Pathology of Gynecological Cancers Associated With Inherited Cancer Susceptibility Syndromes

Karuna Garg MD

University of California San Francisco

UCSF
University of California
San Francisco

Inherited Cancer Susceptibility Syndromes

- No less than 10% of cancers are hereditary
- Numbers increasing

- Important to recognize:
- For patient and family members
- Risk of multiple tumors
- Ability to implement surveillance measures
- Prophylactic surgery
- Prognostic and therapeutic implications

Detection of familial syndromes

Role of the clinician:

Clinical history:

- Patient age
- Personal history
- Family history
- Ethnic background

Drawbacks:

- Clinician dependent
- Limited sensitivity

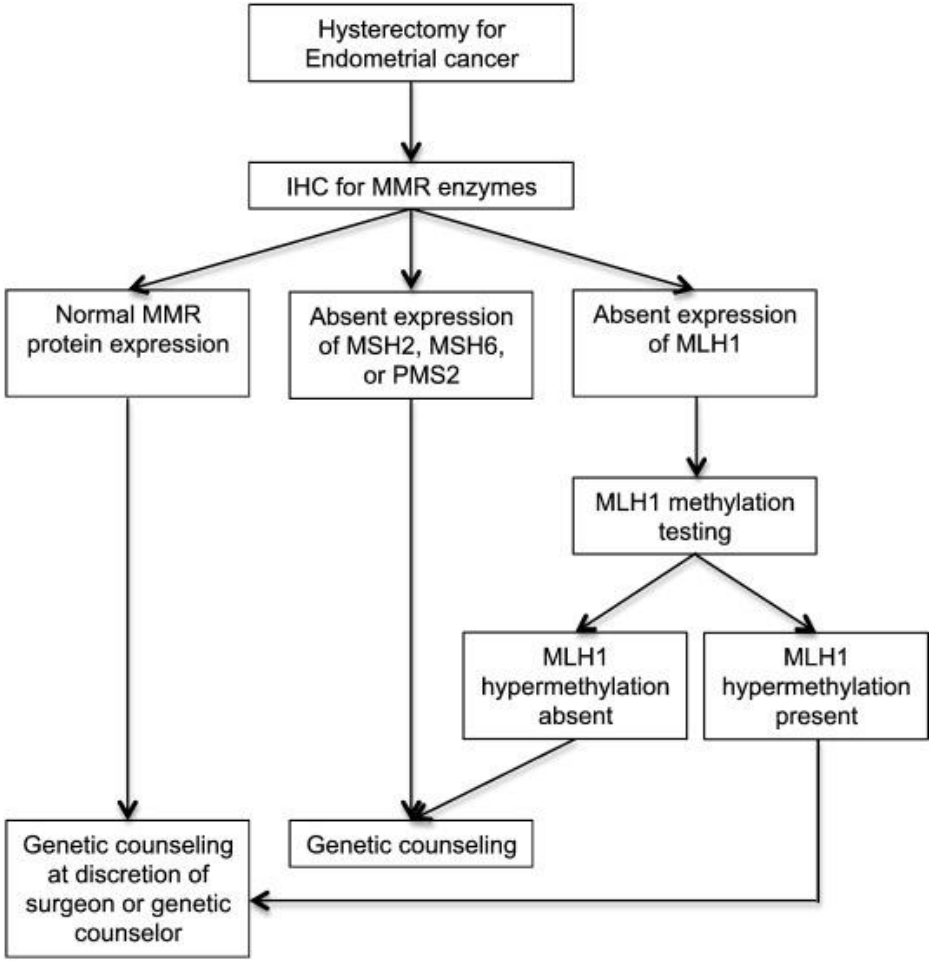
Detection of familial syndromes

Role of the pathologist?

Detection of familial syndromes

Role of the pathologist:

By performing ancillary studies such as MMR IHC with specific screening value



Detecting a familial syndrome

Role of the pathologist:

By recognizing and drawing attention to the association between tumor types or histologic features and predisposition syndromes

- **Uncommon tumor linked to familial syndrome**

- **Common tumor (with specific features) linked to familial syndrome**

- **Combination of multiple tumors (synchronous or metachronous) linked to familial syndrome**

Inherited Cancer Susceptibility Syndromes associated with gynecologic cancers

Syndrome	Responsible gene(s)	Uterus	Ovary	Other
Lynch syndrome	*MLH1, PMS2, MSH2, MSH6*	Endometrial carcinoma	Ovarian carcinoma	Colorectal
Hereditary breast and ovarian cancer syndrome	*BRCA1, BRCA2*, others	?Serous carcinoma	High-grade serous carcinoma	Breast
Cowden syndrome	*PTEN*	Endometrial carcinoma	-	Breast, thyroid
Peutz Jegher syndrome (PJS)	*STK11*	Cervix – Gastric type mucinous carcinoma	SCTAT	
Tuberous Sclerosis complex (TSC)	*TSC1/TSC2*	PEComa family of tumors	-	
DICER1 syndrome	*DICER1*	Cervix – embryonal rhabdomyosarcoma	Sertoli-Leydig cell tumor	Pleuropulmonary blastoma, many others
Rhabdoid tumor predisposition syndrome 2 (RTPS2)	*SMARCA4*	-	Small cell carcinoma, hypercalcemic type	Rhabdoid tumor, sarcomas
Hereditary leiomyomatosis and Renal Cell carcinoma syndrome (HLRCC)	*Fumarate hydratase (FH)*	Leiomyomas	-	Cutaneous leiomyomas, Renal cell carcinoma

Inherited Cancer Susceptibility Syndromes associated with gynecologic cancers

Syndrome	Responsible gene(s)	Uterus	Ovary	Other
Lynch syndrome	*MLH1, PMS2, MSH2, MSH6*	Endometrial carcinoma	Ovarian carcinoma	Colorectal
Hereditary breast and ovarian cancer syndrome	*BRCA1, BRCA2*, others	?Serous carcinoma	High-grade serous carcinoma	Breast
Cowden syndrome	*PTEN*	Endometrial carcinoma	-	Breast, thyroid
Peutz Jegher syndrome (PJS)	*STK11*	Cervix – Gastric type mucinous carcinoma	SCTAT	
Tuberous Sclerosis complex (TSC)	*TSC1/TSC2*	PEComa family of tumors	-	
DICER1 syndrome	*DICER1*	Cervix – embryonal rhabdomyosarcoma	Sertoli-Leydig cell tumor	Pleuropulmonary blastoma, many others
Rhabdoid tumor predisposition syndrome 2 (RTPS2)	*SMARCA4*	-	Small cell carcinoma, hypercalcemic type	Rhabdoid tumor, sarcomas
Hereditary leiomyomatosis and Renal Cell carcinoma syndrome (HLRCC)	*Fumarate hydratase (FH)*	Leiomyomas	-	Cutaneous leiomyomas, Renal cell carcinoma

Well recognized

Inherited Cancer Susceptibility Syndromes associated with gynecologic cancers

Syndrome	Responsible gene(s)	Uterus	Ovary	Others
Lynch syndrome	*MLH1, PMS2, MSH2, MSH6*	Endometrial carcinoma	Ovarian carcinoma	Colorectal
Hereditary breast and ovarian cancer syndrome	*BRCA1, BRCA2*, others	?Serous carcinoma	High-grade serous carcinoma	Breast
Cowden syndrome	*PTEN*	Endometrial carcinoma	-	Breast, thyroid
Peutz Jegher syndrome (PJS)	*STK11*	Cervix – Gastric type mucinous carcinoma	SCTAT	
Tuberous Sclerosis complex (TSC)	*TSC1/TSC2*	PEComa family of tumors	-	
DICER1 syndrome	*DICER1*	Cervix – embryonal [illegible]	Sertoli-Leydig cell [illegible]	Pleuropulmonary blastoma, many others
Rhabdoid tumor predisposition syndrome 2 (RTPS2)	*SMARCA4*	-	Small cell carcinoma, hypercalcemic type	Rhabdoid tumor, sarcomas
Hereditary leiomyomatosis and Renal Cell carcinoma syndrome (HLRCC)	*Fumarate hydratase (FH)*	Leiomyomas	-	Renal cell carcinoma

Relatively well recognized syndromic associations

Inherited Cancer Susceptibility Syndromes associated with gynecologic cancers

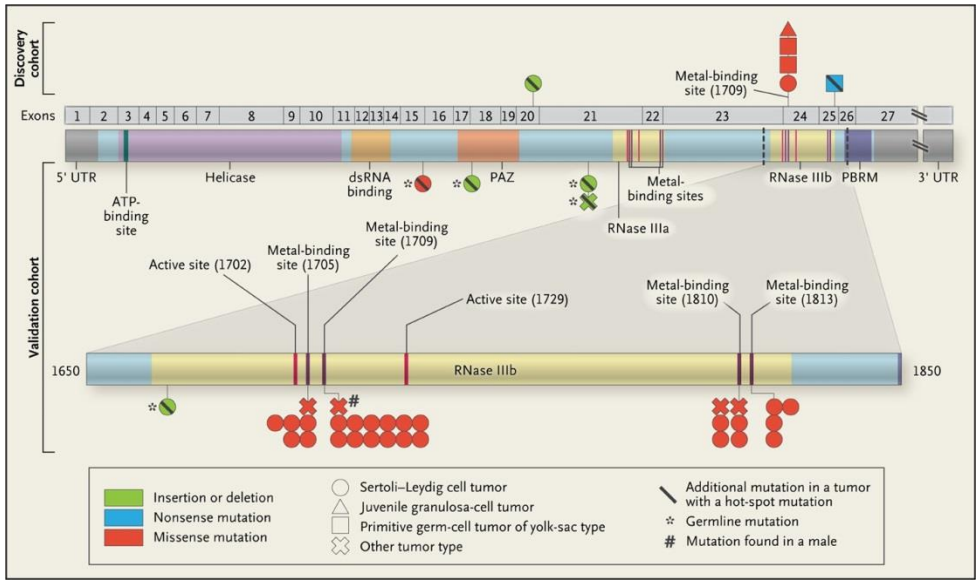
Syndrome	Responsible gene(s)	Uterus	Ovary	Others
Lynch syndrome	*MLH1, PMS2, MSH2, MSH6*	Endometrial carcinoma	Ovarian carcinoma	Colorectal
Hereditary breast and ovarian cancer syndrome	*BRCA1, BRCA2*, others	?Serous carcinoma	High-grade serous carcinoma	Breast
Cowden syndrome	*PTEN*	Endometrial carcinoma		Breast, thyroid
Peutz Jegher syndrome (PJS)	*STK11*	Cervix – Gastric type mucinous carcinoma	SCTAT	
Tuberous Sclerosis complex (TSC)	*TSC1/TSC2*	PEComa family of tumors		
DICER1 syndrome	*DICER1*	Cervix – embryonal rhabdomyosarcoma	Sertoli-Leydig cell tumor	Pleuropulmonary blastoma, many others
Rhabdoid tumor predisposition syndrome 2 (RTPS2)	*SMARCA4*	-	Small cell carcinoma, hypercalcemic type	Rhabdoid tumor, sarcomas
Hereditary leiomyomatosis and Renal Cell carcinoma syndrome (HLRCC)	*Fumarate hydratase (FH)*	Leiomyomas	-	Renal cell carcinoma

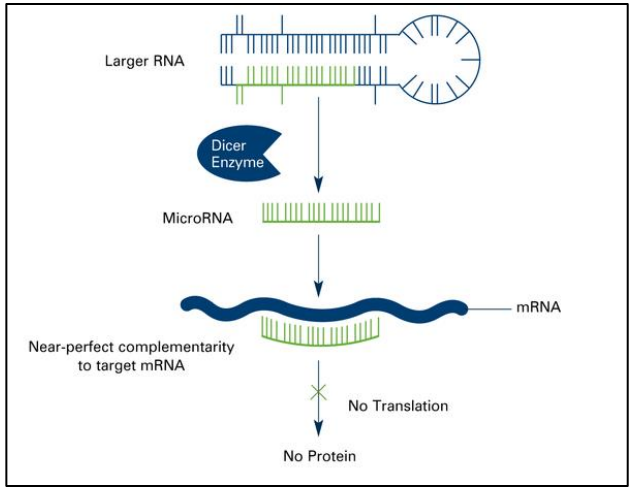
Recently described
Not well known

DICER1 syndrome

DICER1 syndrome

- *DICER1* critical for processing of microRNA
- Germline loss-of-function *DICER1* mutation
- Second hit in the form of a specific missense mutation in the RNase IIIb domain





DICER1 syndrome

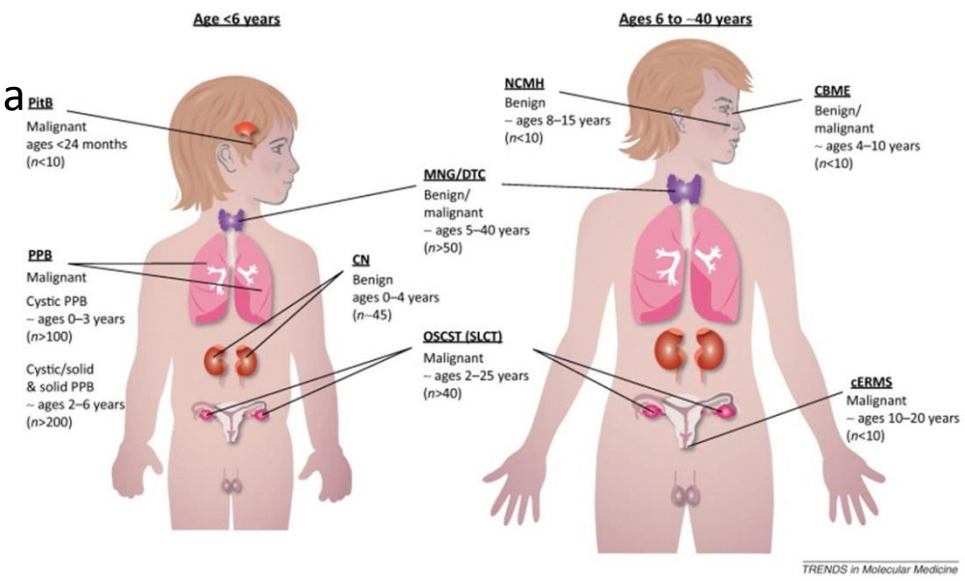
DICER-1 pleuropulmonary blastoma familial tumor predisposition syndrome

- Pleuropulmonary blastoma
- Cystic nephroma
- Multinodular goiter and thyroid carcinoma
- Pituitary blastoma
- Nasal chondromesenchymal hamartoma
- Ciliary body medulloepithelioma
- Renal sarcoma and Wilms tumor

- **Gynecologic tumors:**

1. Ovarian sex cord stromal tumors

2. Embryonal rhabdomyosarcoma of the cervix



DICER1: Ovarian sex cord stromal tumors

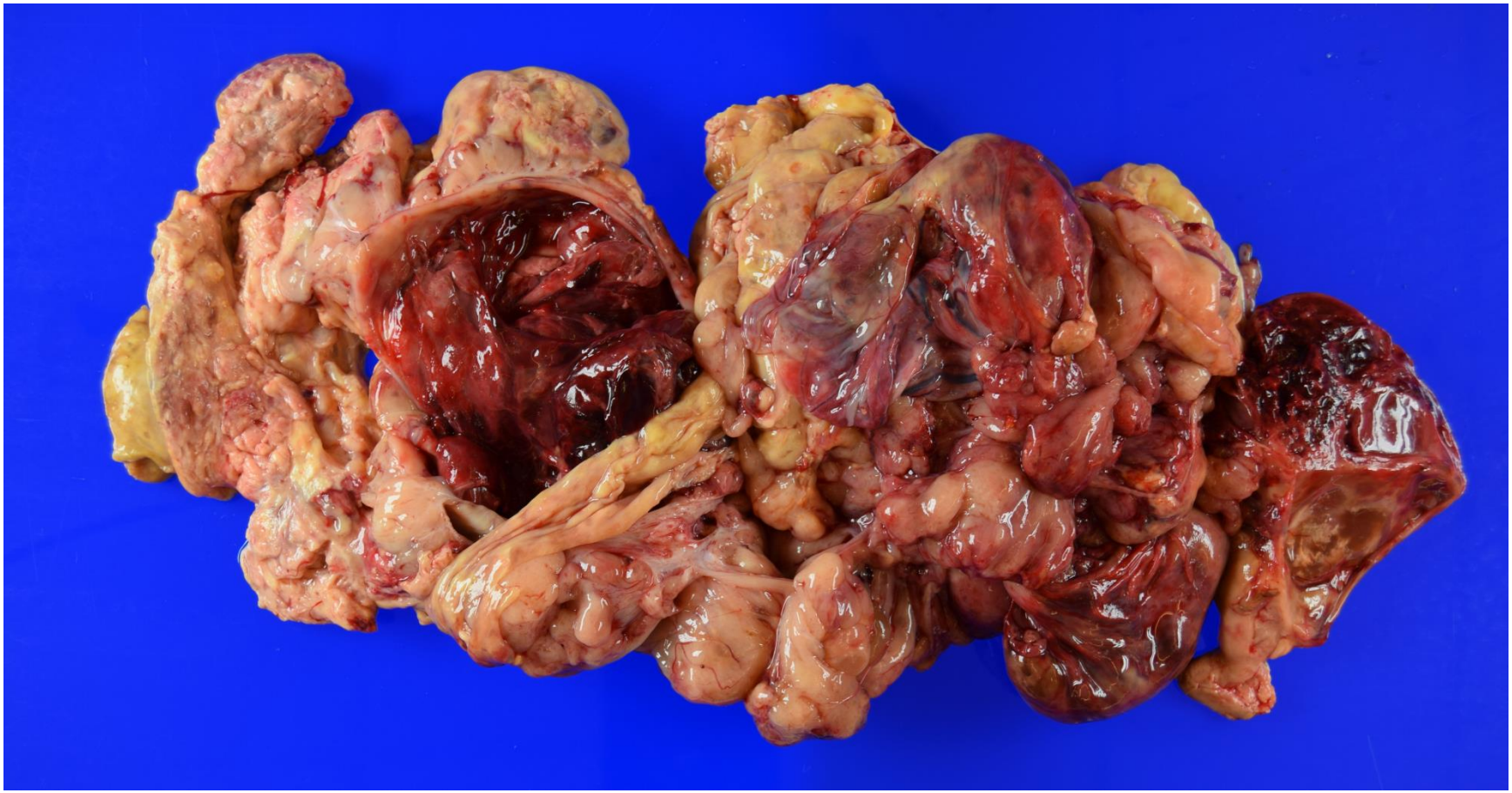
- **Sertoli-Leydig cell tumor (SLCT)**

- Juvenile granulosa cell tumor
- Gynandroblastoma
- Unclassified SCST
- Sertoli cell tumor

Sertoli-Leydig cell tumor

- <0.5% of all ovarian tumors
- Young women (2^{nd}-3^{rd} decade)
- Ovarian mass or virilization symptoms
- Most are stage 1
- Occasionally bilateral
- Generally favorable prognosis (>85% benign)
- Moderate to poorly differentiated tumors (heterologous elements) can have malignant behavior

Sertoli-Leydig cell tumor: Gross

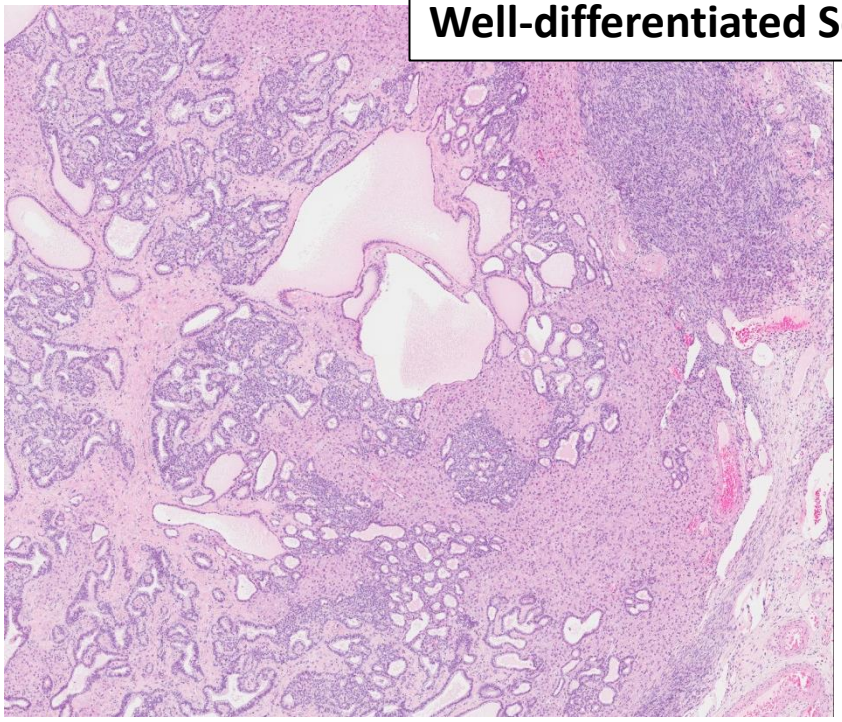


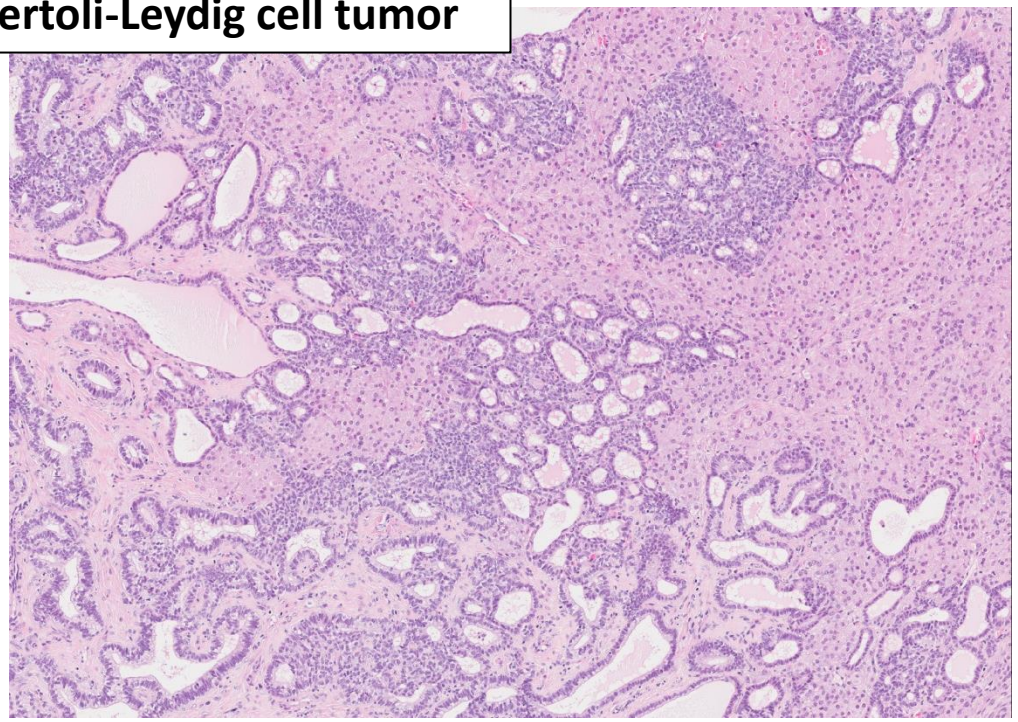
Sertoli-Leydig cell tumor

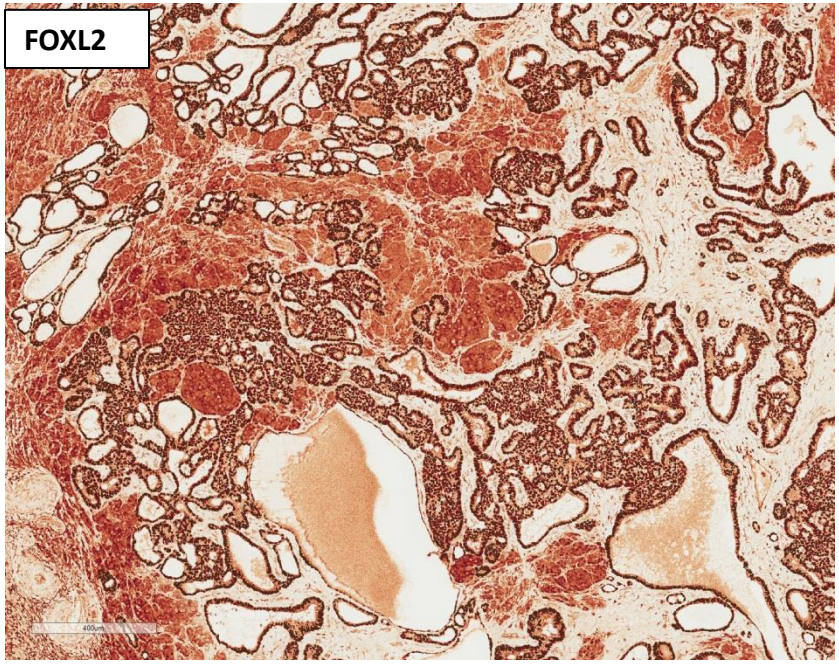
- Sertoli cells and Leydig cells
- Well-differentiated (10%)
- Moderately differentiated (50%)
- Poorly differentiated (35%)

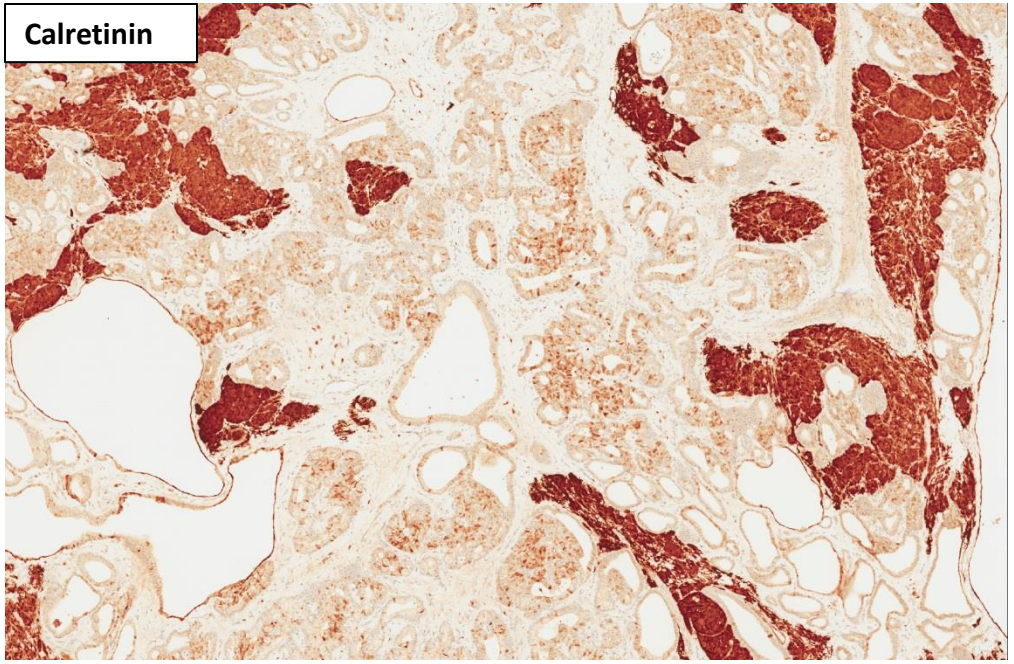
- Can have heterologous elements
- Can have retiform components

Well-differentiated Sertoli-Leydig cell tumor

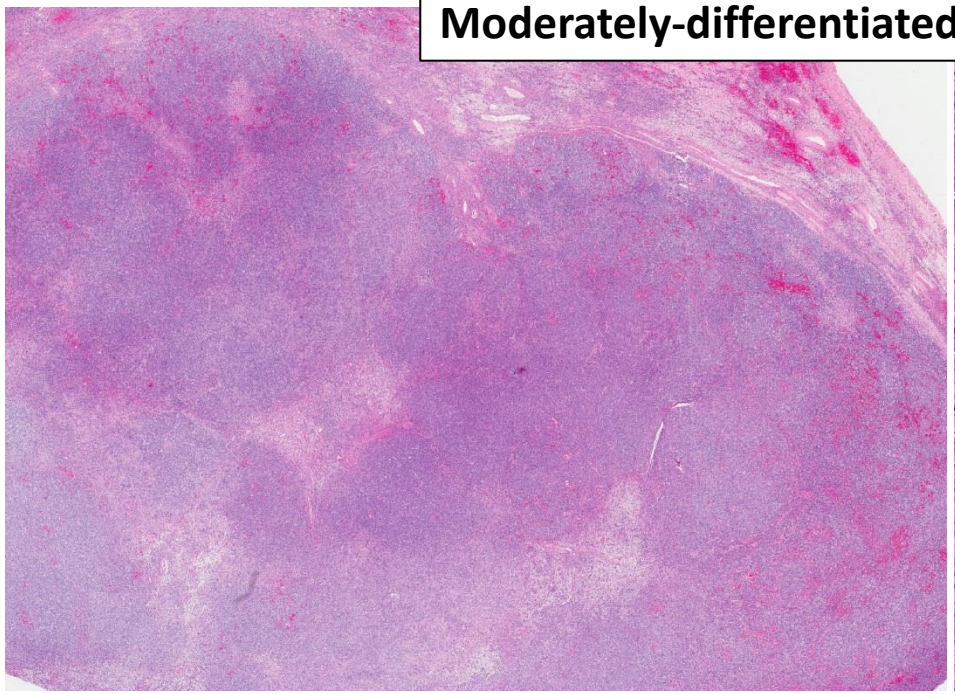


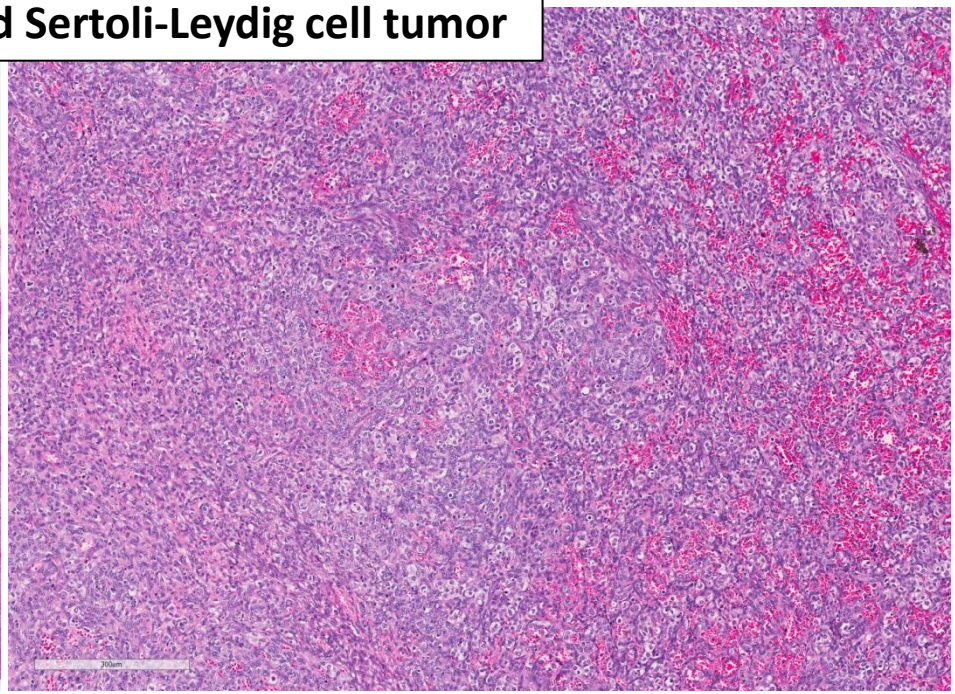




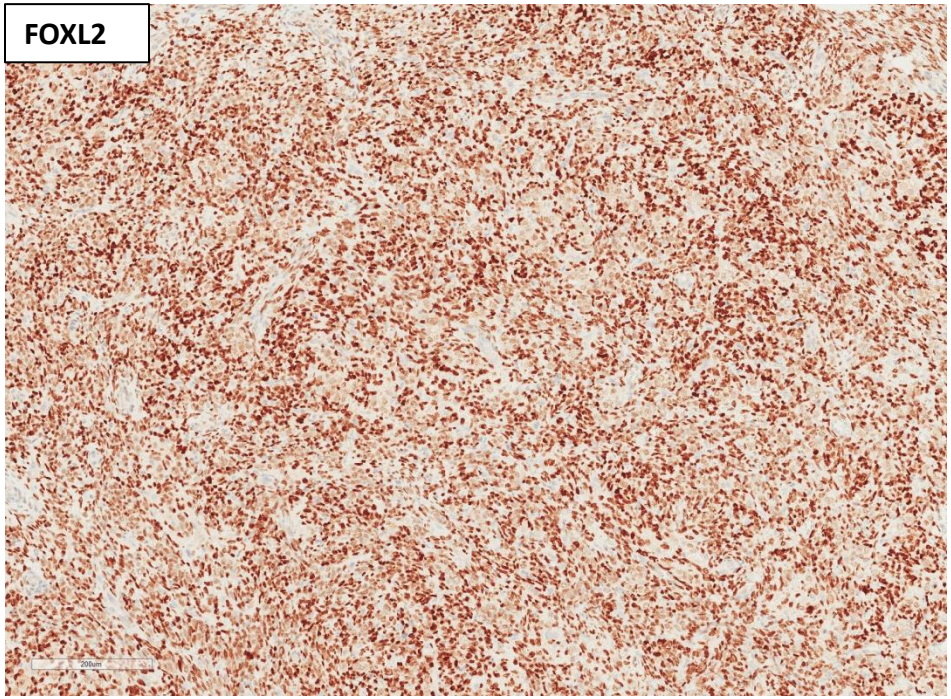


Moderately-differentiated Sertoli-Leydig cell tumor

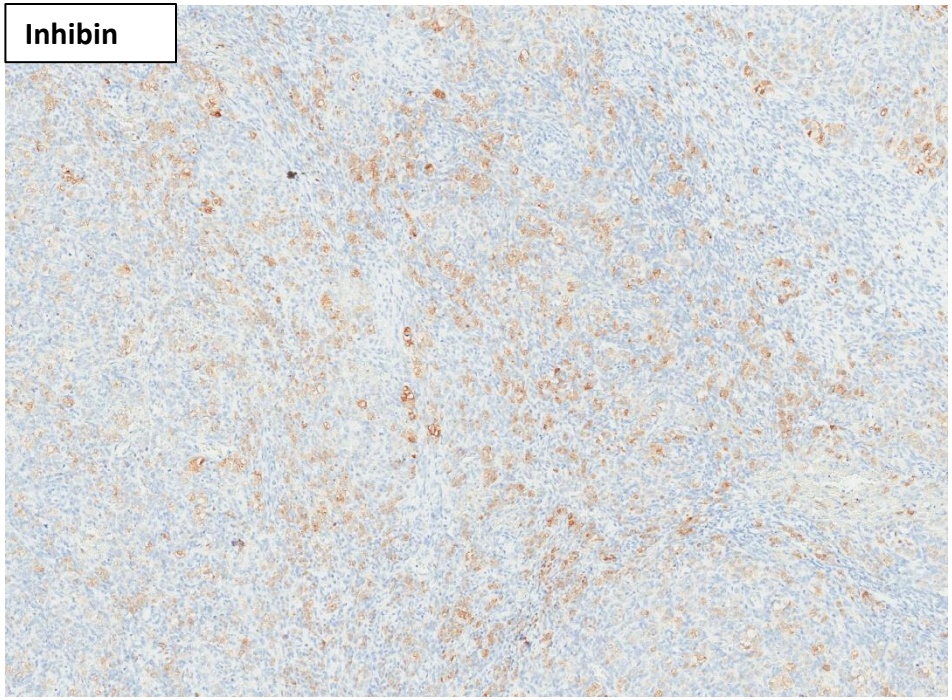




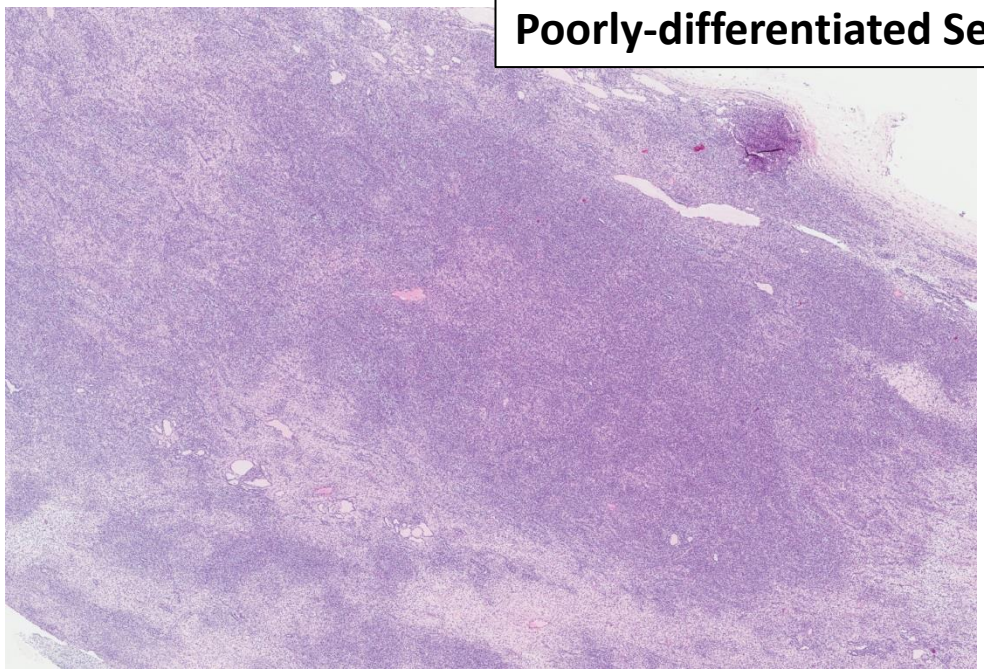
FOXL2

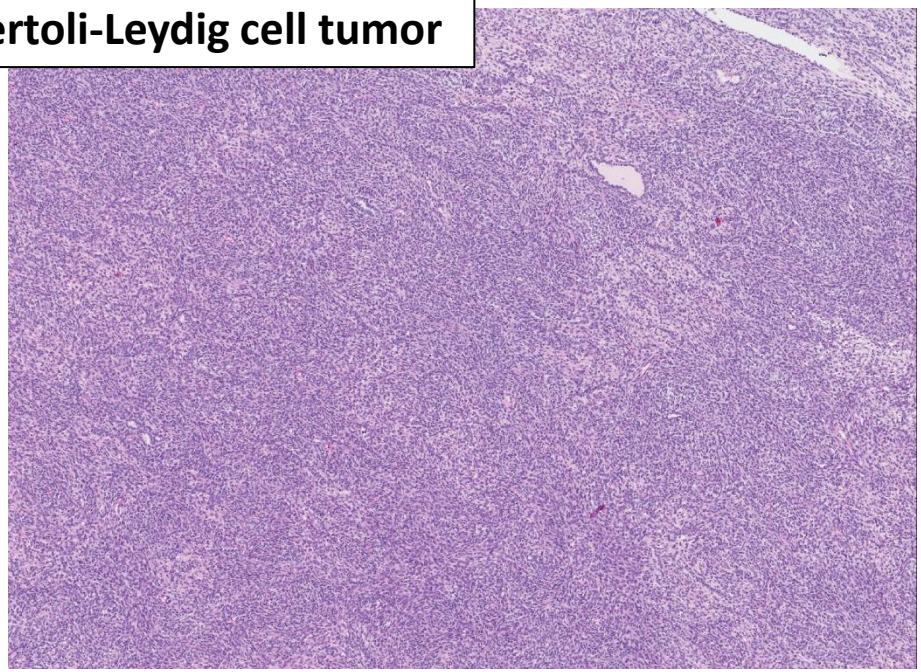


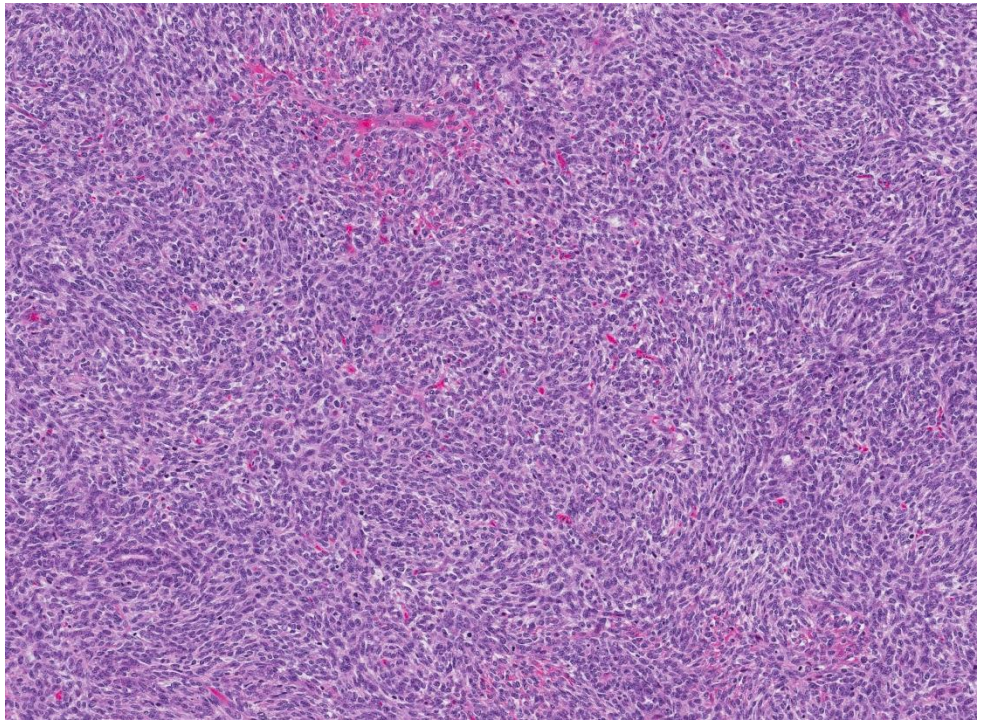
Inhibin

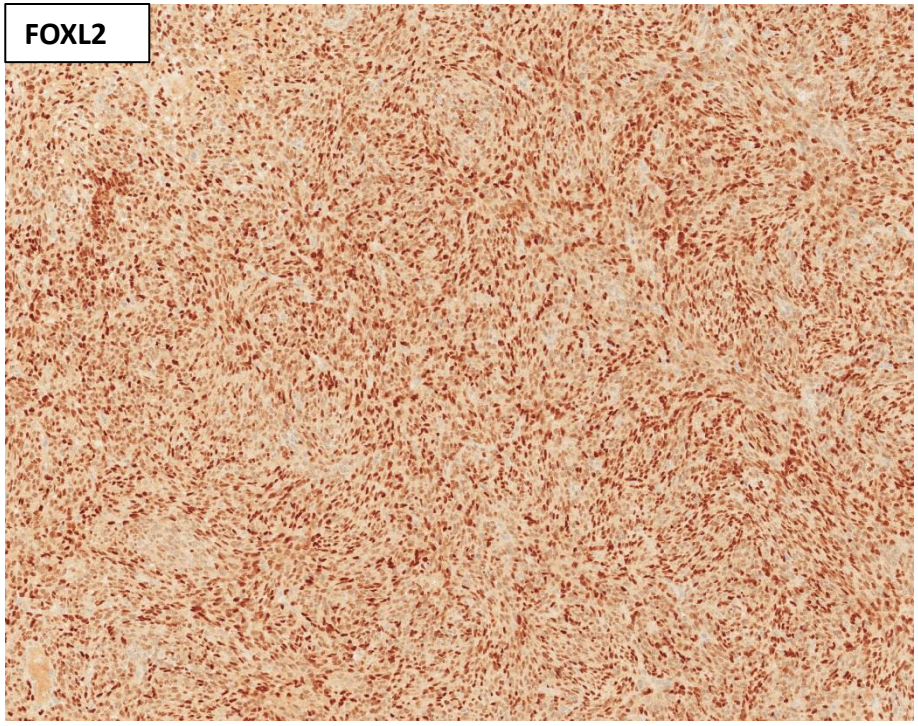


Poorly-differentiated Sertoli-Leydig cell tumor

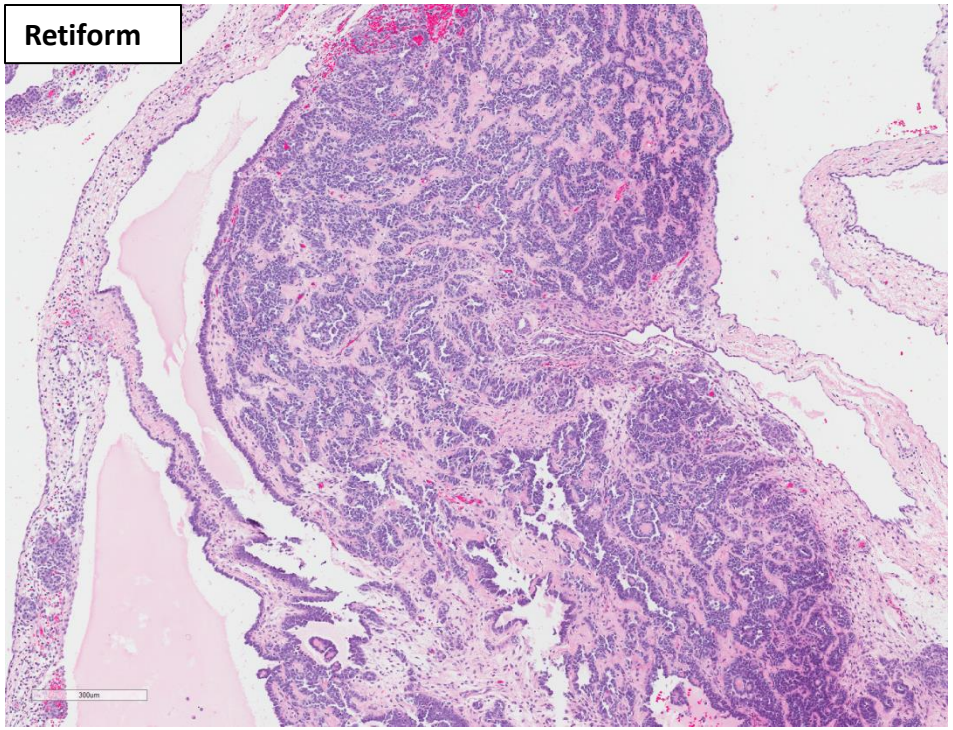




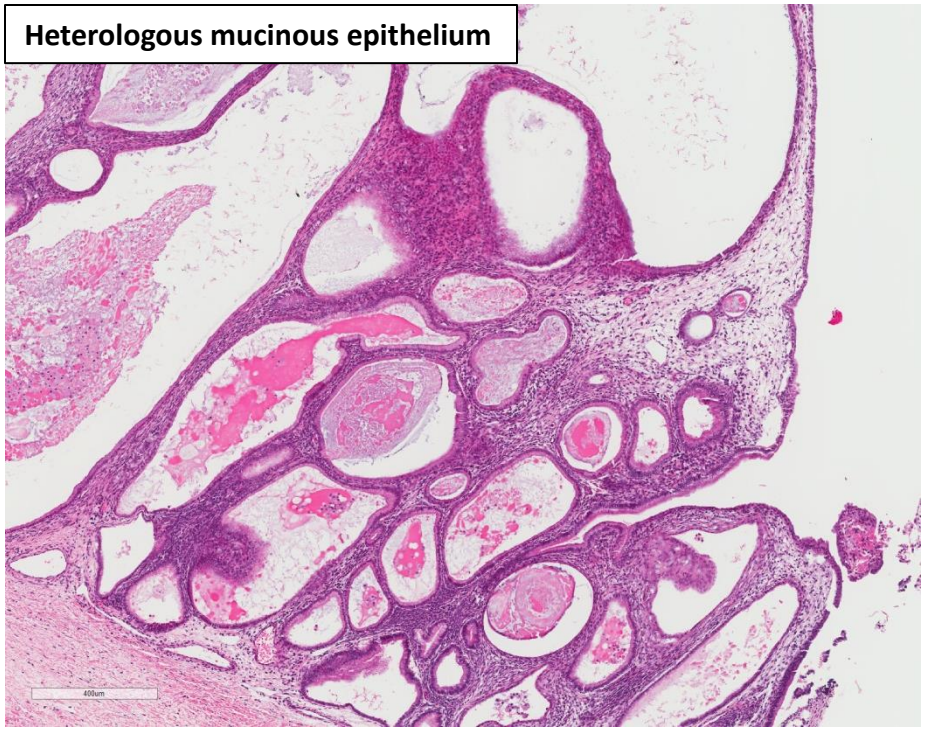




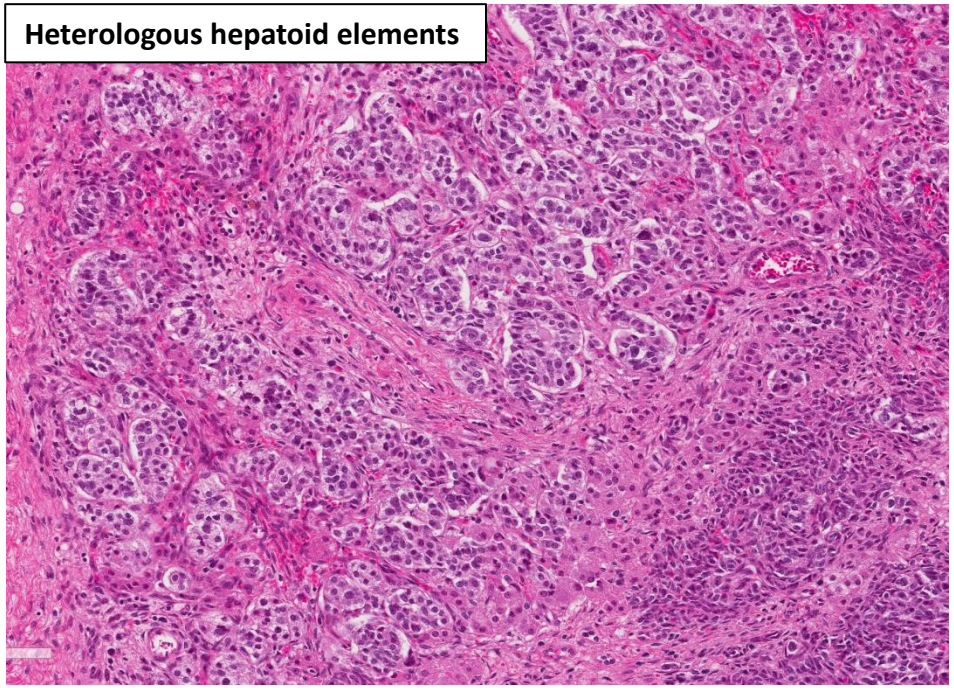
Retiform



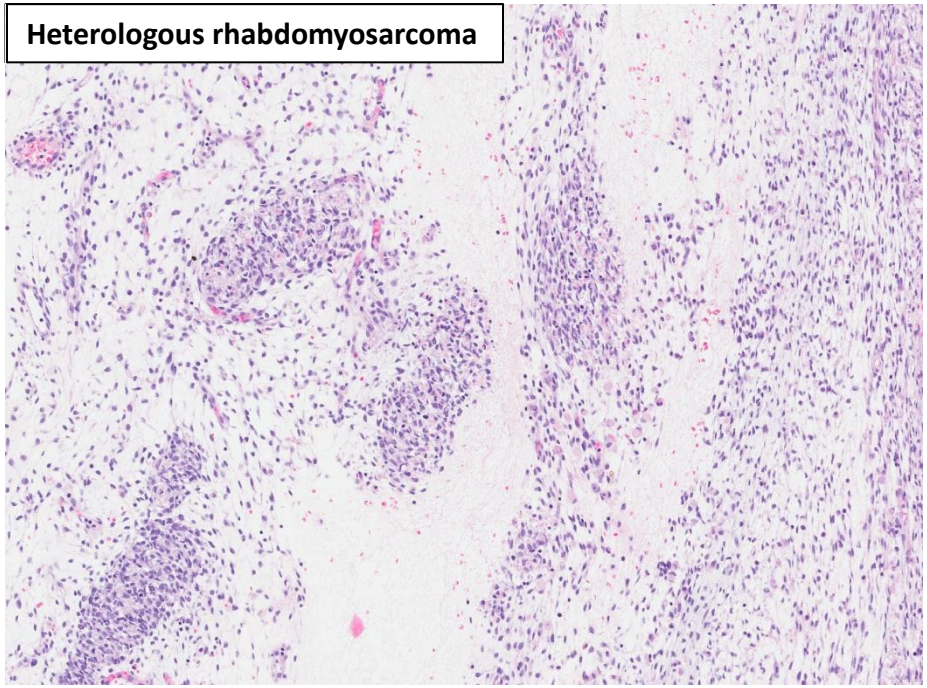
Heterologous mucinous epithelium



Heterologous hepatoid elements



Heterologous rhabdomyosarcoma

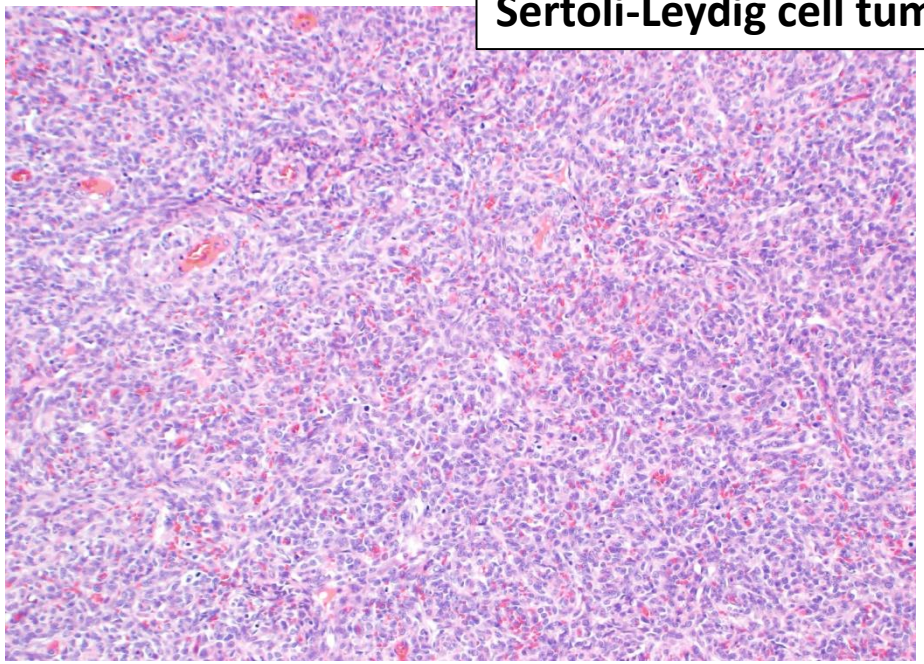


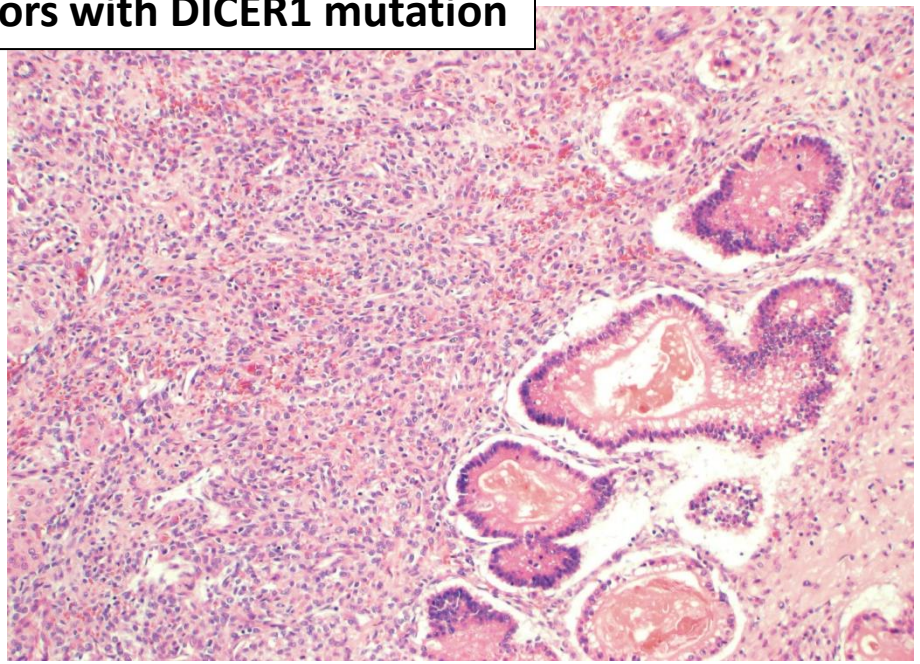
Features of SLCT with DICER1 mutation

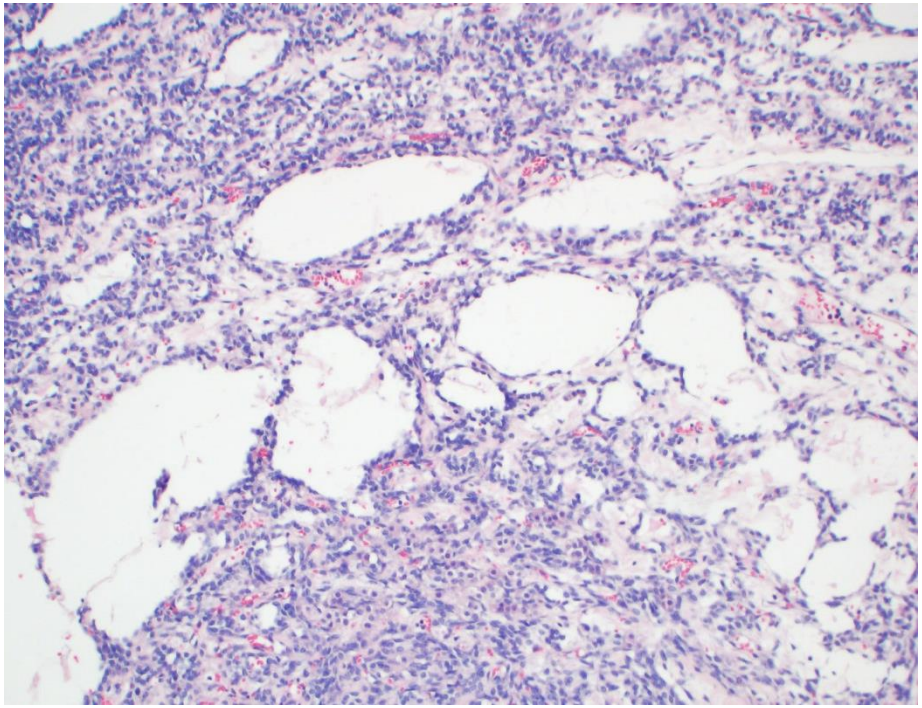
- 60-88% of SLCT have DICER1 mutation (germline or somatic)
- Incidence of germline mutation?

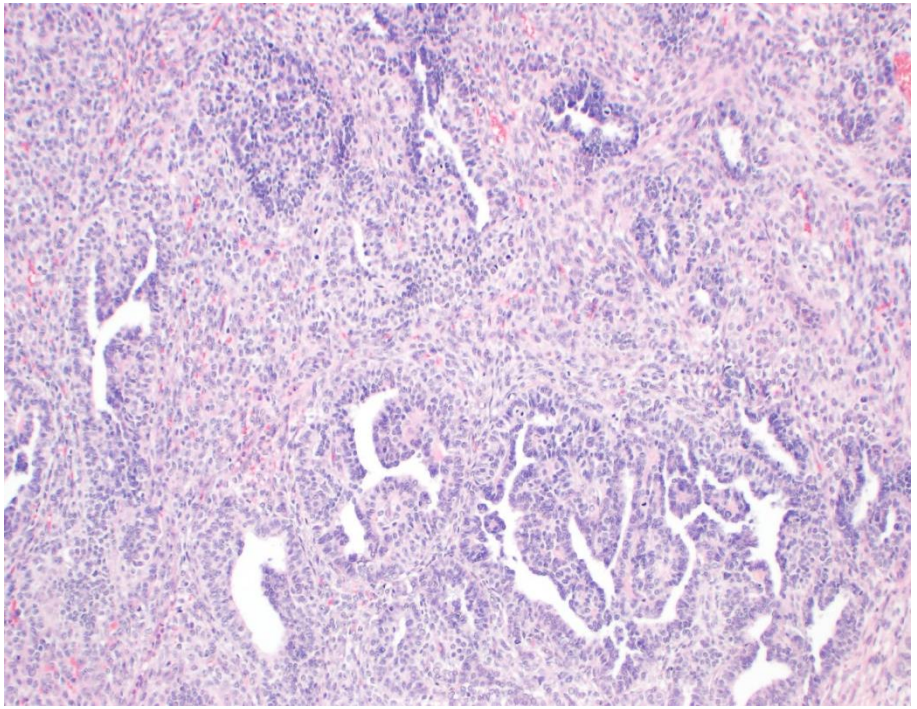
- Younger patients
- Moderately to poorly differentiated SLCT (not well differentiated)
- Can have mixed juvenile granulosa cell-like areas
- Heterogenous morphology and difficult to classify
- Heterologous elements frequent
- Can be retiform

Sertoli-Leydig cell tumors with DICER1 mutation









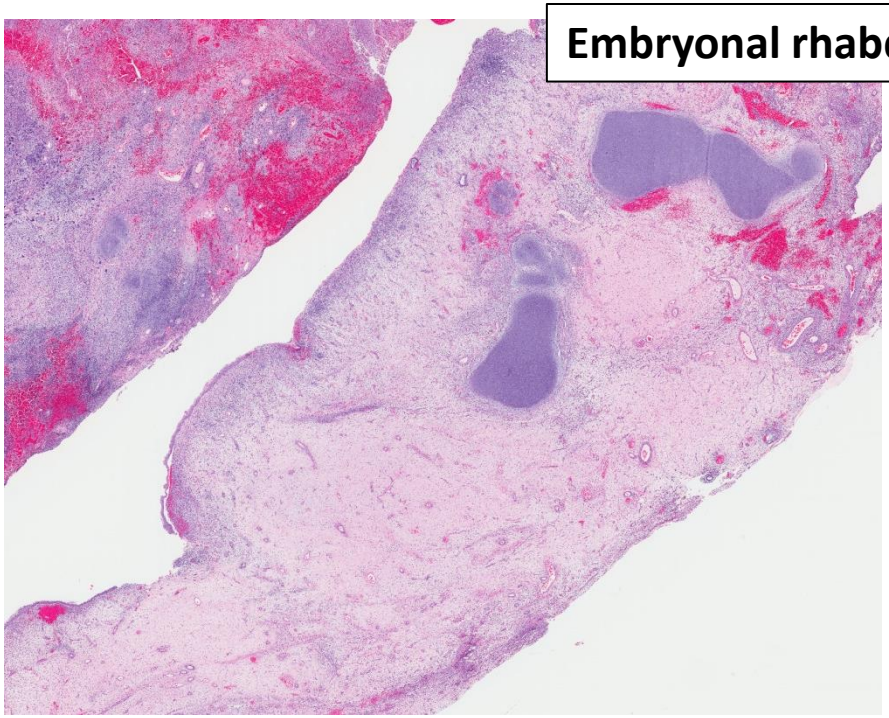
DICER1: Embryonal rhabdomyosarcoma of the cervix

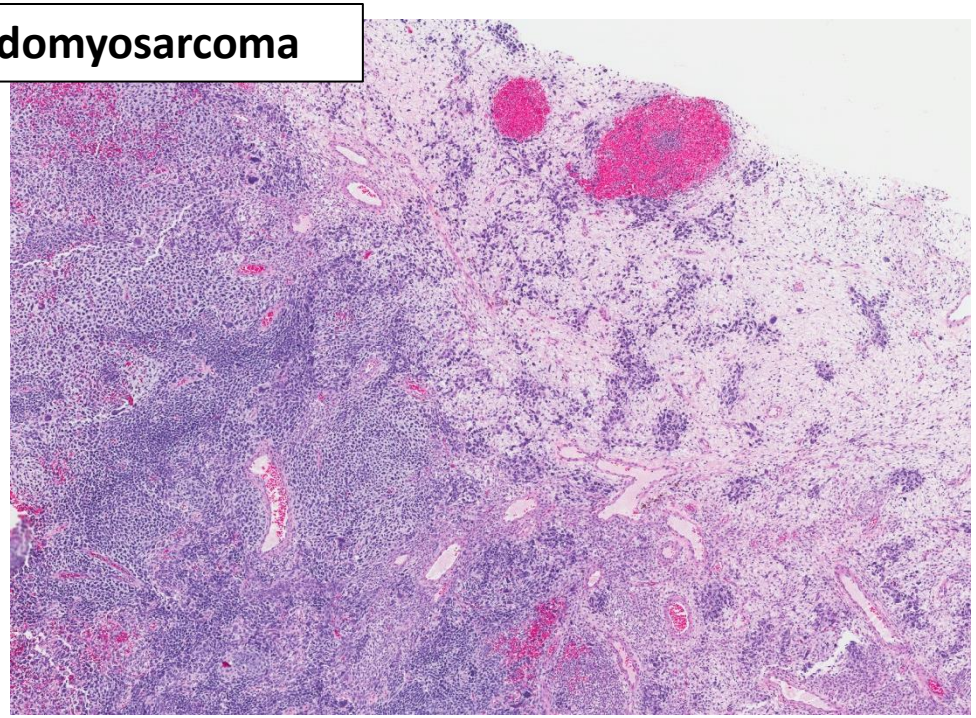
- Polypoid mass (sarcoma botryoides)
- Vaginal bleeding
- Variable age at presentation (can be older than 25 years)

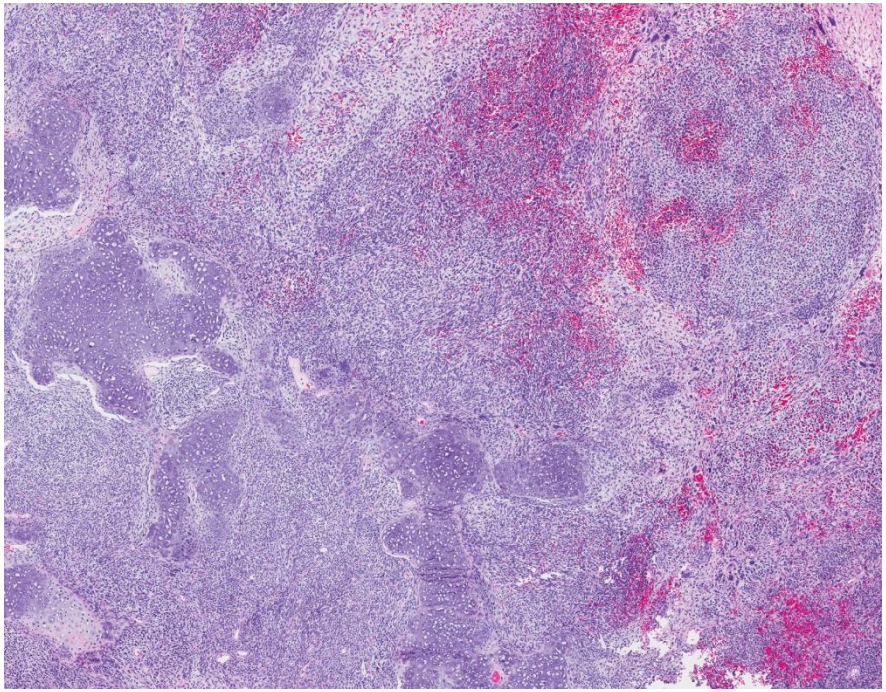
- Most are confined to the cervix and can be excised

- Heterologous differentiation - cartilage

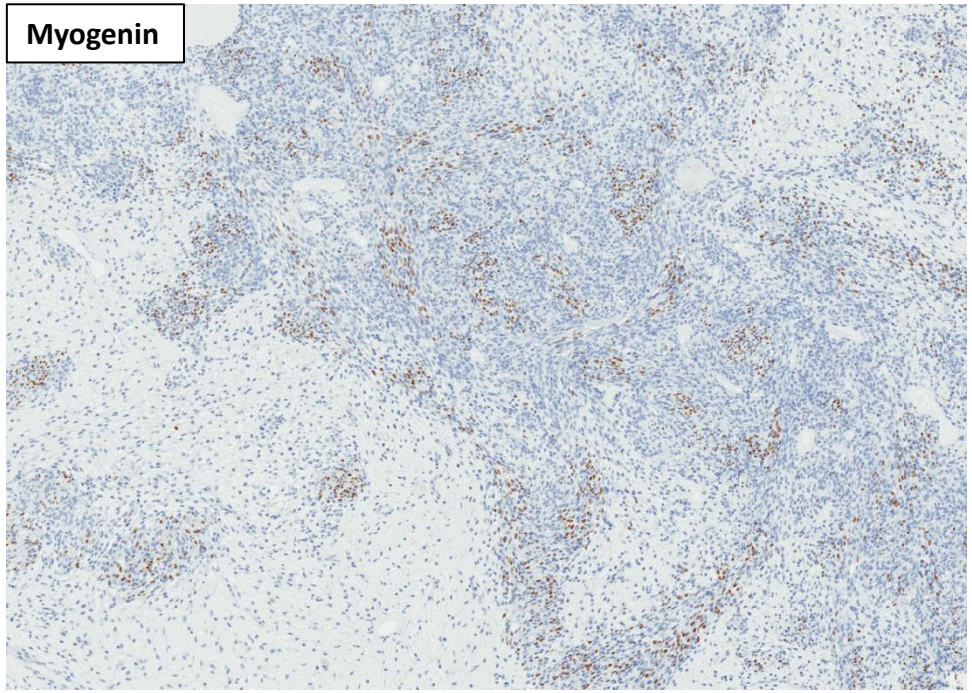
Embryonal rhabdomyosarcoma







Myogenin



DICER1 syndrome

Conclusion:

- All patients with an ovarian Sertoli Leydig cell tumor (or a diagnostically challenging sex cord-stromal tumor with SLCT potentially in the differential) should be referred for genetic counseling and DICER1 testing
- All patients with cervical embryonal rhabdomyosarcoma should be referred for genetic counseling and DICER1 testing

Example of uncommon tumor associated with a familial syndrome

Pathology report example

Diagnosis

Ovary: Sertoli-Leydig cell tumor, moderately differentiated, with heterologous elements; see comment.

Diagnosis comment: Sertoli-Leydig cell tumors of the ovary have been associated with germline mutation in the *DICER1* gene (DICER1 syndrome – provide reference). Thus referral for genetic counseling and testing should be considered.

DICER1 syndrome detection: Clinical implications

1. Surveillance
2. Prenatal management (Pleuropulmonary Blastoma)

Suggested signs and symptoms and imaging surveillance by system for individuals with *DICER1* pathogenic variants

System	Signs/Symptoms to consider	Condition of interest	Screening, Clinical and Radiographic
Lung	Tachypnea, cough, fever, and pain; pneumothorax	- PPB - Lung cysts -Pulmonary blastoma	CXR at birth and every 4– 6 months until 8 years of age, every 12 months 8 –12 years of age; consider a CT of chest at 3 – 6 months of age.* Toddlers: if initial CT normal: repeat between 2–1/2 and 3 years of age.* If mutation detected at > 12 years of age, consider baseline CXR or chest CT.
Thyroid	Visible or palpable thyroid nodule(s) Persistent cervical lymphadenopathy Hoarseness Dysphagia Neck pain Cough	– Multinodular goiter; – Differentiated thyroid cancer	Baseline thyroid US by 8 years of age then every 3 years or with symptoms/findings on physical exam. *With anticipated chemotherapy or radiation therapy: baseline US and then annually for 5 years, decreasing to every 2 to 3 years if no nodules are detected*
Female reproductive tract	Hirsutism Virilization Abdominal distension, pain or mass	– SLCT – Gynandroblastoma – Cervical embryonal rhabdomyosarcoma	For females beginning at 8 – 10 years of age: pelvic and abdominal US every 6–12 months at least until age 40. *End of interval is undetermined but current oldest patient with DICER1–associated SLCT was 61 years of age. Education regarding symptoms strongly recommended.*
Renal	Abdominal or flank mass and/or pain, hematuria	– Wilms tumor – Renal sarcoma – Cystic nephroma	Abdominal US every 6 months until 8 years of age then every 12 months until 12 years of age. If mutation detected at > 12 years of age, consider baseline abdominal US
Gastrointestinal	Signs of intestinal obstruction	– Small intestine polyps	Education regarding symptoms recommended.
Central nervous system **And head and neck (excluding thyroid)**	Headache, emesis, diplopia, decreased ability for upward gaze, altered gait (pineoblastoma); Precocious puberty; Cushing's syndrome (pituitary blastoma); Decreased visual acuity and leukocoria (CBME); Nasal obstruction (NCMH)	– Macrocephaly – Pineoblastoma – Pituitary blastoma – CBME – NCMH	Physical exam. Annual routine dilated ophthalmologic exam (generally unsedated) with visual acuity screening from 3 years of age through at least 10 years of age. Further testing if clinically indicated. Recommend urgent MRI for any symptoms of intracranial pathology.

Key: PPB = pleuropulmonary blastoma; CXR = chest x–ray; CT = computed tomography; US = ultrasound; SLCT = Sertoli–Leydig cell tumor; CBME = ciliary body medulloepithelioma; NCMH = nasal chondromesenchymal hamartoma.

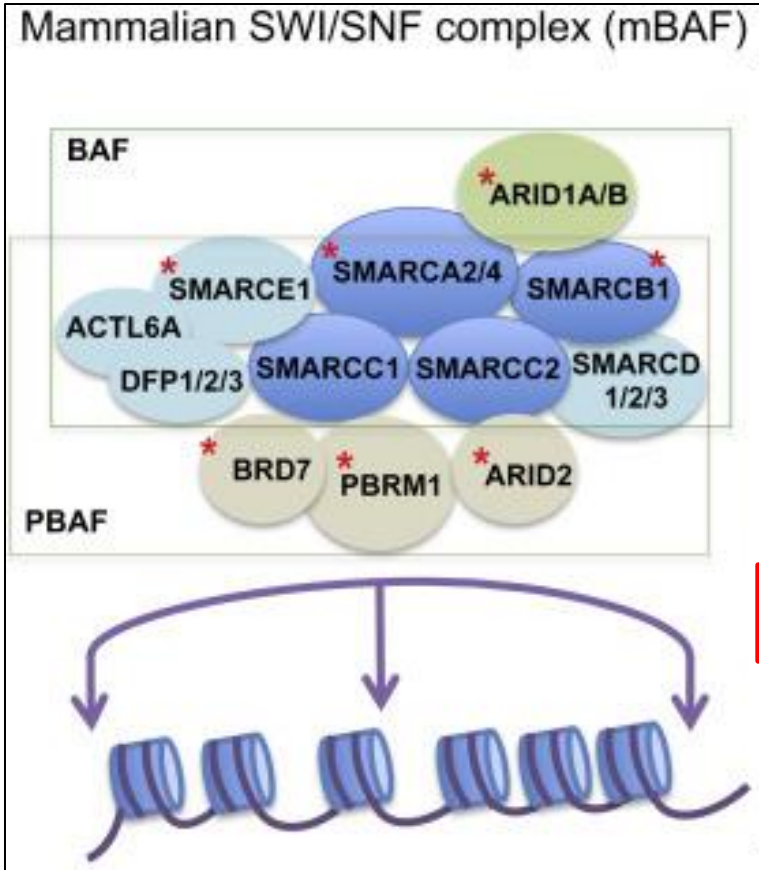
Rhabdoid tumor predisposition syndrome 2 (RTPS2)

Rhabdoid tumor predisposition syndrome 2

- Autosomal dominant
- Germline mutation in *SMARCA4* gene (member of SWI-SNF pathway)

- High grade aggressive tumors with rhabdoid morphology
- CNS: Atypical teratoid/rhabdoid tumor
- Kidney: Malignant rhabdoid tumor
- Gynecologic tract:
- **Ovary: Small cell carcinoma, hypercalcemic type**
- **Uterus: Undifferentiated uterine sarcoma with rhabdoid features**

Hereditary SWI/SNF deficiency syndromes



Subunit	Cancer
ARID1A	Ovarian, hepatocellular, bladder, gastric, endometrioid, pancreatic, colon, lung, neuroblastoma, Burkitt lymphoma
ARID1B	Melanoma, neuroblastoma, hepatocellular, pancreatic, liver
PBRM1	Renal cell carcinoma, breast, gastric, pancreatic
ARID2	Melanoma, hepatocellular, pancreatic
SMARCA2	Lung, colon, breast
SMARCA4	Lung, medulloblastoma, Burkitt lymphoma, SCCOHT
SMARCB1	Rhabdoid tumor, familial schwannomatosis
SMARCE1	Spinal meningioma
BRD7	Breast

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT)

- Uncommon
- <1% of all ovarian cancers
- Unknown histogenesis
- Young patients (mean age 24 years, range 9-44 years)
- Hypercalcemia in up to two-third

- Poor prognosis
- 5-year survival 55% for stage I and 32% for stage II-III

Small cell carcinoma of the ovary, hypercalcemic type: SMARCA4

- Recurrent SMARCA4 mutations (germline or somatic)
- **Germline mutation in up to 43% of tumors**

Small cell carcinoma of the ovary, hypercalcemic type, displays frequent inactivating germline and somatic mutations in *SMARCA4*

Pilar Ramos[1,2,15], Anthony N Karnezis[3,4,15], David W Craig[1], Aleksandar Sekulic[1,5], Megan L Russell[1], William P D Hendricks[1], Jason J Corneveaux[1], Michael T Barrett[1], Karey Shumansky[6], Yidong Yang[6], Sohrab P Shah[3,6], Leah M Prentice[4], Marco A Marra[7], Jeffrey Kiefer[1], Victoria L Zismann[1], Troy A McEachron[1], Bodour Salhia[1], Jaime Prat[8], Emanuela D'Angelo[8], Blaise A Clarke[9], Joseph G Pressey[10], John H Farley[11], Stephen P Anthony[12], Richard B S Roden[13], Heather E Cunliffe[1,14], David G Huntsman[3,4,16], and Jeffrey M Trent[1,16]

Germline and somatic *SMARCA4* mutations characterize small cell carcinoma of the ovary, hypercalcemic type

Leora Witkowski[1–3,26], Jian Carrot-Zhang[3,4,26], Steffen Albrecht[5], Somayyeh Fahiminiya[3,4], Nancy Hamel[1,6], Eva Tomiak[7], David Grynspan[8], Emmanouil Saloustros[9], Javad Nadaf[3,4], Barbara Rivera[1,3], Catherine Gilpin[7], Ester Castellsagué[1,3], Rachel Silva-Smith[1,2], François Plourde[1,2], Mona Wu[1,3], Avi Saskin[3], Madeleine Arseneault[3,4], Rouzan G Karabakhtsian[10,25], Elizabeth A Reilly[10], Frederick R Ueland[10], Anna Margiolaki[9], Kitty Pavlakis[11], Sharon M Castellino[12], Janez Lamovec[13], Helen J Mackay[14], Lawrence M Roth[15], Thomas M Ulbright[15], Tracey A Bender[15], Vassilis Georgoulias[9], Michel Longy[16], Andrew Berchuck[17], Marc Tischkowitz[18], Inga Nagel[19], Reiner Siebert[19], Colin J R Stewart[20], Jocelyne Arseneau[21], W Glenn McCluggage[22], Blaise A Clarke[23], Yasser Riazalhosseini[3,4], Martin Hasselblatt[24], Jacek Majewski[3,4] & William D Foulkes[1–3,6]

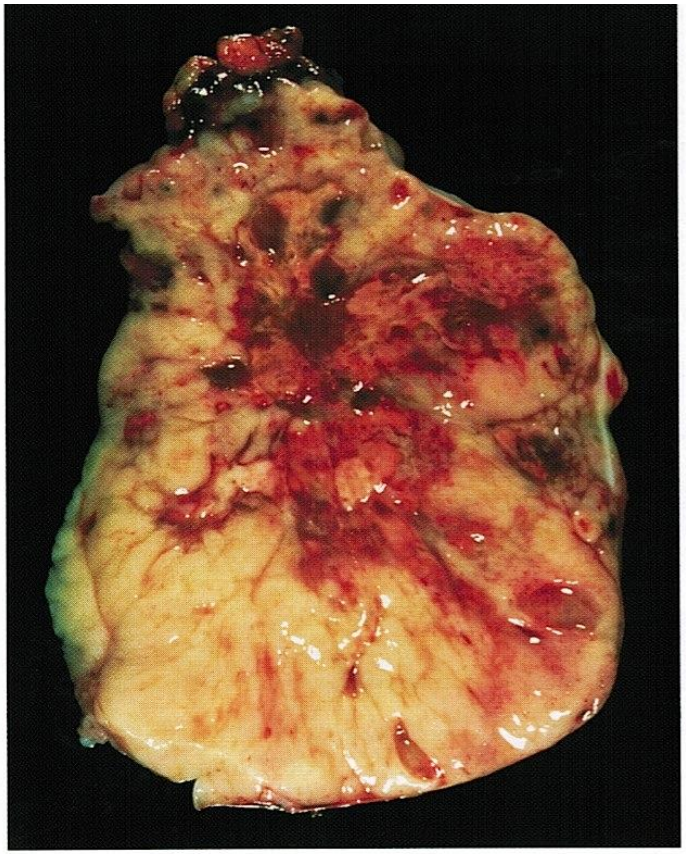
Recurrent *SMARCA4* mutations in small cell carcinoma of the ovary

Petar Jelinic[1,5], Jennifer J Mueller[1,5], Narciso Olvera[1], Fanny Dao[1], Sasinya N Scott[2], Ronak Shah[2], JianJiong Gao[3], Nikolaus Schultz[3], Mithat Gonen[4], Robert A Soslow[2], Michael F Berger[2] & Douglas A Levine[1]

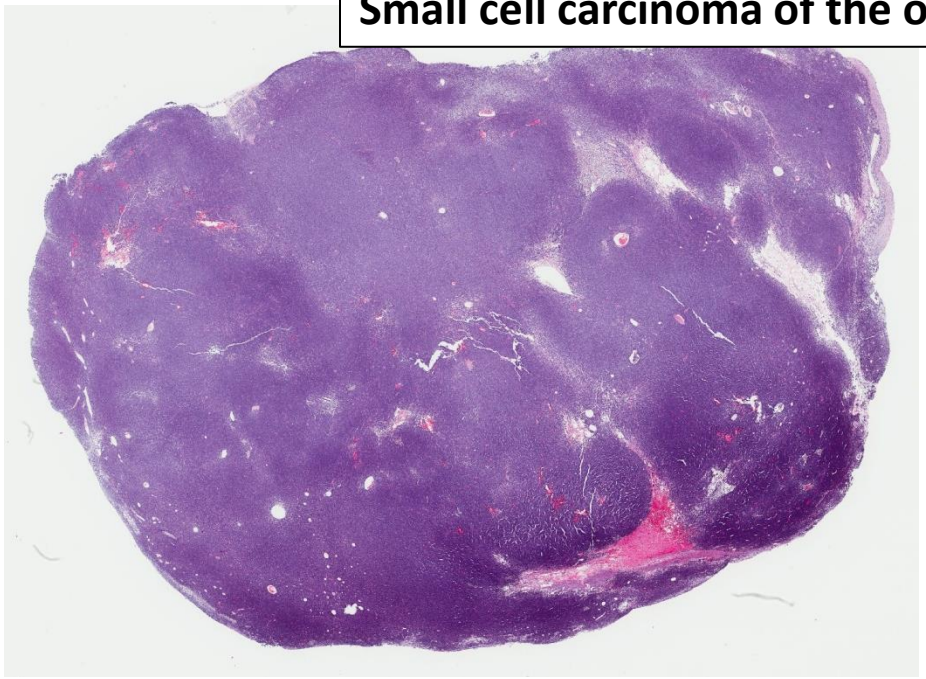
SMARCA4 mutations in all 12 samples is less than 2.22×10^{-16}. Only 4 additional non-recurrent somatic mutations were identified in any of the other 278 genes sequenced across all 12 samples (**Supplementary Tables 2** and **3**). In contrast, an analysis of 4,784 non-hypermutated tumors across The Cancer Genome Atlas (TCGA) identified somatic mutations in an average of 4.3 of these 279 genes for each tumor (s.d. of 4.4). TCGA samples with inactivating *SMARCA4* mutations had more mutations in the other 278 genes sequenced (mean of 14) than the SCCOHT cases. Because the SMARCA2 and SMARCA4 proteins are mutually exclusive

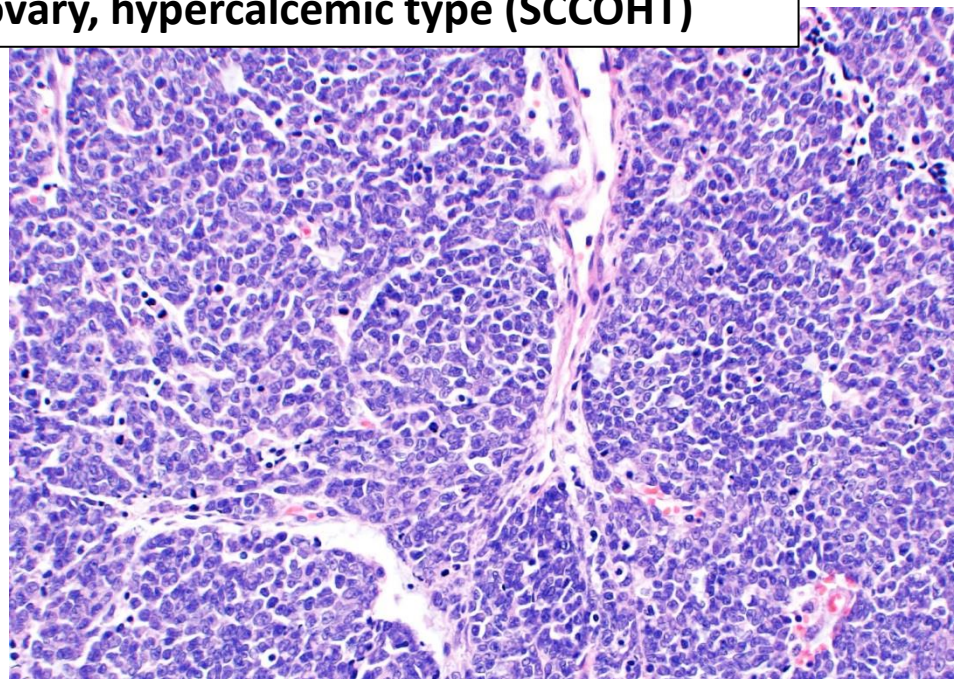
Nature Genetics 2014

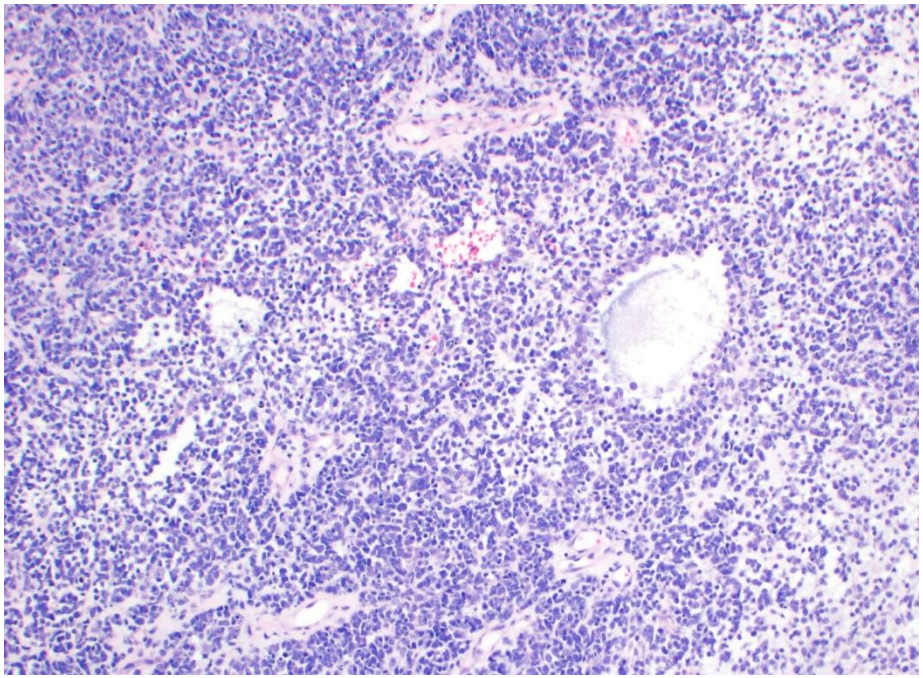
Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT): Gross

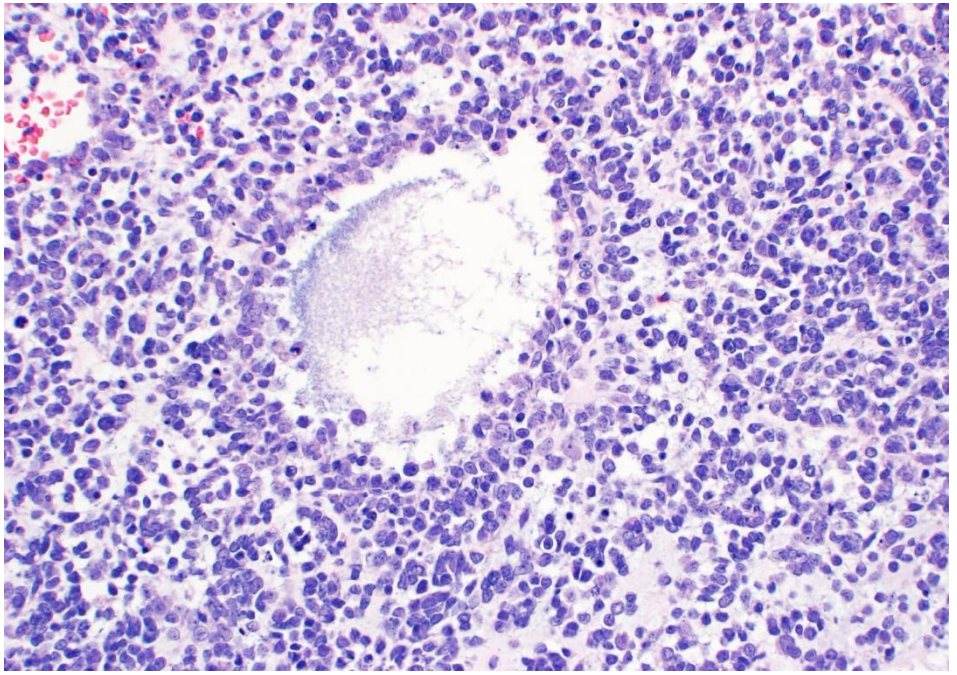


Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT)

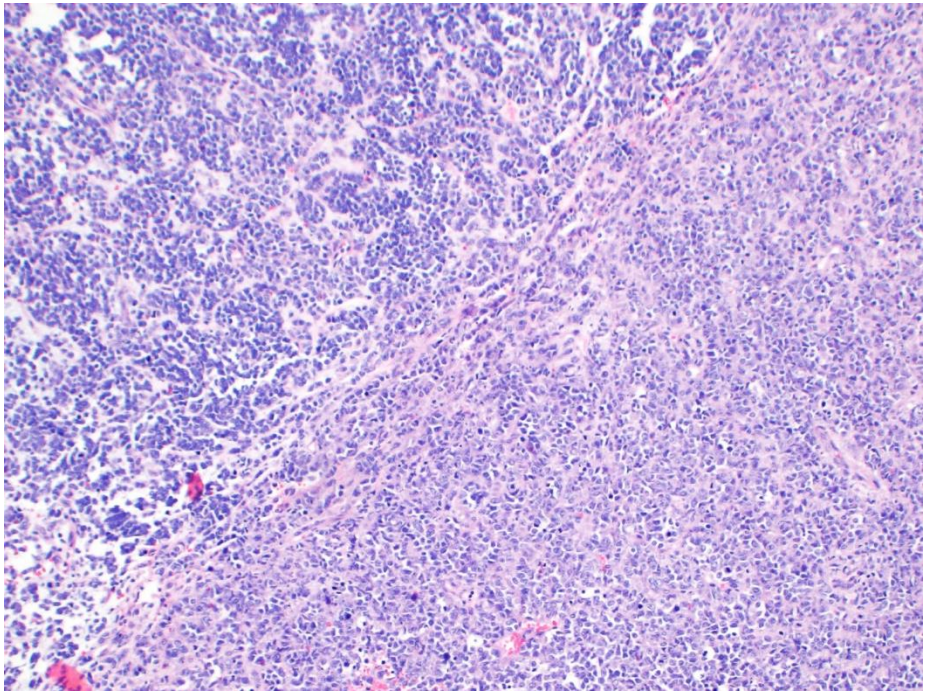


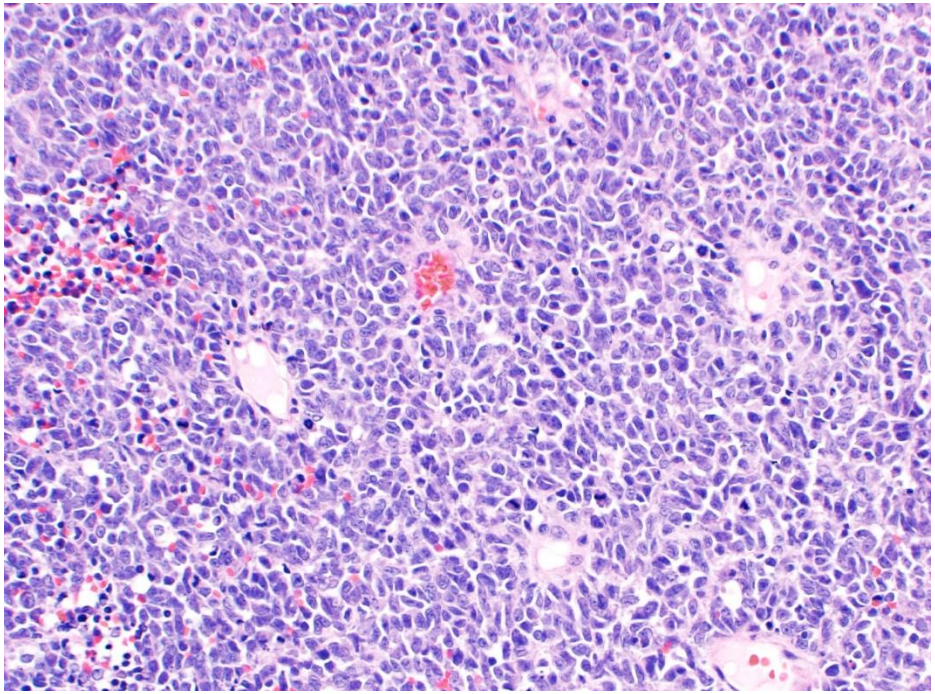






Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT): large cell variant





SCCOHT: Morphology

- Difficult diagnosis
- Wide differential diagnosis
- Sex cord stromal tumors
- Small cell neuroendocrine carcinoma (primary or metastatic)
- Lymphoma

SCCOHT: Immunohistochemistry

- Cytokeratin (AE1/AE3) +
- WT1 +
- EMA +/-
- Sex cord stromal markers –ve

SCCOHT: Immunohistochemistry

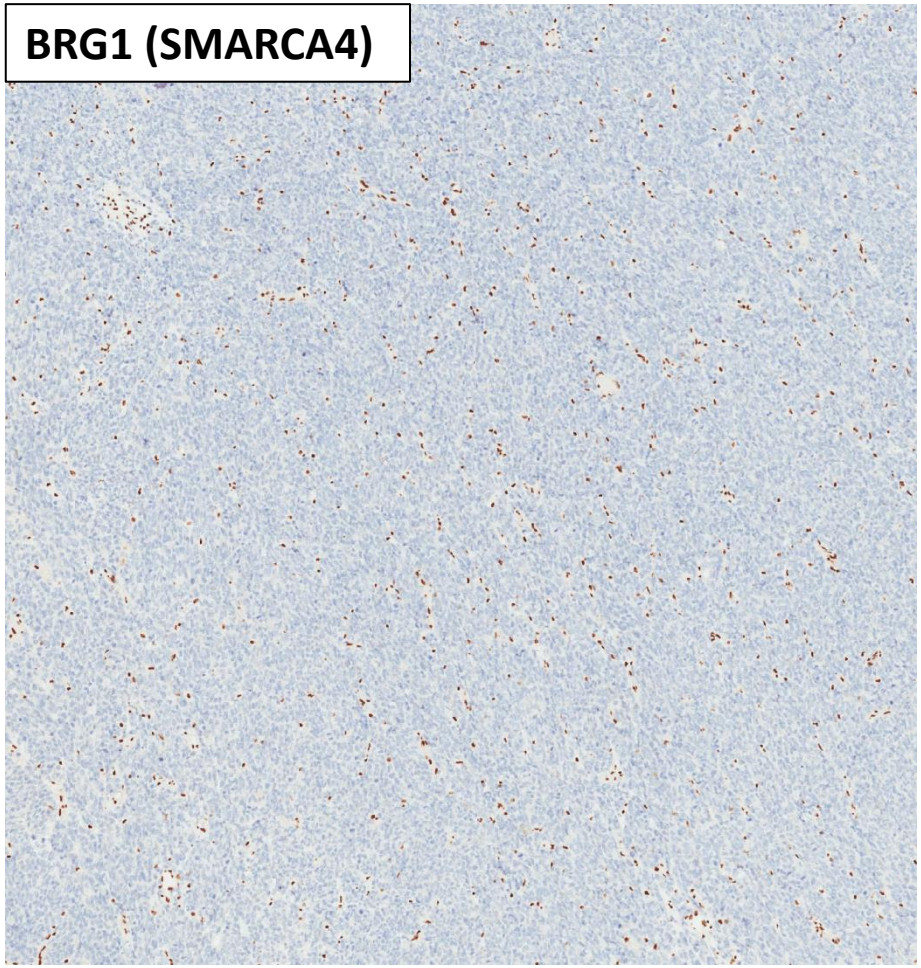
- SMARCA4 mutation correlates with **loss of SMARCA4/BRG1 protein expression by IHC (along with SMARCA2/BRM)**
- Rare exceptions with retained staining– in-frame deletion leads to non-functional protein detected by IHC)

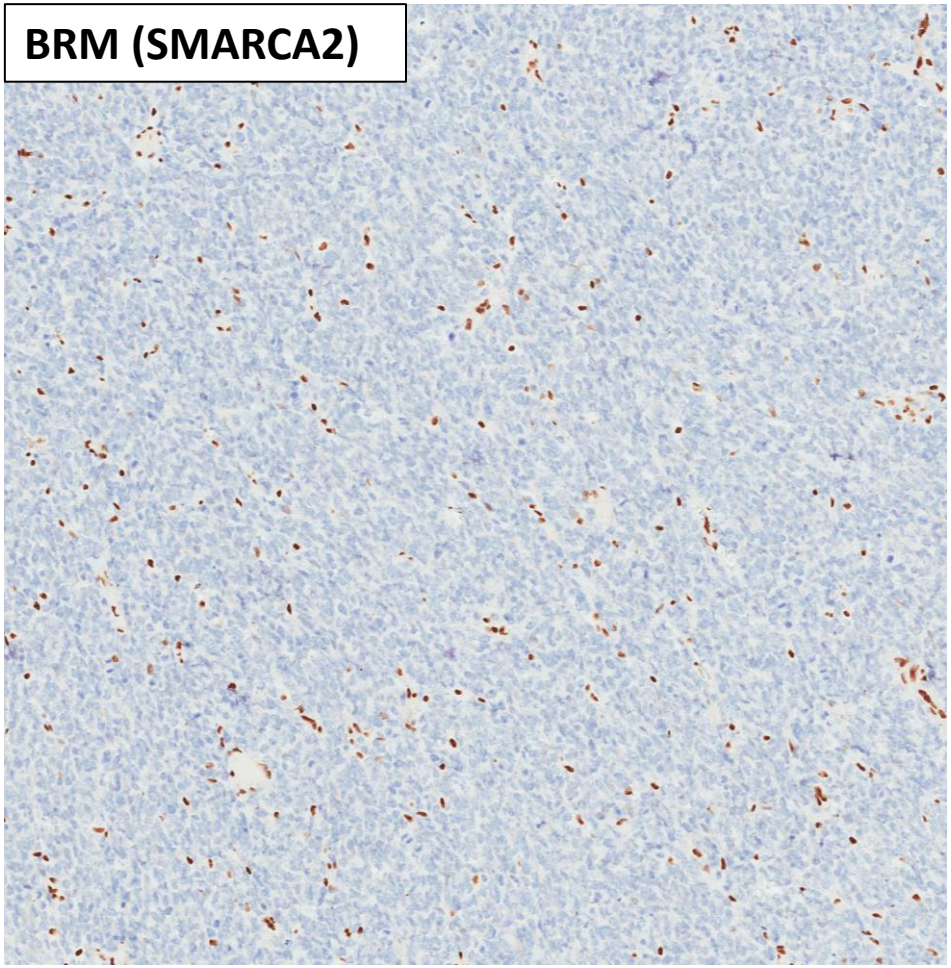
TUMOR TYPE	N	LOSS OF SMARCA4 EXPRESSION
SCCOHT	17	16/17 (94%)
OVARIAN EPITHELIAL TUMORS		
Ovarian SCC, Non-SCCOHT-type	2	0/2 (0%)
Ovarian CCC	37	1/37 (3%)
Ovarian EC	38	0/38 (0%)
Ovarian HGSC	42	0/42 (0%)
OVARIAN SEX CORD STROMAL TUMORS (SCST)		
Ovarian GCT, Adult-type	42	0/42 (0%)
Ovarian GCT, Juvenile-type	11	0/11 (0%)
Ovarian SLCT	6	0/6 (0%)
Ovarian GAB	2	0/2 (0%)
Ovarian SCST NOS	3	0/3(0%)
METASTATIC MIMICS OF SCCOHT		
SCC, Lung	26	0/26 (0%)
SCC, Uterus/Cervix	3	0/3 (0%)
DSRCT	36	0/36 (0%)
Melanoma	31	1/31 (3%)

Other tumors with SMARCA4 loss:
- Clear cell carcinoma
- Endometrioid carcinoma
- Undifferentiated carcinoma
- Endometrial stromal sarcoma

Conlon N, et al. Am J Surg Pathol 2016

SCCOHT: Loss of BRG1 and BRM





Rhabdoid tumor predisposition syndrome 2

Conclusion:

- All patients with small cell carcinoma of the ovary, hypercalcemic type should be referred for genetic counseling and *SMARCA4* mutation testing

Example of uncommon tumor associated with a familial syndrome

Pathology report

Diagnosis

Ovary: Small cell carcinoma of the ovary, hypercalcemic type; see comment.

Diagnosis comment: SCCOHT have been associated with germline mutations in *SMARCA4* gene (RTPS2– provide reference). Thus referral for genetic counseling and mutation testing should be considered.

SMARCA4 germline mutation: Clinical implications

1. Patient with SCCOHT:

Remove contralateral ovary (can be bilateral)

2. Patient without tumor:

?Prophylactic salpingo-oophorectomy

3. Therapeutic implications

SMARCA4 germline mutation: Clinical implications

Prophylactic salpingo-oophorectomy

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gore

Case Report

Prophylactic oophorectomy for hereditary small cell carcinoma of the ovary, hypercalcemic type

Andrew Berchuck [a,*], Leora Witkowski [b], Martin Hasselblatt [c], William D. Foulkes [b]

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

The dilemma of early preventive oophorectomy in familial small cell carcinoma of the ovary of hypercalcemic type

Tanja Pejovic[a,*], W. Glenn McCluggage[b], Adam J. Krieg[a], Fuhua Xu[a], David M. Lee[a], Leora Witkowski[c,d], William D. Foulkes[d]

Table 1
Pros and cons of prophylactic BSO.

	Pro (in favor of early surgical intervention)	Con (against very early surgical intervention)
c.3081 + 1G > T variant, *SMARCA4*	High genetic risk of developing cancer at early age	No direct evidence of pathogenic effect of the mutation, no genetic material available from the mother or aunt
	No screening methods	
	High mortality rate even in early stages	30% long term cure in stage I
	No standardized or effective treatment	
	Psychologic consequences of living with the risk of cancer	Risk of depression and anxiety and fear of premature aging
	HRT available and safe	Increased risk of breast cancer with long term HRT
	Reproductive technique exist to maintain fertility	Freezing ovarian tissue for fertility is experimental

SMARCA4 mutation: Therapeutic implications

Translational Science

Cancer Research

SWI/SNF-Compromised Cancers Are Susceptible to Bromodomain Inhibitors

Tatiana Shorstova[1], Maud Marques[1], Jie Su[1], Jake Johnston[1], Claudia L. Kleinman[2], Nancy Hamel[3], Sidong Huang[4], Moulay A. Alaoui-Jamali[1], William D. Foulkes[3], and Michael Witcher[1]

Therapeu

Histone Deacetylase Inhibitors Synergize with Catalytic Inhibitors of EZH2 to Exhibit Antitumor Activity in Small Cell Carcinoma of the Ovary, Hypercalcemic Type

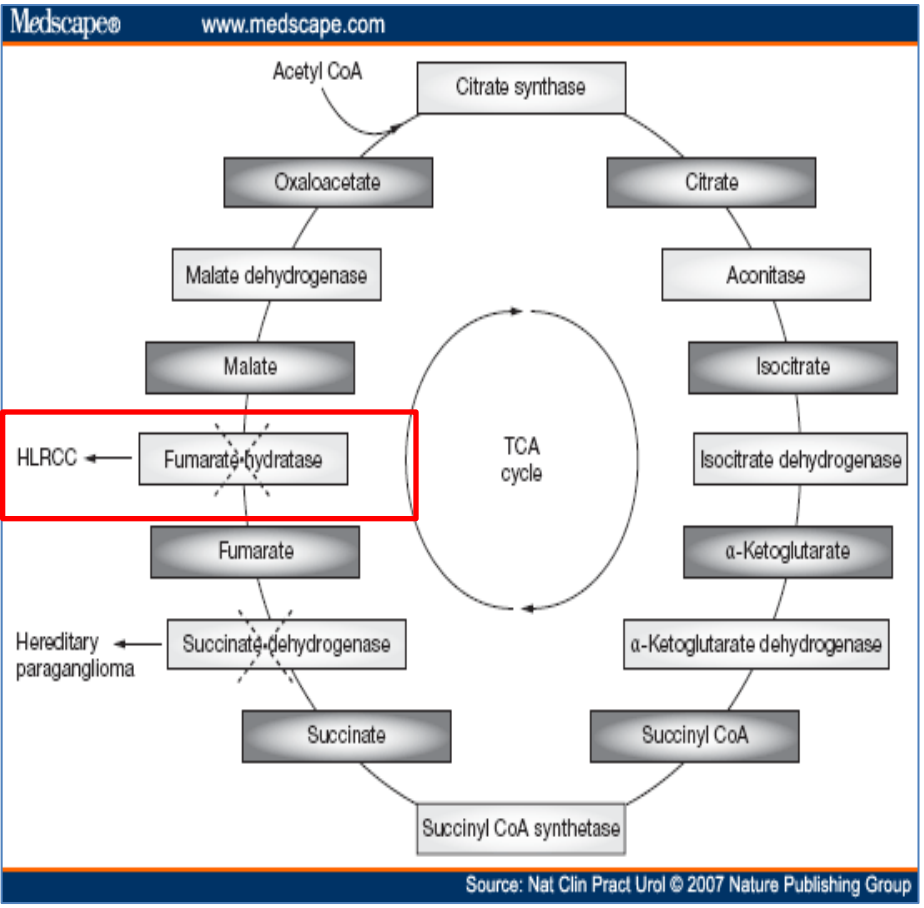
Yemin Wang[1,2], Shary Yuting Chen[1,2], Shane Colborne[3], Galen Lambert[2], Chae Young Shin[2], Nancy Dos Santos[4], Krystal A. Orlando[5], Jessica D. Lang[6], William P.D. Hendricks[6], Marcel B. Bally[4], Anthony N. Karnezis[1,2], Ralf Hass[7], T. Michael Underhill[8], Gregg B. Morin[3,9], Jeffrey M. Trent[6], Bernard E. Weissman[5], and David G. Huntsman[1,2,10]

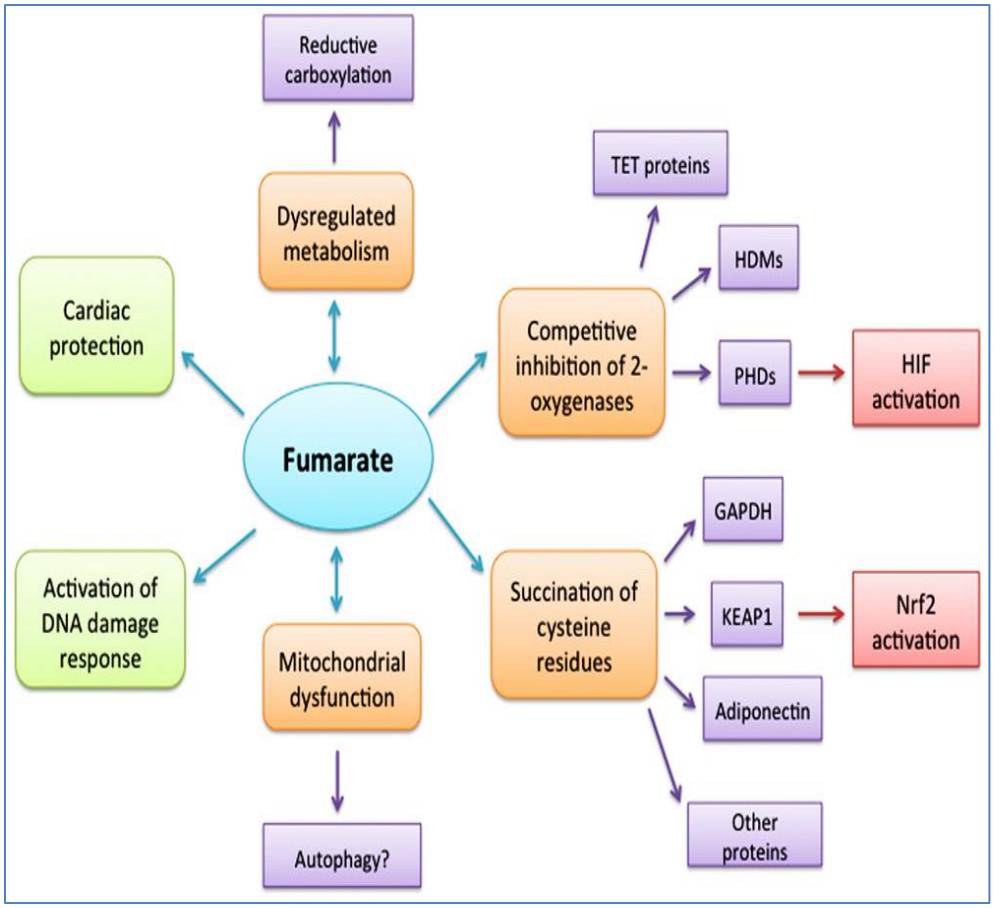
Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome (HLRCC)

HLRCC

- Autosomal dominant
- Germline mutation in *fumarate hydratase (FH)* gene on chromosome 1q42.3
- *FH* acts as a tumor suppressor gene
- Second hit in tumor (often LOH)
- Predisposes to cutaneous and uterine leiomyomas (Reed syndrome) and renal cell carcinoma (variable penetrance)
- Incidence of HLRCC not known but low (estimated 1/10,000-1/50,000)

FH deficiency





1. Germline mutation in *FH* gene: HLRCC
2. Sporadic mutation in *FH* gene: **NOT HLRCC**

HLRCC: Why do we want to detect?

Renal cell carcinoma

- 4th decade
- Typically unilateral single mass
- **High-stage and poor prognosis**

Early detection of HLRCC could decrease morbidity and mortality from aggressive RCC

HLRCC

	Uterine leiomyomas	Cutaneous leiomyomas	Renal cell carcinoma
Penetrance	**~100%**	~75%	~15%
Median age at diagnosis	**2nd-3rd decade**	2nd-3rd decade	4th decade

Uterine leiomyoma: Opportunity for early detection of HLRCC?

Uterine leiomyoma: screening for HLRCC

Problem # 1:

Uterine leiomyomas are common while HLRCC is not

- 20-30% and 80% of all women develop uterine leiomyomas by age 30 and 50 respectively

Problem #2:

Sporadic *FH* mutation more common than germline in uterine leiomyoma

- Similar morphology and IHC results

Uterine leiomyoma: detection of HLRCC

- Clinical presentation
- Personal and family history
- Pathologic features
- Immunohistochemistry (IHC)

Clinical presentation

- Multiple
- Large
- Highly symptomatic
- Young age
- Early surgical intervention

	HLRCC associated ULM	Sporadic ULM
Median age at presentation	28 years	38 years
Age at surgery	<30 years	45 years

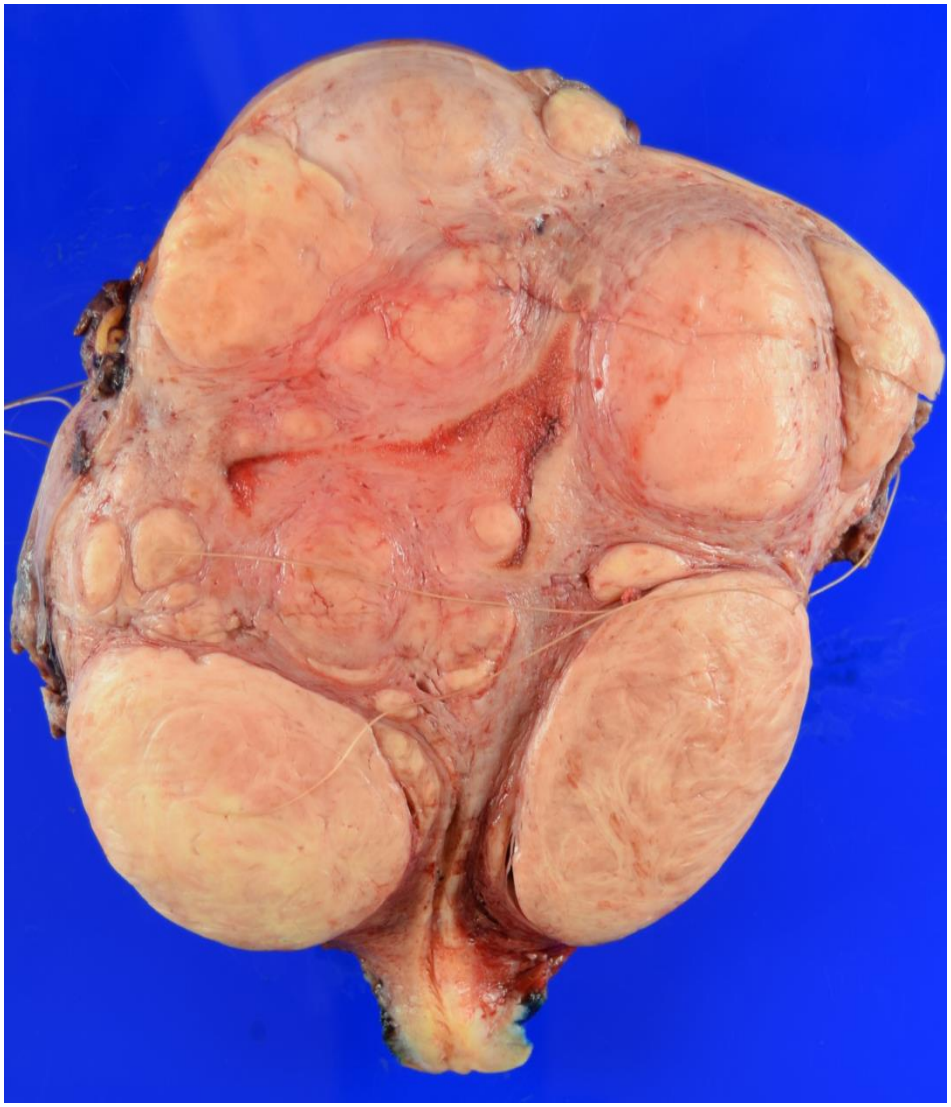
Personal and family history

- Maternal history of early surgery for fibroids
- Personal and/or family history of cutaneous leiomyomas and/or RCC

- Very useful but often not known or provided
- Unreliable due to variable penetrance of HLRCC

Pathologic features: Gross

Multiple large leiomyomas



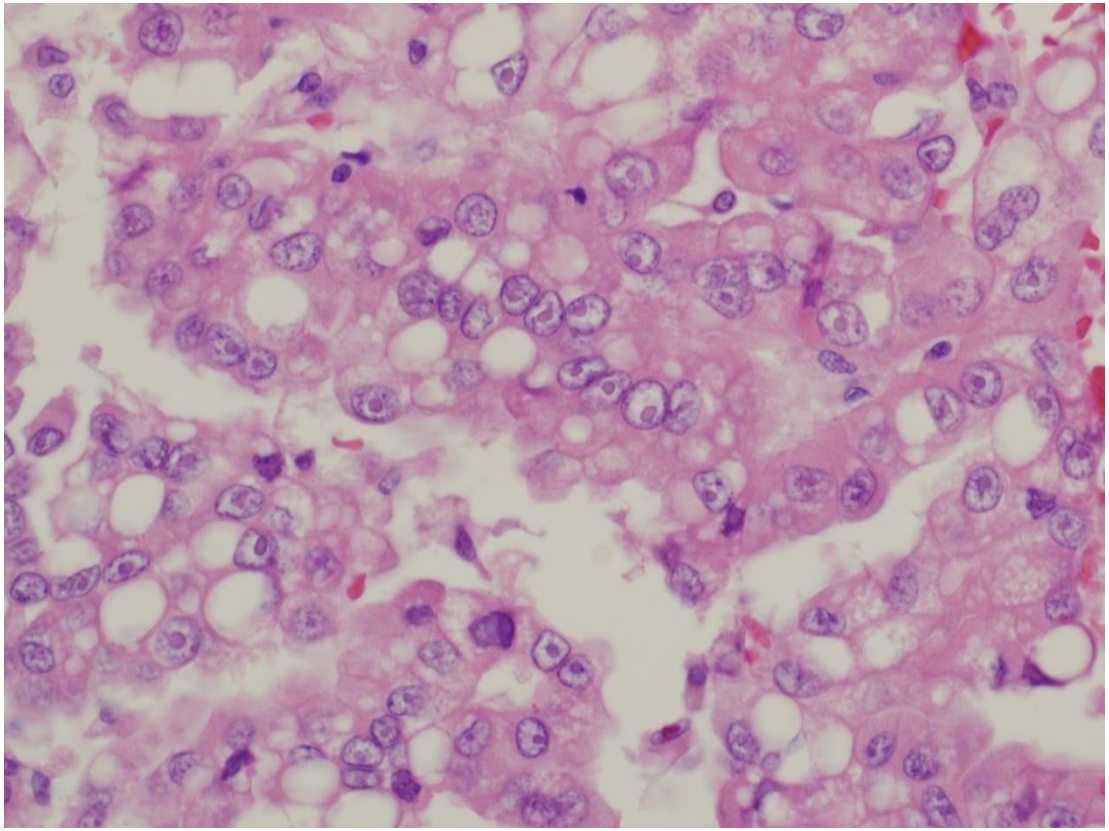
Pathologic features: Microscopic

- Conventional leiomyoma
- Cellular leiomyoma
- Leiomyoma with bizarre nuclei (LBN)

- ?increased risk for leiomyosarcoma or STUMP (probably not)

Pathologic features: Morphology

- First reported in renal cell carcinoma
- Prominent eosinophilic nucleoli surrounded by perinucleolar halos

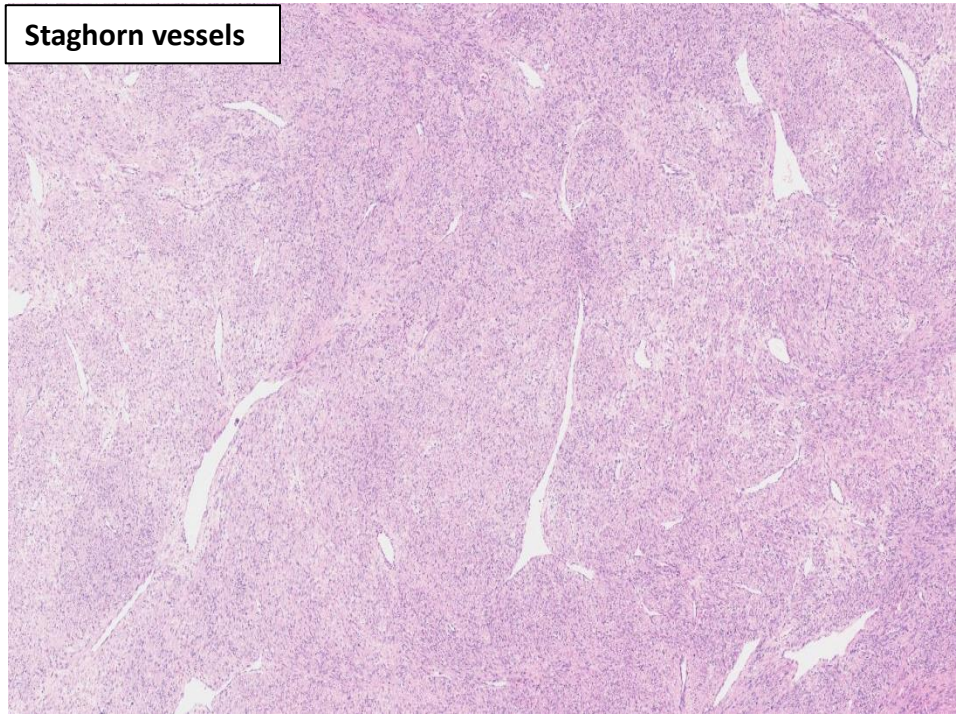


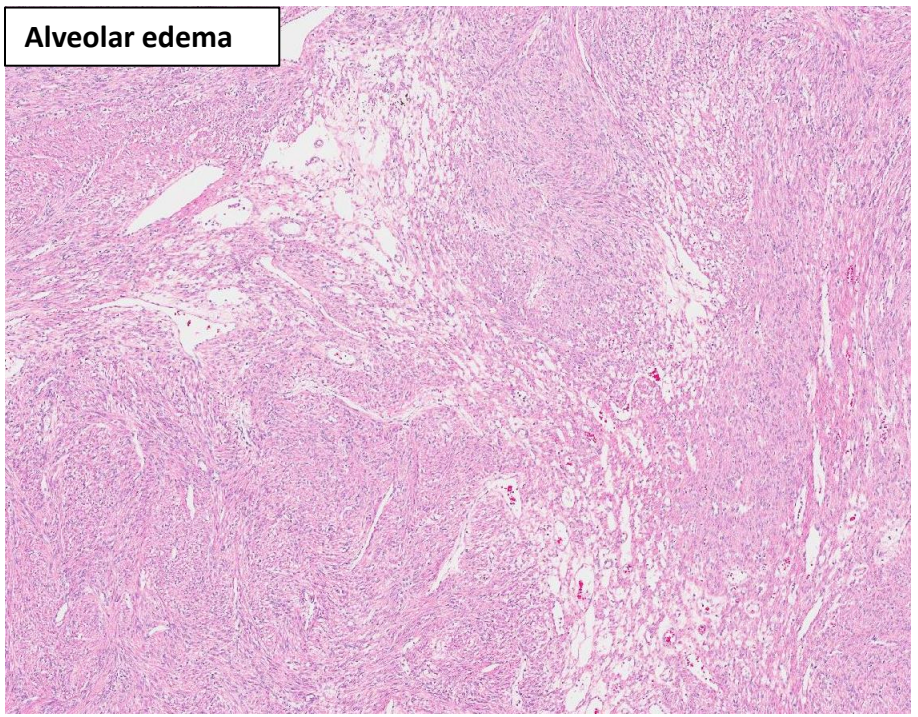
Merino MJ, et al. AJSP 2007

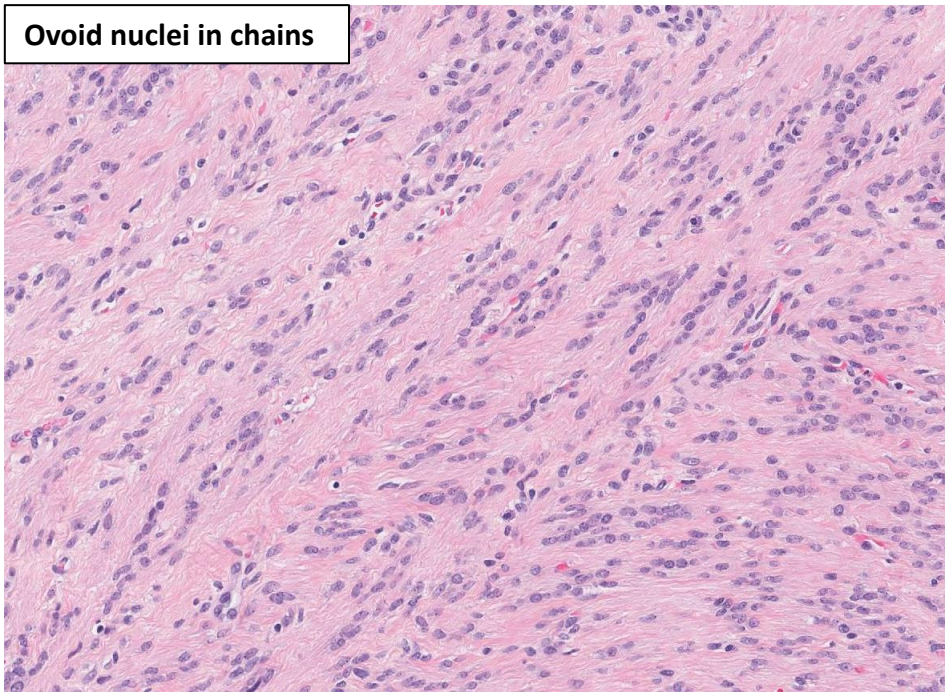
Pathologic features: Morphology

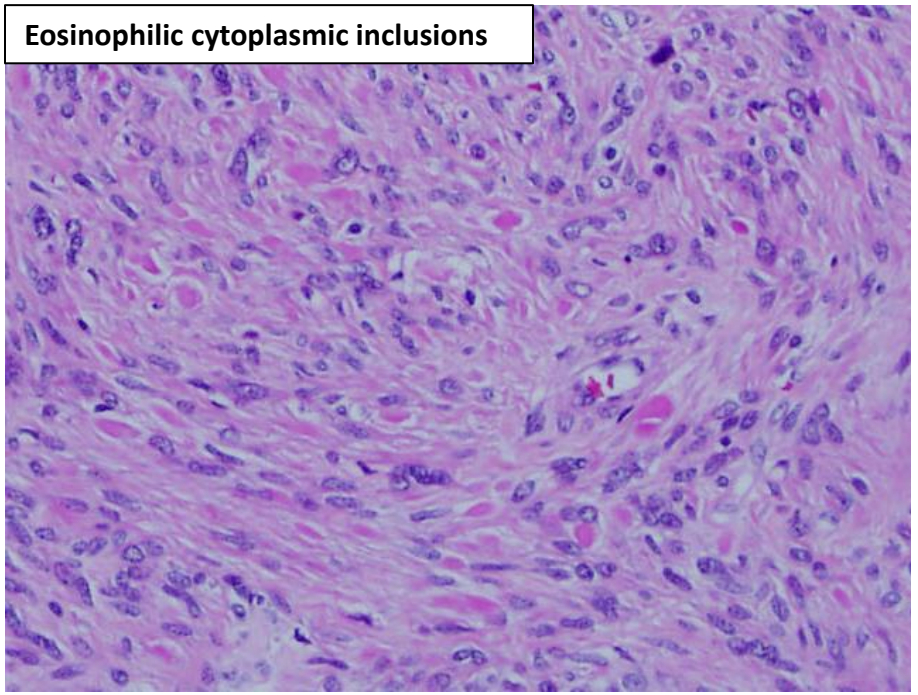
- Staghorn blood vessels
- Alveolar edema
- Ovoid nuclei arranged in chains
- Eosinophilic cytoplasmic inclusions
- Prominent eosinophilic macronucleoli surrounded by clear halos
- Schwannoma-like growth

Sanz-Ortega J, et al. Am J Surg Pathol 2013
Reyes C, et al. Mod Pathol 2013

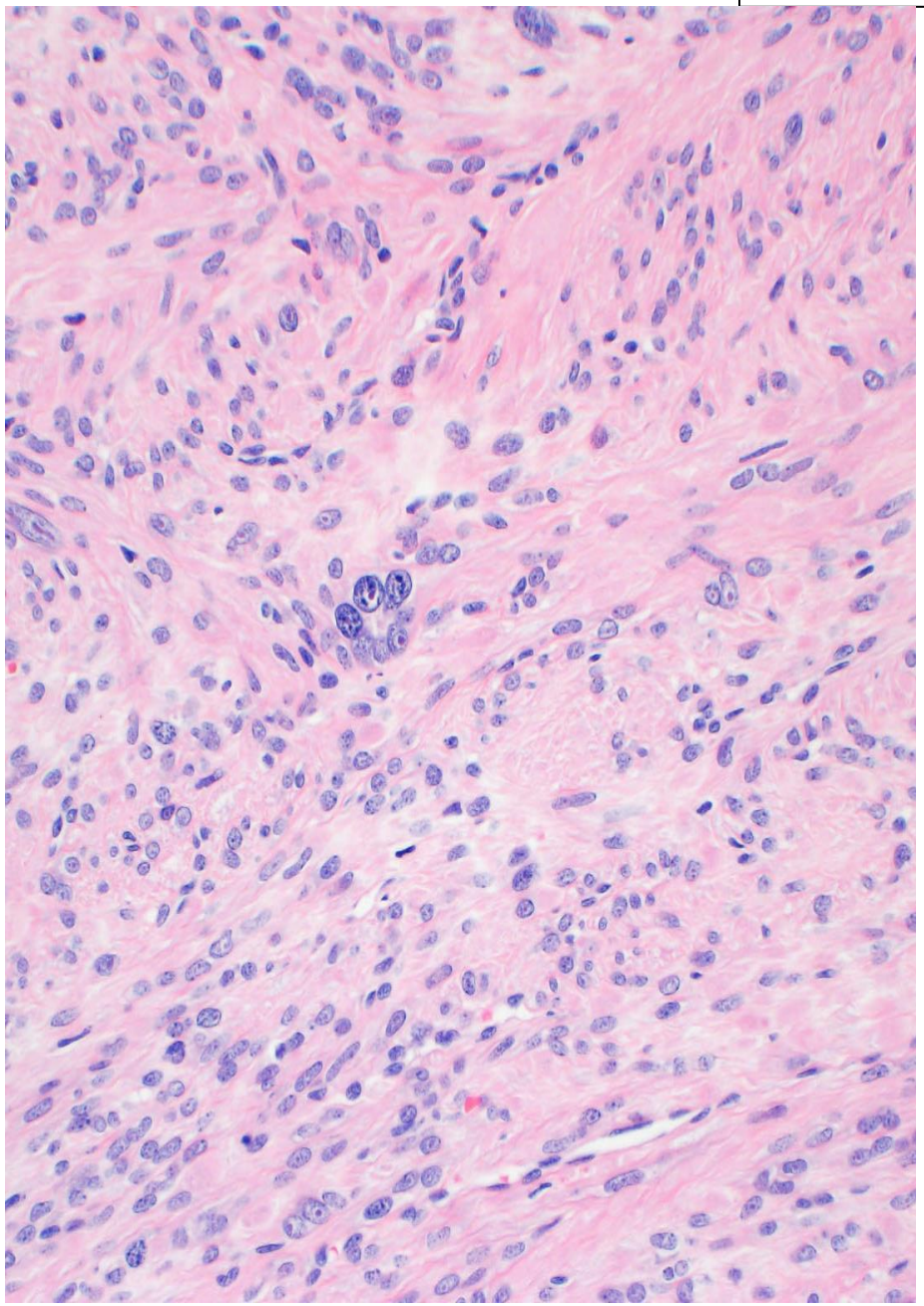

Staghorn vessels

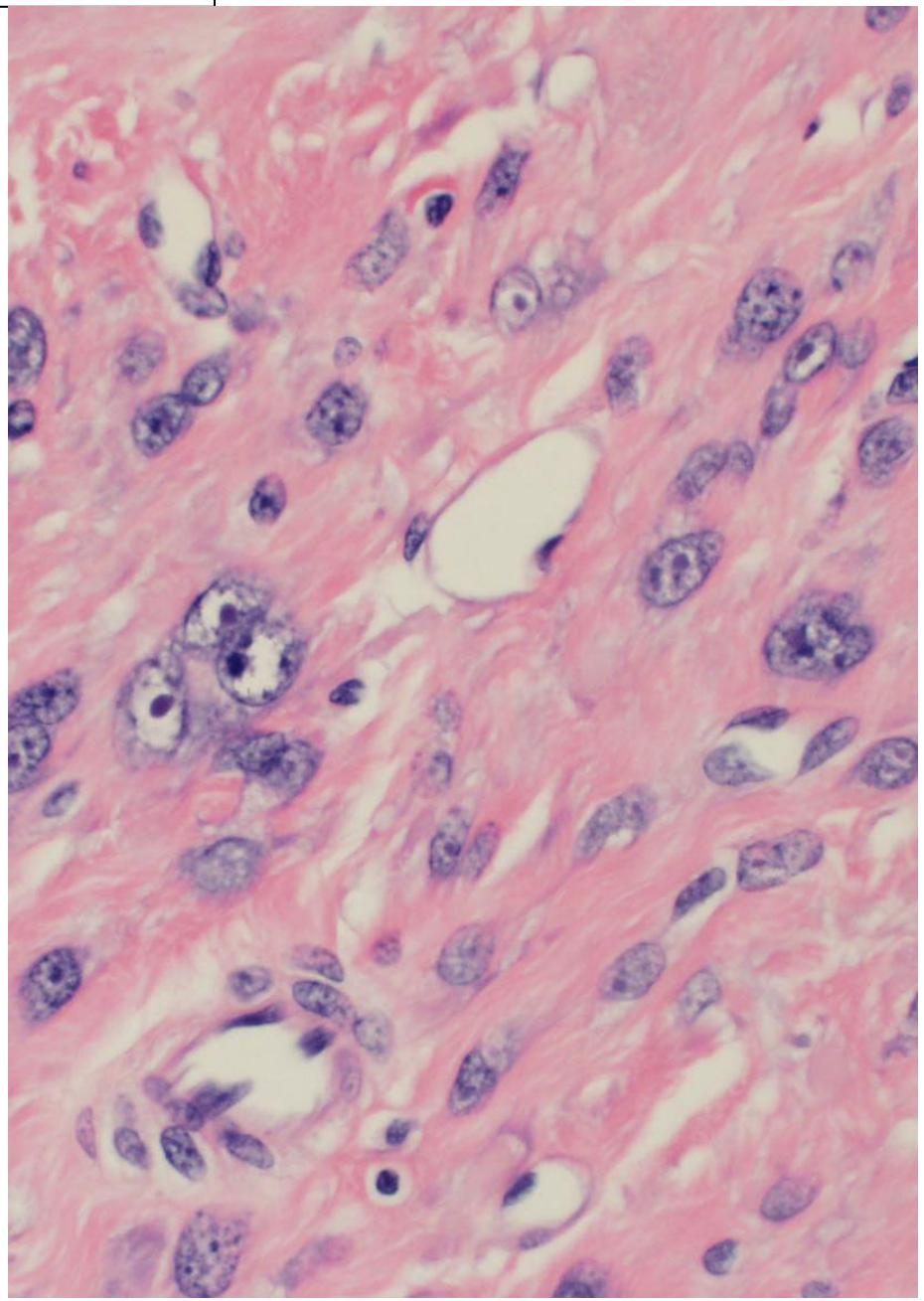

Alveolar edema

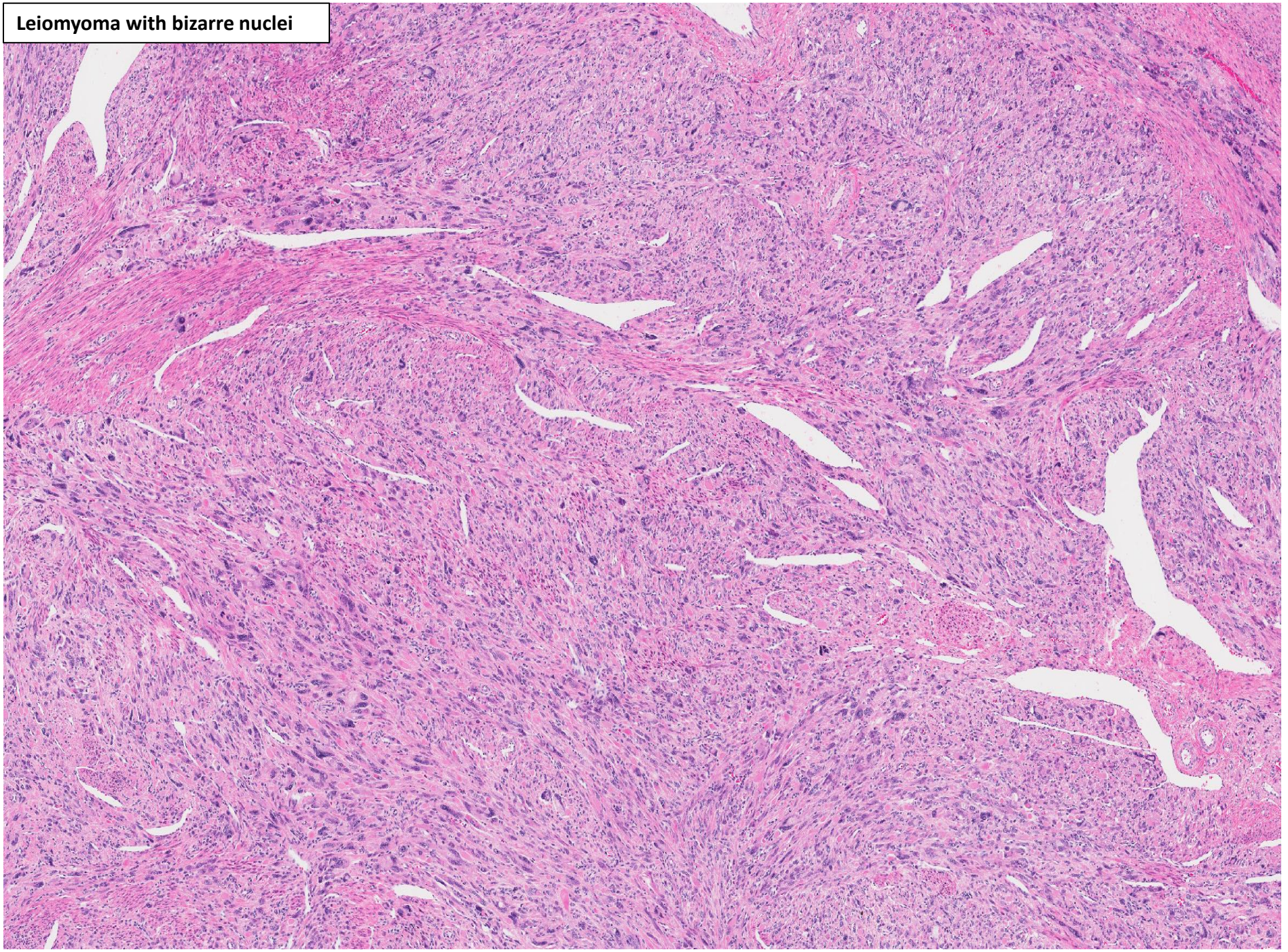

Ovoid nuclei in chains


Eosinophilic cytoplasmic inclusions

Nuclear features





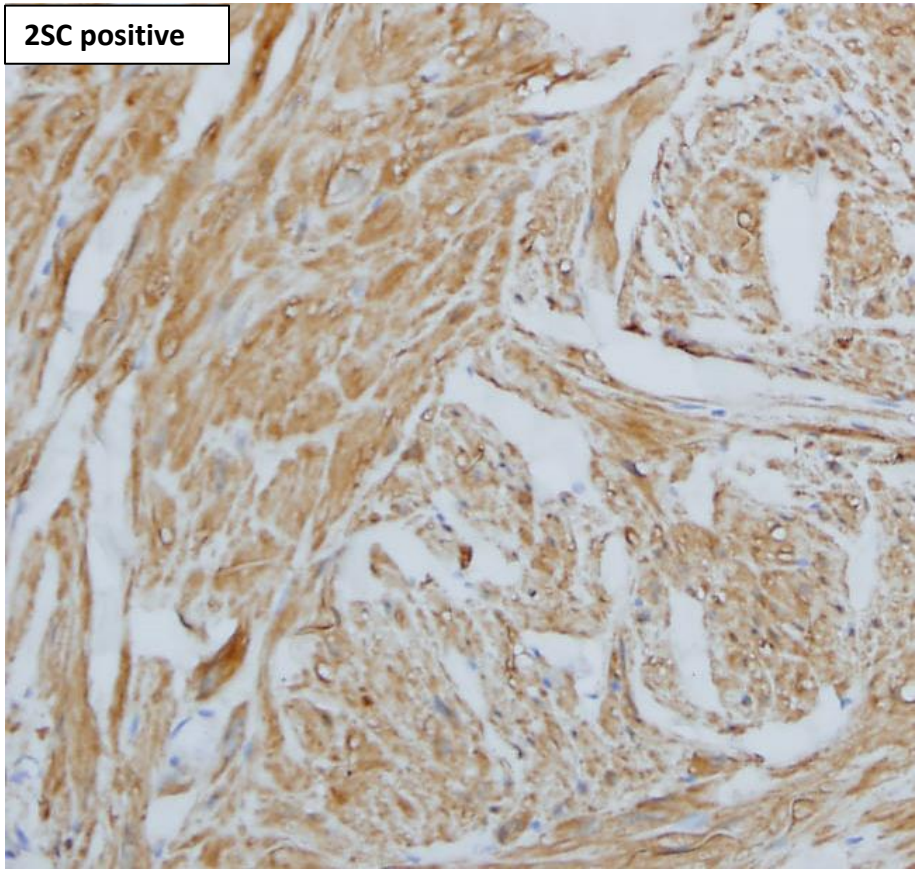

Leiomyoma with bizarre nuclei

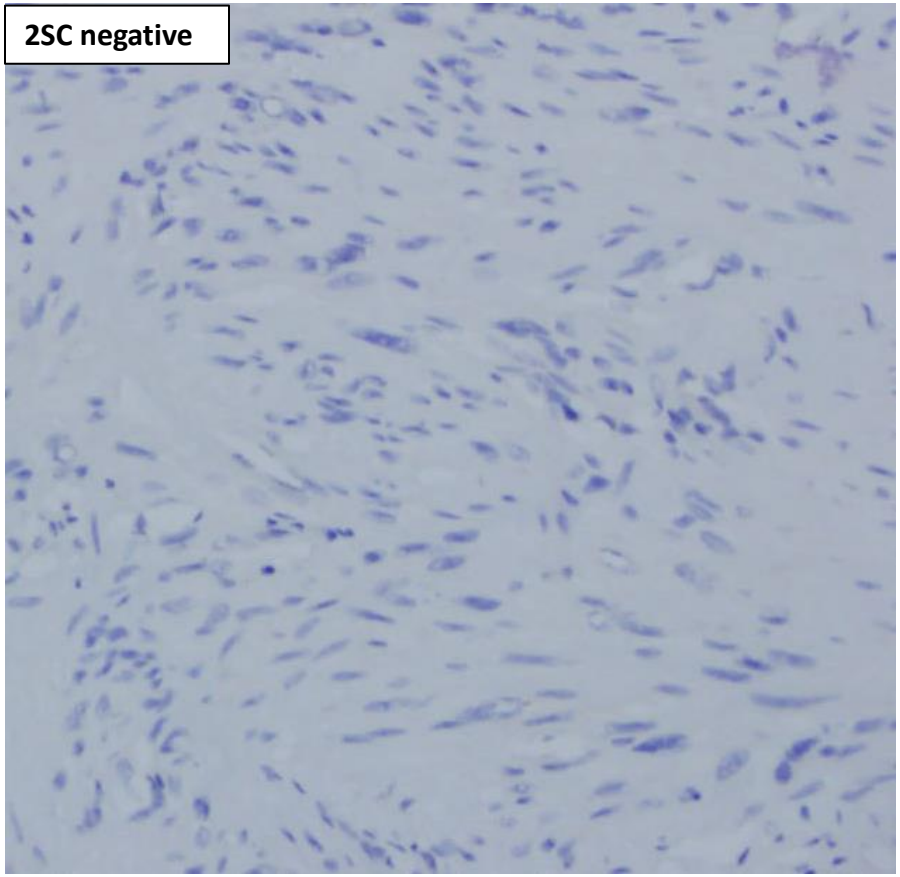
FH deficiency: Immunohistochemistry

- 2SC (2 succinocysteine)
- FH (fumarate hydratase)

2SC IHC

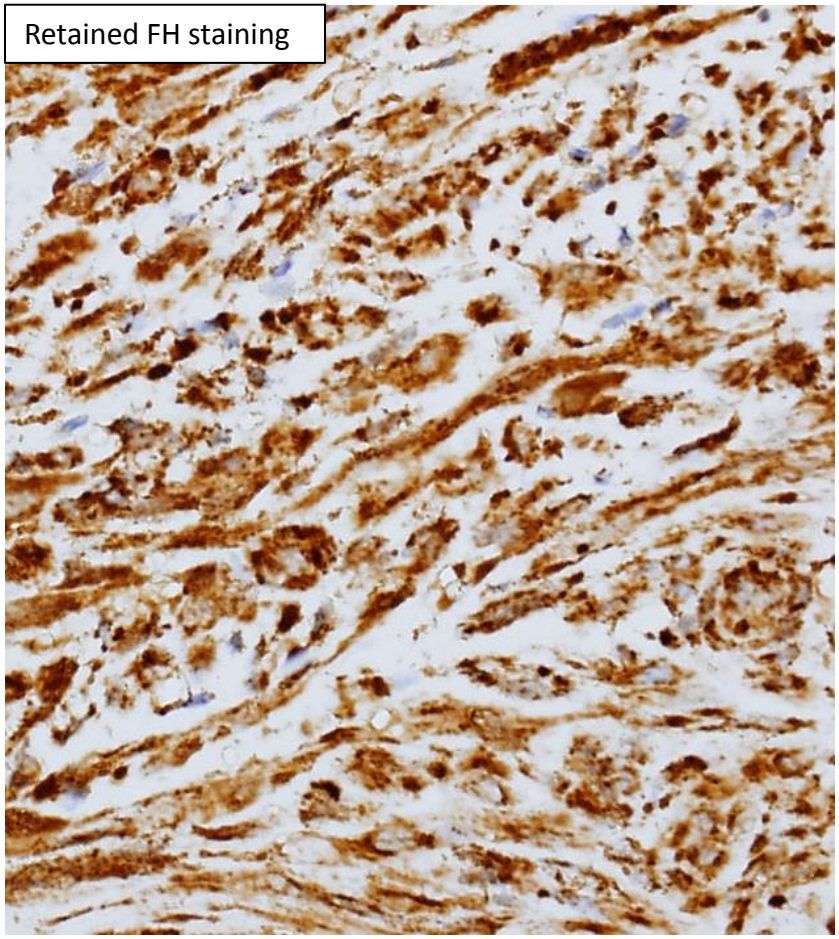
- **Positive staining for 2SC** correlates with *FH* gene mutation
- Sensitive and specific
- **Not commercially available (may have just become available!)**

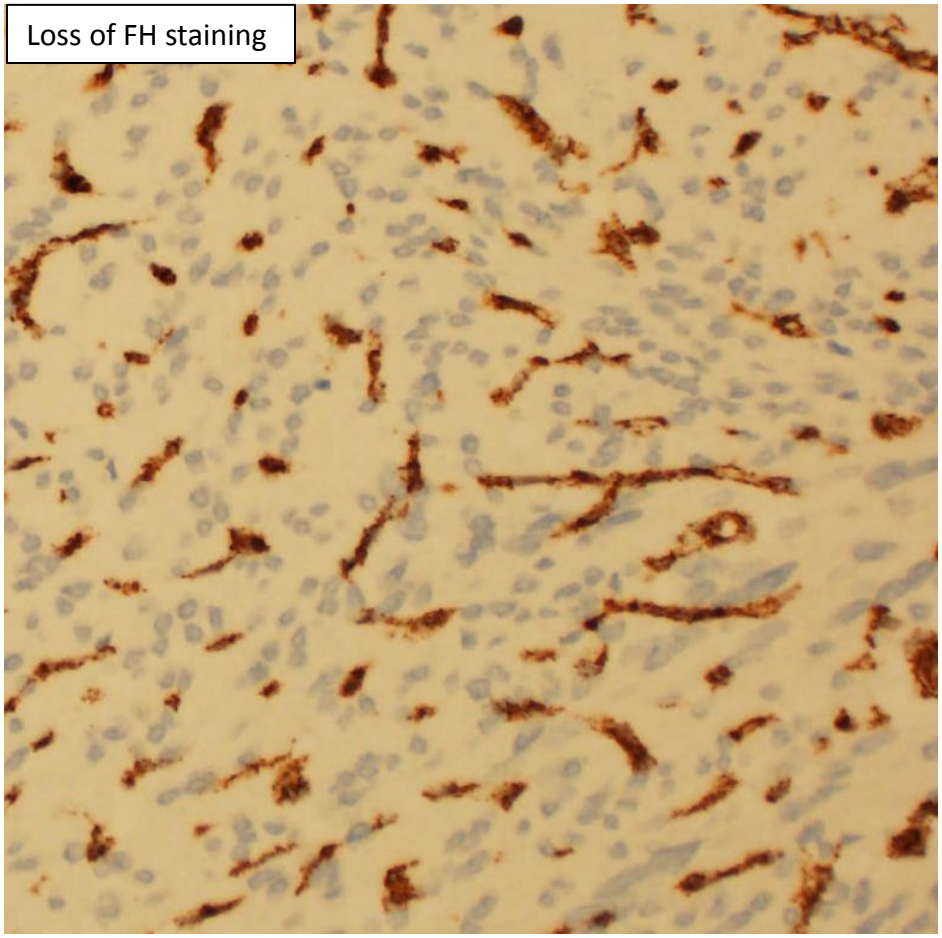




FH IHC

- Complete loss of FH staining correlates with *FH* gene mutation





FH IHC

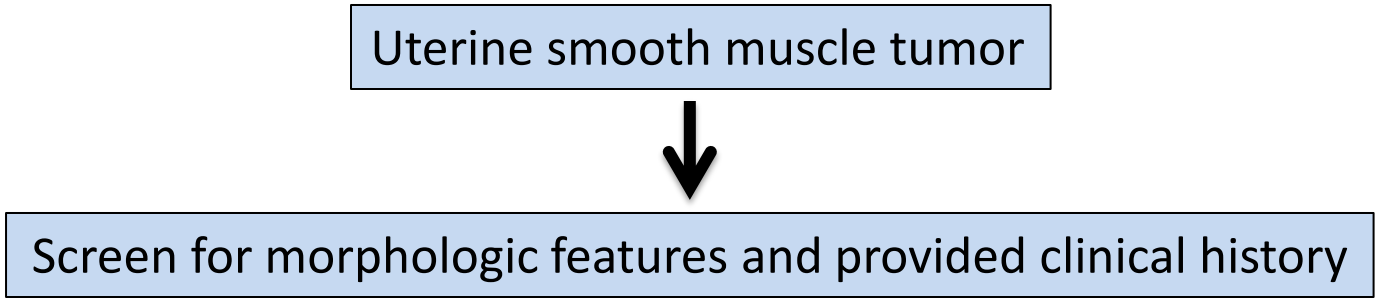
Pros:

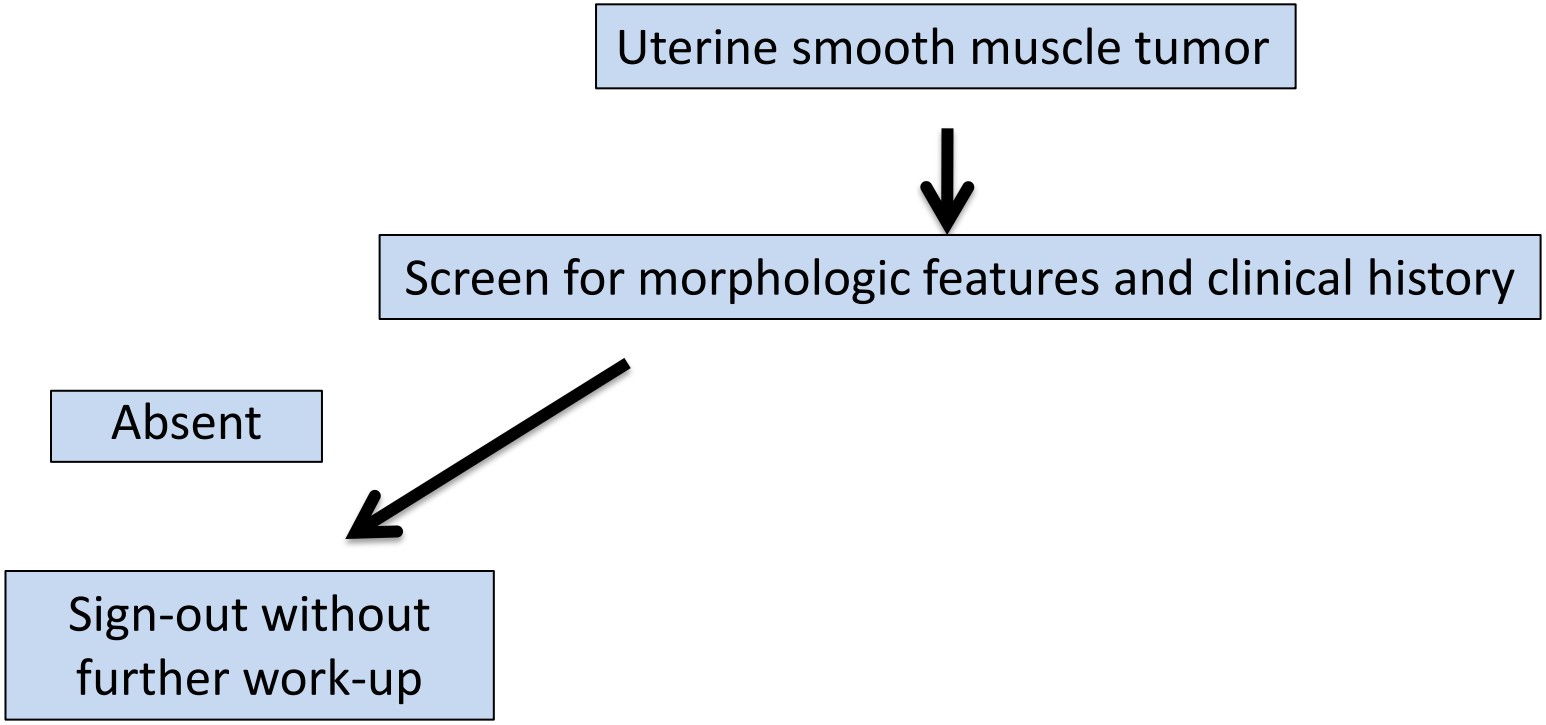
- Specific
- Commercially available

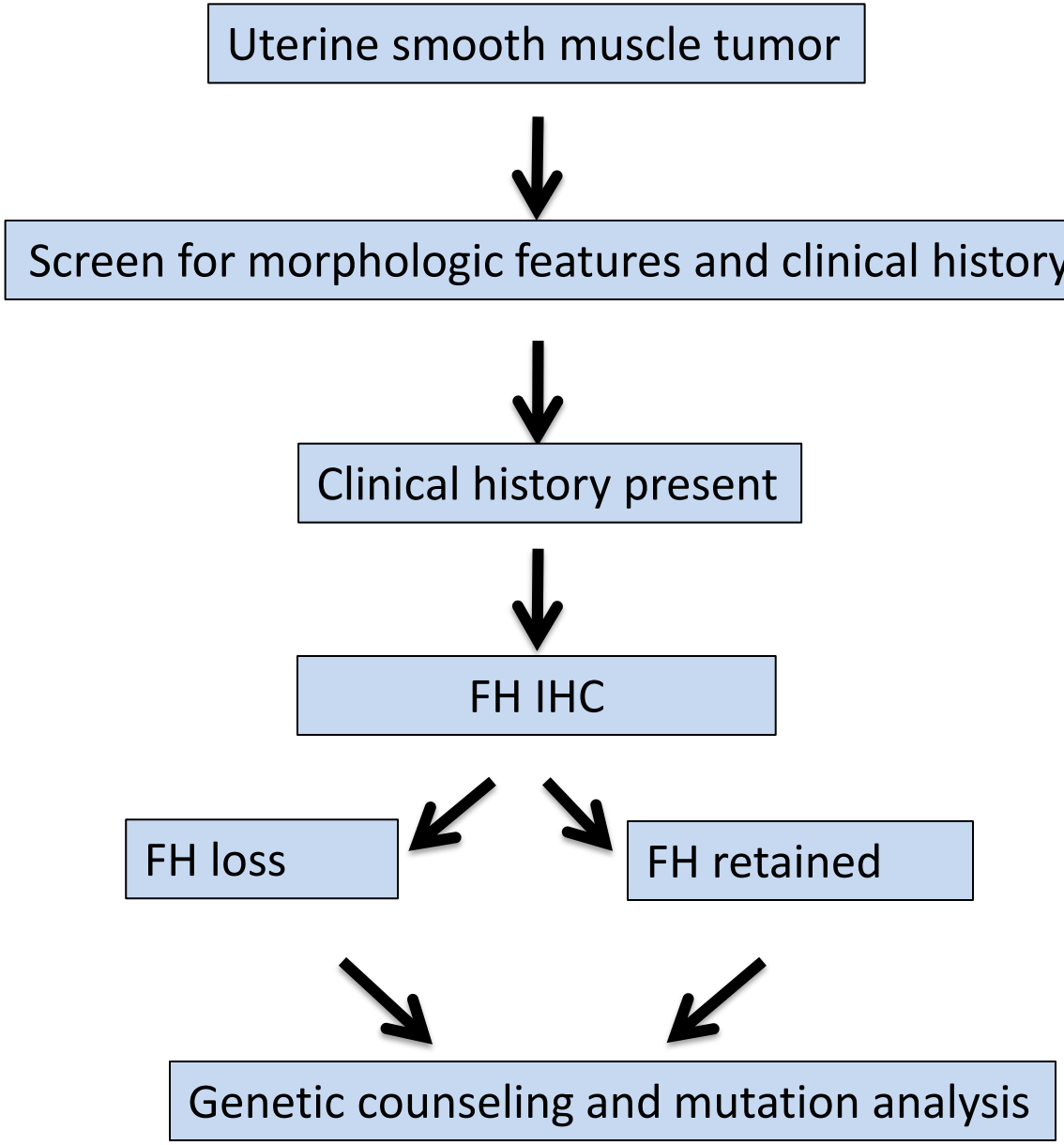
Cons:

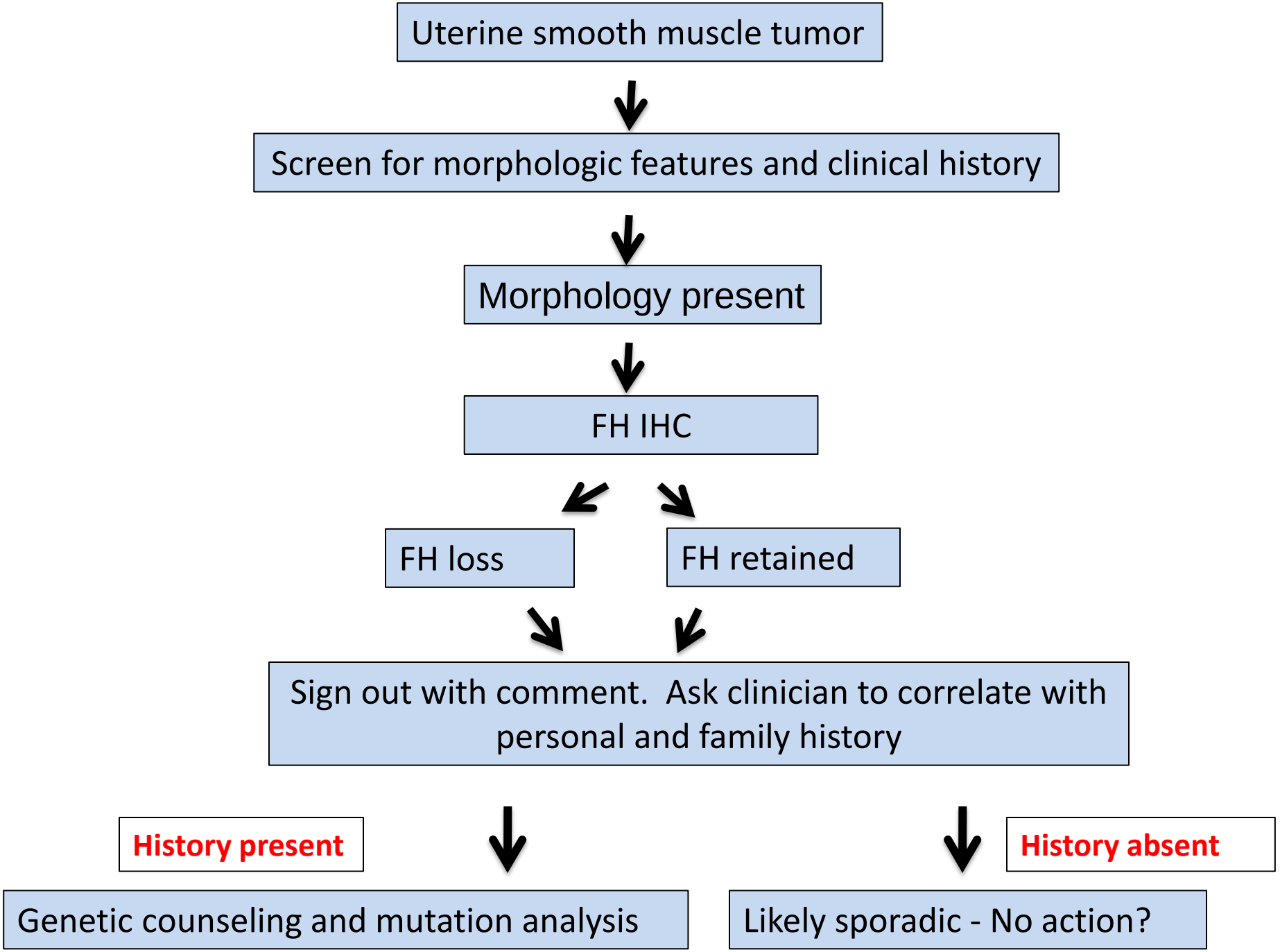
- **Low sensitivity: Retained staining in the presence of *FH* gene mutation (missense mutation)**

Proposed algorithm




Uterine smooth muscle tumor
Screen for morphologic features and clinical history
Absent
Sign-out without further work-up


Uterine smooth muscle tumor
Screen for morphologic features and clinical history
Clinical history present
FH IHC
FH loss
FH retained
Genetic counseling and mutation analysis


Uterine smooth muscle tumor
Screen for morphologic features and clinical history
Morphology present
FH IHC
FH loss
FH retained
Sign out with comment. Ask clinician to correlate with personal and family history
History present
History absent
Genetic counseling and mutation analysis
Likely sporadic - No action?

UCSF experience

Prospective Detection of Germline Mutation of *Fumarate Hydratase* in Women With Uterine Smooth Muscle Tumors Using Pathology-based Screening to Trigger Genetic Counseling for Hereditary Leiomyomatosis Renal Cell Carcinoma Syndrome

A 5-Year Single Institutional Experience

Joseph T. Rabban, MD, MPH, Emily Chan, MD, PhD,* Julie Mak, MS, LCGC,† Charles Zaloudek, MD,* and Karuna Garg, MD**

- 5 years
- FH-d morphology reported in 30 out of 2060 women with uterine leiomyomas (1.3%)
- **10 of 30 underwent genetic counseling and mutation testing**
- **5 germline *FH* mutations and 1 variant of unknown significance (VUS) detected**
- Screening program led to a confirmed genetic diagnosis of HLRCC syndrome in 0.24% of all women with any type of uterine smooth muscle tumor

HLRCC

- **Conclusions:**

Consider raising the possibility of HLRCC/FH deficiency if a uterine leiomyoma shows characteristic morphologic features (FH-d morphology) irrespective of FH IHC staining result

Example of common tumor associated with a familial syndrome

Pathology report

Diagnosis:

- Uterus, myomectomy: Leiomyoma with features of FH deficiency; see comment.

Diagnosis comment: The leiomyoma shows morphologic features that have been described to be associated with FH deficiency. This could be due to sporadic or germline (HLRCC) *FH* mutation. Correlation with personal and family history is recommended. If there is any suggestive history – patient should be referred for genetic counseling and mutation testing

HLRCC: Clinical implications

- **Surveillance for renal cell carcinoma:**

Annual MRI (with renal protocol) starting at age 8 years

Recommendations for surveillance in HLRCC reported in literature

Age to start surveillance	Modalities for surveillance	Interval between imaging procedures	Remarks	Reference
5 years	CT, MRI, ultrasound	6 months	Baseline CT followed by ultrasound; MRI if available	23
20 years	MRI, ultrasound	6 months	Alternating MRI and ultrasound	6
18-20 years	Contrast-enhanced MRI	at least every 12 months	Option for surveillance < 18 years in families with very early onset RCC	7
8 years	Contrast-enhanced MRI	12 months		HLRCC Family Alliance 2013; National Cancer Institute; http://www.hlrccinfo.org
10 years	MRI	12 months		Expert National Center for Rare Cancers PREDIR 2012; French National Cancer Institute; http://www.predir.org/View/maladies.aspx

Menko, et al. Fam Cancer 2014

Summary

- **Rare gynecologic cancer predisposition syndromes**
  - **DICER1**
  - **RTPS2**
  - **HLRCC**

- **Role of the pathologist**

- **Surgical pathology report**

Thank you!