Uveal Melanocytic Neoplasia

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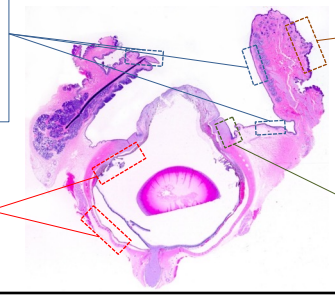
Diagnosis of Ocular/Periocular Melanocytic Tumors

Not all black masses are made equal!

- Species differences
  - Dogs ≠ Cats ≠ Horses
- Location differences
  - Uveal ≠ Conjunctival ≠ Eyelid skin ≠ Limbal

Conjunctival
Palpebral, bulbar & 3rd eyelid
- Melanomas > melanocytoma
- Often recur, rarely met.
- Can be multifocal – pagetoid spread

Uveal
- Melanocytoma > Melanomas
- Iris/CB > Choroid
- Rarely met. or recur



Eyelid, *Cutaneous*
- Identical to cutaneous other sites
- Melanocytoma > Melanomas

Limbus
- Limbal melanocytoma
- Almost always benign

2

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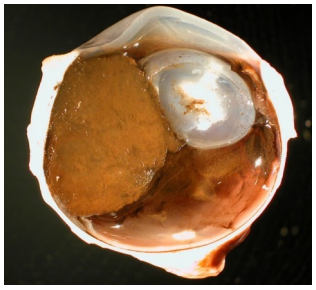
2135/5722 Canine Melanocytic Tumors
(numbers from 2012)

- Most common ocular neoplasms in dogs
- Affecting the Globe: 1871
  - Anterior Uveal Melanocytoma: 1245
  - Anterior Uveal Malignant Melanoma: 312
  - Limbal Melanocytoma: 213
  - Choroidal:
    - 86 Melanocytoma
    - 11 malignant Melanoma
  - Metastatic Melanoma: 15



1. Giuliano EA, Chappel R, Fischer B, **Dubielzig RR.** (1999) A matched observational study of canine survival with primary intraocular melanocytic neoplasia. *Vet. Ophthal*. 2: 185-190.

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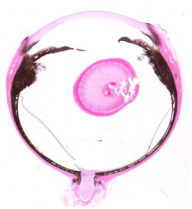
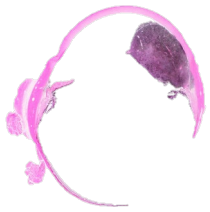
Ocular Pigmented Melanocytic lesions in dog

Diagnosed at COPLOW:

- Heavily pigmented globe
- Ocular melanosis
- Melanocytoma
- Melanoma (malignant)





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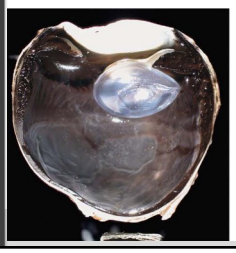
Heavily pigmented globe

- Cairn terriers, Boxers Labradors, Rottweilers.
- Normal phenotype
- Normal architecture

Ocular Melanosis

- Cairn terriers, Boxers and Labradors.
- Increase numbers and size of melanocytes
- Uveal distortion



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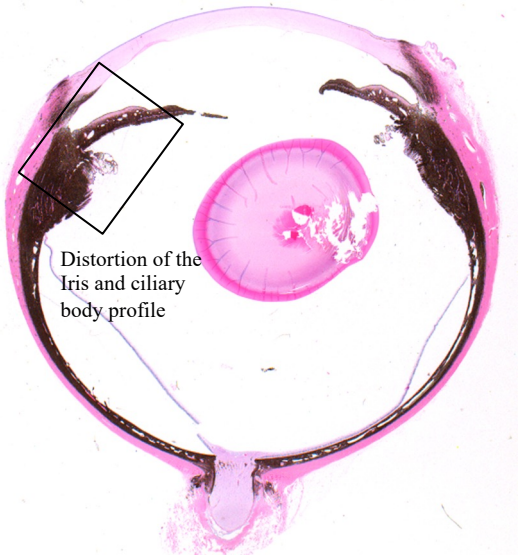
Ocular Melanosis



1. Heavily pigmented eye
The uveal profile is maintained

2. Ocular melanosis
Uveal profile disrupted
Entirely pigmented round cells

3. Melanocytoma
Either a double population
Round and spindle cells
Or a clear mass
Can arise in melanosis

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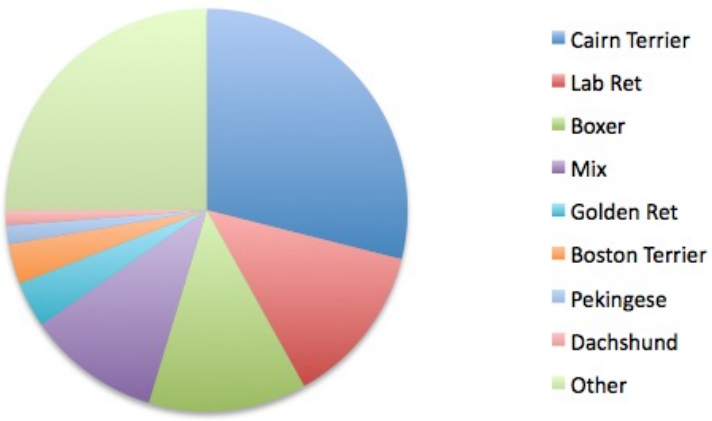
Canine Ocular Melanosis



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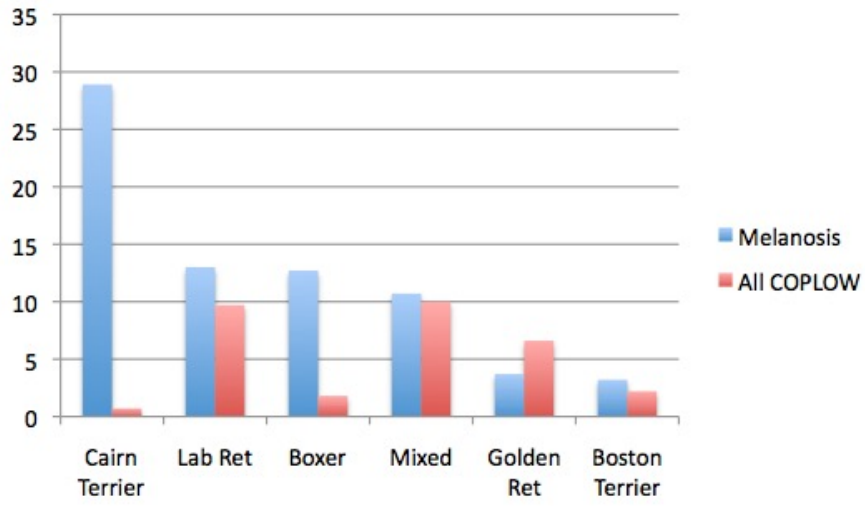
Ocular Melanosis



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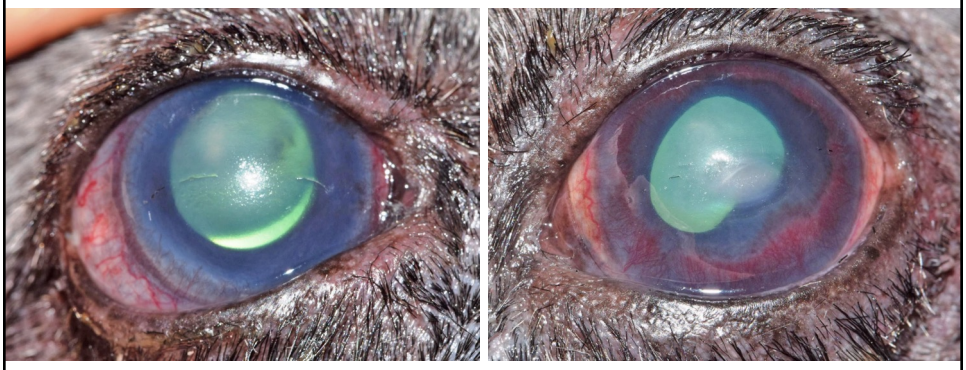
Ocular Melanosis



Hyperpigmented and distorted iris

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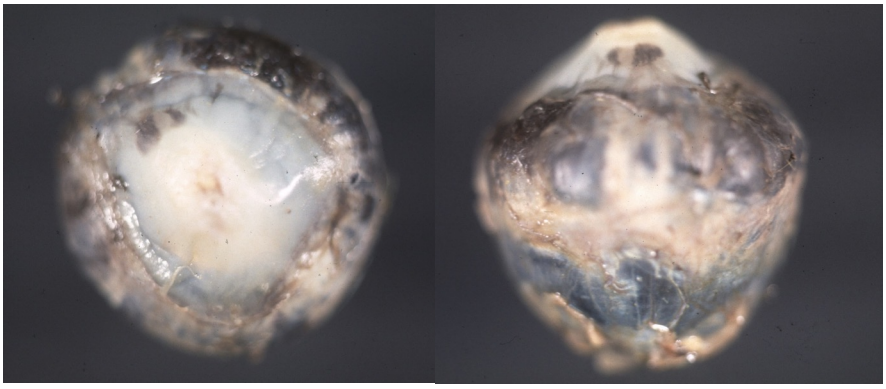
Ocular Melanosis



Hyperpigmented uvea, sclera and no mass lesion
and no double papulation (spindel and round)

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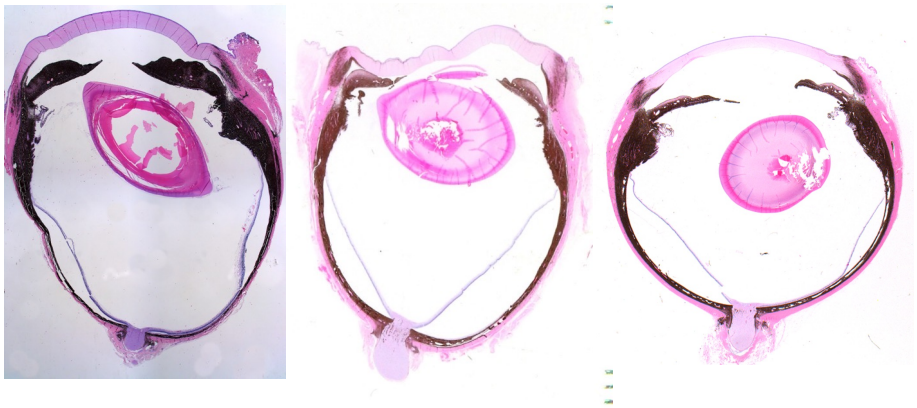

Excessive pigmentation often seen throughout the uvea

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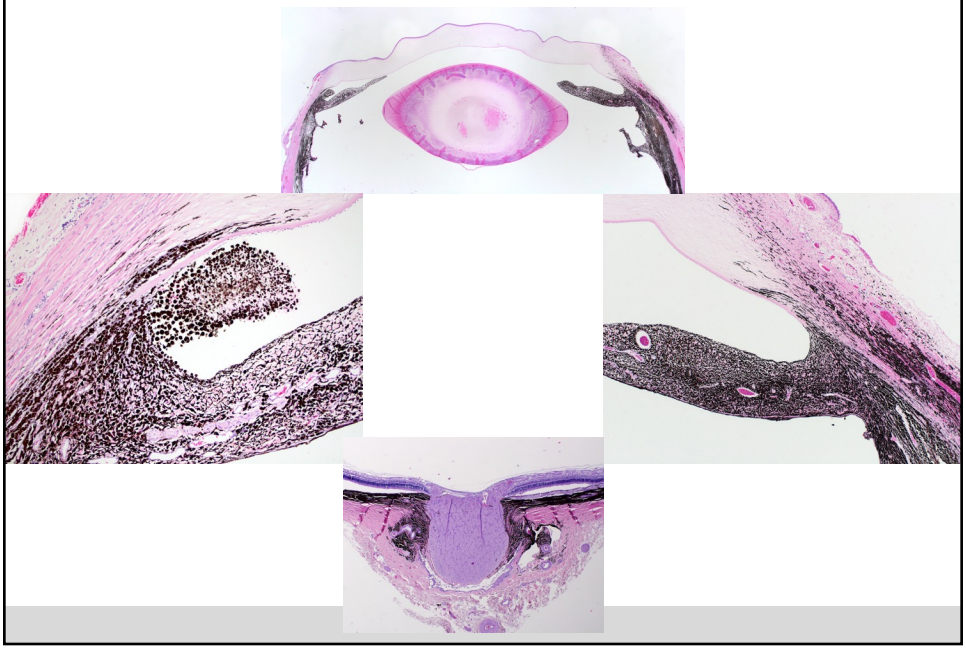

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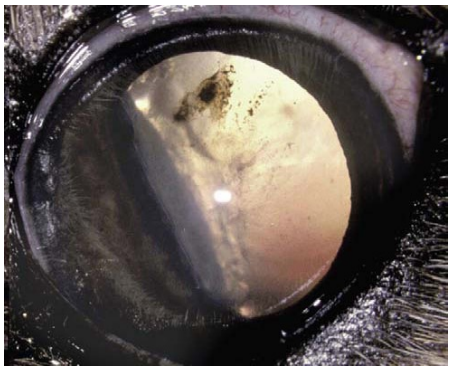
Uveal Melanocytoma

- Most common in the iris and ciliary body, typically affecting both
- 94% anterior, 6% choroidal
- 75% of anterior melanocytic neoplasms are benign
- 85% of choroidal melanocytic neoplasms are benign



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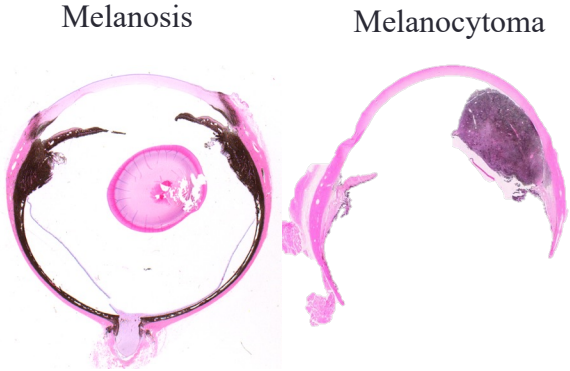
Anterior Uveal Melanocytoma

Many cases arise within ocular melanosis or heavily pigmented globes

Melanocytoma:

- Distinct mass lesion or
- Double population of spindle and round cells



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Uveal Melanocytoma

- Similar histologic appearance independent of their location
- Variable proportions of heavily pigmented spindle cells and discohesive heavily pigmented plump polyhedral cells
- Mitotic count of < 3-5 in 10 HPF (2.37 mm^2)
- Readily efface the iridocorneal angle
- Many expand along the corneoscleral meshwork in the deep peripheral corneal stroma
- Scleral and extrascleral extension is common (not a feature of malignancy)

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Uveal Melanocytoma

- Individualized pigmented cells may be seen in the anterior and posterior chambers and vitreous
- Necrosis and infiltration of melanophages are common
- Secondary findings: Intraocular hemorrhage, pre-iridal fibrovascular membrane, asteroid hyalosis, and glaucoma
- Retinal detachment is expected with choroidal melanocytomas

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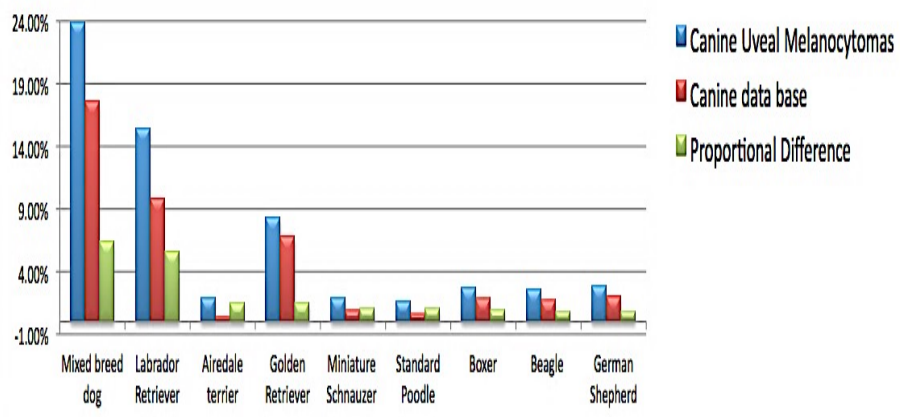
Uveal Melanocytoma

2372 Casos



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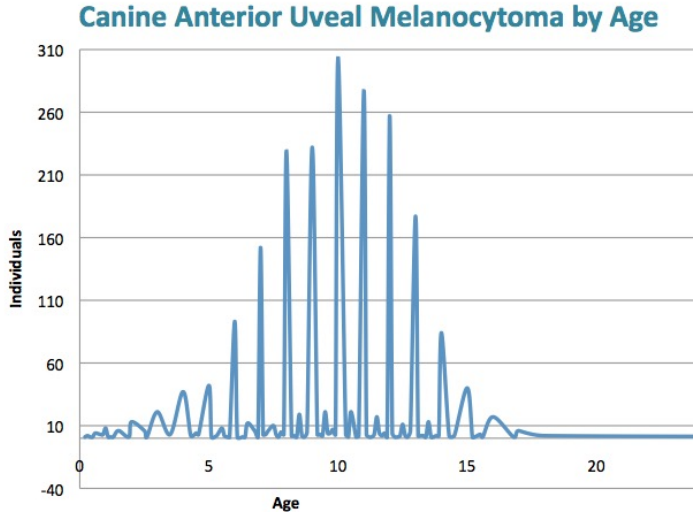
Uveal Melanocytoma



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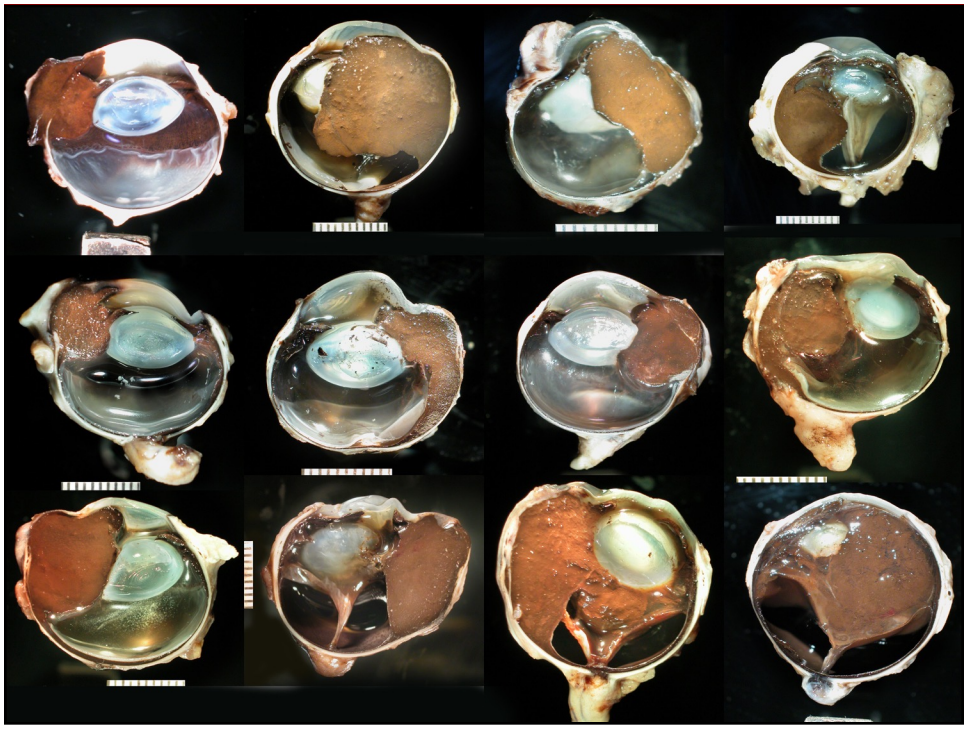

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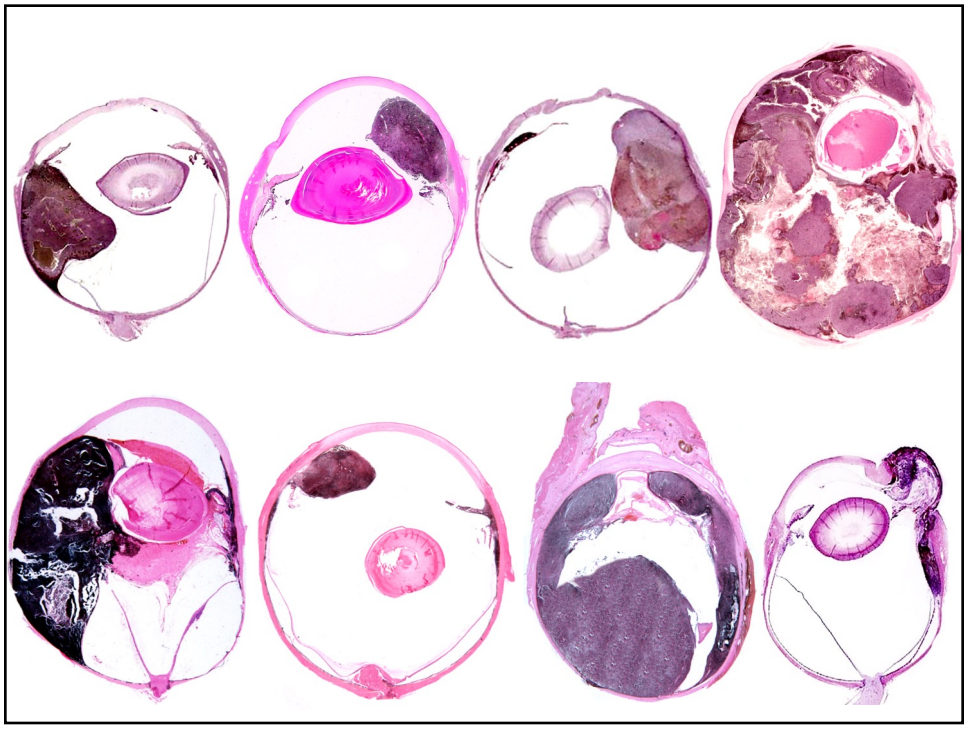

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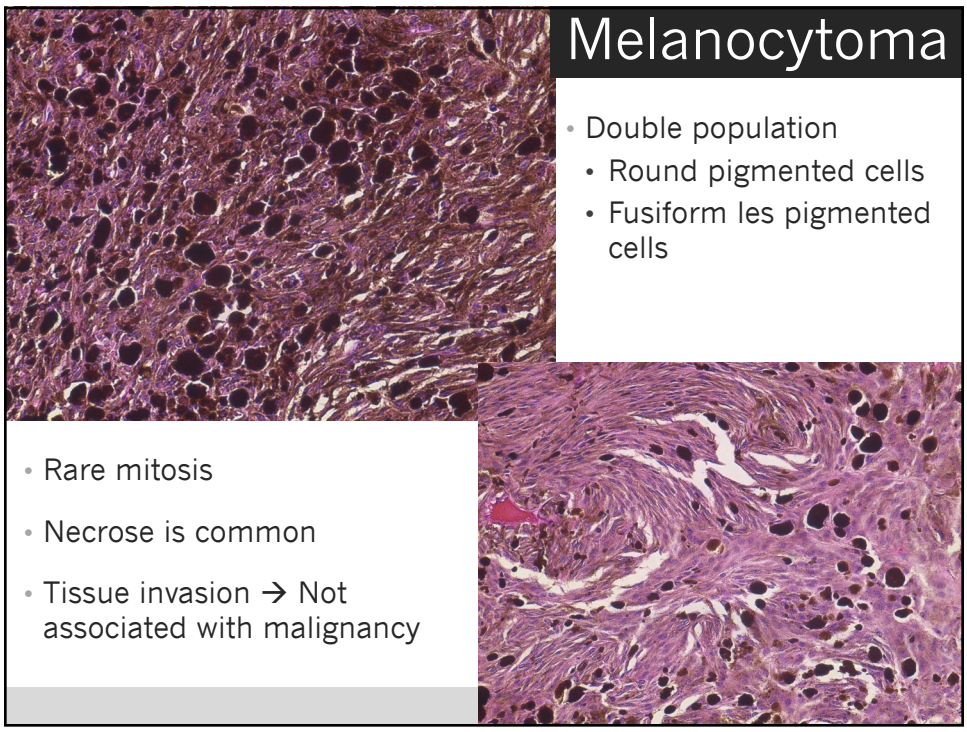
Melanocytoma
• Double population
• Round pigmented cells
• Fusiform les pigmented cells
• Rare mitosis
• Necrose is common
• Tissue invasion → Not associated with malignancy

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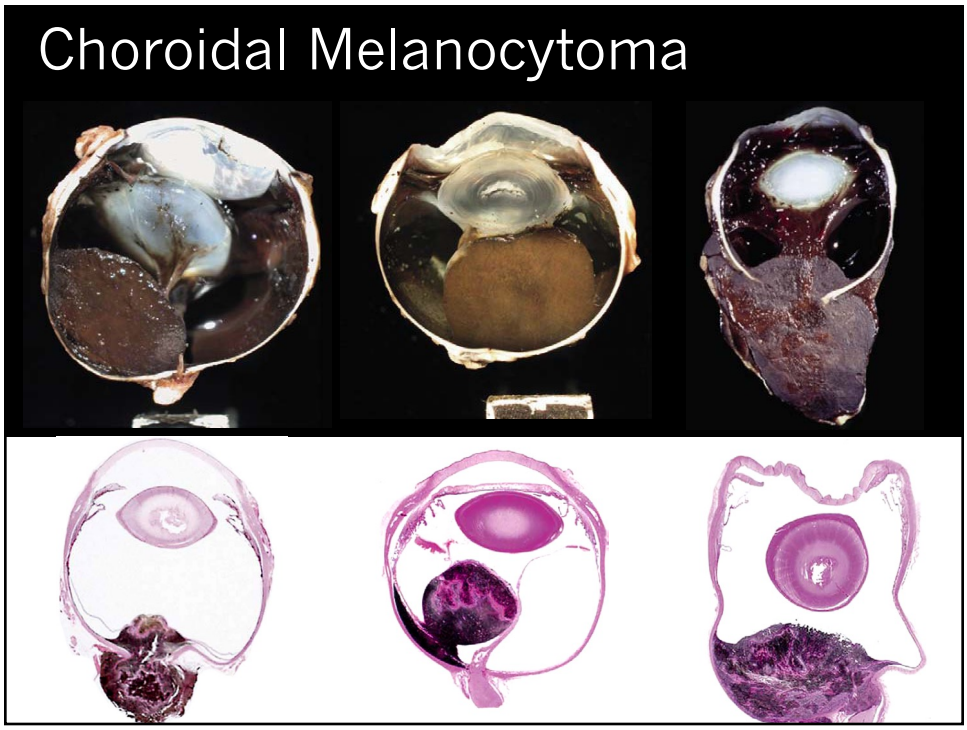
Choroidal Melanocytoma

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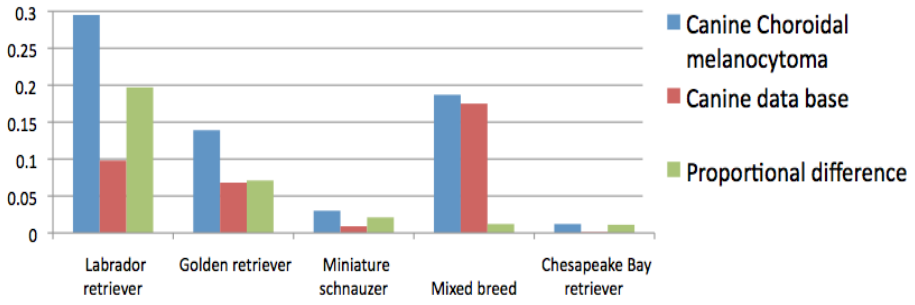
Choroidal Melanocytoma

Canine data base - 29,760 records
Canine Choroidal Melanocytoma - 166 records
Overrepresented



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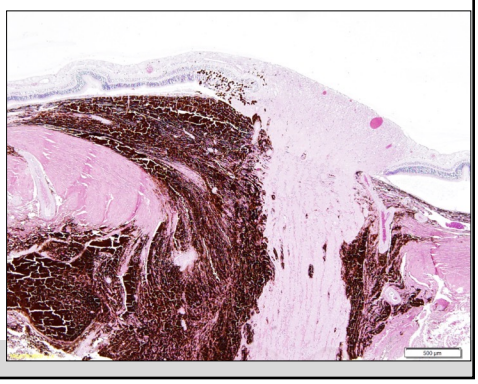
Choroidal Melanocytoma

After 4 years the dog developed neurologic disease, presumed to be secondary to invasion of the optic foramen

After 2.5 years this dog developed neurologic signs and was euthanized.



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Anterior Uveal Malignant Melanoma 312 cases

- Most common in the iris and ciliary body, typically affecting both
- 97% anterior, 3% choroidal
- 25% of anterior melanocytic neoplasms are malignant
- 15% of choroidal melanocytic neoplasms are malignant
- No histologic features can reliably predict metastasis
- Anecdotal metastatic rate <5%

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Anterior Uveal Malignant Melanoma

- Similar histologic appearance independent of their location
- Spindle cells to polygonal cells
- Variably pigmented
- Moderate to severe pleomorphism
- Mitotic count of 3-5 or more in 10 HPF (2.37 mm2)
- Readily efface the iridocorneal angle
- Many expand along the corneoscleral meshwork in the deep peripheral corneal stroma
- Scleral and extrascleral extension is common

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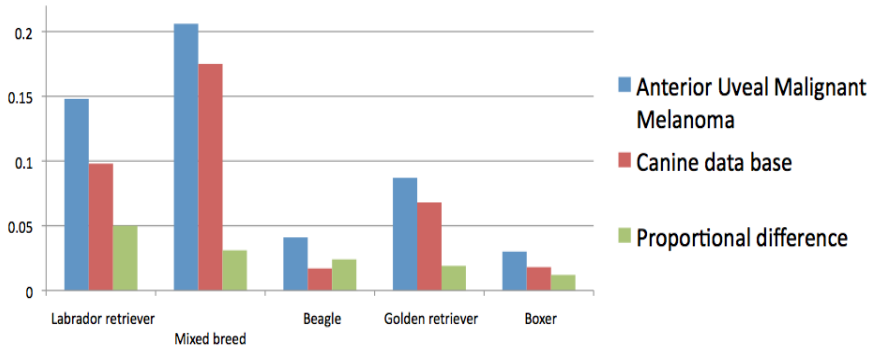
Malignant Melanoma

Canine data base - 29,760 records
Canine Anterior Uveal Malignant Melanoma - 635 records
Overrepresented breeds



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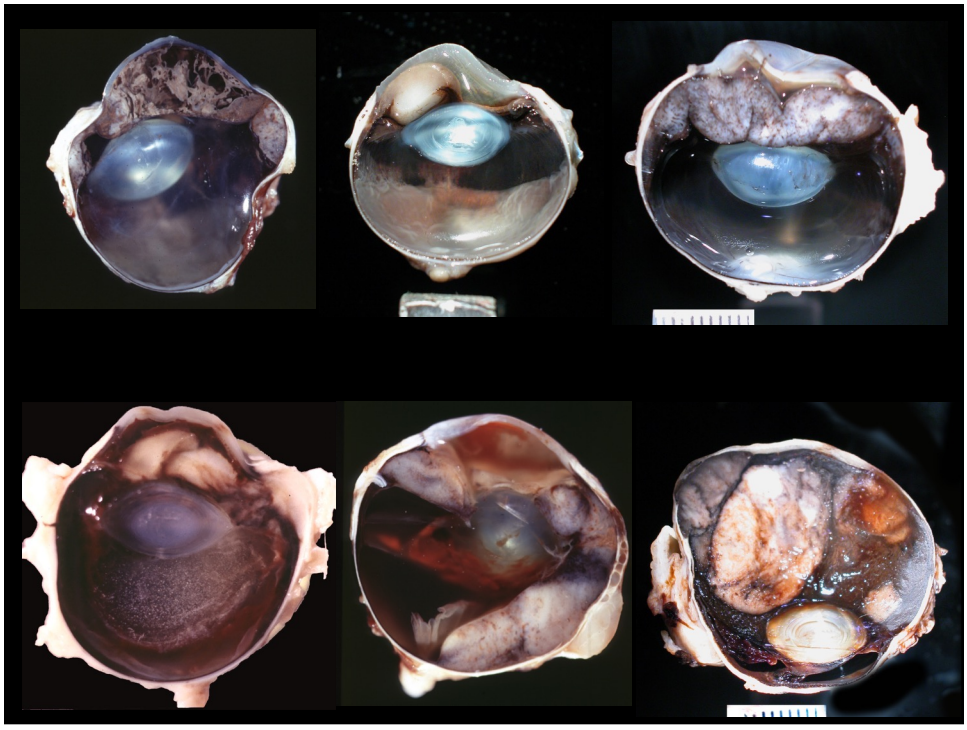

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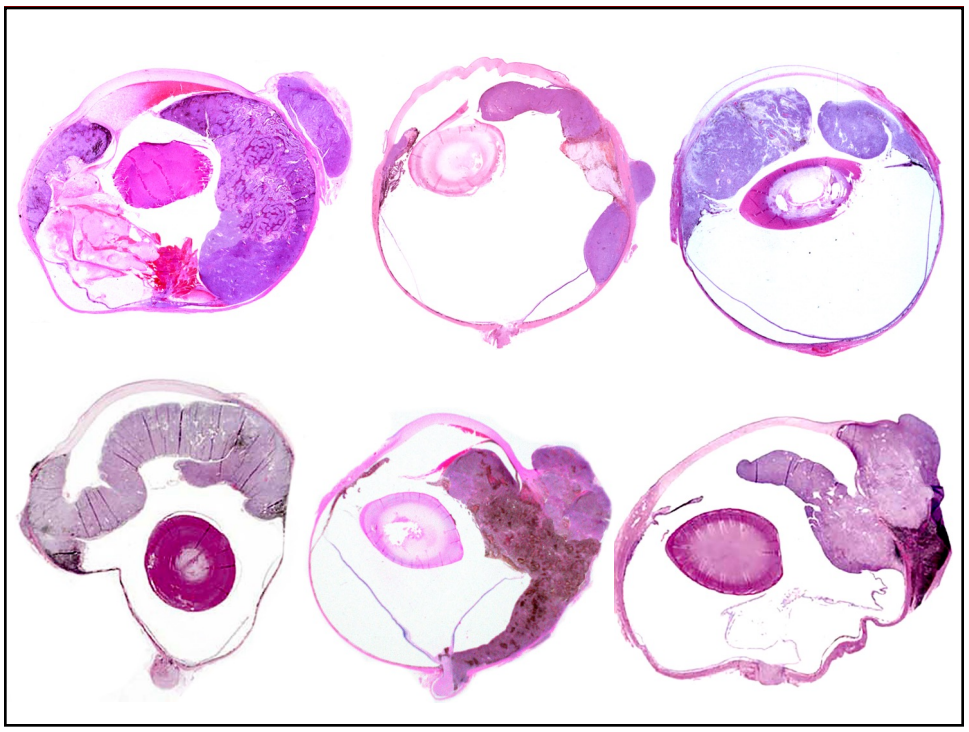

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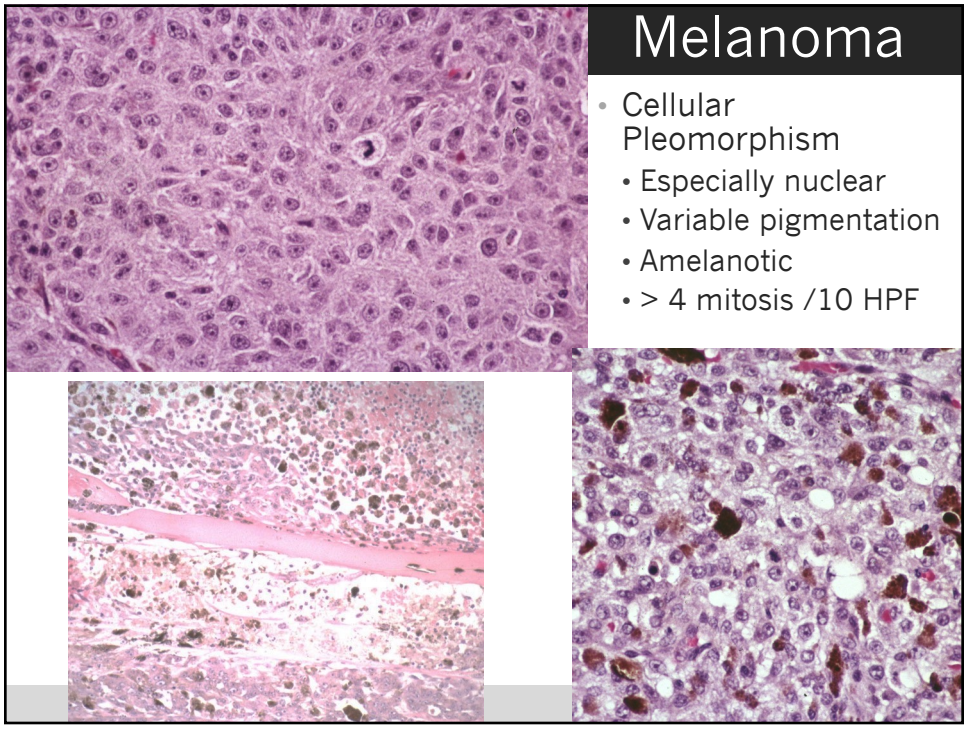
Melanoma
• Cellular Pleomorphism
• Especially nuclear
• Variable pigmentation
• Amelanotic
• > 4 mitosis /10 HPF

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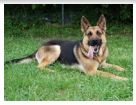
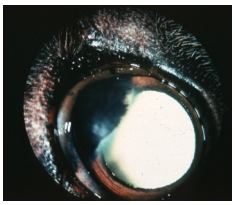
Limbal Melanocytoma (epibulbar)



- Brown to black
- Almost all benign (melanocytomas)
- Broad-based nodule
- Arise from the melanocytes that demarcate the limbus at the junction of the corneal stroma and sclera



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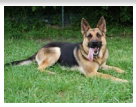
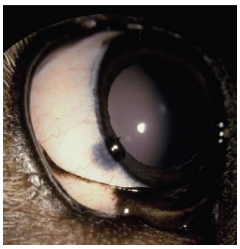
Limbal Melanocytoma (epibulbar)



- Discohesive heavily pigmented plump polyhedral cells often admixed with fewer pigmented spindle cells
- No atypia, mitoses are rare to absent
- Expands along the planes of least resistance: conjunctiva > corneal stroma
- Necrosis in approx. 20% of cases
- May extend intraocularly
- Rare limbal malignant melanomas
- Some benign neoplasms include areas with atypical cells



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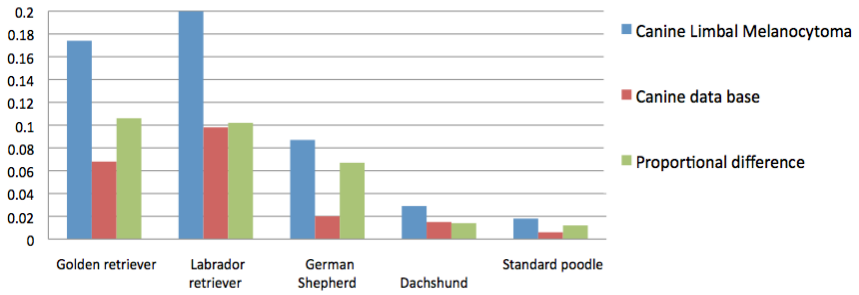
Limbal Melanocytoma

Canine data base - 29,760 records
Canine Limbal Melanocytoma - 380 records
Overrepresented



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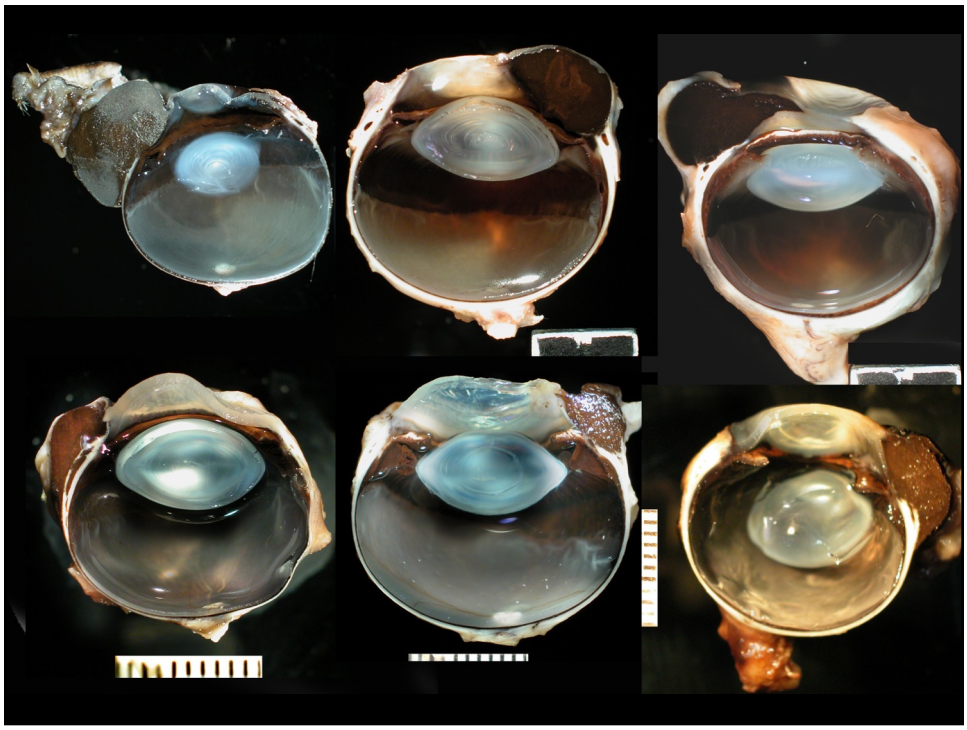

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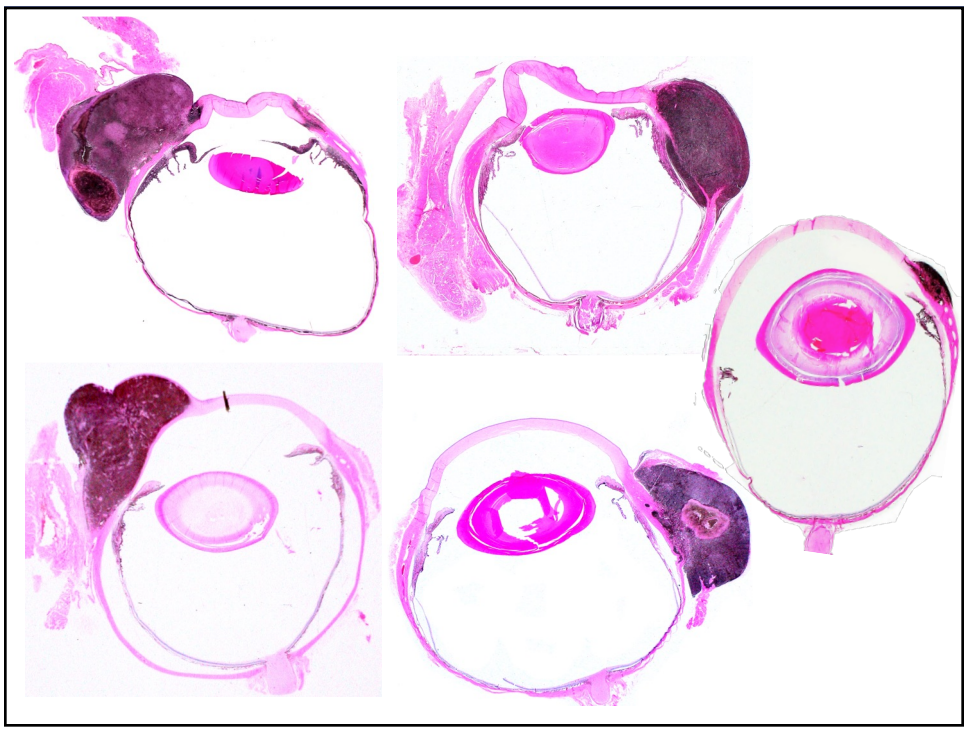

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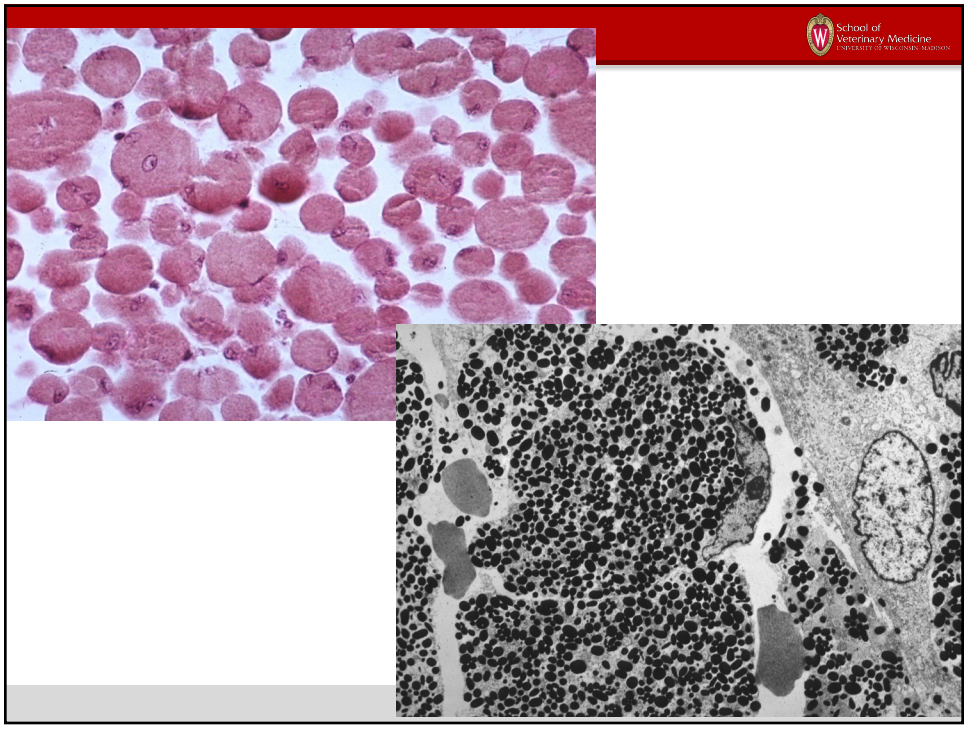

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Melanocytic tumors in cats:

- Feline diffuse iris melanoma (FDIM)
- Feline choriociliary melanoma (FCCM)

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Melanocytic tumors in cats:

- Feline diffuse iris melanoma (FDIM)

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Feline diffuse iris melanoma (FDIM)

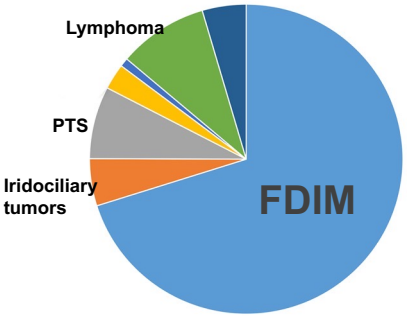
- Most common feline ocular tumor

Diffuse Iris Melanoma > 4000 cases

- Approx. 27% of all feline submission
- Approx. 50% of all feline tumors
- Approx. 70% of all feline intraocular tumors

Progressive and insidious melanocytic neoplasm that diffusely infiltrates the uveal tissue

COPLOW database



Kalishman JV, Chappell R, Flood LA, Dubielzig RR (1998). A matched observational study of survival in cats with enucleation due to diffuse iris melanoma. *Vet. Ophthal.* 1: 25-29.

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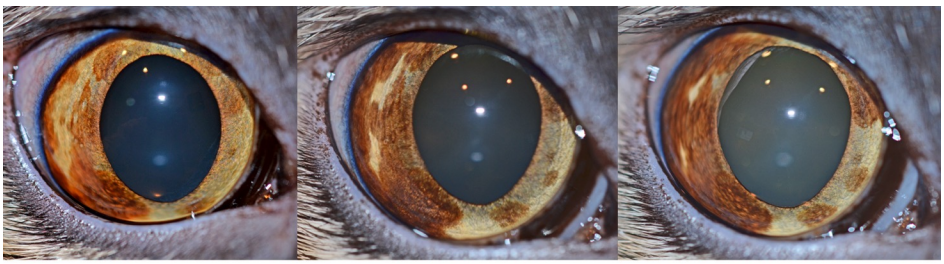
Typical Clinical Appearance of Feline Diffuse Iris Melanoma



Photos by Chuck Stuhr

2 Months

4 Months

Asymmetrical Darkening of the Iris

This process can occur rapidly or take years

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FDIM Histologic Features

Key histologic features:

- Distribution
  - Multifocal to diffuse
  - Iris surface – Stroma – Extension to rest of uvea, sclera, etc.
- Pigment (variable)
  - Pheomelanin vs eumelanin
- Anisocytosis/anisokaryosis - kareyomegaly
- Cytoplasmic invaginations into nucleus (pseudoinclusions)
- IHC: Express Melan-A, PNL-2, +/- E-cadherin

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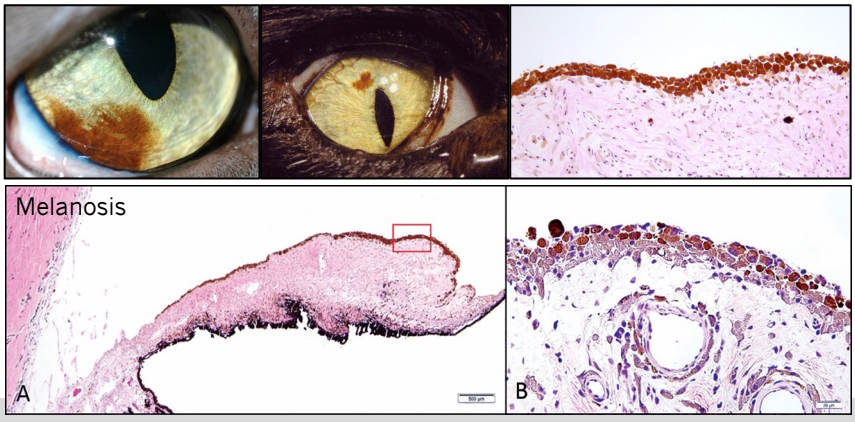
FDIM Histologic Classification

Melanosis vs FDIM

- Melanosis – Pre-neoplastic lesion. Only iris surface
- FDIM – Infiltration of the iris stroma



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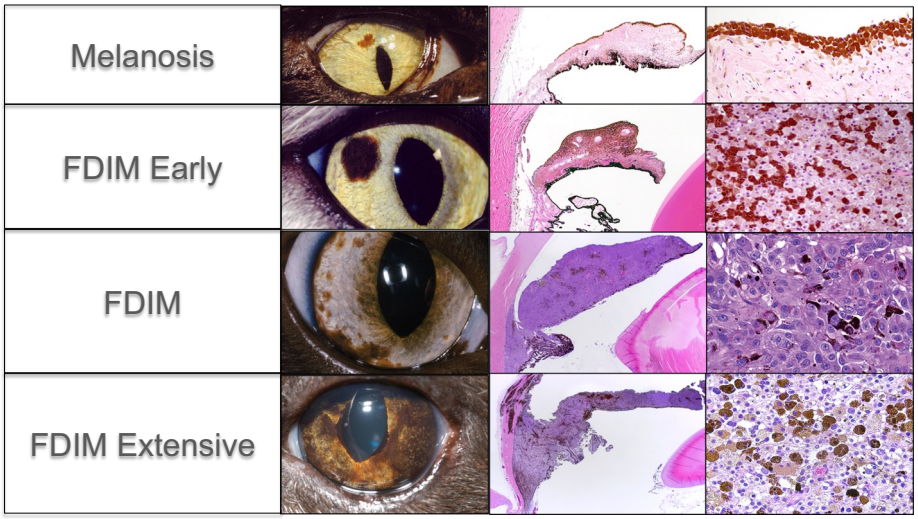
FDIM - Histologic Classification

Based on extent of neoplastic infiltration:



Kalishman, Chappell, Flood, Dubielzig. A matched observational study of survival in cats with enucleation due to diffuse iris melanoma. *Veterinary Ophthalmology* (1998) 1, 1, 25-29

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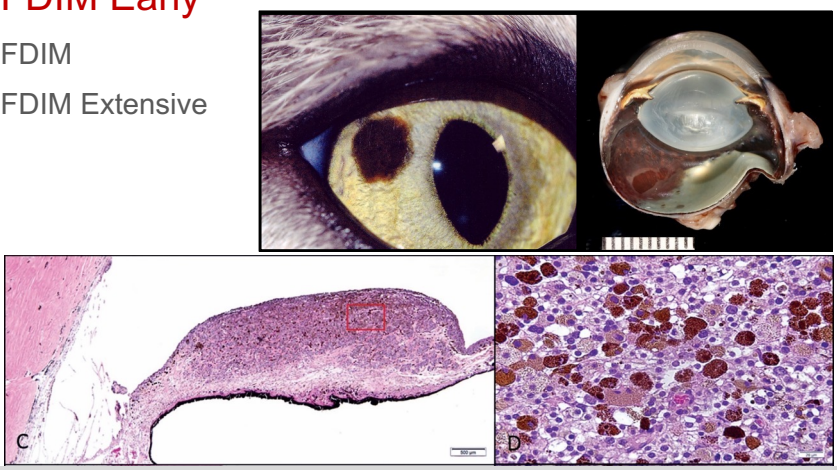
FDIM Histologic Classification

- FDIM Early
- FDIM
- FDIM Extensive



Kalishman, Chappell, Flood, Dubielzig. A matched observational study of survival in cats with enucleation due to diffuse iris melanoma. *Veterinary Ophthalmology* (1998) 1, 1, 25-29

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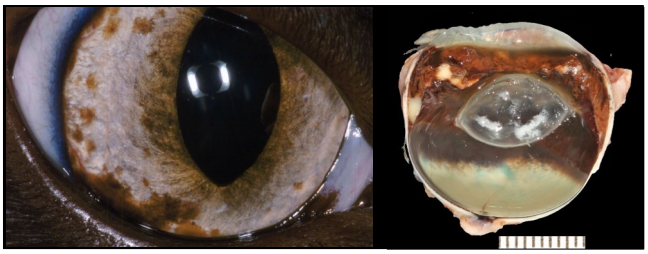
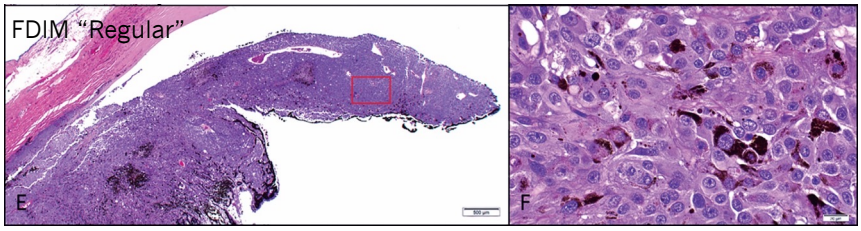
FDIM Histologic Classification

- FDIM Early
- **FDIM**
- FDIM Extensive





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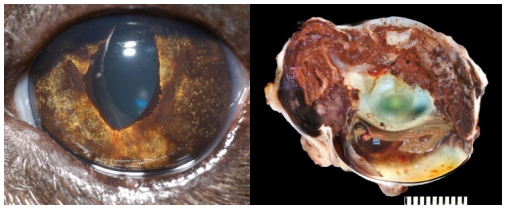
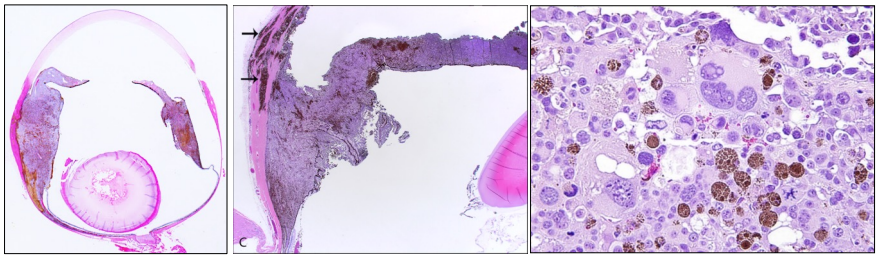
FDIM Histologic Classification

- FDIM Early
- FDIM
- **FDIM Extensive**



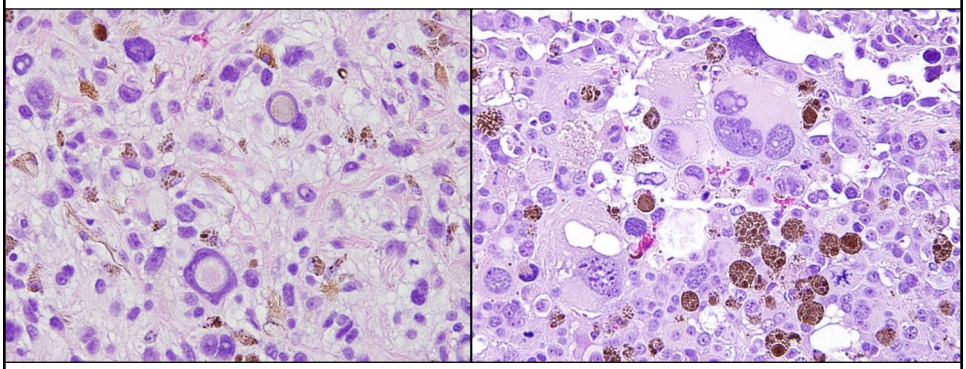


Kalishman, Chappell, Flood, Dubielzig. A matched observational study of survival in cats with enucleation due to diffuse iris melanoma. *Veterinary Ophthalmology* (1998) 1, 1, 25-29

46

FDIM Cytologic Features

- Suggests Malignancy
  - Mitotic figures
  - Nuclear atypia



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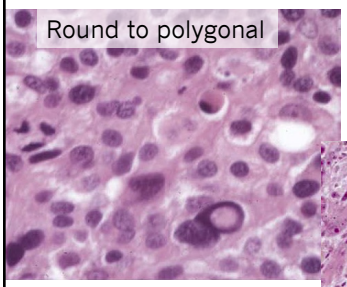
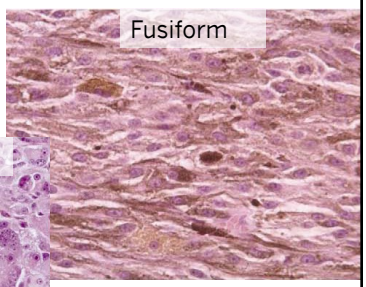
FDIM Cells

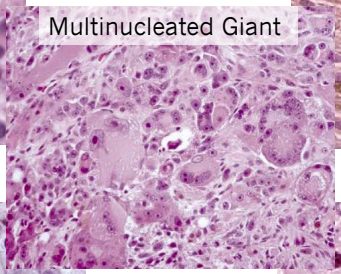
Round to polygonal



Fusiform

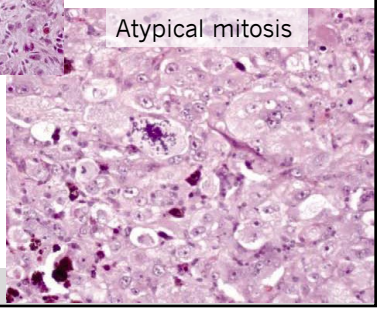


Multinucleated Giant



Balloon cells

Atypical mitosis



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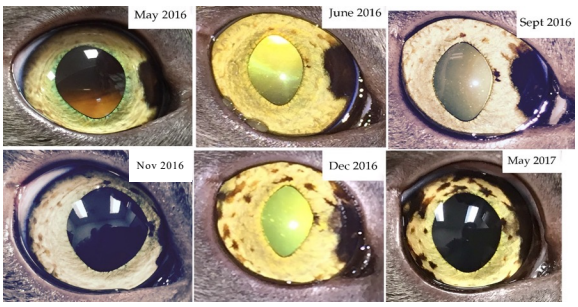
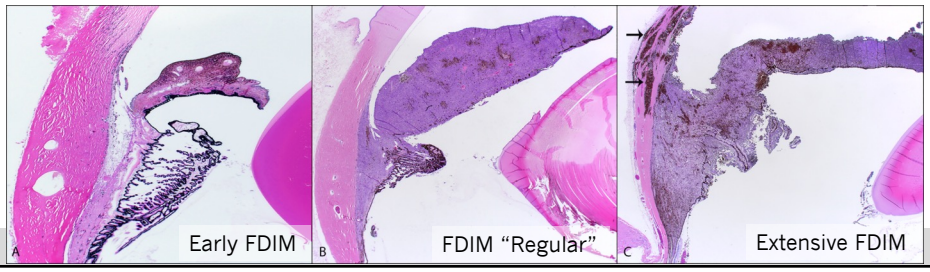
FDIM Progression





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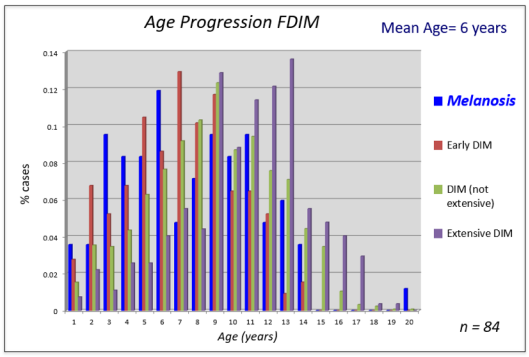
Ages of Cats with Melanosis, Early Melanoma, Melanoma, and Extensive Melanoma

- Approx. 6-year age difference between cats with eye removed in the earliest and latest stage of disease
- Suggests tumor takes 6 years (average) to progress to advanced levels
- In practice rate of progression is highly variable
  - Some cases taking decades or never becoming extensive
- Currently we cannot predict this variability



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Ages of Cats with Melanosis, Early Melanoma, Melanoma, and Extensive Melanoma

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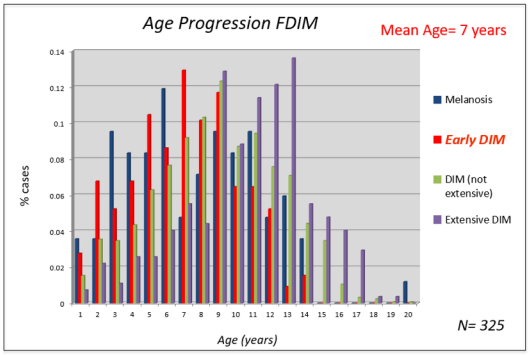

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Ages of Cats with Melanosis, Early Melanoma, Melanoma, and Extensive Melanoma

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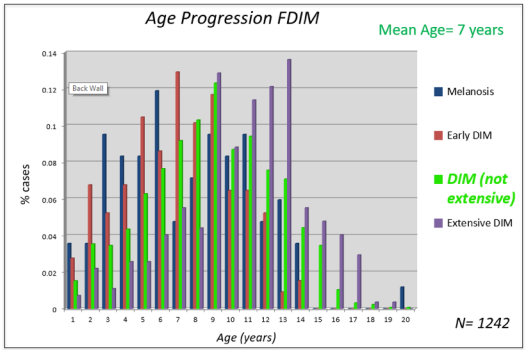

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Ages of Cats with Melanosis, Early Melanoma, Melanoma, and Extensive Melanoma

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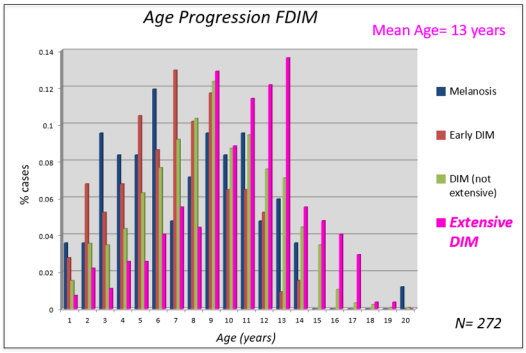

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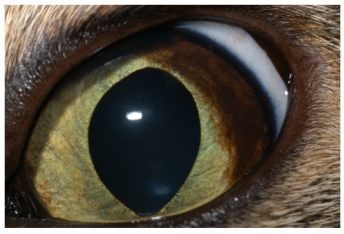
Prognostic Indicators

Clinical

- Secondary glaucoma[2]

Histologic

- Higher mitotic index[1,3]
- Areas of necrosis[3]
- Scleral venous plexus invasion[1,2]
- Ciliary body stromal or choiroidal and/or intrascleral extension[2]
- Choroidal or extrascleral extension[3]
- Confinement to anterior iris improves prognosis [1,2]



1 Duncan & Peiffer, 1991
2 Kalishman et al, 1998
3 Wiggans et al, 2016

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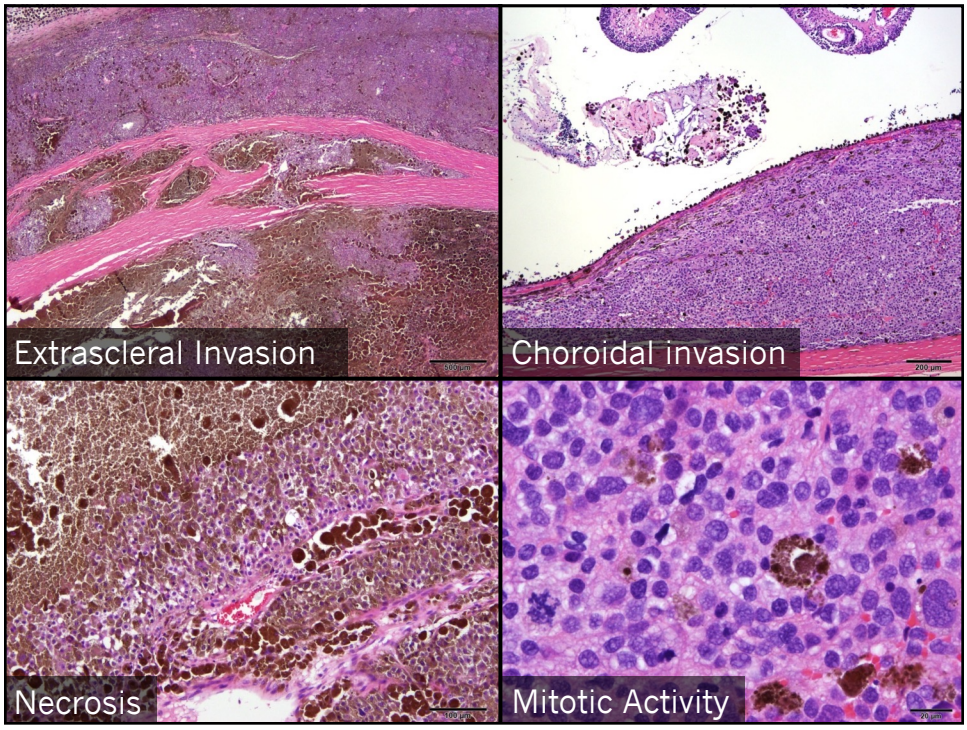

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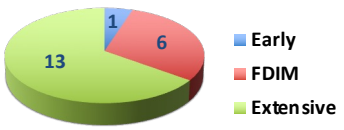
Metastatic Potential of FDIM

- Metastatic rates of 19-63% have been reported[5,2]
- Typically to distant organs - liver, lung, spleen, lymph nodes, and bone[1-4]
- Progression and metastasis are unpredictable
  - Some early tumors can metastasize rapidly[1]
  - Many extensive neoplasms never metastasize
- **Caveats**
  - Hard to follow up on cats
  - Cases often enucleated early

Distribution of Metastatic FDIM based on the histological subtype (n:20)



1. Patnaik & Mooney. Feline melanoma: a comparative study of ocular, oral, and dermal neoplasms. *Veterinary Pathology* 1988; 25:105–112.
2. Duncan & Peiffer. Morphology and prognostic indicatorsof anterior uveal melanoma in cats. Progress in Veterinary and Comparative Ophthalmology 1991; 1:25–32.
3. Kalishman *et al*. A matched observational study of survival in cats with enucleation due to diffuse iris melanoma. Veterinary Ophthalmology 1998; 1:25–29.6.
4. Planellas *et al*. Unusual presentation of a metastatic uveal melanoma in a cat. Veterinary Ophthalmology 2010; 13: 391–394.
5. Wiggans *et al*. Histologic and immunohistochemical predictors of clinical behavior for feline diffuse iris melanoma. Vet Ophthalmol. 2016 Jul;19 Suppl 1:44-55.

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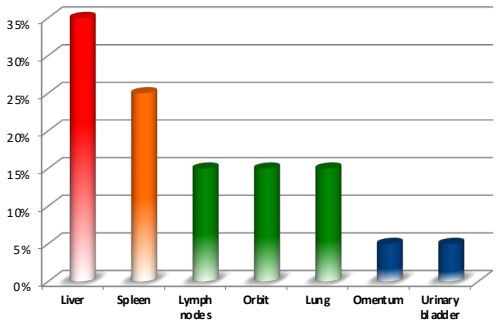
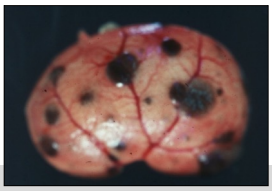
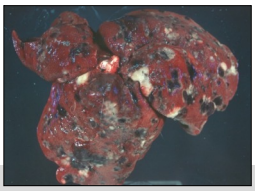
Frequency of metastatic sites on FDIM (n:20)







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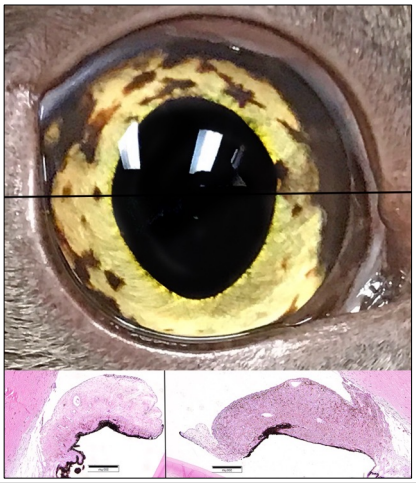
Pitfalls of Interpretation

- Location of biopsy
- Area of sectioning of globe
  - Multifocal lesions
- Poorly pigmented or poorly differentiated tumors
  - Differentials
  - IHC



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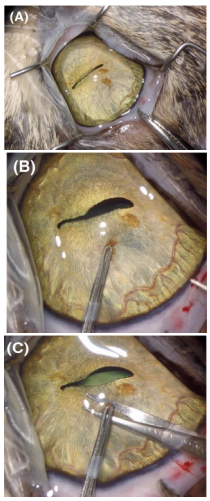
Iris biopsy FDIM

COPLOW numbers

- Iris biopsies in cats – 37 cases
  - Melanocytic lesions (FDIM or Melanosis) - 34
    - FDIM – 30
    - Feline melanosis – 3
    - Non-diagnostic – 1
  - Biopsy + Enucleation – 14 cases
    - All biopsies diagnosed as FDIM
    - Enucleation
      - Early FDIM – 6
      - Regular FDIM – 8



Images from: Featherstone et al. 2020 Vet Ophthalmol.

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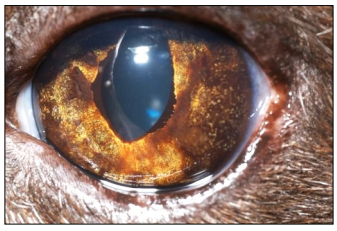
Iris biopsy FDIM

Diagnostic limitations

- Limited anatomical distribution
  - Melanosis vs Melanoma
- Size of samples
  - Orientation during embedding
  - Multiple step sections
- Representative tissue
- Handling artifact



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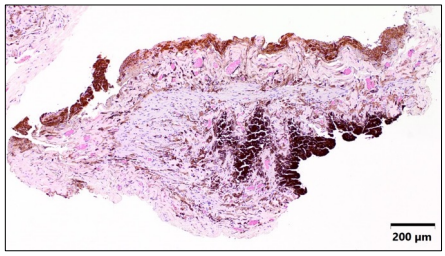
Iris biopsy x Histopathology Correlation

10-year-old, FS, DSH cat

First Biopsy – August 2012 (1 y/o)

Dx: Uveal melanosis



Second Biopsy – June 2021

Dx: Feline diffuse iris melanoma

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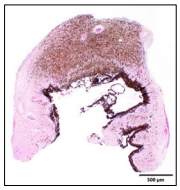
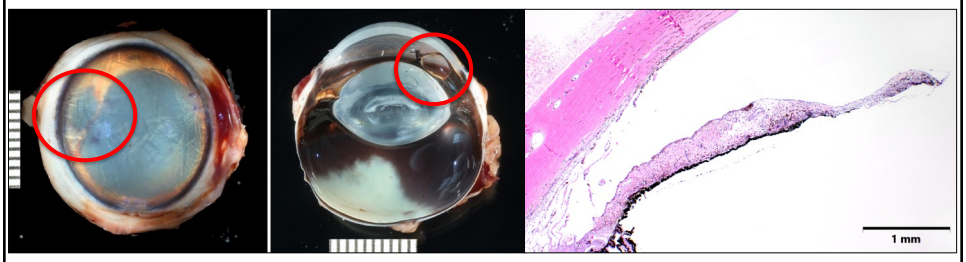
Iris biopsy x Histopathology Correlation



10-year-old, FS, DSH cat

Enucleation – November 2021

Dx: Feline diffuse iris melanoma, early



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Diagnostic value of iris biopsies for the assessment of iris pigment changes and diffuse iris melanoma (DIM) in cats: A descriptive histopathological study

Veterinary Pathology
OnlineFirst

https://doi.org/10.1177/03009858251403170

Sabine Beetz [1], Robert Klopfleisch [1], Carolina Naranjo [2], Emma Scurrell [3], Judith Bushe [4], Annika Lehmbecker [5], Gerhard Loesenbeck [6], Sophie E. Merz [5], Hannah Pischon [5], Ingo Spitzbarth [5], Birgit Müller [7], Katharina Thieme [1], Sixta Wellen [8], and J. Corinna Eule [1]

- Iris biopsies can a useful diagnostic tool for identifying FDIM
- **Sample size, quality, and tissue handling -** Heavily influence diagnostic value of biopsies
- Early FDIM 79.7% concordance
- Advanced FDIM 91.1% concordance

Clinicians must weigh the benefits and limitations of iris biopsies in their decision-making process on a case-by-case basis

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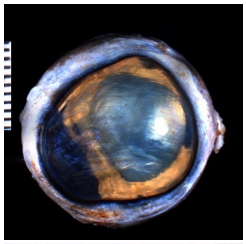
Feline choriociliary melanoma (FCCM)

Atypical Primary Ocular Melanoma

Definition

- Uncommon variant of uveal melanoma in cats
  - "Unusual" distribution ≠ FDIM
  - Primarily affect the ciliary body, choroid and retina
  - Bland, heavily pigmented cellular morphology



COPLOW numbers

- 93 cases in the COPLOW collection
- ≅ 1% of all feline neoplasms
- No breed or sex predisposition.
- Median age of 12 years old (range 5-18).
- Both eyes are affected equally.

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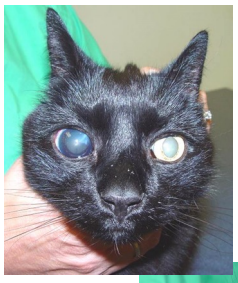
Feline choriociliary melanoma (FCCM)

Atypical Primary Ocular Melanoma

Clinical presentation

- Focal heavily pigmented mass in the ciliary body and posterior segment +/- iris.
- Retinal detachment and glaucoma is common.



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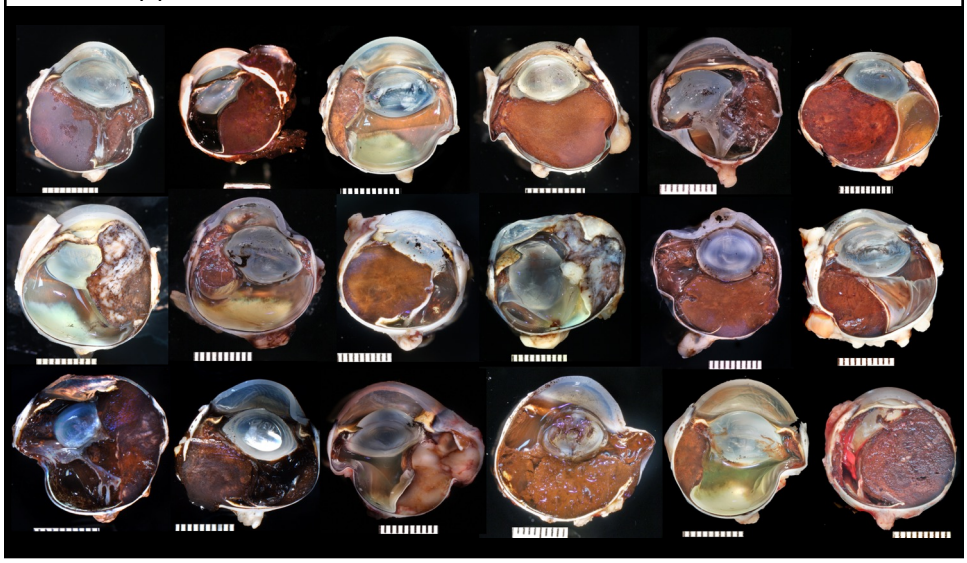
Feline choriociliary melanoma (FCCM)

Gross Appearance



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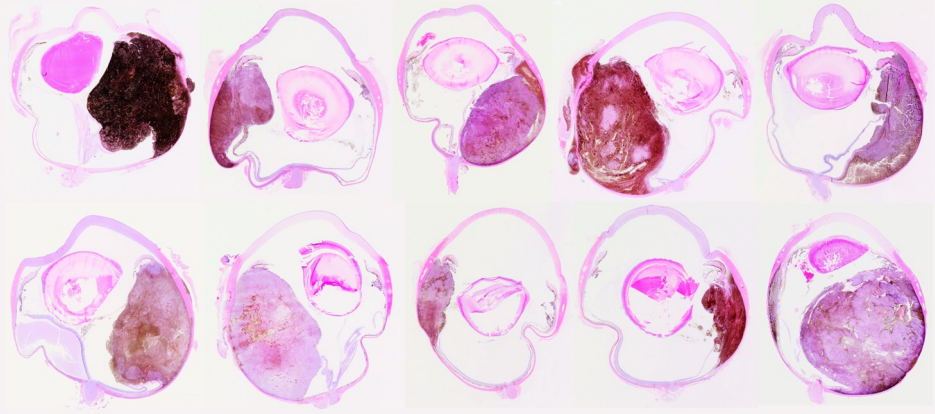
Feline choriociliary melanoma (FCCM)

Atypical Primary Ocular Melanoma

Subgross



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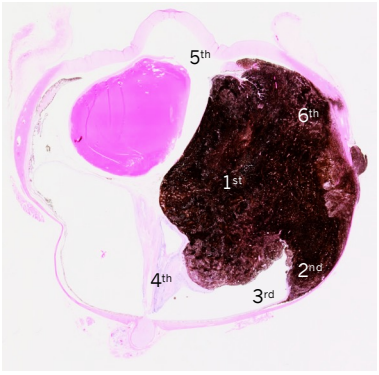
Feline choriociliary melanoma (FCCM)

Atypical Primary Ocular Melanoma

Neoplasia distribution

Tissue	N cases affected (/87)	%
Ciliary body	86	98.8
Choroid	85	97.7
RPE	83	95.4
Retina/sub-retinal space	72	82.8
Iris*	58	66.7
Iridocorneal angle	40	46.0



* Extension from the posterior mass - Base of the iris or iris effacement
Not anterior iris surface down like FDIM

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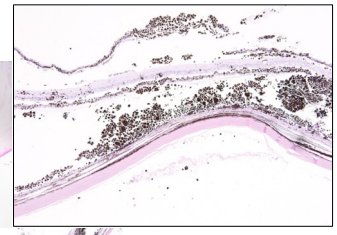
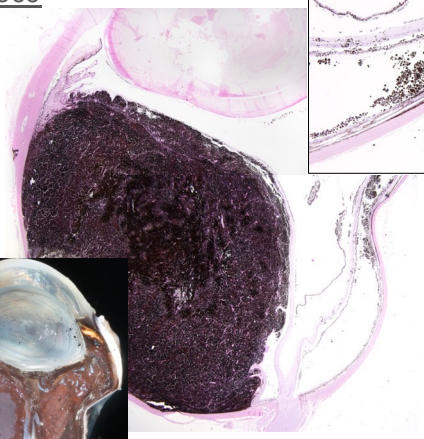
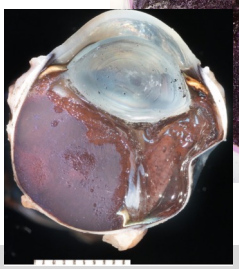
Atypical Feline Diffuse iris Melanoma

Subgross







- Heavily pigmented mass
- Ciliary body and posterior
- Sparing of iris
- Retinal detachment and subretinal neoplastic clumps

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Feline choriociliary melanoma (FCCM)

Atypical Primary Ocular Melanoma

Prognosis

- Follow-up received for 32/87 (36%) cases *(ongoing)*
- Local recurrence – 3/32 (9%)
  - All 3 had dirty surgical margins on histopath*
  - All 3 recured in the orbit

Survival

- 21/32 (65%) Still alive at last contact
- 6/32 (19%) Dead
  - 5/6 euthanized due to tumor-related reasons
  - 1/6 died due to chronic kidney disease

Median survival time after enuc. 326 days*
(152-608 days)*≅10 months

Metastasis

- 10/32 (31%) - Signs of metastatic disease
  - 4/6 Confirmed metastasis (biopsy/cytology least one organ) *Skin, liver, regional LN, lungs and spleen*
  - 6/6 Suspected metastasis (Metastatic pattern on imaging) *Lungs, liver and spleen*
- 10/32 (31%) No signs of mets at last contact
- 12/32 (38%) No info on metastatic status

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Feline choriociliary melanoma (FCCM)

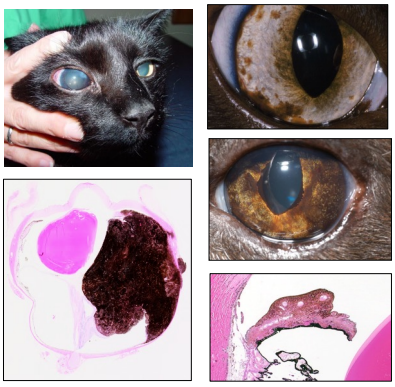
Atypical Primary Ocular Melanoma

Conclusions

- In contrast to FDIMs:
  - FCCM present as a localized mass with bland cellular features
  - Primarily affect the ciliary body, choroid and retina
  - Worst prognosis
    - Higher metastatic rates (31%)
    - Invasion and local recurrence

Propose a new nome: **Feline choriociliary melanoma**

FCCM vs FDIM



Pang DH, Shaw GC, Teixeira LBC. *Clinicopathologic study of feline ocular choriociliary melanomas: a retrospective study.* 2025 ACVP Annual Meeting, New Orleans, Louisiana.

1st Place, Veterinary Student Poster Award (Natural Disease)

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Equine Intraocular Melanocytic Neoplasia (*EIMN*)

- Benign appearing melanocytic neoplasm
  - Often diagnosed as melanoma (no obvious reason)
- Most common intraocular tumor in horses
- 86 cases in the COPLOW database
- Arabian was the most common breed (27%)[1]
- Gray was the most common coat color (85%)[1]

1. Labelle AL, Gemensky Metzler AM, McMullen RJ Jr, Wiggans KT, Labelle P, Hamor RE. Equine intraocular melanocytic neoplasia. Can Vet J. 2024 Oct;65(10):1048-1054.

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Equine Intraocular Melanocytic Neoplasia (*EIMN*)

- Equine melanoma - multicentric disease.
  - *67% have cutaneous melanoma*[1]
  - Gray horses are overrepresented
    - Up to 80% of horses affected in some breeds.
    - Autosomal dominant gene syntaxin-17 (STX17)[2,3]
      - Controls gray coat color
      - Strongly associated with melanoma formation
  - Lipizzaner horses
    - Gene DPF3 - Candidate for development of melanoma[4]
  - Gray Quarter horses[5]
    - Melanoma prevalence and severity is lower than other breeds[5]

1. Labelle AL, et al. Equine intraocular melanocytic neoplasia. Can Vet J. 2024 Oct;65(10):1048-1054
2. Seltenhammer, et al. Equine melanoma in a population of 296 grey Lipizzaner horses. Equine Vet J 2003;35:153–157.
3. Curik I, et al. Complex inheritance of melanoma and pigmentation of coat and skin in grey horses. PLoS Genet 2013;9:e1003248.
4. Druml T, et al.. DPF3, a putative candidate gene for melanoma etiopathogenesis in gray horses. J Equine Vet Sci 2022;108:103797.
5. *Teixeira RB et al. Coat color genotypes and risk and severity of melanoma in gray quarter horses. J Vet Intern Med 2013;27:1201–1208.*

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Equine Intraocular Melanocytic Neoplasia (*EIMN*)

- **Iris most commonly affected**
  - But can originate anywhere in the uvea
  - Some cases appear to originate in the *corpora nigra*
  - Few (11 cases) exclusively limbal/episcleral

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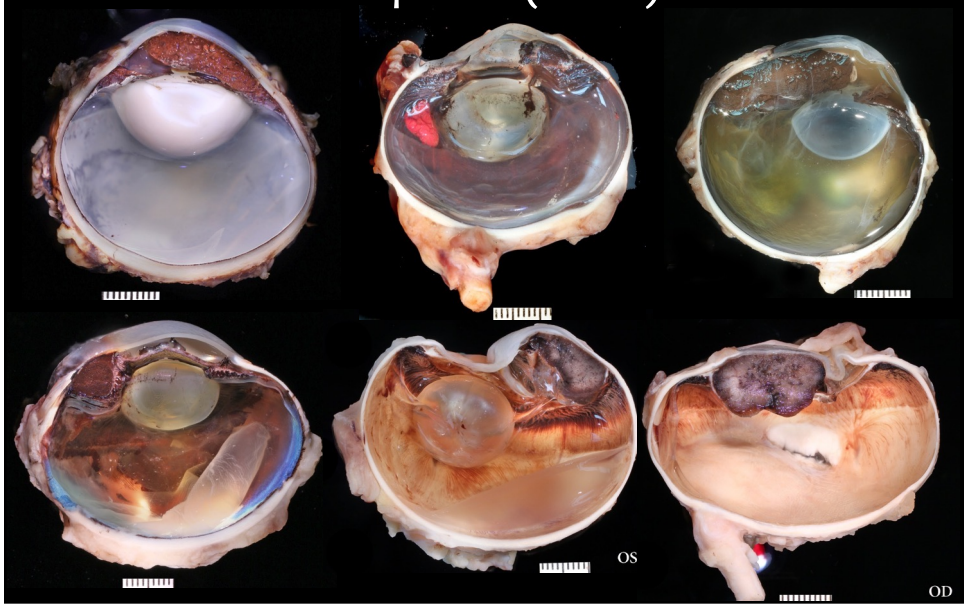
Equine Intraocular Melanocytic Neoplasia (*EIMN*)



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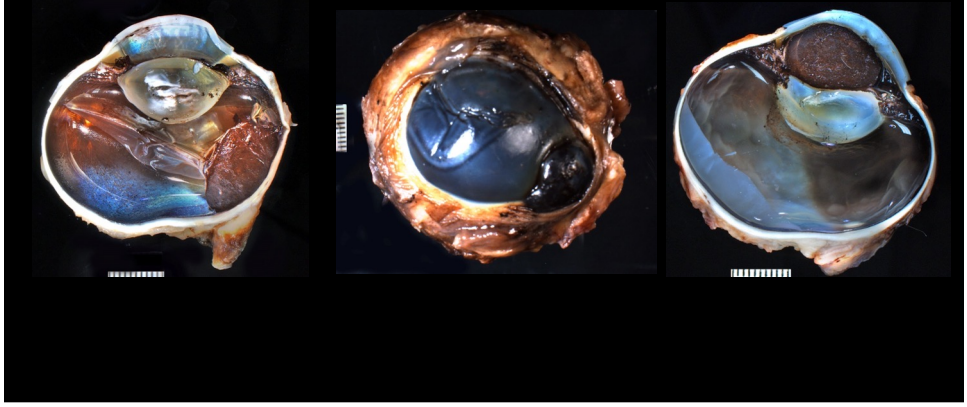
Equine Intraocular Melanocytic Neoplasia (*EIMN*)

Choroidal | Limbal/episcleral | *Corpora nigra*



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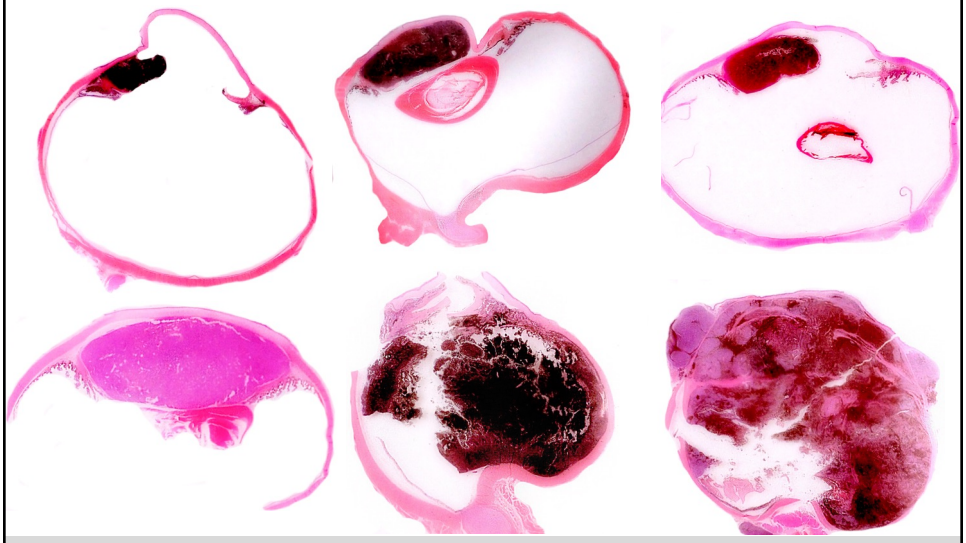
Equine Intraocular Melanocytic Neoplasia



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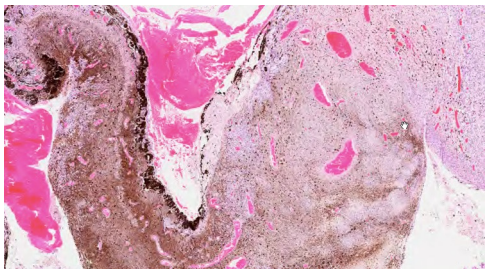
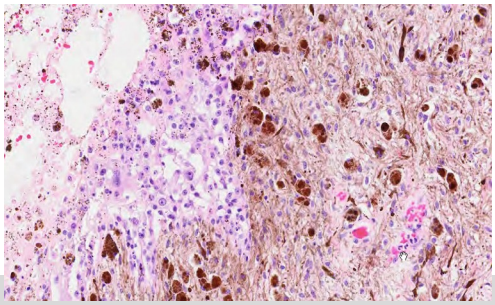
Equine Intraocular Melanocytic Neoplasia

- Mixed cell type, low mitotic index
- Necrosis/melanophages,
  - Preiridal fibrovascular membranes,
  - Pigment in corneal endothelium





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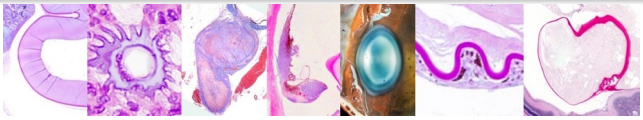
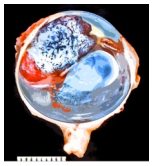
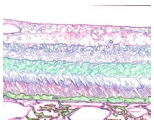
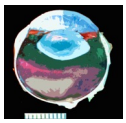
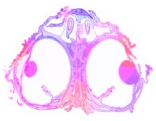


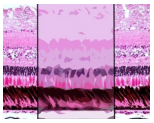
Questions?

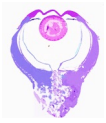


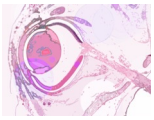












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