates, and this alone is strong evidence for a hereditary cause behind the tragic deaths found in this RR family. Dr. Meurs and her coworkers collected pedigree information for the deceased dogs and examined 21 closely related dogs, including littermates and parents when available. A substantial number of these closely related dogs displayed a particular cardiac arrhythmia, and it was reasonable to hypothesize that the Sudden Death Dogs likely also had this arrhythmia and that this was related to the sudden death.

Before going further, I will briefly describe what is meant by arrhythmia and how arrhythmia is detected and quantitated. 'The heartbeat is normally controlled by the electrical system of the heart, . . . [which] consists of the sinoatrial (SA) node, the atrioventricular (AV) node and special tissues in the ventricles that conduct electricity."(2) "Arrhythmias are abnormalities of the heartbeat. There are several types of arrhythmia, and they are classified by . . . where they begin in the heart (the atria, AV node, or the ventricles). . . . . Generally speaking, . . . those that come from the ventricles are called ventricular arrhythmias."(3)

The type of arrhythmia that is the focus in RR IVA manifests itself by numerous premature ventricular contractions (PVCs) or sometimes ventricular premature complexes (VPCs, ref. **1**). PVCs are heartbeats that occur earlier than they should in the normal heart rhythm. They are relatively common, both in people and in dogs. A juvenile Rhodesian Ridgeback has on the order of 100,000 heartbeats in 24 hours and the occurrence of fewer than 50 PVCs is generally considered normal.(4)

An accepted experimental method used to detect cardiac arrhythmias is called an ambulatory electrocardiogram (ECG), which employs a monitor attached to the thorax of the dog by electrodes. The dog wears the monitor for 24 hours and a continuous electrocardiogram is recorded. Evaluation of the ECG trace can be carried out by a trained technician, either manually or by using a computer analysis, to identify PVC events. The recording device is called a "Holter monitor," after the name of the scientist who invented it. Holter monitors are commonly used to evaluate cardiac function in humans as well as in dogs.(5)

PVCs can occur as singlets (one occurrence), doublets (two occurrences – also called couplets), triplets or longer runs. This terminology refers to whether the irregular heartbeat is followed by a normal run of heartbeats (PVC singlet) or as a sequence of multiple consecutive irregular beats (doublets, triplets, etc). Three or more consecutive PVCs before the normal heart rhythm resumes is

called ventricular tachycardia (VT).(6) Multiple PVCs, especially VT, are considered more serious than singlet PVCs, as described later.

The four Sudden Death Dogs that prompted Dr. Meurs' investigation were from two related families, I and II, stemming from a bitch bred to two different stud dogs, as illustrated by the pedigree graphic depicted in Figure 1, taken from the 2016 Meurs article:(7)

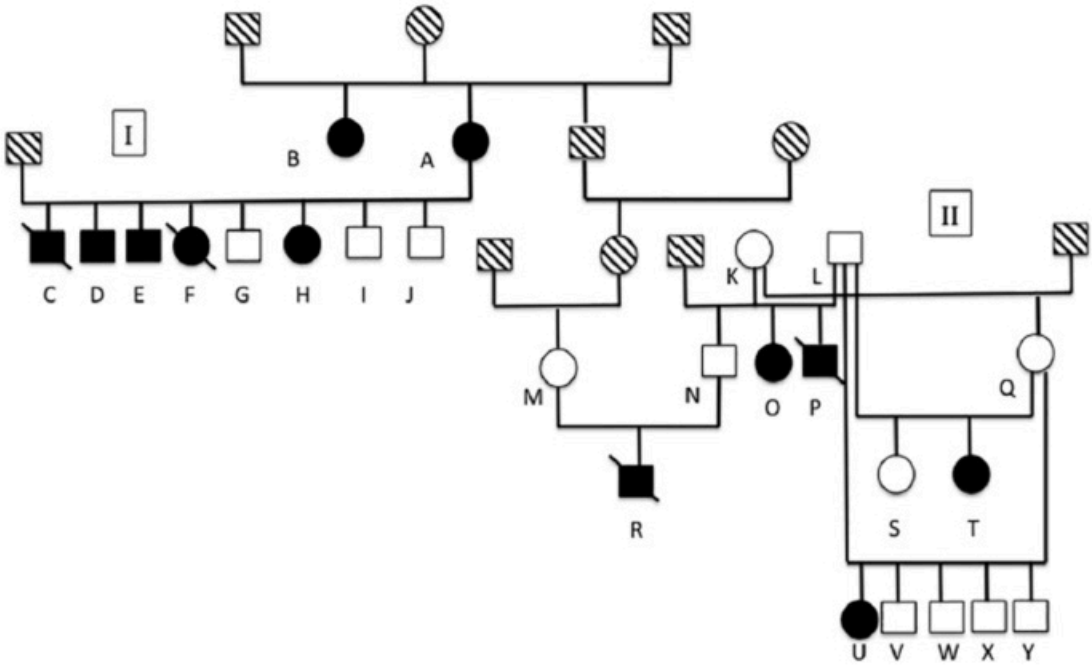


Figure 1. Reproduction of Figure 1 from Meurs, K. M. *et al.*, *JAVMA*, **2016**, *248*, 1136.

In this family tree gender is depicted as a round figure for females and a square figure for males. The 12 solid black symbols represent dogs identified as affected (8 who had frequent or complex PVCs, and the 4 Sudden Death Dogs depicted with a line through the symbol), the 13 solid white symbols represent dogs deemed to have normal cardiac electrical function, and the 10 diagonally shaded symbols represent dogs that were not available for evaluation.

In Family I, the two Sudden Death Dogs (male C and female F) died within 11 days at the age of 7 months. All six littermates of the two deceased dogs were evaluated by 24-hour ambulatory ECG (Holter monitor test) at 8 months of age. Three littermates were found to have frequent ventricular irregularities (male D: 1,240 PVCs/24 hours [all singlets], male E: 5,335 PVCs/24 hours [singlets and doublets] and female H: 8,700 PVCs/24 hours [singlets with ventricular tachycardia]. The other three littermates (males G, I and J) had no detectable PVCs. The dam (female A) was Holter-monitored at 6 years of age, with reported results of 90 PVCs (singlets with ventricular tachycardia), which exceeded the 50 PVC top of the normal range.

Family II included five parents (males N and L and females K, M and Q) and all five of these dogs were determined, after Holter-monitoring, to be within the normal range of PVCs. These included male N and female M (parents of the Sudden Death Dog R) and male L and female K (parents of the Sudden Death Dog P). In this family II, three females were identified as affected (O: 803 PVCs/24 hours (all singlets), T: 792 PVCs/24 hours (singlets with one triplet) and U: 3,913 PVCs/24 hours (singlets, doublets,

triplets and ventricular tachycardia). Five other dogs in Family II (female S and males V, W, X and Y) were found to be in the normal range of PVCs.

The definition of "affected" used by Dr. Meurs in the NCSU publication and webinar is based mainly on the number of PVCs; only secondary attention seems to be given to the complexity of PVCs (*i.e.* triplets or longer runs that are associated with ventricular tachycardia).(8) However, Figure 2, the one graphic illustrating the disease in Dr. Meurs' 2016 article and webinar shows ventricular tachycardia with a run of 6 consecutive PVCs in a 13-month old Rhodesian Ridgeback (this appears to be female H in the foregoing family tree, who also had 8,913 PVCs/24 hours).

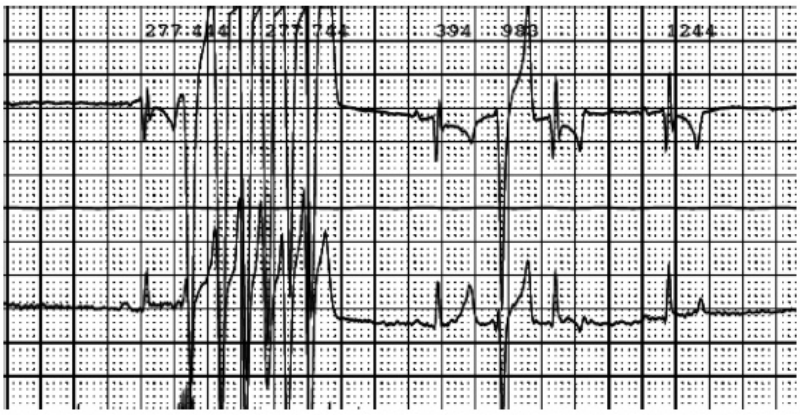


Figure 2—Representative ECG tracings (leads II and III) obtained from a 13-month-old Rhodesian Ridgeback with VPCs. Notice the short run of ventricular tachycardia and a single VPC. Paper speed, 25 mm/s; 1 cm = 1 mV.

Figure 2. Reproduction of Figure 2 from Meurs, K. M. *et al.*, *JAVMA*, **2016**, *248*, 1137.

Dr. Meurs has concluded that RRs with RR IVA have the following characteristics:

- Affected dogs exhibit an abnormally large number of PVCs when tested by 24-hour ambulatory ECG (Holter test). Dogs with more than 50 PVCs in the 24-hour test or with complexity (doublets, triplets, VT) are considered to be affected.9
- The condition is normally found in juvenile RRs and Dr. Meurs hypothesized that most affected RRs normally outgrow the condition by the age of 36 months.(10) The age of onset has not been determined, but is generally believed to develop between the ages of 4-36 months. One puppy has been identified with RR IVA at 4 months of age. Dr. Meurs and her associates are currently studying this aspect.(11)
- Dr Meurs presumes that the Sudden Death Dogs had ventricular arrhythmia. This is a hypothesis, since no reported RR who suddenly died at a young age had been previously tested by ambulatory ECG. However, as described above, littermates and other close relatives of these Sudden Death Dogs were found to display an abnormally large number of PVCs. This provides support for the hypothesis that the sudden deaths may be associated with ventricular arrhythmia or ventricular tachycardia.

There seems to be a belief in the Ridgeback community(12) that the frequent VPCs are more common in Rhodesian Ridgebacks than in other breeds of dogs,(13) and this may turn out to be the case. However, as yet, I am not aware of a publication that discloses data to fully support this generalization. In a 2001 article, Dr. Meurs and coworkers reported the use of Holter monitoring to evaluate healthy dogs for PVCs.(14) This study concluded that "healthy mature dogs have infrequent VPC in a 24-hour period . . . " Although this study included 28 dogs representing 12 breeds and 22 mixed-breed dogs, there was little information about the ages of the dogs except that there was one as

young as 1-year old and the subject dogs were generally considered to be "mature" with an average age of 5 years. Therefore, this study does not appear to give information that can be compared with the juvenile arrhythmia seen in Rhodesian Ridgebacks.

Extensive studies of Inherited Ventricular Arrhythmia and sudden death in German Shepherd Dogs have been published(15) and, to date, the described characteristics of GSD IVA strongly parallel some characteristics of RR IVA. The detailed GSD IVA studies included as the main analytical technique 24-hour ambulatory ECGs (Holter tests). A 2009 review of GSD IVA contained the following preamble:(16)

> "Spontaneous ventricular arrhythmia (VA) and sudden death occur in young German Shepherd Dogs (GSDs). The disorder ranges in severity from infrequent and non-life- threatening single premature ventricular complexes (PVCs) to multiple episodes of rapid polymorphic ventricular tachycardia (VT). Dogs with VT are most likely to die suddenly. No other clinical indicators of abnormality are apparent, and pathological examination of the hearts of dogs that die suddenly reveal morphologically normal hearts. A window of vulnerability for the presence of VA and sudden death exists between approximately 3 and 18 months of age, with peak affectedness occurring at approximately 6–7 months of age. Affected dogs rarely have VA after ~24 months of age, and when they do, it is infrequent. The trait of VT is most commonly observed in dogs lying at rest and during rapid eye movement sleep. Because of the age and behavioral dependence of the expression of this disease, extensive observation via 24-hour ambulatory ECG monitoring (Holter monitoring) is often required to ascertain disease presence and its severity."

An important conclusion that emerged from the GSD study is that sudden death only occurred in dogs with rapid polymorphic ventricular tachycardia (VT) (ref. 15a). Figure 3 in Moïse's 1994 article on GSD IVA shows a portion of the ECG traces of five GSDs that died suddenly during the study. The legend of this Figure states: "Electrocardiographic recordings from five German shepherd dogs . . . that died suddenly. Each of these dogs had multiple runs of rapid polymorphic ventricular tachycardia of at least six consecutive ventricular complexes with a rate of ≥480 beats/min. Most frequently, the ventricular tachycardia was preceded by a long RR interval." Although it is notable that each of these sudden death dogs had runs of six or more consecutive ventricular contractions, it was also noted that ". . . the presence of VT is not an exact surrogate for sudden death [since] . . . 50% of dogs that had VT survived the first 2 years of life and subsequently lived a normal lifespan without cardiac compromise such as heart failure or syncope [fainting]." (ref. 16).

In contrast to the GSD IVA studies, to date, there is no previous ECG data on any of the Sudden Death Rhodesian Ridgebacks. Accordingly, we do not know if those Sudden Death Dogs were affected by simple ventricular arrhythmia or, like the GSDs documented in the Moïse study, had rapid polymorphic ventricular tachycardia (VT), or if some other unidentified issue was related to their deaths.

The RR IVA DNA Test

In her first webinar, Dr. Meurs described the availability of a DNA test that is marketed by NCSU and is intended to be predictive of dogs that are disposed to RR IVA.(17) Results are reported as "negative", "positive heterozygous", or "positive homozygous." These three results mean that the dog has 0, 1, or 2 copies of a DNA mutation at a particular allele that makes the dog at risk for IVA.

Although NCSU does not publish results or disclose them to anyone except the owner of the tested dog, a community initiative18 resulted in a tabulation of results from 244 dogs, and is believed to provide a reasonable estimate of the prevalence of the DNA mutation (Figure 3).

Negative	Positive Heterozygous	Positive Homozygous	Total
43	117	84	244
17.6%	48.0%	34.4%	

Figure 3. Summary of RRIVA DNA test results; data volunteered to the author by various members of the RR community.

As yet, there has been no publication that discloses details of how this DNA test was devised and validated. The test is said to be diagnostic for identifying dogs that are positive (either heterozygous or homozygous) and, therefore are "at risk for the disease" (ref. 11).

In her February 10, 2017 webinar, Dr. Meurs illustrated DNA sequencing data for seven dogs with a graphic that is intended to illustrate "a genetic mutation that was associated with the development of arrhythmia and sudden death". In the webinar, which is the only place this information has been made public, the graphic is entitled "Rhodesian Ridgeback Inherited Ventricular Arrythmias, Through DNA sequencing we identified a genetic mutation that was associated with development of the arrhythmia and sudden death." The graphic shows a series of traces representing DNA sequencing results (Figure 4):

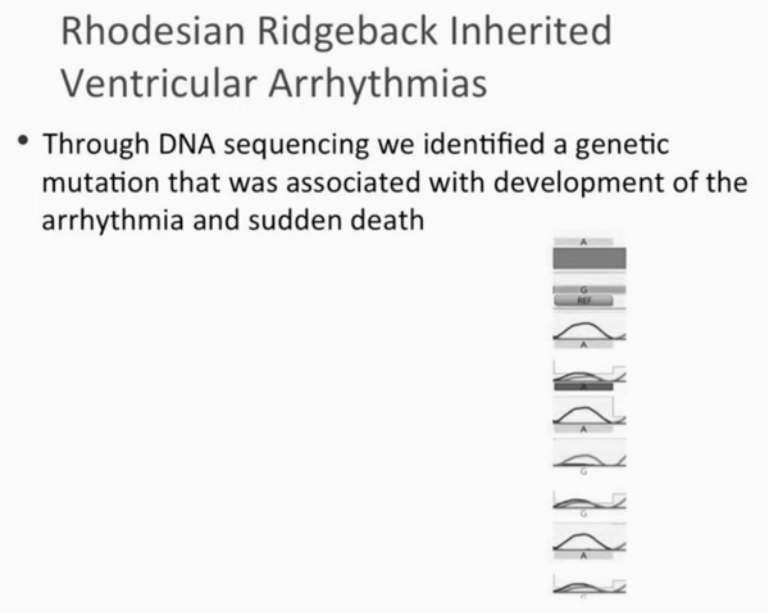


Figure 4. Graphic from Meurs Webinar, February 10, 2017. [In the original graphic the lines corresponding to the letters G and A are yellow and red, respectively.]

Although details of the experiments that gave rise to these partial traces have not been disclosed, the traces appear to represent a particular position on the genomes of seven subject dogs where there can be either A or G.(19) In her first webinar, Dr Meurs described this graphic by saying that the three traces labeled G were for "normal" dogs and the four labeled A were for "abnormal" dogs. Furthermore, it was stated in the webinar that these results "demonstrated to us that these dogs absolutely did have an abnormal genetic sequence that was associated with the development of arrhythmia an sudden death." To date, no information has been provided with regard to what criteria were used to define "abnormal" or to the phenotypes of the seven dogs that supplied the DNA depicted in Figure 4.

However, the foregoing description of the seven traces is not correct. At each position on the genome (called an allele), an individual can have two "letters", one from the sire and one from the dam. If the individual inherits the same letter from both parents you will see only one line. For example, the 4th trace from the top has one line that corresponds to the letter G, so this allele is GG. Since GG is what is found in the consensus canine genome at this allele, that sample is called "wild type." On the other hand, the 2nd, 5th and 7th traces from the top show two lines, one corresponding to the letter G and one corresponding to the letter A. These dogs had one copy of the G that is commonly found at this position in the consensus canine genome and one copy of A, resulting from a mutation. These three samples would therefore be AG, which is called heterozygous. Finally, the 1st, 3rd and 6th traces show just one line that corresponds to the letter A, so these three are homozygous since both of the genetic letters are the mutated version, A. So in actuality, although the seven traces are labeled as A, A, A, G, G, A, G, they should actually be labeled AA, AG, AA, GG, AG, AA and AG. In other words, three are homozygous A, and three are heterozygous (AG)(20) and one is homozygous G (wild type). It is not clear how these results could possibly correlate with "affected" or "non-affected" phenotypes. That is, the data presented in the graphs shows that six of the seven dogs represented had a mutation at the particular allele illustrated, with G having been mutated to A, with three of the six having one copy of the mutation and three having two copies. However, the data represented in these graphs does not in itself demonstrate that this mutation is associated with IVA.(21)

No association data have been published that shows a clear association of the DNA result with actual ventricular arrhythmia. The DNA test report that is provided by the NCSU Veterinary Cardiac Genetics Laboratory includes the statement:(22)

> "Dogs that are positive for the test will not necessarily develop significant heart disease (arrhythmias) and die from the disease. Our current results suggest that about 60% of the dogs that are positive will develop a cardiac arrhythmia and may need treatment. Many dogs appear to outgrow the disease between 2 and 3 years of age. We recommend that dogs that are positive have a Holter monitor performed periodically between 6 months to 3 years of age."

In a later webinar (December 5, 2017), Dr. Meurs stated that about 40% of dogs testing positive, either heterozygous or homozygous, will be found to be affected by Holter monitor.(23)

In the fall of 2017 the author initiated a survey using the Facebook Rhodesian Ridgeback IVA page. The survey gathered DNA and Holter test results for dogs under 36 months of age (Figure 5; a somewhat less granular summary is found in Appendix B).

DNA Test Result	Number	Affected	% Affected
Homozygous Positive	54	13	24%
Heterozygous Positive	48	10	21%
Negative	23	4	17%
No Test	3	0	0%
Total	128	27	21%

Figure 5. Relationship between RRIVA DNA test results and Holter test results

This data shows that the NCSU DNA test is not useful for making breeding decisions because it appears that the test does not even associate with juvenile arrhythmia, to say nothing of sudden death. For this group of >120 dogs, the fraction found to have arrhythmia at the "affected" level (>50 PVCs/24h) is essentially the same, irregardless of the results of the DNA test.

The most critical data in the foregoing table is that for the four dogs that test Negative on the NCSU RRIVA DNA test and yet were found to have juvenile arrhythmia when tested by the Holter method. Because of the importance of these four cases, each is described in detail below.

- Dog A is a bitch who was found to have have 9403 PVCs/24h with 10 doublets when first tested at the age of 7 months. She was placed on sotalol medication and retested at the age of 20

months, when she was found to have 375 PVCs/24h, all singlets. Her DNA test was done in duplicate and gave a result of negative both times.

- Dog B is a dog who was tested at the age of 14 months and found to have 2052 PVCs/24h with 37 doublets. He was retested at the age of 15 months and found to have 683 PVCs/24h with one doublet. Although this dog is "negative by parentage" since both his sire and dam tested negative on the DNA test, he was tested by the NCSU DNA test and confirmed to be negative.
- Dog C is a bitch who was tested at the age of 22 months and found to have 7484 PVCs/24h, all singlets. She was tested again at the age of 22 1⁄2 months and found to have 119 PVCs/24h, all singlets. She was tested again a week later and found to have 195 PVCs/24h, with one doublet and one triplet.(24) She was tested twice by the DNA test and found to be negative both times.
- Dog D is a bitch who was tested at the age of 15 months and found to have 125 PVCs/24h, all singlets.
- One other DNA-negative dog showed abnormal Holter results on one test, but was in the normal range on two other tests. This is a bitch who was first tested at the age of 6 months and found to have 35 PVCs/12h. This corresponds to 70 PVCs/24h and would therefore be "affected". However, she was tested again at 7 months had found to have 15 PVCs/24h and again at 11 months and found to have 4 PVCs/18h.

Conclusions

Arrhythmia is widespread in juvenile Ridgebacks, as shown by the experimental observation of arrhythmia in about 20% of the dogs tested by the Holter method.

Dr. Meurs and her coworkers have identified a mutation that is common in Ridgebacks relative to the consensus canine genome. This mutation is very widespread, with about 85% of Ridgebacks having either one or two copies of the mutation. However, this mutation seems to be unrelated to observable arrhythmia.

I would like to express a note of caution about the level of anxiety, worry and fear that seems to be occurring in some quarters on social media. While the sudden death of any young dog is admittedly tragic, we must avoid the instinct to panic.

Even if there is a malfunctioning gene that is responsible for ventricular arrhythmia we can nevertheless conclude that the lethality of this particular genetic defect is low. This conclusion is based on the following analysis:

- So far, of the RRs for whom Holter test data have been collected, about 20% have been found to have arrhythmia at the level of >50 PVCs/24h.
- There are about 750 Ridgeback litters registered with the American Kennel Club per year. At an average litter size of 7, the number of puppies born each year in registered litters would be about 5,250.
- If 20% of these dogs show arrhythmia on a juvenile Holter test, it follows that each year there are born about 1050 AKC-litter-registered Rhodesian Ridgebacks that have ventricular arrhythmia as juveniles, which is not detected because there are no obvious symptoms and dogs appear to outgrow the condition by the age of 3.
- Although there are no comprehensive data for sudden cardiac deaths in juvenile ridgebacks, there are anecdotal reports of about two dozen sudden deaths over the last 20 years. Although this number may be under representing, it is far less than the many thousands of RRs who must have had juvenile arrhythmia over this period of time.
- Finally, the very fact that the condition of juvenile arrhythmia is so widespread in the general population underscores the low probability of lethality in the general ridgeback population.

It is likely that there are degrees of risk for a dog identified as having VA by ECG test. In most cases, I believe it is benign, but in rare sudden death cases there is some other system failure – perhaps genetic in nature – as yet unidentified. It is this lethal factor that should be sought.

How do we apply the information available through the existing tests? It should be noted that so far, more than two years after the 2016 Meurs JAVMA article, hundreds of RRs have been tested by the NCSU DNA test and/or by the Holter test. To my knowledge, none of the RRs tested by either of these methods has died suddenly.

Furthermore, it appears that the DNA test was not adequately validated before being placed on the market. The data that has been collected indicate that the test does not correlate with juvenile arrhythmia. Therefore, at the moment, RR owners and breeders should be skeptical of the test, which appears to have no predictive value.

Holter monitoring is a different matter because it actually identifies arrhythmia. The test measures an actual physical condition – there is no issue of incomplete penetrance or false positive results; PVCs are either above the normal range or not. Consequently, the Holter test gives a much richer set of data than the DNA test, which has only three possible results – negative, positive heterozygous or positive homozygous.

Furthermore, a given dog can have a wide range of PVCs, from zero to many thousands per 24 hours and the PVCs can be singlets or complex, including ventricular tachycardia. Moreover, dogs with <50 PVCs/24 hours are considered "unaffected" or "normal" while those with >50 PVCs/24 hours are considered "affected".(25) Of course, this is just an arbitrary cutoff – it seems obvious that a dog that has a few hundred PVCs/24 hours would be less at risk than one with thousands of PVCs.

As a practical matter, we must recognize that in most cases information about the presence and degree of ventricular arrhythmia will not be available to a breeder, unless the dog to be bred was Holter-tested during the susceptible age range. Unfortunately, the vast majority of breeding candidates have not been tested during the juvenile age range and, if affected with VA, have likely outgrown the arrhythmia by the time he or she is ready to be bred. Going forward, we need to continue to gather information that will let us understand the risk factors for sudden death of young RRs. For that reason, I recommend that breeders continue to Holter-test as many juveniles as possible over the susceptible age range of 6-15 months and make the results available in a database to be established.

Although, to my knowledge there has not yet been a sudden cardiac death of a young Ridgeback previously Holter-tested, or whose parents or other ancestors were Holter-tested, this will probably happen at some time in the future. When this occurs, DNA profiling of this young dog, and its parents and littermates, might be instrumental in developing a more reliable DNA test which is actually predictive of sudden death ventricular arrhythmia in juvenile ridgebacks. As of this date, however, according to publications, there is no such conclusive DNA test for predicting sudden deaths in ridgebacks.

Finally, I am not opposed to breeding dogs who demonstrated ventricular arrhythmia (but not ventricular tachycardia) as juveniles, provided, however, that the dog was determined by Holter testing to be normal by age 2-3 years. I think it is incumbent on the breeder who breeds a dog (male or female) who had abnormal Holter results as a juvenile, to examine all of the puppies by Holter test at the age of 9 months of age.

I recommend caution in breeding parents or littermates of Juvenile Sudden Death Dogs.

Summary:

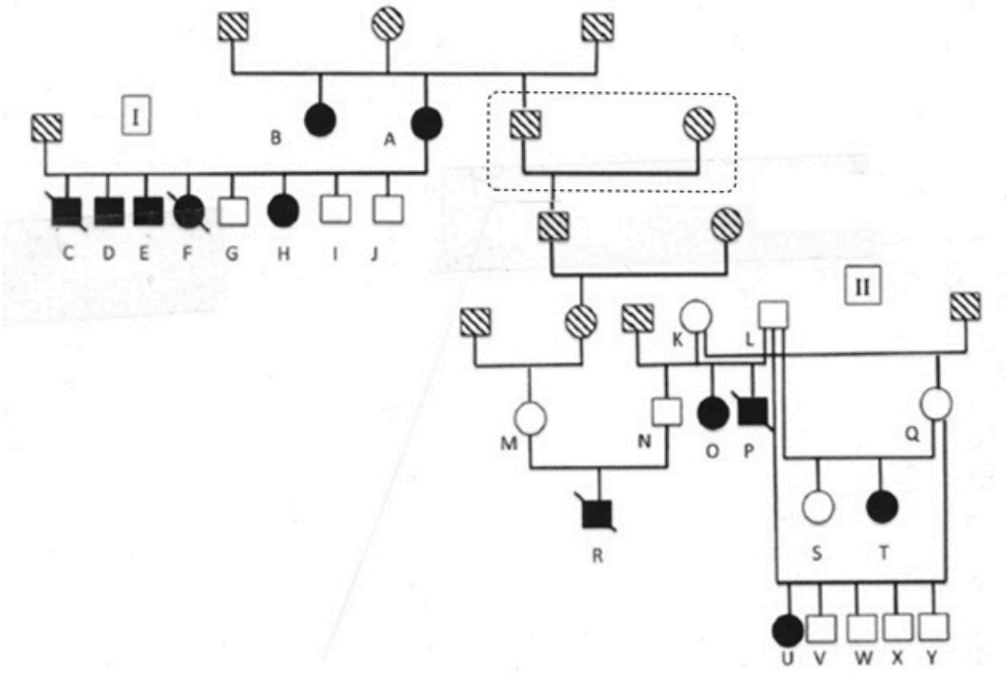
- Ventricular arrhythmia, as measured by Holter testing, is common in young Rhodesian Ridgebacks.
- A very small fraction of juvenile dogs died suddenly – presumably from ventricular arrhythmia or tachycardia. The vast majority of juvenile ridgebacks testing positive for VA by Holter testing appear to outgrow the condition. At present, the actual risk of sudden cardiac death to juveniles who manifest the ventricular arrhythmia appears to be quite low.
- Much more data must still be collected on the time course of the condition – ages at which the ventricular arrhythmia begins and declines, and I endorse the NCSU program to collect this

valuable data. However, in my opinion the program should have many more subject dogs than the 20 currently enrolled.

- The RR IVA DNA test that is being marketed by NCSU – which does not predict ventricular arrhythmia nor predict sudden cardiac death – is of no use. There clearly are other factors that need to be identified to unequivocally identify dogs that carry a "sudden cardiac death" gene or gene cocktail.

APPENDIX A

One generation is missing from the family tree depicted in Figure 1 of the 2016 Meurs article. The correct tree is shown below. The omitted generation is indicated by the dashed box.



APPENDIX B

- DNA Negative: 20 dogs age 7-36 mos
  - o 16 with <50 PVCs (0-8)
  - o 4 with >50 PVCs (125, 195, 683, 9403)

- DNA Heterozygous positive: 48 dogs age 5-36 mos
  - o 38 with <50 PVCs (0-35)
  - o 10 with >50 PVCs (57, 69, 543, 656, 1170, 1279, 3062, 3473, 3847, 10475)

- Homozygous positive: 54 dogs age 5-36 mos
  o 41 with <50 PVCs (0-44)
  o 13 with >50 PVCs (50, 97, 117, 117, 168, 190, 275, 287, 601, 792, 3913, 5203, 15412)

1 (a) Meurs, K. M. *et al.*, "Ventricular arrhythmias in Rhodesian Ridgebacks with a family history of sudden death and results of a pedigree analysis for potential inheritance patterns," *JAVMA*, **2016**, *248*, 1135-1138. (b) See also Meurs webinar, February 10, 2017: https://cvm.ncsu.edu/genetics/rhodesian-ridgeback-inherited-arrhythmia-rr-iva/
2 "Premature Ventricular Contractions (PVCs, PVC)," https://www.medicinenet.com/premature_ventricular_contractions/article.htm
3 "Arrhythmias (Heart Rhythm Disorders)," https://www.emedicinehealth.com/heart_rhythm_disorders/article_em.htm
4 Meurs, K. M., *et al.*, "Familial Ventricular Arrhythmias in Boxers," *J. Vet. Intern. Med.*, **1999**, *13*, 437-439.
5 A **Holter monitor** is a battery-operated portable device that measures and records your heart's activity (ECG) continuously for 24 to 48 hours or longer depending on the type of monitoring used. The device is the size of a small camera. It has wires with silver dollar-sized electrodes that attach to your skin.
6 "Three or more beats in a row on an ECG that originate from the ventricle at a rate of more than 100 beats per minute constitute a ventricular tachycardia." https://en.wikipedia.org/wiki/Ventricular_tachycardia
7 The tree depicted as Figure 1 in the 2016 Meurs article is slightly incorrect, as one generation was omitted in the family II part of the tree. For the corrected tree see the Appendix. This corrected tree was constructed by the author on the basis of interviews with the breeders of the various depicted dogs and the Pedigree Online Search Tool, POST.
8 Meurs *et al.* state that "Holter-monitor data was evaluated for presence of abnormal pauses, bradyarrhythmias, or tachyarrhythmias that could be associated with a fatal cardiac event. The number of VPCs/24 hours and their complexity (eg, single monomorphic VPCs [singlets]; bigeminy; trigeminy; couplets; triplets; R-on-T phenomenon; or ventricular tachycardia) were tabulated." However, this data was not presented in the publication. (ref. **Error! Bookmark not defined.**a)
9 Meurs 2016, at 1136: "If a ventricular arrhythmia was present, it was interpreted as a normal finding if there were <50 VPCs/24 hours and all were single beats." See also Meurs, K. M., *et al*. Use of ambulatory electro-cardiography for detection of ventricular premature complexes in healthy dogs. *J Am Vet Med Assoc* **2001**, *218,* 1291–1292.
10 Note that bitch A in the foregoing family tree is an exception to this generalization, as she was found to still have an abnormally large number of PVCs and even ventricular tachycardia at 6 years of age.
11 https://cvm.ncsu.edu/research/clinical-trials/list/?ID=462191
12 Rhodesian Ridgeback Inherited Arrhythmia (RR IVA); https://www.facebook.com/groups/1346498062074178
13 This assumption is also implicit in the name "inherited Rhodesian Ridgeback ventricular arrhythmia."
14 Meurs, K. M. *et al.*, "Use of ambulatory electrocardiography for detection of ventricular premature complexes in healthy dogs," *JAVMA*, **2001**, *218*, 1291-1292.
15 (a) N. S. Moïse, *et al.*, "Inherited Ventricular Arrhythmias and Sudden Death in German Shepherd Dogs," *JACC*, **1994**, *24*, 233-243. (b) N. S. Moïse, *et al.*, "Age dependence of the development of ventricular arrhythmias in a canine model of sudden cardiac death," *Cardio. Res.*, **1997**, 483-492. (c) N. S.

Moïse, “Inherited arrhythmias in the dog: potential experimental models of cardiac disease,” *Cardio. Res.*, **1999**, 37-46.
16 J. Cruickshank, *et al.*, “Genetic Analysis of Ventricular Arrhythmia in Young German Shepherd Dogs,” *J. Vet. Intern. Med.*, **2009**, *23*, 264-270.
17 https://cvm.ncsu.edu/genetics/rhodesian-ridgeback-inherited-arrhythmia-rr-iva/
18 Information was solicited and tabulated in mid-2017 by the author from participants in the Facebook page devoted to Rhodesian Ridgeback Inherited Ventricular Arrhythmia.
19 The letters A and G stand for adenine and guanine, two letters of the genetic code.
20 It is not clear why the 2nd and 7th trace are both labeled A but the 5th trace is labeled G, since all three seem to be heterozygous AG.
21 I thank James Han, who is a genome and bioinformatics scientist with 15 years of experience analyzing DNA sequence, for bringing this to my attention and for useful discussions. 22 This statement, which does not appear to be supported by current knowledge, was still being used as recently as April 2018.
23 NCSU CVM: Genetics Webinar – Rhodesian Ridgeback Update. https://mymediasite.online.ncsu.edu/online/Play/27ce4b919ddc485aaefbb353193e750c1d, at 10:25.
24 The large range in the PVC counts for this dog is notable and as yet, not fully understood. The first Holter was done with a DR180 monitor and the second with a DR200 monitor. To test if the difference could be due to the equipment, we carried out a third Holter test, with the original DR180 monitor. This time the test showed 195 PVCs/24h. So, while this bitch is definitely "affected", we don't fully understand why there was such a difference in the test results. One clue may lie in the hourly profile for her last test. The full report for the 24h test showed that she had 39 PVCs in the 18.5-hour period from 10:40 am until 6:00 am the next day (she had only 2 for the 6-h period from 1-7 pm and only 1 for the 7-h period from 11 pm-6 am), then had 156 in the 4.5- hour period from 6:00 am until 10:40 am. This shows that results of a 24-h Holter test are qualitative but not quantitative as a large fraction of the total PVC count can occur in just a small amount of the total measurement time.
25 In her article on RR IVA, Dr. Meurs considers more than 50 PVCs/24h to be “affected”. Other authors have used different measures. For example, Moise (ref. 15b) considers dogs with “less than 10 PVCs on any 24-h ECG recording” to be “within the normal variation” and “these animals were defined as unaffected.” Cruickshank (ref. 16) categorized dogs as affected or unaffected on the basis of three traits. Cruickshank’s cutoff values for affectedness were >100 PVCs, >4 couplets or >2 VT in 24h.