THE KENNEL CLUB

Genetics and Health Testing

Dr Joanna J. Ilska

Talk Outline

1. Genetic basis of disease
2. Hip and Elbow Dysplasia – KC/BVA Scheme data for BMD
3. Estimated Breeding Values (EBVs)
4. Genetic diversity

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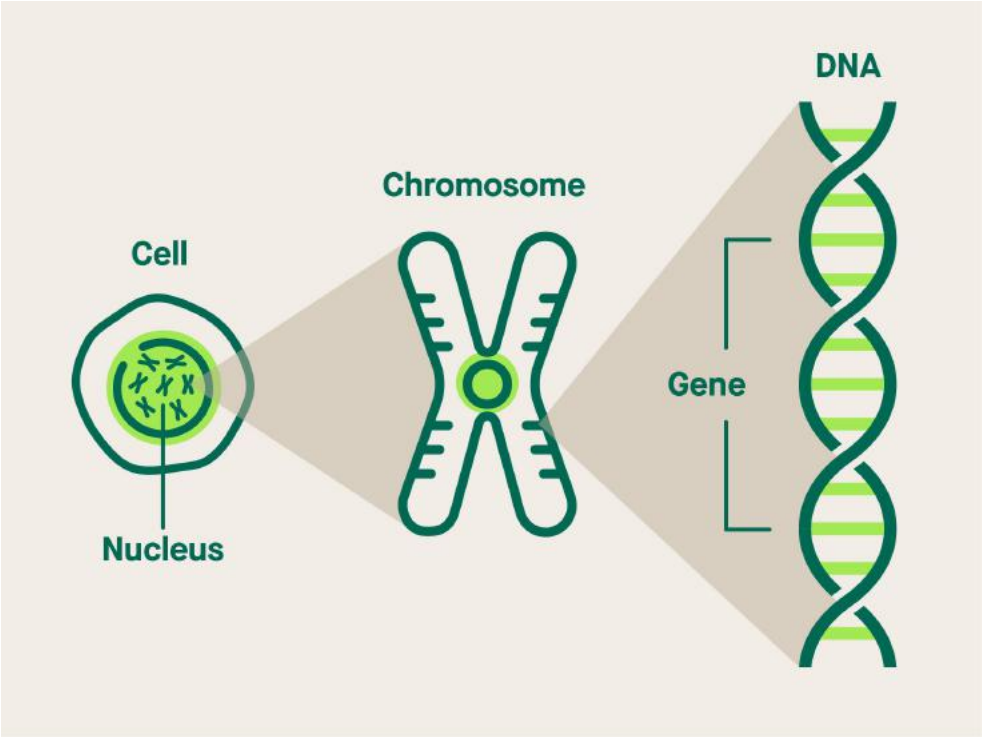
Genetic basis of disease

Genetic basis of variability



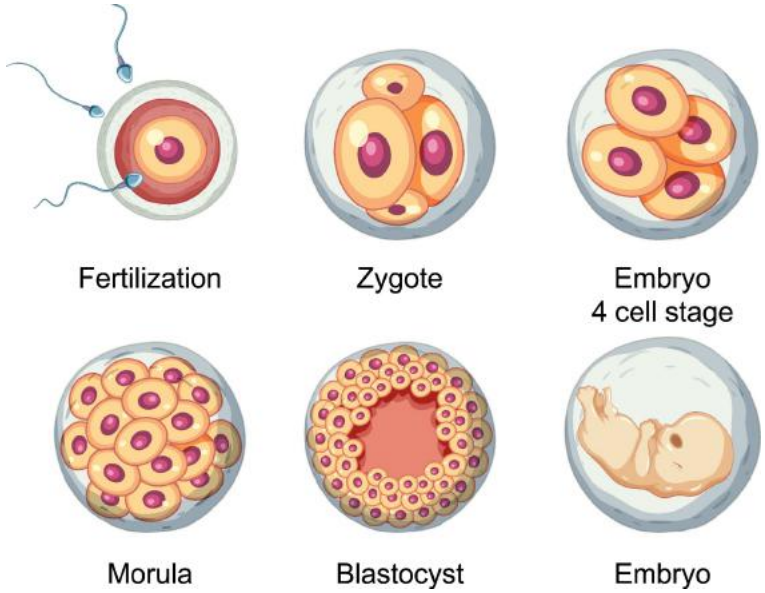
Dogs genome

2.5 billion base pairs

~19K genes

Genetic basis of variability

1. Growth, life cycle → new cells (including reproductive cells) → DNA needs to be replicated

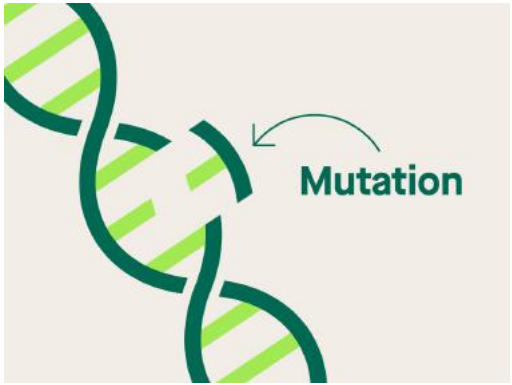


Genetic basis of variability

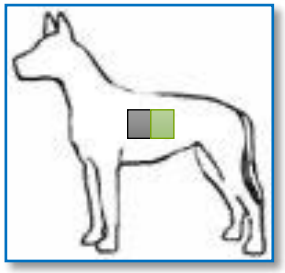
1. Mutation:
    1. Typically small alteration in DNA code
    2. May change the protein the DNA codes for:
        1. Mostly deleterious
        2. Some can be beneficial
        3. May be silent - neutral (no effect)

ALL organisms have mutations

Every person in this room has ~70 completely novel mutations

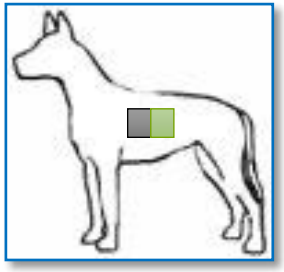


Basic terms



- **Allele** – a single copy of a gene. Different alleles are created through mutation
- Each individual has 2 alleles of each gene – the pair is called a **genotype**

Basic terms



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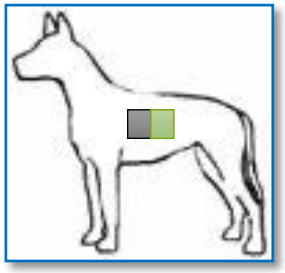
Dog's Genotype – a set of genotypes across all genes

Basic terms



- **Allele** – a single copy of a gene. Different alleles are created through mutation
- Each individual has 2 alleles of each gene – the pair is called a **genotype**
- Visible/measurable characteristic - **phenotype**

Dog's Genotype – a set of genotypes across all genes

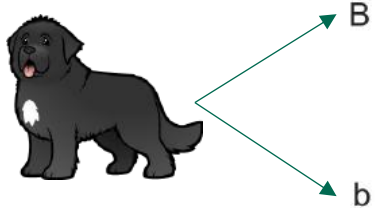
Single gene traits

1. Simplest scenario:
    1. Phenotype completely controlled by a single gene
    2. Bi-allelic – only two alleles possible (e.g. ‘B’ – black coat, ‘b’ – brown coat)
    3. Recessive – two copies of the mutant allele needed for the mutation to change the phenotype (dog’s coat visibly brown)

Single gene traits

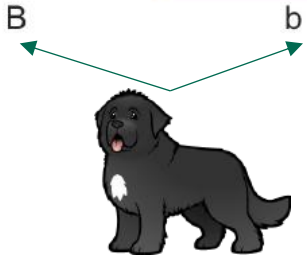
25% chance of BB
50% chance of Bb
25% chance of bb

1. 1 gene → 2 alleles → 3 possible genotypes:
    1. BB – normal, black coat
    2. Bb – carrier, black coat, but can pass brown to progeny
    3. bb – both alleles are mutant, brown coat



Punnett Square

	B	b
B	BB	bB
b	Bb	bb



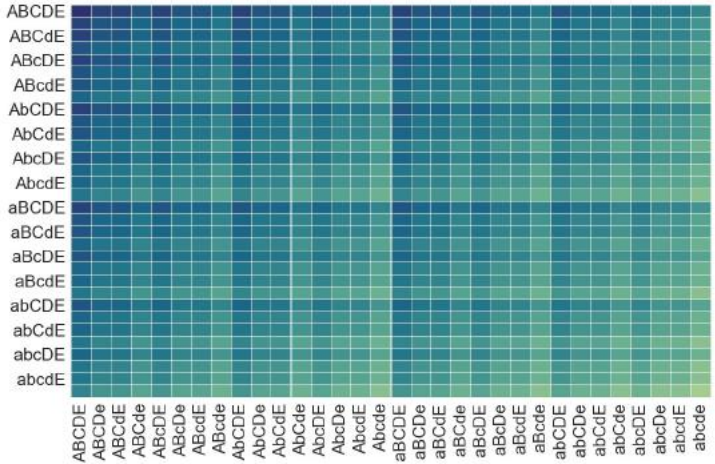
Polygenic traits

1. The number of possible genotype combinations increases with the number of genetic variants involved

$$Number\ of\ unique\ genotypes = 3^{number\ of\ genes}$$

# Genes	# Genotypes
1	3
3	27
5	243
10	59,049

Punnett Square



Polygenic traits

1. The number of possible genotype combinations increases with the number of genetic variants involved
2. The effects of individual genes are typically very small – total genetic value is the sum of individual gene effects

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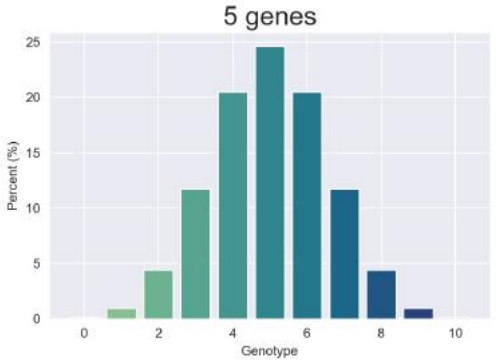

Polygenic traits

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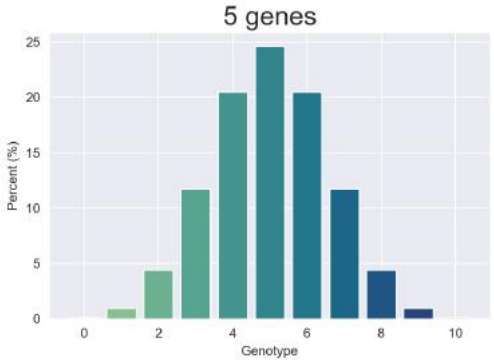
    - The same effect produced by many combinations of genotypes

When considering complex traits, we want to assess the overall genetic merit of the dog, rather than track individual gene variants.

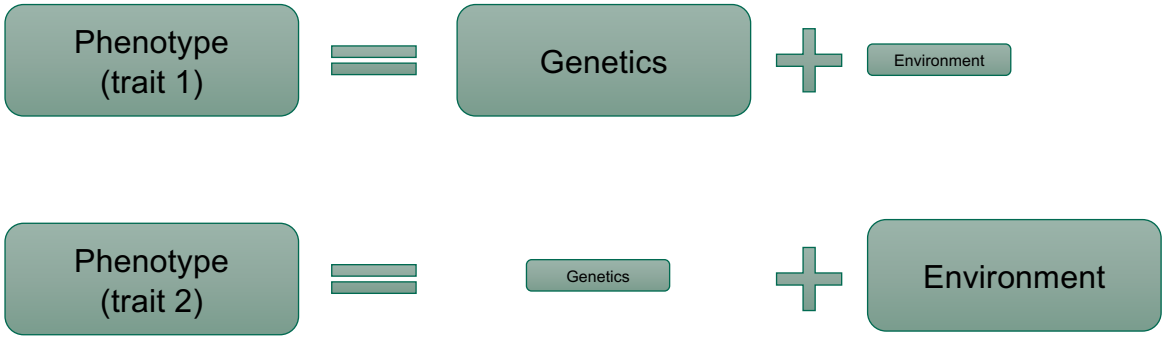


Polygenic traits

1. The number of possible genotype combinations increases with the number of genetic variants involved
2. The effects of individual genes are typically very small – total genetic value is the sum of individual gene effects
3. Frequently affected by environment

Heritability (h^2)

- Heritability - how much of the variation we see in the trait can be explained by genetics?
  - h^2 = 0% → all variation comes from environment
  - h^2 = 100% → all variation comes from genetics



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- Heritability - how much of the variation we see in the trait can be explained by genetics?
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- Heritability is a parameter of a “trait in a population”, not an absolute value for the trait!

Identical genetics (twins, clones)

h^2 ~ 0%

Environment ~ 100%
Genes ~ 0%

Identical environment

h^2 ~ 100%

Environment ~ 0%
Genes ~ 100%

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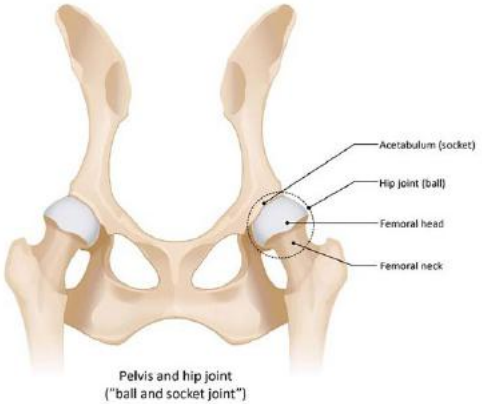
Hip and Elbow Dysplasia in BMD

Hip dysplasia (HD)

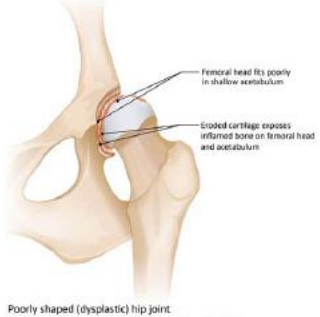
- Developmental orthopaedic disorder of the hip joint
- Malformation and laxity of the joint lead to osteoarthritis (OA)
- OA is irreversible



Pelvis and hip joint
("ball and socket joint")

Laxity → Altered growth/remodelling of the joint surfaces → Abnormal forces → Osteoarthritis → Pain, lameness

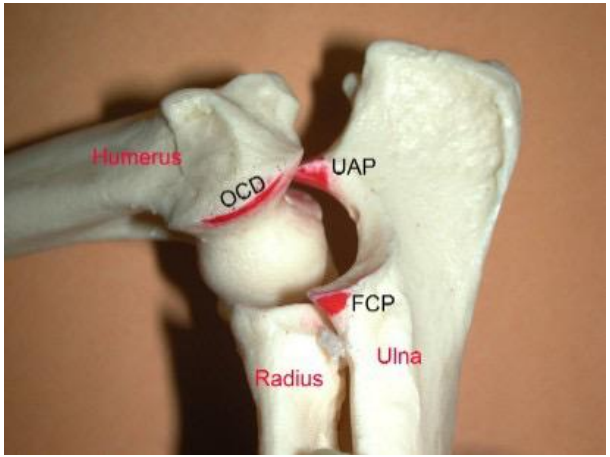
Normal hip joint



Poorly shaped (dysplastic) hip joint
with secondary bone damage and inflammation (osteoarthritis)

Very deformed (severley dysplastic) hip joint with gross secondary bone damage
and inflammation (advanced and very painful osteoarthritis)

Elbow dysplasia (ED)



- Developmental orthopaedic disorder of the elbow joint
- Primary lesions:
  - Fragmented or ununited medial coronoid process (FCP)
  - Osteochondritis dissecans (OCD or OD)
  - Ununited anconeal process (UAP)
- Primary lesions lead to OA, which is irreversible

Primary lesions → Altered growth/remodelling of the joint surfaces → Abnormal forces → Osteoarthritis → Pain, lameness

HD/ED in BMD

1. Hip Dysplasia – OR = 7.2
2. Elbow Dysplasia:
    1. FCP OR = 140
    2. UAP OR = 50

Odds ratio (OR):

OR >1, breed more at risk of developing condition than control

OR = 1, breed at the same risk as control

OR < 1, breed less likely to develop the condition than control

LaFond, E., Breur, G. J., & Austin, C. C. (2002). Breed susceptibility for developmental orthopaedic diseases in dogs. *Journal of the American Animal Hospital Association*, *38*(5), 467-477.

BVA/KC Hip/Elbow Dysplasia Schemes

- Xray of dogs when >1 year old (at GP vets)
- Xray sent to BVA
- Panel of scrutineers – specialists

BVA/KC Hip/Elbow Dysplasia Schemes

Hip Dysplasia

- Range 0 – 53 per hip, 0 – 106 total

CERTIFICATE OF SCORING

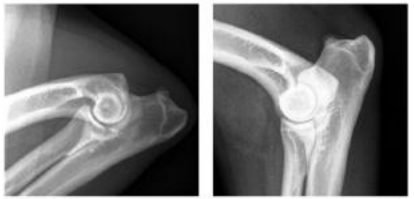
HIP JOINT	Score Range	Right	Left
Norberg angle	0-6	3	1
Subluxation	0-6	3	2
Cranial acetabular edge	0-6	2	2
Dorsal acetabular edge	0-6		
Cranial effective acetabular rim	0-6		
Acetabular fossa	0-6		
Caudal acetabular edge	0-5		
Femoral head/neck exostosis	0-6		
Femoral head recontouring	0-6		
TOTALS	(max possible 53 per column)	8	5

13 Total score (max possible 106)

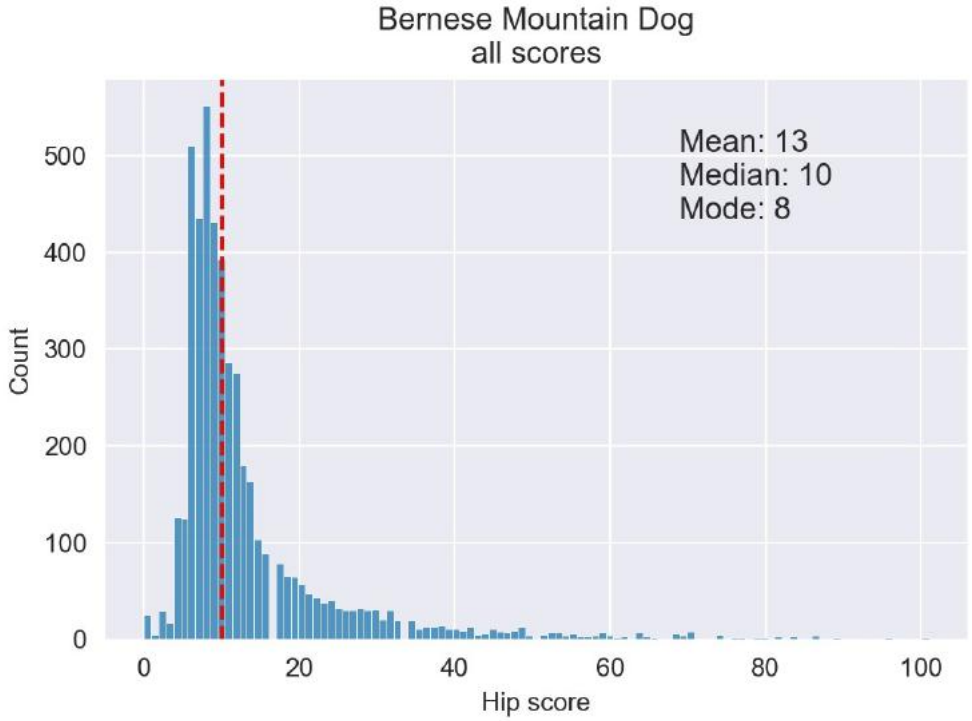
Elbow Dysplasia

- Grades:
  - 0 – radiographically normal
  - 1 – Mild osteoarthritis (OA)
  - 2 – Moderate or a primary lesion with no OA
  - 3 – Severe OA or a primary lesion with OA

	RIGHT	LEFT
GRADE (range 0-3)	1	2
OVERALL GRADE (max possible 3)	2	



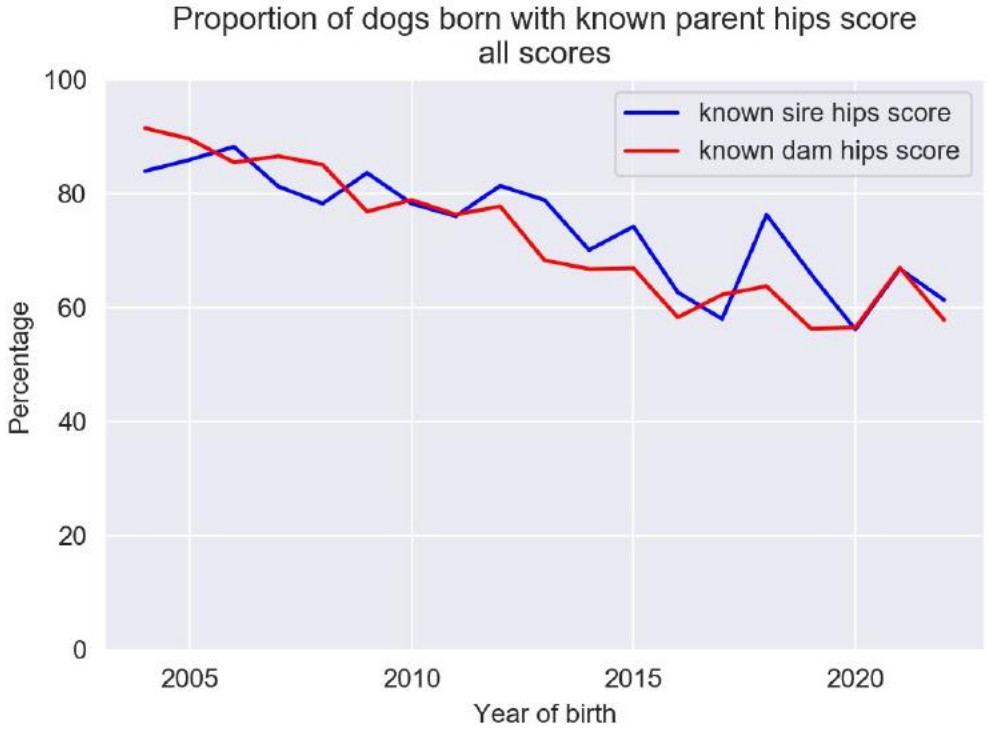
BVA/KC Hip Dysplasia Scheme



BVA/KC Hip Dysplasia Scheme
Total of 4,746 hip scores (BMD)

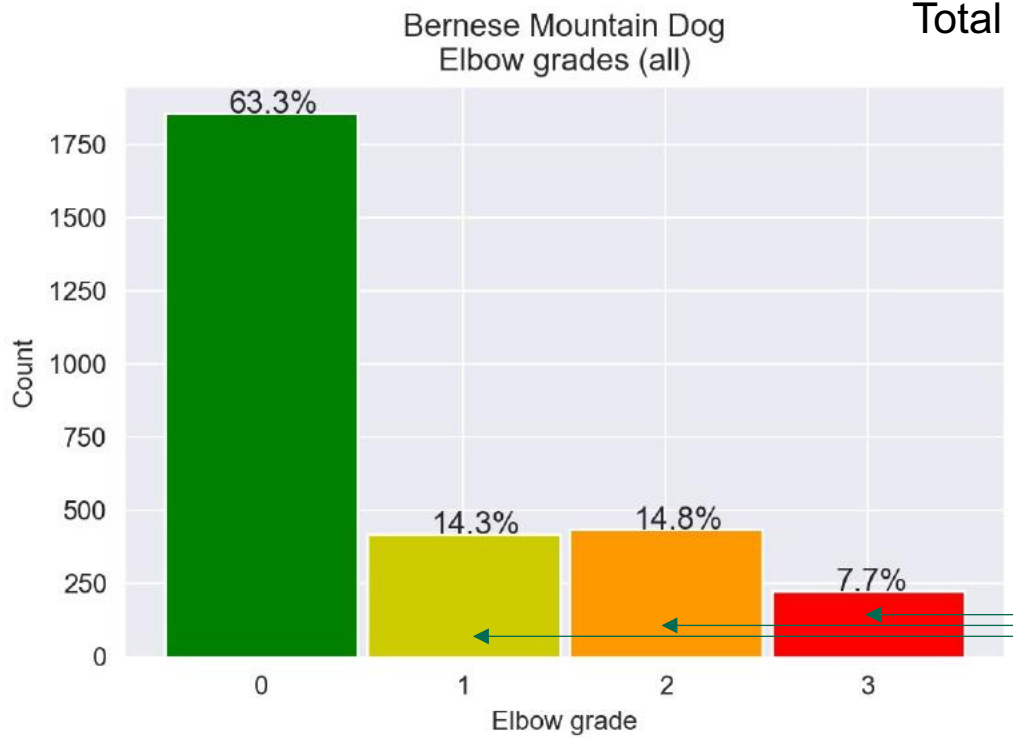
Breed	Mean	Median
Labrador	11	9
German Shepherd	15	11
Rottweiler	10	8

BVA/KC Hip Dysplasia Scheme



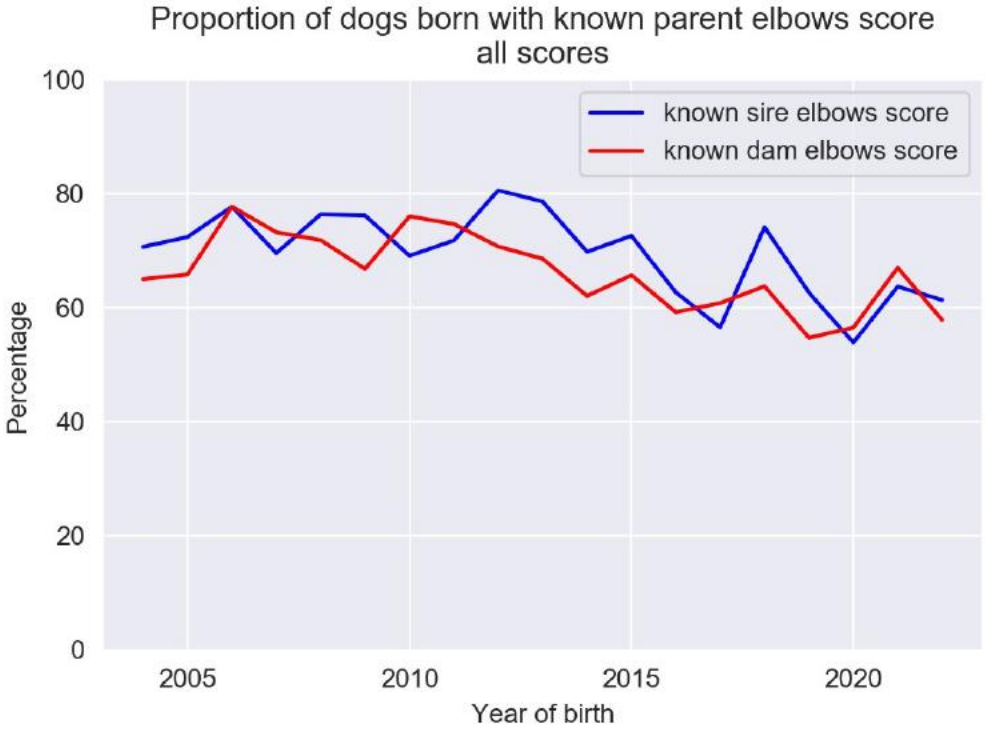
BVA/KC Elbow Dysplasia Scheme

BVA/KC Elbow Dysplasia Scheme
Total of 2,936 elbow grades



37% some degree of elbow dysplasia

BVA/KC Elbow Dysplasia Scheme



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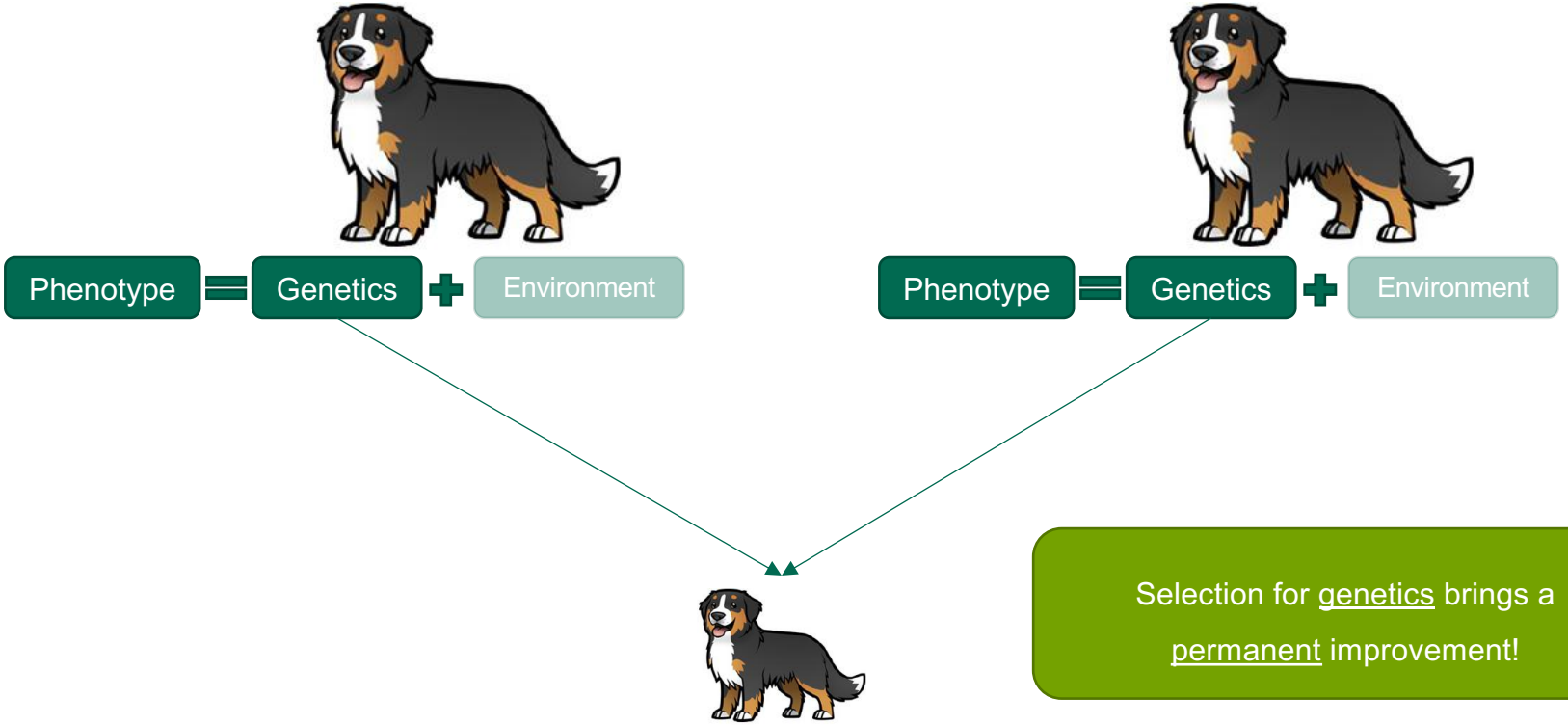
Genetics of Hip and Elbow Dysplasia

Phenotype = Genetics + Environment

Phenotype = Genetics + Environment

Genetics – focus for breeders!



Selection for genetics brings a permanent improvement!

Heritability

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h^2 of HD in BMD
37%

h^2 of ED in BMD
27%

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"Only 37% of your dog's hip score is due to genetics"

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h^2 of HD in BMD
37%

h^2 of ED in BMD
27%

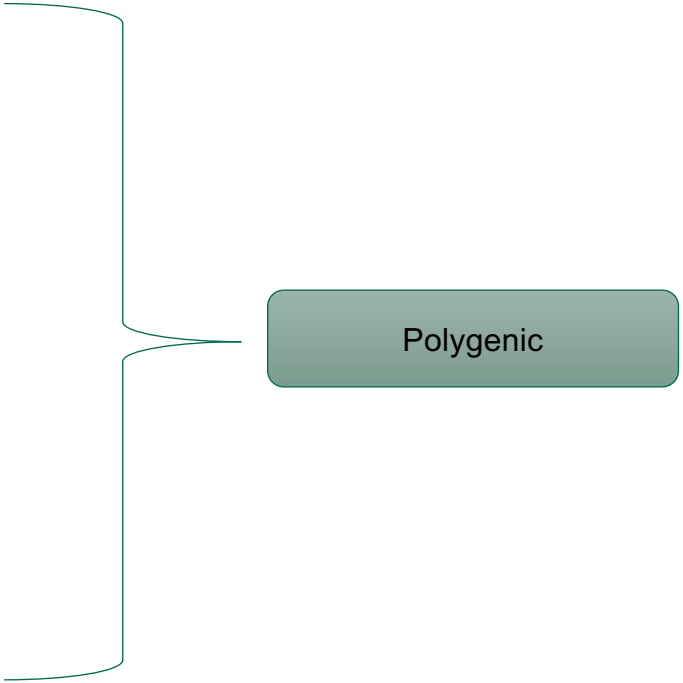
~~*"Only 37% of your dog's hip score is due to genetics"*~~

37% of the variation in the hip score <u>in the breed</u> can be explained by genetics

Genetics of hip/elbow dysplasia

1. Genes involved:
    1. Conformation of the hip and elbow joint
    2. Laxity
    3. Growth and maturity rates – hormonal activity?
    4. Bone mass and density?
    5. Muscle development?
    6. Cartilage matrix composition?

    7. *(Temperament? Preferred activities? Appetite?)*



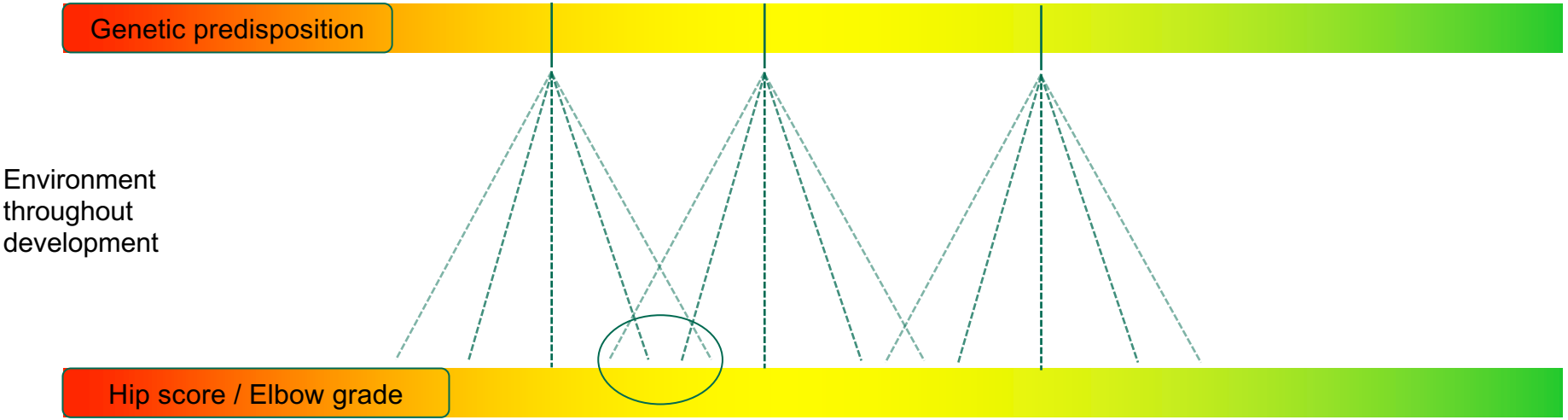
Complex Traits

Genetic predisposition

Environment throughout development

Hip score / Elbow grade

Complex Traits



Complex Traits

Prevalence and inheritance of and selection for elbow arthrosis in Bernese Mountain Dogs and Rottweilers in Sweden and benefits:cost analysis of a screening and control program

Swenson et al (1997)

	% with ED	% with severe ED
Grade 0 x Grade 0	31	11
Grade 0 x Grade 1	44	19
Grade 0 x Grade ≥ 2	56	27
Grade ≥ 2 x Grade ≥ 2	59	29
Grade 0 x Not tested	40	18
Not tested x Not tested	60	32
Grade ≥ 2 x Not tested	51	29

Complex Traits

How the Orthopedic Foundation for Animals (OFA) is tackling inherited disorders in the USA: Using hip and elbow dysplasia as examples

G. Gregory Keller[a,*], Edmund Dziuk[a], Jerold S. Bell[a,b]

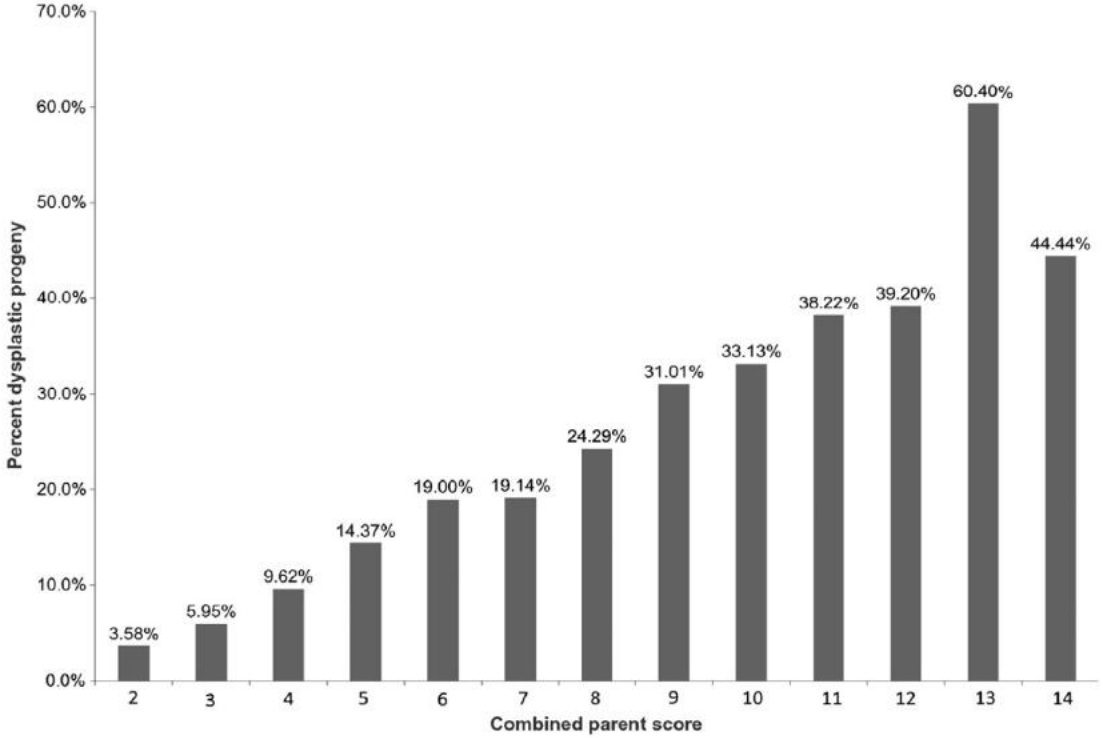
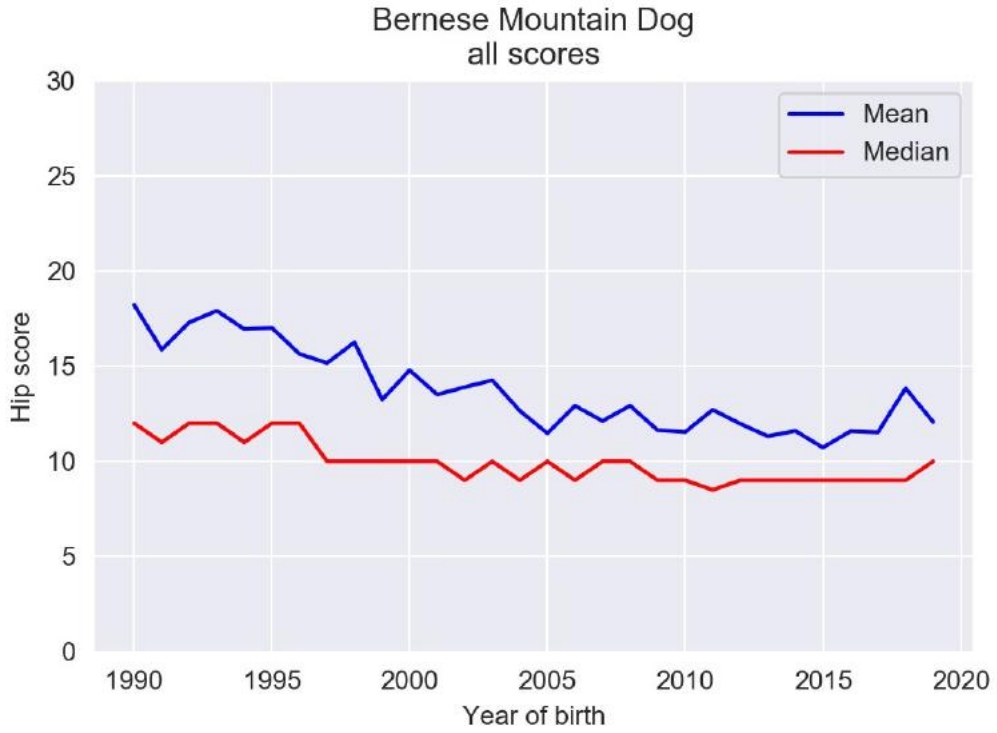


Fig. 1. Relationship of Combined Parent Score to percentage of hip dysplastic progeny.

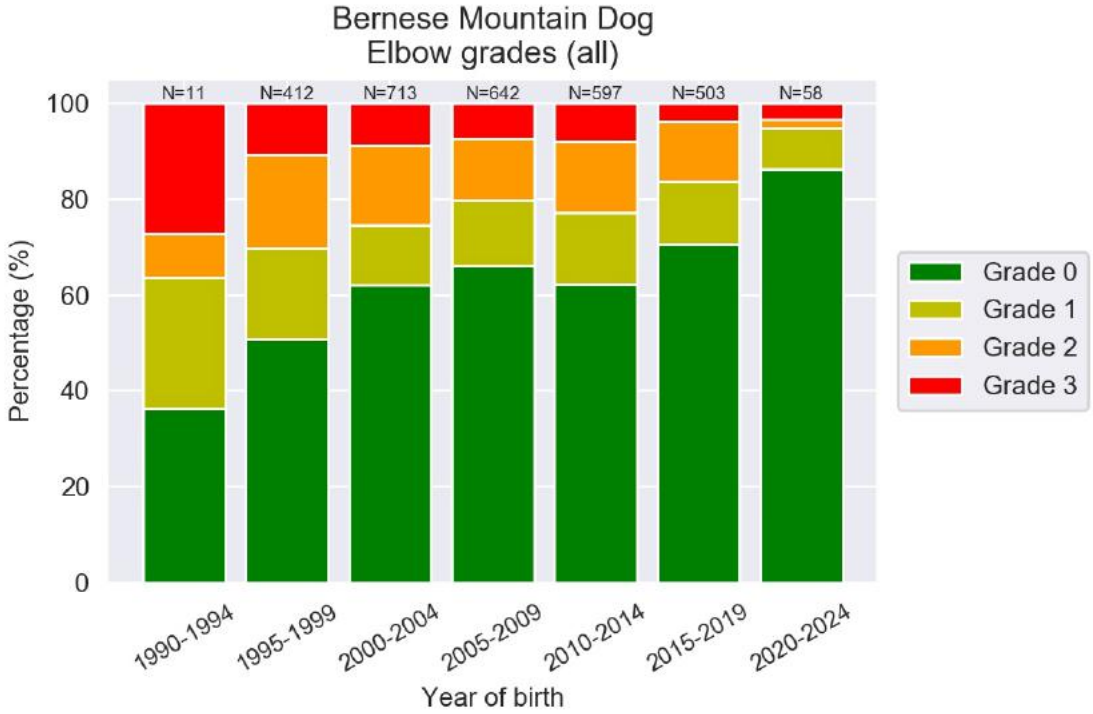
Phenotypic selection

1. Use in breeding only dogs with hip score <10, ideally elbow grade 0

BVA/KC Hip Dysplasia Scheme



BVA/KC Elbow Dysplasia Scheme



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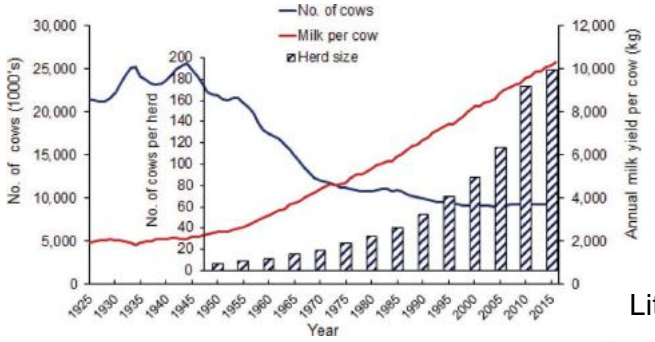
Estimated Breeding Values

EBVs

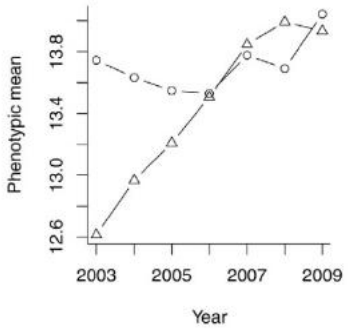
EBVs – primary tool in livestock breeding

1. More accurate estimation of the genetics – more precise selection, better response to selection



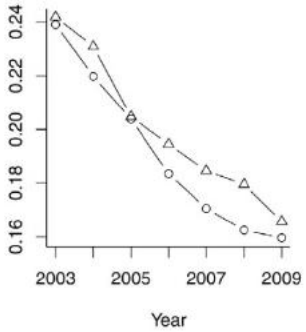
J. Dairy Sci. 100:10292–10313
https://doi.org/10.3168/jds.2017-12959

Litter size

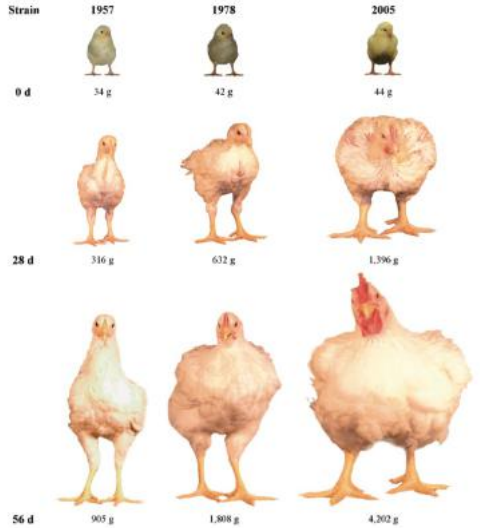


J. Anim. Sci. 2013.91:2575–2582
doi:10.2527/jas2012-5990

Mortality



Zuidhof et al., 2014
Poultry Science 93:2970–2982



Know your line!

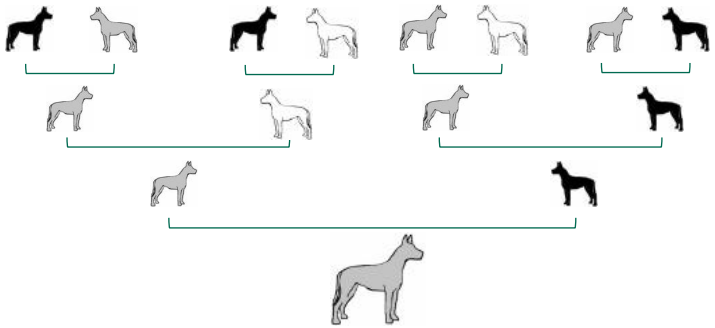
1. Genetic variation → resemblance between relatives
2. The degree of similarity ~ degree of relationship

Know your line!

Rover
Mild hip dysplasia

Fido
Mild hip dysplasia

Know your line!



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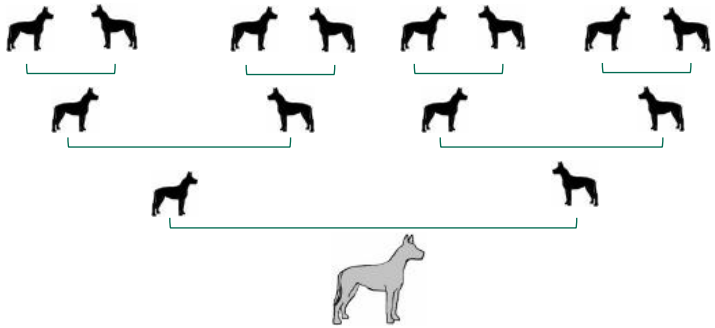


Fido
Mild hip dysplasia

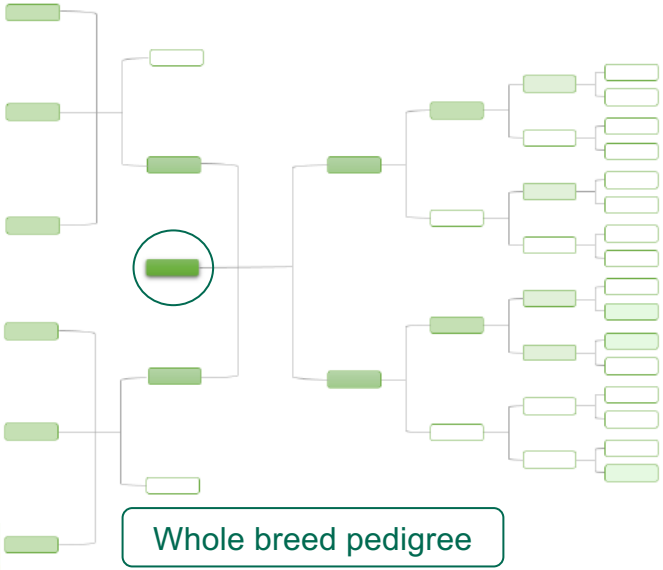
Excellent hips

Mild hip dysplasia

Severe hip dysplasia

EBVs – know your pedigree!

Hip scores of relatives, weighted by the degree of relationship



Whole breed pedigree

sex

litter

age

Time trend

Statistical model

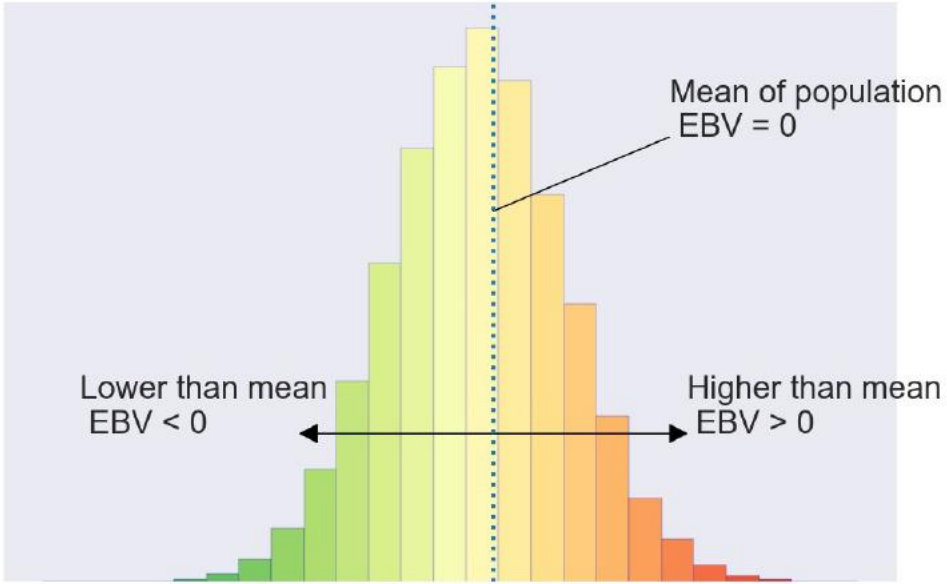
Estimated Breeding Value (EBV)

for all dogs in pedigree

Environmental “noise”

Estimated Breeding Values (EBVs)

1. Breeding value – how does offspring of an individual compare to the mean of the population? By how much?



Estimated Breeding Values (EBVs)

1. Breeding value – how does offspring of an individual compare to the mean of the population? By how much?

2. “Genetic merit” of an individual – can be used to predict phenotype, but it doesn’t account for environment! Dogs with the same EBV could have different phenotypes!

Estimated Breeding Values (EBVs)

1. Breeding value – how does offspring of an individual compare to the mean of the population? By how much?

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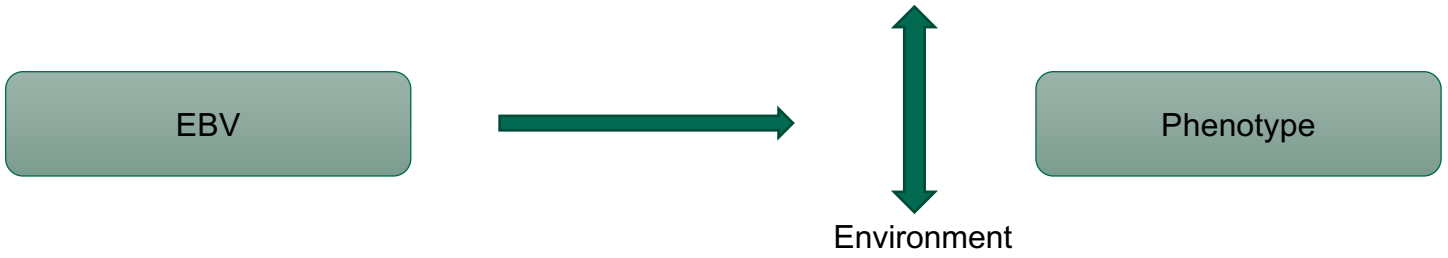


How to use EBVs

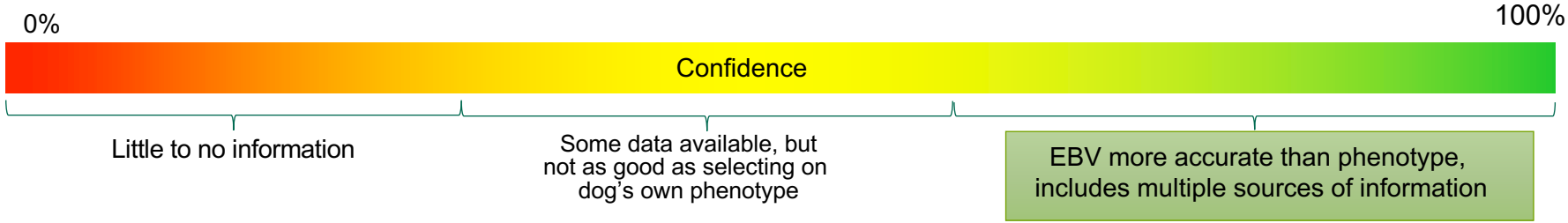
1. Used to rank individuals

2. Selecting individuals that are better than the breed average – not necessary to select the “best of the best” (easier to avoid popular sires!)

3. Gradual improvement

Confidence of EBVs

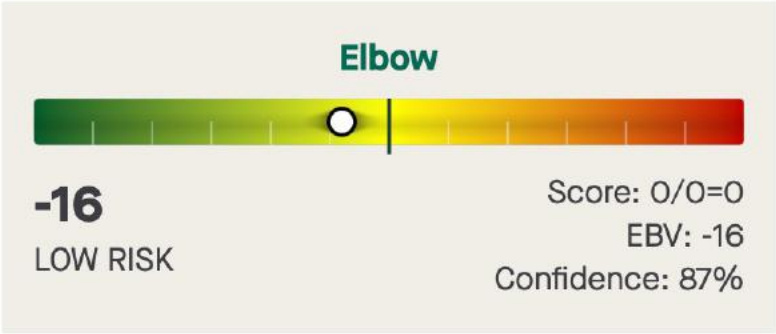
1. EBVs are calculated for all dogs in pedigree
2. Confidence – correlation between EBV and True BV
3. Confidence of the EBVs varies between dogs, depending on amount of information

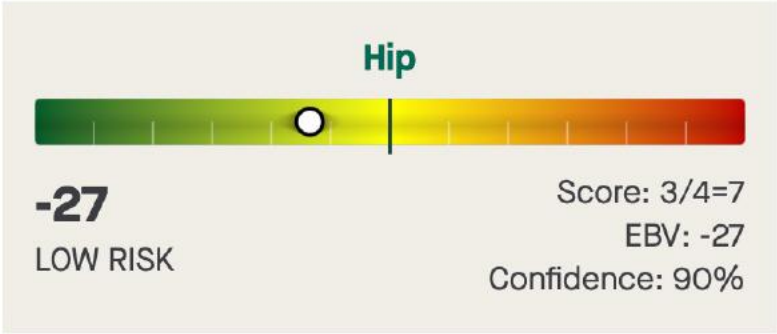


https://www.thekennelclub.org.uk/search/health-test-results-finder

EBVs at The Kennel Club

1. EBVs for HD and ED produced since 2014
2. Both HD and ED EBVs available for BMDs





EBV results last updated 27 July 2022.

Using EBVs in practice

Rover

Hip

Confidence: 97%

Fido

Hip

Confidence: 96%

Using EBVs in practice

Rover

Hip

Score: 4/2=6

Confidence: 97%

Fido

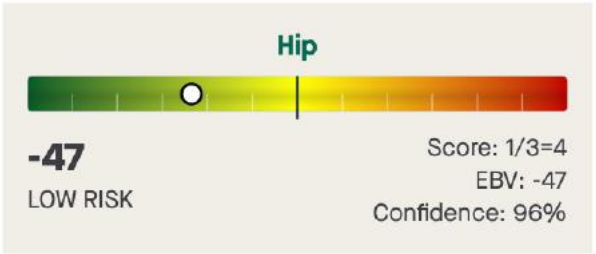
Hip

Score: 1/3=4

Confidence: 96%

Breed median hip score = 10

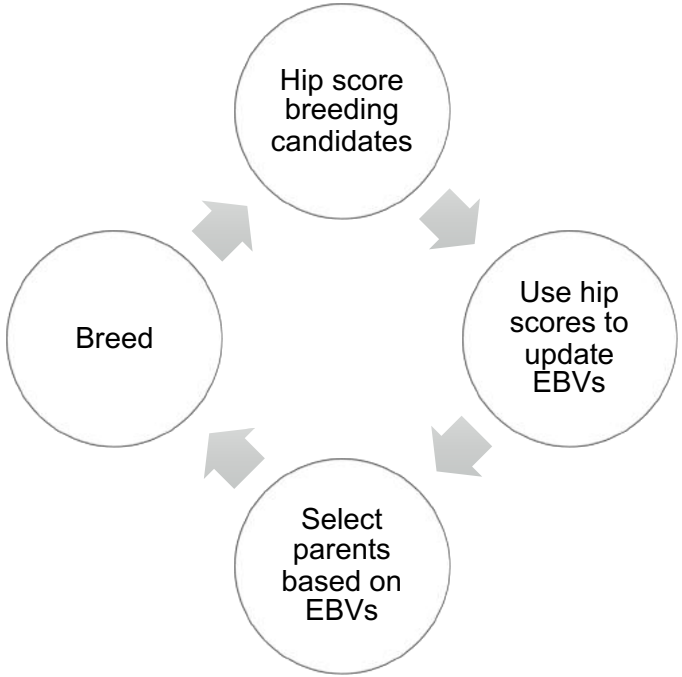
Using EBVs in practice



Breed median hip score = 10

EBV does NOT replace hip scoring/elbow grading!

You can’t improve what you don’t measure!



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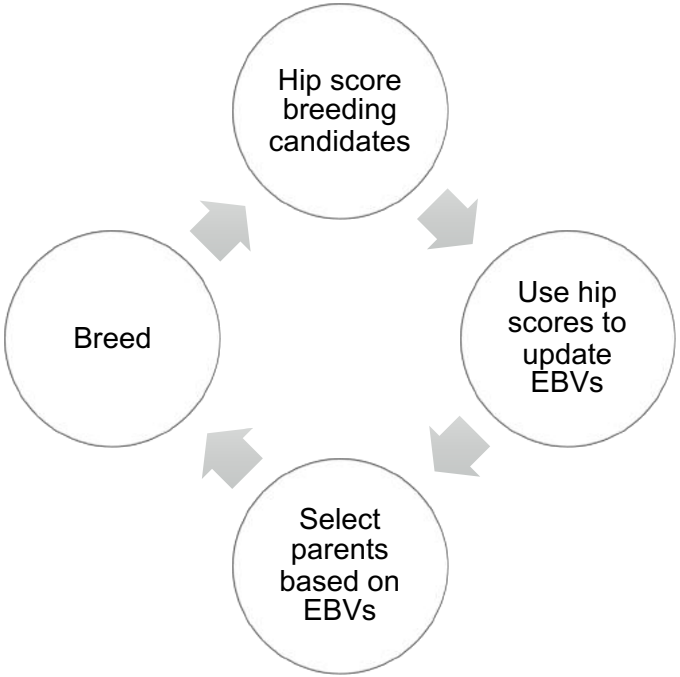

Hip scoring and elbow grading:

- Improves the knowledge about your own dog
- Provides basic information on whether your dog is a good breeding candidate
- Improves your breeding program
- Optics

EBV does NOT replace hip scoring/elbow grading!

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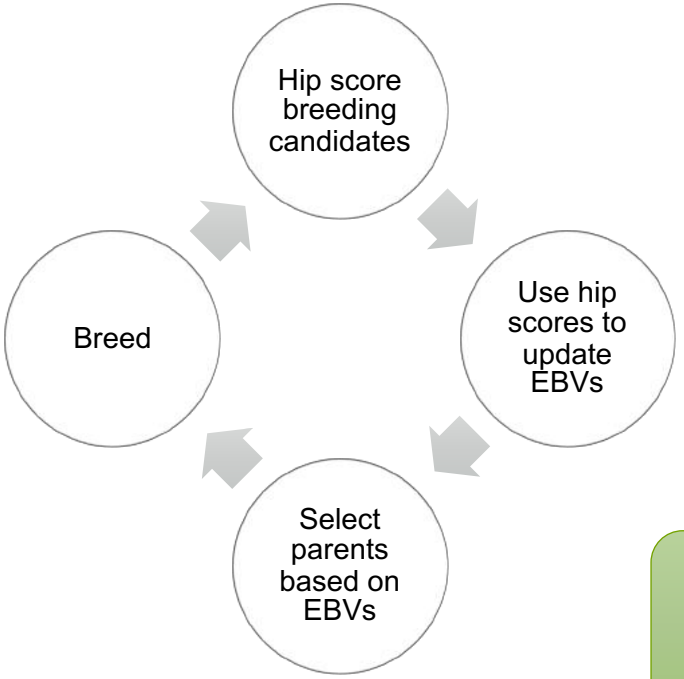


Hip scoring and elbow grading:

- Improves the knowledge about your own dog
- Provides basic information on whether your dog is a good breeding candidate
- Improves your breeding program
- Optics

By testing your dog, you improve the accuracy of EBVs for all dogs in your line, but also for all other relatives!

Conclusions

1. Evidence that HD and ED are a problem in Bernese Mountain Dog
2. Declining number of dogs tested
3. HD and ED – complex trait
4. Difficulty in selection – environmental effects
5. EBVs offer a solution

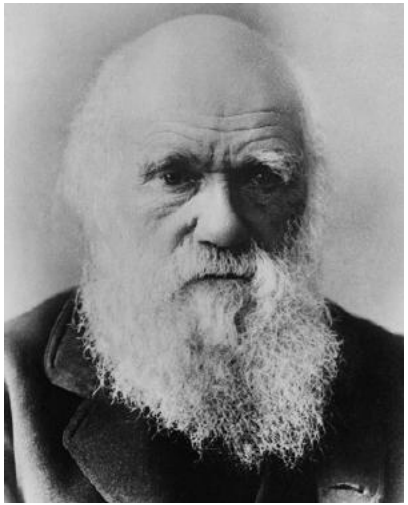
THE KENNEL CLUB

Inbreeding and genetic diversity

Consequences of inbreeding

- Charles Darwin – outcrossing in plants favoured over self-fertilization

- C. Darwin married his first cousin:
  - 10 kids
  - 3 died early in life
  - 3 were infertile



1802 - 1882

Consequences of inbreeding

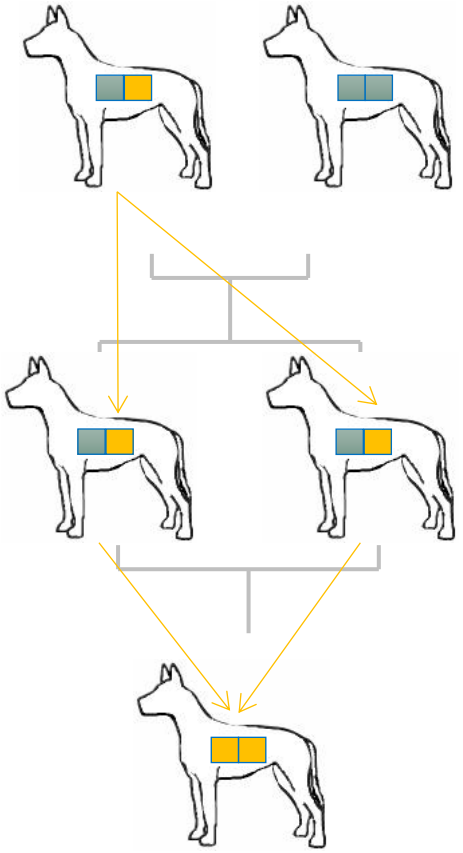
1. Major abnormalities
2. Early life mortality
3. Lowered fitness:
    1. Survival (infections)
    2. Growth rate
    3. Fertility

Inbreeding

1. Inbreeding – probability that the two copies of a gene come from the same ancestor

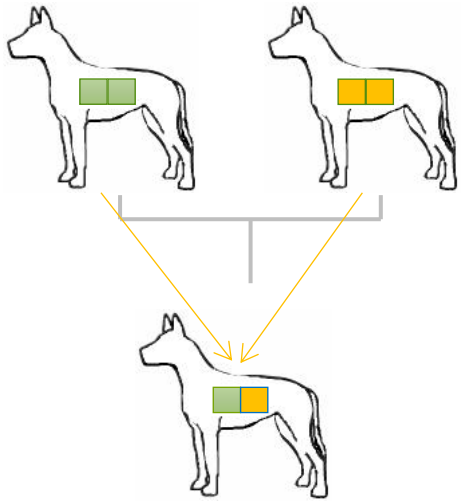
- **25%** for offspring of a full sib mating or a parent/offspring mating
- **12.5%** for offspring of a half sib mating
- **6.25%** for offspring of 1st cousins
- etc

Measure of risk – not a guarantee



Inbreeding

1. Inbreeding – probability that the two copies of a gene come from the same ancestor
2. New mutations – mostly deleterious, unknown
3. Inbreeding is NOT inherited



Age of inbreeding

- We all have:
  - 2 parents
  - 4 grand parents
  - 8 great grand parents
  - 16 great great grandparents

$$2^n$$

where *n* = generations back

25 generations ago was the 1300s

To be completely non-inbred we would need >33.5 million unrelated ancestors

Total human population in 1300's = ~400M

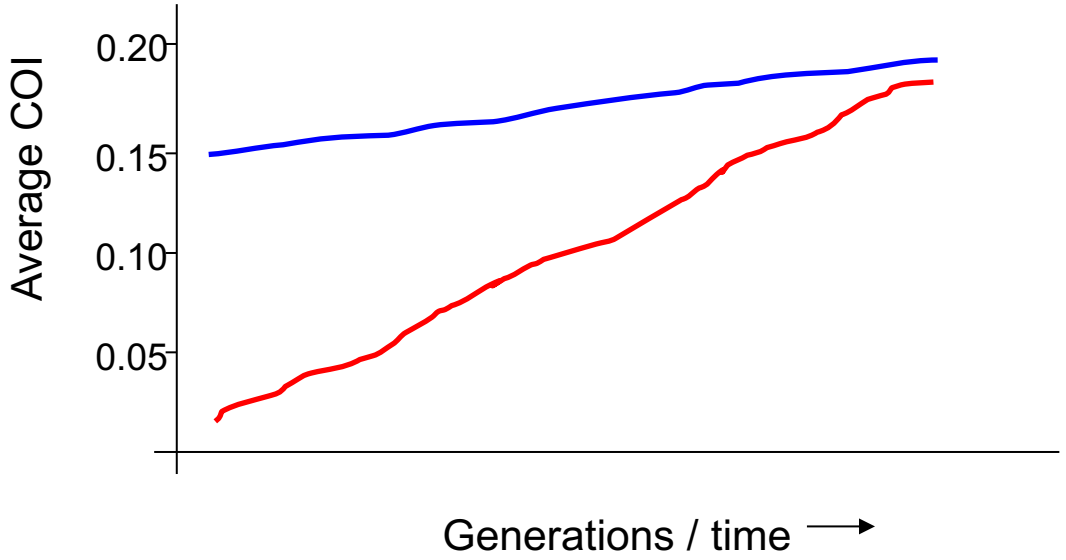
Age of inbreeding

1. Inbreeding on distant ancestors appears less harmful than on recent ancestors
    - Natural selection acts against deleterious mutations – purging selection

Some mutations may remain in population at low frequencies!

Age of inbreeding

1. Rate of inbreeding (ΔF) – how quickly is it accumulated over time?
2. High ΔF – high loss of diversity
3. ΔF = 0.5% sustainable



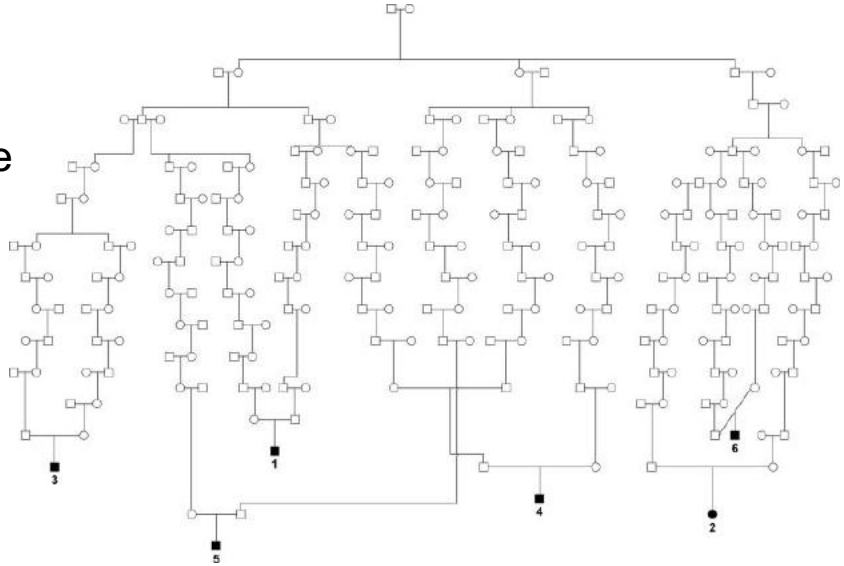
Danger of popular sire

1. Every individual carries new mutations

2. Most of the time, not a problem, as they are rare and usually recessive

3. If two descendants of the same sire are mated, they could have the same mutation
   - their offspring could inherit two copies, and fall sick

4. Loss of diversity from other sires



COI at the Kennel Club

1. COI calculator available since 2012
2. Minimise inbreeding in produced litters

1. Breed average:
    1. COI calculated for all dogs using complete pedigree
    2. Average of the COI calculated for dogs born in previous yea
    3. Current breed average for BMD = 3%

Inbreeding Coefficient (COI) lookup Results

☆ MOST DIVERSE MATCH

Inbreeding coefficient for ARGUS ELECTRA PETARDA (IMP POL) and DINASTII THE PHENOMENAL is 1.7%.

The breed average is 3.7%
11 generations available of which 5 are complete

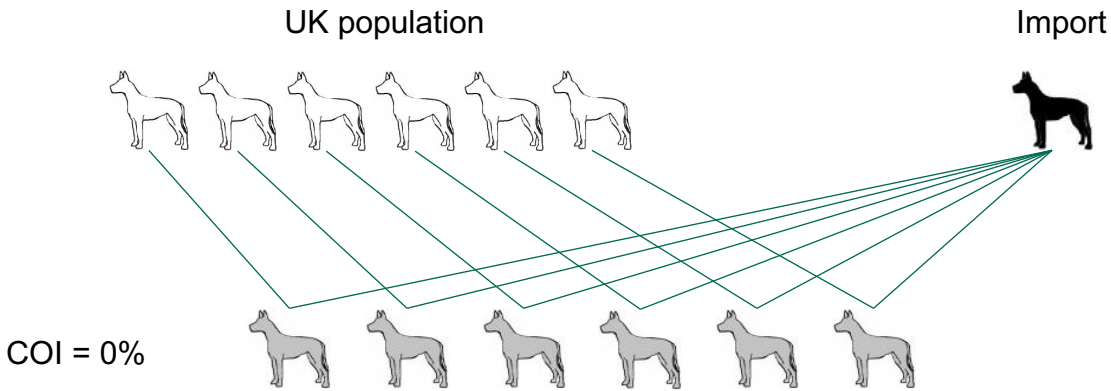
Inbreeding coefficient for ARGUS ELECTRA PETARDA (IMP POL) and SIBIRSKI MEDVED VESELY RODZHER (IMP RUS) is 2.1%.

The breed average is 3.7%
11 generations available of which 4 are complete

https://www.thekennelclub.org.uk/search/inbreeding-co-efficient/
https://www.thekennelclub.org.uk/health-and-dog-care/health/getting-started-with-health-testing-and-screening/inbreeding-calculators/

COI - limitations

1. Retrospective!



COI - limitations

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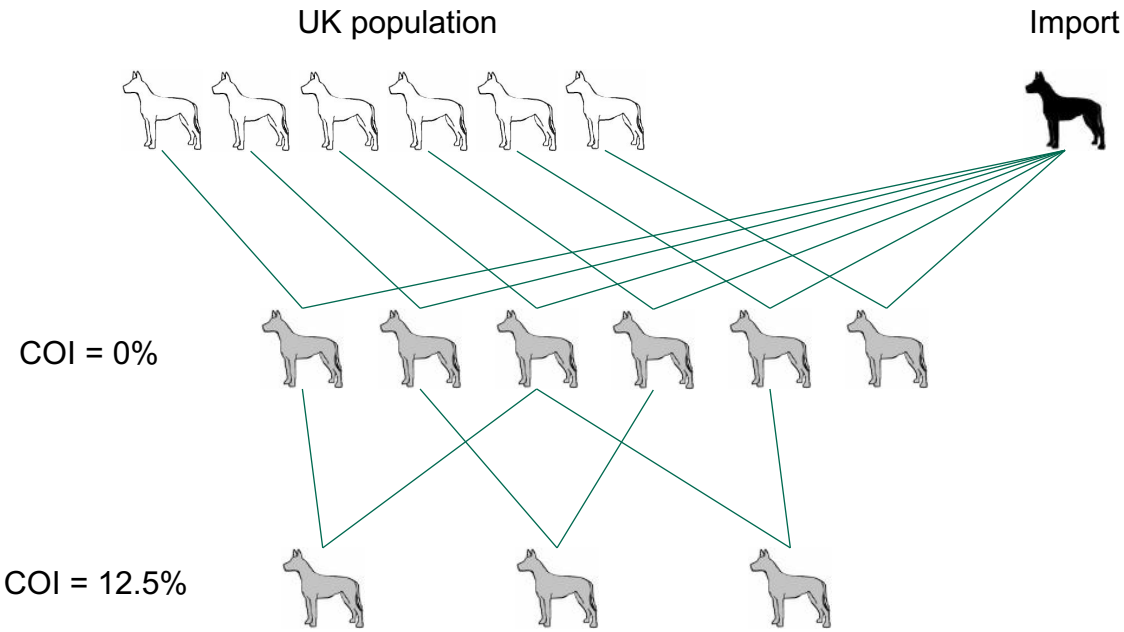
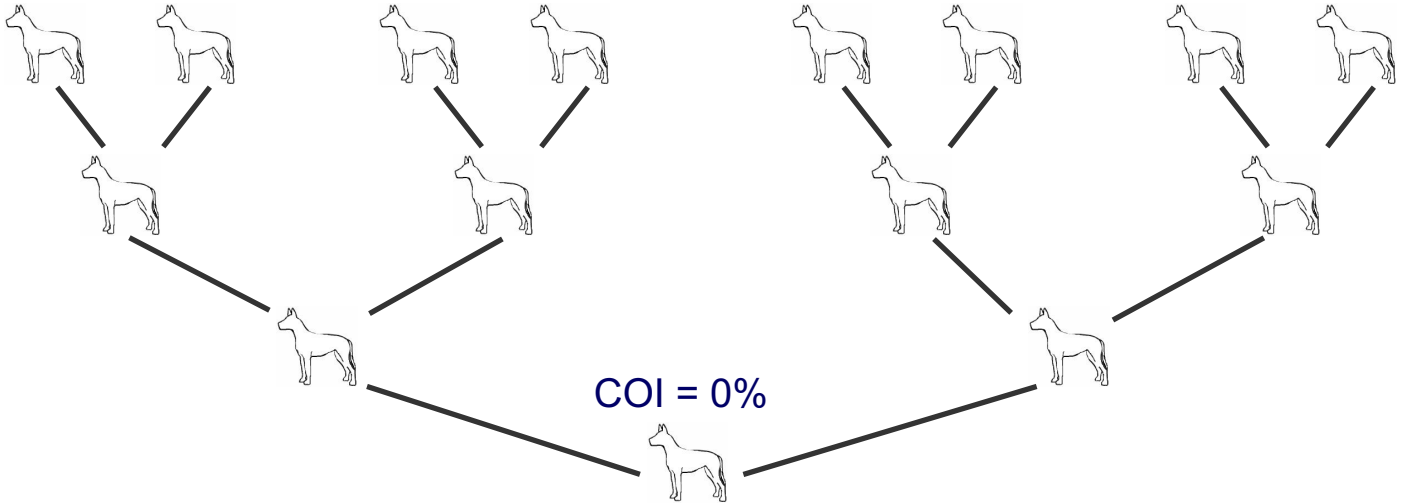
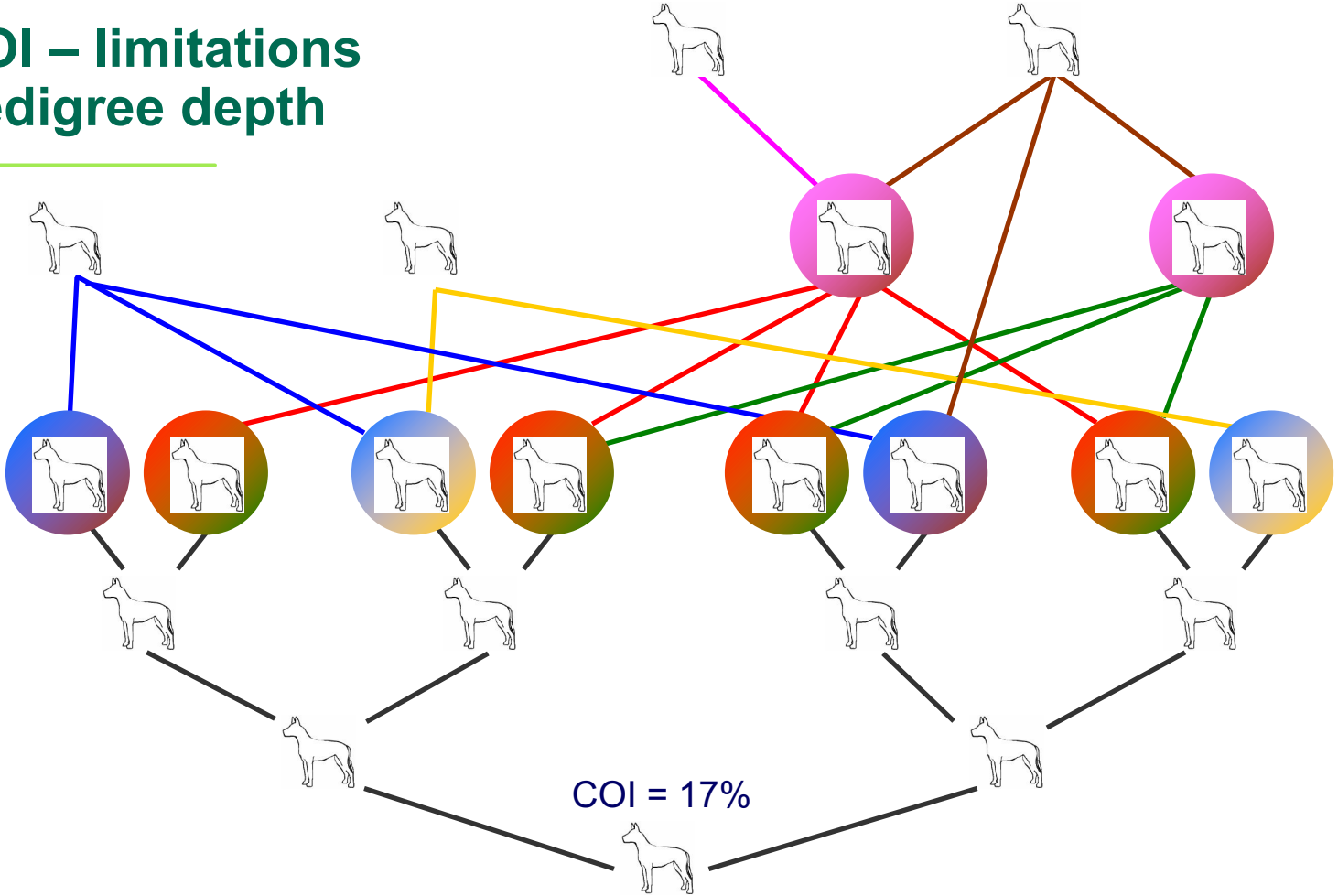


COI – limitations
Pedigree depth

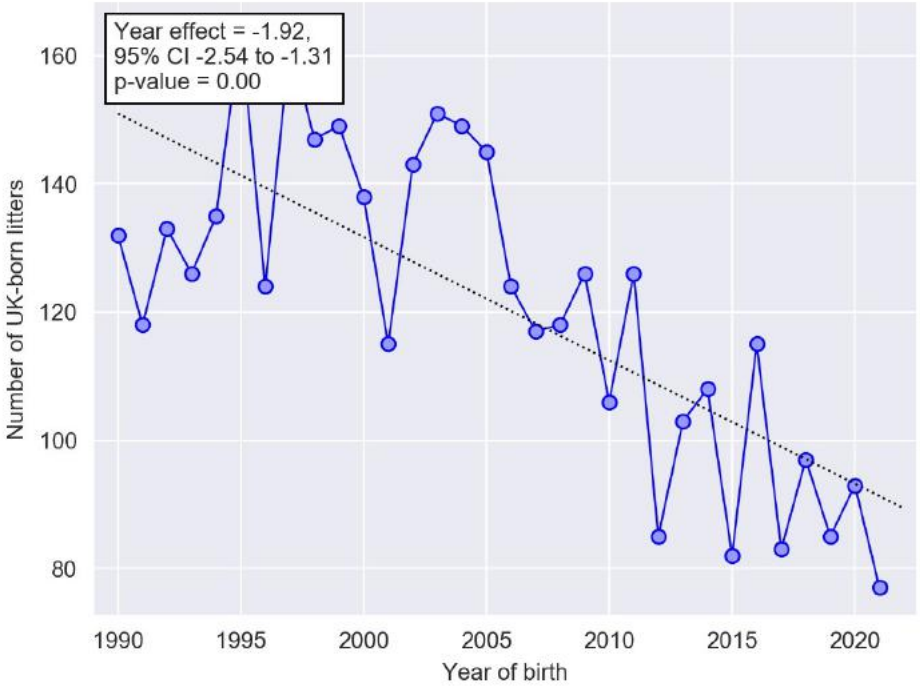


COI – limitations
Pedigree depth



Bernese Mountain Dog population

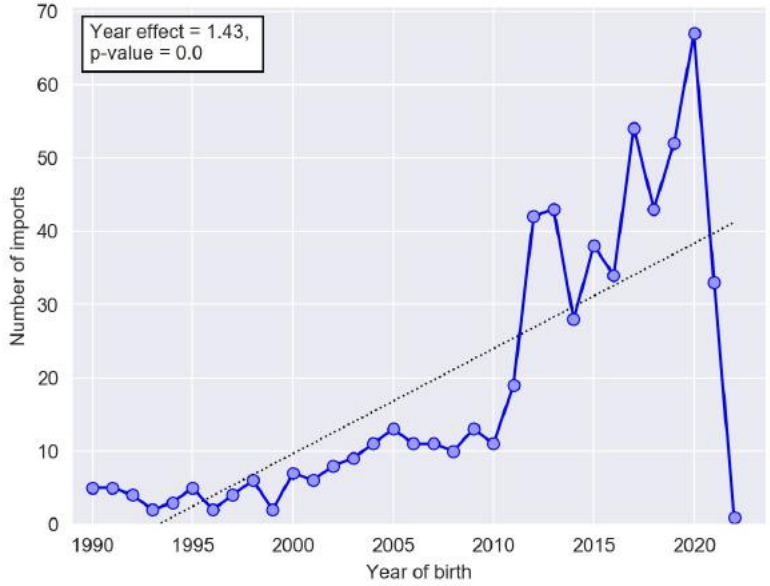
1. Complete pedigree
    - 31K dogs in total
    - 26K dogs in litter registrations



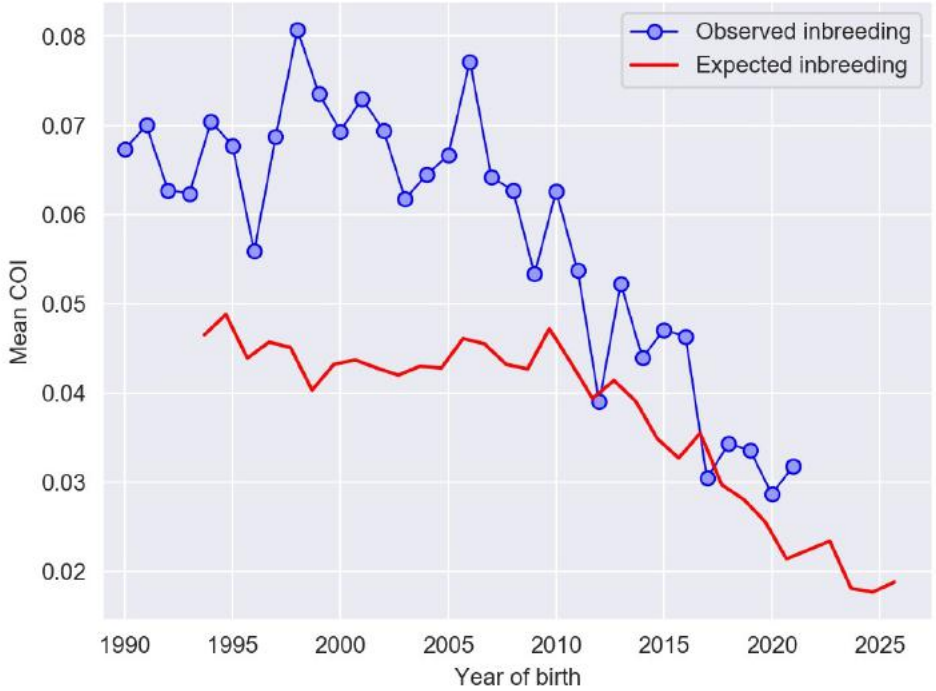
Bernese Mountain Dog population

1. Imports:
    - 1,2K total
    - 42 countries (>50% from top 8 countries)

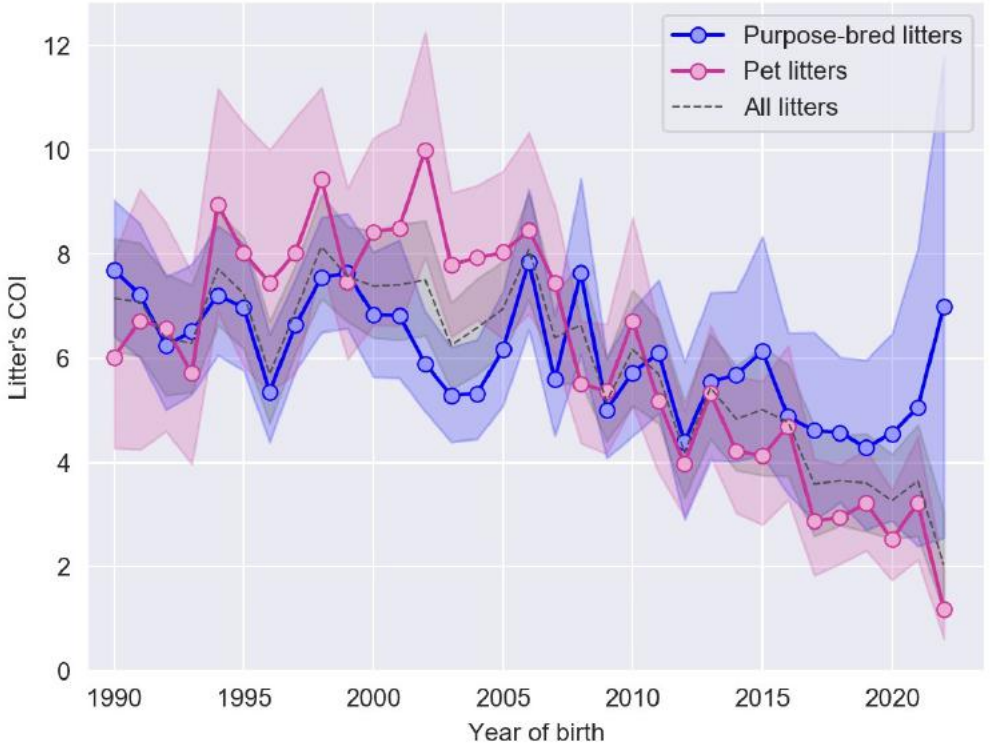
Country	imports	% of imports
Poland	526	10%
Belgium	450	9%
Switzerland	341	7%



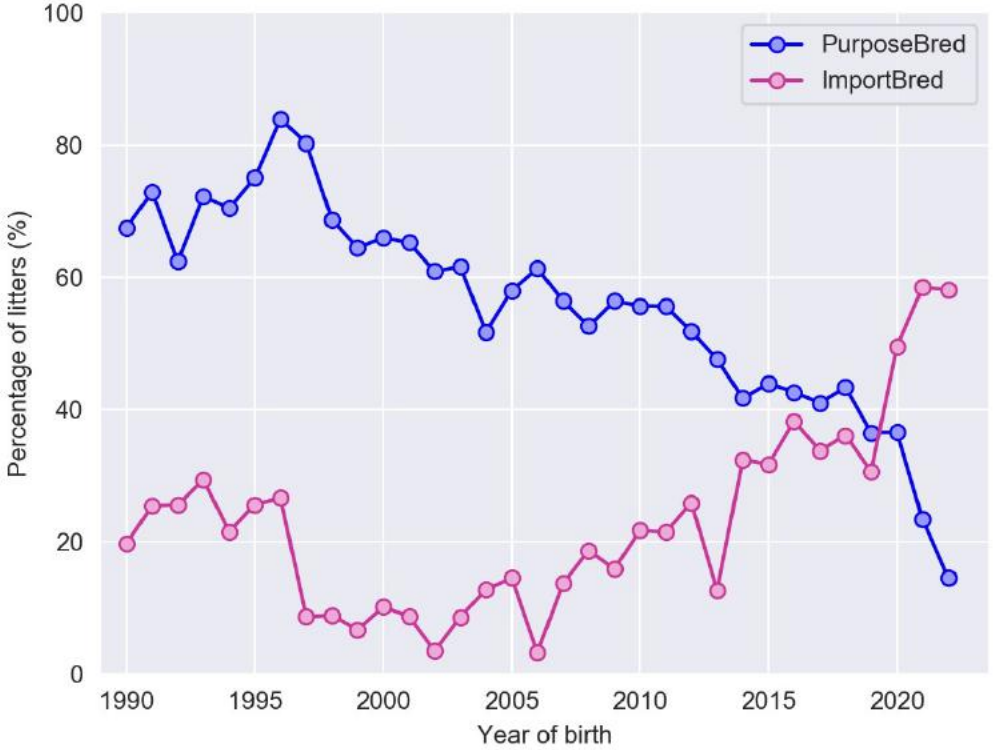
Bernese Mountain Dog population



Bernese Mountain Dog population



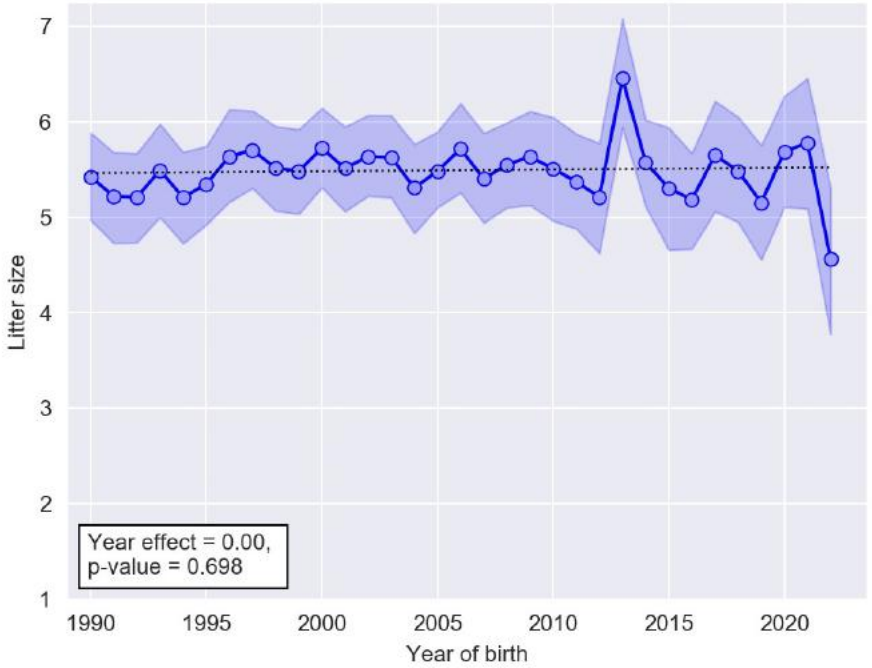
Bernese Mountain Dog population



Bernese Mountain Dog population

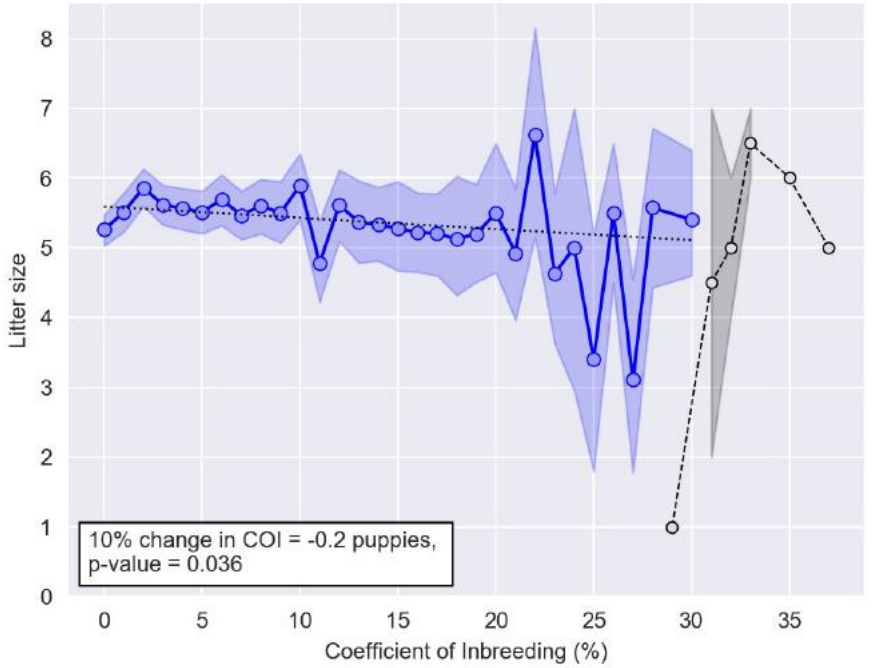
- Litter size statistics:
  - Range: 1 to 15
  - Median: 6
  - Mean: 5.5

- No changes over time



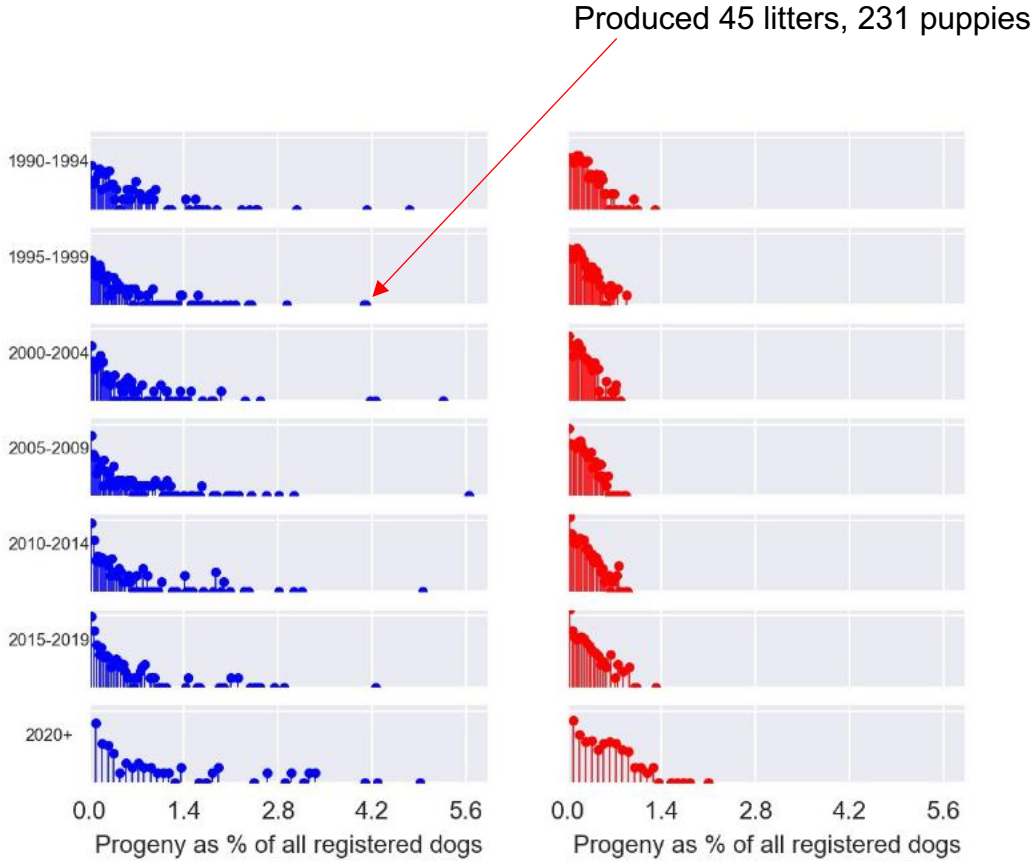
Bernese Mountain Dog population

1. COI and litter size



Bernese Mountain Dog population

- Popular sires

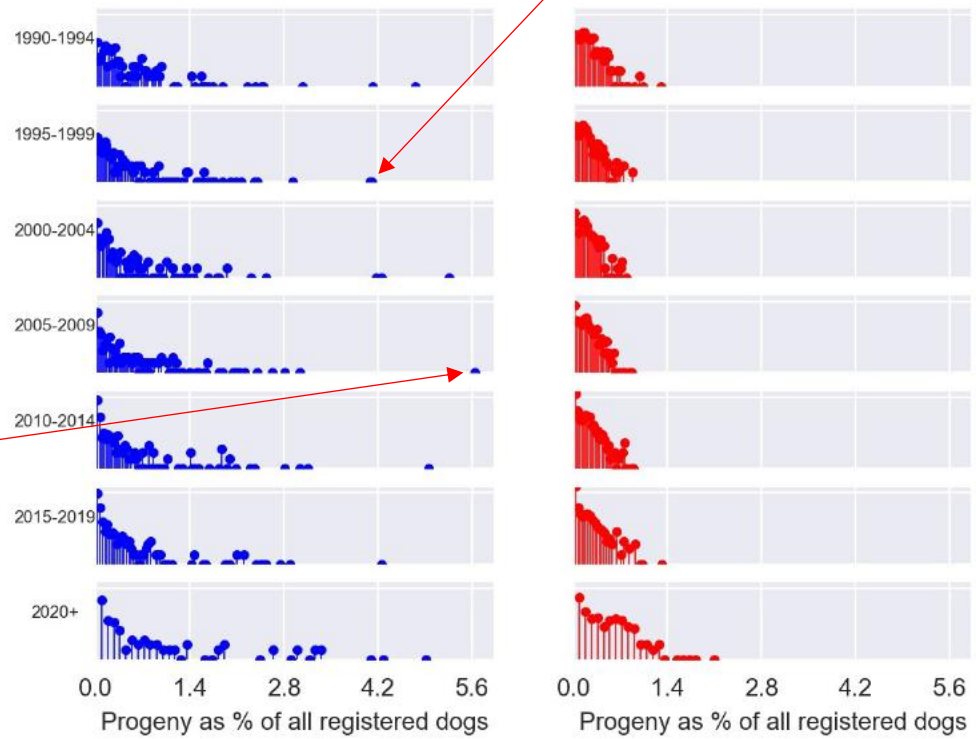


Bernese Mountain Dog population

- Popular sires

Produced 45 litters, 231 puppies

Produced 38 litters, 201 puppies



Genetic diversity in Bernese Mountain Dog (UK)

1. Appears to be relatively good – low mean COI
2. Beware of pedigree depth!
3. Avoid popular sires – and their sons!
4. Monitor genetic diversity across the breed

THE KENNEL CLUB

Breeding for health – group responsibility!

Questions

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