B - Breeding
O - Out
A - Abnormal
S - Sounds

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Preventative Medicine!

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How Can We Breed Healthier Dogs?

- BOAS is complex
- Let's approach this problem with a simpler example

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Better Health

4 fundamental questions:

1. How impactful is this trait to the individual?
2. Is this trait heritable?
3. If the trait is heritable, how do we effectively screen for it?
4. How impactful is this trait to the breed?

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1. Impact on the Individual

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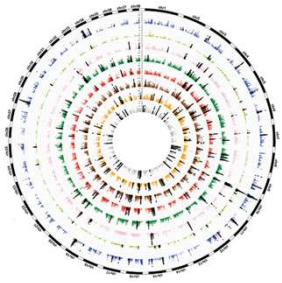
2. Determining How Heritable A Trait Is

- **Marker-assisted tests**
- **Genome-wide association studies (GWASs)**
  - **Single-nucleotide variants (SNV) → marker**

Canine Genome



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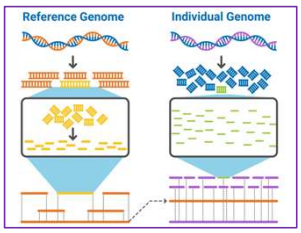
2. Determining How Heritable A Trait Is

Whole Genome Sequencing



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2. Is DM Heritable?

- **Yes**

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Better Health

4 fundamental questions:

1. **How impactful is this trait to the individual?**
2. **Is this trait heritable?**
3. **If the trait is heritable, how do we effectively screen for it?**
4. **How impactful is this trait to the breed?**

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3. How Do We Screen For Heritable Traits?

- **Genetic testing**
- **Health screening → complex traits**

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Online Mendelian Inheritance in Animals Database (OMIA)

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Interpreting Genetic Tests

- **Individual - Will this dog get this disease?**
  - **Simple fully penetrant diseases**

- **Combining individuals: Possible consequences to the progeny of combining 2 individuals**
  - **Autosomal recessive**
  - **Autosomal dominant**
  - **X-linked dominant**
  - **X-linked recessive**

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3. How Do We Screen For DM?

- **Genetic testing**

OMIA:000263-9615 : Degenerative myelopathy in *Canis lupus familiaris* (dog)

Categories: Nervous system phene
Possibly relevant human trait(s) and/or gene(s)s (MIM numbers): 105400 (trait) , 147450 (gene) , 618598 (trait)
Links to MONDO diseases: No links.
Mendelian trait/disorder: yes
Mode of inheritance: Autosomal recessive
Considered a defect: yes

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	R	R
R	RR	RR
R	RR	RR

	R	r
R	RR	Rr
R	RR	Rr

	r	r
R	Rr	Rr
R	Rr	Rr

	R	r
R	RR	Rr
r	Rr	rr

	r	r
R	Rr	Rr
r	rr	rr

	r	r
r	rr	rr
r	rr	rr

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RR – Normal
Rr – Carrier (not affected)
rr – "At risk"

	r	r
R	Rr	Rr
R	Rr	Rr

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	R	r
R	RR	Rr
R	RR	Rr

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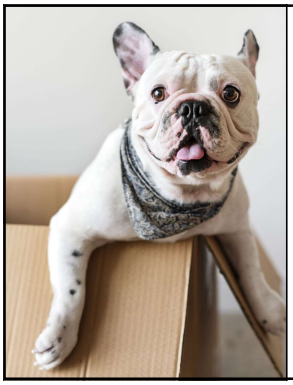

- DNA tests are used to maximize genetic diversity, not to maximize the exclusion of animals
- Breeds where the genetic diversity is low, excluding animals will be far more dangerous in the long run than breeding them wisely

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Better Health

4 fundamental questions:

1. How impactful is this trait to the individual?
2. Is this trait heritable?
3. If the trait is heritable, how do we effectively screen for it?
4. How impactful is this trait to the breed?

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4. How Impactful Is This Trait to the Breed?

- Genetic Diversity
  - Coefficient of Inbreeding (COI)
- Gene Pool Size
  - Effective Population Size (EPS)
- Disease Prevalence and Penetrance

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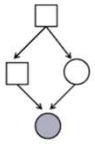
Genetic Diversity

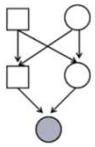
- Coefficient of Inbreeding (COI)
  - Pedigree vs Genome
  - <10%

Half sibling: 12.5%



F=0.125

Parent/Offspring: 25%
Full Sibling: 25%



F=0.25

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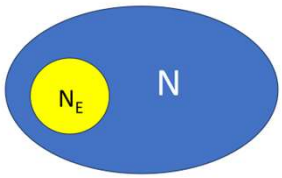
Gene Pool Size

- Effective Population Size (EPS)
- >100

$$N_E = \frac{4N_M N_F}{N_M + N_F}$$



N_E = Effective Population Size
N_M = Number of breeding males
N_F = Number of breeding females

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Genetic Diversity

Penetrance
- Probability of observing a specific phenotype given a certain genotype

- Genetic diversity is dangerously low in certain breeds and disease prevalence can be extremely high at the same time

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Prevalence of DM Genotype in the PWC

- RR – 14.1%
- Rr – 32.4%
- rr – 53.5%

https://ofa.org/diseases/disease-statistics/

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4. Impact to the Breed

Genetic Diversity

Poor

Average Coefficient of Inbreeding: 13.2%

Gene Pool Size

Poor

Effective Population Size: 42.60

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4. Impact to the Breed

- RR – 53.2%
- Rr – 38.1%
- rr – 8.7%

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Better Health

4 fundamental questions:

1. How impactful is this trait to the individual? ☑ ☑
2. Is this trait heritable? ☑ ☑
3. If the trait is heritable, how do we effectively screen for it? ☑
4. How impactful is this trait to the breed? ☑

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BOAS = Complex Trait

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1 & 4. Impact of BOAS to the Individual and the Breed

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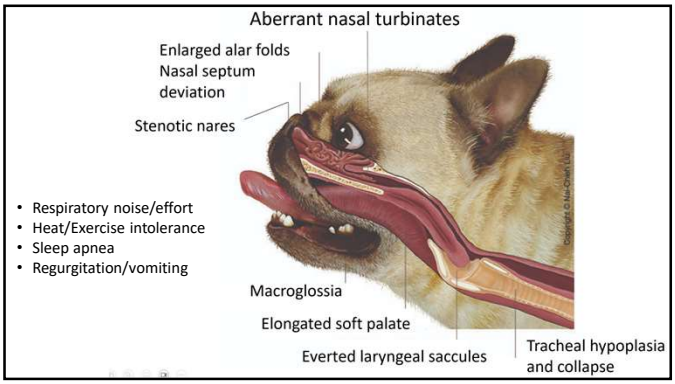

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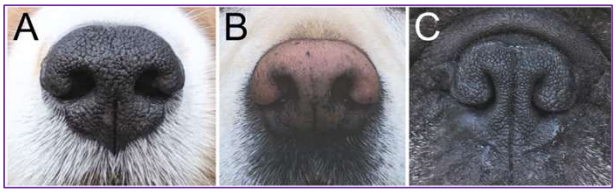
BOAS

Anatomical features of BOAS:

• **Stenotic nares**



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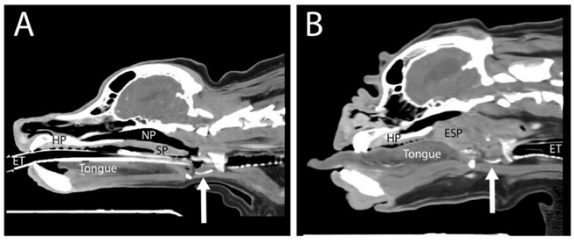

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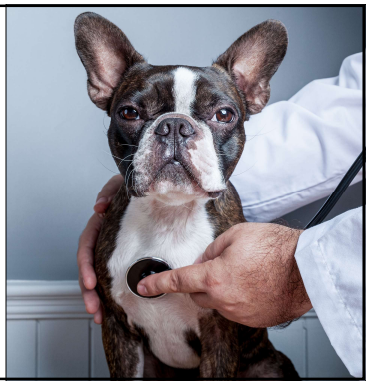
BOAS Treatment

Surgical correction includes:
- Staphylectomy
- Tonsilectomy
- Rhinoplasty
- Laser-assisted turbinectomy

Not curative!
- Reduce clinical severity
- Improve welfare
- Slow the rate of secondary lesion development



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Brachycephaly

BOAS

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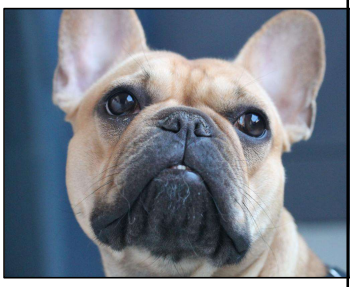
Brachycephalic Obstructive Airway Syndrome (BOAS)

- **20-40% are affected by moderate to severe disease**



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1 & 4. Impact of BOAS to the Individual and the Breed

Genetic Diversity

Average

Average Coefficient of Inbreeding: 4.8%

Gene Pool Size

Average

Effective Population Size: 132.3

DogBreedHealth.com

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Better Health

4 fundamental questions:

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2. Is this trait heritable?
3. If the trait is heritable, how do we effectively screen for it?
4. How impactful is this trait to the breed?

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2. BOAS Heritability

- BOAS risk factors
- Heritability difficult to determine due to defining the presence and severity of the disease
- GWAS on 172-210 dogs
- Heritability estimates of 40-60% for BOAS
- Multiple loci (8-11 per breed)

Kalmar et al.
Yang et al.

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3. How Do We Screen For Heritable Traits?

- Genetic testing
- Health screening → complex traits

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BOAS Genetic Testing

- In the works!
- Will involve a substantial number of alleles

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Health Screening

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Mission Statement:
"To improve the health and well-being of companion animals through a reduction in the incidence of genetic disease"

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OFA Tests

- **Things we know are heritable and what we can screen for**
- **GP screening tests**
- **Specialist screening tests**
- **Breed specific lists**

Diseases
Hip Dysplasia
Elbow Dysplasia
Eye Disease
Cardiac Disease
Respiratory Function
Patellar Luxation
Thyroid
Other Phenotypic Evaluations
DNA Based Disease Tests
Disease Statistics

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French Bulldog Health Screening

Screening	Testing options
Hip Dysplasia	*One of the following:* OFA Radiographic Hip Evaluation PennHIP Evaluation. Results registered with OFA.
ACVO Eye Exam	Annual Eye Examinations. Results registered with OFA
Patellar Luxation	Veterinary Evaluation of Patellar Luxation. Results registered with OFA.
Cardiac Evaluation	*One of the following:* Congenital Cardiac Exam - Echocardiagrams recommended but not required Advanced Cardiac Exam - Echocardiograms recommended but not required Basic Cardiac Exam - Echocardiagrams recommended but not required
Autoimmune Thyroiditis	*(Optional but recommended)* Autoimmune Thyroditis Evaluation from an approved Lab. Results registered with OFA.
Elbow Dysplasia	*(Optional but recommended)* OFA Radiographic Elbow Evaluation
Tracheal Hypoplasia	*(Optional but recommended)* OFA radiographic evaluation for Tracheal Hypoplasia.

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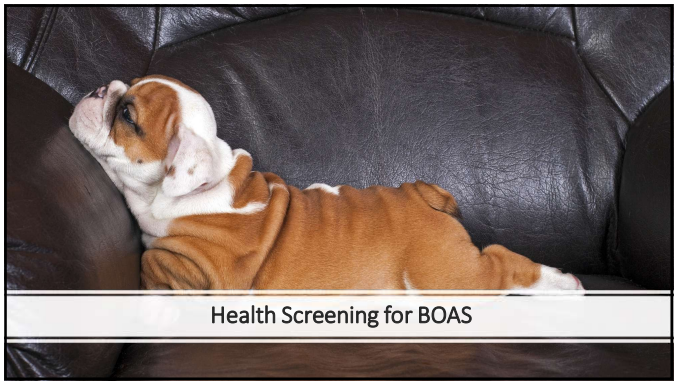

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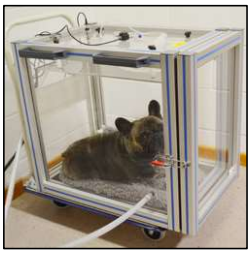
Whole-Body Barometric Plethysmography (WBBP)

- Non-invasive objective measurement of respiratory function
- Constant ventilating airflow
- Monitors pressure changes from dog breathing
- BOAS Index (0-100%)



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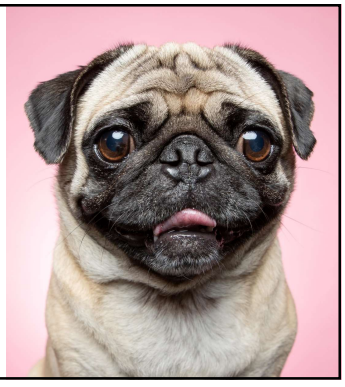
BOAS Diagnosis

- Current standard: Radiographs, CT, anesthesia, etc
- Gradient scale of the disease



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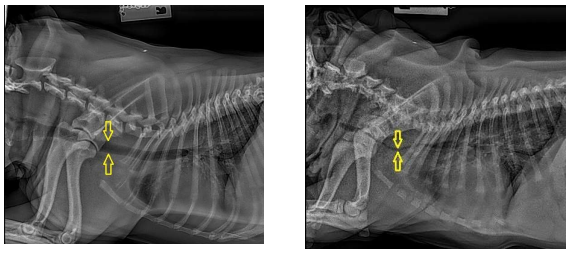
Tracheal Hypoplasia



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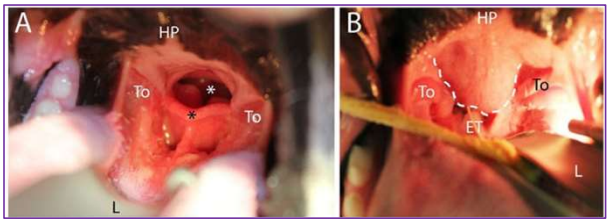
Elongated Soft Palate



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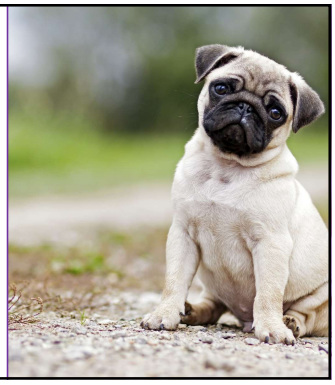
BOAS Screening

- **Exercise and respiratory assessment test**



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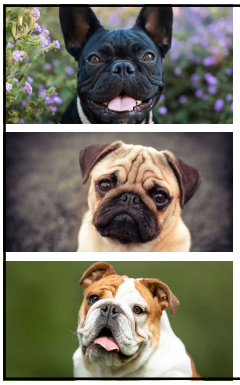

OFA Screening for BOAS

- New pre-breed screening in the works
- Exercise test and respiratory assessment
- Cambridge and UK Kennel Club

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Received: 7 August 2018 | Revised: 28 November 2018 | Accepted: 16 December 2018
DOI: 10.1111/vsu.13159

WILEY

ORIGINAL ARTICLE – CLINICAL

Validation of exercise testing and laryngeal auscultation for grading brachycephalic obstructive airway syndrome in pugs, French bulldogs, and English bulldogs by using whole-body barometric plethysmography

Julia Riggs MA, VetMB, DipECVS | Nai-Chieh Liu DVM, MPhil, PhD | Dawn R. Sutton BVSc | David Sargan MA, PhD | Jane F. Ladlow MA, VetMB, DipECVS

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Validation of ET

- Riggs et al.
- Incorporation of an exercise test (ET) to challenge upper respiratory tract function to identify clinically relevant airway obstruction when clinical signs are mild or dynamic
- Hypothesis: 3-minute trot test will have a positive correlation with WBBP data

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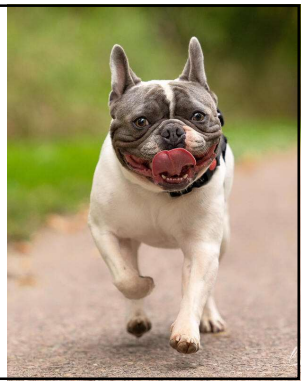
BOAS Exercise Test

- Airway evaluation at rest:
  - Stenotic nares
  - Laryngeal auscultation
  - Respiratory effort
- Baseline clinical grade given
- ET: 3-minute trot test (speed of 4-5 MPH)
- Immediately after ET, airway evaluation repeated



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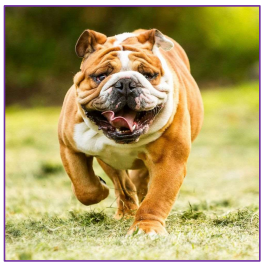
Materials and Methods

- Hx and full PE = Comorbidities excluded
  - Ortho, neuro, cardiopulmonary
- Respiratory distress, cyanosis, collapse, or regurgitation during the test = Grade 3
- 44 dogs, >12 months old



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Materials and Methods

- WBBP = objective assessment of upper airway obstruction after chamber acclimation
- Respiratory function was assessed over 20 min
- 30+ min between ET and WBBP
- BOAS indices
  - Categorized BOAS+ or BOAS-
  - Based on predefined, breed-specific thresholds

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Grade	Pre-ET /Post-ET	Abnormal Respiratory Noise	Inspiratory Effort	Dyspnea/Cyanosis /Syncope
Grade 0	Pre-ET	-	-	-
	Post-ET	-	-	-
Grade 1	Pre-ET	-/+, nasal stertor when sniffing	-	-
	Post-ET	+, nasal stertor when sniffing	-/+	-
Grade 2	Pre-ET	+/++	+/++	-
	Post-ET	++/+++	++/+++	Dyspnea +
Grade 3	Pre-ET	++/+++	++/+++	Dyspnea ++/+++, +/- cyanosis
	Post-ET	+++	+++	Dyspnea +++, +/- cyanosis or syncope

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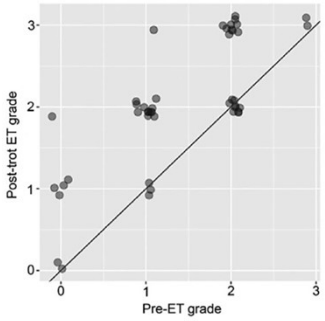

Significance P < 0.025

- **Bonferroni correction for multiple comparisons**
- **Correlation via Spearman's rank correlation**

Riggs et al.

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Results

Comparing functional grades to WBBP:

- **Sensitivity:**
  - **56.7% pre-ET**
  - **93.3% post-ET**
- **Specificity:**
  - **100% pre-ET and post-ET**

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Breeding Recommendations

- Grade 3 dogs withdrawn from breeding programs
- Grade 2 only bred to Grade 1 or 0
- 15 - 20% reduction

Sire

Dam: RFG Grade for each dog	Grade 0	Grade 1	Grade 2	Grade 3
Grade 0				
Grade 1				
Grade 2				
Grade 3				

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Future OFA Testing

- Training at CE events
  - GP too!
- Slow change, not one generation

Society for Theriogenology
Veterinarians Dedicated to Animal Reproduction

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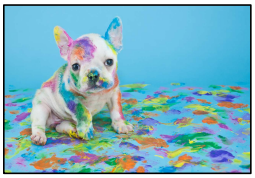
Pearls of Wisdom



- Genetic testing:
  - Inclusion of breeding dogs
- Genetic diversity
- Complex genetic traits:
  - Screening and removal of dogs with extreme traits
- Reduce BOAS by:
  - Making informed breeding decisions
  - Health screening

We can prevent disease and breed healthier dogs!

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