To test or not to test….

Is that a question? Actually yes, this is very realistic question. The fact that you can test for a certain condition, is certainly not always a reason to introduce a mandatory test for it. But please realise that I am talking about a policy on population level. That means that I am not talking about individual dogs or breedings, but about what a club could do to preserve the health quality of the breed. If a test for a certain condition is not mandatory, I can only applaud for breeders/owners that still test their dog for it. However, if a test for a certain condition is mandatory, it certainly is against all ethics not to do so.

There are several reasons to test structurally for a certain condition:

1. The condition is serious and affects the dogs quality of life.
2. The population characteristics like incidence and prevalence are not known (yet).
3. Test results are believed to make it possible to eradicate the problem or to minimise it in the population, i.e. it is believed to be DNA mediated or genetically predisposing individual dogs for the problem.
4. A test result should and can lead to interventions. Testing without the option for actions makes hardly any sense. Interventions can be for example breeding guidelines (not mating grade X with grade Y), imposing tests or (extra) dog assessments.

But you have also to consider the type of test, as that is very relevant for the way it can be used/interpreted.

DNA testing

Basically, the ideal test for every condition is a DNA-test. This offers the best decisive information in the case of autosomal inheritance. That means, that there is one mutation responsible for the condition. A dog needs two copies of it to become affected. The test, if performed by a reliable, authorized laboratory, can tell whether a dog doesn't have the bad mutation at all (N/N, "free"), has one mutation (N/A, "carrier") or two mutations (A/A, "affected"). A carrier will stay free of the condition but will pass on the mutation to 50% of its offspring. The 50% is a statistical number, and therefore even none or all of his offspring could carry the mutation. However, an A/A dog will develop the condition, but you will not know at what age. An affected dog will pass on the "bad gene" to all of his offspring.

A "hybrid" DNA test is the test for degenerative myelopathy (DM). The SOD mutation is believed to be involved in DM, or at least partly responsible, but not every affected dog will develop clinical symptoms. Does it say something about a variable time to emergence of the symptoms, or is there another gene involved as well? We don't know yet.

But for many conditions, it seems that more genes/mutations can be held responsible or that external factors, like activity or nutrition contribute to the phenotype (the way it looks). In these cases a clinical test is the only solution.

Clinical tests

If there is no DNA test available, you have to fall back to clinical tests. These tests give a "phenotypical" result: the result tells you whether the condition is present or not. These tests are used for conditions for which no clear mutation is known, or where environmental influences play a role. Examples are hip dysplasia (HD), osteochondritis dissecans (OCD), patella luxation (PL) and many eye conditions. But only for the HD, PL and eye conditions there are standardized tests and protocols available, however for OCD, that is not the case.

Now let's have a look at some conditions that are relevant for the kuvasz. I will discuss hip dysplasia (HD) and Progressive Retina Atrophy (PRA).

Hip dysplasia

Hip dysplasia is one of the oldest conditions that has been held accountable for very severe disabling of dogs suffering from it. It is thought that mainly large dogs were vulnerable, but that is not true. Also smaller breeds can become affected.

Nutrition and the amount and type of activity were held co-responsible for the emergence of severe forms, like HD D and E. But inheritance is certainly involved. Sceptical breeders will point out that out of combinations of HD A and HD A, not rarely an affected dog with grade D or E is born, and vice versa: that affected dogs produced HD A dogs. These observations are totally correct, but one should not look at a single generation, but at many, over a long period.

In The Netherlands, kuvasz breeding only really started in the 70's. Many dogs from that breeding stock were HD ± (HD C) and HD + (HD D). If these dogs would have been excluded from breeding programmes in those days, there would probably never have been a kuvasz population in our country at all. But when we look at the statistics over 30 years, we can note a significant improvement and severe cases are very rare nowadays. We believe that the basis for this development were clear mandatory guidelines for combinations of HD grades (no breeding with D and E, and grade C only with grade A) and the promotion of outcrossing (or limiting inbreeding).

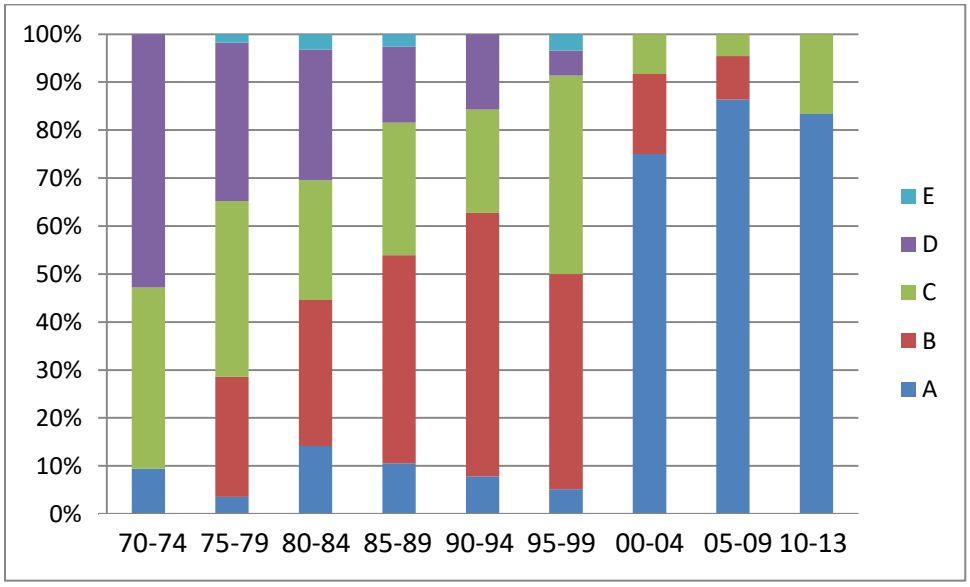


Figure 1 Percentages of HD grades per birth year (The Netherlands)

So the conclusion must be that in the long term you can breed away from a condition that was diagnosed on phenotype, but that it takes a long time. The same we noticed with cochlear deafness, which can be diagnosed at an early age by the BAER test. But by using secondary phenotypical markers to breed away from (i.e. pigmentation defects), we seldom find these cases of deafness anymore.

Progressive Retina Atrophy

First of all some remarks on the condition PRA as such. PRA is a container word for many, if not all, degenerative processes of the retina. The one found in the Kuvasz is the **p**rogressive **r**od and **c**one **d**egeneration in the retina, hence the name prcd-PRA. The responsible mutation was identified by Optigen when a blood sample of an affected kuvasz in the USA was submitted to them. We were lucky: the responsible mutation was detected only about a year after the first clinical cases were published and a clinical test became mandatory in Western Europe and Scandinavia. The identification of the mutation was a major, but lucky, step forward, and made it possible to prevent any clinical cases to emerge. So following the guidelines as they are mandatory in Scandinavia and Western Europe, it is very effective to prevent the emergence of prcd-PRA. No breeding is allowed with affected (A/A) dogs, and carriers (N/A) may only be mated to free (N/N) dogs.

But there are many types of PRA. Laboklin for example offers 14 different tests for PRA. Many tests are breed specific. The prcd-PRA is the most widely spread form between breeds. But when there are so many forms, does it make sense to test only for one form of PRA in the kuvasz? YES, it certainly does. The prcd-PRA is till now the only form that has been diagnosed in the kuvasz. All cases of PRA as known today can be linked to the mutation for the prcd-form. Shouldn't we test for all other thirteen forms? NO, that makes no sense at all. It would mean a waste of money... at this moment.

One other note on this. A dog born from parents that tested free from the prcd-PRA form by the Optigen test can be considered genetically "free by parentage". Theoretically in those dogs the mutation can happen again, but we have no clue how often/soon that will happen. So some day we have to decide how many generations can be declared free by parentage after two DNA tested ancestors.

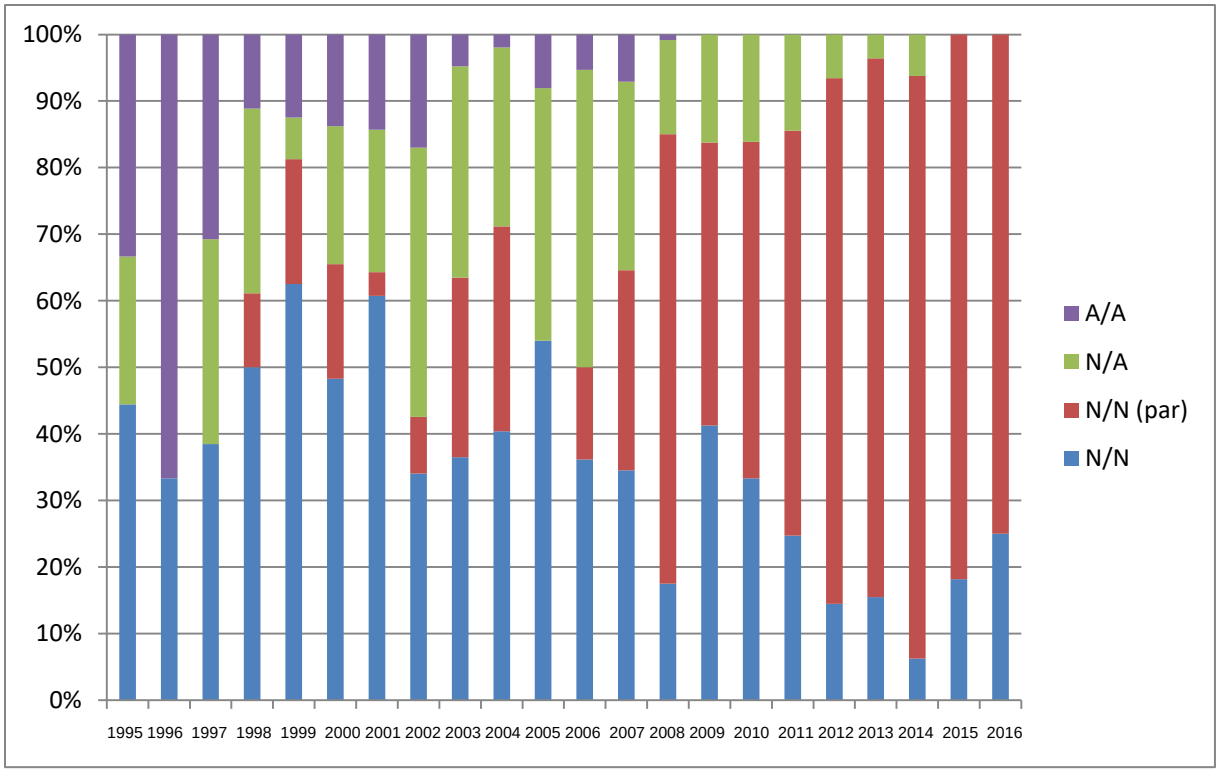


Figure 2 Percentages of PRA test results by birth year (DNA only, worldwide)

I just said, that no other forms have been detected. However, in one case, blindness was diagnosed in a prcd-PRA carrier. Did this case indicate another form of inherited PRA? Personally I don't think so. And why? Because the course of the condition didn't look like an inherited form. The blindness in this dog emerged within a few weeks, and such a quick progression is certainly not typical for an inherited form. It does however remind me of SORD (Sudden Onset Retinal Dysplasia), which causes blindness in a few weeks, but for which no cause could be identified yet. However, the German clubs initiated the ECVO eye test to become mandatory to be sure that any form would be detected.

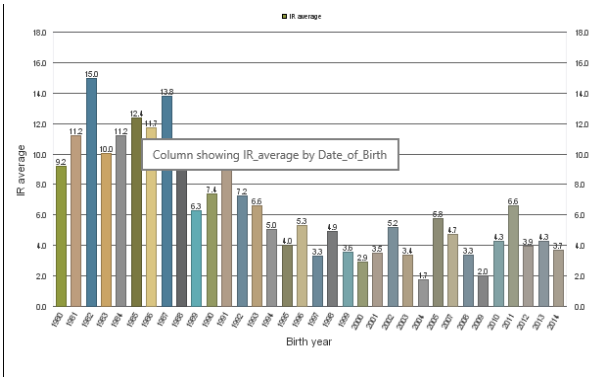
Despite this, this emergence of a second form is very well possible. In my other breed, the Lancashire Heeler, the DNA test for Primary Lens Luxation (PLL ADAMTS17 mutation) disclosed a till then unrecognized and still unidentified form, when carriers of the ADAMTS17 mutation and even dogs that were free of it, developed lens luxation. Research is now ongoing to identify this mutation too.

The downsides of testing

The examples of hip dysplasia (clinical test) and PRA (DNA test) illustrate how successful an intervention in the long term could be. However, there are also downsides to consider. If the tests lead to exclusion of many dogs, the overall effect could be disastrous by the increase of inbreeding ratios IR, also called Inbreeding Coefficient) in the population. Based on an 8 generation analysis according to Wright's algorithm, this is however not (yet) the case in the kuvasz. I give here two examples: The Netherlands and Hungary (please keep in mind that the Hungarian data are incomplete, so actual numbers might be different, but the point I want to make is about the trend).

A risk of increasing inbreeding ratios is the clinical emergence of other bad genes. Every dog has thousands of bad genes, of which some might cause severe problems. When we exclude large

numbers of dogs with problem A, problem B, C or D might get the chance to develop within the breed. So a careful selection policy, monitored by the IR over years, is mandatory.



Figuur 3 IR in The Netherlands

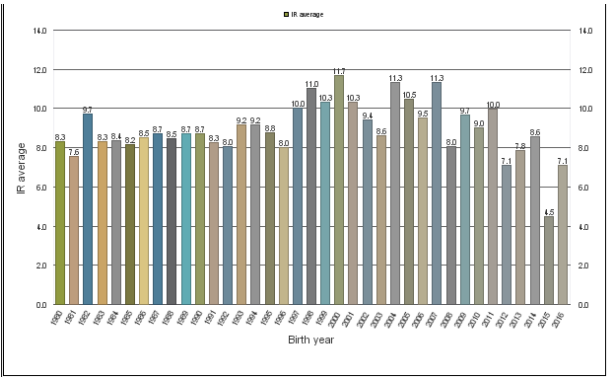


Figure 4 IR in Hungary

Another issue could be that you detect new problems. Examples are the PPM (Persistent Pupillary Membranes) and distichiasis. These were found “thanks” to the ECVO test. Were they not present before the test was done? Of course they were. Did they cause any problems? Not that I am aware of. So you really should wonder whether these “collateral findings” should lead to any intervention. Based on my experience in my other breed, and the opinion of leading ophthalmologists in The Netherlands, I would say that PPM is rather innocent and can be ignored until the opposite is proven. Distichiasis might be different, but I am not sure about that.

Conclusions

Coming back to the question I started with: Yes, testing makes sense and can be effective. I have been discussing tests for populations, but I sincerely believe that no individual breeder can run away from the fact that testing with subsequent interventions have a positive effect. Not always a test result is very pleasant, but in the end, the breed will benefit.

On the other hand, breed clubs should be careful with imposing new tests for or limitations due to newly found anomalies. Severity and importance should be weighed carefully against the potential decrease of the gene pool.

In the end, the choice to impose a test scheme is the result of a balance between the severity and the incidence of the condition, the availability of a relevant and reliable test and the options for interventions of any kind. One last note: if the incidence of a significant anomaly is unknown, that is, as such, an indication to start testing (but without any implications for breeding programmes till more is known).

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