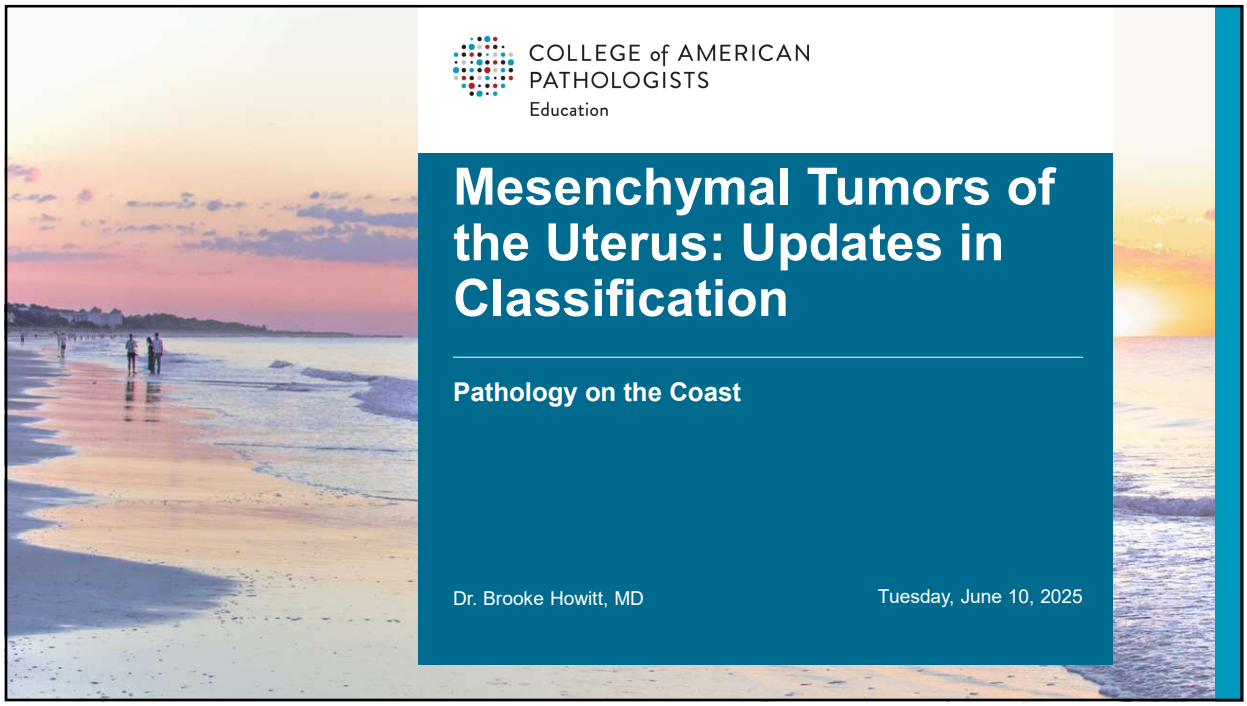
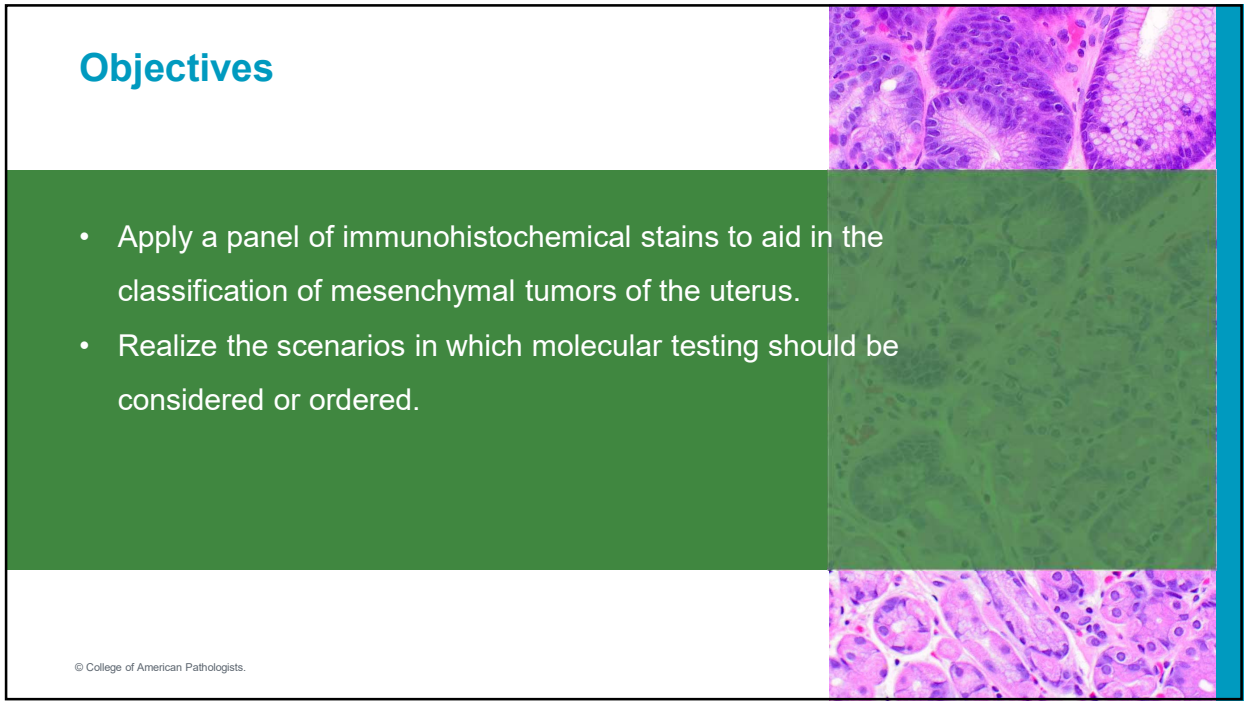
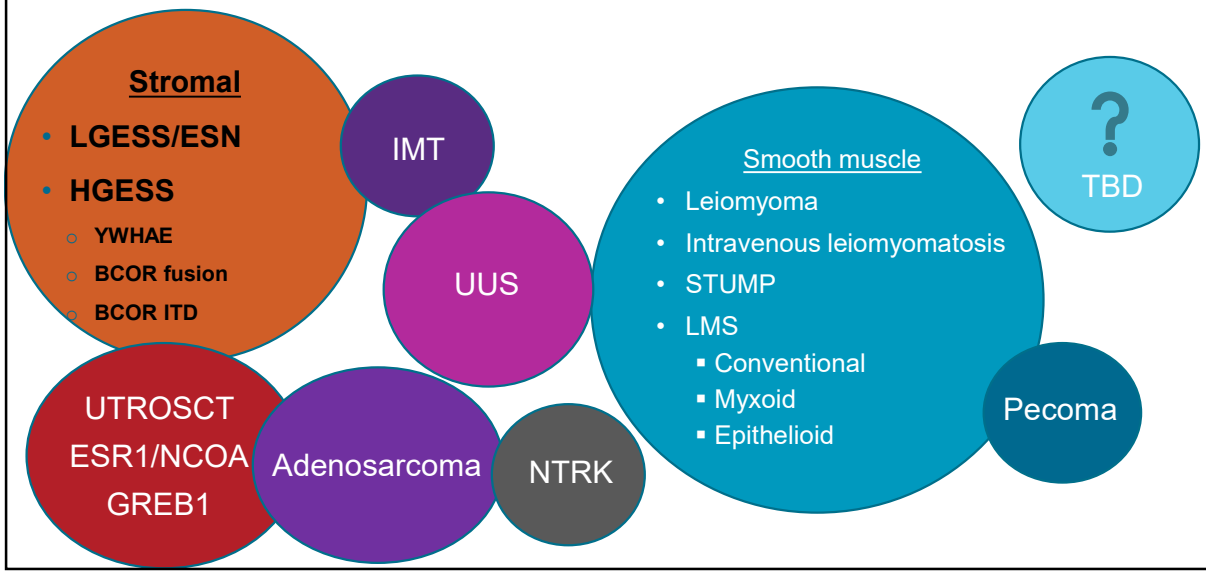


1



2

The ever-growing list of uterine sarcomas and mesenchymal tumors



3

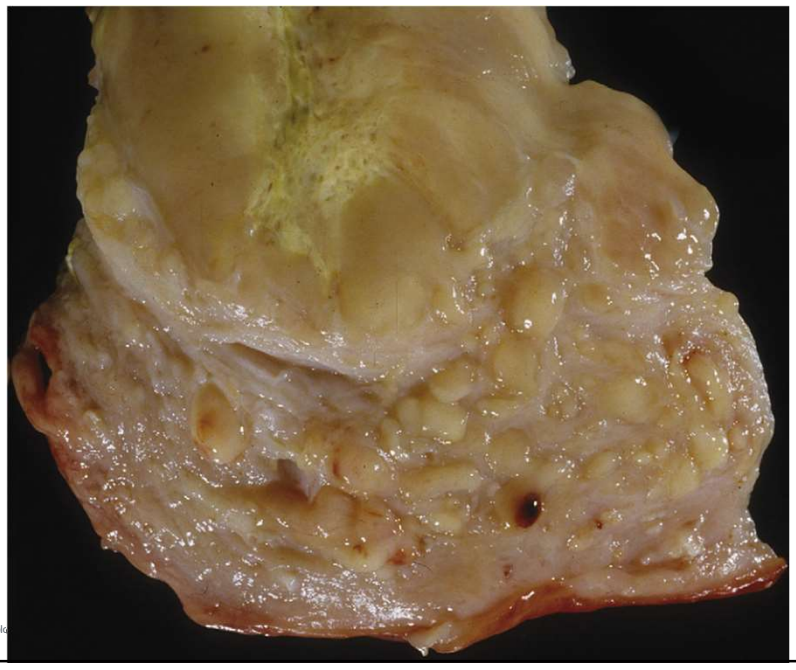
Outline

1. **Classification of endometrial stromal sarcomas (ESS)**
   - A. **LGESS**
   - B. **YWHAE-HGESS**
   - C. **BCOR-HGESS**
2. **UTROSCT**
3. ***NTRK*-sarcoma**
4. ***KAT6B/A::KANSL1* sarcomas**
5. **SMARC-deficient uterine sarcoma (SDUS)**
6. **Adenosarcoma**
7. ***ERBB2* (HER2) mutated tumors/sarcoma**

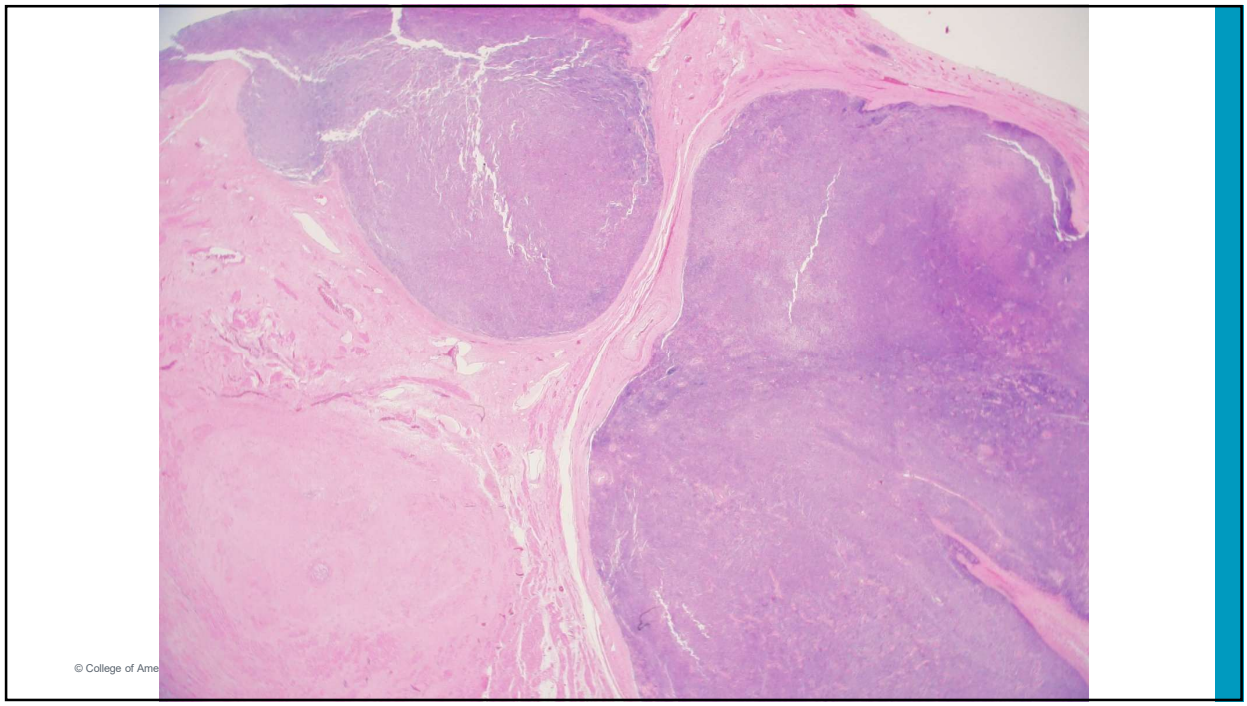
4

Part 1: Classification of endometrial stromal sarcomas

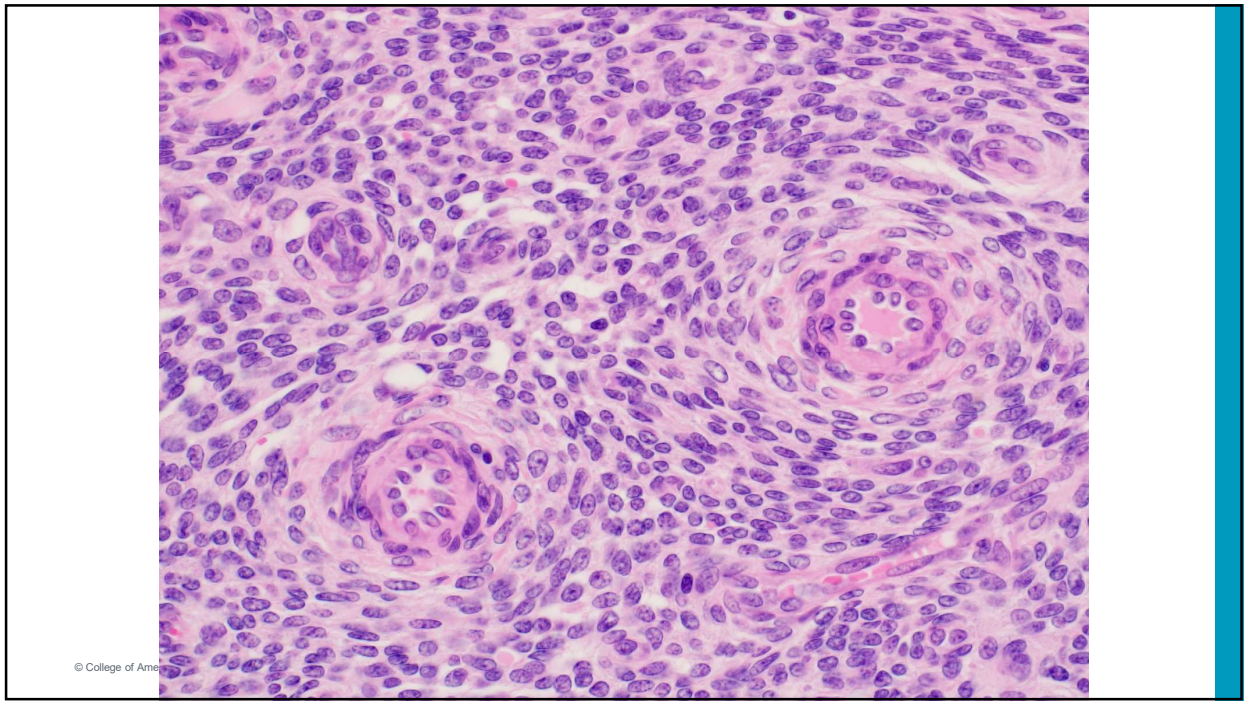
5



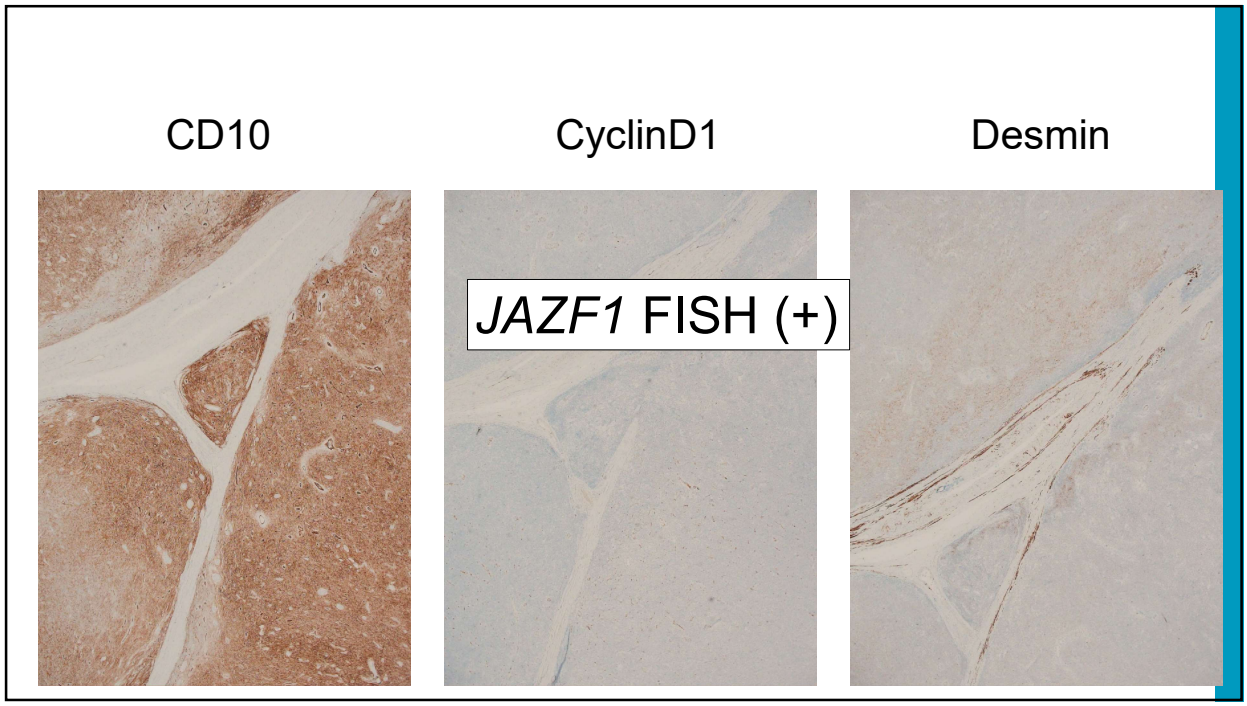
6



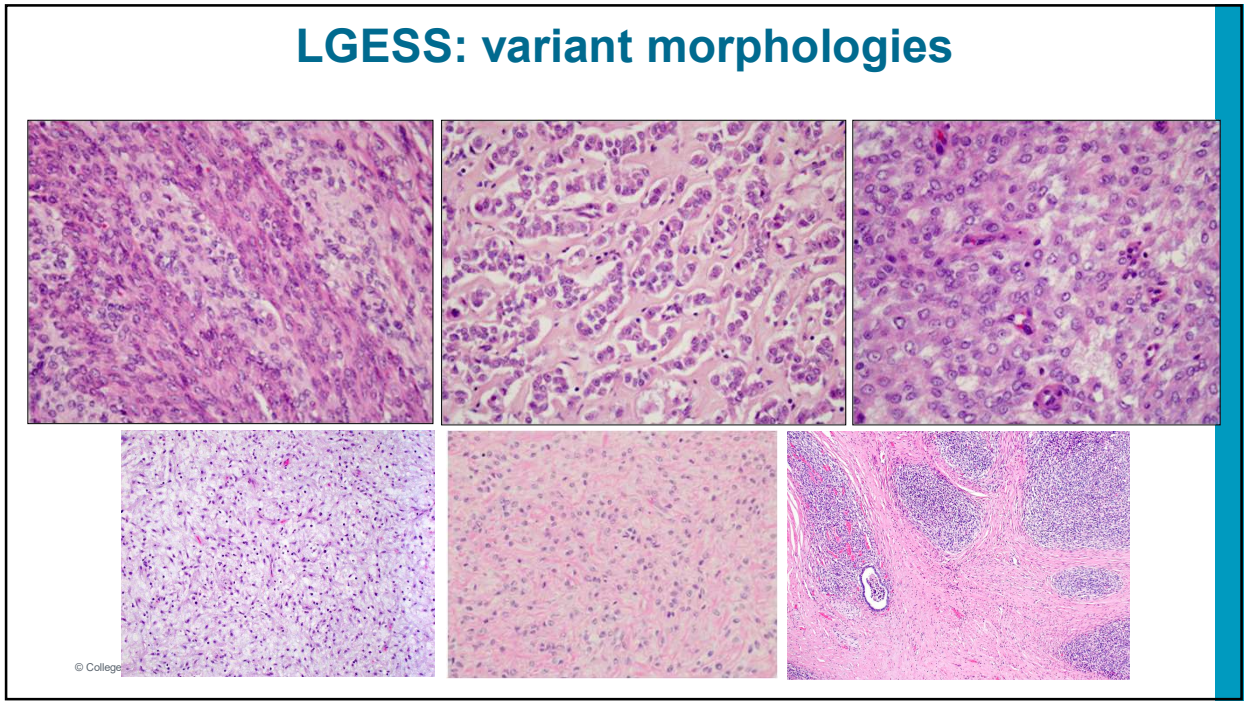
7



8



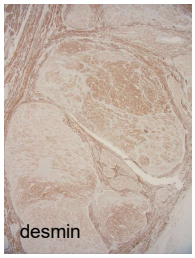
9

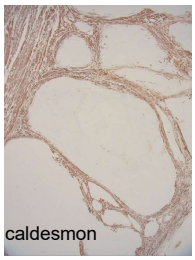


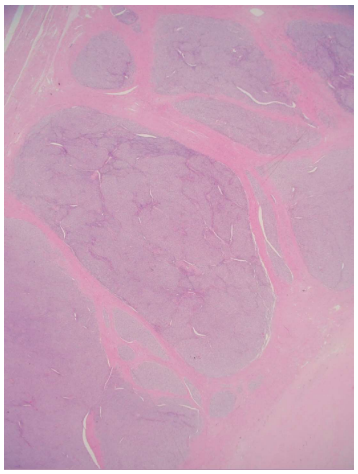
10

LGESS: IHC Ancillary tests

- **Immunohistochemistry**
  - **(+) CD10, ER/PR**
  - **(-) CyclinD1, smooth muscle markers***



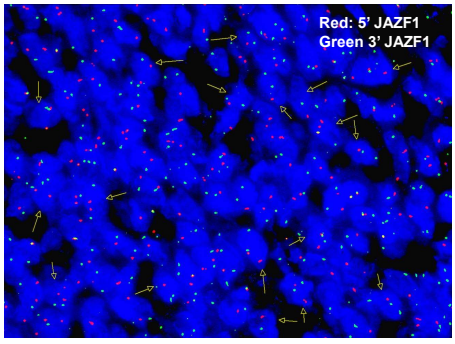




11

LGESS: Molecular/CG Ancillary tests

- **Conventional karyotype, FISH, RNAseq**



- **t(7;17) (most common)**
  - ***JAZF1::SUZ12***
- t(6;7)
  - *JAZF1::PHF1*
- t(6;10)
  - *EPC1::PHF1*
- Some cases lack demonstrable genetic rearrangements

12

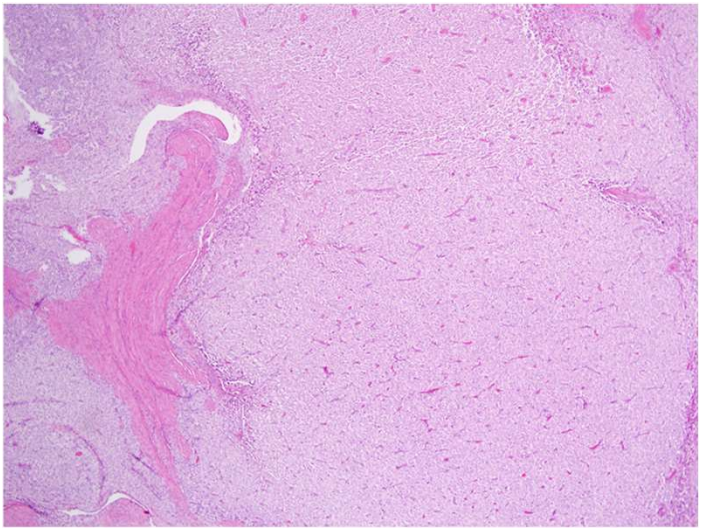
High grade endometrial stromal sarcoma (HGESS)

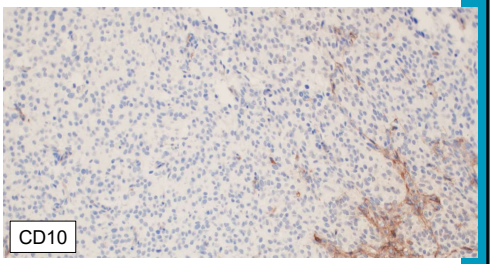
1. ***YWHAE*-rearranged**
2. ***BCOR*-rearranged**
3. ***BCOR* ITD**

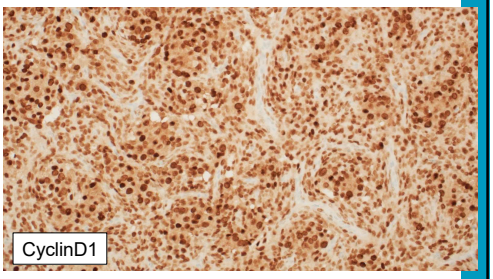
2020 onward:
LGESS
HGESS=YWHAE, BCOR
UUS

13

YWHAE-rearranged HGESS







14

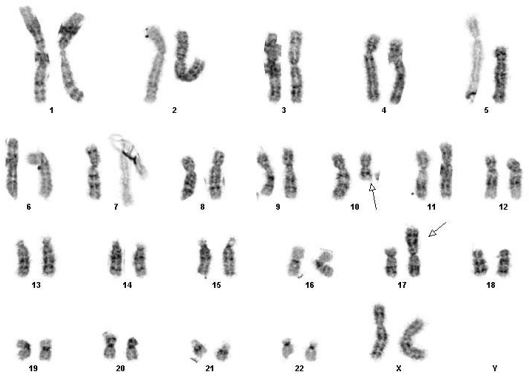
YWHAE-rearranged HGESS: Ancillary tests

- **Immunohistochemistry:**
  - **CD10, ER usually negative but may be positive**
  - **CyclinD1: typically strong and diffuse (even in LG areas)**
  - **BCOR: typically strong and diffuse**

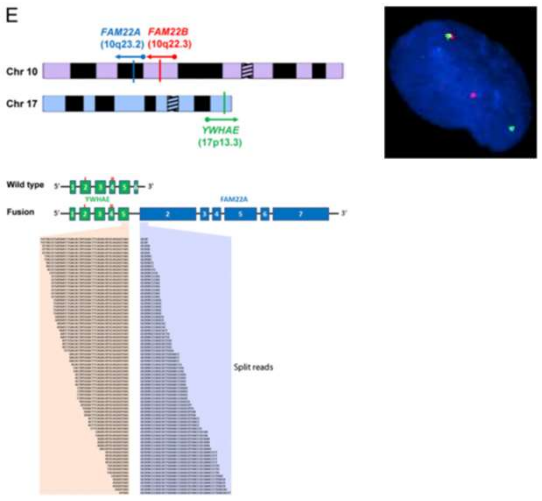
15

YWHAE-rearranged HGESS: Ancillary tests

- **Conventional karyotype, FISH, RNAseq**



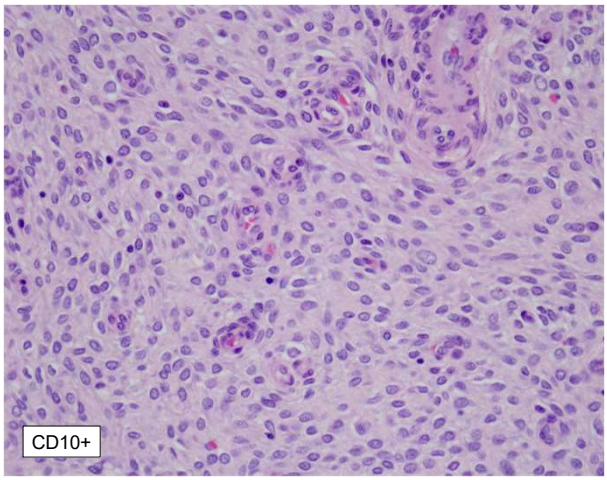
t(10;17)

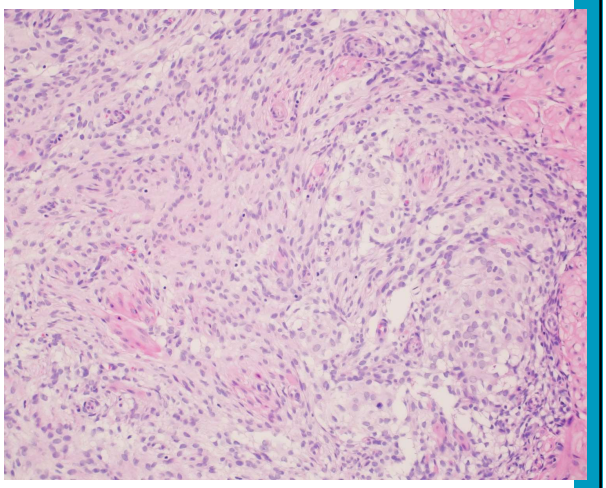


Lee CH, et al. PNAS. 2012 Jan 17;109(3):929-34.

16

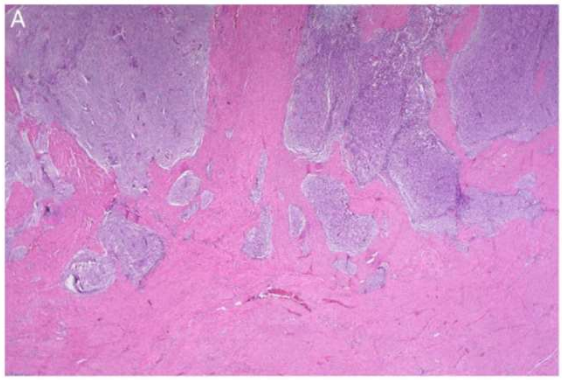
Challenging areas in the diagnosis of *YWHAE*-HGESS

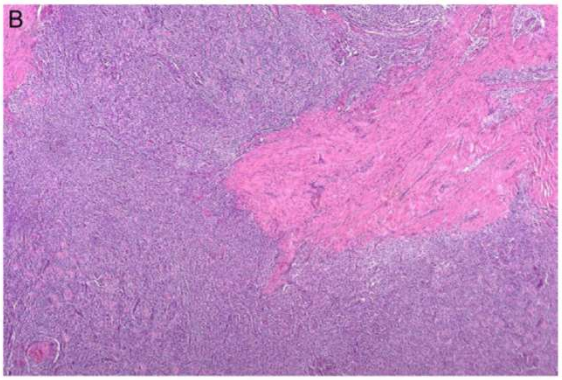




17

In some YWHAE-ESS, the tumor is entirely low-grade morphology

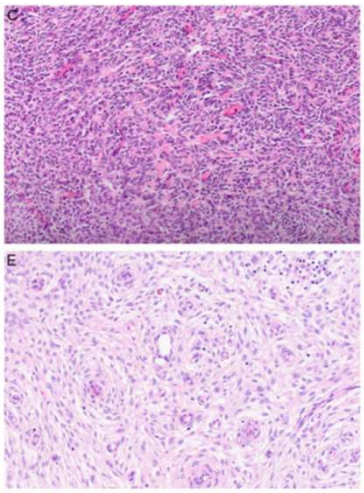




Devins et al. Am J Surg Pathol Volume 47, Number 6, June 2023

18

In some YWHAE-ESS, the tumor is entirely low-grade morphology

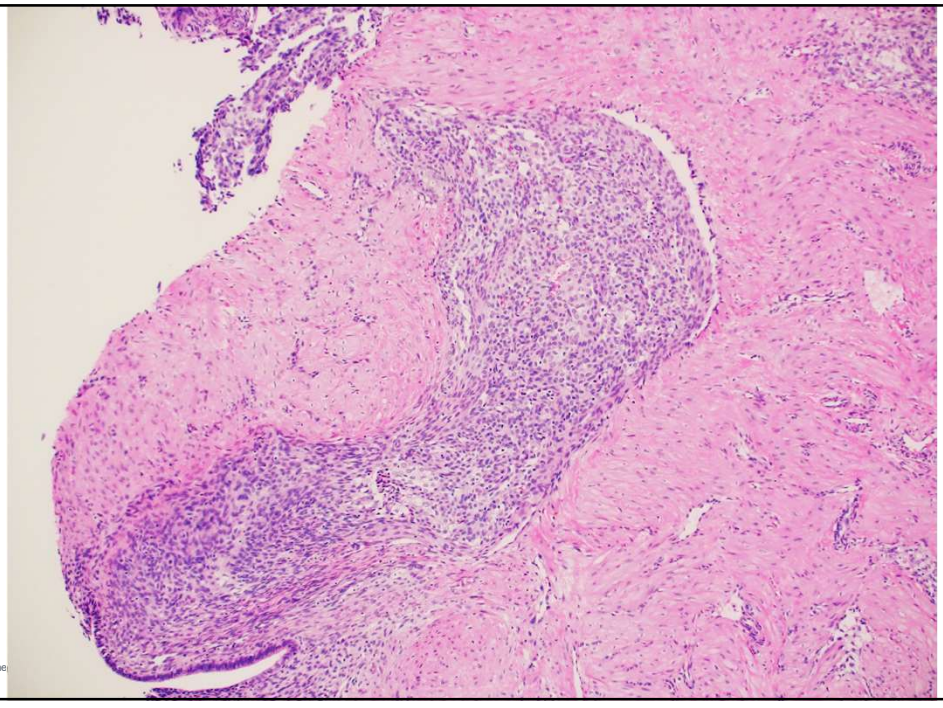


Typical LGESS morphology with focal collagen

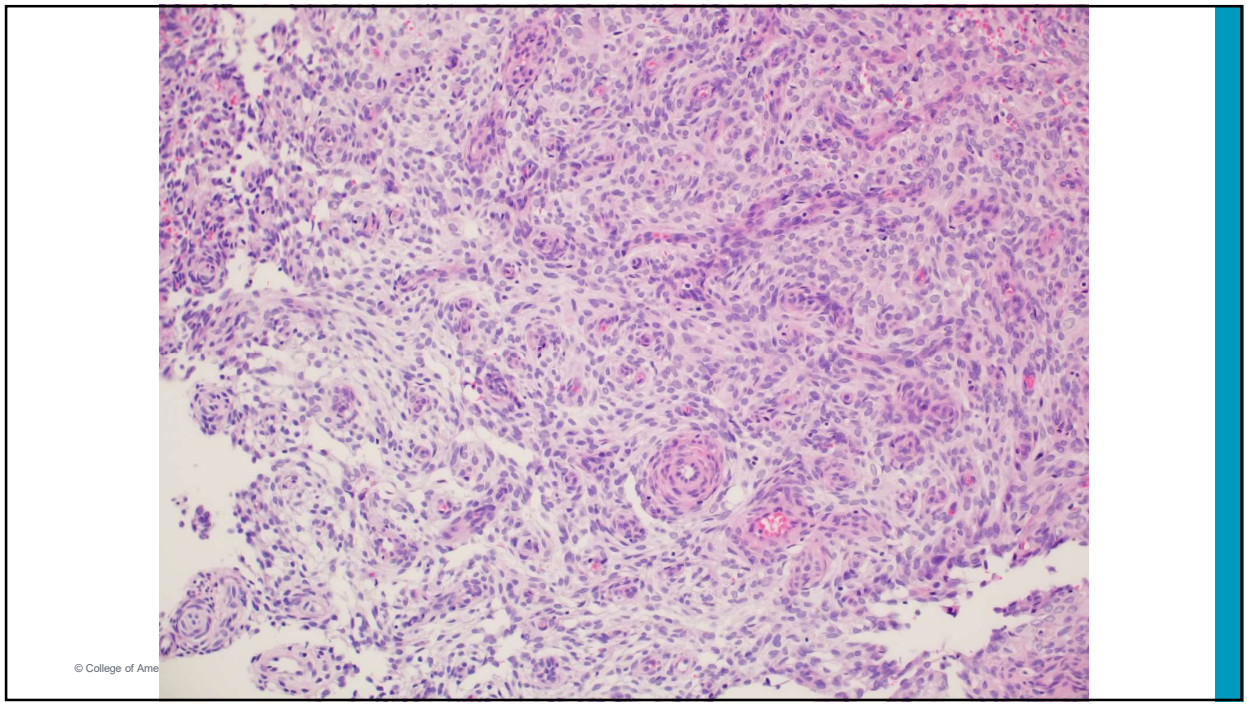
Fibromyxoid LGESS morphology

Devins et al. Am J Surg Pathol Volume 47, Number 6, June 2023

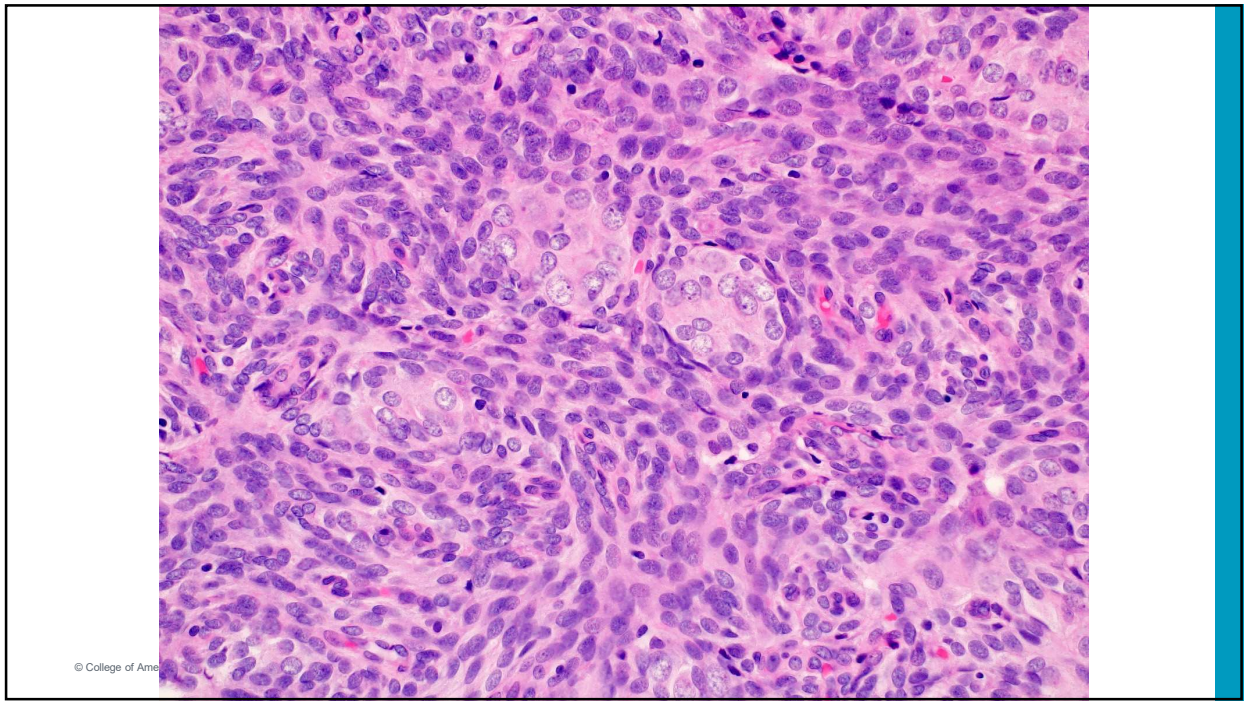
19



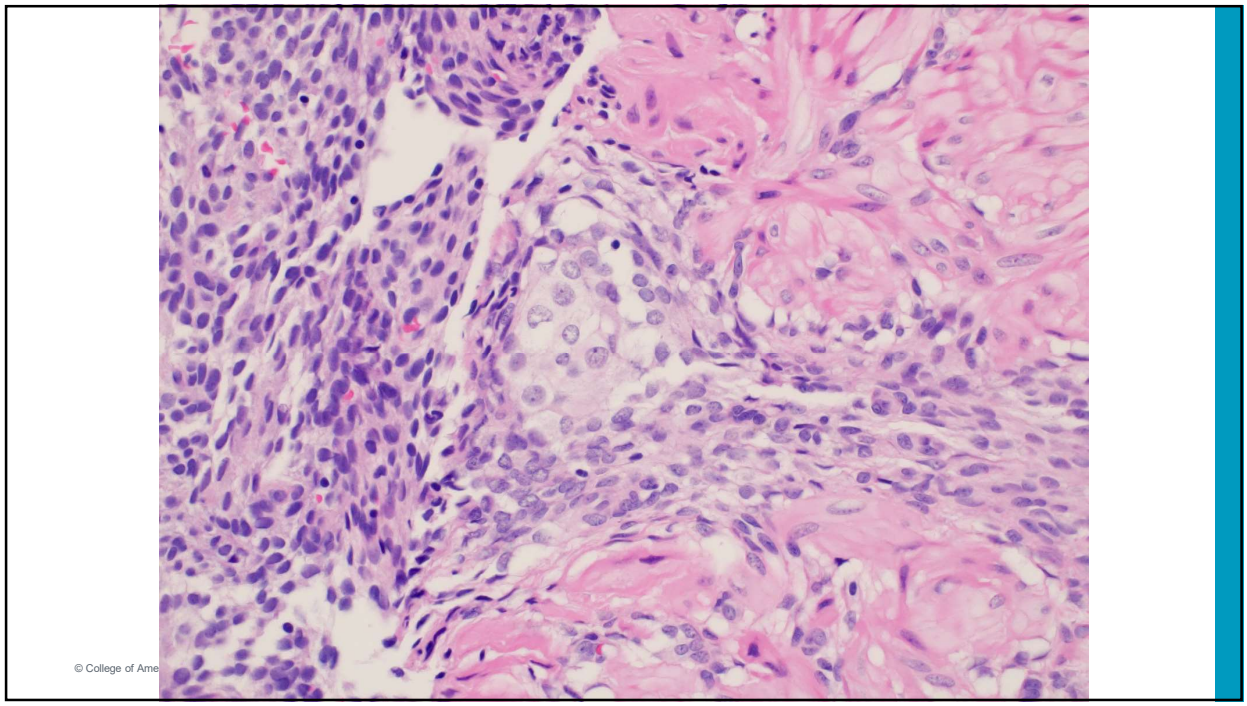
20



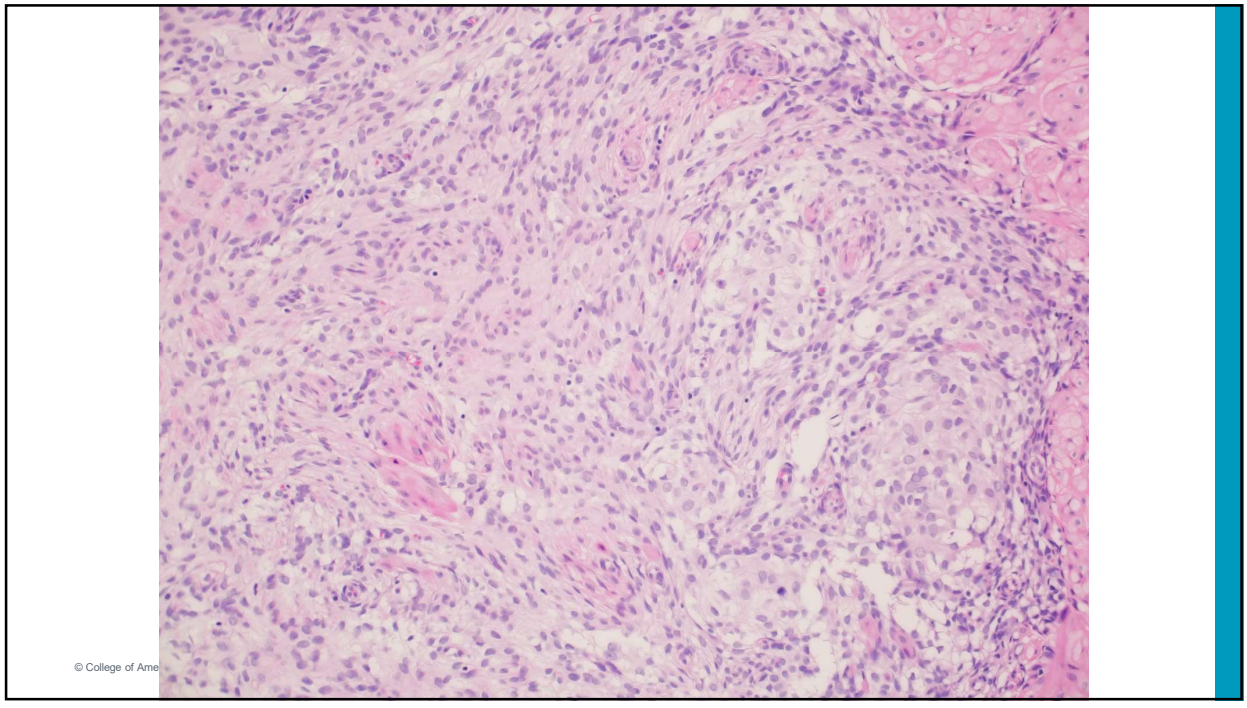
21



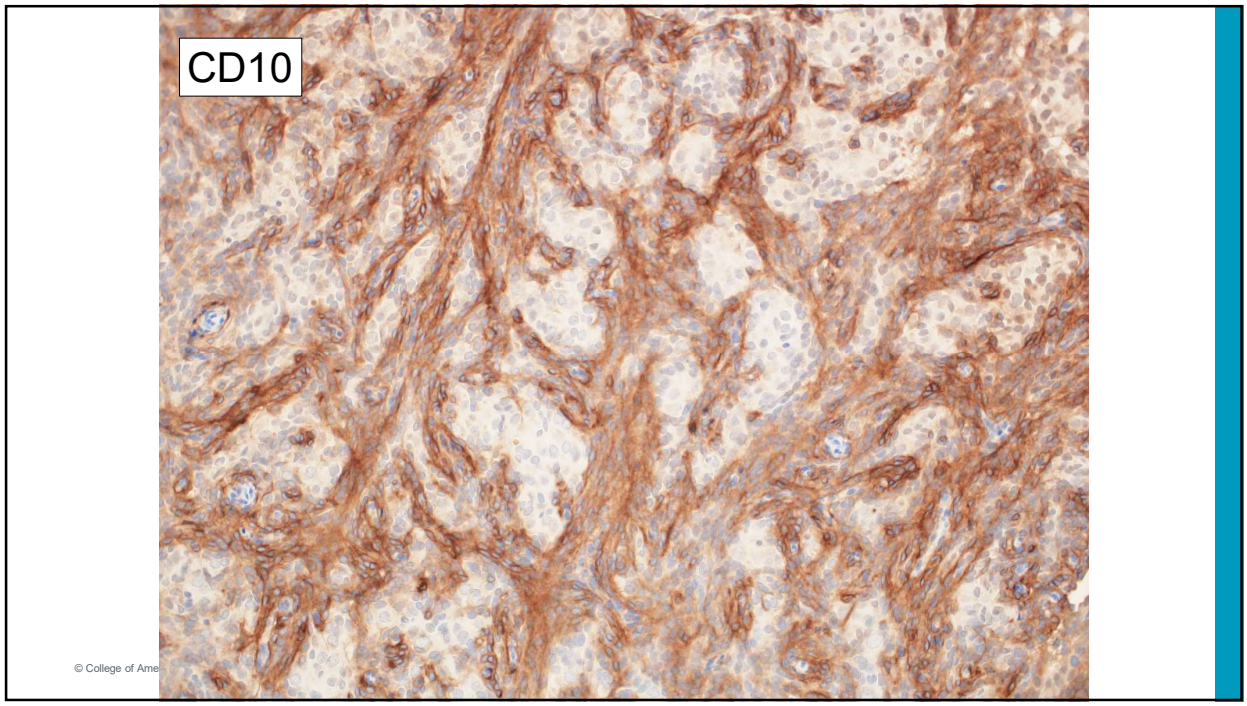
22



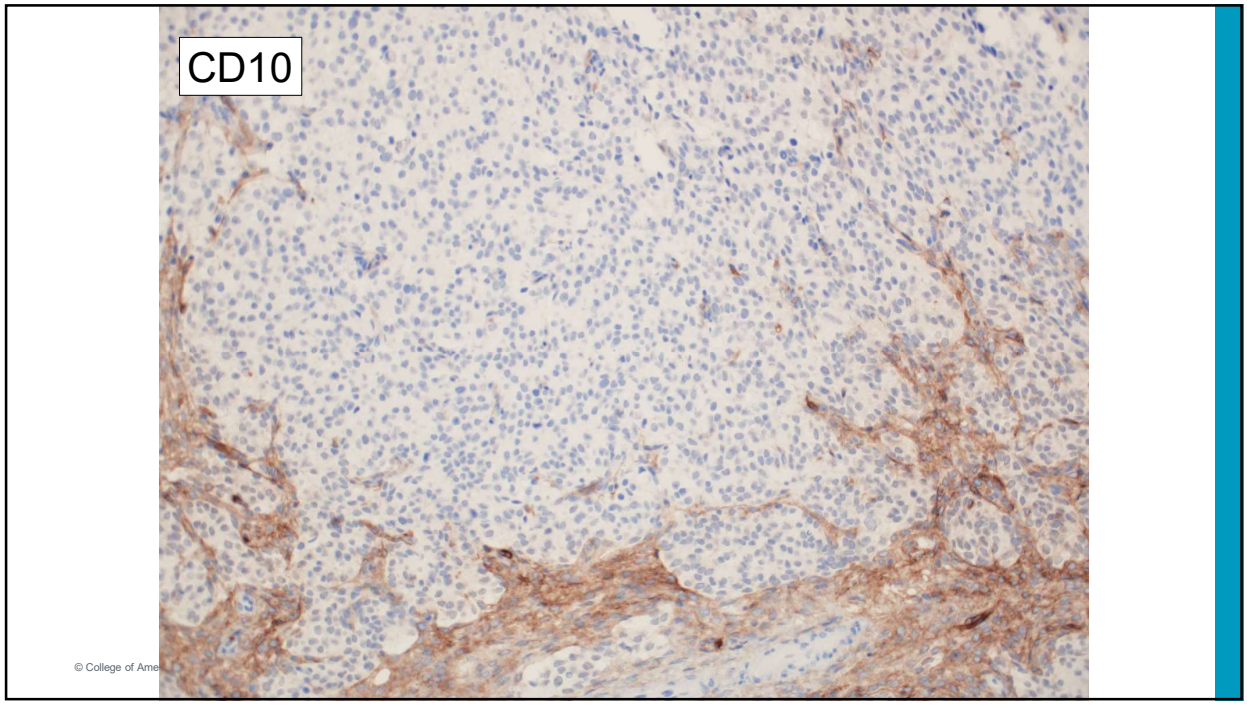
23



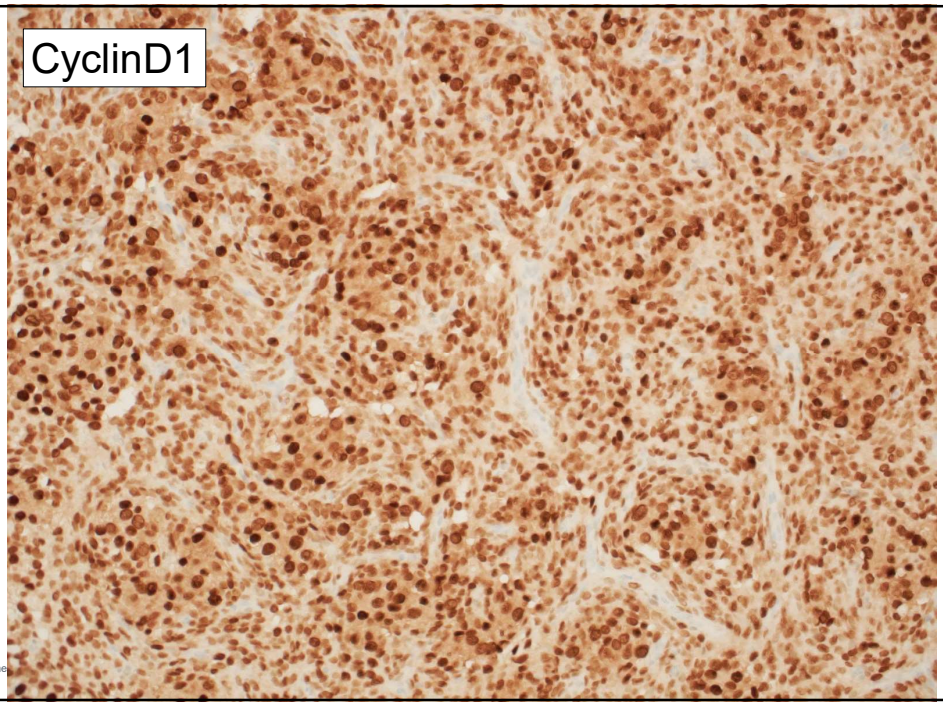
24



25



26



27

High-grade endometrial stromal sarcoma

- **Positive for *YWHAE* rearrangement by FISH**

28

Clues to recognizing HGESS masquerading as LGESS

- **Fibromyxoid morphology**
- **CD10 negativity or only focal staining**
- **Only limited/focal ER/PR positivity**
- **CyclinD1 positivity**

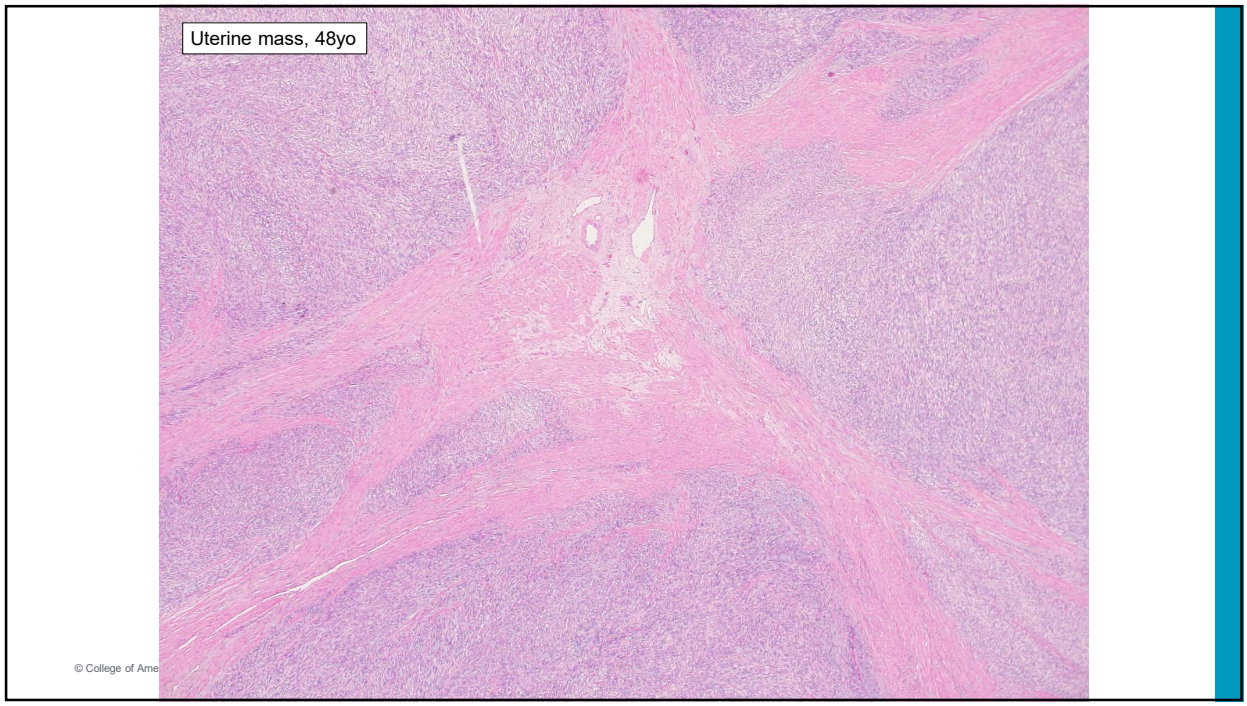
- **Unclear if these tumors are best considered/diagnosed as LGESS (morphology) or HGESS (molecular) for diagnostic/treatment purposes**

29

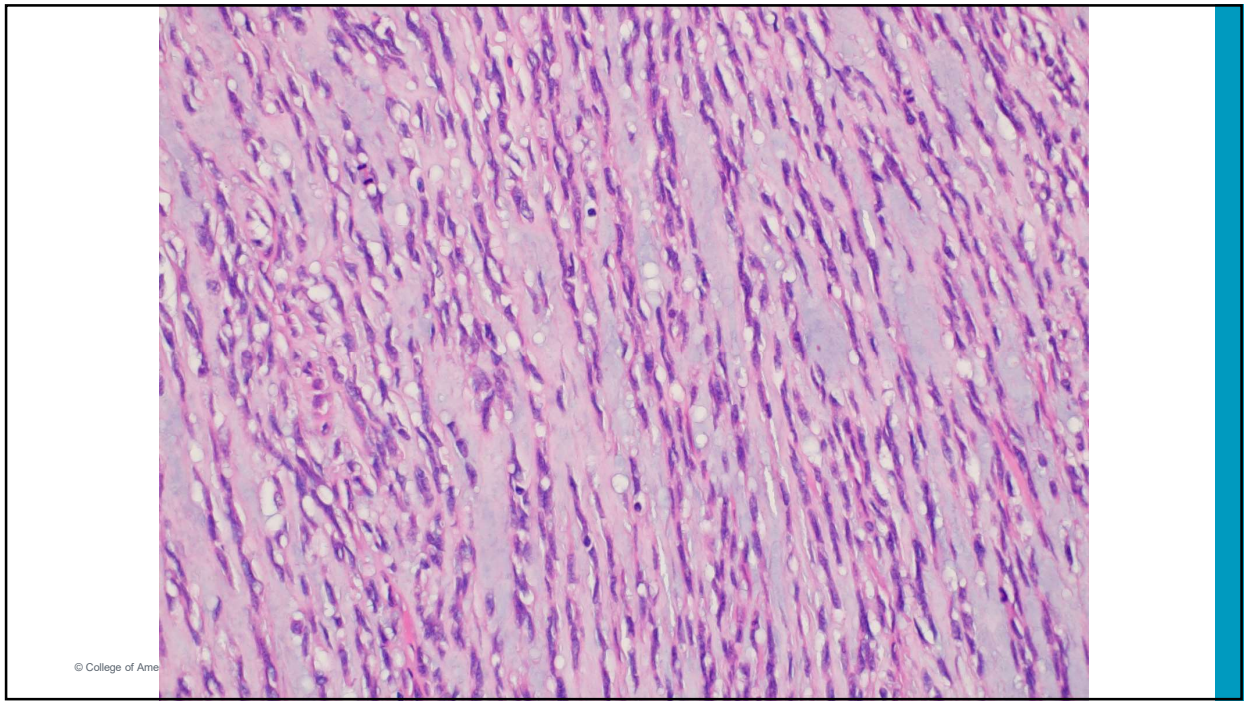
Practical pearl

- **Careful selection of blocks for IHC is critical and guided by morphology; however underlying molecular fusion is consistent throughout tumor (FISH/RNAseq)**

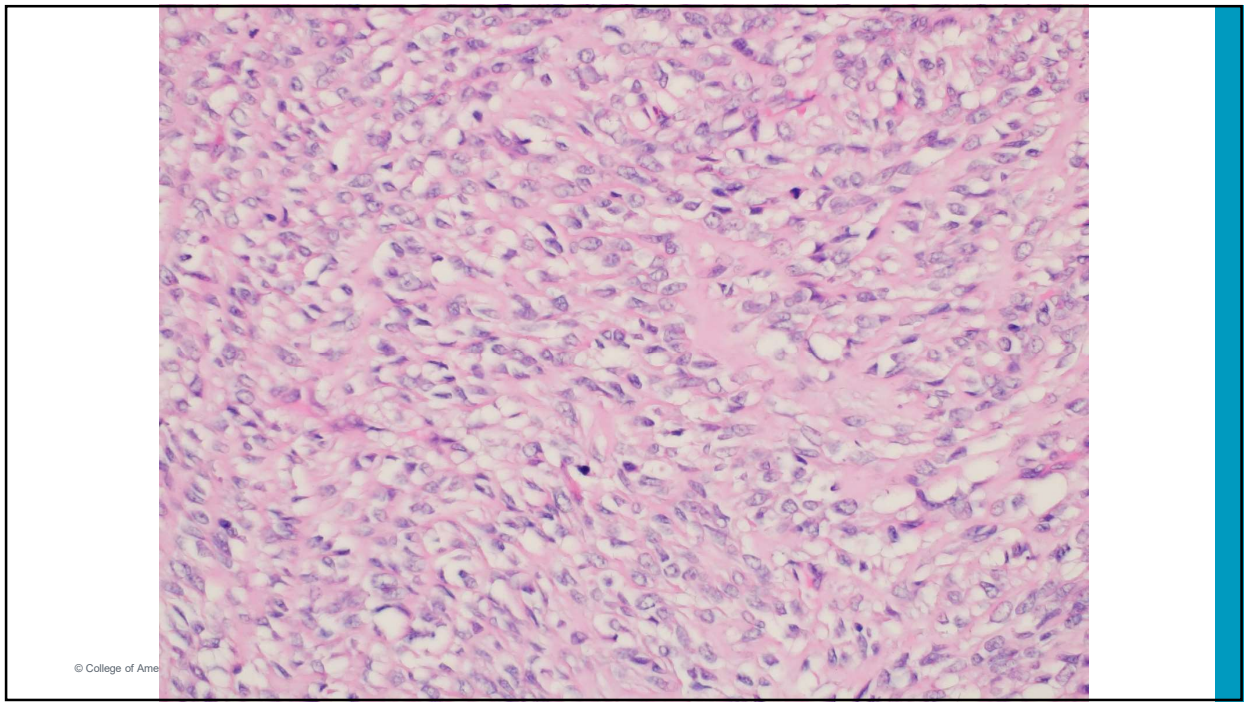
30



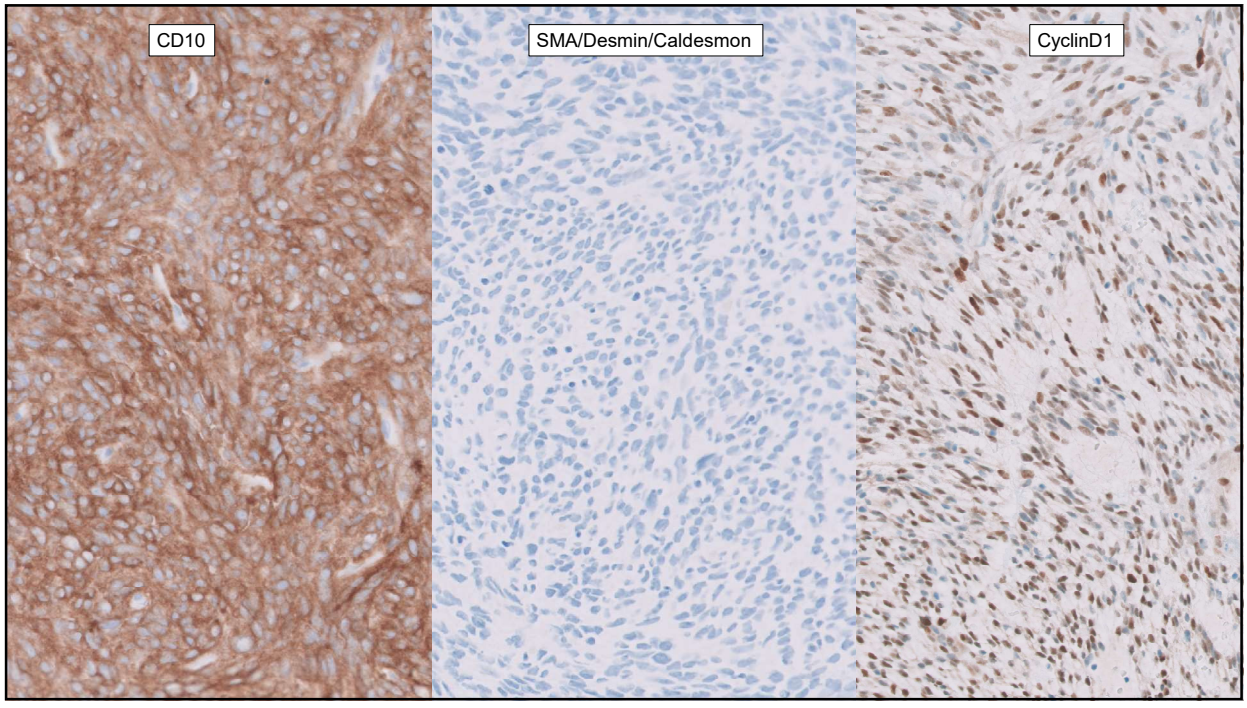
31



32



33



34

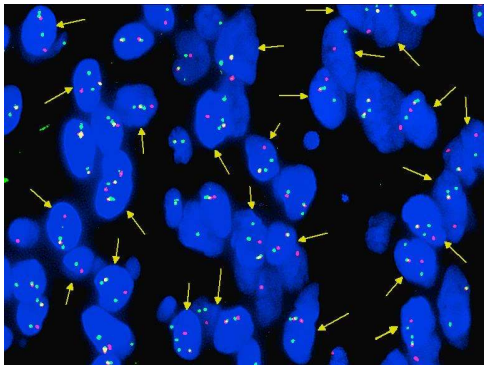
Diagnosis: BCOR-altered HGESS

- ***BCOR::ZC3H7B* gene fusion identified by RNAseq**

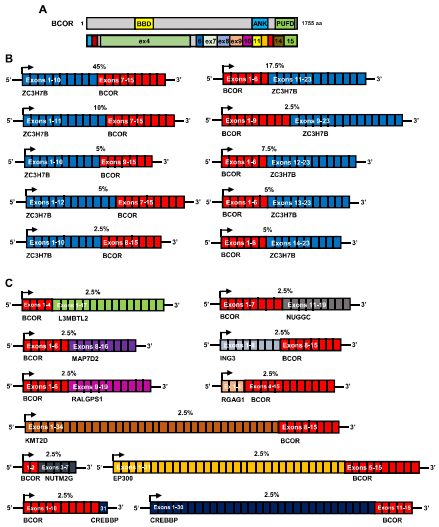
35

BCOR-rearranged HGESS: Ancillary tests

- **Conventional karyotype, FISH, RNAseq**

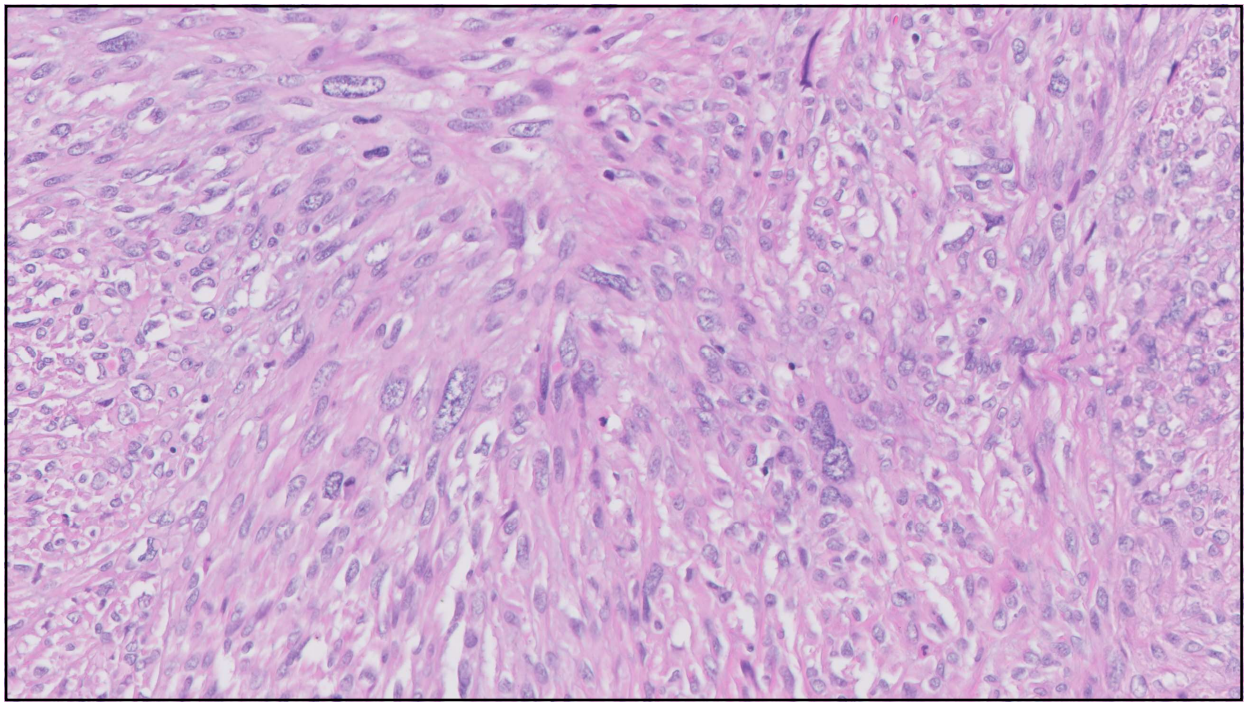


t(X;22)(p11;q13)

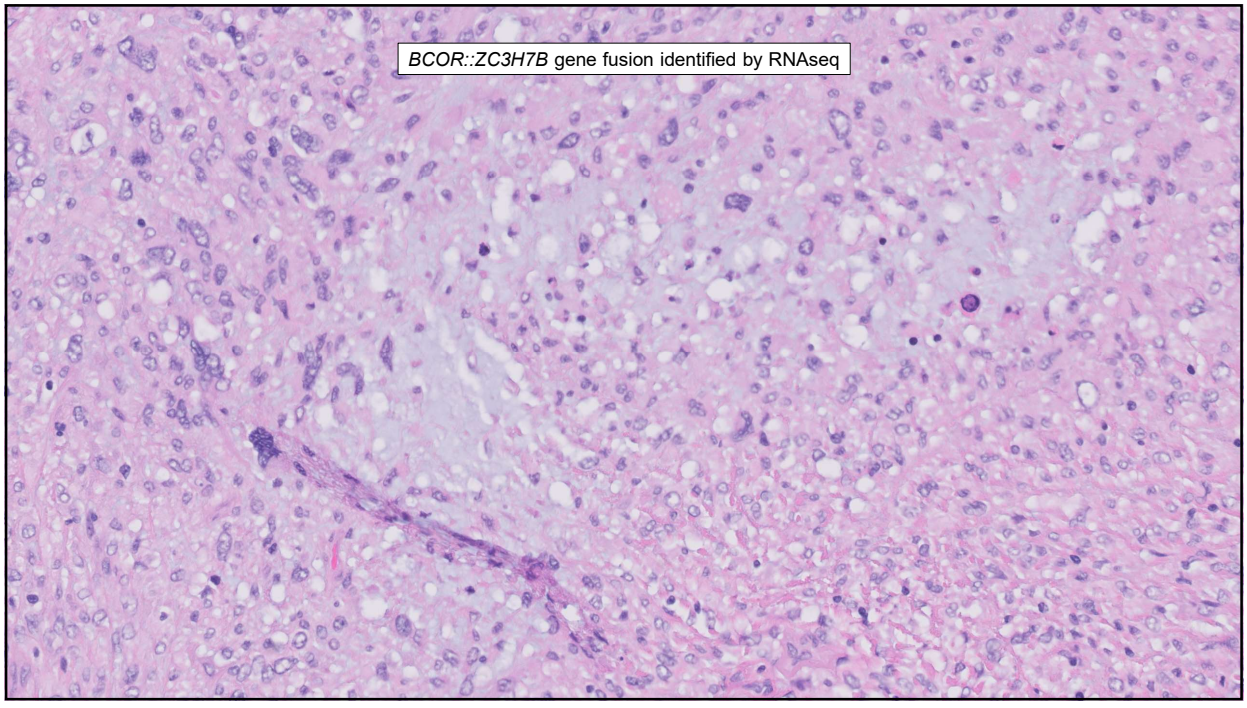


Lin DI et al. Gynecol Oncol. 2020 May;157(2):357-366.

36



37



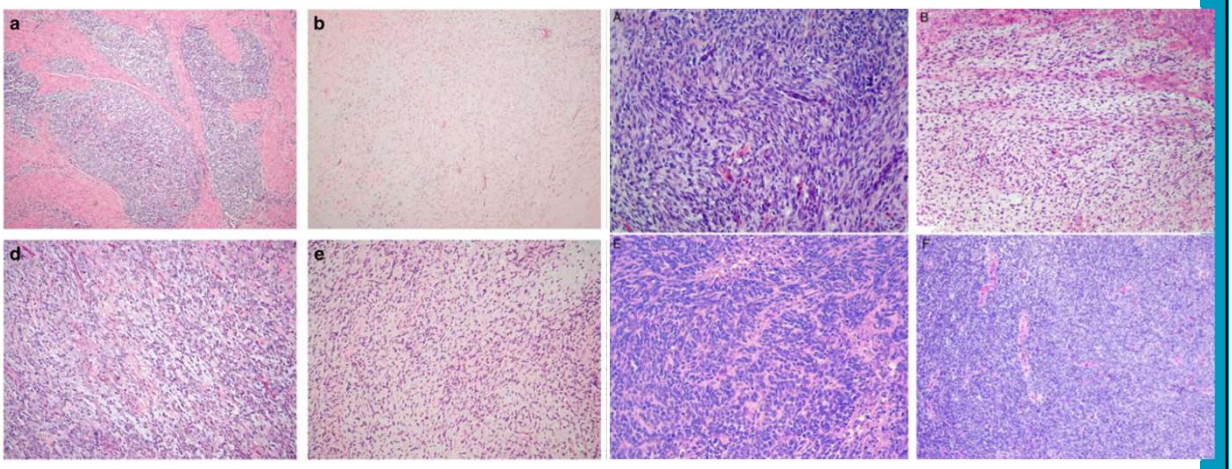
38

Practical pearls: BCOR breaks the rules

- **Consider *BCOR*-HGESS for uterine sarcomas with spindled and round cell morphology with at least focally myxoid stroma**
- ***BCOR* fusion sarcomas CAN have significant nuclear atypia and pleomorphism**
  - **CD10 can be strongly positive**
  - **Desmin may be focal/limited (+)**
  - **BCOR fusion sarcomas may be negative for BCOR IHC (~50%), even in the setting of FISH/fusion (+)**

39

BCOR-internal tandem duplication (ITD) HGESS



Modern Pathology (2017) 30, 1251–1261

Am J Surg Pathol 2018;42:335–341

40

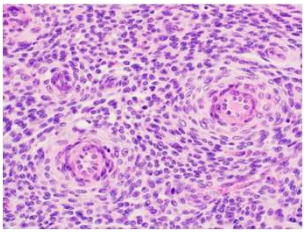
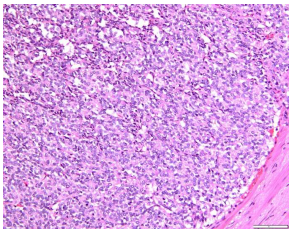
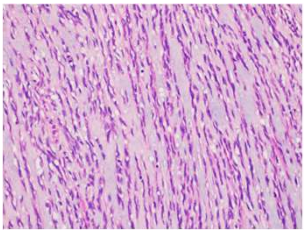
BCOR-ITD HGESS: Ancillary tests

BCOR ITD HGESS will be NEGATIVE for *BCOR* gene rearrangement by FISH assay

Some NGS assays can detect ITDs (need to check)

Cotzia P, et al. Am J Surg Pathol. 2019 May;43(5):662-669.

41

	LGESS	HGESS (YWHAE)	HGESS (BCOR)
CD10	+	- (except LG areas are +)	+/-
CyclinD1	-	Strong diffuse +	Strong diffuse +
BCOR	-	+	+/-
ER/PR	+	-	Neg or focal
FISH/fusion	JAZF1, PHF1	YWHAE	BCOR (BCOR ITD will be FISH negative)
Clinical	Relatively good prognosis for stage I	More often present at advanced stage	Worse than LGESS, may be comparable to YWHAE

42

Practical approach to IHC workup in suspected endometrial stromal neoplasms

- **Panel of CD10, ER, PR CyclinD1 generally sufficient with typical LGESS morphology**
- **If unusual morphologic features present:**
  - **Consider smooth muscle markers (SMA, desmin, caldesmon)**
  - **Consider sex cord markers (keratin, SF1, etc)**
- **Specific block/area of tissue selected for IHC DOES matter.**

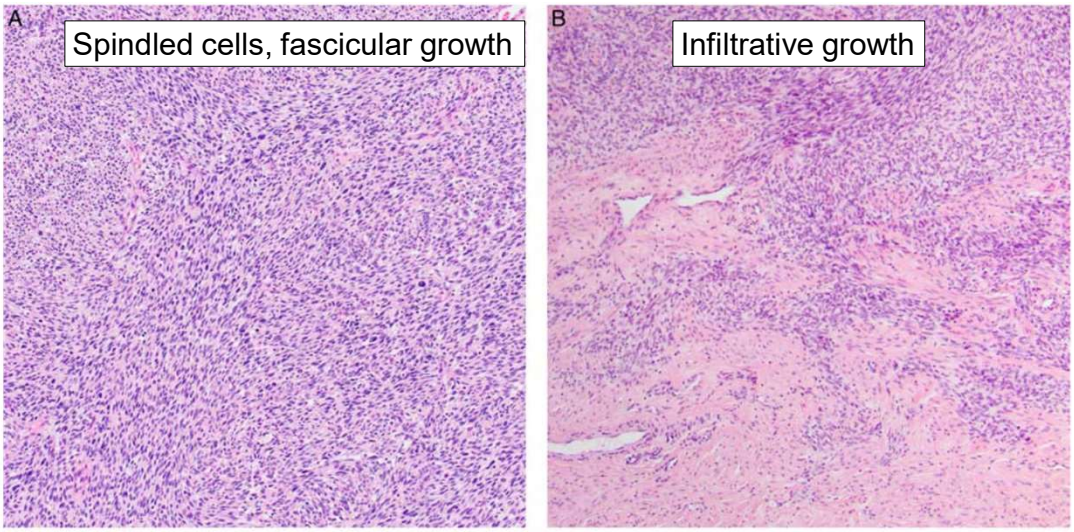
43

A practical approach: When to consider FISH in endometrial stromal neoplasms?

- Before diagnosing an undifferentiated uterine sarcoma that has uniform nuclear morphology, I test for both *YWHAE* and *BCOR* alterations (FISH or fusion assay)
  - **High stage or recurrent disease**

44

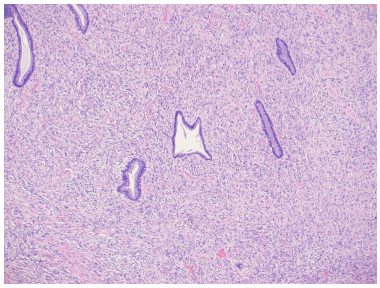
NTRK-rearranged uterine sarcoma

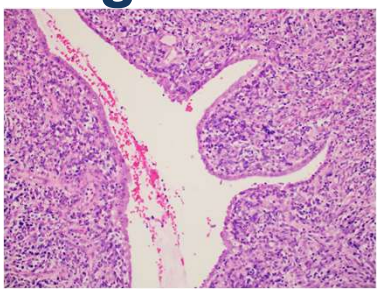


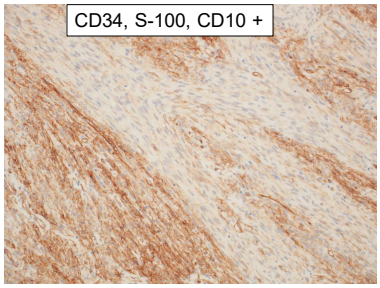
Costigan et al. Am J Surg Pathol Volume 46, Number 10, October 2022

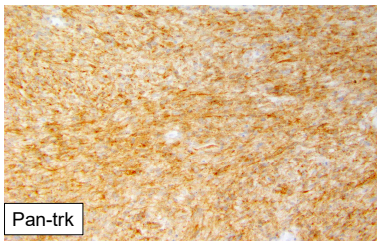
45

NTRK-rearranged uterine sarcoma









Harbor *NTRK1* or *NTRK3* gene fusions

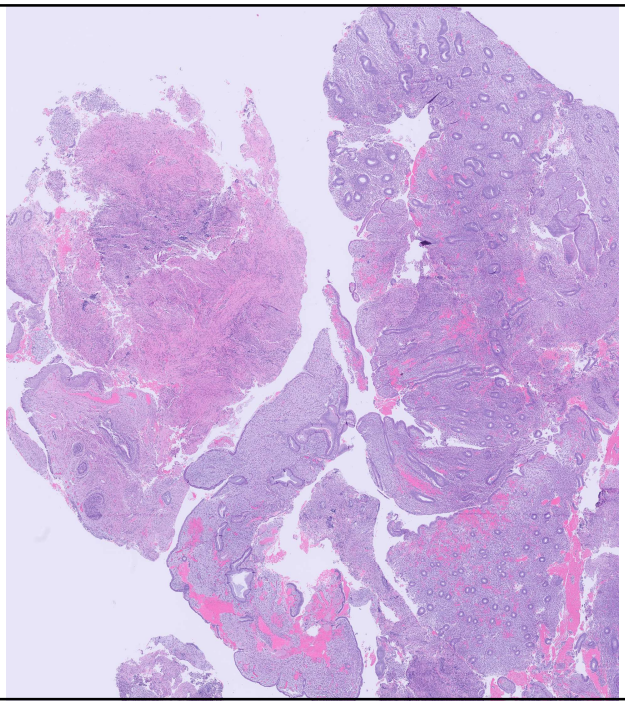
Can use pan-Trk IHC as screen for fusion status
→Pan-trk IHC positivity however is NOT specific!
→Other uterine sarcomas may show positive pan-trk staining
Findings must be confirmed with molecular assays

46

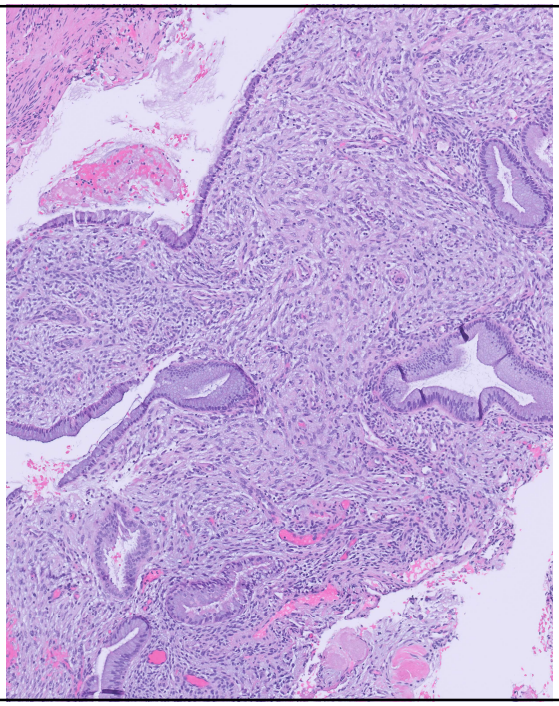
NTRK-rearranged uterine sarcoma

- S100+ (80-90%), CD34+ (60%)
  - When CD34+, S100 also positive
- SOX10, desmin (-)
- Harbor *NTRK1* or *NTRK3* gene fusions
- Can use pan-Trk IHC as screen for fusion status
  - →Pan-trk IHC positivity however is NOT specific!
  - →Other uterine sarcomas may show positive pan-trk staining
    - Often BCOR-HGESS are positive for pan-trk
- Findings must be confirmed with molecular assays (RNAseq/FISH)

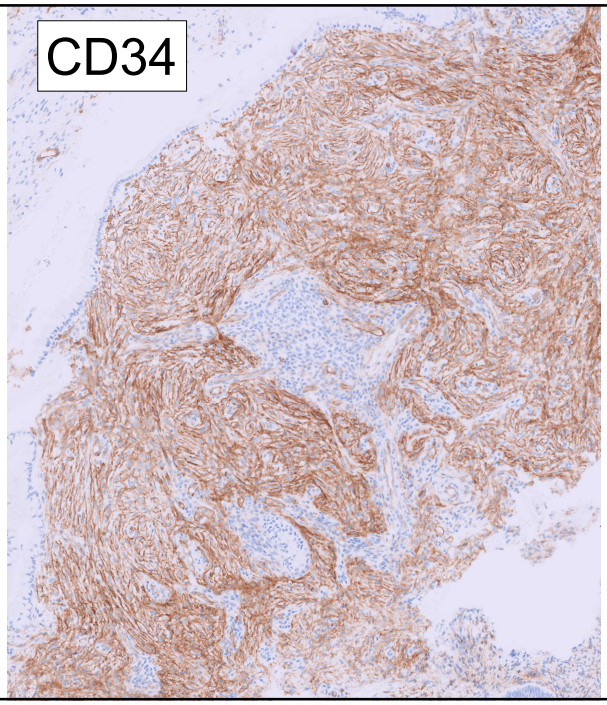
47



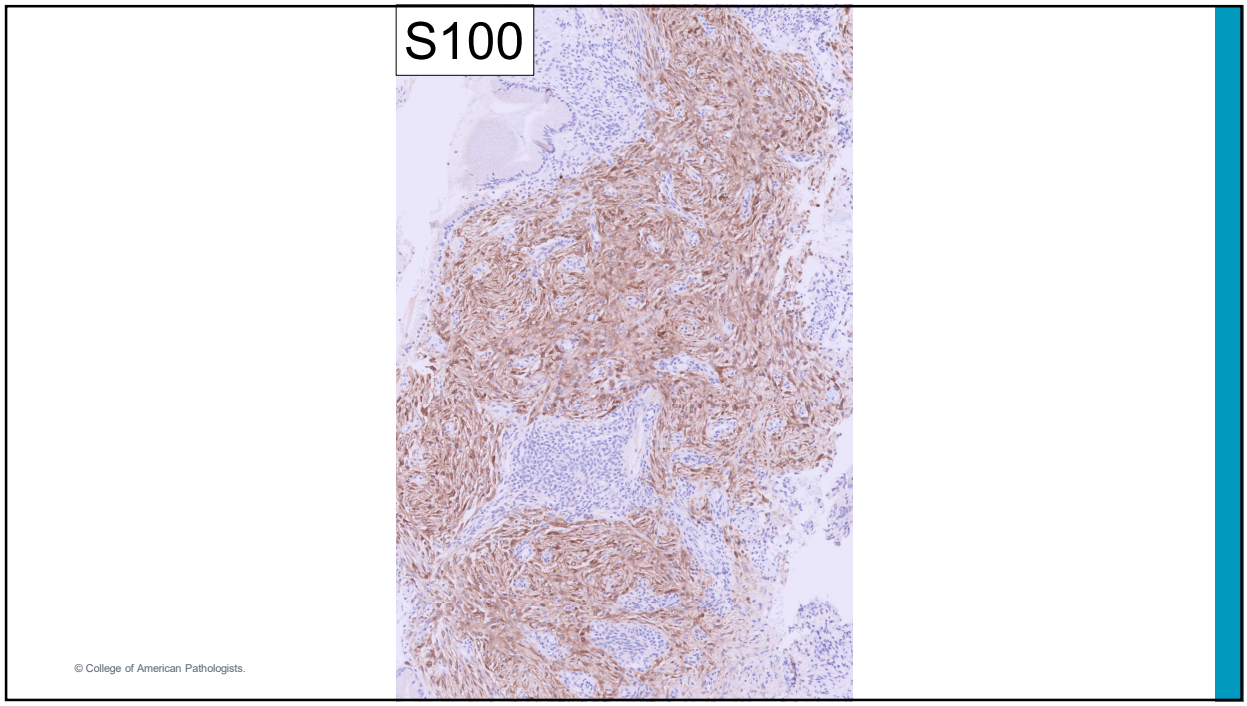
48



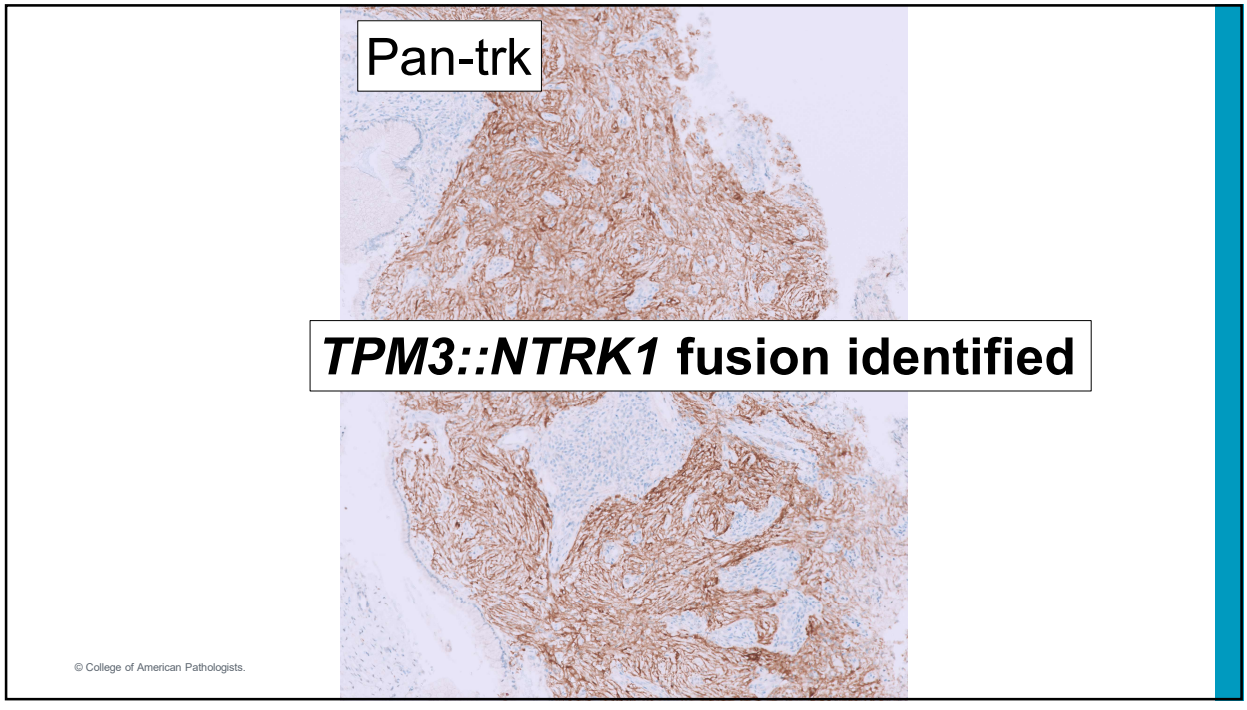
49



50



51



52

Prognostication in *NTRK*-sarcoma

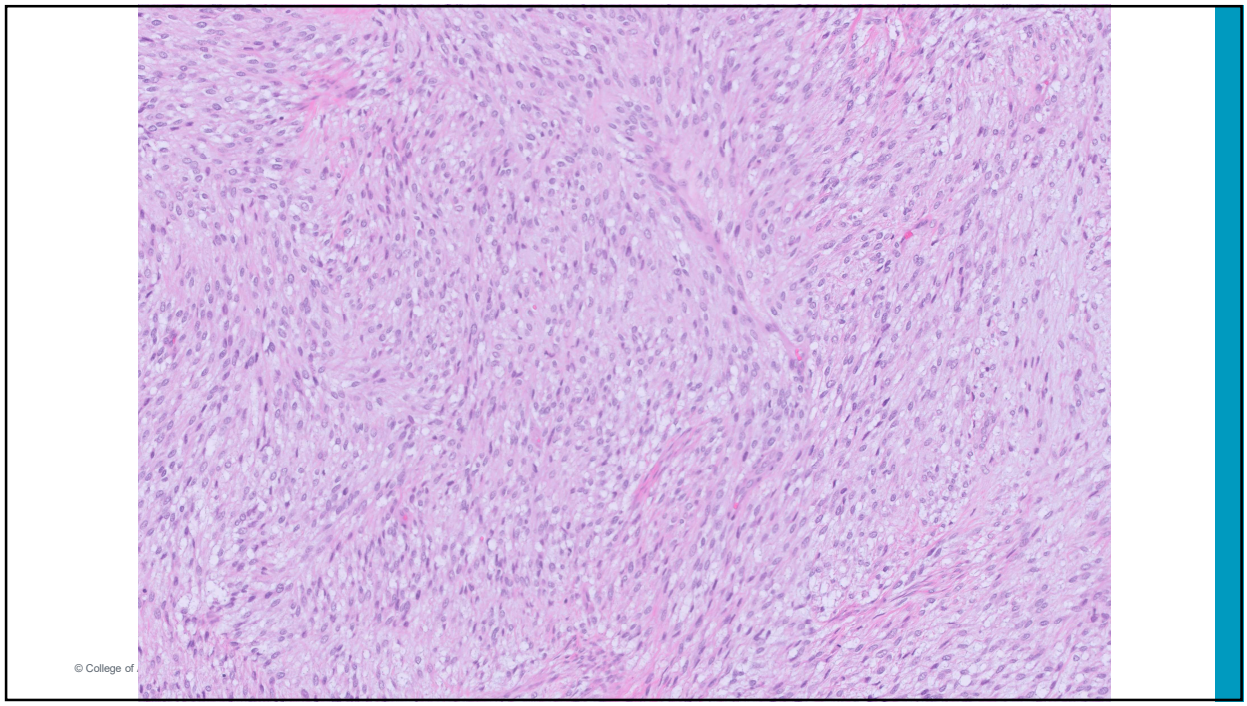
- **Features associated with increased risk of recurrence:**
  - **Necrosis**
  - **LVI**
  - **Mitoses > or = 8 per 10 HPFs**
  - ***NTRK3* fusion**
- **Tumors lacking all 4 of these features did not recur (limited #'s)**
- **Targeted therapy for *NTRK*-sarcomas:**
  - **Entrectinib, Larotrectinib, Repotrectinib**

Costigan et al. Am J Surg Pathol Volume 46, Number 10, October 2022

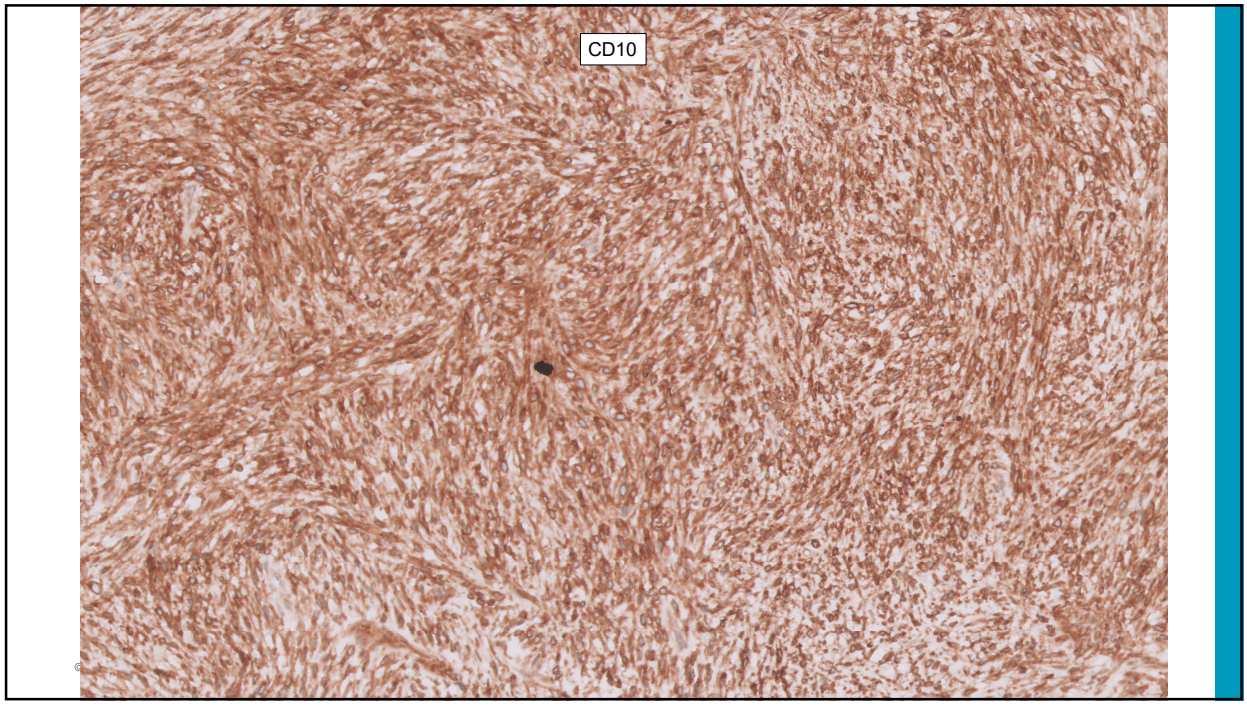
53

What about this case?

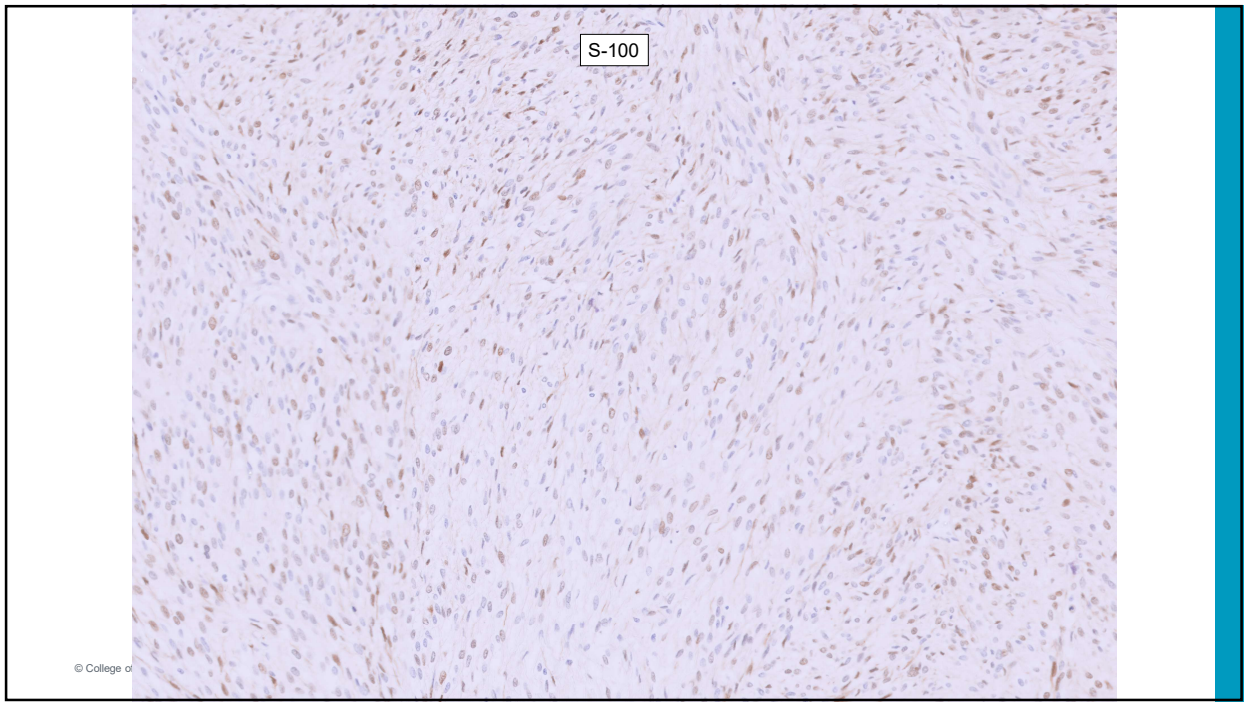
54



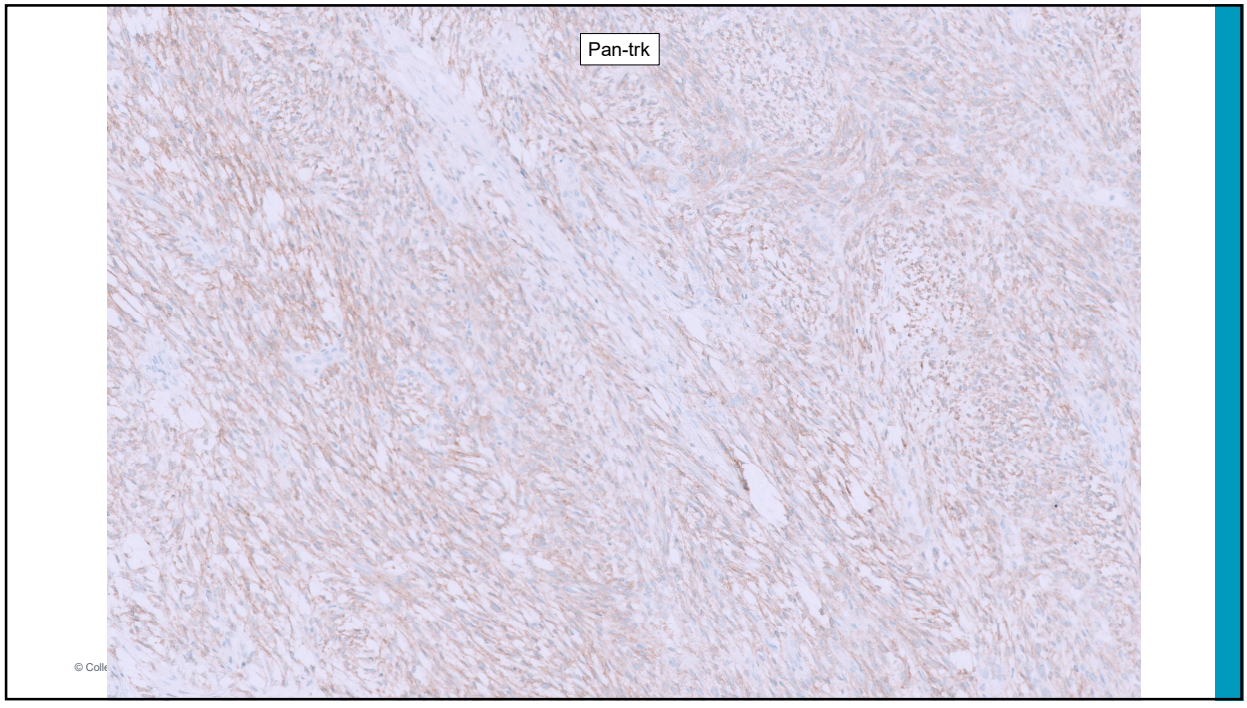
55



56



57

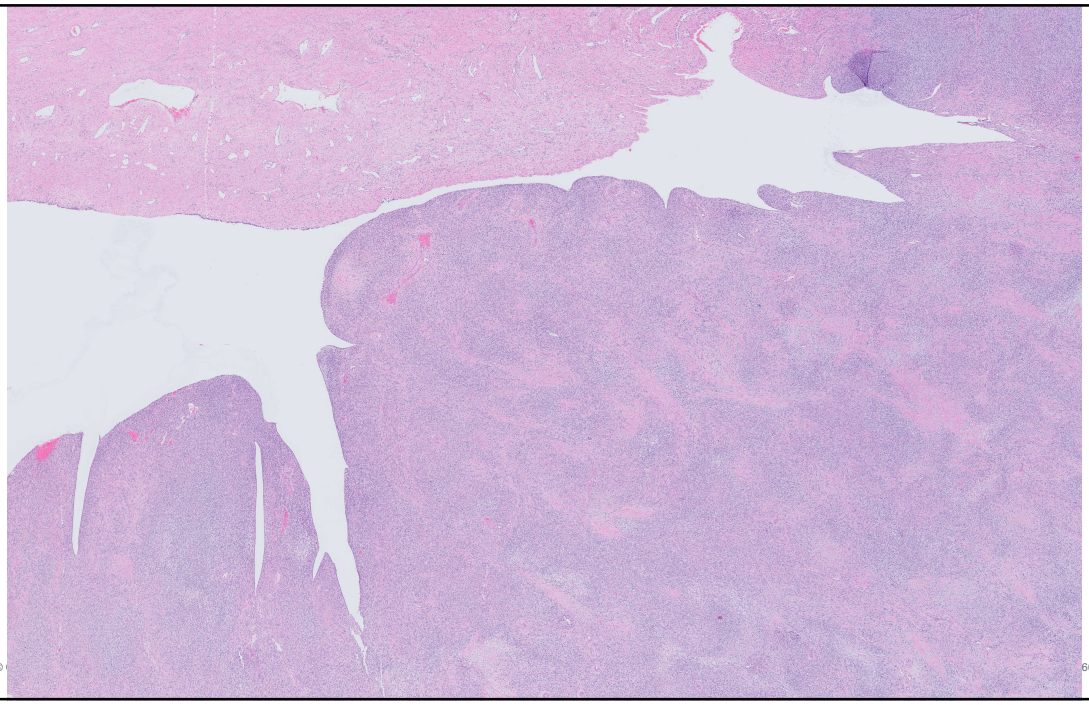


58

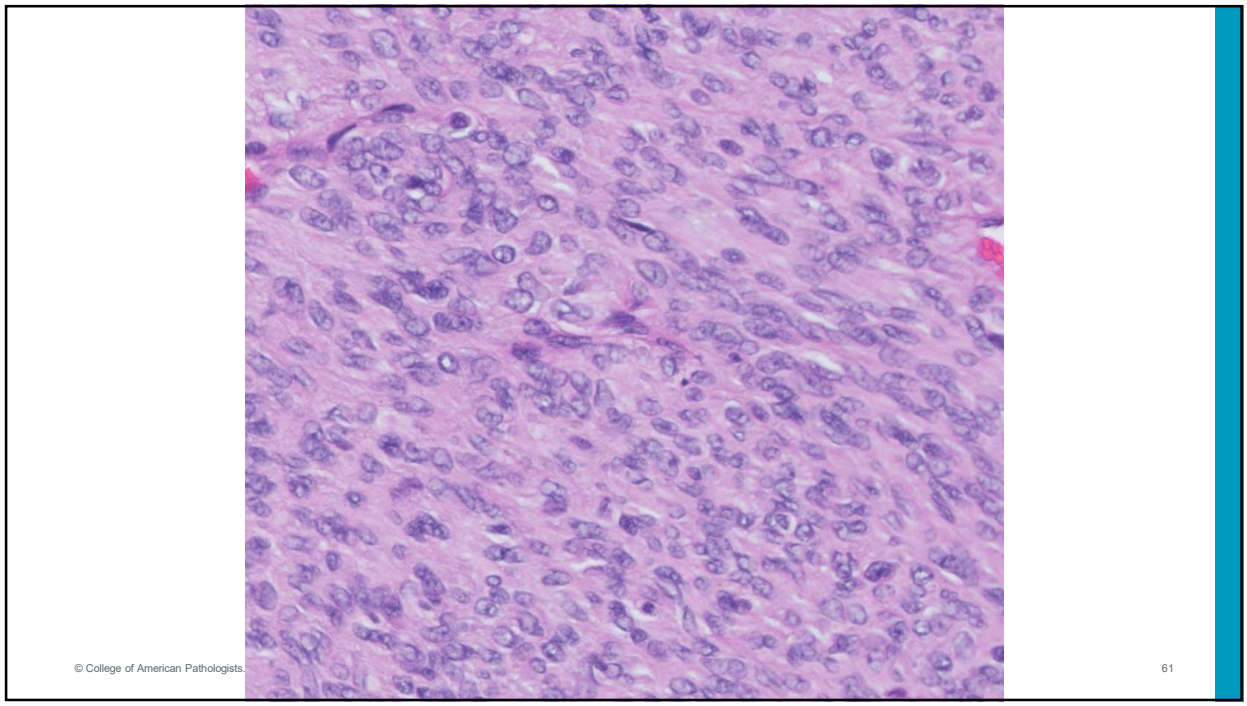
Diagnosis: BCOR-altered HGESS

- ***BCOR::ZC3H7B* gene fusion identified by RNAseq**

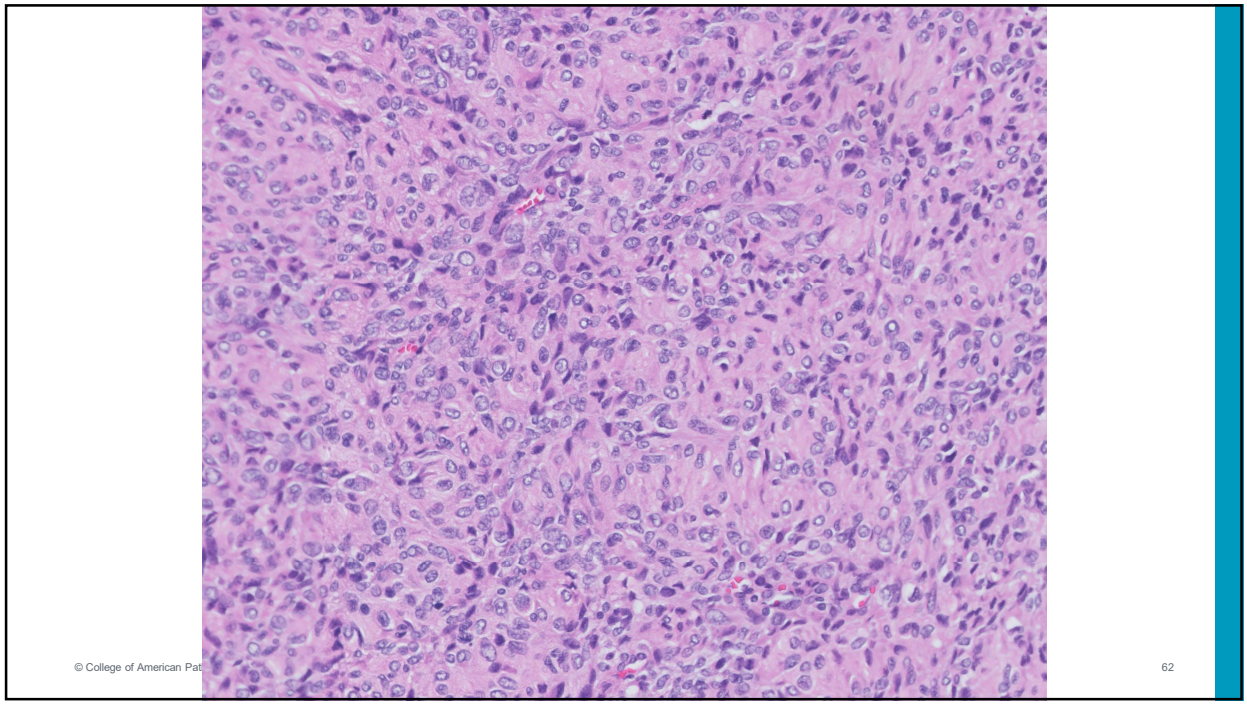
59



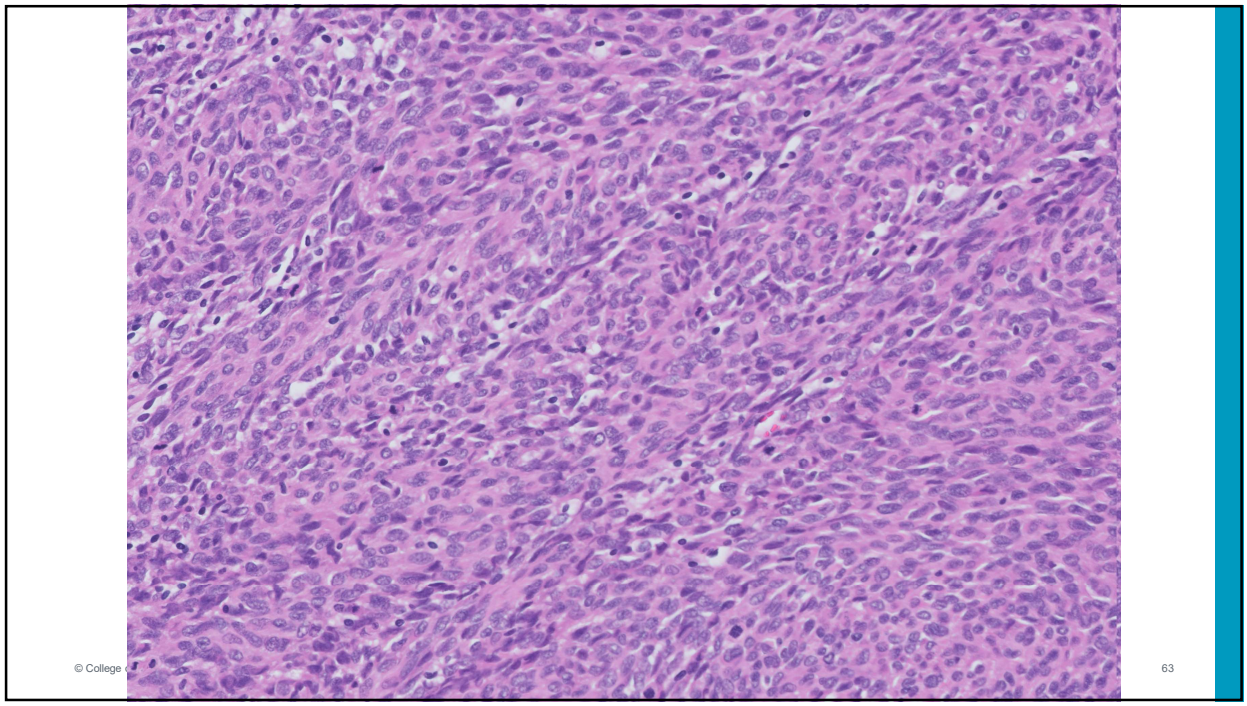
60



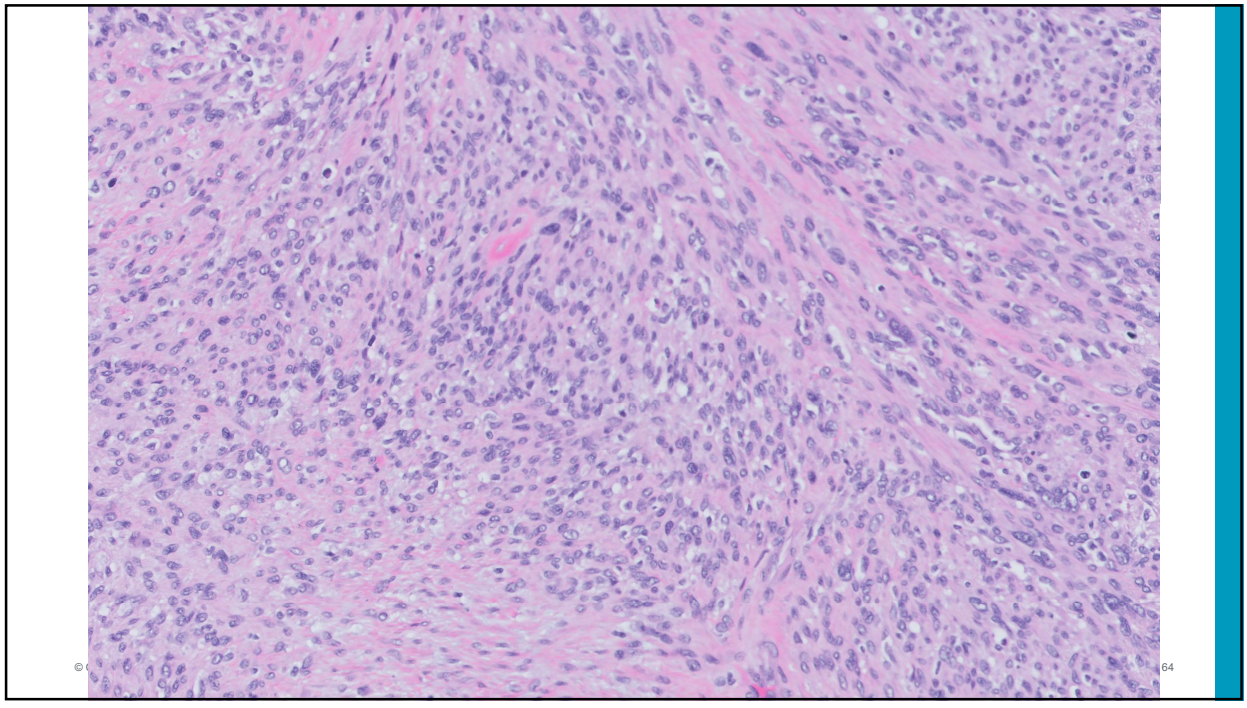
61



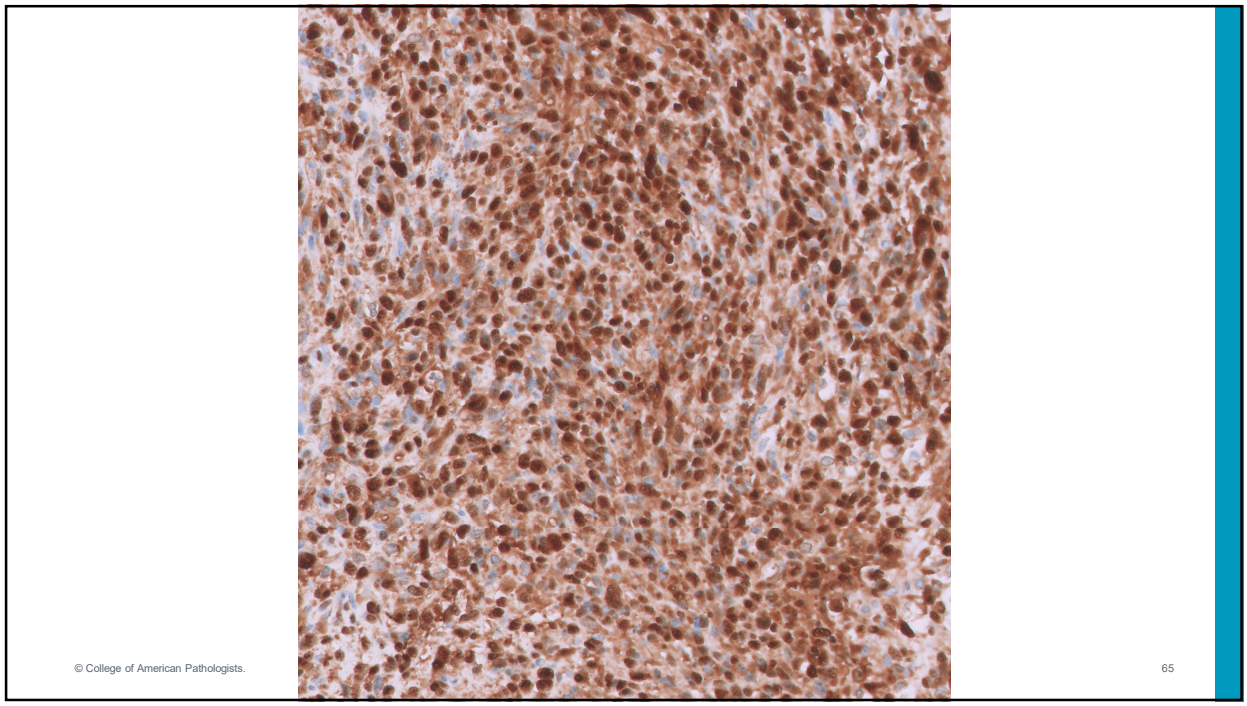
62



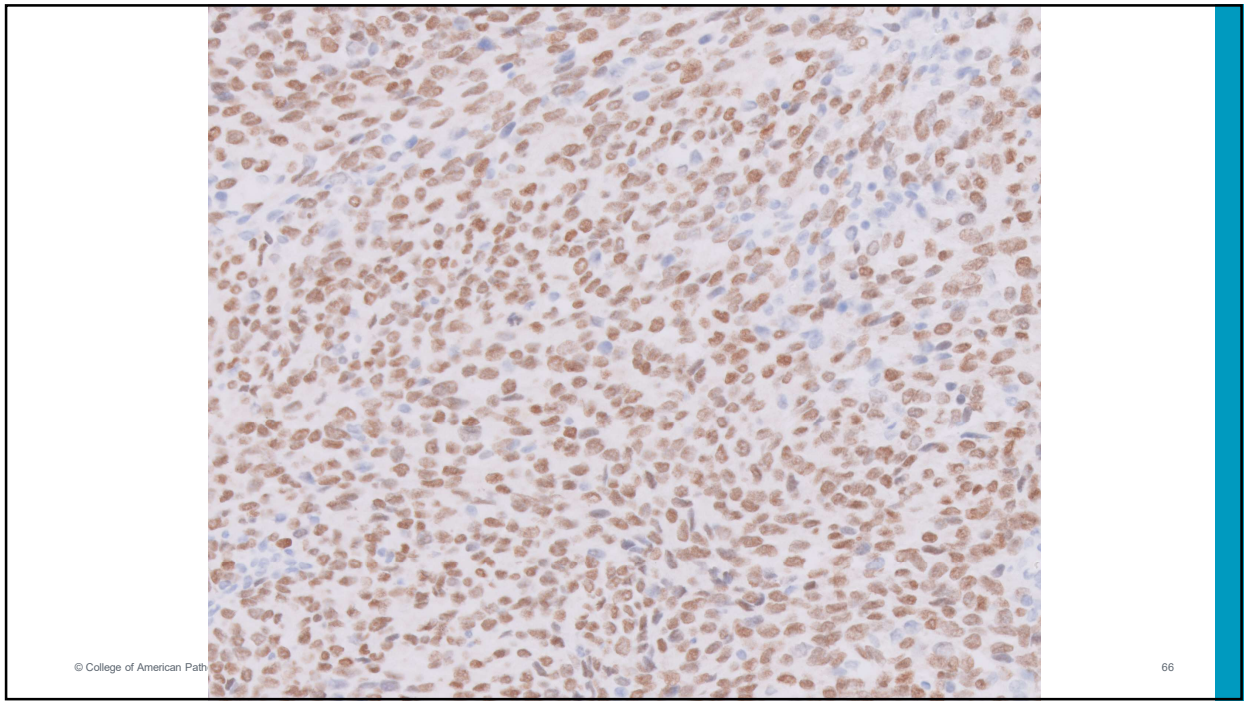
63



64



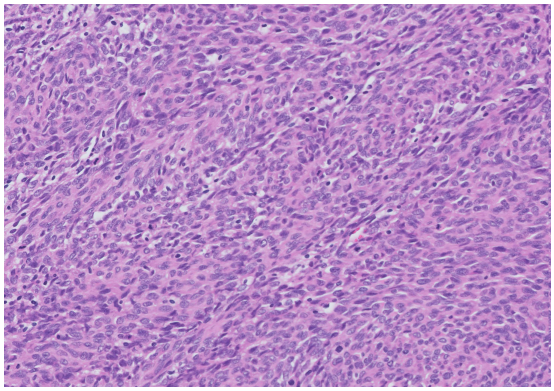
65

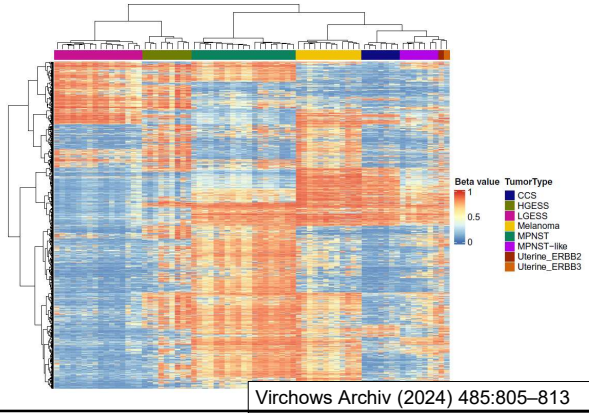


66

Evolving entity: *ERBB2*-mutated tumors (cervix)

- **S100/SOX10 + HER2 IHC variable**
- **Uncertain histogenesis, ? Sarcoma vs melanoma**



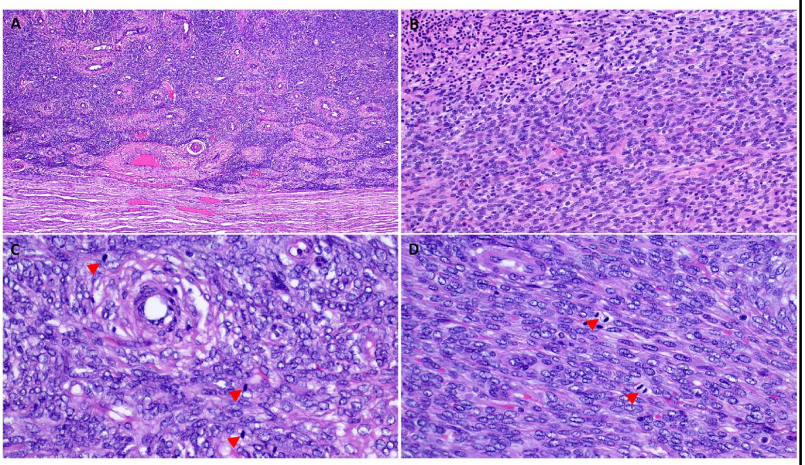


Virchows Archiv (2024) 485:805–813

67

New entity: Uterine Sarcoma with *KAT6B::KANSL1* Fusion

- **Tumor with hybrid morphologic features of endometrial stromal tumors and smooth muscle tumors**
- **May also have sex cord morphology**
- **Demonstrate both smooth muscle marker and CD10 positivity**
- **Associated with aggressive clinical behavior, despite a relatively bland histologic appearance**
  - **27% DOD at a median of 10 months**
  - **Some aggressive tumors with mitotic count of 1 per 10 HPF**

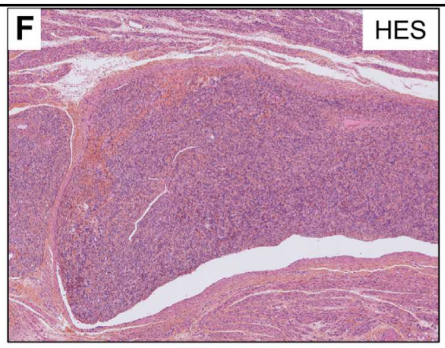


Trecourt A, et al. *Modern Pathology* (2023)
Agaimy et al. Am J Surg Pathol 2022;46:1298–1308

68

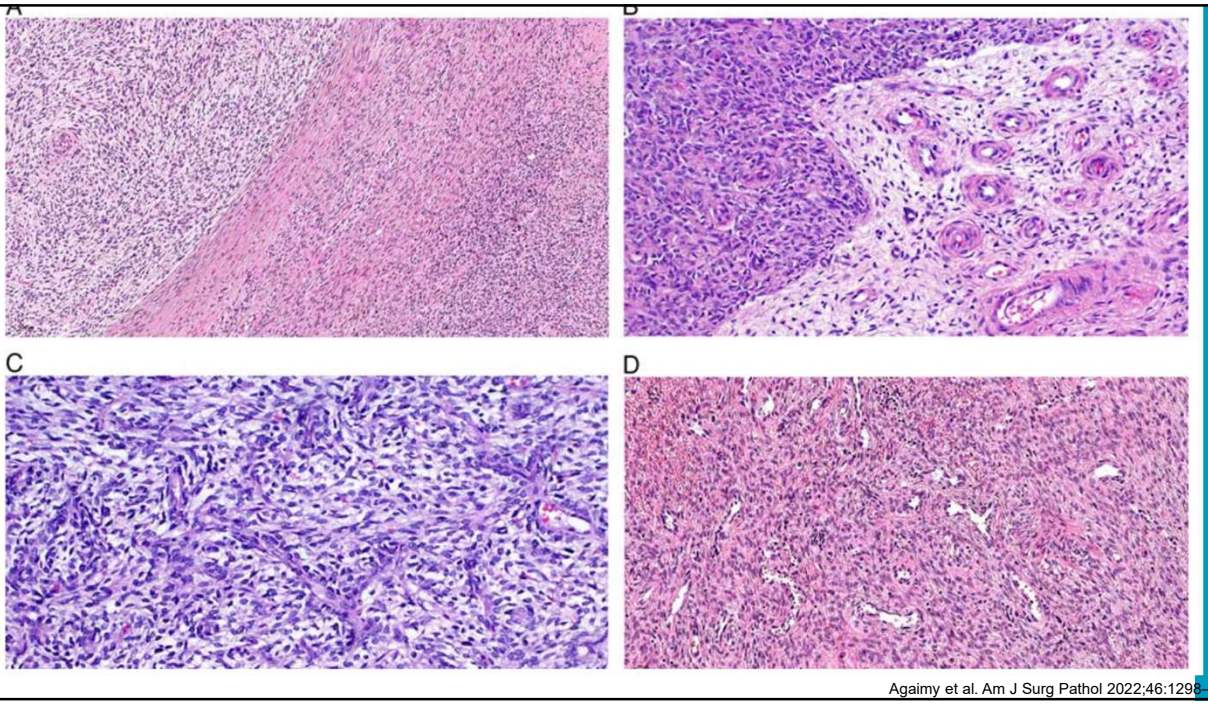
Agaimy et al. Am J Surg Pathol 2022;46:1298–1308

Some tumors bear striking morphologic resemblance to smooth muscle tumors, and multiple cases have been reported as uterine or retroperitoneal leiomyomas in the literature



Trecourt A, et al. *Modern Pathology* (2023)

69



Agaimy et al. Am J Surg Pathol 2022;46:1298–1

70

Highly variable IHC in *KAT6B::KANSL1* fusion tumors

TABLE 3. IHC Findings in *KAT6B/A::KANSL1* Fusion-positive Uterine Sarcomas

Case No.	Desmin	SMA	h-CD	CD10	Cyclin D1	ER	PR	Calretinin	Inhibin	CK	WT1
1	−	+	−	−	−	++	+++	−	−	−	−
2	−	++	−	+++	+++	+++	+++	−	−	−	−
3	−	+	−	+++	−	++	+++	−	−	−	−
4	−	−	−	+++	−	NA	NA	NA	NA	NA	NA
5	++	NA	NA	+++	NA	NA	NA	++	+	++	+++
6	−	++	−	+	−	+++	+++	NA	NA	−	NA
7	NA	NA	NA	+++	++	+++	+++	++	−	++	+
8	+	+++	+	+++	+	+++	+++	NA	NA	++	+++
9	−	+	−	+	++	−	−	NA	NA	NA	NA
10	−	++	+	+	−	−	−	NA	NA	NA	NA
11	+++	+	NA	+	NA	+++	+++	+	−	−	NA
12	−	−	−	+	−	−	−	−	NA	+	NA
13	+	+	−	+++	+	+++	+++	−	−	+	+++

+: <25%.
++: 25% to 50%.
+++: > 50%.
− indicates negative; CK, cytokeratin; ER, estrogen receptor; h-CD, h-caldesmon, NA, not available; PR, progesterone receptor; SMA, smooth muscle actin.

Agaimy et al. Am J Surg Pathol 2022;46:1298–13

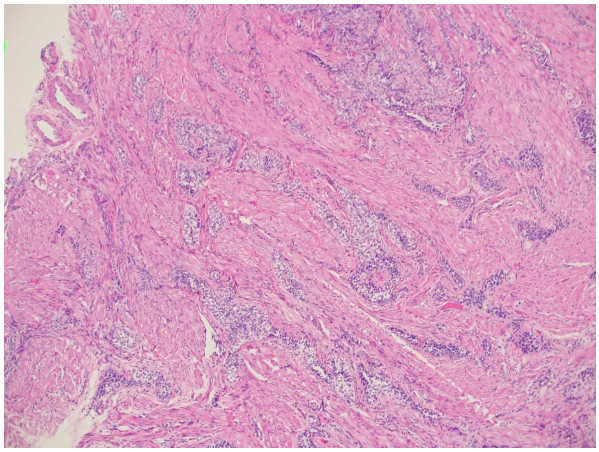
71

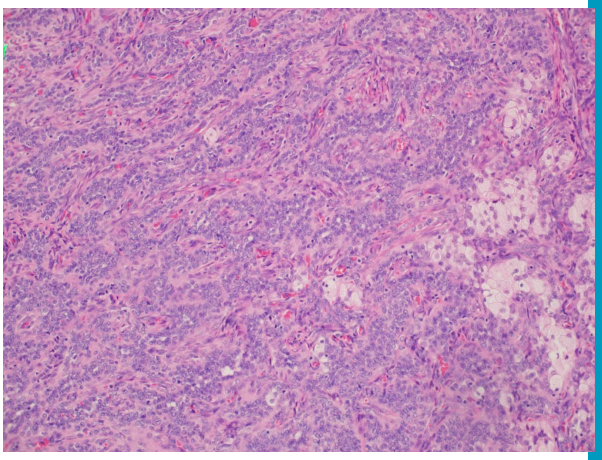
KANSL1-rearranged sarcoma: new entity, new headache

- **Distinction from LGESS:**
  - **Best done with FISH or RNAseq to identify known LGESS rearrangements/fusions**
  - **Negative ESS FISH results does not entirely exclude LGESS**
- **Distinction from cellular smooth muscle tumors can be quite challenging**
  - **No readily available assay in most labs for *KANSL1* or *KAT6A/B***
  - **Morphologic features not entirely specific**
  - **Important distinction as cellular smooth muscle tumors are benign and *KANSL1-rearranged* sarcoma often recur, some with no necrosis and few mitoses**

72

Uterine Tumor Resembling Ovarian Sex Cord Tumor (UTROSCT)





Tumor with wide variety of morphologic appearances and architectural growth patterns- both epithelioid and spindled components typically present

73

UTROSCT: Ancillary Studies

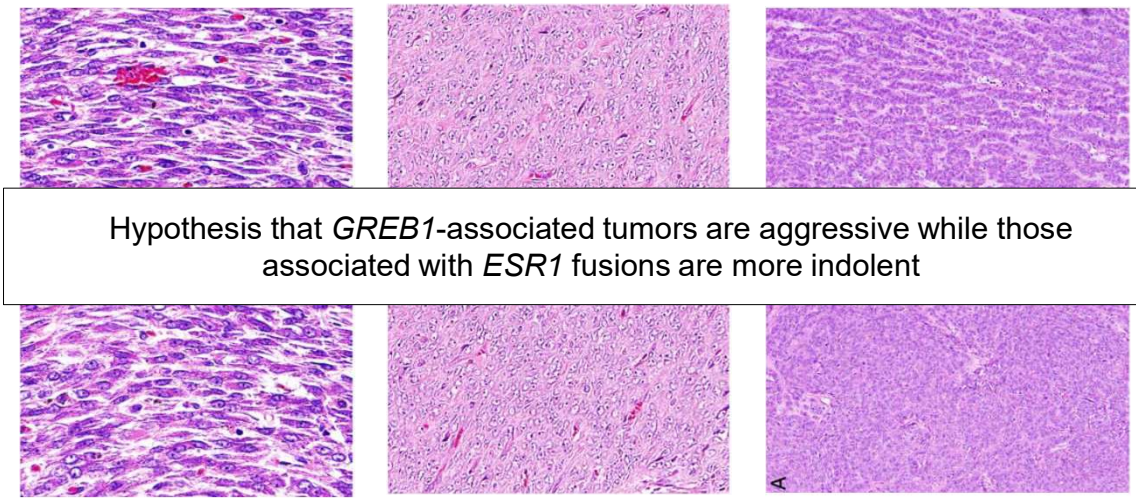
- **Immunohistochemistry:**
  - **(+/-): SF-1, calretinin, inhibin, keratins, smooth muscle, HMB-45/melanA**
  - **All quite variable within and between tumors**
  - **CD10 should NOT be significantly positive in these tumors!**

- **Molecular features of UTROSCT**
  - ***ESR1::NCOA3***
  - ***ESR1::NCOA2***
  - ***GTF2A1::NCOA2***
  - ***…***

- *GREB1::NCOA2*
- *GREB1::NCOA1*
- *GREB1::CTNNB1*
- *GREB1::SS18*
- *GREB1::NR4A3*

74

GREB1-rearranged UTROSCT



Hypothesis that *GREB1*-associated tumors are aggressive while those associated with *ESR1* fusions are more indolent

Kao YC, Lee JC. Genes Chromosomes Cancer. 2021 Mar;60(3):180-189.

75

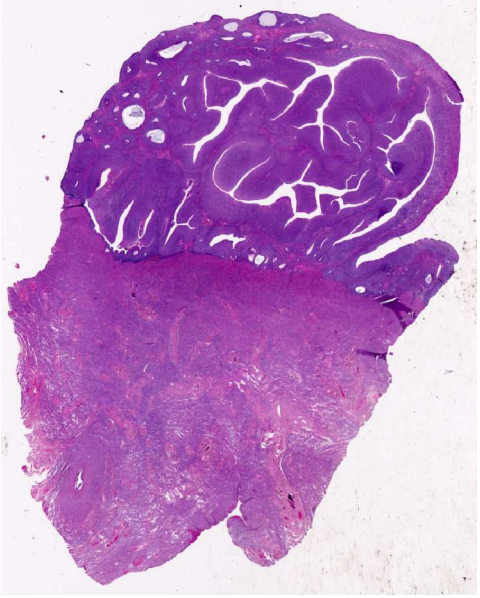
Can we recognize *GREB1* vs *ESR1* tumors without molecular testing?

ESR1-rearranged "UTROSCT"	*GREB1*-rearranged tumors
• More likely to have overt sex cord differentiation by morphology and IHC	• May have less obvious or more poorly developed sex cord morphology
• Postmenopausal	• May be less likely to have significant sex cord IHC positivity
• Molecular not always needed for diagnosis	• Usually younger women (premenopausal)
	• Molecular usually needed for diagnosis

76

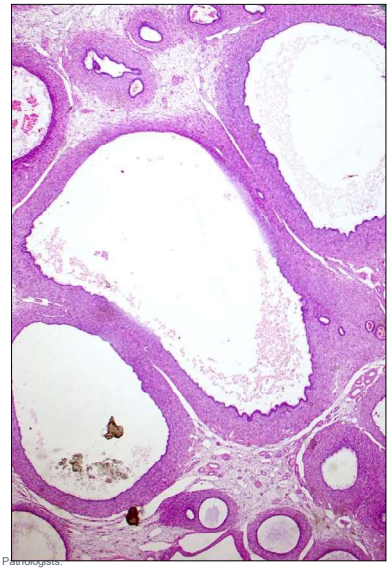
Adenosarcoma

- **Microscopic Features:**
  - **Broad, leaf-like architecture reminiscent of phyllodes tumors of the breast**
  - **“rigid” cysts**
  - **Periglandular cuffing of malignant stroma around benign-appearing glands, with sub-epithelial condensation**
  - **Stromal cytologic atypia**
  - **Stromal mitotic activity ≥ 2 per 10 HPFs**

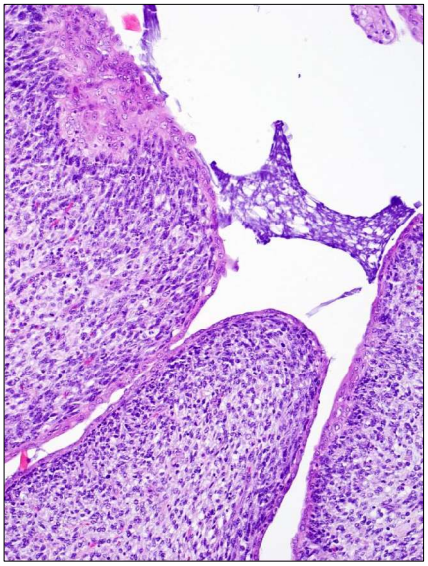


77

Rigid cysts



Cambium layer



78

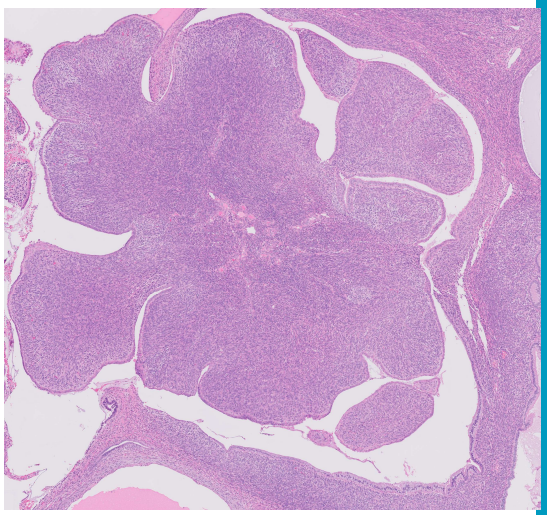
Adenosarcoma

- **Pathologic Features:**
  - **Sarcomatous overgrowth (SO):**
    - **>25% of the tumor is composed of sarcoma without any associated epithelial component**
  - **Heterologous elements:**
    - **Present in ~1/4 of MASO**
    - **Rhabdomyosarcoma (DOES count as sarcomatous overgrowth)**
    - **Sex cord elements (** does NOT count as sarcomatous overgrowth)**

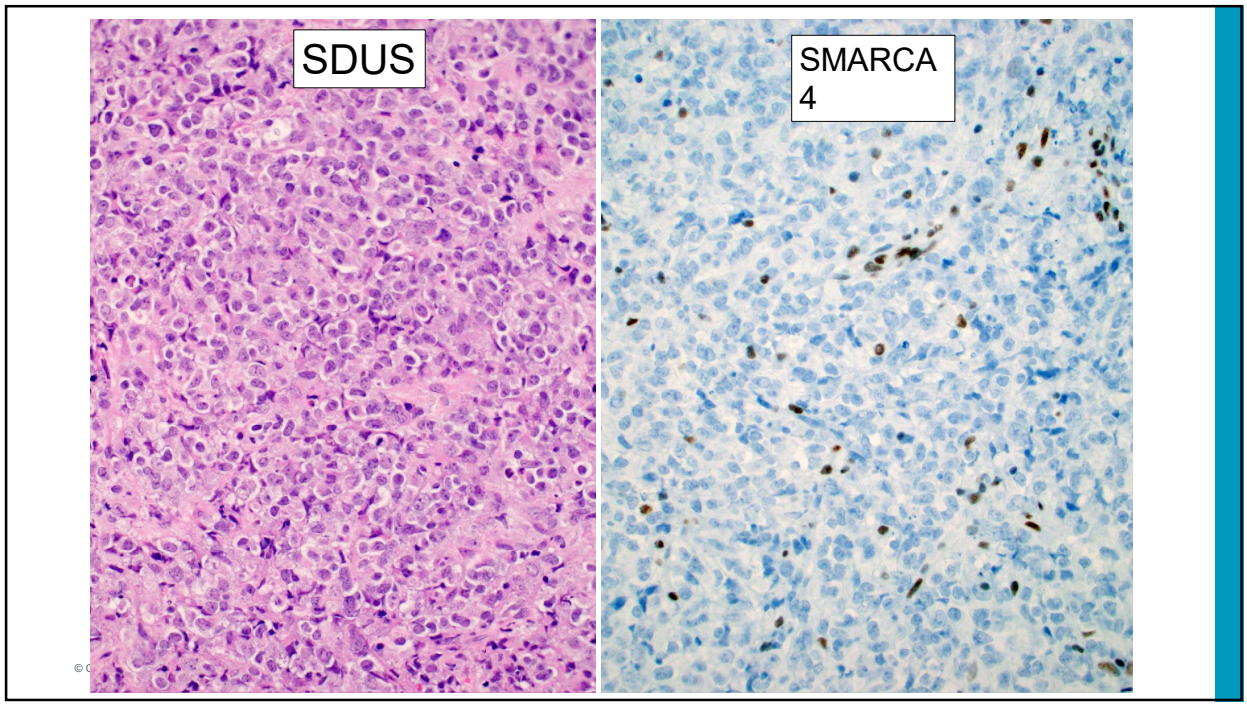
79

Adenosarcoma

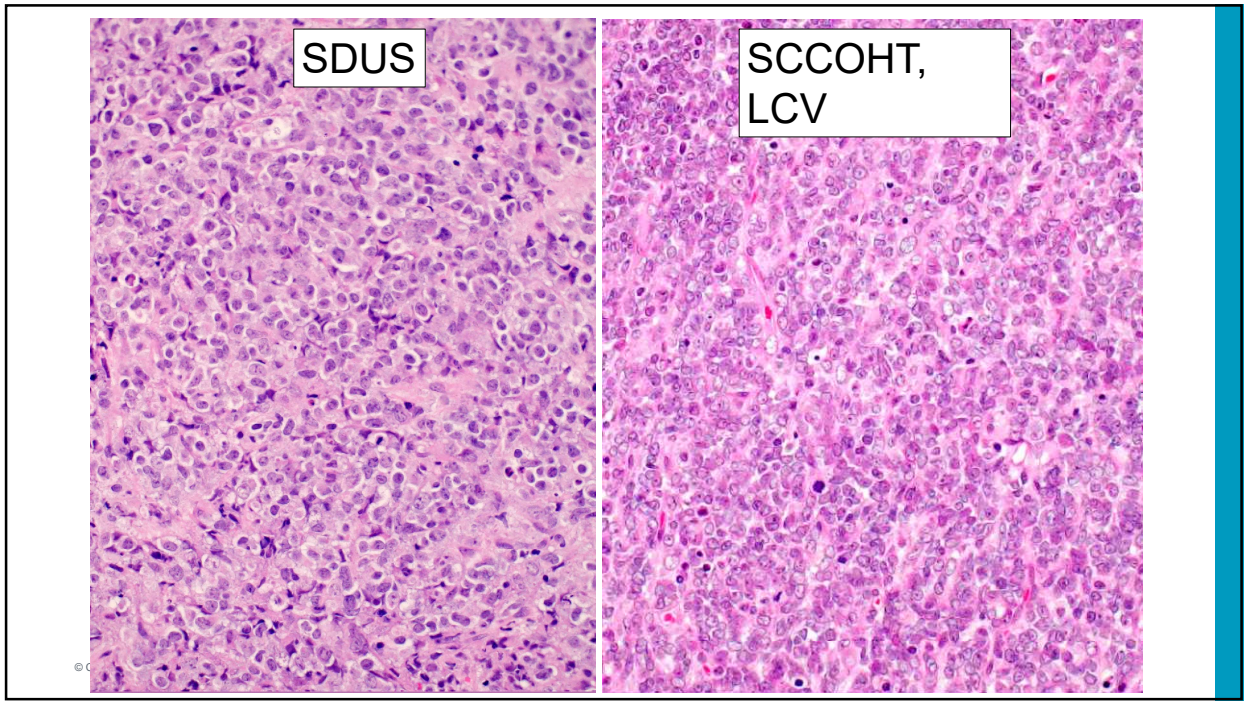
- **Biphasic tumor demonstrating overlapping features with a variety of tumors:**
  - ***NTRK*-sarcoma**
  - **UTROSCT (NCOA fusions)**
  - **Embryonal rhabdomyosarcoma (*DICER1* mutations)**
  - **BCOR-HGESS**
  - **SDUS**



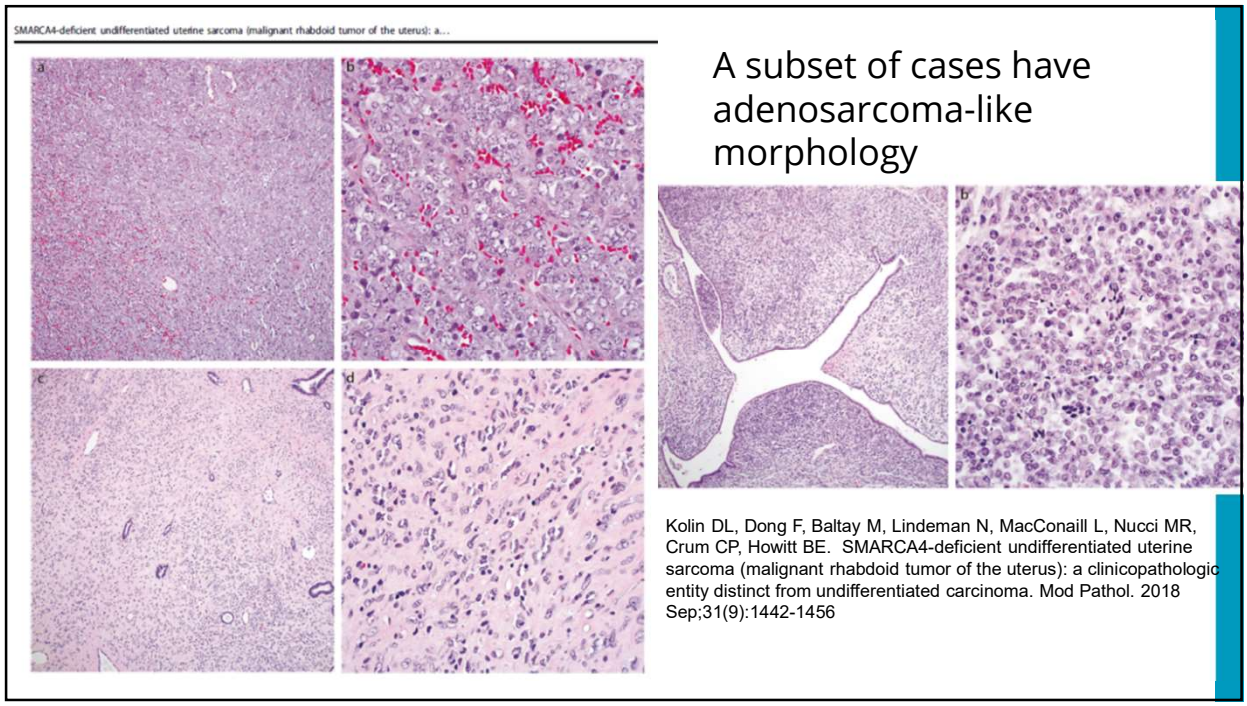
80



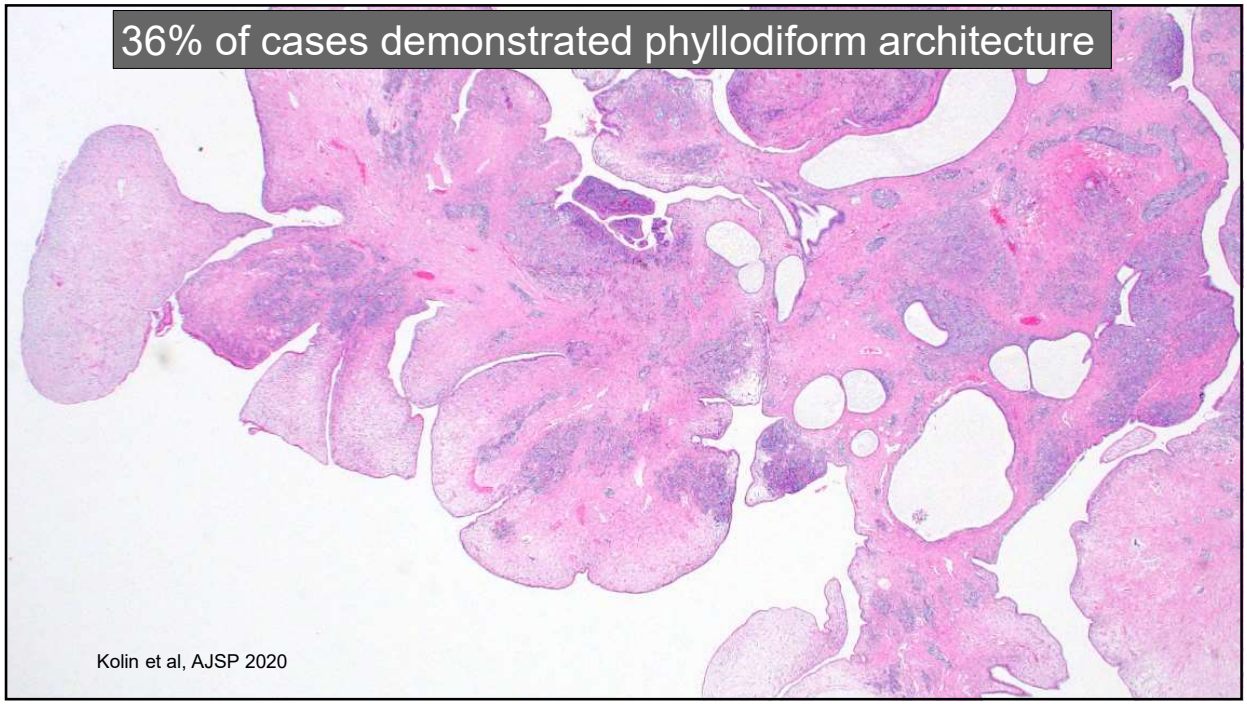
81



82



83



84

SMARC-deficient uterine sarcoma (SDUS)

- Previous reports of "malignant rhabdoid tumor of uterus"
- *SMARCA4* mutations (loss of SMARCA4 IHC) with few other genomic alterations
  - No *PTEN*, *KRAS*, *PIK3CA*, *TP53*, *CTNNB1* mutations or MSI
- Young patients (~20s-40s, occasionally older), aggressive course (<1 yr survival)
- Morphologic, immunohistochemical, molecular similarities to the large cell variant of small cell carcinoma of the ovary, hypercalcemic type (some cases have classical small cell morphology)
  - Rare keratin, EMA, focal ER, may have some CD10
  - May be WT-1 positive
- May be associated with germline mutation, so important to recognize
  - Vast majority involve *SMARCA4*; one case has had *SMARCB1* alteration and IHC loss

85

Summary

- Endometrial stromal neoplasms may be divided into:
  - Low grade endometrial stromal tumors (JAZF1/PHF1/etc)
  - High-grade ESS with *YWHAE* rearrangement
  - High-grade ESS with *BCOR* alterations (rearrangement or ITD)
  - Unclear where *KANSL1*-rearranged sarcomas fit
- A panel of IHC, sometimes supplemented with molecular studies, can generally classify stromal neoplasms and distinguish them from morphologic mimics

86

Summary: IHC

- **CD10 positivity does not indicate LGESS**
  - **Smooth muscle tumors, HGESS, NTRK-sarcoma, and adenosarcoma also CD10+**
- **KANSL1-fusi… …se without molecular co…**
- **NTRK-sarcor…**
  - **Pan-trk IHC is n…**
- **S100 and CD34 may be helpful as part of panel**
  - ***NTRK* sarcomas CD10+, CD34/S100 +**
  - ***ERBB2* mutated tumors S100/SOX10 +**

Virtually all workup of uterine mesenchymal tumors requires a PANEL of IHC markers

87

Summary: Molecular

- **Molecular confirmation in the setting of unusual morphology or immunophenotype, as well as high stage/recurrent tumors**
- **Recognition of the other "flavor" of HGESS (BCOR) has significantly broadened ddx**
  - **Myxoid LMS**
  - **NTRK-sarcoma**
  - **Adenosarcoma**
- **BCOR ITD HGESS will be negative via FISH assays, but may be detectable via NGS**
- **LGESS vs HGESS based on morphology vs molecular status remains somewhat controversial**
  - **I tend to classify based on molecular status when ambiguous**

88

Questions?

89

COLLEGE of AMERICAN PATHOLOGISTS

90