

Improving health using EBVs: Elbow, Skin, and Mast Cell Tumors

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2023 Breeders Workshop

Introduction

- Goal = select new, young breeders less likely to produce affected offspring
- EBVs **DO NOT** identify genetic cause and effect.
- Traits must be measurable, have variation, and be heritable (i.e., significant portion due to genetics) to make worthwhile improvements through breeding.
- Need lots of consistent and accurate data on many (ideally all) dogs.

Skin (Atopy)

Skin: Atopy Criteria

Diagnostic criteria of canine atopic dermatitis, according to Willemse (4, 9)

Major features

- Pruritus
- Facial or digital involvement (At Guiding Eyes- mostly digital)
- Lichenification of the flexor surface of the tarsal joint or the extensor surface of the carpal joint
- Chronic or chronically relapsing dermatitis
- Individual or family history of atopy
- Breed predisposition

Features observed in Guiding Eyes for affected dogs

Minor features

- Onset of symptoms before the age of three years
- Immediate skin test reactivity to inhalant allergens
- Elevated serum concentrations of allergen-specific IgGd
- Elevated serum concentrations of allergen-specific IgE
- Xerosis
- Recurrent superficial staphylococcal pyoderma
- Recurrent *Malassezia pachydermatis* infection
- Recurrent bilateral otitis externa
- Bilateral recurrent conjunctivitis
- Facial erythema and cheilitis (sore lips)
- Sweating

Skin Trait = Lowest Skin Score of “Allergy Diagnoses”

- Diagnoses presumed related to allergies are assigned score 5 to 1
- Database assigns dog lowest score as skin score
- Normal skin & ears
 - Has been examined age 15 mo. or later and was normal
 - ≥ 3 yrs. old and no diagnoses scoring 1-4

Diagnosis	Score
Normal skin/ears	5
Pododermatitis predisposing factor, not allergy	4
Pyoderma superficial- not likely allergy caused	4
Rash, mild	4
skin lesions	4
Acute moist dermatitis, predisposing factor	3
Contact dermatitis	3
Interdigital pyoderma	3
Otitis externa both ears	3
Otitis externa left ear	3
Otitis externa right ear	3
Salivary staining	3
Staph folliculitis	3
Allergic dermatitis (inhalant)	2
Flea allergy dermatitis	2
Follicular conjunctivitis	2
Food allergy dermatitis verified	2
Generalized pyoderma deep skin	2
Metatarsal Fistula	2
Otitis externa persistent-not fully resolved or recurs readily	2
Pyoderma (deep) unspecified*	2
Pyoderma superficial- allergy cause possible	2
Acute moist dermatitis - suspect allergy caused	1
Atopy	1
Chronic allergies skin	1
Interdigital dermatitis allergy caused	1
Otitis externa chronic-3+ episodes/12 mo	1

Skin Data: Dogs that leave the program

- Annually survey owners for health updates, ideally lifelong but at least until 5 yrs. old (average 3 yr. old age of onset + catch the older tail of presentation)
- Use consistent definitions to assign diagnoses based on feedback
- Options for survey collection:
 - Survey Monkey or similar service
 - New electronic health survey form via IWDR beginning test, expected available around August: <https://www.tfaforms.com/5053016>

Maintaining Lifelong Health Surveys

- **Send to all dogs produced** (Released, retired, active working, breeders)
- **Get agreement from adopters & clients to supply information**
- **Keep contact information as current as possible**
- **Response rates:**
 - Improved with time as new owners gained experience in filling out surveys.
 - Volunteer provides phone call follow-up as needed.

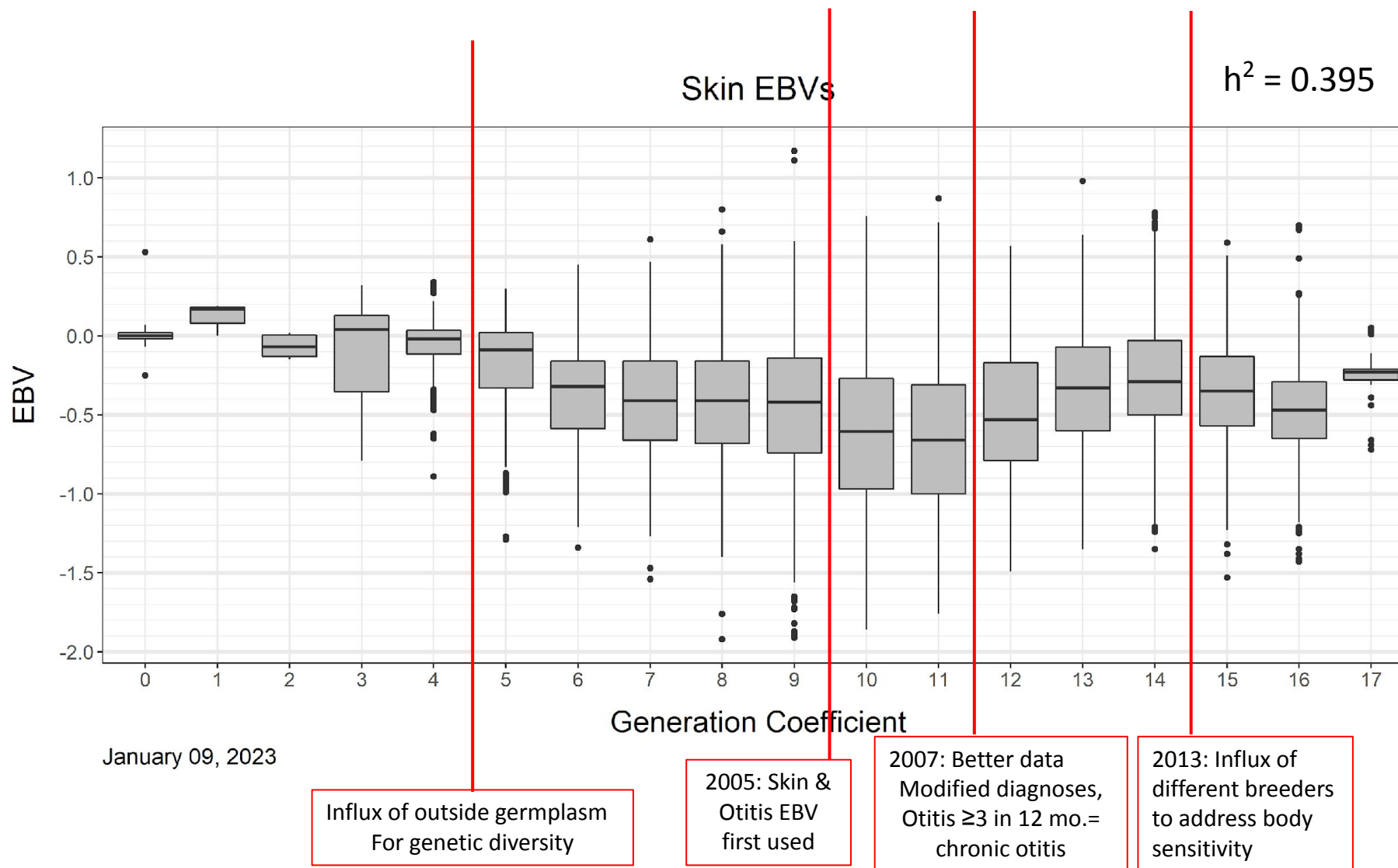
IWDR* Skin EBV Model

	Labrador Retriever	German Shepherd	Golden Retriever
Heritability	0.353	0.279	0.459

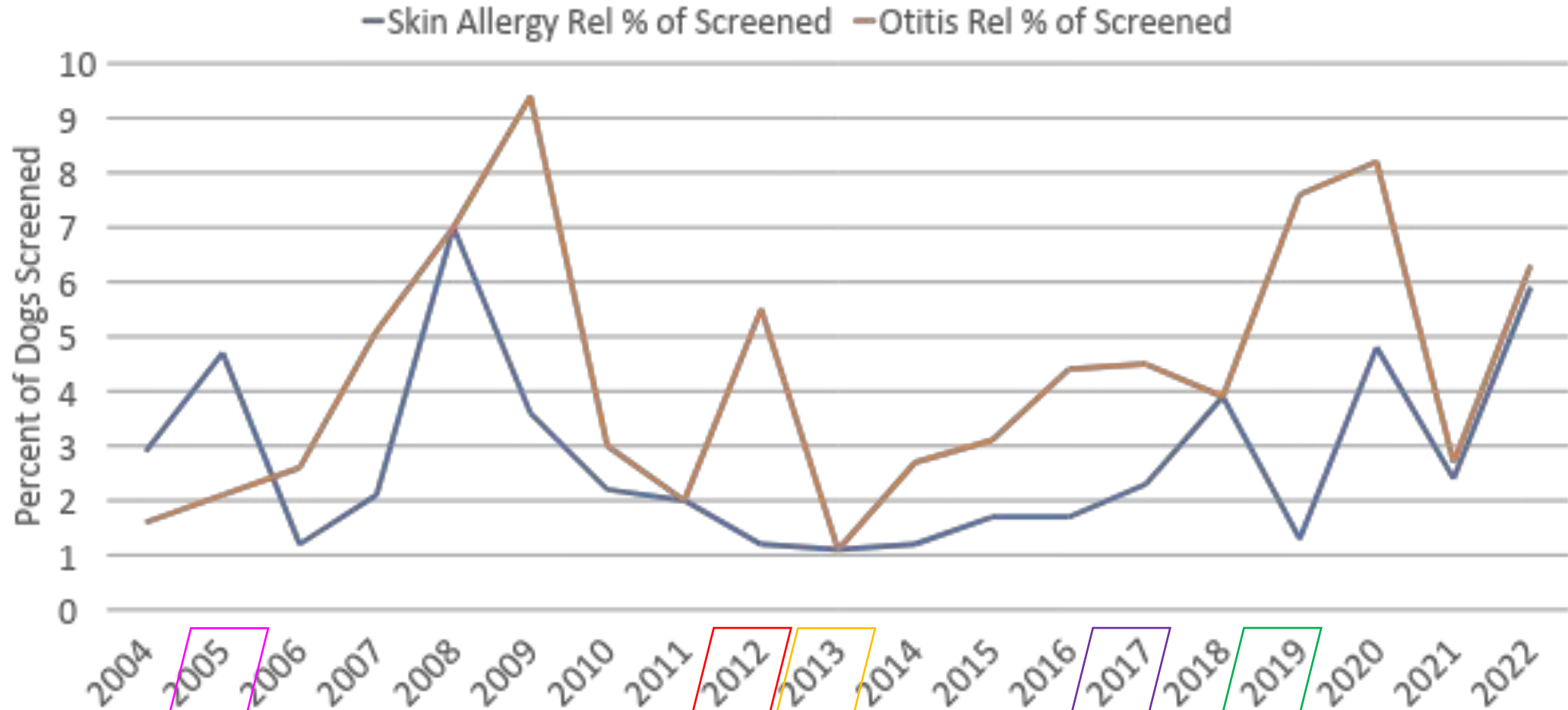
- **Trait:** score of lowest-scored (most undesirable) skin diagnosis
- **Fixed effects:** sex
- **Covariates:** percent inbreeding
- **Random effects:**
 - Age of dog in days when diagnosis was made providing lowest score
 - Dog ID

**GEB model for Labradors shown following – from which IWDR was based – is similar.*

Skin Genetic Trend – GEB Data



% Skin Allergy & Otitis Releases of Screened LR by Year Released



2005: EBV implemented

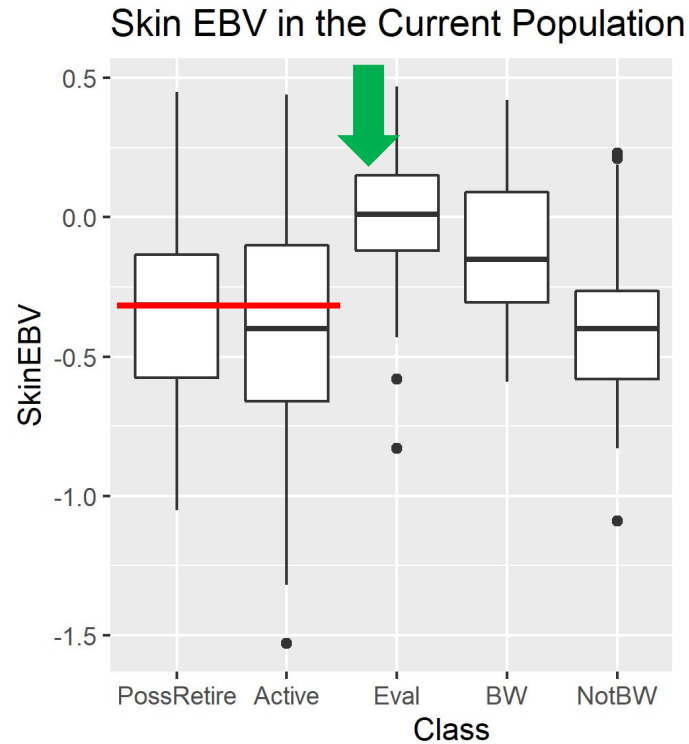
2012: Environmental change e.g. kennels more humid than usual?

2013: Breeding priority shifted away from skin/otitis

2017: Influx of outside studs

2019: Focus shifting back to skin/otitis

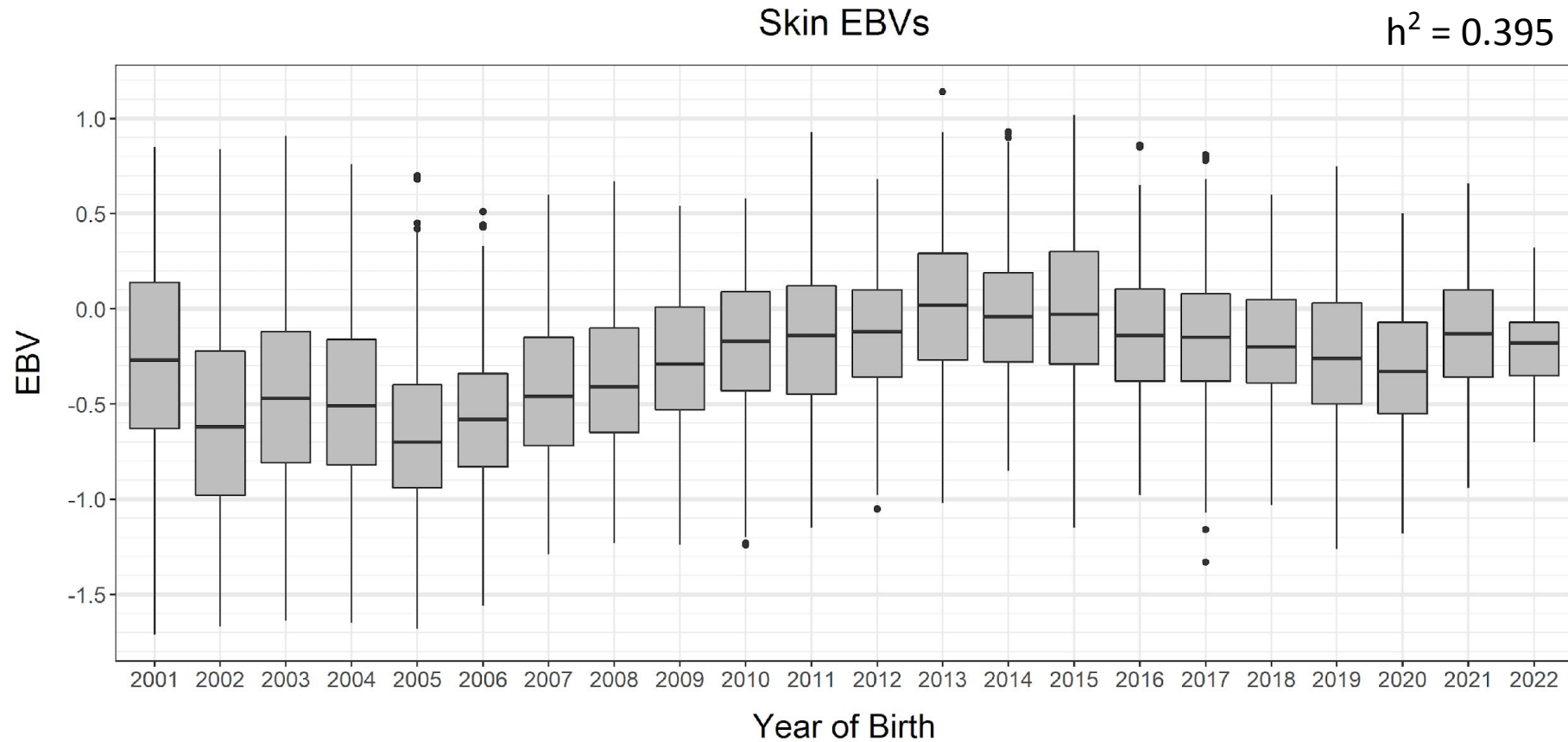
Timeline of Genetic Progress: GEB Skin Data



January 09, 2023

- **Progress lost** when **dogs leaving the colony were stronger**
- **Progress made** when **new dogs kept are stronger than dogs not kept/leaving**

Skin Genetic Trend by Year of Birth



January 24, 2023

Summary: Skin

- Responds well to genetic selection. Select young breeders from families with lowest incidence of skin allergy and otitis.

	Labrador Retriever (GEB)	Labrador Retriever (IWDR)	German Shepherd (IWDR)	Golden Retriever (IWDR)
Heritability	0.395	0.353	0.279	0.459

- Requires accurate data on many relatives & can be later onset: Annual health survey of dog’s owners helps track changes with age. **Continue getting data on all relatives at least until at least 5 years of age.**



Elbow Dysplasia

Radiograph Views For Elbow Diagnoses

Multiple conditions = need different views to correctly identify.



Elbow Diagnosis	ML Flexed	ML extended	Cranial Caudal	Cranial Caudal Oblique
Medial Coronoid (MCD) previously FCP		x		x
Ununited anconeal process (UAP)	x			
Osteochondrosis (OCD)			x	
Kissing lesions – look like OCD but are secondary to MCD	x	x		
Incongruity		x		

Summary from IWDR: <https://www.iwdr.org/elbow-dysplasia-screening/>

PowerPoint download from FCI website: <http://www.fci.be/medias/SCI-ART-DYS-COU-MDU-en-1744.ppt>

Identifying Elbow Dysplasia (Radiographs)



ML flexed



ML extended



Cranial Caudal



Cranial Caudal
Oblique

- **Measure:** <https://www.iwdr.org/elbow-dysplasia-screening/>
 - 4 views is best
 - Read by certifying agency (FCI, OFA, BVA), not a local veterinarian
- **Age:**
 - **IDEAL:** 15-18 months old
 - **Minimum:** 12 months old
 - **Breeders:** Re-screen at 36 months (3 years) old
- **Which Dogs:** All dogs (breeders, working candidates, released of appropriate age)

Identifying Elbow Dysplasia (CAT Scan)

- Alternative way of measuring elbow quality gaining popularity in some parts of the world
- Accuracy for selection is better than radiographs.
- May be able to identify MCD at younger ages than radiographs.
- May be cost prohibitive and/or less available in some places.
- See extra slides for references/further reading.

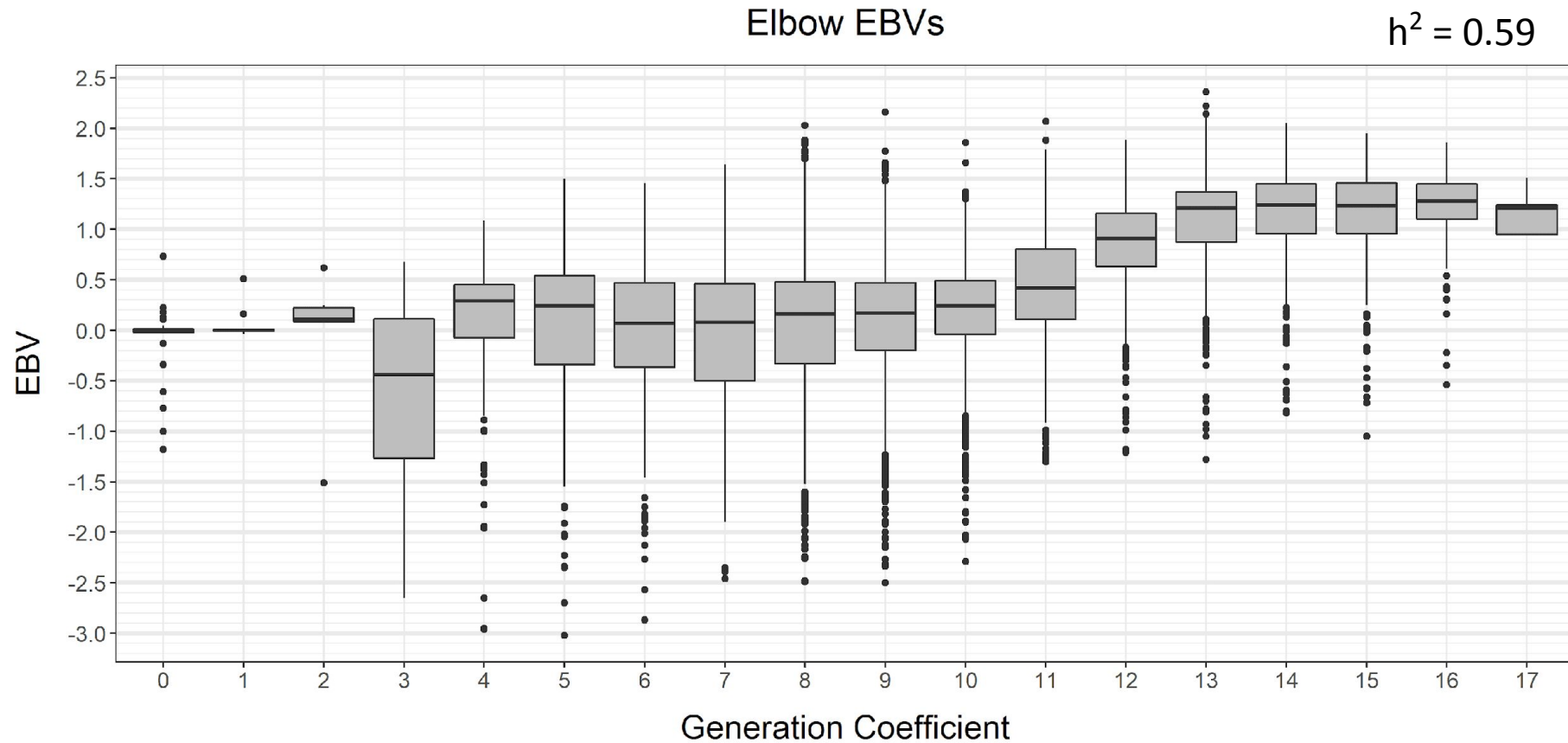
IWDR* Elbow EBV Model – same as Skin

	Labrador Retriever	German Shepherd	Golden Retriever
Heritability	0.312	0.268	0.204

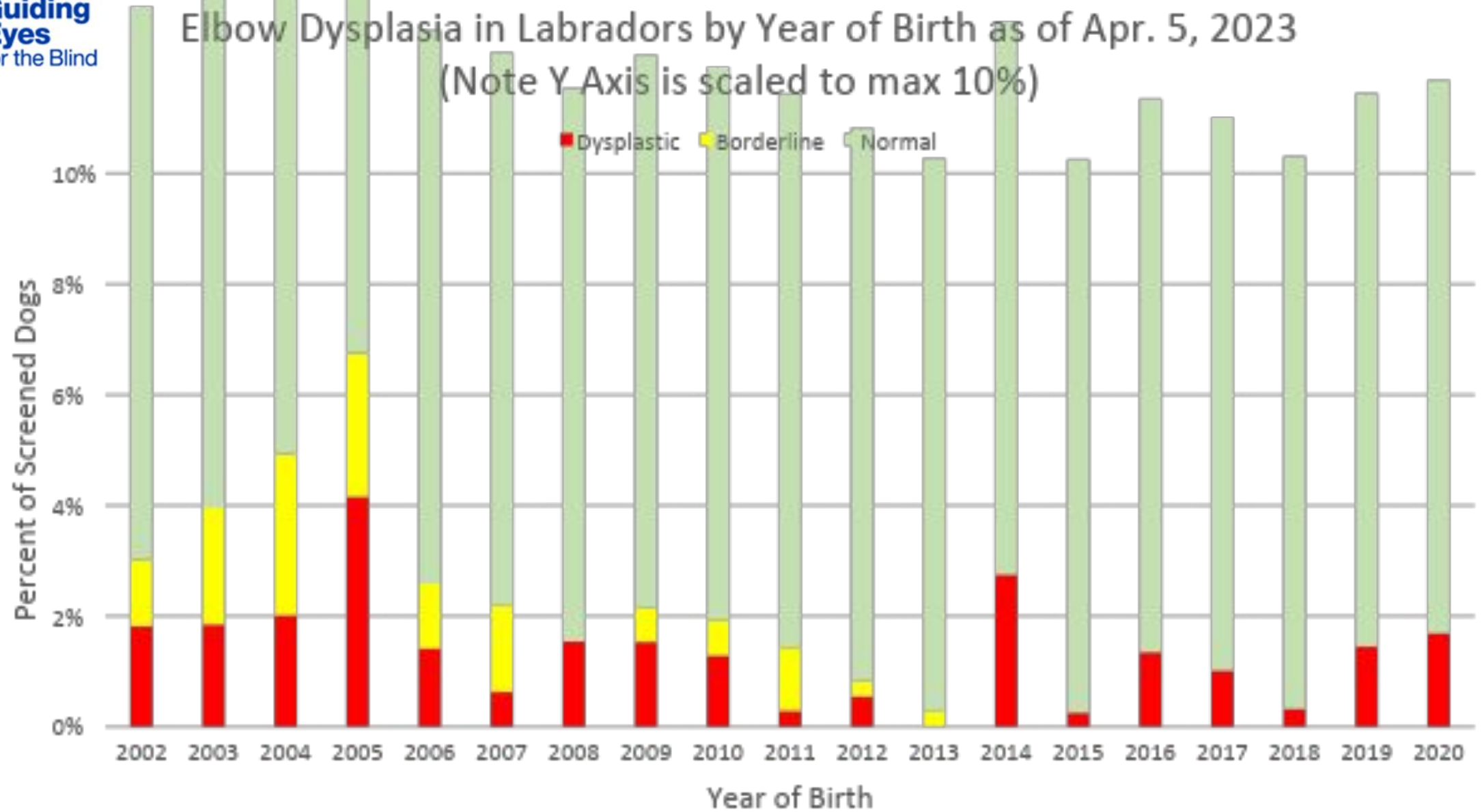
- **Trait:** score of lowest-scored (most undesirable) elbow diagnosis
- **Fixed effects:** sex
- **Covariates:** percent inbreeding
- **Random effects:**
 - Age of dog in days when evaluated for elbow quality
 - Dog ID

**GEB model shown next differs.*

Elbow Genetic Trend by Generation



January 09, 2023



*Birth years 2021 and 2022 excluded due to low number of dogs screened to-date.

Summary: Elbow Dysplasia

- Consists of several diseases seen with different radiographic views
- Screen all dogs ideally at 15-18 months old but no younger than 12 months old. Recheck breeders at 36 months.
- Responds to genetic selection, but several radiographic views read by certifying agency (not a local vet) or CAT scan are necessary to get accurate data for accurate selection.

	Labrador Retriever (GEB)	Labrador Retriever (IWDR)	German Shepherd (IWDR)	Golden Retriever (IWDR)
Heritability	0.594	0.353	0.279	0.459

Mast Cell Tumors

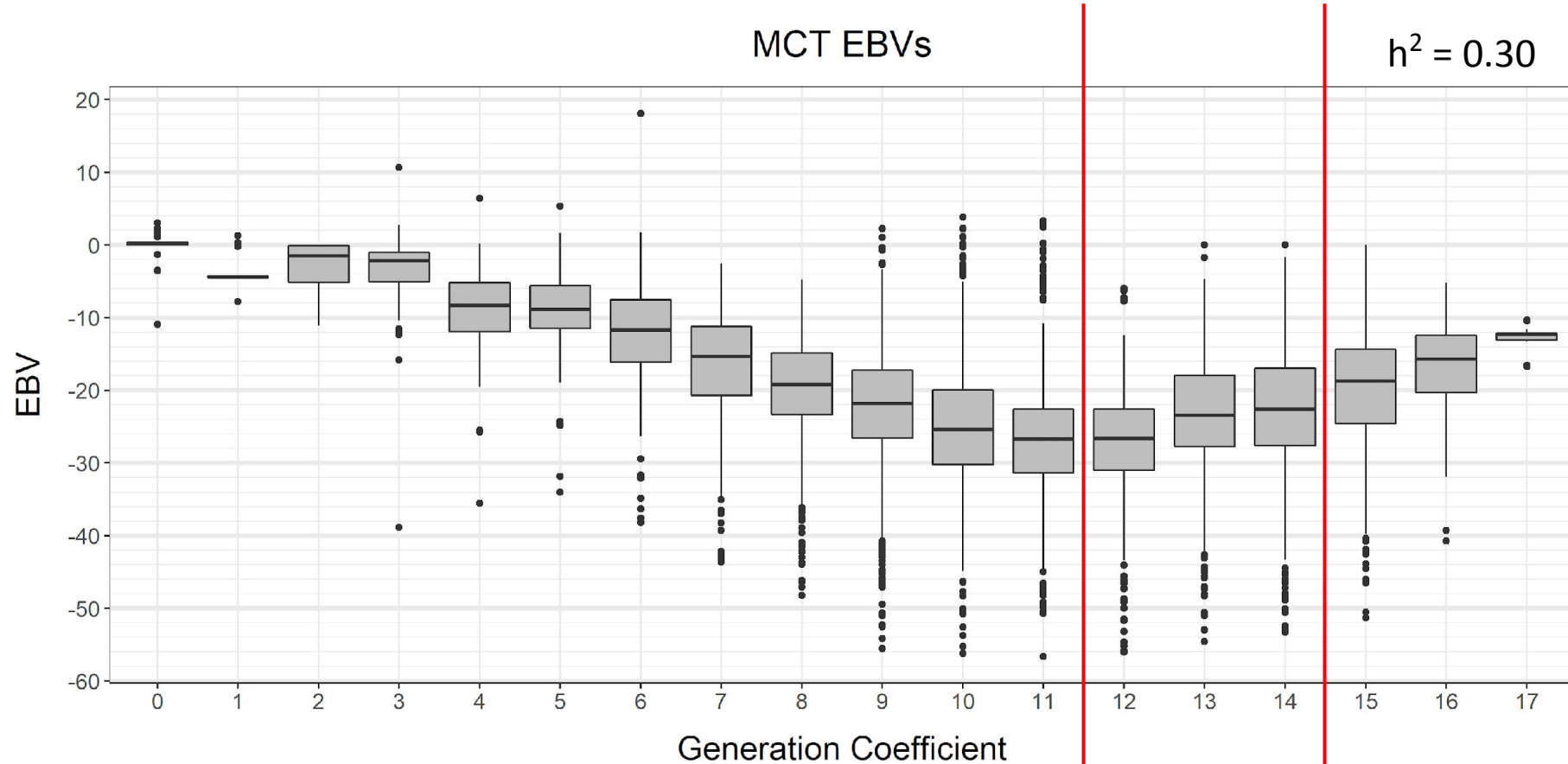
Mast Cell Tumors

- Common type of malignant skin tumor.
- Can be graded by biopsy/histopathologic analysis: Lower grades are less aggressive.
- Average age of onset in GEB colony = 7 years old, so need to survey dog owners/handlers about health through advanced ages.

Mast Cell Genetic Model (GEB Labradors)

- Doesn't currently have an IWDR EBV
- **Heritability** about 30%
- **Trait:** Age of onset (2 parts: min and max age. Driving toward later onset – using score did not drive continued improvement.)
 - **Cases:** min age = max age
 - **Controls:**
 - Min age is 6 or less depending on last exam
 - Max age is infinity (did not get disease)
- **Fixed effects:** Sex
- **Random effects:** Dog ID

Mast Cell Genetic Trend by Generation



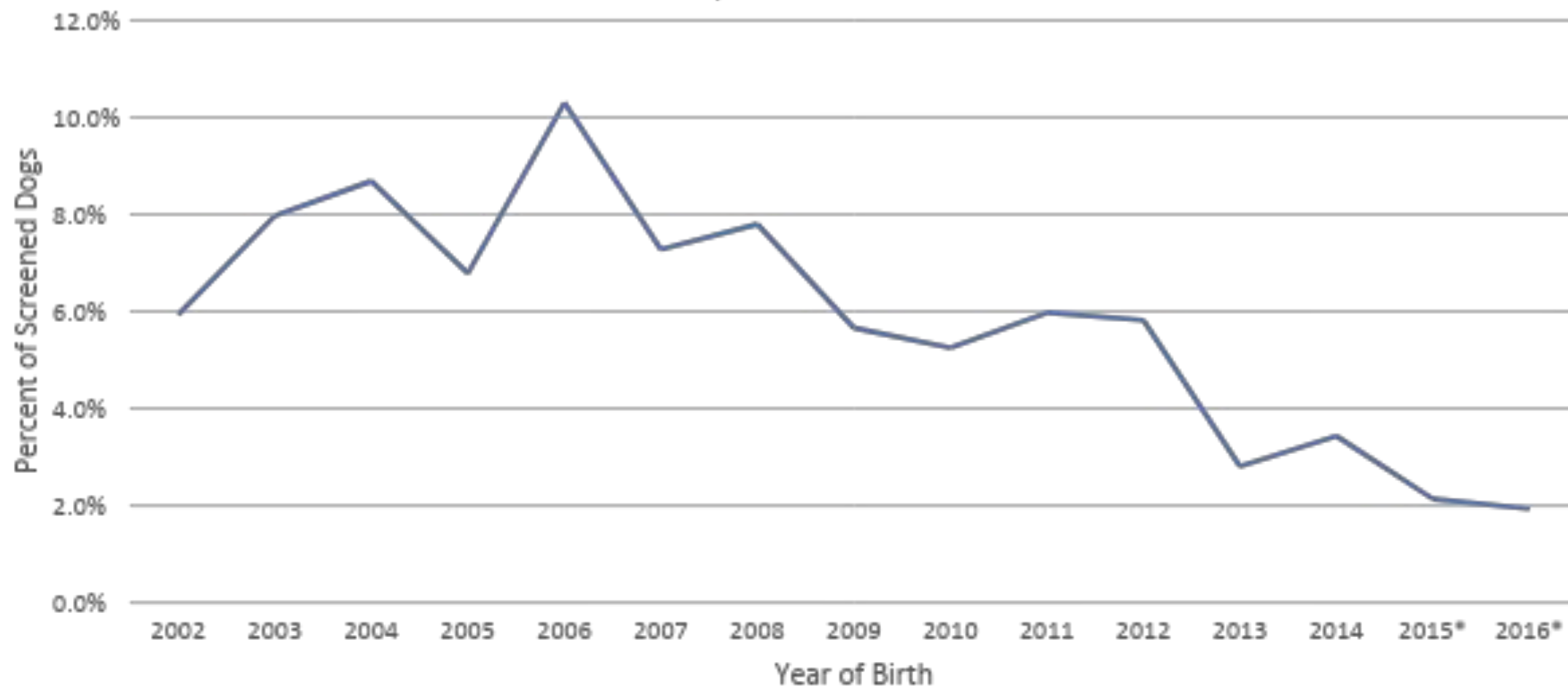
EBV based
on grading

EBV model changed to
consider age of onset as trait

Mast Cell Cancer in Labradors

Percent Affected of Dogs Screened by Year of Birth

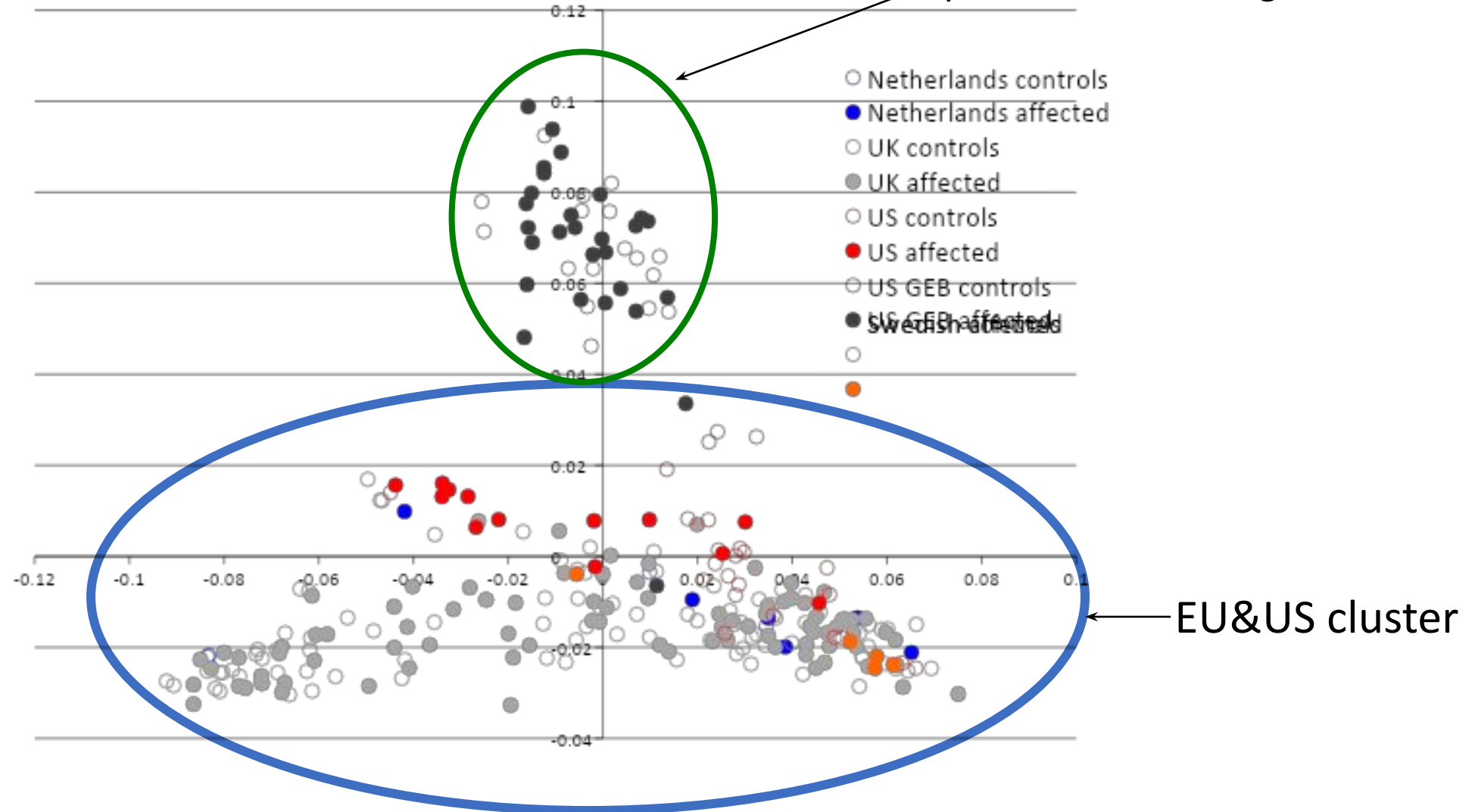
April 5, 2023



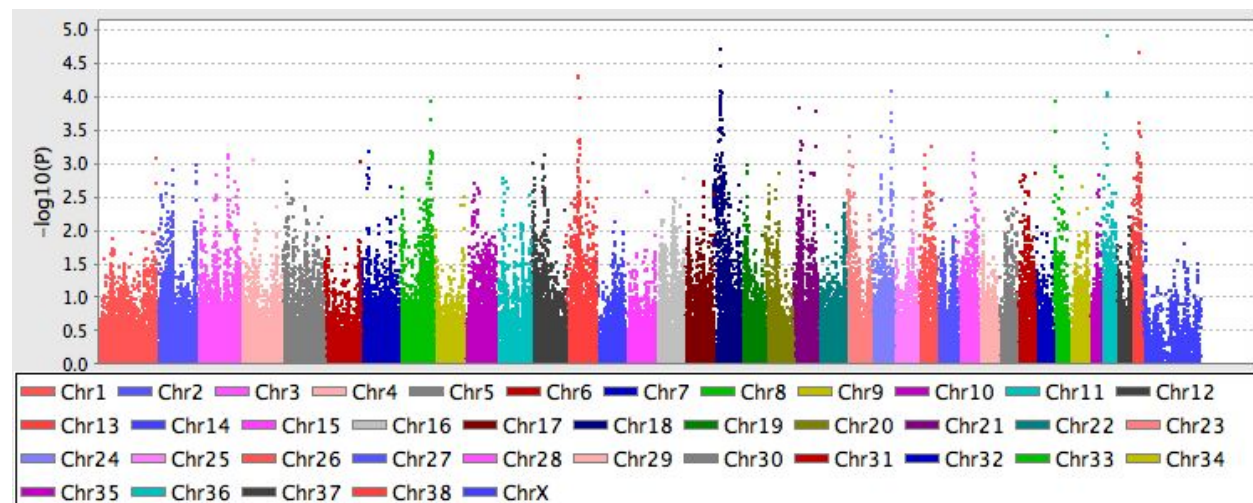
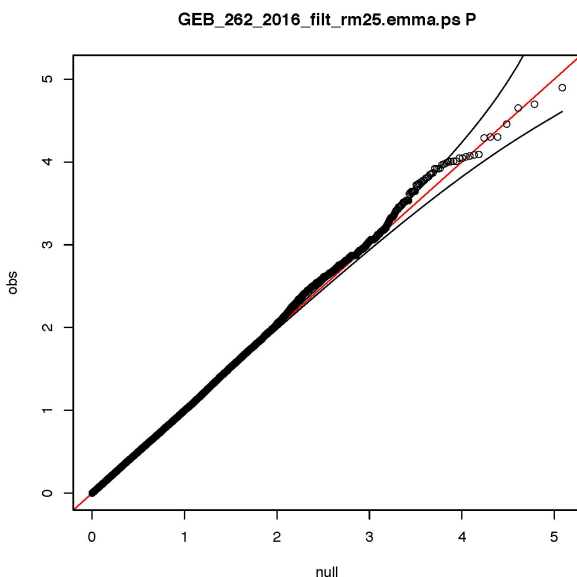
EU & US cluster

The outlier group consists of the Guiding Eyes for the Blind dogs.

114 affected, 119 controls. Inflation factor 1.08.



GEB GWAS analysis based on mast cell tumor cases and controls



•No significant association identified

261 individuals 141 cases 120 controls (recently updated phenotypes) after removing individuals related more than 25% there are 101 cases and 64 controls. Analysis performed using the emmax software. No deviations from the expected p-values in the qq-plot are seen.



- QQ plot to the left shows expected versus observed p-values, a deviation from the expected normal indicates significance. 95% confidence interval is indicated by thin black line.
- Manhattan plot to the right shows dots for each SNP in the analysis. Location of each SNP is on the x-axis and on the y-axis the $-\log_{10}(p)$ value is noted.

Summary: Mast Cell

- Need substantial longevity data, ideally lifetime (average age of onset is 7 in GEB colony – want to capture at least through then)
- Responds to selection, especially when considering age of onset (goal = never get it, but if they do, it happens at more advanced ages)
- Can be genetically different between colonies/populations. EBVs can still help if populations mix providing everyone is collecting data.

Questions?



Extra/alternative slides

Some References for CT Scans for detecting Elbow Dysplasia

- Hazewinkel, H.A.W. and Lau, S. F. Pathogenesis of fragmentation of coronoid process. Proceedings of the 34th IEWG Meeting, Nice, 2022.
- Lau S.F., Wolschrijn, C.F., Hazewinkel, H.A.W., Siebelt M., Voorhout G. The early development of medial coronoid disease in growing Labrador retrievers: radiographic, computed tomographic, necropsy and micro-computed tomographic findings. *Vet J.* 2013;197:724–30.
<https://doi.org/10.1016/j.tvjl.2013.04.002>
- Villamonte-Chevalier, A., van Bree, H., Broeckx, B., Dingermanse, W., Soler, M., Van Ryssen, B., and Gielen, I. Assessment of medial coronoid disease in 180 canine lame elbow joints: a sensitivity and specificity comparison of radiographic, computed tomographic and arthroscopic findings. *BMC Vet Res* 11, 243 (2015).
<https://doi.org/10.1186/s12917-015-0556-9>

Summary of Health Measures Needed

<https://www.iwdr.org/master-knowledge-base/what-data-should-i-collect/>

Health Trait		Need	
	Which Dogs	Age	Best Method
Elbow	All	≥12 mos Ideally 15-16 mos Repeat 36 mos	4 radiographic views read by certifying organization or CAT scan <ul style="list-style-type: none">• https://www.iwdr.org/elbow-dysplasia-screening/• http://www.fci.be/medias/SCI-ART-DYS-COU-MDU-en-1744.pdf
Skin	All	All diagnoses, lifetime or at least 5 years	Use definitions to assign diagnoses. Owner survey for dogs not in organization's direct care.
Mast Cell	All	All diagnoses, lifetime or at	Owner survey as dogs age –

Data Used in Addition to Health Data

1. Sex of the dog (males vs. females; fixed effect)
2. Age in days when phenotype was measured (covariate)
3. **Inbreeding level**- determined by which male is chosen to be the father (covariate)

Blue Color- You influence these data

Heritability of Health Traits

Trait	GEB LR	LR	IWDR	
			GS	GR
Skin	0.395	0.353	0.279	0.459
Elbow	0.594	0.312	0.268	0.204
MCT	0.298	NA	NA	NA

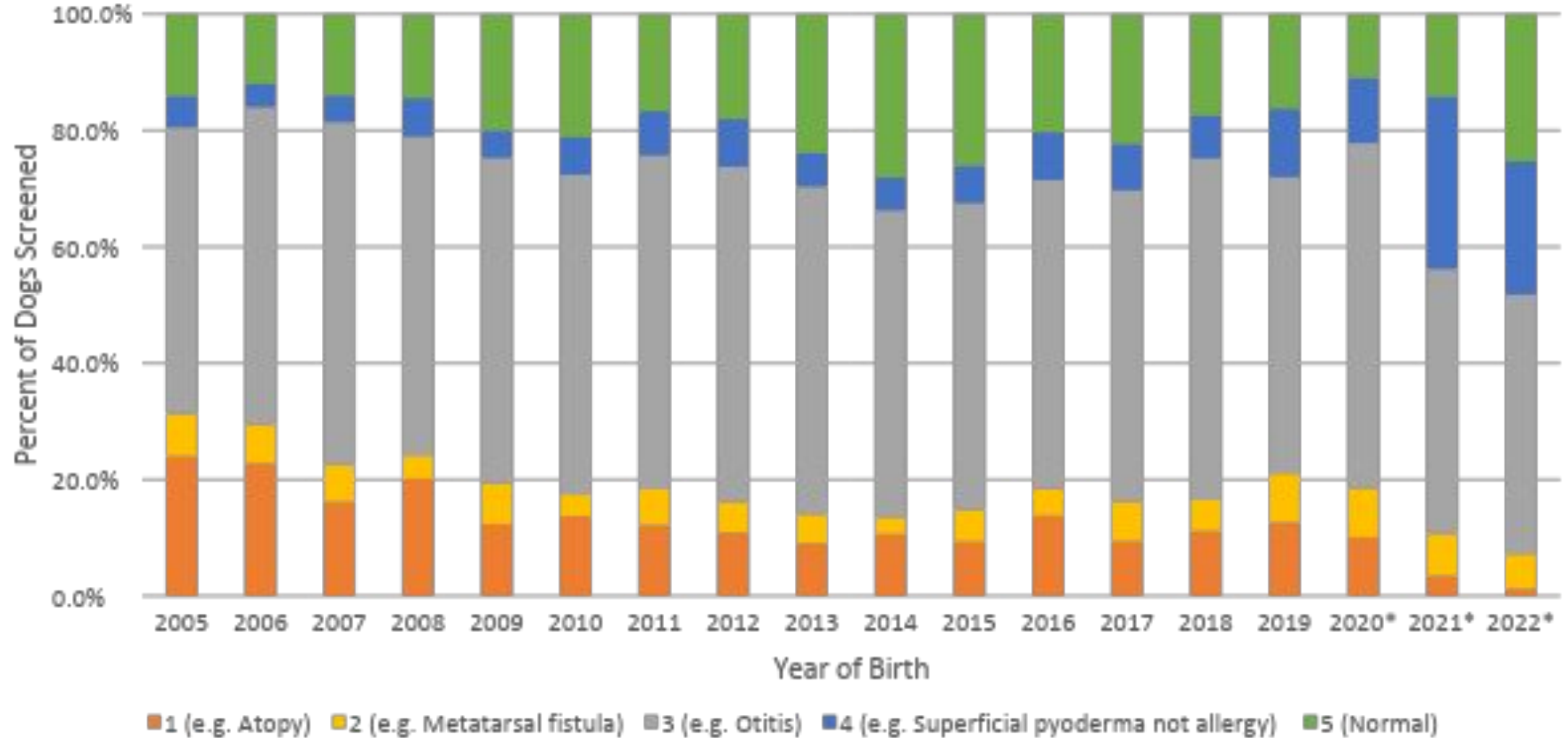
Challenges of Each Condition

- Skin:
 - Average age of onset can be later – need health survey to get longevity data
 - Interpreting owner responses can be intensive if the survey is not coded
- Elbow:
 - Need multiple radiographic views read by a certifying agency to properly identify several relevant diagnoses. May miss incidences otherwise.
- Mast Cell:
 - Average age of onset is at an advanced age – need health survey as with skin, but to an even later age.
- Overall: Change in observable trait lags a few years behind change in EBVs.

Principles to Keep in Mind

1. Look at the whole dog & whole picture.
 - If it matters for long term longevity, it must have measures in place
 - Focus on the priorities
 - Consequence of not doing this = making improvements one trait while something else is inadvertently worsened
2. It takes a long time to “turn around the airship.”
 - EBV trend changes before phenotype changes, especially with lower heritability
 - Usually ~3 generation lag
3. Occasionally choose mates that BOTH have strong EBVs to avoid accidentally losing exceptionally good genetic merit

Worst Skin Score (LR) by Year of Birth 1/25/2023 (2022 n=83 where others are >200)



**Data still accumulating – distribution likely to change*