Strategies to Control Canine Hip Dysplasia: The Need for Veterinarian and Breeder Alliance

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ABSTRACT

Genetic control of CHD requires: a) a knowledge of the principles of quantitative genetics, b) an accurate screening method keyed to a phenotype with optimal heritability, c) an organized screening program based on a proven screening phenotype, d) a centralized database containing essential phenotypic and pedigree information, and e) trust and cooperation between breeders and the veterinarians who perform the screening procedure.

THE RELATIONSHIP BETWEEN PHENOTYPE AND GENOTYPE

Controlling diseases of complex inheritance (aka, polygenic diseases) like CHD requires a concerted and coordinated effort on the part of breeders and veterinarians. As importantly, the integrity of the test used to screen for CHD is central to reducing the frequency of hip disease (**Figure 1**).

The principal objective of selective breeding is to maximize the pairing of good genes by breeding dogs not overtly affected with (and preferably, not susceptible to) CHD. The purpose of the screening test is to evaluate hip phenotype (that which you can see or measure) as an estimate of the genotype (that which you can't 'yet' see or measure). The relationship between phenotype and genotype is embodied in the concept of heritability represented by the symbol, h^2. Heritability denotes the reliability of the phenotype in predicting the genotype. A high heritability, say approaching 1, means that the phenotype closely reflects the genotype. Or put in other words, all the variation in the phenotype is explained by the genes. Environmental factors, such as diet or exercise, have no influence on the phenotype. In contrast, a heritability of 0 means that a disease is not influenced whatsoever by genes and accordingly variation in expression is purely environmental.
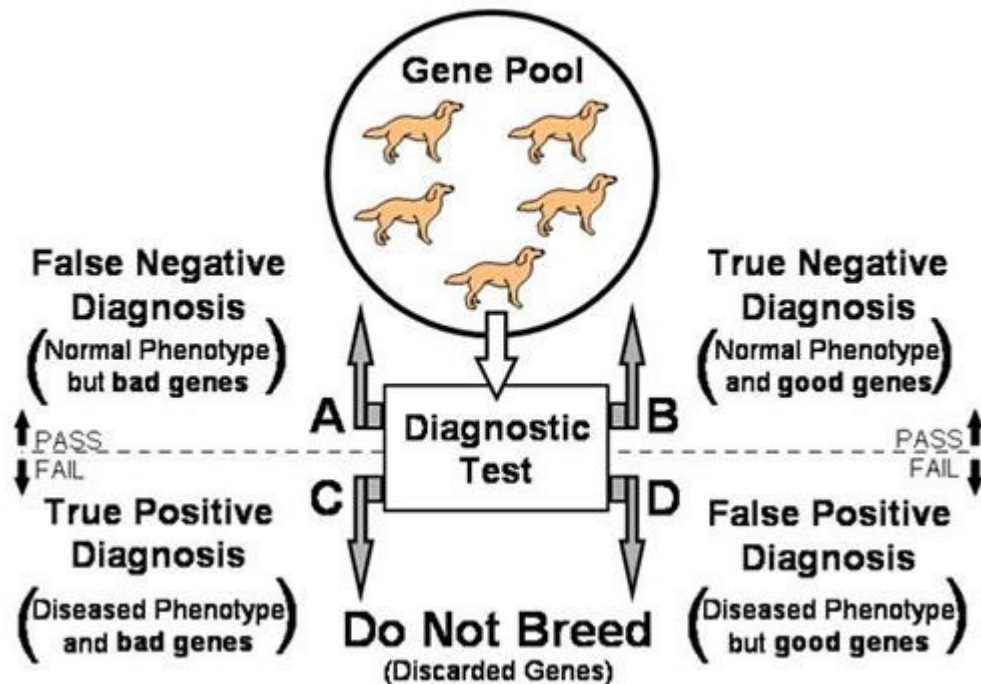
Heritability is mathematically defined as the ratio of additive genetic variation to the total phenotypic variation of a given trait ($h^2=V_G/V_P$). And the total phenotypic variation, V_P, in turn is defined as the sum of the genetic variation, V_G, plus the variation owing to environment factors, V_E, (sometimes termed nongenetic factors). Then,

$$h^2=V_G/ (V_G + V_E)$$

One can see from this simple relationship that when environmental factors do not influence the trait of interest (i.e., V_E is small) then, h^2 approaches 1 and the trait or disease of interest can be considered purely genetic. Similarly, as environmental factors cause increasingly more variation in the phenotype, h^2 approaches 0.

Examples of environmental factors that contribute to variation in the denominator of the heritability relationship above include diet, exercise, gender, age, and diagnostic error. These factors increase the total phenotypic variance in the denominator of this relationship, V_P, and therefore they have the effect of lowering estimates of heritability, the significance of which will be emphasized later. So, polygenic traits are influenced by both environmental and genetic effects. For example, a dog's weight is partly influenced by environmental factors in terms of how much it is fed and how much exercise it gets. However, it is known that body weight can also be influenced by genetic factors, i.e., obese parents tend to have obese offspring.

Role of the Screening Test in Selective Breeding

Gene Pool

False Negative Diagnosis (Normal Phenotype but **bad genes**)

True Negative Diagnosis (Normal Phenotype and **good genes**)

A | **Diagnostic Test** | B

PASS / FAIL — — — — — — PASS / FAIL

True Positive Diagnosis (Diseased Phenotype and **bad genes**)

C | D

False Positive Diagnosis (Diseased Phenotype but **good genes**)

Do Not Breed (Discarded Genes)

Figure 1: The Role of a Screening Test in Improving the Gene Pool. The objective of any screening test for a genetic disease is to lower the frequency of 'bad genes' in the gene pool. This entails using what can be seen', as a result of the diagnostic test (the phenotype) to estimate 'what can not be seen' (the genes). Dogs are permitted to enter the gene pool based on normal results of the test (arrow A or B). A perfect test (arrows B and C only) would be capable of accurately separating 'good genes' from 'bad genes' on the basis of the phenotype alone (i.e., the test result), thereby quickly and effectively ridding the gene pool of bad genes (arrow B ➜good genes enter the gene pool: arrow C ➜bad genes are not returned). Unfortunately, no screening test is 100% accurate. For example, a test result may wrongly exclude from breeding a dog that tests positive for a diseased phenotype even though it harbors good genes (arrow D). This would be an unfortunate missed opportunity, as some good genes would not re-enter the gene pool. However, this mistake would not appreciably harm the gene pool. Of much greater potential damage to the gene pool is a test result that indicates a dog has a normal phenotype (negative) but which, in fact, harbors many bad genes (arrow A). Such a mistake would recycle bad genes through the gene pool, resulting in a steady-state level of disease in the offspring derived from that gene pool, despite the best efforts at selection (e.g., breeding excellent to excellent). The frequency of disease coming from the gene pool will depend on the sensitivity of the test to detect bad genes. This sensitivity is directly related to the **heritability** of the phenotype used for screening, therefore the higher the heritability, the better the test, and the more rapid the genetic change.

IMPORTANCE OF HERITABILITY

Worldwide, the predominant mode of choosing breeding stock is to make selections based on the individual animal's hip phenotype, so-called mass selection. It must be stressed, however, that this is not the most effective method to select breeding candidates. More rapid genetic change can be accomplished if the hip phenotypes of relatives are incorporated into the selection decisions. By incorporating data from relatives, one can calculate so-called 'breeding values' for each individual dog. Although this method facilitates more accurate selection decisions, it is not widely employed because of the need for extensive record keeping coordinated with the availability of accurate pedigree information. The breeder should recognize, however, that there are better tools to help in making selection decisions than just resorting to the individual dog's phenotype, eg, hip score.

The common practice of selecting breeders by using only the individual animal's phenotype makes knowledge of the magnitude of heritability of utmost importance. Why is heritability so important in this regard? Because, for a quantitative trait, the rate of expected genetic change in the next generation, (ΔG), from mating a dog and a bitch is equal to the product of the heritability, (h^2), times the selection pressure that is applied (Relationship 1 below). Selection pressure is defined as the deviation of the parental mean, eg. hip laxity, from the population mean.[1]

$$\Delta G = h^2 \times (Avg_{Parents} - Avg_{Pop.}) \quad (1)$$

Where:

ΔG = the expected change in average litter phenotype after one generation

h^2 = heritability of phenotype, eg. DI or subjective hip score

$Avg_{Parents}$ = average hip phenotype of the parents

$Avg_{Pop.}$ = average hip phenotype of the population from which parents were derived.

Therefore, the higher the heritability of a specific trait and the greater the selection pressure applied, the more rapid the expected genetic change per generation of breeding. Estimates of heritability above 0.4 make feasible selection based on the individual phenotype. These concepts applied to PennHIP data are illustrated in the actual mating of 2 tight-hipped German Shepherd dogs (**Figure 2**). In this example, extreme selection pressure has been applied because the sire and dam are drawn

from the tightest 5th percentile of the breed. One can see that the mean hip laxity of the litter derived from these 2 parents is 0.27. From formula 1, it is possible to calculate the 'realized heritability' of any metric, for example, DI. The GSD population average DI is 0.39 and the parental average DI is 0.2, therefore the selection pressure applied was 0.19 DI units. Again, the average DI for the 9 puppies was 0.27. Therefore the realized heritability from this single mating can be found by rearranging terms in Relationship 1:

$$h^2 = \Delta G / (Avg_{Parents} - Avg_{Pop})$$

Plugging in data from the mating in Figure 2

$$h^2 = (0.39-0.27)/(0.39-0.20) = 0.63$$
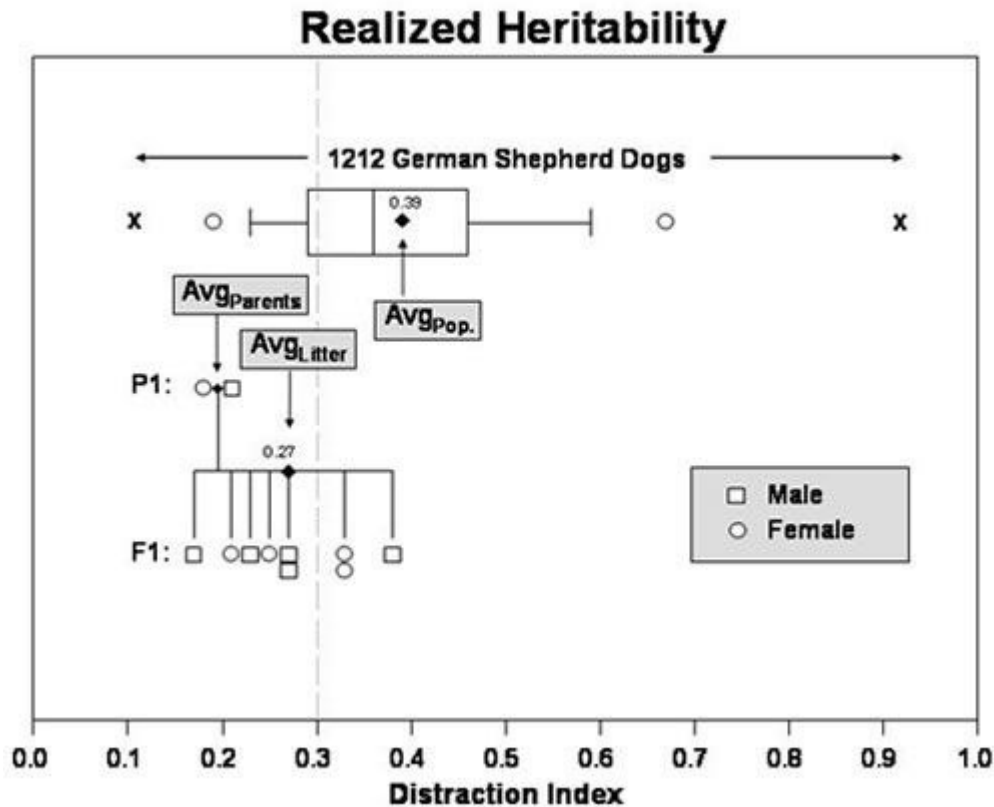
Figure 2: Calculation of Realized Heritability from a Single Mating. See text for full description. This illustration shows the relative relationships of passive hip laxity of, 1) the German Shepherd dog breed at large, 2) the dog and bitch, P1, and, 3) the litter, F1. Note that the mean litter DI moved approximately 60% of the distance from the mean of the GSD population toward the mean of the parents. Plugging these averages in hip laxity into Relationship 1 yields a realized heritability of approximately 0.6. It is notable that all 9 puppies showed hip laxity below the average for the breed and that hip laxity in 6 of the 9 puppies fell below a DI of 0.3, indicating little to no susceptibility to DJD.

Currently there are no published estimates of heritability for subjective (OFA) hip scores for the most popular breeds of dogs. A retrospective analysis from the OFA showed heritability in 4 less common dog breeds to average 0.26.[4] Phenotypes with heritability of this magnitude would be considered to be lowly heritable[1] meaning that genetic change will be slow (only 25% of of the applied selection pressure will be passed on in each generation of breeding- see Relationship 1). These figures are corroborated by 2 well-executed studies of subjective hip score (OFA-type scoring), which yielded similar estimates of heritability of 0.22 [2] and 0.43 [3] for German Shepherd Dogs.

The magnitude of selection pressure applied is the other important factor in relationship 1 above. With successful application of selection pressure, offspring within generation will begin to look similar, eg, more dogs will be normal, meaning that the phenotypic and genotypic variance will get smaller. However, with decreasing variation in the hip phenotype (for example, in subjective score), there may come a point, a steady state, at which little additional incremental selection pressure can be applied by using the subjective score as a selection criterion. That is, if the application of maximum selection pressure (e.g., breeding 'excellent' to 'excellent', see arrow A in **Figure 1**) still produces affected progeny, no more genetic progress can be expected (short of incorporating estimated breeding values in making selection decisions, mentioned above). Such has been the experience of The Seeing Eye, Inc. after 17 years of selection against hip dysplasia using a subjective scoring scheme similar to, but more strict than, that of the OFA.[5]

Heritability of a given phenotypic trait is a property of the population under study. Therefore heritability of each trait or diagnostic phenotype must be calculated for each breed and each population of dogs. An example of a calculation of realized heritability was illustrated in Figure 2, however, estimates of heritability can also be calculated by other methods. For example, the upper limit for heritability of DI can be estimated as the intraclass correlation coefficient for longitudinal repeatability of hip score, e.g., DI measurements, over time.[1] In one study of German Shepherd Dogs, the intraclass correlation coefficient of repeatability of DI was between 0.67 and 0.74, indicating a high upper limit of heritability for DI and in line with the realized heritability calculated above.[6] In contrast, in the same study the longitudinal repeatability of subjective score over the same interval from 4 months of age to 24 months of age was 0.08 and not statistically significant.

Heritability can also be estimated by analyzing resemblance between parents and offspring in terms of hip laxity (DI). To accomplish this, a regression analysis of litter mean DI phenotype, can be plotted against parent mean DI, to yield a line whose slope is an estimate of heritability. This method was employed in the publication of heritability estimates from the OFA, mentioned above.[4] Using a similar method, estimates of heritability of DI (unpublished) for a group of German Shepherd Dogs was between 0.42 and 0.65, and the upper limit for heritability of DI among a group of Labrador Retrievers was 0.92. For Golden Retrievers the estimate for heritability of hip laxity from an analysis of 265 dogs comprising 47 litters was 0.64.[7] For comparison, the estimate of heritability for subjective hip score (slope of regression line) in the study of Golden Retrievers was 0.22 and not statistically significant.

The most valid estimates of heritability of DI or subjective hip score are derived by incorporating knowledge of relevant phenotypes in the context of the full pedigree. The Seeing Eye, Inc. has maintained a closed colony of dogs intended for use as dog guides for the blind. Leighton, et al invoked rigorous mathematical methods that incorporated the full pedigree structure, and found the heritability of DI to be 0.46 for German Shepherd Dogs and 0.46 for Labrador Retrievers.[8] The corresponding heritability estimates for subjective hip score (determined by a board-certified veterinary radiologist) were lower at 0.34 for German Shepherd Dogs and 0.34 for Labrador Retrievers. This low heritability of subjective hip score in German Shepherd dogs is supported by a recent study from Finland by Leppanen et al.[9] Applying BLUP (best linear unbiased prediction) procedures to analyze 10,335 GSDs from 1985 to 1997 these investigators found that using subjective hip score as a selection criterion over this 12-year time interval failed to produce genetic improvement.

Heritability analyses using these newer, more sophisticated statistical methods are needed for all hip screening methods applied to all breeds of dogs. Results thus far are promising that the heritability of DI will be considerably higher than the heritability of subjective hip scoring. These findings have great clinical significance owing to the abundant evidence linking hip laxity as measured by DI with osteoarthritis of the hip. (Figure 3).[10] Currently there are no published estimates of the heritability of other diagnostic hip phenotypes including the DLS score[11], the DAR score[12], and the scores of Fluckiger[13], Barlow test, Bardens test, or Ortolani test. Such studies are necessary to determine the relative merit of these diagnostic tests as candidate hip screening methods for selecting breeding stock.
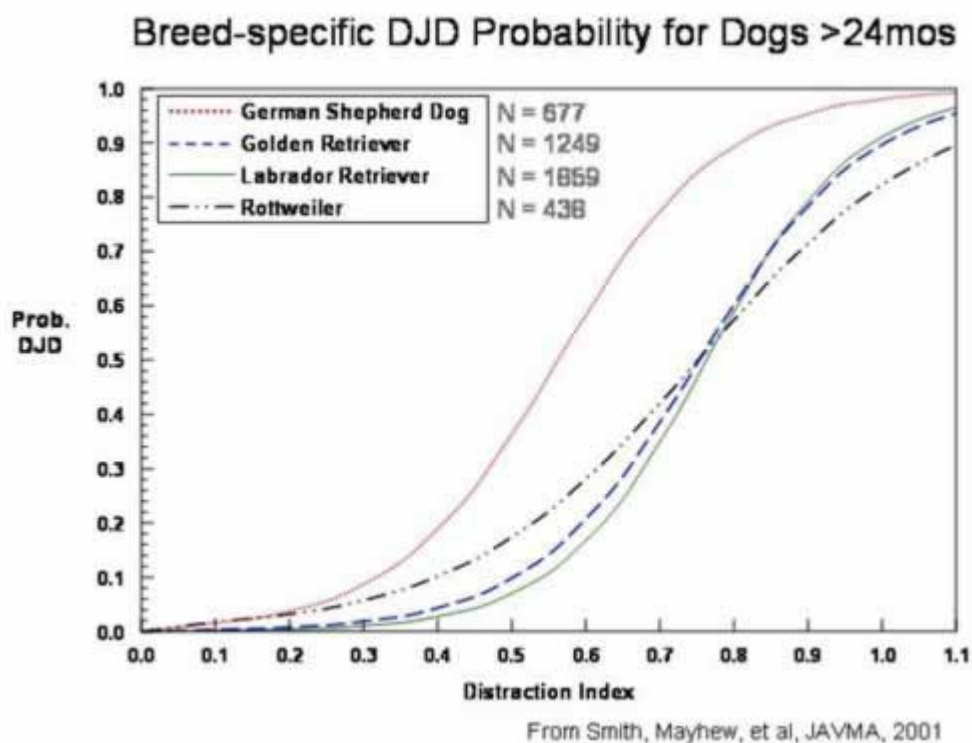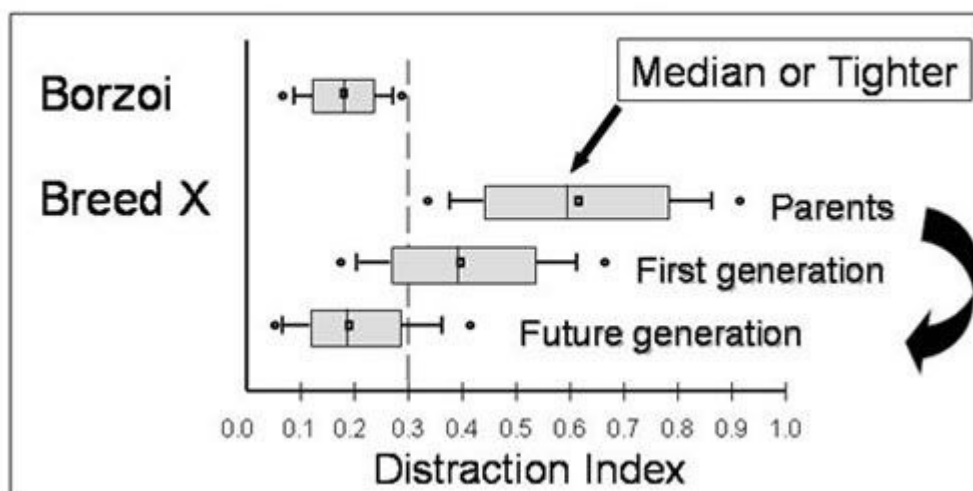

Figure 3: Breed Specific DJD Probability based on DI for Dogs $\geq$ 24 Months of Age. Probability of radiographic evidence of degenerative joint disease (DJD) as a function of distraction index (DI) for dogs $\geq$ 24 months old of 4 common breeds. Note the spatial shift to the left for the German Shepherd Dog breed indicating an increased probability of DJD for any given DI compared to the three other breeds.

SELECTION PRESSURE TO PRODUCE RAPID GENETIC CHANGE IN CHD

Breeders cannot influence the magnitude of the heritability of the phenotype, but they can control the magnitude of applied selection pressure (i.e., the difference between the mean of the parents and the mean of the population at large, see Relationship1). Therefore, to the extent that breeders select breeding candidates, they can control the rate of improvement in hip phenotype in each generation. For the most rapid genetic change, the breeder can decide to mate only the tightest-hipped dogs within the breed (those with the lowest DI) and then continue to inbreed for tight hips. This approach would maximize the difference between the parent average and population average (i.e., the selection pressure, the second term on the right side of Relationship 1, would be large). There would therefore be a greater expected change in each generation assuming constant heritability. This approach, however, creates concern that founding a breeding program on only a few dogs, and inbreeding on these dogs, would reduce the overall genetic diversity in the gene pool and could contribute to the loss of some desirable traits or the expression of some undesirable traits. This reality affects some breeds more than others. For example less than 5% of golden retrievers have hip laxity in the 'tight-hipped' range below a DI of 0.3. If one were to require that breeding candidates conform to this standard and must come from this small pool of dogs, the result would be a serious reduction in genetic diversity, not to mention that the strategy would neither be practical nor unacceptable to breeders.

To avoid these potential problems accompanying this 'extreme' selection, a 'moderate' approach has been suggested to go hand in hand with PennHIP testing, particularly in breeds with few or no members having tight (DJD-unsusceptible) hips. In such breeds it is recommended that breeders choose breeding stock from the tightest half of the breed, thereby maintaining an acceptable level of genetic diversity while still applying meaningful selection pressure (**Figure 4**). Clearly the more selection pressure applied, the more rapid the genetic change. The PennHIP database ranks each dog relative to other members of the breed making it possible for the breeder to identify dogs whose DI will apply meaningful selection pressure (**Figure 5**). By applying at least moderate selection pressure, eventually the average of the population will shift with each generation toward tighter hips, increasingly tightening the minimum standard for breeding. By following these time-tested principles, eventually, fewer dogs will be at risk for developing DJD. Understandably, more rapid genetic change could be achieved by imposing greater selection pressure or by using estimates of breeding value from incorporation of the pedigree. These strategies are recommended for the aggressive breeder wishing to achieve the most rapid hip improvement. Even absent these measures, however, the principle of mass selection if linked to a highly heritable phentoype, such as the PennHIP DI, holds great promise for reducing the frequency and severity of DJD in future generations of dogs.

Figure 4: Proposed Minimum Laxity-based Breeding Criteria. By using the generational median (or mean) as the minimal criterion for breeding, one can expect genetic change to occur. Breed X displays a range and distribution of hip laxity not unlike the golden retriever breed, for example. Genetic change toward tighter hips can be expected in each subsequent generation by breeding dogs in the tighter half of the distribution (and preferably much tighter). The goal of this strategy is to tighten the hips of Breed X until matching the range and distribution of hip laxity of the Borzoi. Obviously, based on Relationship 1, the tighter the parents, the greater the selection pressure, and the more rapid the expected genetic change toward hip improvement. This logic follows well-established principles of quantitative genetics.
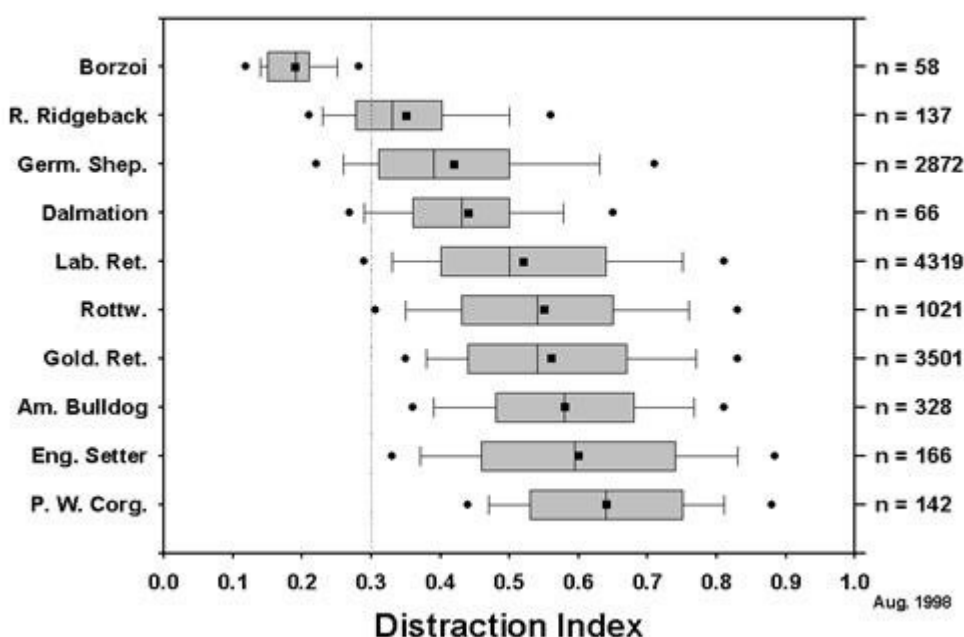
Figure 5: Breed Distribution of Distraction Index -- Box and Whisker Plots of Passive Hip Laxity by Breed. Data is drawn from the PennHIP database (Aug. 1998) and shows breed-specific passive hip laxity. Note that the Borzoi breed has no members with hip laxity greater than a DI of 0.3. Note also that the golden retriever breed has few if any members with hip laxity less than a DI of 0.3. The obvious objective of selective breeding is to move the laxity profiles of the looser CHD-prone breeds, like golden retrievers, into the hip-laxity range approximating that of the Borzoi, a breed of dog that has an extremely low incidence of CHD.

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