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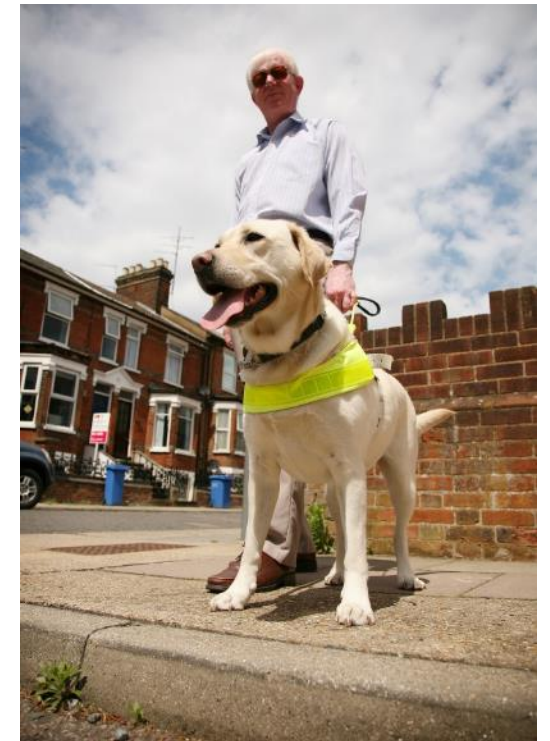


Implementation of Estimated Breeding Values (EBVs) for health and behavioural traits at Guide Dogs UK

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Work undertaken at University of Nottingham
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Introduction

- Guide Dogs is the largest breeder and trainer of working dogs in the world.
- Guide Dogs is currently responsible for more than 8,000 dogs including breeding stock and retired animals.
- Approximately 5,000 guide dog owners in the UK.



GUIDE
DOGS



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59%

Golden Retriever Crosses
(with Labradors or German Shepherds)



25%

Labradors



8%

Golden Retrievers



3%

German Shepherds



5%

Other breeds and crosses





Breeding

- The organisation breeds the majority of its own dogs.
- Approximately 86 stud dogs and 256 brood bitches.
- Purpose-built National Breeding Centre (NBC) opened in 2011 giving capacity to breed 1500 puppies a year.
- 1324 puppies were born in 2016.





Qualification rate

- Nearly 70% of puppies bred by Guide Dogs successfully become working guide dogs or breeding stock.
- Could this proportion be increased further using quantitative genetic techniques?





Starting point



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- What traits (behaviour, health, physical appearance) matter to Guide Dogs?
- What data are available?
 - Pedigree file
 - Health records
 - Behavioural assessment results:
 - Puppy profiling assessment (PPA)
 - Character assessment tracker (CAT)
 - Canine assessment summary (CAS)





Requirements for heritability analyses

1. Pedigree file

- All dogs represented in the pedigree should be clearly identified and not duplicated
- All familial relationships should be accurately reflected
- Both of these things were not always true – duplicates have now been removed and familial relationships identified where possible
- Contained 52275 individuals in January 2016

2. Phenotypic information on as many individuals as possible

- accurate identification of cases of a disease condition and those dogs which were definitely free of the condition
- behavioural assessment scores



Health records 1

- Mined Guide Dogs' database, dated February 2012 (then an SQL Server database)
- Considered dogs with complete health records – only dogs born since the beginning of 1995
- Considered only the 7 most numerous breeds and their crosses. Subsequently reduced to only GSDs, Labradors, Golden Retrievers and Lab x Golden
- Approximately 21000 dogs, reduced to 19000 when other breeds excluded
- Collected information on confirmed cases of any disease condition with a fair number of affected individuals



Health records 2

- Each time a dog belonging to Guide Dogs sees a vet, the vet completes a health slip
- Slip contains details of the consultation, any procedures carried out, medication given, diagnoses made and if any test results are awaited
- Slip then submitted to whichever site is responsible for that dog. Contents of slip entered into dog's health record in Guide Dogs Interactive by a support worker
- Entry checked and coded by a trained Dog Care & Welfare Advisor



Health records 3

- Old coding system used only 200 codes
- Replaced in 2009 with new system including approximately 2100 codes
- Codes may indicate:
 - a clinical sign eg polyuria
 - a procedure eg routine worming
 - a diagnosis eg chondrosarcoma



Example health record 1

- Flurry
- 27/09/2011
- Routine health check. Vaccinated with Nobivac PL. Waxy ears – Surolan. Slight tartar on carnassials.
- Codes:
 - Routine 6 monthly check
 - Routine vaccination
 - Wax in ear
 - Tartar



Example health record 2

- Kyran
- 09/01/2009
- X-ray shows very mild HD, no treatment now, possibly in future. ED confirmed via arthroscopy book in for arthrotomy.
- Codes:
 - Radiography of hindleg
 - Arthroscopy



Health records 4

- In order to pick up as many cases of a condition as possible, multiple codes were checked for most conditions
- For hip dysplasia, codes checked were: hip dysplasia, bilateral dysplastic hip, unilateral dysplastic hip, osteoarthritis of hip, osteoarthritis, chronic osteoarthritis, arthritis, degenerative joint disease, disorder of hip, hindlimb lameness, abnormal hindlimb gait, radiography of hindleg, radiography of hip, radiography of hip bilateral
- Cases of 46 disease conditions were collated



Identifying “non-cases”

- Clear definition needed, as for cases
- For cruciate ligament disease:
 - Health records from less than 1 year of age to at least 8 years of age
 - Not more than 1 year gap between health record entries
- To avoid confounding, in 2012 analyses only cases and non-cases born between 1995 and 2004 were included



Health records – key points 1

- Errors crept in at many stages in the process of entering health records into Guide Dog's database
 - Adequate training of staff required
 - Minimise number of staff involved in data entry
 - Situation improved since 2012
- A large number of dogs were lost to follow-up when they left Guide Dog's programme and had to be discounted from analyses
 - This could be addressed by requiring adopters to participate in annual health surveys
 - Survey of rehomed GSDs undertaken January 2016, enabled EBVs for an additional health trait



Health records – key points 2

- Initial data-mining exercise was extremely time-consuming
- Where possible the errors have been corrected in the master database
- Database has now been migrated from SQL Server platform to cloud-based Salesforce platform
- Reports created for each condition with all codes which need to be checked, only records created since last date undertaken need checking – much quicker

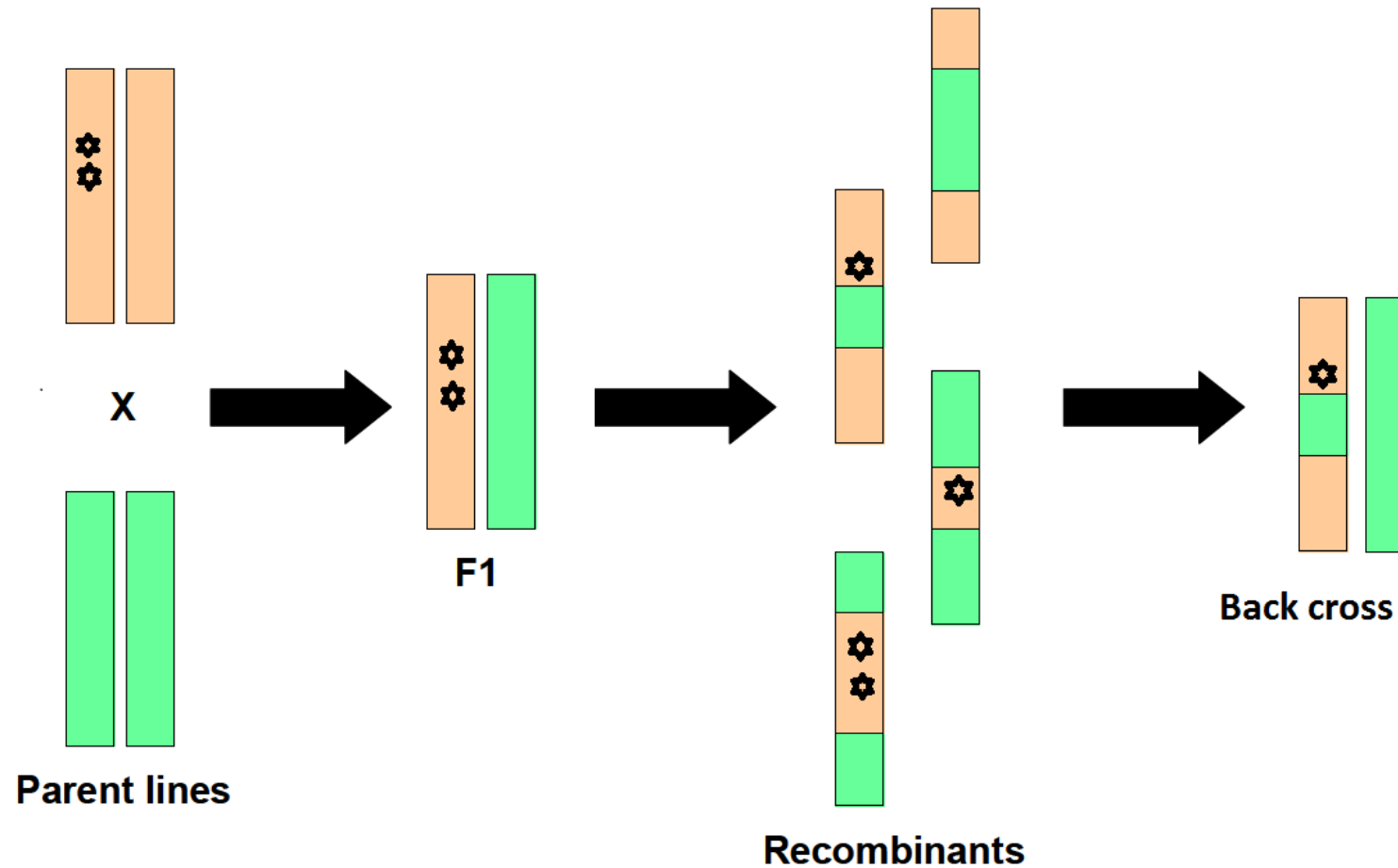


Heritability analyses 1

- Datasets prepared using Access and MATLAB
- Analyses performed in ASReml
- Univariate mixed linear models, treating diseases as binary (affected/unaffected) traits
- Fixed effects in the purebred models were gender, year of birth, inbreeding coefficient and whether the dogs were bred by Guide Dogs or not (and colour for Labradors)
- Crossbreed models the same but in addition breed fraction, heterosis and recombination loss were included as covariates
- Litter was included as a random effect



Heterosis and recombination loss





Heterosis and recombination loss 2

- Expected heterosis value is the probability that the two alleles at any one locus originate from different breeds.
- Expected recombination loss value is the probability that any two loci inherited from the same parent originate from different breeds.





Heritability analyses 2

- Successful heritability estimates:
 - Purebred Labradors: atopic dermatitis, cruciate ligament disease, diabetes mellitus, distichiasis, elbow dysplasia, entropion, hip dysplasia, laryngeal paralysis, multifocal retinal dysplasia, panosteitis, patellar luxation and seizures
 - Purebred Golden Retrievers: atopic dermatitis, congenital ichthyosis, entropion, Horner's syndrome and panosteitis
 - Purebred German Shepherd Dogs: atopic dermatitis, hip dysplasia, panosteitis and sebaceous cysts



Heritability analyses 3

- Successful heritability estimates:
 - Crossbreed models (include pure Labs, pure Golden Retrievers and any crosses between these 2 breeds): atopic dermatitis, cruciate ligament disease, elbow dysplasia, entropion, hip dysplasia, Horner's syndrome, panosteitis and seizures
 - The results of crossbreed models suggest that there are small health benefits of heterosis (hybrid vigour) for the first generation (F1) cross
 - These appear to be lost in the backcrosses (produced by breeding an F1 individual with one of the pure breeds)



A few interesting heritability estimates...

Labrador models:

Disease condition	Heritability (standard error)
Diabetes mellitus	0.08 (0.03)
Entropion	0.11 (0.04)
Laryngeal paralysis	0.11 (0.04)
Panosteitis	0.18 (0.04)





Behavioural assessment scores

- PPA – work previously described (at IWDC, La Grande Motte, 2015), looks promising but needs further work.
- CAT – insufficient data
- CAS – best option currently.





CAS – brief description

- Came into use in 2002
- 25 different “dimensions” are scored by trained staff, of which 3 are only scored during puppy walking and 6 only during early and advanced training
- Elements scored 1- 4 (training phase elements scored 1-7) with 1 always being the best score e.g. most confident or least distractible
- Work by Lucy Asher showed that scores at some time points are more predictive of qualification than others:
 - First visit, 5, 8 and 12 months in puppy walking
 - First assessment in early training
 - First assessment in advanced training



CAS – example element definition

- “Distraction” refers to the degree to which the dog focuses on the stimuli within the environment that interfere with its attention to the handler, training activity or guiding task.





CAS – example scoring

- Scoring for distraction:
 1. Seldom displays any distraction and its attention to the handler, activity or task is easily regained.
 2. Occasionally displays a moderate level of distraction but its attention to the handler, activity or task is easily regained.
 3. Occasionally displays a moderate to high level of distraction that interferes with its attention to the handler, activity or task.
 4. Frequently displays a high level of distraction that significantly interferes with its attention to the handler, activity or task.



CAS heritability analyses 1

- Insufficient data in the GSD currently.
- Heritability analyses undertaken for Labrador, Golden Retriever and crosses between these breeds for all CAS elements at all 6 time points identified as being most predictive of qualification.





CAS heritability analyses 2

- Datasets prepared using Access and MATLAB.
- Analyses performed in ASReml.
- Univariate mixed linear models.
- Fixed effects in the purebred models were gender, year of birth, age (in days) at assessment, inbreeding coefficient and whether the dogs were bred by Guide Dogs or not (and colour for Labradors).
- Crossbreed models the same but in addition breed fraction, heterosis and recombination loss were included as covariates.
- Litter and assessor were included as a random effects.



CAS model results

- Heritability estimates ranged from 0 to 0.24.
- No heritability estimates were detectably larger than zero for any CAS element at the first assessment in puppy walking.
- CAS element scores at the first CAS assessment in advanced training were generally more heritable than those during puppy walking or at the first assessment in early training.
- Estimates of litter effect were all small and mostly not detectably larger than zero.



CAS model results 2

- Different assessors appeared to have more of an effect on CAS scores than genetics.
- This environmental “noise” may be lowering the heritability estimates.
- Reducing the number of people assigning CAS scores, or working to make the scoring system even more standardised, may help to reduce this.





CAS model results 3

- Out of 120 univariate models, only 14 yielded heritability estimates detectably larger than zero in the purebred Golden Retriever models – smallest datasets.
- 42 univariate models yielded heritability estimates detectably larger than zero in the purebred Labrador models – datasets more than twice as large.
- 69 univariate models yielded heritability estimates detectably larger than zero in the crossbreed models – by far the largest datasets.



CAS model results 3

- The three “task acquisition” elements (handler position in busy areas, handler position in quiet areas and speed control), which are only scored in puppy walking, all had non-significant heritability estimates and large assessor effect estimates.
- The six “skills acquisition” elements (kerb work, locating objectives, on/off kerb work, right shoulder work, straight line work and traffic) which are only scored in early and advanced training all had non-significant heritability estimates and low to moderate assessor effect estimates.



Crossbreed CAS model results 1

- Six CAS elements (alertness, body sensitivity, distraction, interaction with people, stress resilience and suspicion) showed small to moderate beneficial effects of heterosis (hybrid vigour).
- This may relate to the higher success rate seen in the Labrador Retriever cross Golden Retriever compared to either pure breed.





Crossbreed CAS model results 2

- Three CAS elements (body sensitivity, eagerness and stress resilience) showed slight detrimental effect estimates for recombination loss.
- Recombination loss occurs in second generation crosses between F1 hybrids, or in backcrosses, due to re-pairing of genes during meiotic recombination resulting in the loss of beneficial associations between genes which are close together in the pure breeds.
- This suggests that some of the benefits in behaviour, as measured by CAS scores, seen in the F1 may be at least partially lost in the backcrosses.



PhD endpoint:

- Many (health and) behavioural traits found to be heritable
- Which ones of most importance?





Determination of selection priorities

- Determined collaboratively
- Factors considered for each health and behavioural trait:
 - Impact on welfare of affected dog
 - Impact on the guide dog owner
 - Estimated life time cost of the trait (health only)
 - Percentage of dogs affected by the condition but not withdrawn (health only)
 - Percentage of dogs withdrawn due to the trait each year



Selection priorities for Labrador Retrievers

Condition/trait	Impact on welfare of the dog (Score 0 to 100)	Impact on the Guide Dog Owner (either as a result of managing the condition or reduced mobility) (Score 0 to 100)	Estimated lifetime cost of the condition (Score 0 to 100)	Percentage of dogs affected but not rejected (actual percentage)	Percentage of dogs rejected out of those bred each year (actual percentage)	Cost of reduction in working life (Score 0 to 100)	Total score (divided by 600 for health traits and 400 for behavioural traits)	Ranking
Elbow dysplasia	60	100	80	1.63	2.77	85.46	0.55	2
Hip dysplasia	50	50	50	2.07	1.21	75.33	0.38	9
Atopy	55	65	90	3.30	1.70	44.58	0.43	6
Panosteitis	25	0	0	3.84	0.05	0	0.05	21
Entropion	10	0	10	1.08	0	0	0.04	22
Horner's syndrome	10	5	5	0.25	0	0	0.03	23=
Cruciate disease	55	70	40	1.14	0.21	29.36	0.33	12
Seizures	30	85	15	1.17	0.48	53.74	0.31	13
Diabetes mellitus	45	90	20	0.48	0.02	22.35	0.30	14=
Distichiasis	10	0	5	0.37	0	0	0.03	23=
Laryngeal paralysis	25	20	10	1.60	0.02	66.58	0.21	19
Patellar luxation	40	100	35	0.45	0.17	66.64	0.40	8
Vaginal strictures	0	0	0	0.94	0	0	0.002	26
Cystic endometrial hyperplasia	0	0	5	0.96	0	0	0.009	25
Aggression animals	45	90	X	X	0.83	64.78	0.50	3
Aggression people	55	100	X	X	2.12	79.46	0.59	1
Attentiveness	5	70	X	X	4.31	62.89	0.36	10=



Most important heritable health traits

Trait	GSD h ²	Lab h ²	GRet h ²	Crossbreed h ²
Atopic dermatitis	0.24 (0.11)	0.14 (0.04)	0.18 (0.07)	0.11 (0.02)
Cruciate ligament disease	-	0.14 (0.05)	0.26 (0.12)	0.10 (0.03)
Elbow dysplasia	-	0.35 (0.06)	NS	0.23 (0.04)
Hip dysplasia	0.30 (0.12)	0.15 (0.06)	NS	0.12 (0.03)
Patellar luxation	-	0.10 (0.04)	-	-
Seizures	-	0.13 (0.05)	NS	0.11 (0.03)



Most important heritable CAS traits 1

Trait	Lab h^2	GRet h^2h^2	Crossbreed h^2
Aggression towards people	0.08 (0.03)	NS	0.03(0.01)
Aggression towards animals	0.07 (0.03)	NS	0.05 (0.01)
Suspicion	0.07 (0.03)	0.21 (0.10)	0.10 (0.02)
Stress resilience	NS	NS	0.05 (0.02)



Most important heritable CAS traits 2

Trait	Lab h^2	GRet h^2	Crossbreed h^2
Body sensitivity	0.15 (0.04)	NS	0.15 (0.02)
Confidence	NS	NS	0.05 (0.01)
Distraction	0.10 (0.04)	0.12 (0.08)	0.15 (0.02)
Attentiveness	0.15 (0.04)	0.09 (0.06)	0.11 (0.02)



CAS genetic correlation estimates 1

Trait	Crossbreed (Lab x Golden)
Aggression animals – aggression people	0.56 (0.17)
Aggression animals - suspicion	NS
Aggression people - confidence	0.47 (0.16)
Aggression people – stress resilience	0.54 (0.16)
Aggression people - suspicion	0.54 (0.13)



CAS genetic correlation estimates 2

Trait	Crossbreed (Lab x Golden)
Attentiveness - confidence	0.26 (0.14)
Attentiveness - distraction	0.74 (0.27)
Attentiveness – stress resilience	0.28 (0.13)
Attentiveness - suspicion	0.26 (0.12)
Body sensitivity - confidence	0.48 (0.11)



CAS genetic correlation estimates 3

Trait	Crossbreed (Lab x Golden)
Body sensitivity - distraction	-0.25 (0.11)
Body sensitivity – stress resilience	0.30 (0.04)
Body sensitivity - suspicion	0.36 (0.10)
Confidence – stress resilience	0.80 (0.08)
Confidence - suspicion	0.91 (0.06)
Stress resilience - suspicion	0.91 (0.05)

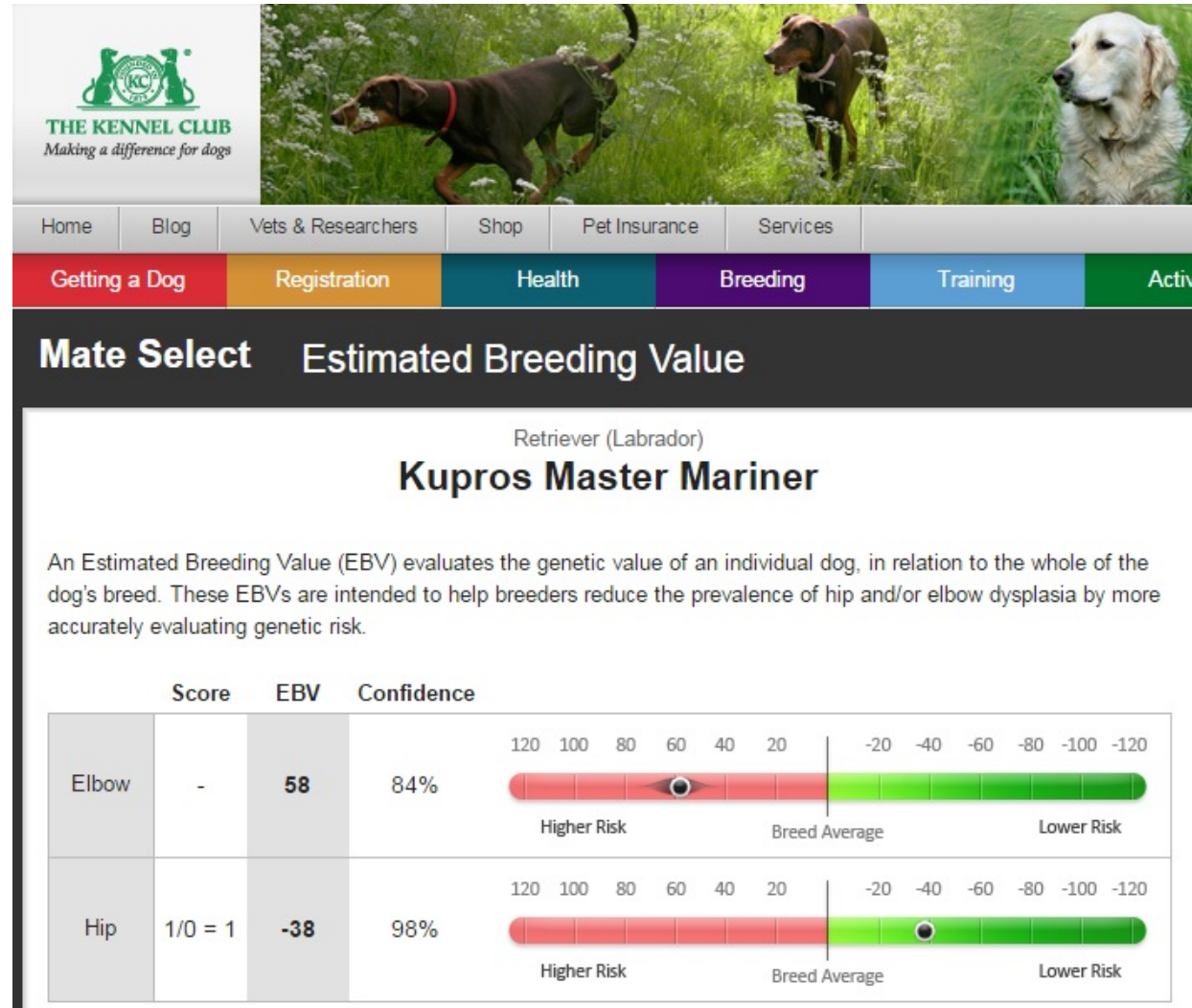


What happens now?

- Starting to use health trait EBVs
 - GSDs: atopy, hip dysplasia
 - Pure Golden Retrievers: atopy, cruciate ligament disease
 - Pure Labrador Retrievers: atopy, cruciate ligament disease, elbow dysplasia, hip dysplasia, patellar luxation and seizures
 - Crossbreed models: atopy, cruciate ligament disease, elbow dysplasia, hip dysplasia and seizures
- 8-trait CAS selection index for Labs, Goldens & their crosses
- Genetic diversity appears to be being maintained well, continue to monitor

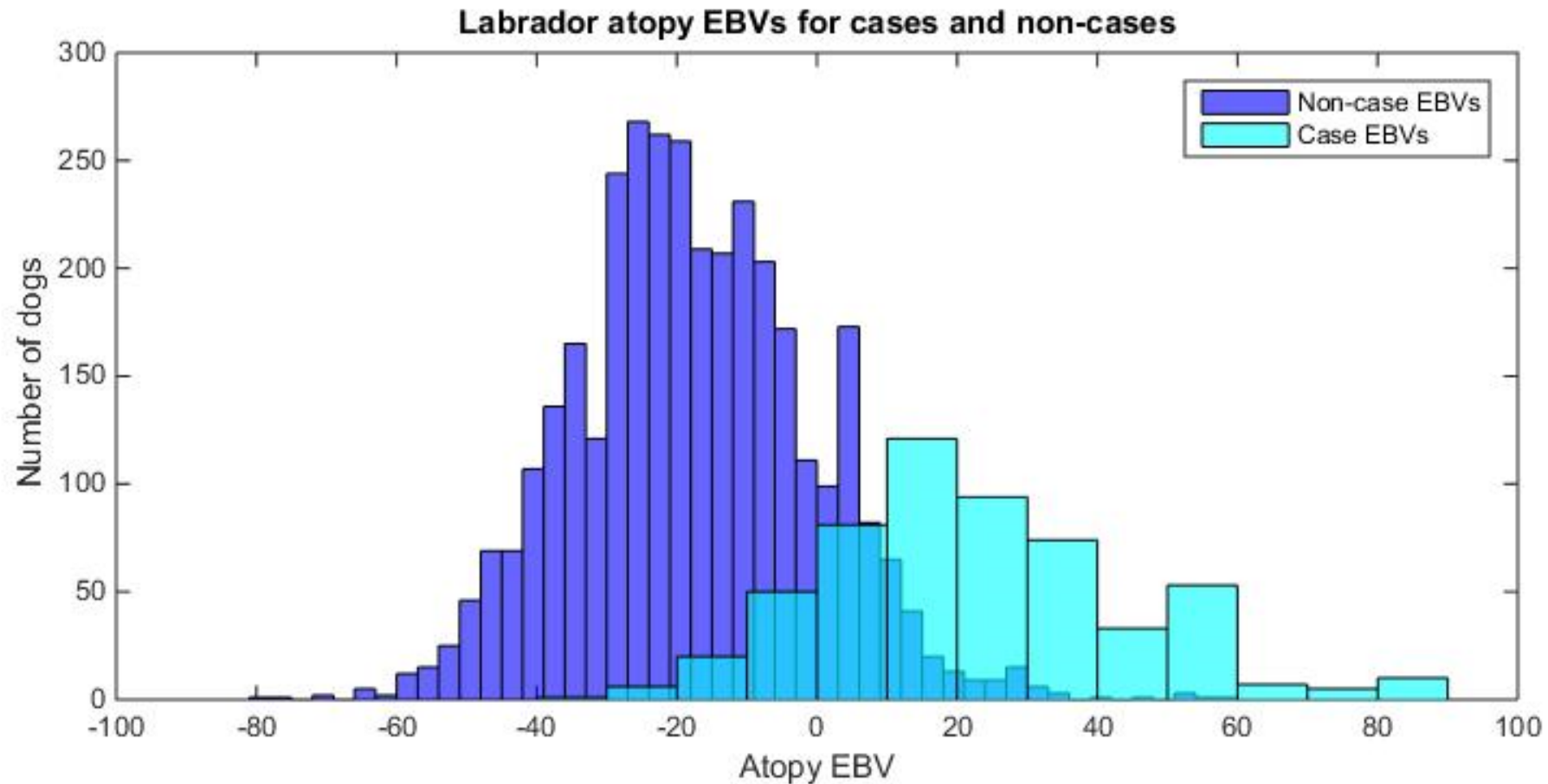


EBV visual example





Atopy EBVs – cases and non-cases





Pure breed vs crossbreed health EBVs

- High correlation coefficients between population's pure and crossbreed EBVs for the 5 health traits which have both models (0.81 – 0.94)
- Striking differences between pure and crossbreed EBVs for some individuals
- Example Golden Retriever stud dog:
 - Pure breed atopy EBV -16.49 (accuracy 0.75)
 - Crossbreed atopy EBV +20.37 (accuracy 0.89)





CAS selection index 1

- A selection index is a means of combining several individual EBVs into one numerical value per dog.
- Individual elements of the selection index are “weighted” differently according to their relative importance.





CAS selection index 2

- 8-trait CAS selection index now available for Labs, Golden Retrievers & their crosses
- Based on scores received at the first assessment in advanced training
 - Not all dogs reach this assessment, so not the time point with the largest dataset
 - However the heritability estimates were largest, and assessor effect estimates smallest, at this time point
- Traits weighted using scores from selection priorities work
- Estimated selection accuracy of 40%





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