Update on DNA-Testing

Carrier Distribution, Consequences and possible Strategies in ISDS Border Collies

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Abstract

This article gives a view on the current status of gene testing in ISDS Border Collies via a representative sample. It is based on test results from ISDS dogs. Totals of tested dogs were for CEA (791), IGS (697), TNS (530) and SN (281). Carrier percentages were for CEA (22,0%), for IGS (9,6%), for TNS (13,6%) and for SN (10,3%). 214 dogs were tested against all four diseases. 45% of those were carriers for at least one disease, and only 55% were completely free.

Diseases, numbers and their relevance are discussed further down, and causes for the rise in the last years discussed.

Population genetics show that the relationship between individual dogs rises in a closed breed and after a good 100 years seems to reach a critical limit which brings out recessive diseases. As far back as 2002, Teun van den Dool calculated that the total influence of „key dogs“ on then current population of pups was 72,4%. This development will have accelerated in the last 15 years, and it is the main reason we see these „new diseases“.

The speed of growing homozygosity in a dog breed is dependent on the number of founder dogs, the length of generation cycles, the amount of line breeding, and the use of popular sires.

Dangers for the breed obviously lie in uncontrolled increase of carriers and, further down the road, in affected. The same applies to well-meant but counter-productive actions.

Legal consequences can stem from consumer protection or animal welfare legislation. The English Animal Welfare Regulations of 2018 or the Irish Dog Breeding Establishment Guidelines (2019) include much stricter conditions for dog breeding and higher responsibilities for breeders. Wales and Scotland don’t have these regulations (yet), whereas most countries on the Continent do.

Further down in the article, common recommendations to control recessive diseases are listed, and their merit or potential for damage discussed and whether there should be the same rules for all dogs. Different dogs can have a very different impact on the breed. The average ISDS Border Collie has 20 pups, and every tenth dog will is bred from. If all breeding was done by that average, genetic diversity would be high, genetic diseases would be small problems, and mostly locally restricted. If less dogs are used to breed the same amount of pups, diversity obviously shrinks. Dogs with high offspring numbers have a higher impact on the breed than the average dog. This relates to desirable recessive traits like working ability the same as to undesirable recessive traits.

Selection against genetic diseases can be done negatively, positively, or not at all:

Negative selection works by excluding dogs from breeding, f.i. excluding carrier x carrier matings and carrier x affected matings.

Pro: Young dogs can be used for breeding because info about their genetic status can be obtained.

Con: Every genetic disease must be accessed individually, which can result in a considerable number of tests. It is a costly way to keep the breed healthy and puts a lot of burden on the one time breeder, who will not see returns of the costs.

Positive selection for health means breeding for longevity, health and healthy offspring, using only proven older and still healthy dogs, preferable with healthy offspring.

Pro: It is the most sustainable option, and it describes the history of the working Border Collie.

Con: As a modern guideline with most working dogs not working full time, and the amount of money turned over in the industry, it is unrealistic.

A compromise, to keep carrier numbers from rising uncontrollably and to keep ISDS rules compliant with new animal welfare legislation, could be testing of dogs that have a high impact on the breed. Concentrating on dogs with a high impact would save the majority of owners and breeders the hassle of additional testing, while probably keeping carrier numbers under control. It would, however, not totally eradicate the possibility of affected dogs or unknown carriers, and the viability in view of the animal welfare laws would need to be explored.

The last option is do nothing, and hope the bad stuff will go away by itself. That „solution“ is very popular. It has led to the multitude of destroyed pet dog breeds. Breeders ignored the warning signs when their breeding stock were only carriers until a big percentage of them were affected, which makes a way back near impossible.

ISDS Border Collies still are among the healthier breeds. It would be wise to keep it that way.

Introduction

In the last ten years, a number of „new“ genetic diseases in Border Collies have generated attention. These diseases have one thing in common, they all are inherited via a single gene mutation (monogenetic), and for all of them a gene test is available. From testing for CEA only, there now is the option to test for 4 to 5 different diseases.

When more pups and dogs got ill or died from IGS,TNS or SN, owners of closely related dogs were happy to have a tool to find out, whether their own dog was a carrier or even affected. If you step back from the individual case and look a the breed as a whole, testing is a fact finding mission. Widespread testing was vital to recognize whether there might be a real problem, or whether all was just a hype, possibly created by labs that wanted to market their tests.

The crucial questions to estimate a potential problem are, a) how big a percentage of dogs actually are carriers for the testable diseases, and b) how many affected dogs are there? While the second question won’t be answered anytime soon unless more people come forward, the first was the reason why I negotiated for a reasonably priced panel with Laboklin/Labogen. As many owners as possible should be encouraged to test their dogs. It is €89 for CEA, IGS, TNS and SN for the ABCD/ISDS panel, but more tests and parentage testing are available via the special form.

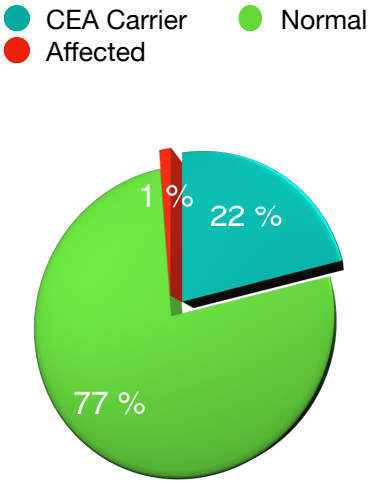
With the first hundreds of results coming in, it is important not to jump to conclusions straight away. Quite obviously, people who own a relative of a carrier or an affected dog are keener to test as others who don’t see a problem in their kennel. This gives a slanted view. In the beginning of testing, carrier percentages are overrepresented in comparison to the whole of the breed. This is the so-called negative bias. To get results without a big negative bias, as many random dogs as possible need to be tested. To achieve this, testing needs to be easy and not too expensive.

Now, with many hundreds of dogs tested, a first interpretation of the carrier numbers is viable.

The Diseases

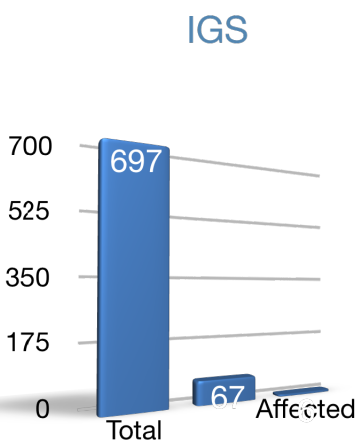
CEA

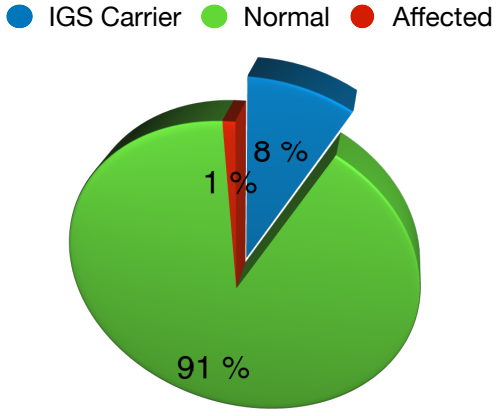
Collie Eye Atrophy is well known and widely spread through our breed. The gene test has come under fire in the last years, because the most debilitating condition of CEA, the coloboma, is not covered in the gene tests. On the other hand, there are dogs who are homozygously affected and still have passed their eye exam with flying colours and have perfect eyesight. CEA can render dogs blind, but among the testable diseases it is the most harmless one. The percentage of carriers and affected can be found in the adjacent diagram.



IGS

Imerslund-Grasbäck Syndrome describes an inability to ingest Vitamin B12 from the food. Vit B12 is a large molecule, too big for diffusion, so the body needs special transport proteins to pump it from the intestine into the blood stream. In dogs with IGS, a mutation of one responsible gene has occurred, and consecutively the encoded transport protein is defect.



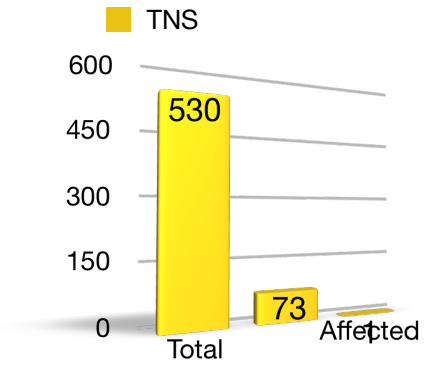


Symptoms are explained by the lack of Vit B12. Dogs stop to thrive around 6-12 months, they are thin, bad eaters, and can show chronic diarrhea, anemia, and progressive brain damage. Therapy consists of regular injections with Vit B12. It is a cheap and easy therapy, that will roll back all symptoms if started early enough.

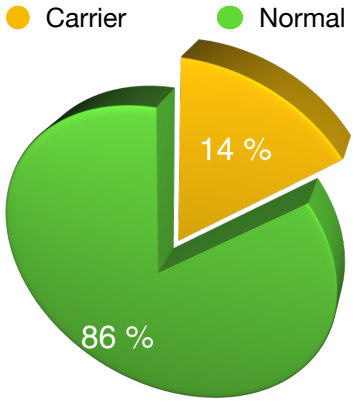
IGS is not totally rare. A carrier frequency of 8,1% is high enough to warrant attention.

TNS

Trapped Neutrophil Syndrome describes an inability to release the vital white blood cells from the bone marrow into the blood stream, they are trapped at their production site. White blood cells are the body's police force, without them no dog can survive any infection. TNS typically hits pups at the time around the first vaccination, because then the maternal antibodies are declining. It can be earlier, or in very rare cases even later, but any little infection will kill the pup. Symptoms can be multiple, depending on what kind of infection they catch.



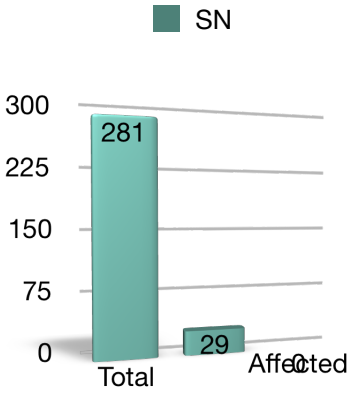
Interestingly, affected pups can have a typical appearance as well, a bit like Jack Russels, small, and with a long nose.



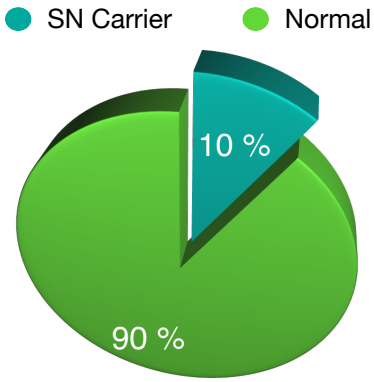
A carrier frequency of nearly 14 % is worrying. There is no way to evade that problem. CEA used to have a carrier frequency of 25%. It is now down to 21% due to the use of the gene test. A carrier frequency in the double digits warrants some action.

SN

Sensory Neuropathy is a degenerative disease of the peripheral nerves. It starts in the hind legs and wanders up. Pups lose sensation in their back legs, start swaying and might mutilate themselves, because they don't feel the pain. It is a deadly disease and pups should be euthanized before they suffer gravely. As with TNS, this is the reason that the statistic doesn't show any affected, it is not that there had not been any.



The SN test is the newest one, which is mirrored in the lower total number. Carrier numbers must be judged very carefully, they probably contain a negative bias of unknown size.



Causes

Are these diseases really new? Or have they always been around, and people are just fussier nowadays? The mutations have probably been around for a long time, but were so scarce that they didn't meet very often to form a recessive pair of genes (affected).

Basically, the whole breed is based on the first dogs' genes, which are mixed and remixed. This gives a lot of variation for a long time. Teun van den Dool identified 643 dogs maximum as founder dogs.

Still, over time it is inevitable that the relationship between dogs becomes closer. With closer relationship comes genetic conformity (homozygosity), because more identical genes are handed down from the parents. In other words, the longer a breed exists the higher is the probability that similar genes meet. It's why any farmer will buy in rams or bulls, and not just rely on his own flock. After a good hundred years of breeding, signs of rising homozygosity usually can be seen in dog breeds. These are speeded up by line breeding, short generation cycles or the use of popular studdogs. It is a balance. Everything, that contributes to more conformity will on the other hand also decrease diversity. While conformity in reliable working ability is a commendable breeding goal, the same conformity usually leads under the surface to a rising number of recessive defects.

We are lucky, that the ISDS has historically only used working ability as a criterion, so that selection used to be based on ability, longevity, good temperament, stamina and resilience.

What also contributed to diversity was regional breeding. Most stud dogs had a regional influence, and only very few had an impact on the whole breed. Those are the key dogs. Nowadays, with easy transportation and artificial insemination top dogs are bred to bitches all over the world, and the regional pockets of diversity get lost.

In former years, the odd carrier of a disease would not make an impact on the whole breed. When major stud dogs happen to be carriers of recessive diseases, the odds are shifting massively.

As early as 2002, Teun van den Dool calculated „The total influence of the 'key dogs' on the current population of pups born during the last five year, is 72.4 percent." This percentage is bound to have risen in the last 15 years. If one of these key dogs were found out to carry some rare recessive mutation this would explain rising carrier and affected numbers even decades later.

With some popular stud dogs being proven as carriers of IGS, TNS or SN by their offspring or by direct testing, we have seen rising carrier frequencies. Since, on first glance unrelated popular dogs still might have inherited the defective gene from some former common ancestor, this could explain the relatively high carrier frequencies we see in our sample.

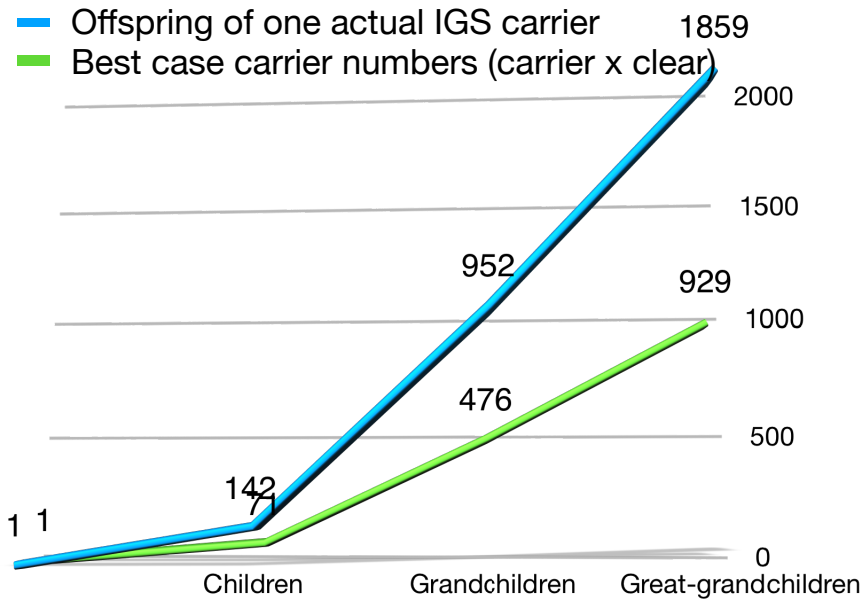
Consequences for Breeding

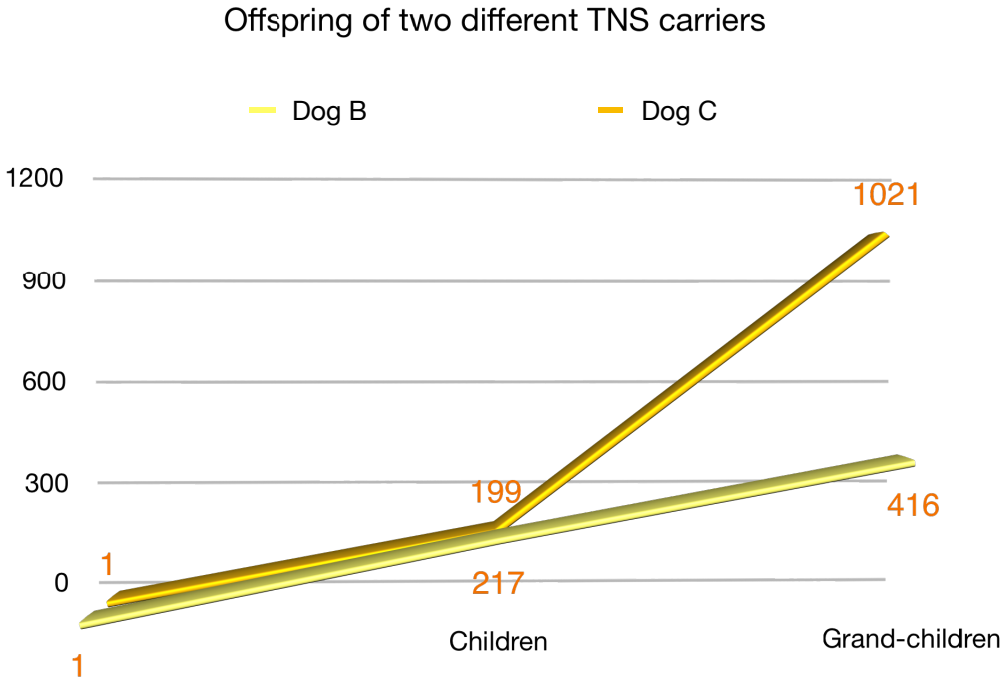
In a mating between a carrier and a clear the average distribution among the pups is 50% clear and 50% carriers. In a mating between two carriers, the pups will be 25% clear, 50% carriers and 25% affected. In a mating between a carrier and an affected, half of the pups will be carriers and the other half

affected. While this won't happen with TNS and SN because they are self-limiting, it is easy to imagine an undiagnosed IGS dog breeding.

So, even under the best circumstances half of the offspring of a carrier will also be carriers. When bred to carriers or affected the carrier numbers skyrocket. Knowing about the genetic status is the only way to keep carrier numbers under control.

A dog, that only breeds a couple of times in his life, has a very small impact on the breed. A dog, that breeds several hundred pups obviously has a much higher impact on the breed. If such a dog is a carrier of a genetic disease, the repercussions will be felt by many people. This is the situation we find ourselves in.

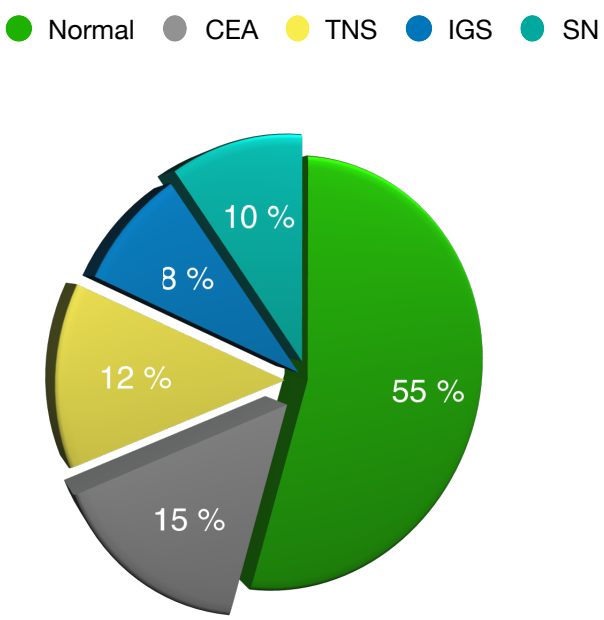




The use of popular sires has greatly contributed to the carrier numbers we see nowadays.

We used to look at pedigrees, trying to work out who might be a founder for a certain disease, nowadays with the help of gene tests we can watch the development in real time…

The most important number in all the gene results is the carrier frequency. It tells us, how likely it will be that in a mating two carriers might meet. The graph shows the percentages of carriers. From 214 dogs who had all four tests done, 45% were found to be a carrier for at least one disease.



This is a fairly shocking number. It predicts more and more double or triple carriers in the future if no steps are taken.

In the face of this graph it needs mentioning though, that ALL dogs carry hidden recessive mutations for deleterious conditions (reckoning is about 50), and the difference between a tested and an untested dog is only the knowledge about the tested status. Carriers of deleterious mutations are just as valuable as other dogs, on the contrary due to individual performance they can be highly desirable to breed from! Obviously, they also have the same worth for diversity as any clear dog.

Legal Consequences

With the English Animal Welfare Regulations 2018 and other likewise regulation in other countries having come up, a new kind of responsibility has arisen.

„6.5 No dog may be kept for breeding if it can reasonably be expected, on the basis of its genotype, phenotype or state of health that breeding from it could have a detrimental effect on its health or welfare or the health or welfare of its offspring.

Guidance:

- License holders must take all reasonable steps to ensure that the dogs are of good physical and genetic health, of acceptable temperament and fit for function (e.g. be able to see, breathe normally, and be physically fit and able to exercise freely). License holders must be aware of any health risks that may be specific to that type or breed. Where appropriate veterinary advice on the suitability of an animal for breeding must be sought.“

The same rules can be found in Germany, and probably in quite a few other countries with associated societies. The Irish Dog Breeding Guidelines (2019) are not quite as severe, but it is a reasonable assumption, that pressure on breeders will rise everywhere. To keep them safe from

exaggerated claims by buyers, breeding societies are well advised to create rules for dealing with genetic diseases. These should be based on scientific evidence, and preferably not harm the breed.

Possible strategies

There have been a number of recommendations put forward to deal with genetic diseases.

1. Banning carriers from breeding: This is a clearly counterproductive measure. No breed can afford to lose 40% of their breeding stock, and that is even without carriers for the polygenetic diseases like epilepsy and HD. It's an old recommendation and can safely be forgotten.

2. Restricting the number of bitches for every stud dog: This is a very popular measure in FCI clubs in hopes to slow down the rising level of relationship in a breed. This also does not work.

It has been shown, that breeders use close relations of a popular stud dog, if they cannot get the „real thing". These related dogs often lack in the individual genetic make-up for performance (otherwise they would be a popular sire in their own right), while all of their other genes are pretty similar because of the close relationship. They do not really help to keep a population genetically diverse. With this strategy, loss of working ability is traded against a small or no gain in diversity.

3. Breeding carriers only to clear partners: This is a well-known strategy, and it works as can be seen with the low CEA cases and sinking carrier percentages. The downside is that with the growing number of dual or even triple carriers breeding, options can get small. This is also the major argument to implement a sound policy before things deteriorate further.

The downside is that some promising matings cannot be made, and all owners of stud dogs and brood bitches are forced to take tests before they can even breed one litter. Quite obviously, results need to be made available, as has already been done by a multitude of conscientious breeders and studdog owners.

4. Testing only dogs with a high impact, then act as mentioned in point 3: Since not every stud dog has the same impact on the population, starting with the ones that have a major influence gives the best effect with fairly small effort. A potential cut-off number could be 30 pups or 5 litters.

This would keep the majority of breeders safe from too much bureaucracy and costs, while still avoid massive spread of known defect genes in the breed. It is a compromise, and a breeding society would be well advised to react, should the measure prove to be insufficient. This could easily be done by long-term statistics.

5. Reduce the relationship coefficient by aiming for a low inbreeding coefficient of the pups. By avoiding to breed a carrier of a defect to a same carrier, the risk of producing affected is prevented. Keeping the relationship in the whole breed as small as possible aka keeping the diversity as high as possible by encouraging breeders to use many different dogs and not overly focus on a few above average ones, will reduce the general risk and slow down the trend to homozygosity.

For a small fee, Teun van den Dool sells predictive pedigrees for a planned mating, which shows the expected COI (inbreeding coefficient) of the offspring.

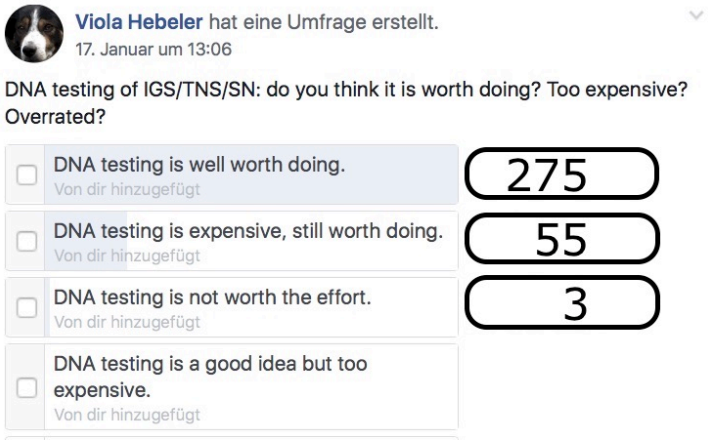
Teun's website www.bcdb.info must get a special mentioning at this point. It is a terrific fountain of knowledge about our breed, and a must-see for breeders, who are interested in genetics.

6. The only positive option to get out of this vicious circle is breeding for longevity, health in old age and stamina. This includes the use of older proven dogs, who have stayed healthy in spite of hard work, and have produced healthy offspring. The same goes for bitches, but their breeding age obviously is more limited.

Unfortunately, the conditions are not a given any more, since a too high percentage of working Border Collies don't do hard work on a daily basis for a number of years. The ones that do, and reach retirement are very valuable breeding material in this respect. On the other hand, the industry flourishes which is a good thing, and dogs with champion pedigree are the most sought world wide. So, the last strategy got a mention solely for the sake of completeness.

As to the acceptance of further DNA testing, I did a spontaneous poll among ISDS members in a Facebook group („ISDS Working Border Collies", 9,500 members) which resulted in an overwhelmingly positive response for DNA testing, with less than 1 percent voting it were not worth the effort. (Picture shows results after 24 hours)

Interestingly, the answers included not only hobby handlers but also dedicated breeders and owners of famous stud dogs.



Author's remark

This article does not claim to contain all knowledge on the subject. It is an attempt to give a distilled overview about the underlying theories and submit the most recent numbers for carriers in the ISDS population.

It was written to the best of the author's knowledge.

Major thanks go to Doris Brand for keeping all data conscientiously up to date, to Teun van den Dool for additional statistical background, and to both of them for their dedicated work for the breed over the last decades.

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ABCD Studbook Committee