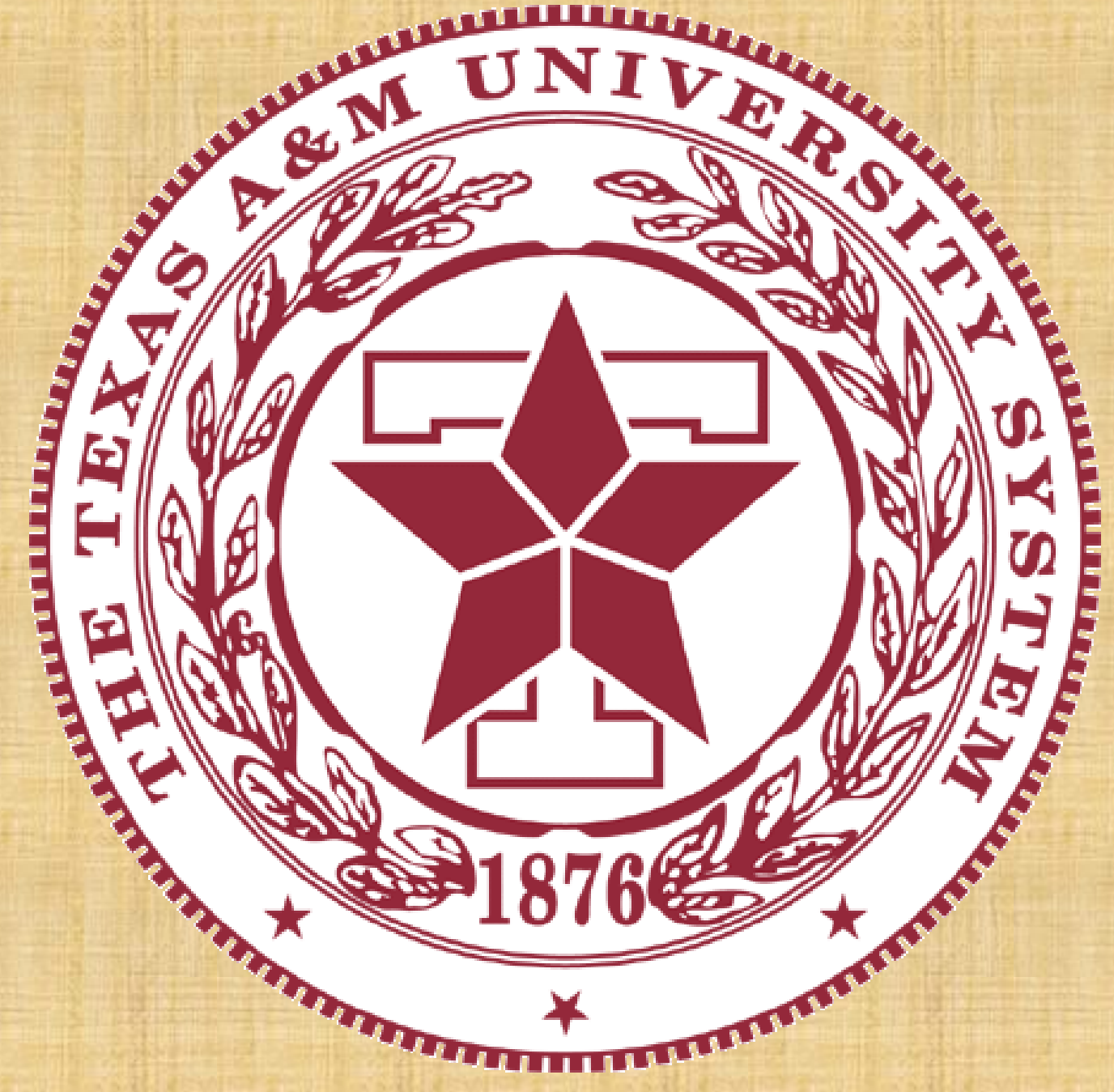


# The Dog as a Novel Animal Model for Leiomyoma Research

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## Introduction

Dogs are the only domestic species that commonly develop leiomyomata in female reproductive tracts. Up to 25% of mature female dogs with intact ovaries ("bitches") have leiomyomata in their vaginas. Usually, there are usually multiple leiomyomata and the bitch has not been pregnant. Tumors can get large, over 10 cm in dimensions.

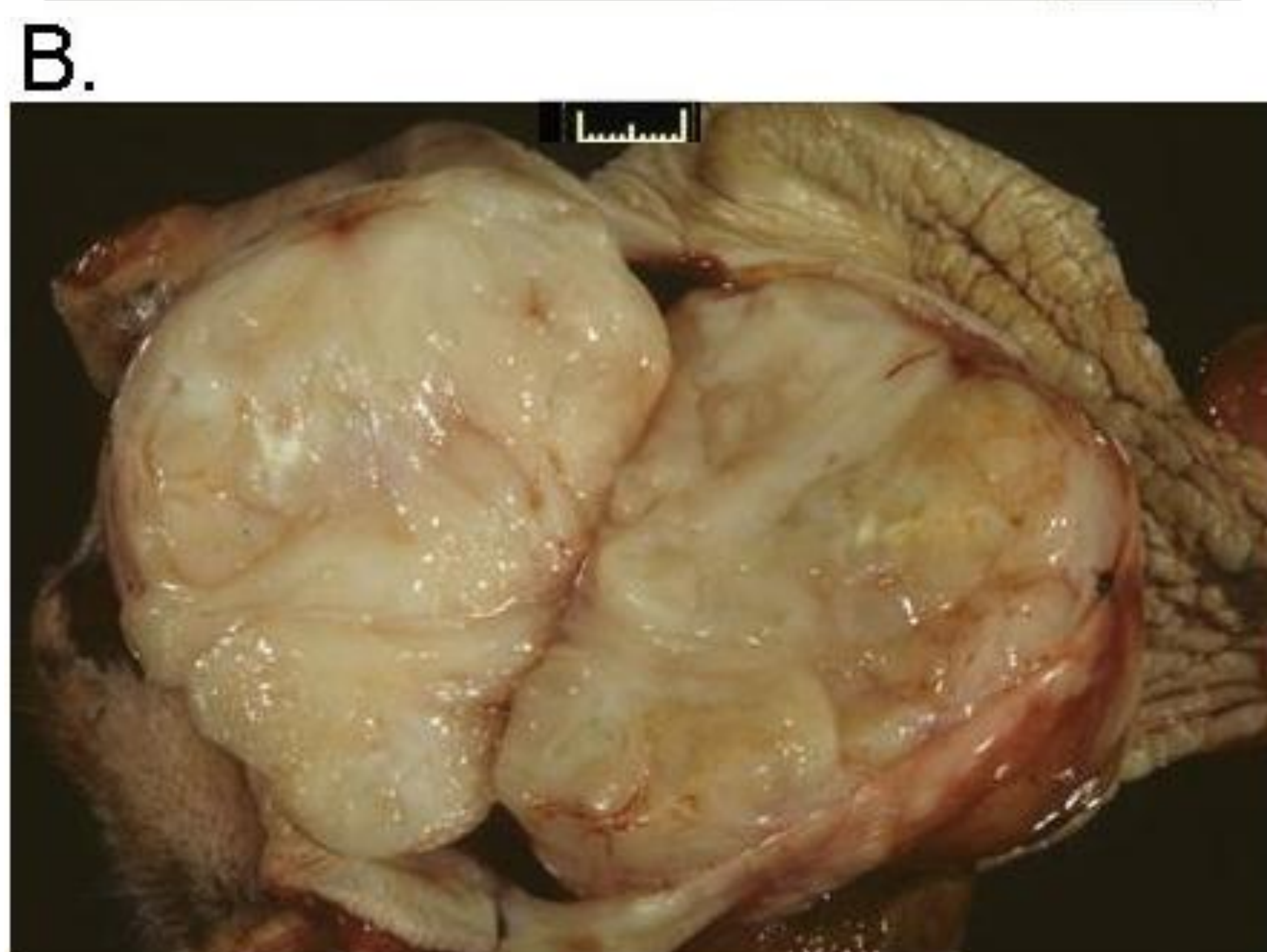
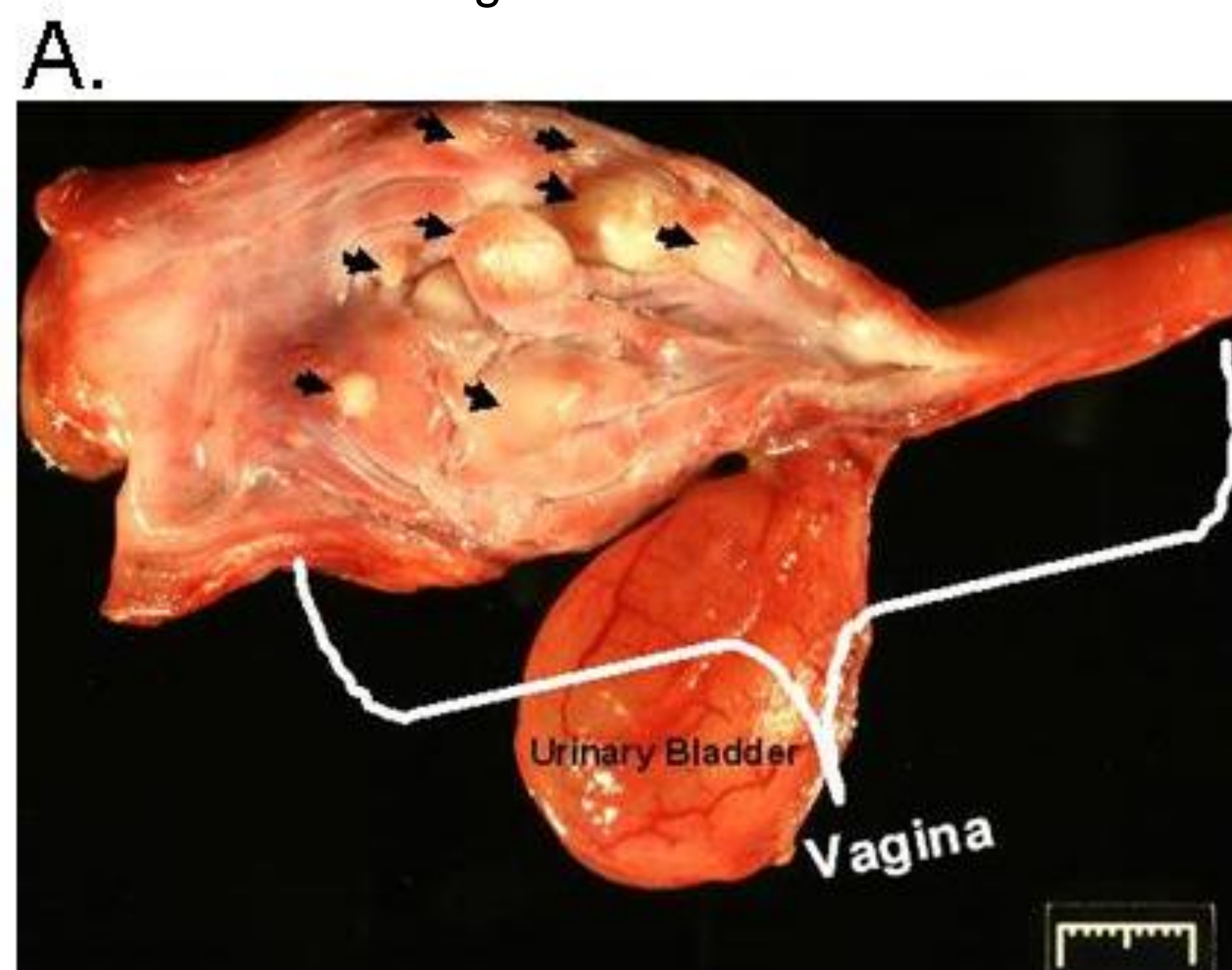
Steroid hormones from the ovary drive the growth of leiomyomata in dog vaginas. Leiomyomata do occur in ovariectomized dogs and do not recur after ovariectomy.

Leiomyoma growth can be rapid when ovaries are active. Regression with antiprogesterin treatment is also rapid (50% in 3 months).

The following study was performed to assess how similar the leiomyomata in dog vaginas are to the uterine tumors of women.

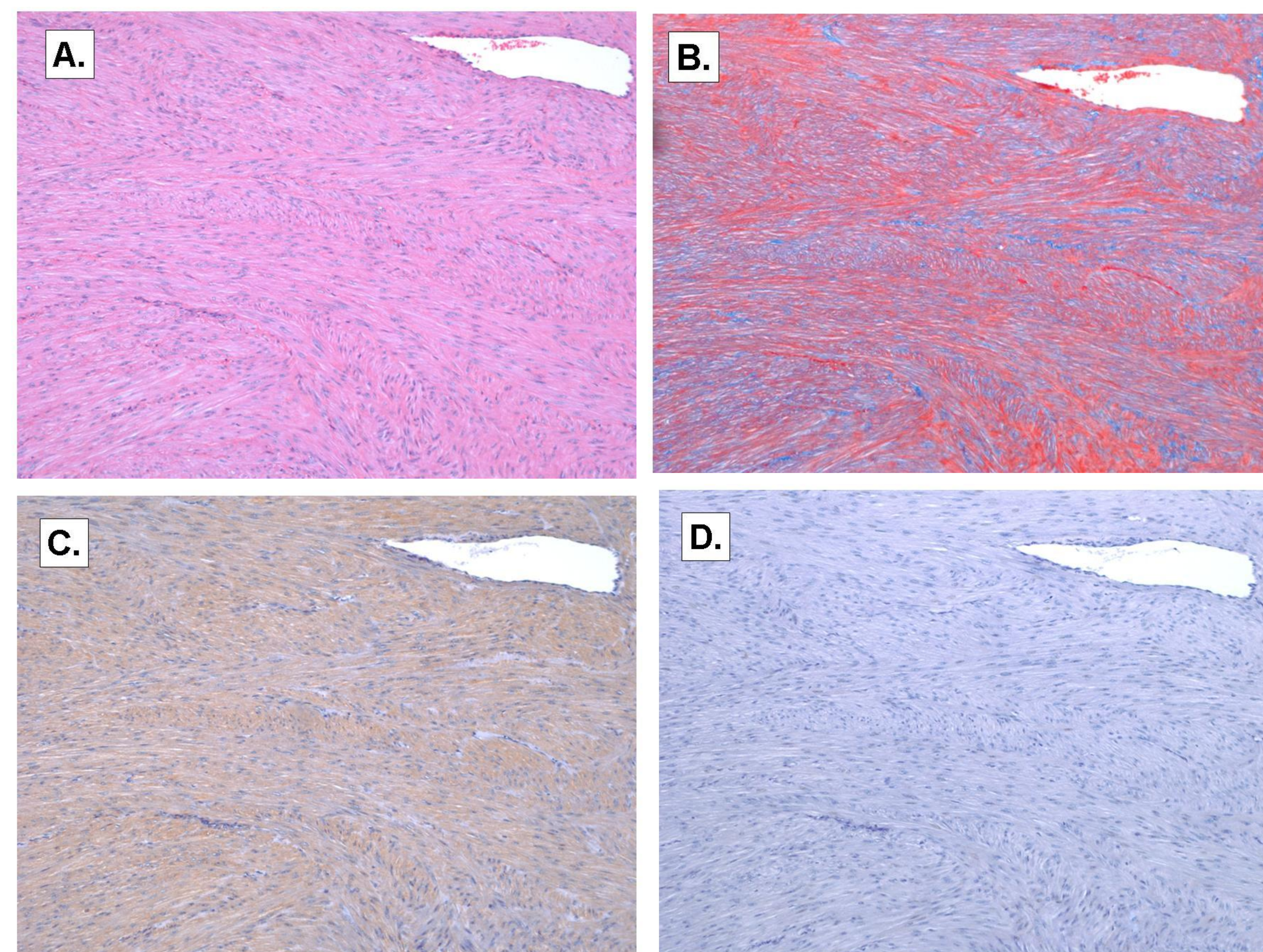
## Gross Pathology

Photographs of two cases of vaginal leiomyomata in the bitch are shown. The vaginas (incised dorsally) are oriented with the vulva at left and cervix at right. **A.** A 12 year old Pomeranian (toy breed) bitch has 8 small leiomyomata with the largest in the caudal vagina. **B.** The vagina of a ten year old Beagle bitch has a 6 X 4 cm leiomyoma, with the cut surface exposed to show the typical whorled appearance of the tumor. Two other leiomyomas (4 cm and 0.8 cm in largest dimension) are also present but are occluded from view. Marker is 1 cm long.



## Histological Pathology

Histology of a 6.5 X 4 X 4 cm leiomyoma from the vagina of an 11 year old Labrador bitch. **A.** H & E staining shows the typical morphology of leiomyoma cells: spindle-shaped with elongated nuclei that are associated in intersecting fascicles. **B.** Trichrome staining shows collagen (blue) staining between and around the leiomyoma cells. **C.** Immunostaining shows smooth muscle actin (SMA) protein detection (brown) with hematoxylin counterstain. **D.** Negative control for SMA staining (replace primary antibody with nonimmune serum??) shows hematoxylin stain only.



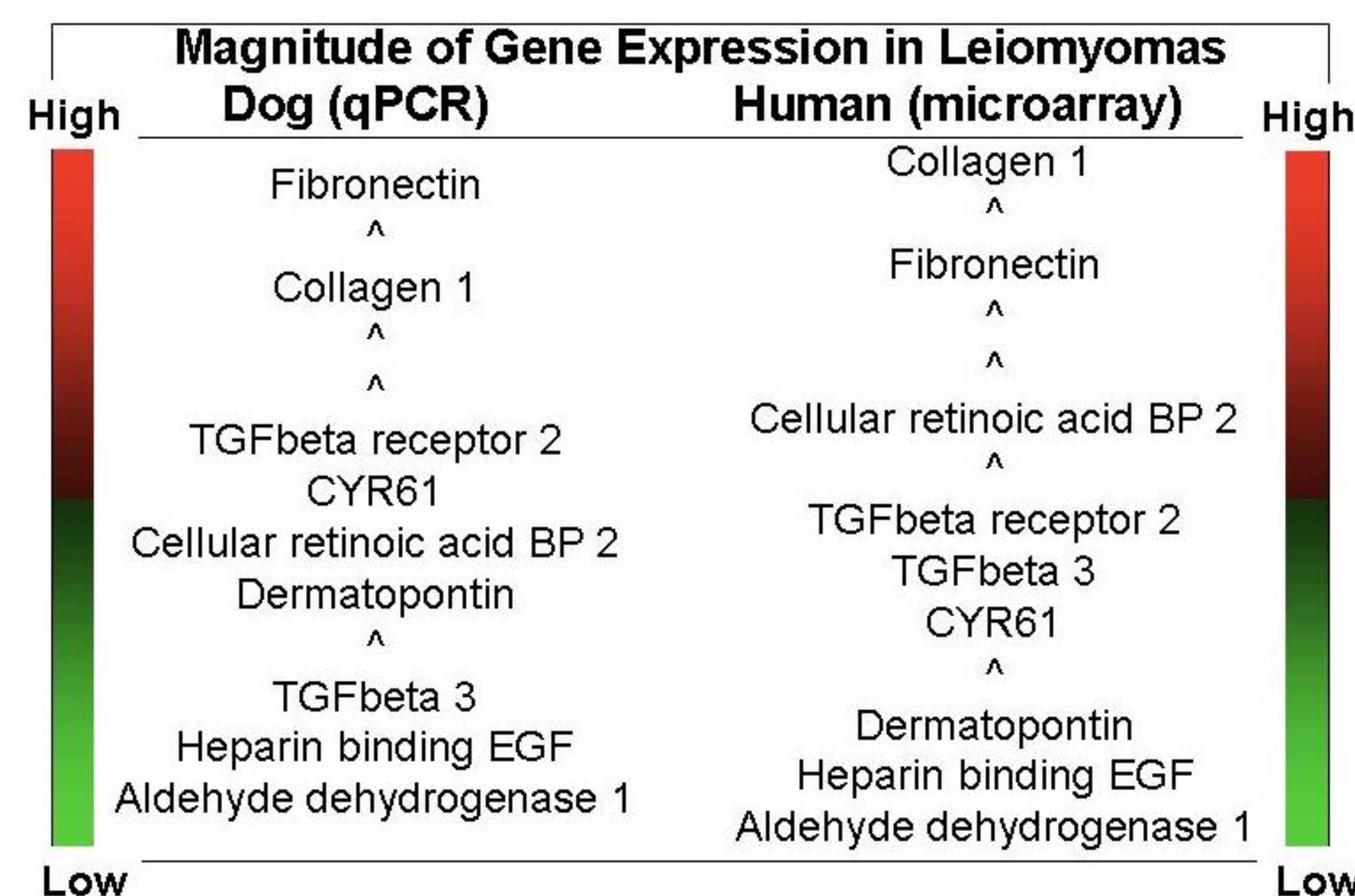
## Gene Expression Signature - II

Relative mRNA concentrations were analyzed in dog leiomyomata for 9 mRNAs reported to be differentially expressed in uterine leiomyomata of women compared to myometrium. RNA was extracted from formalin-fixed paraffin-embedded leiomyomata (n = 4) and uterine (n = 5) tissues. Reverse transcription with random octamers lead to real time PCR with optimized human primers adapted to dog genome sequence for the 9 mRNAs and GAPDH mRNA and 18S rRNA for normalization. Fold difference (leiomyoma/uterus) are graphed for 7 differentially expressed mRNAs. Results for TGFbeta receptor 2 and dermatopontin were variable in the leiomyomata. These data are consistent with that from uterine leiomyomata of women.

### Fold differences in gene expression between leiomyoma and uterus

Gene Expression (Tumor/Uterus):	Decrease	Increase
	10 5 1	1 5 10
Fibronectin		----->
Collagen 1		--->
Cellular retinoic acid binding protein 2		----->
Transforming growth factor beta (TGFB) 3		-->
Heparin-binding epidermal growth factor	<--	
Cysteine-rich, angiogenic inducer 61	<--	
Aldehyde dehydrogenase 1	<-----	

## Gene Expression Signature – I



## Conclusions and Future Directions

Our initial characterization of leiomyomas from dog vaginas indicates that their histopathology and molecular signature of gene expression are indistinguishable from uterine leiomyomata of women. Therefore, dogs may provide a new animal model for advancing our understanding of the basic biology of leiomyomas, such as identification of the gene pathways involved in the steroid hormone dependent growth of the tumors.



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## References