

A photograph of the Harvard Medical School building, a grand neoclassical structure with a portico supported by columns. The words "HARVARD MEDICAL SCHOOL" are visible on the pediment. The building is set on a green lawn with trees in the foreground and modern buildings in the background.

# Recent Discoveries on the Diagnosis and Pathogenesis of Mesothelioma

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Harvard Medical School

Senior Pathologist  
Brigham and Women's Hospital

# Mesothelioma

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- **Introduction**
- **WHO Update on Classification**
  - **Morphologic features**
    - Histologic subtypes with clinical significance
    - Grading
  - **Immunohistochemical features**
- **Genetics and Pathogenesis**

# Mesothelioma

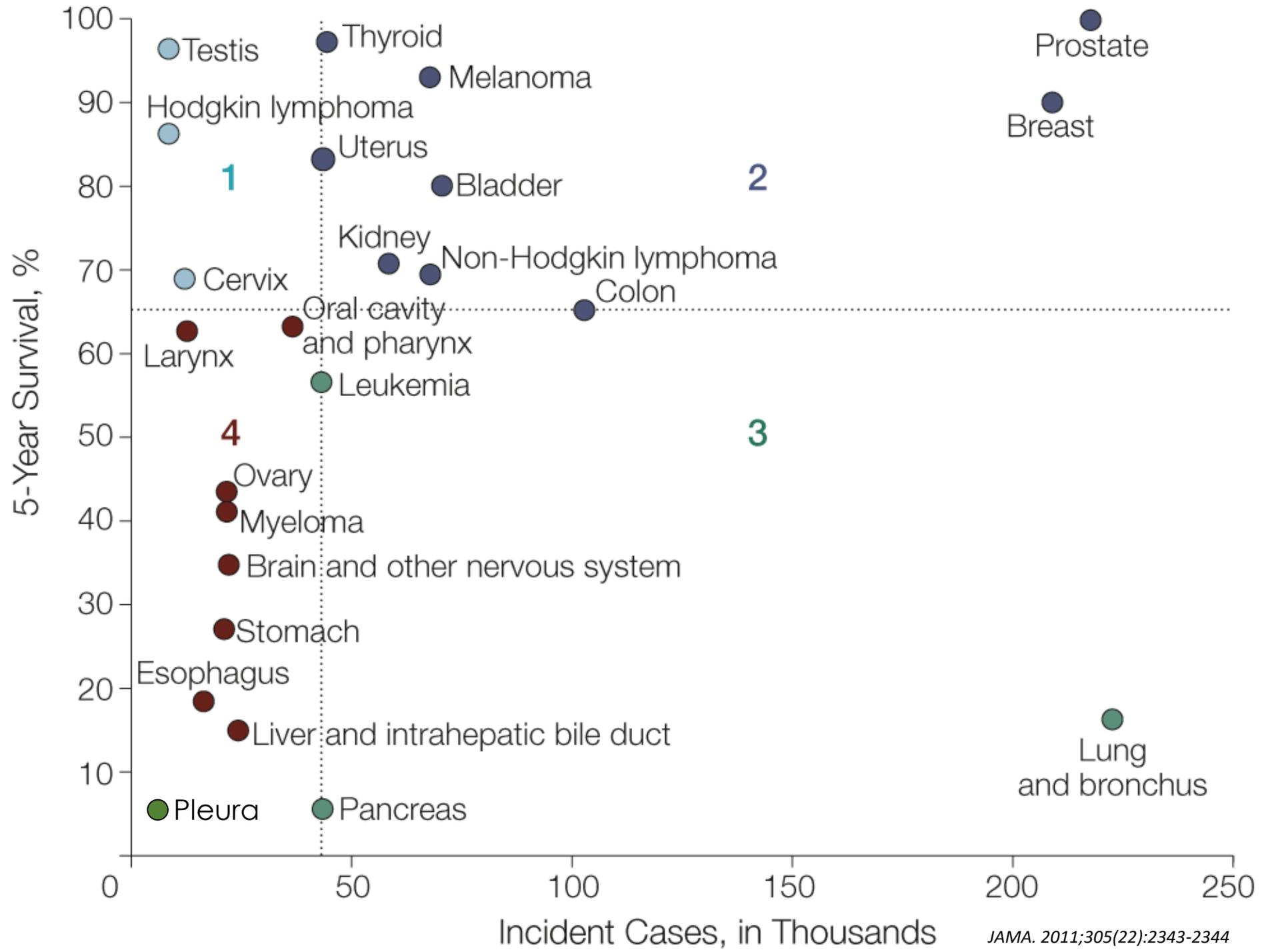
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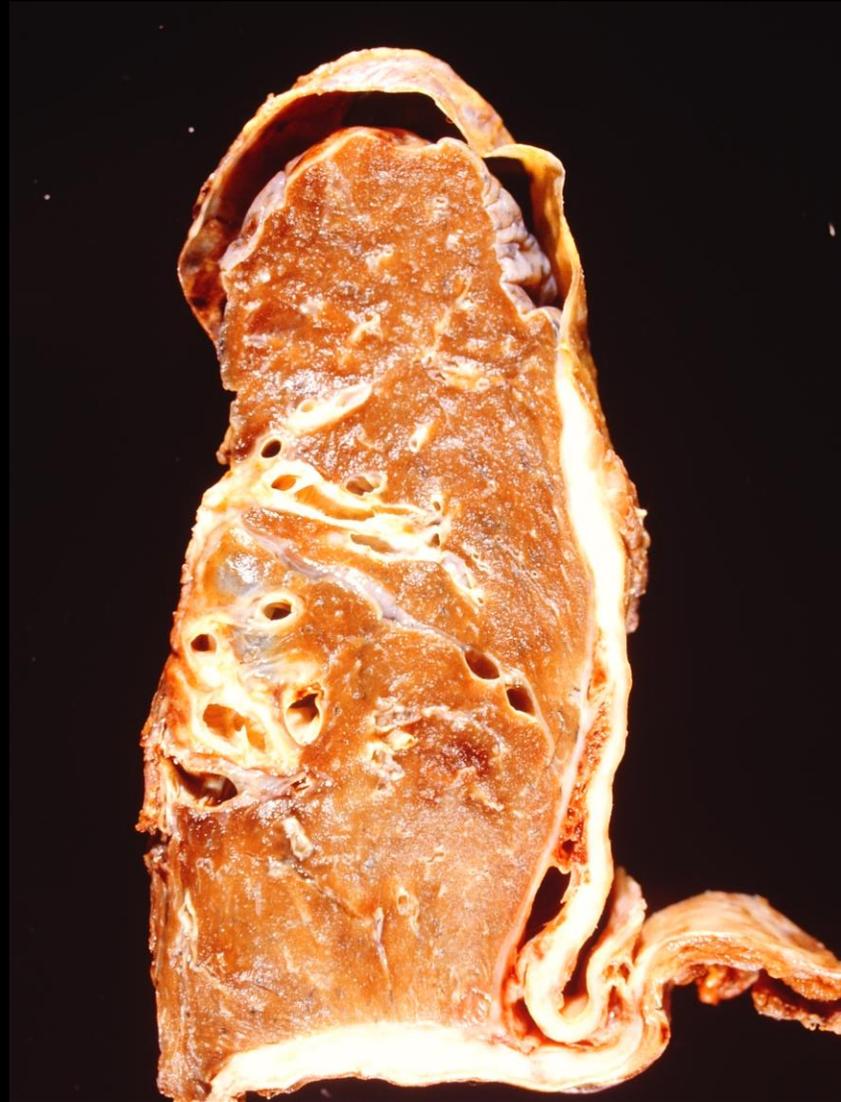
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- **Introduction**
  - Annual incidence in USA is 3000 cases
  - Pleural mesothelioma accounts for 90%, peritoneal 9%, pericardium and tunica vaginalis testis the remainder
  - Median overall survival is 1 year
  - 5-year survival is about 5%
  - Mainly seen in older men, median age at diagnosis 72
  - Asbestos exposure reported in 80%, usually decades earlier
  - Work exposure is most common route



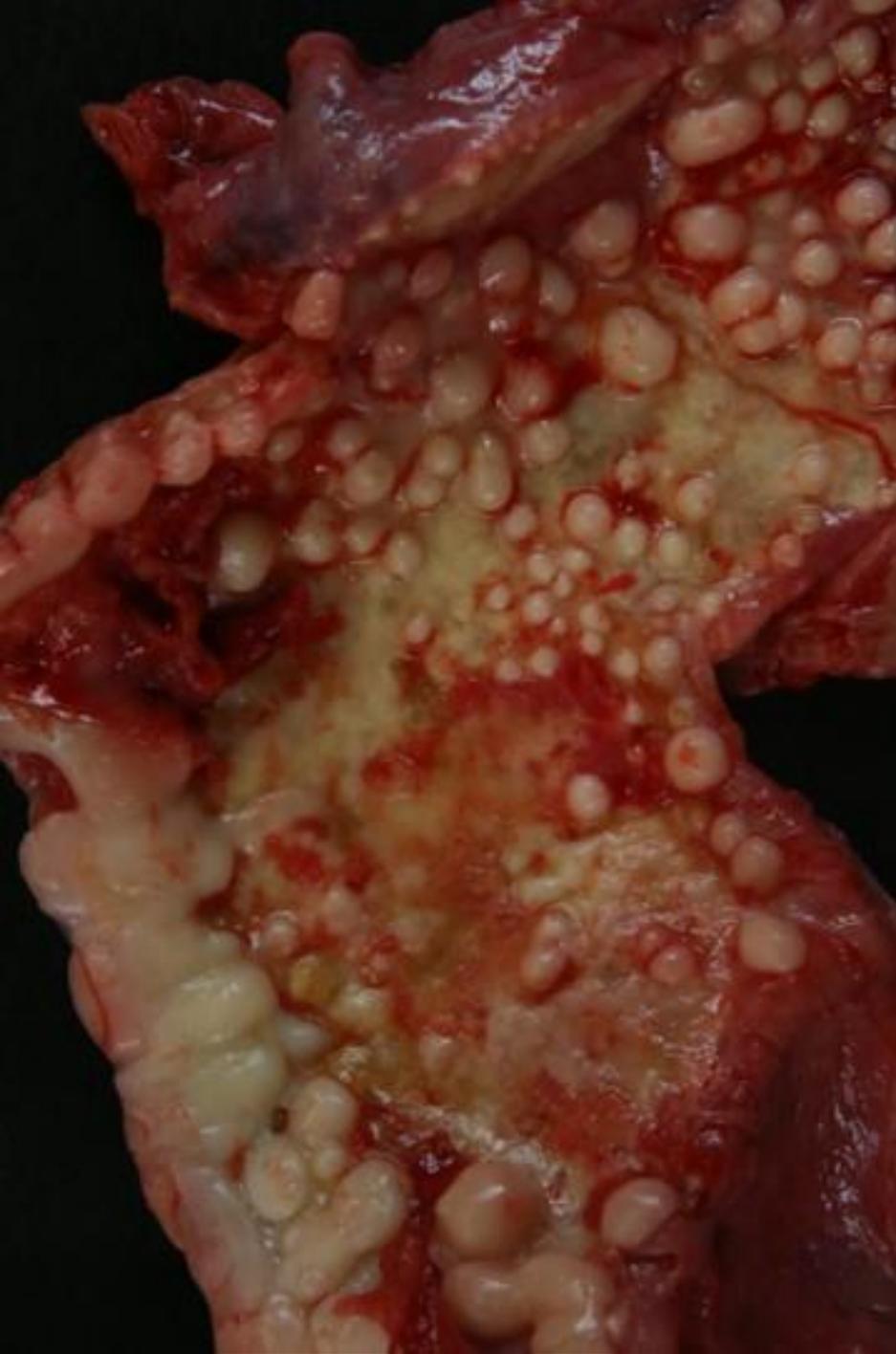


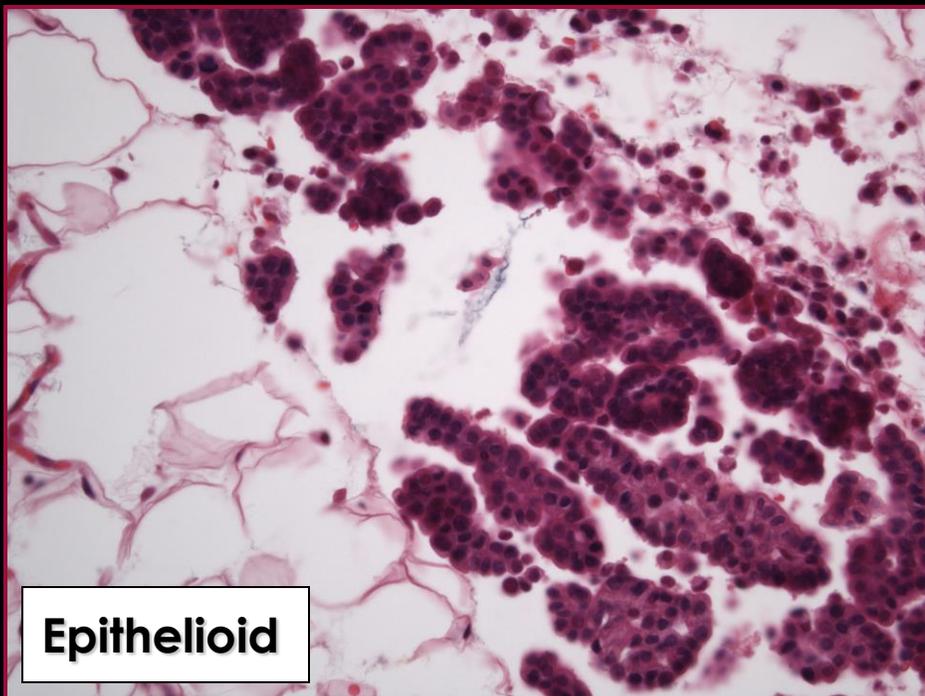
Mesothelioma in 18-year-old woman metastatic to lymph nodes.  
No known asbestos exposure.



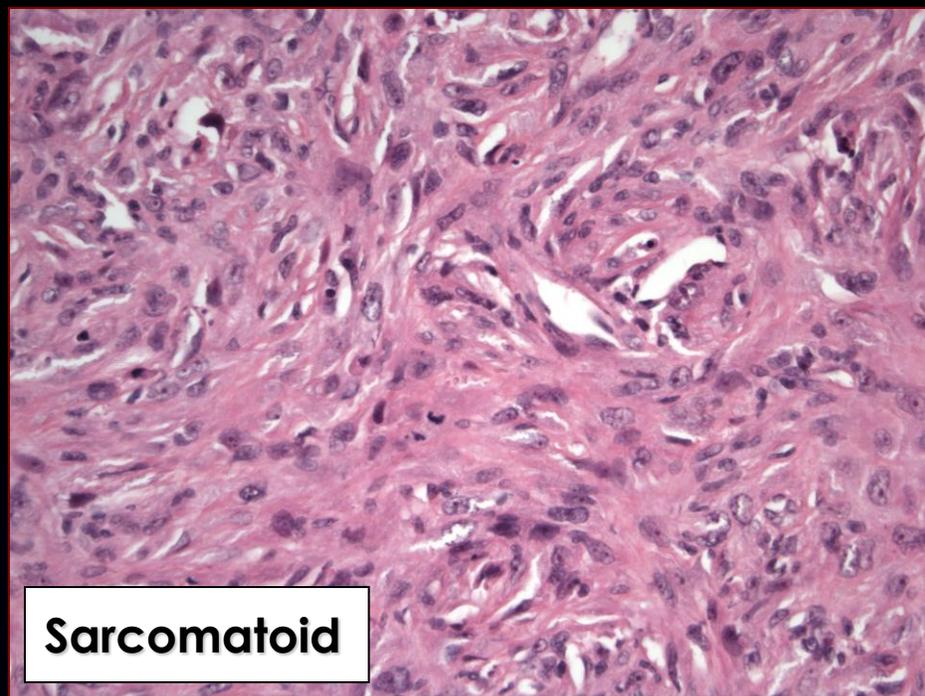
Mesothelioma, sarcomatoid type in a man.

Courtesy, Tyler Janovitz, M.D., Ph.D.

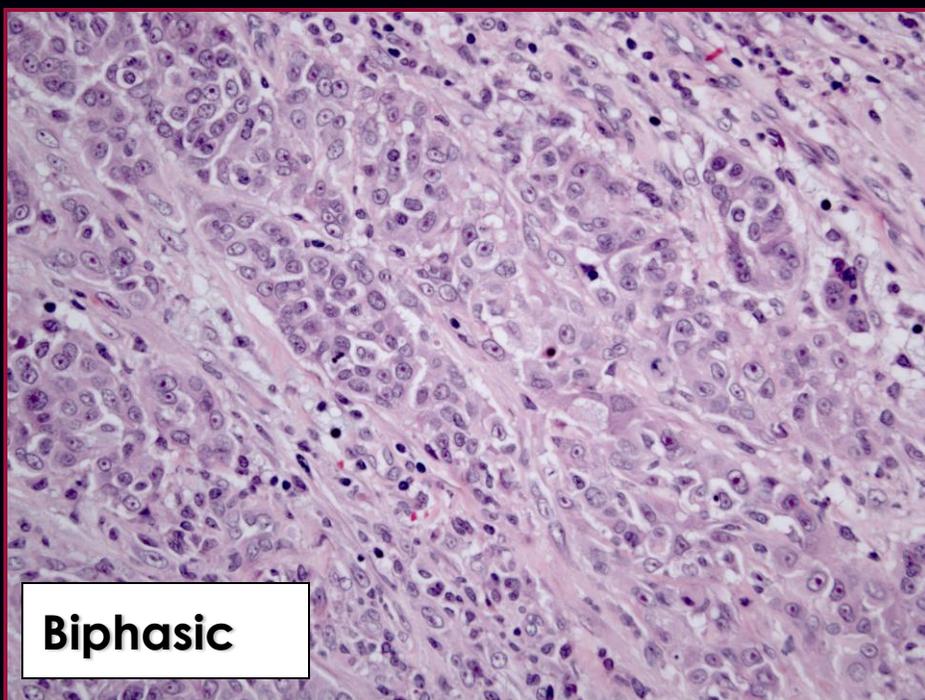




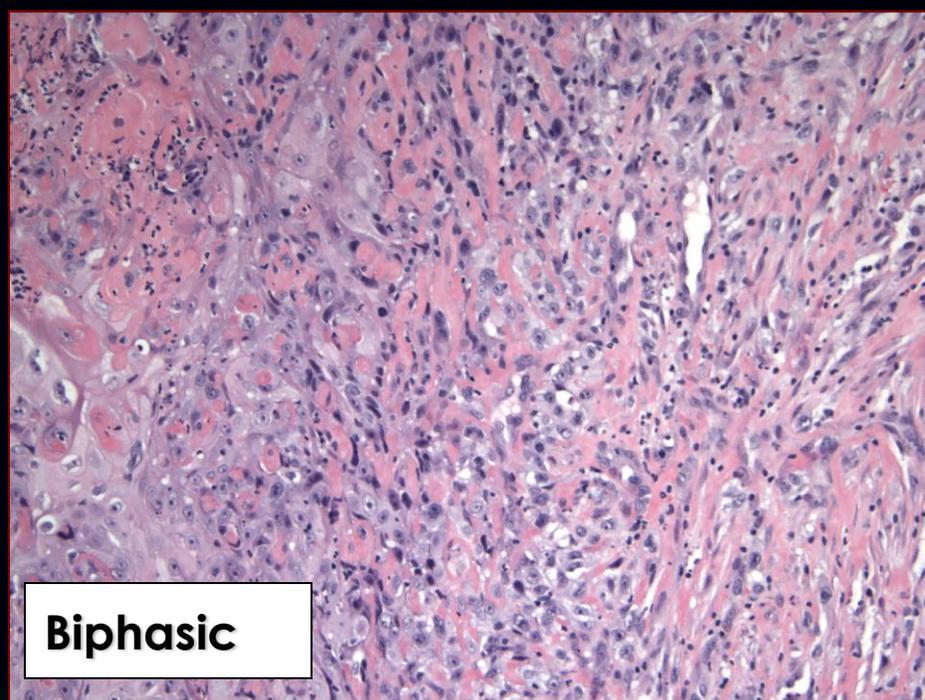
**Epithelioid**



**Sarcomatoid**

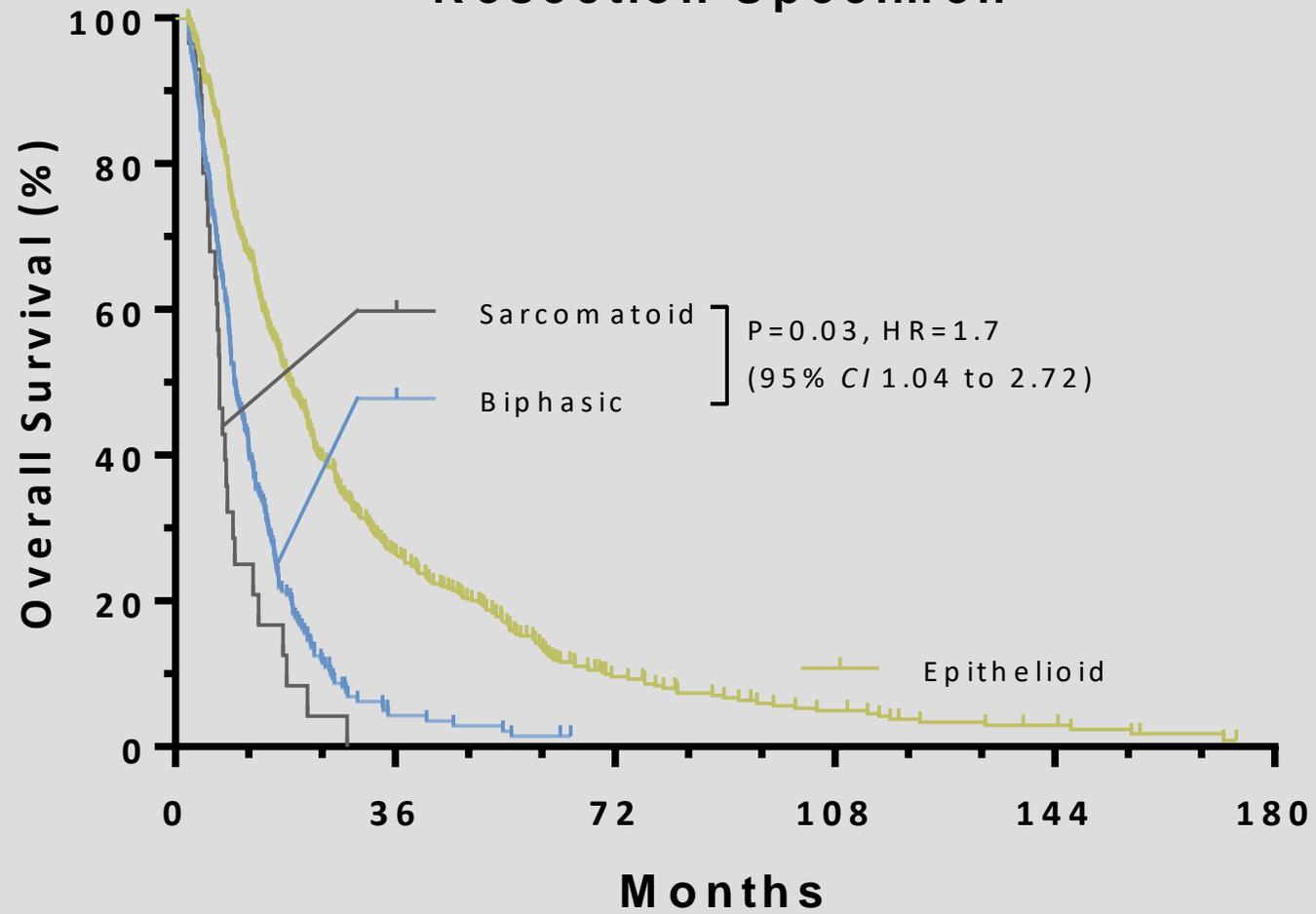


**Biphasic**



**Biphasic**

# Resection Specimen



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# WHO Classification of Tumors

IARC 2021 5<sup>th</sup> ed; vol 5

Changes from the Previous 2015 Edition

- **New entity:** Mesothelioma in Situ
- **New Terminology:** Diffuse ~~Malignant~~ Pleural Mesothelioma
- **New Terminology:** Localized ~~Malignant~~-Pleural Mesothelioma
- **New Terminology:** Well-differentiated papillary mesothelial mesothelioma tumour (WDPMT)
- **New cytological features:** Transitional features is now classified under sarcomatoid mesothelioma.
- **Genetic tumour syndromes involving the thorax:** BAP1 tumour predisposition syndrome is a hereditary cancer syndrome caused by heterozygous germline pathogenic variants in the *BAP1* (BRCA1 associated protein 1) gene.

# Histologic Subtypes and Patterns of Mesothelioma

## ■ Epithelioid Mesothelioma

- Tubulopapillary
- Micropapillary
- Trabecular
- Acinar
- Adenomatoid
- Solid
- Clear cell
- Deciduoid
- Adenoid cystic
- Signet ring cell
- Small cell
- Rhabdoid
- Pleomorphic

## ■ Sarcomatoid Mesothelioma

- Conventional, spindle cell
- Desmoplastic
- Heterologous differentiation (osteosarcomatous, chondrosarcomatous, etc.)
- Lymphohistiocytoid (may also be classified as epithelioid)
- Transitional

## ■ Biphasic/Mixed

# Histologic Subtypes and Patterns of Mesothelioma

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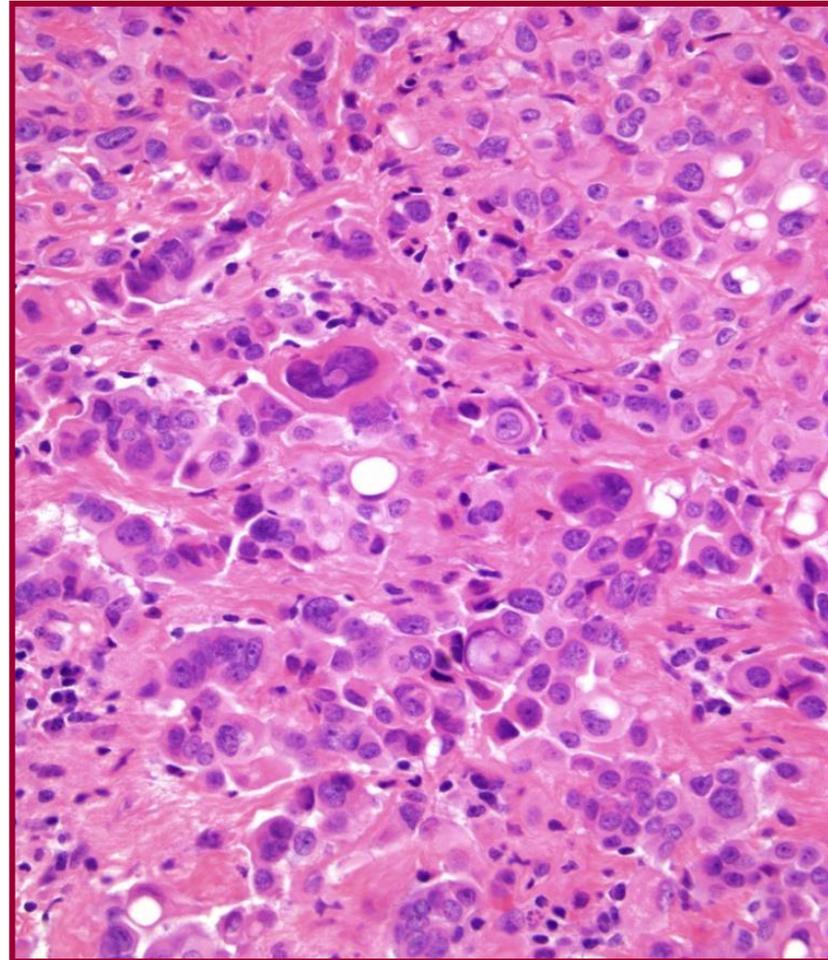
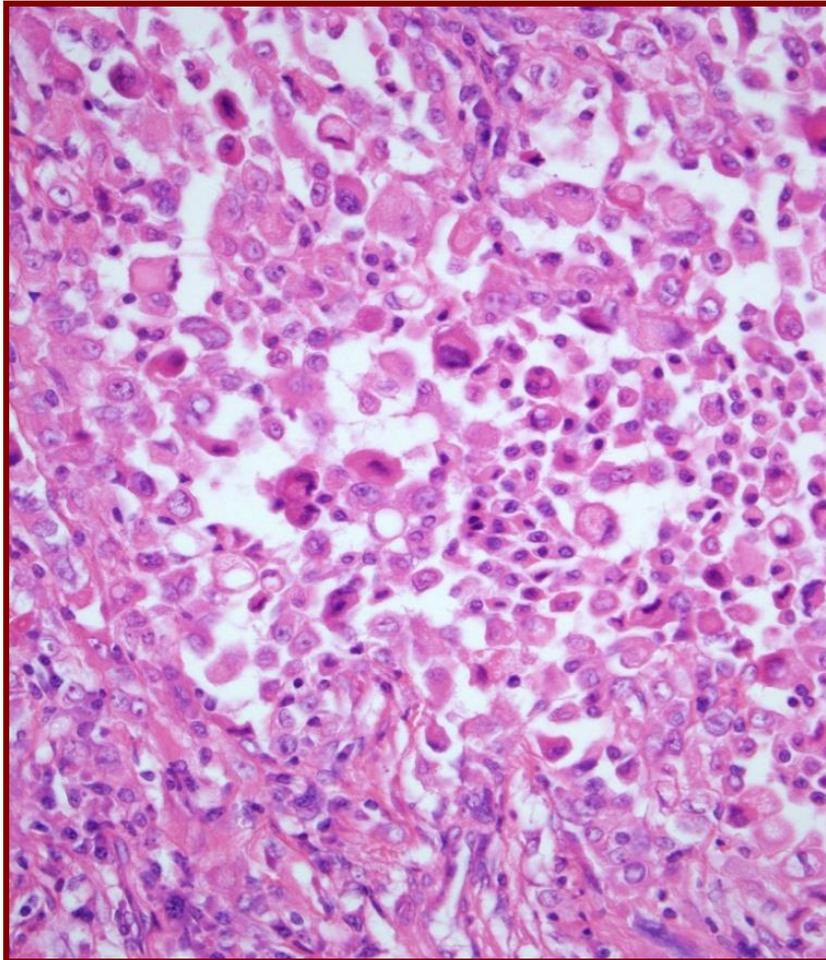
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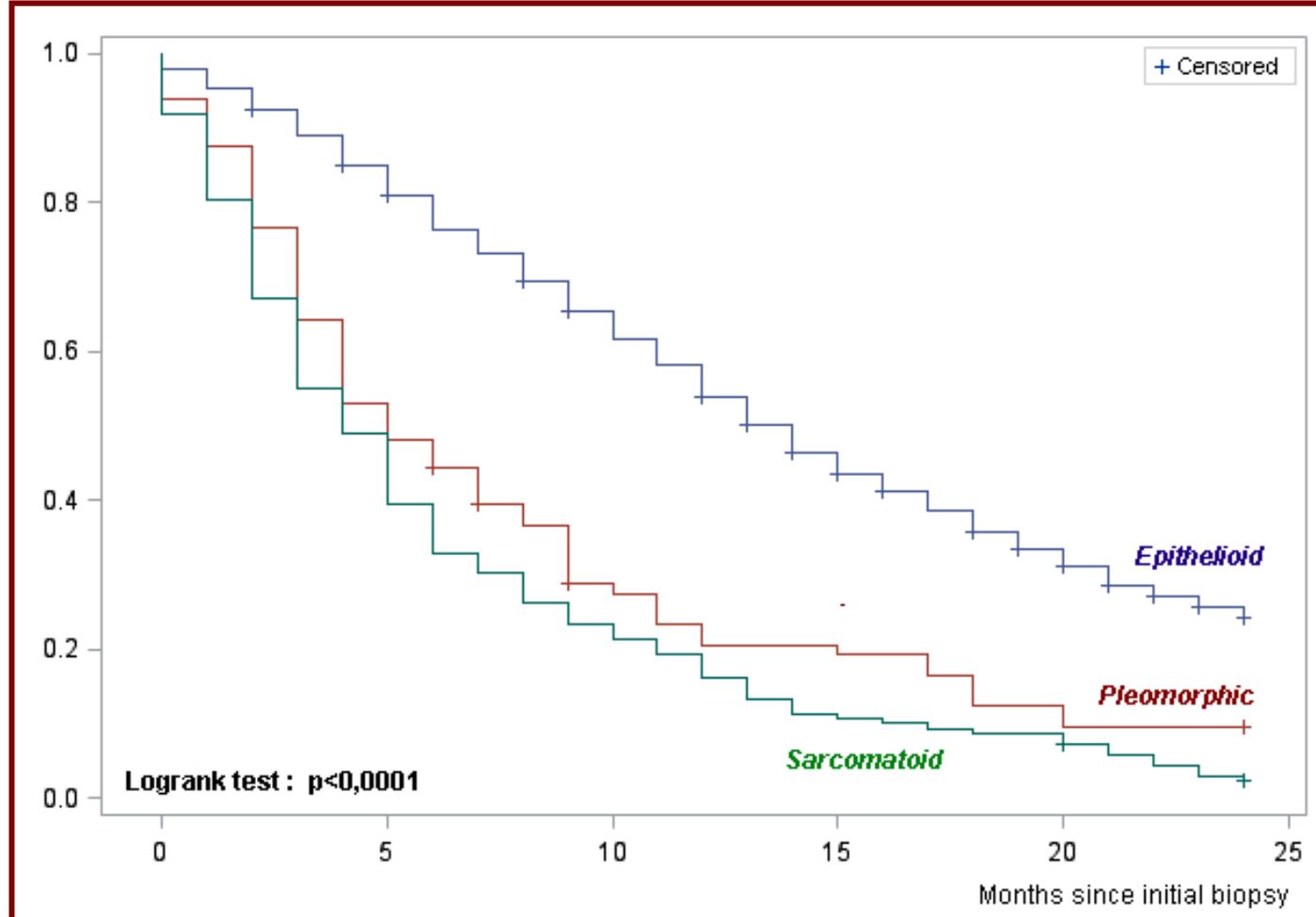
## ■ Biphasic/Mixed

# Mesothelioma

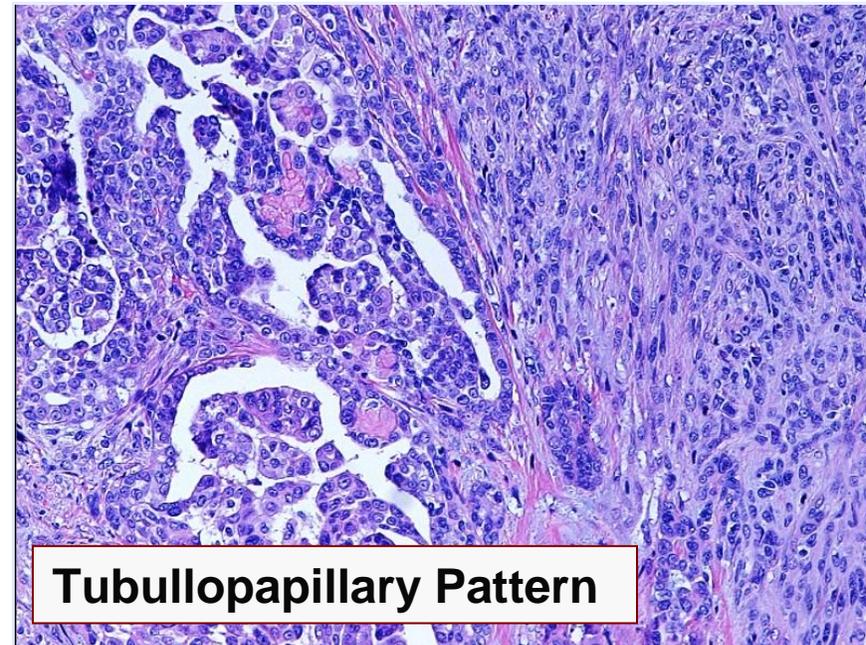
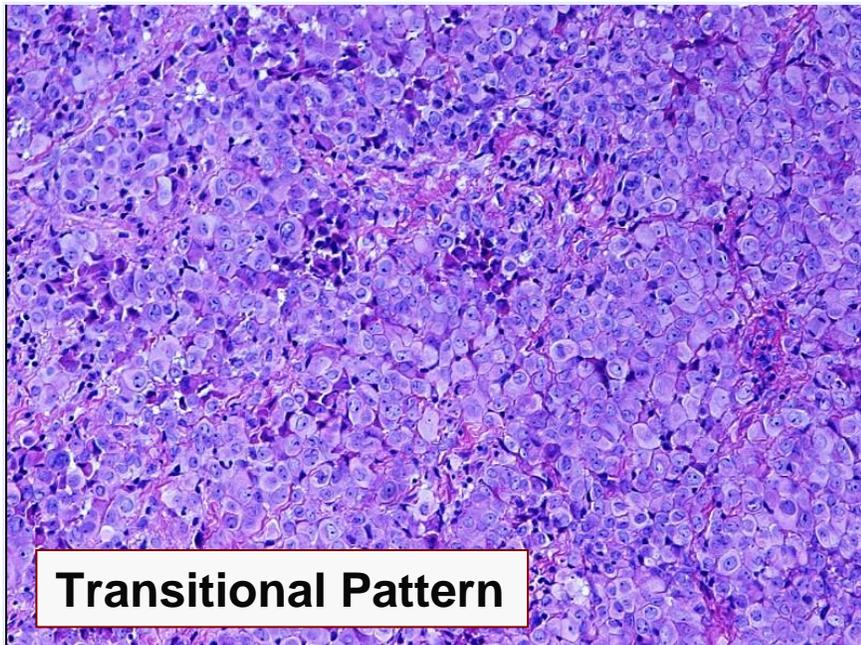
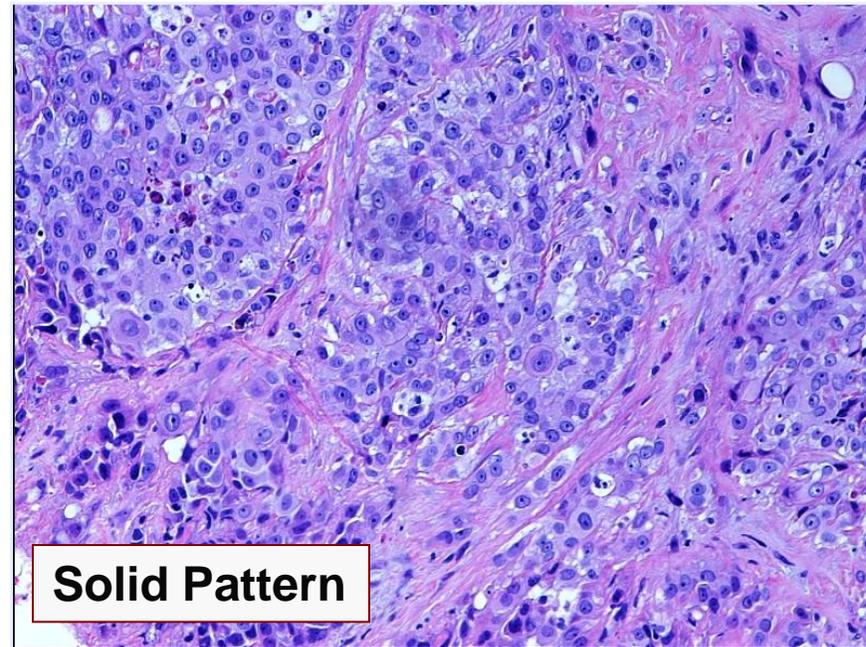
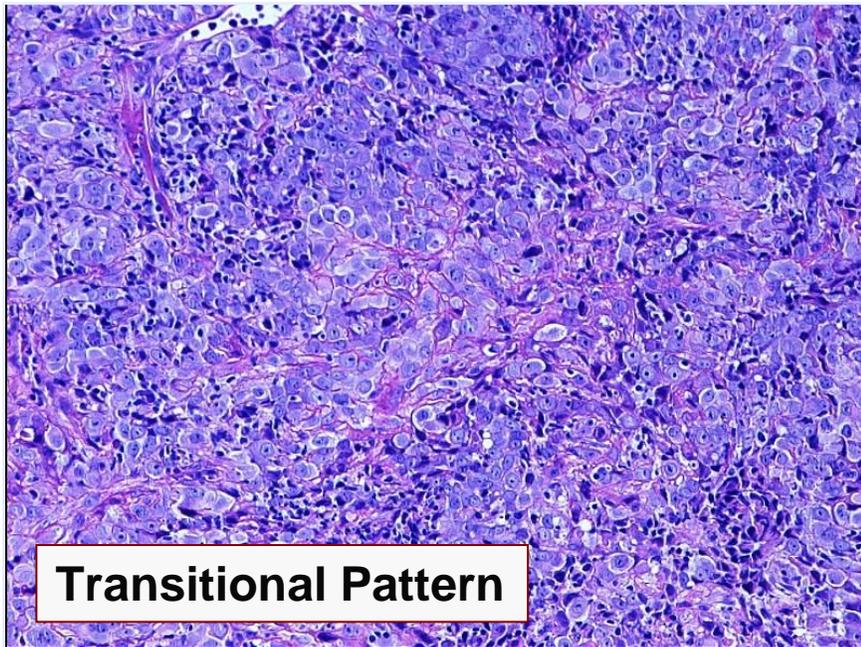
## Pleomorphic Histology

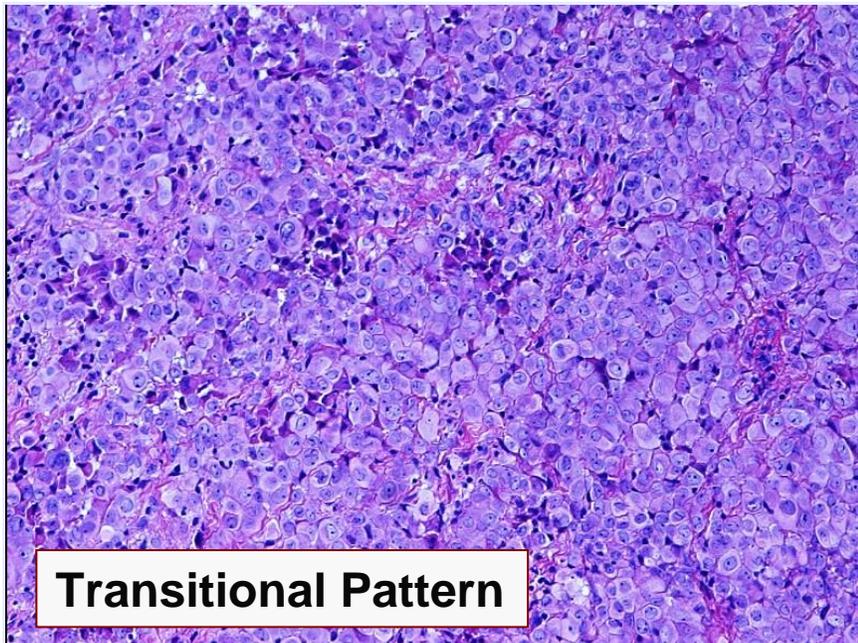
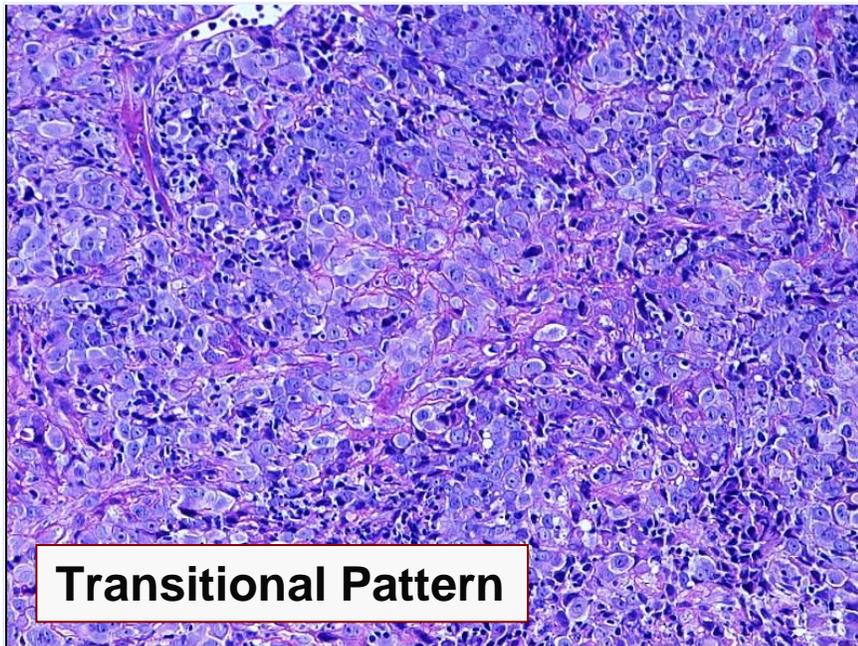


# Overall survival by histologic type in 2582 patients with diffuse pleural mesothelioma



Vivero M, et al.

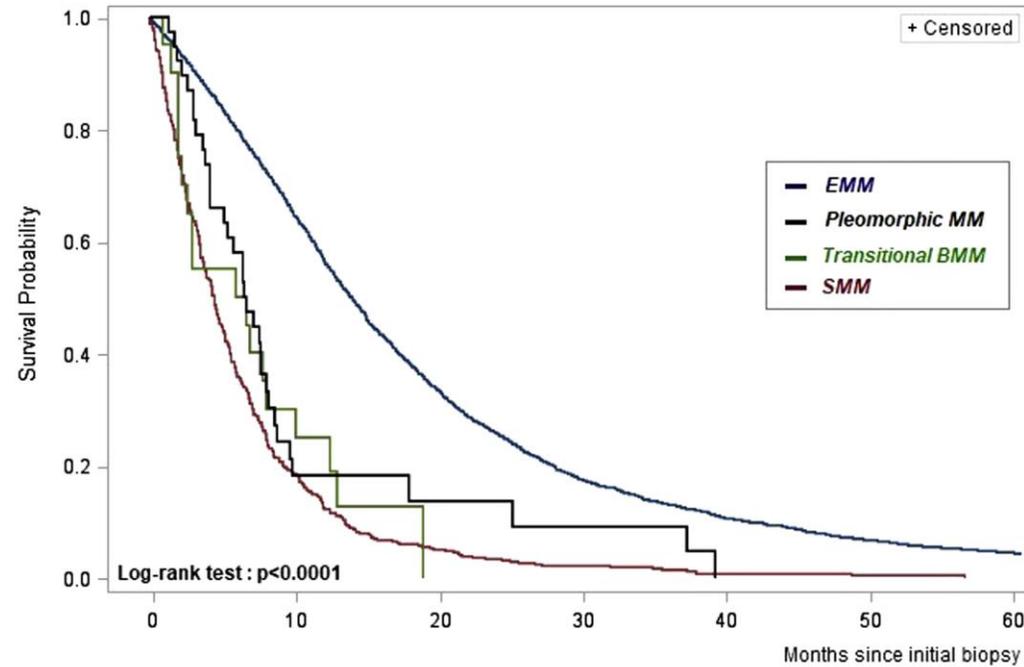




## TRANSITIONAL PATTERN

- Sheets of plump cells starting to lose their epithelioid morphology.
- But not overtly spindle shaped.
- And lacking frank sarcomatous features.
- The transitional pattern could be diffuse covering the entire sample or only focal.

# Overall Median Survival Curves by Histologic Types and Comparison with Transitional and Pleomorphic Patterns



	N	Median	1 yr-survival [CI95%]	2 yrs-survival [CI95%]	5 yrs-survival [CI95%]
EMM	5219	14 mos	55% [53%; 57%]	24% [23%; 26%]	4% [3%; 5%]
Pleomorphic MM	40	7 mos	18% [5%; 31%]	13% [1%; 25%]	0%
Transitional BMM	16	6 mos	19% [0%; 38%]	0%	0%
SMM	465	4 mos	12% [9%; 15%]	3% [1%; 5%]	0%

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## Diagnostic Utility of Detection Assays for Distinguishing Epithelioid Mesothelioma From Reactive Mesothelial Proliferation

**Table 1. Methylthioadenosine Phosphorylase (MTAP) and BRCA-Associated Nuclear Protein 1 (BAP1) Loss by Immunohistochemistry in Reactive Mesothelial Proliferations, Malignant Epithelioid Mesotheliomas, and Lung Adenocarcinomas**

	No.	MTAP Loss, No. (%)	BAP1 Loss, No. (%)	MTAP or BAP1 Loss, No. (%)
Reactive mesothelial proliferation	17	0 (0)	0 (0)	0 (0)
Malignant epithelioid mesothelioma				
Pleural	18	12 (67)	11 (61)	17 (94)
Peritoneal	2	1 (50)	0 (0)	1 (50)
Total	20	13 (65)	11 (55)	18 (90)
Lung adenocarcinoma	21	4 (14)	0 (0)	0 (0)
High-grade serous ovarian carcinoma	12	1 (8)	0 (0)	1 (8)

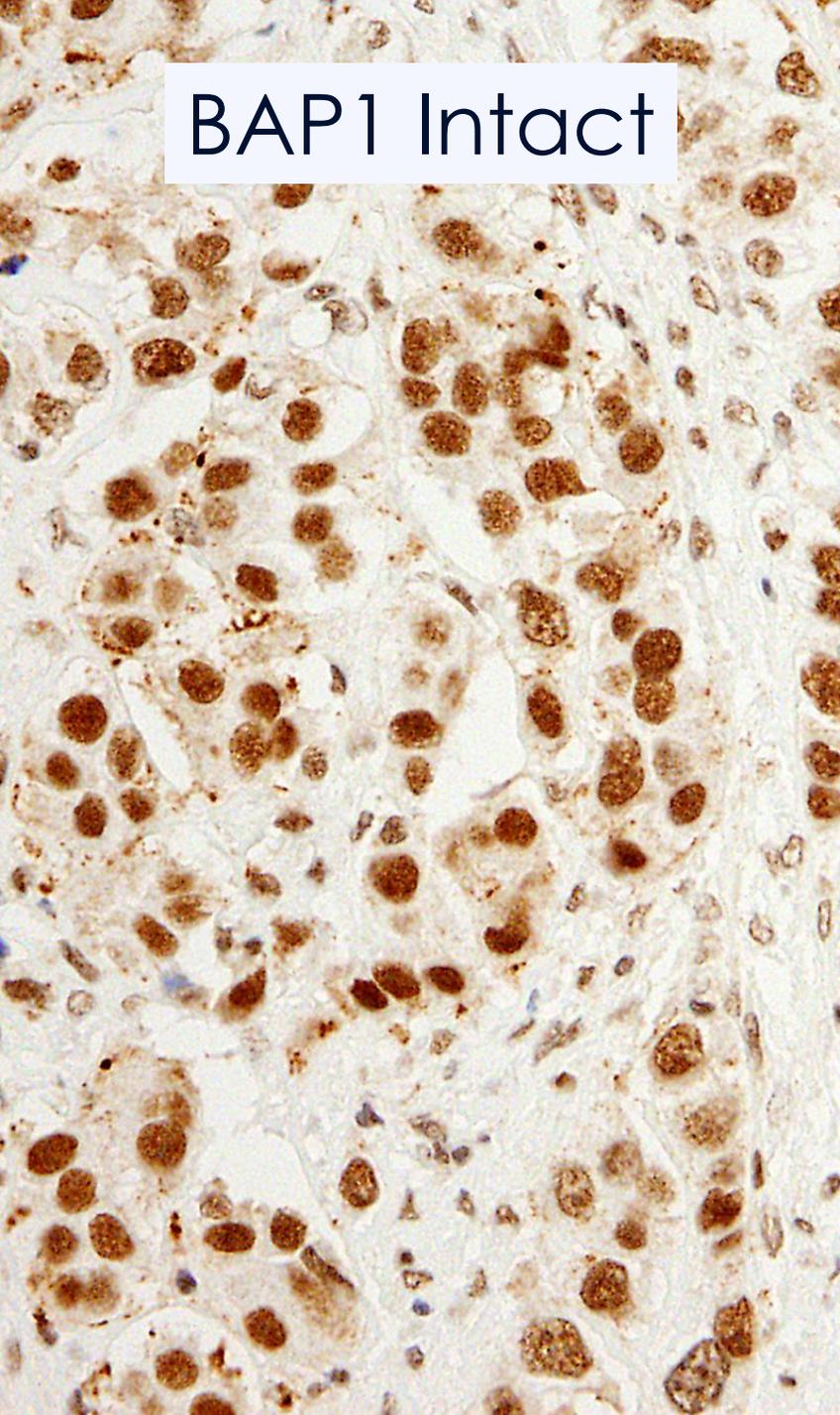
## Sensitivities of BAP1 Immunohistochemistry and MTAP Immunohistochemistry

	BAP1 Loss (%)	MTAP Loss (%)
<b>Mesothelioma Histotype</b>		
Epithelioid	60-70%	50%
Sarcomatoid	20%	90%
<b>Mesothelioma Primary Site</b>		
Pleural	50-60%	50%
Peritoneal	60-70%	5-10%

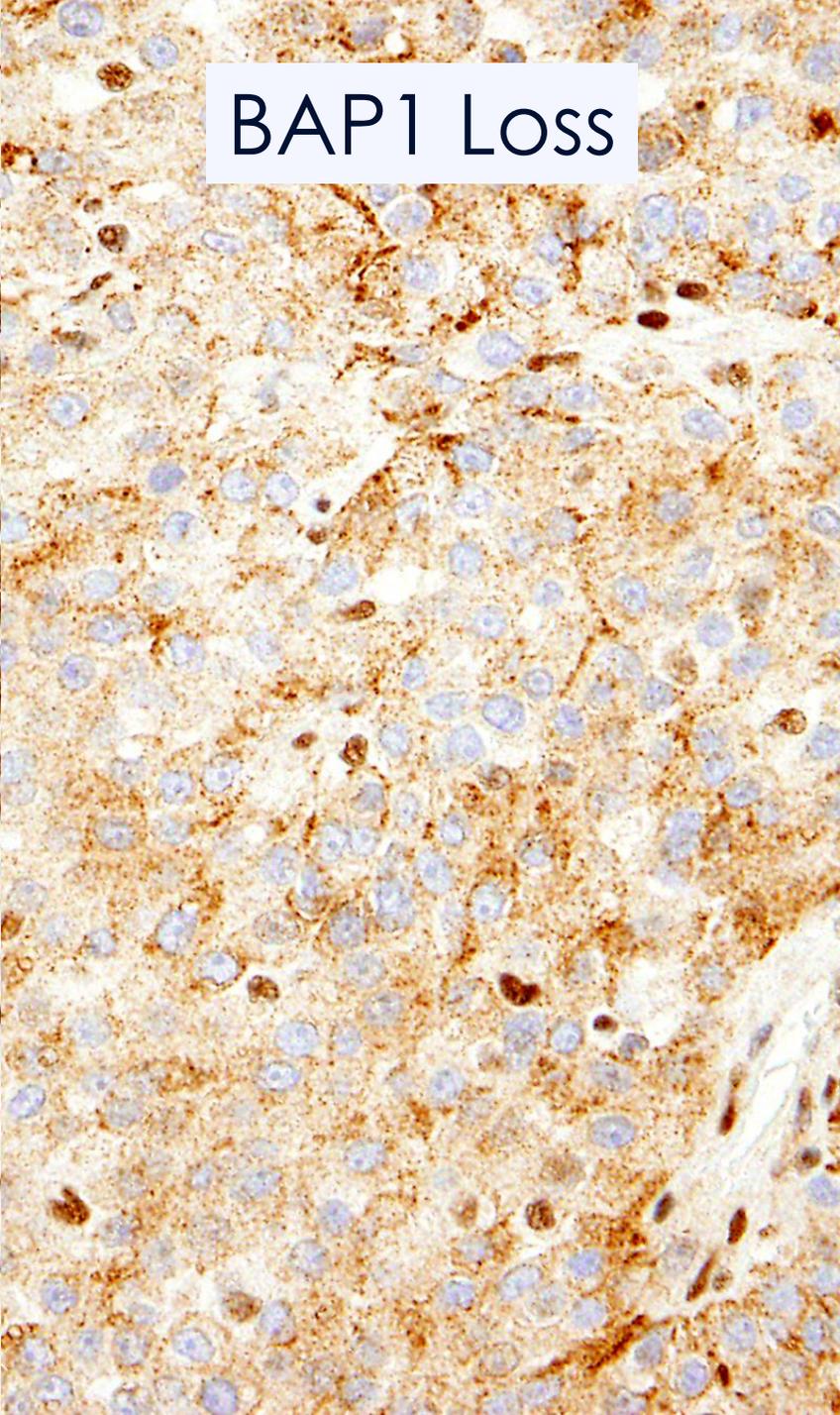
*Should be interpreted with a positive internal control:  
intratumoral inflammatory or stromal cells*

*Adapted from Husain et al.*

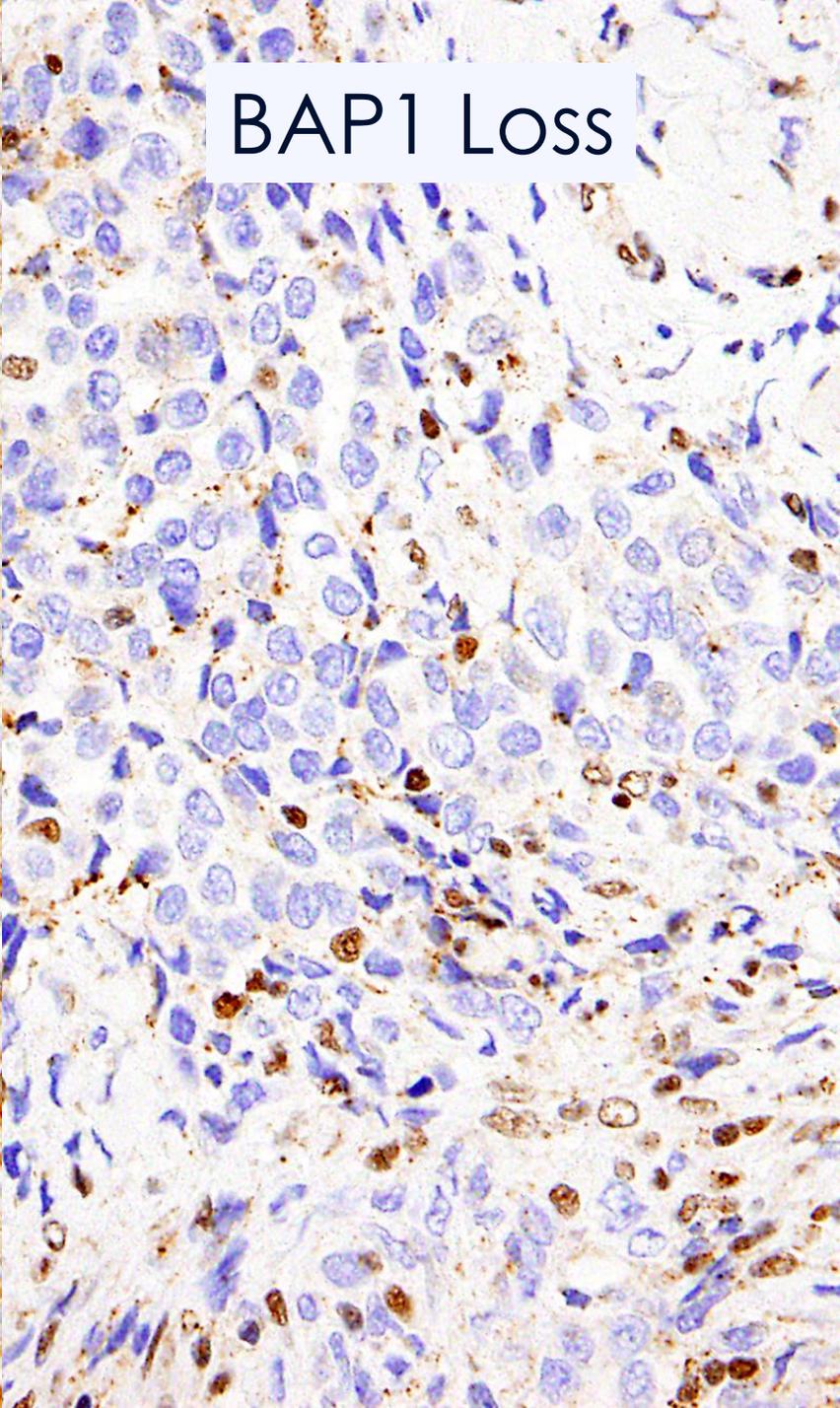
BAP1 Intact

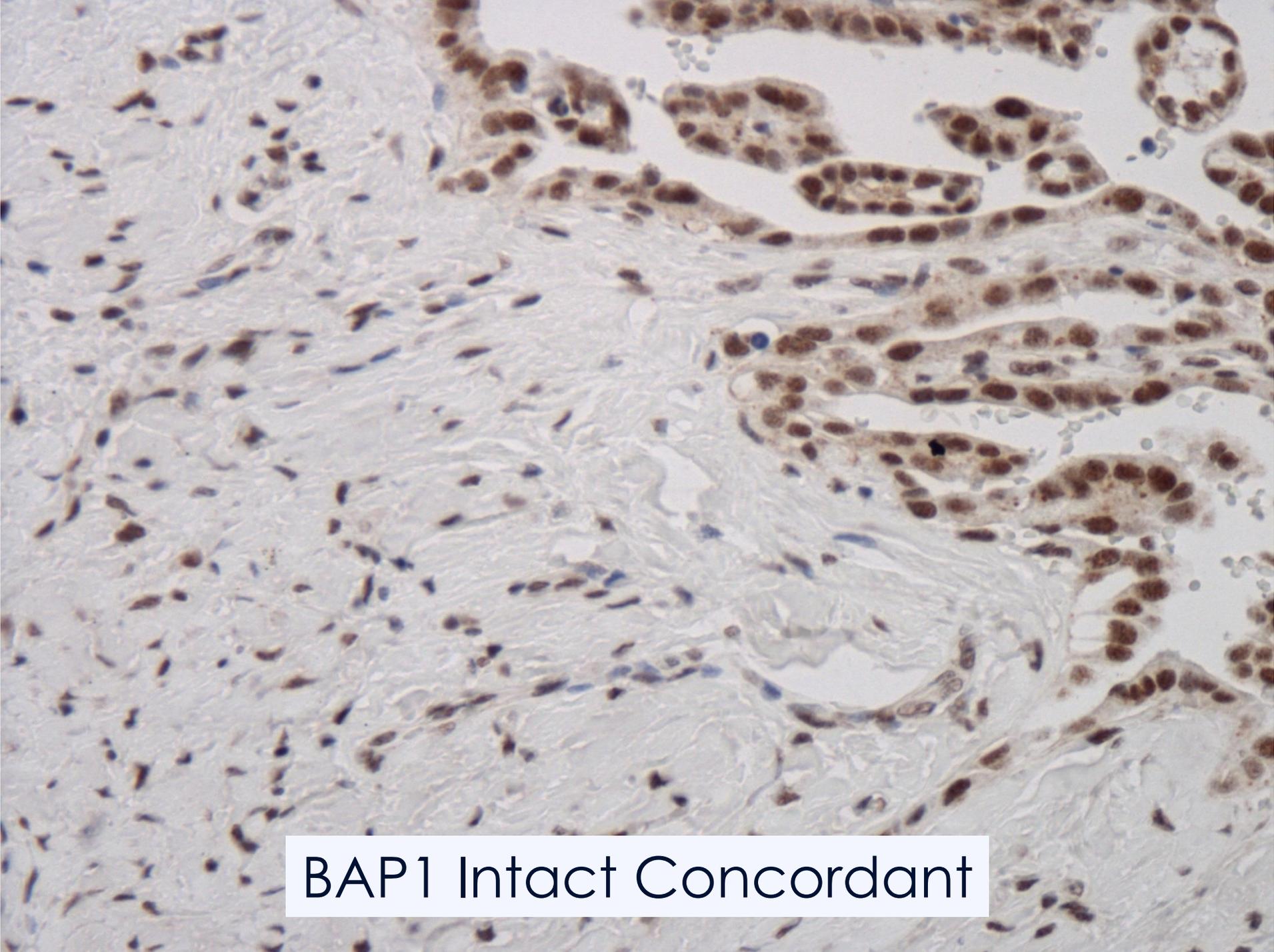


BAP1 Loss

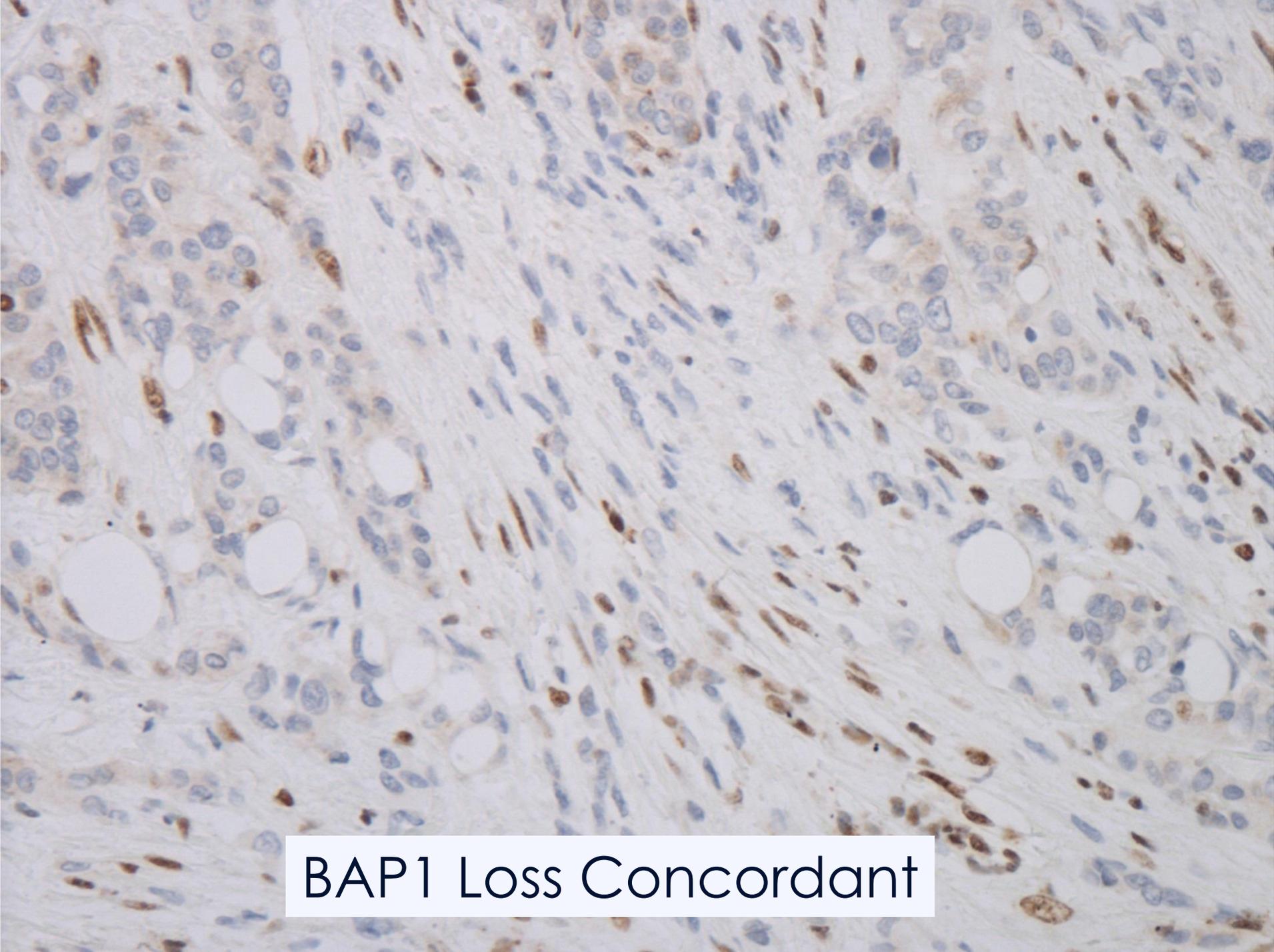


BAP1 Loss

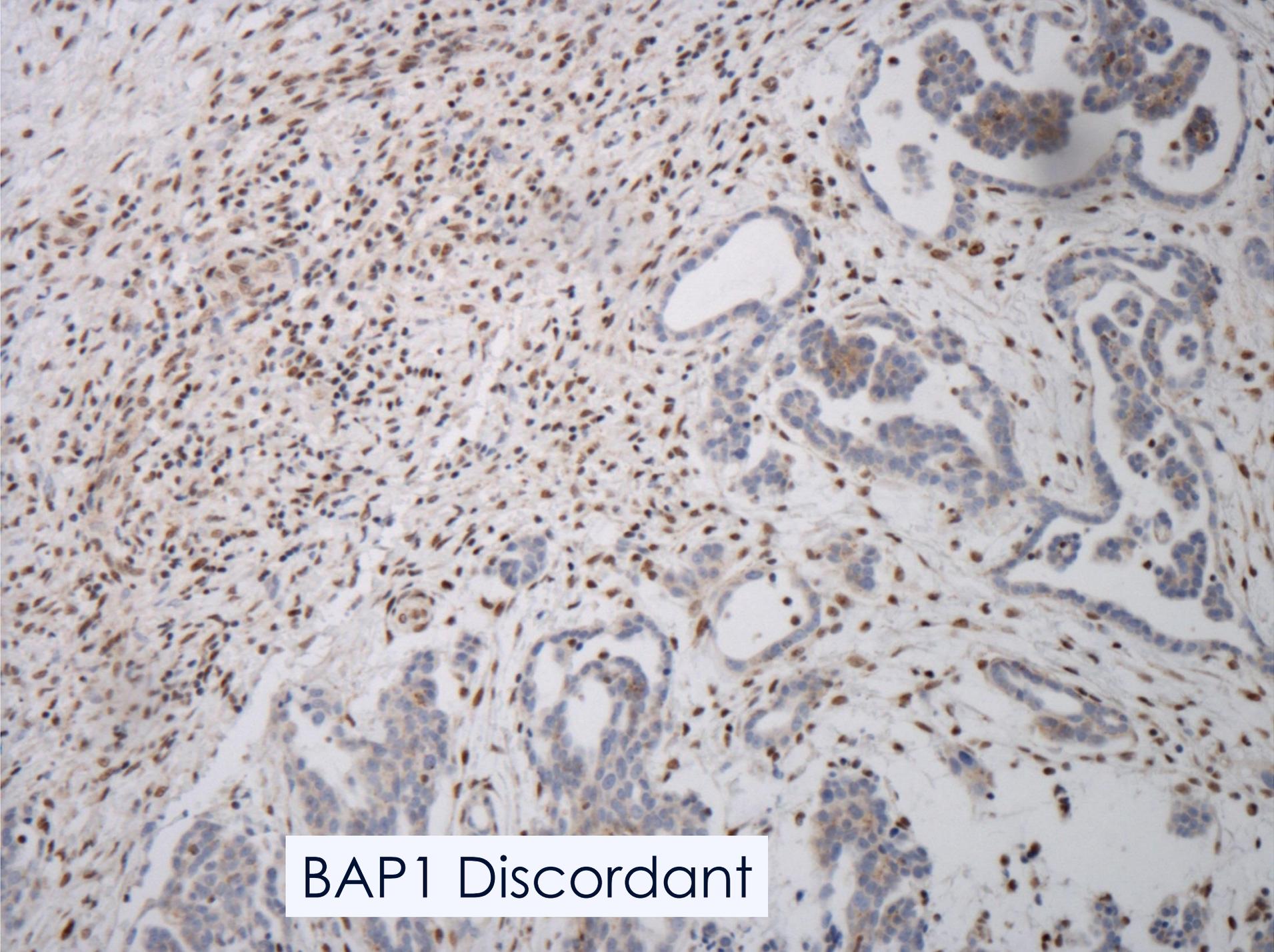




BAP1 Intact Concordant



BAP1 Loss Concordant

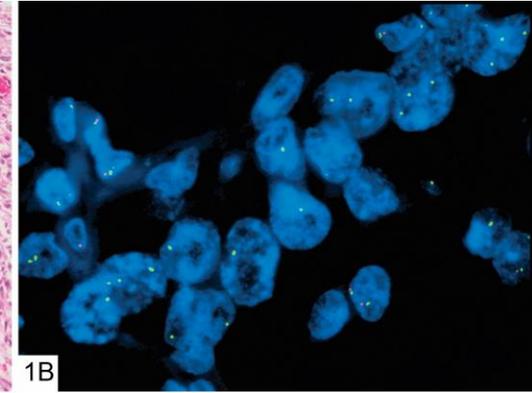
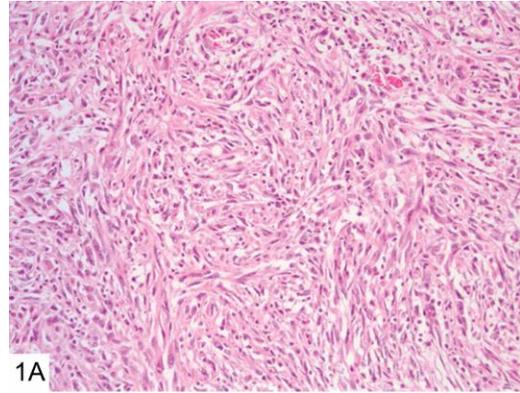


BAP1 Discordant

# *p16* Deletion in Sarcomatoid Tumors of the Lung and Pleura

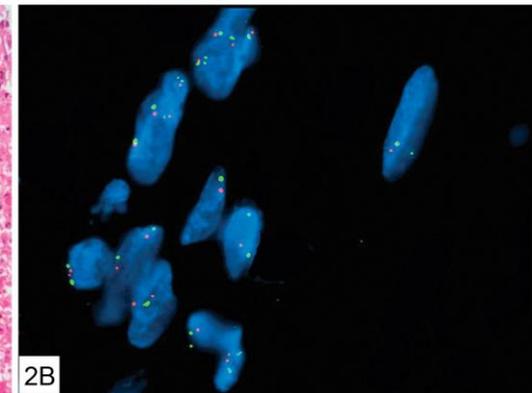
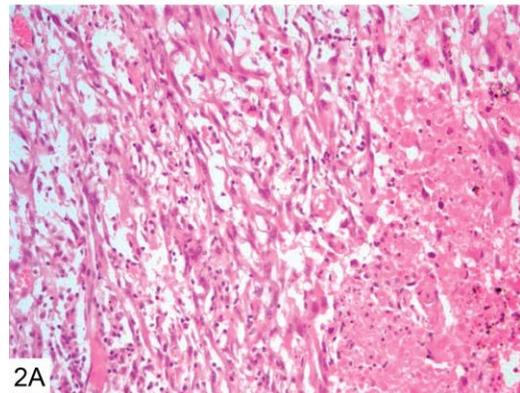
## **Sarcomatoid Mesothelioma**

9p21 homozygous deletion



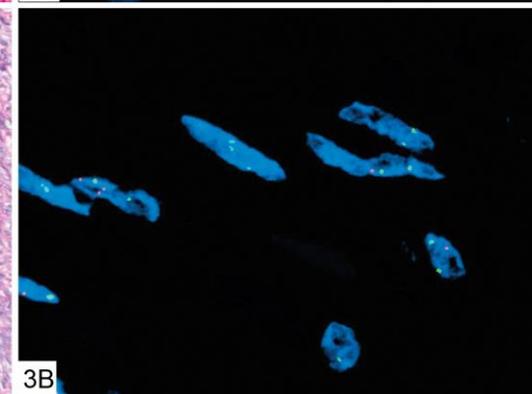
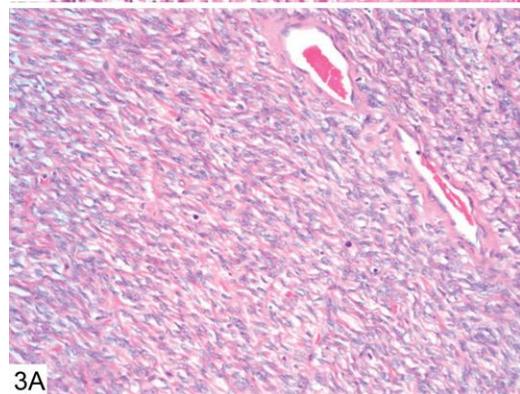
## **Sarcomatoid Carcinoma**

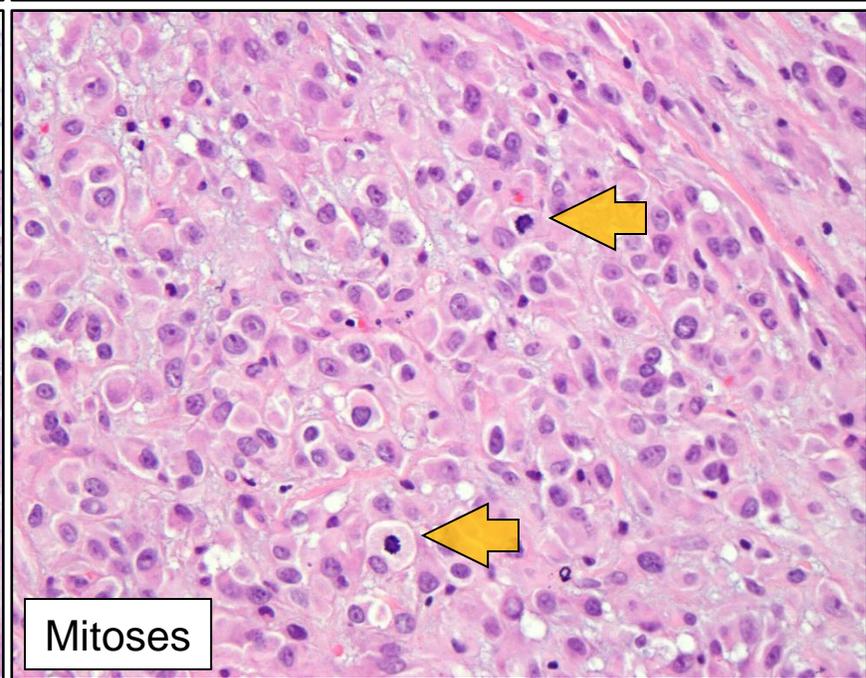
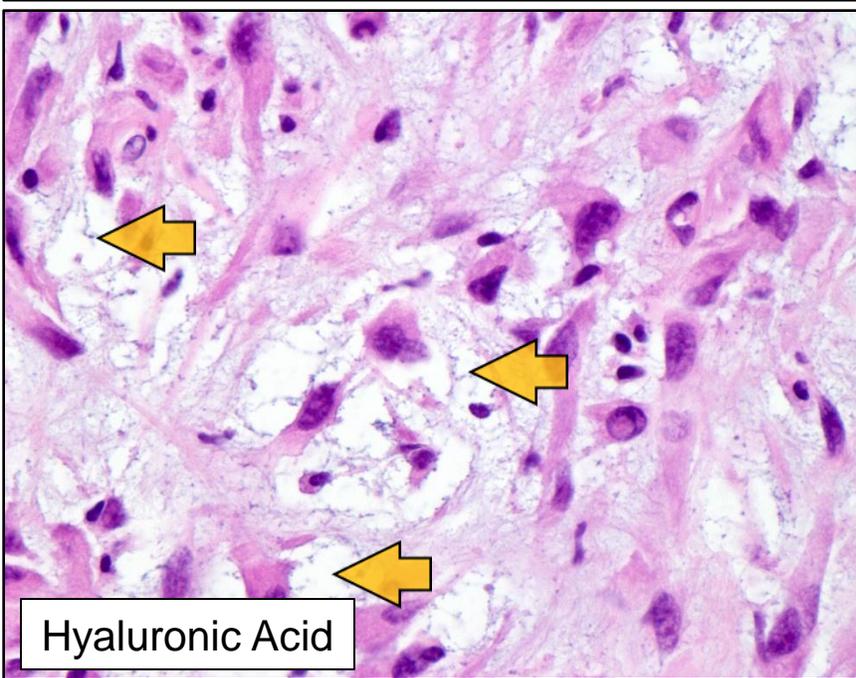
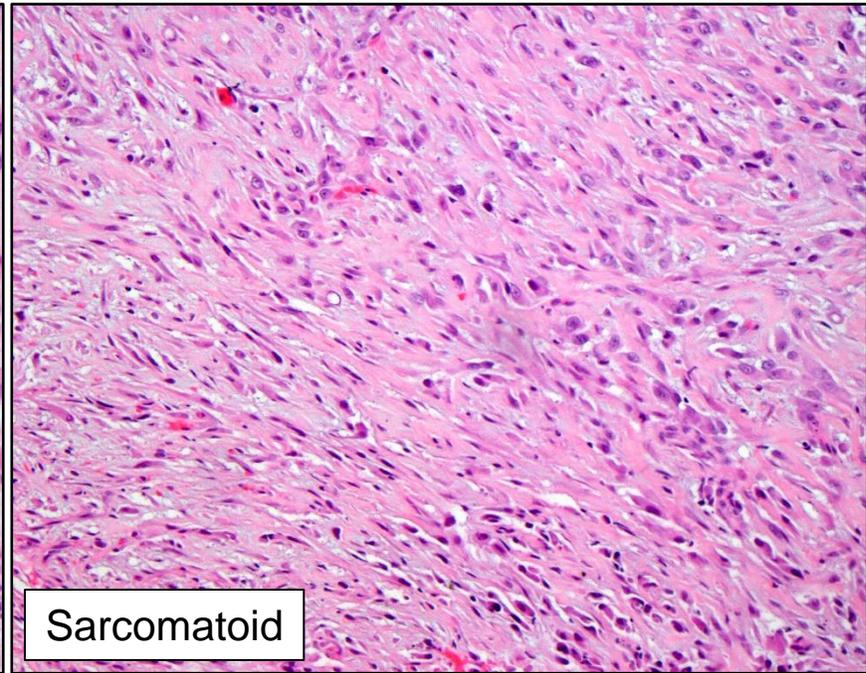
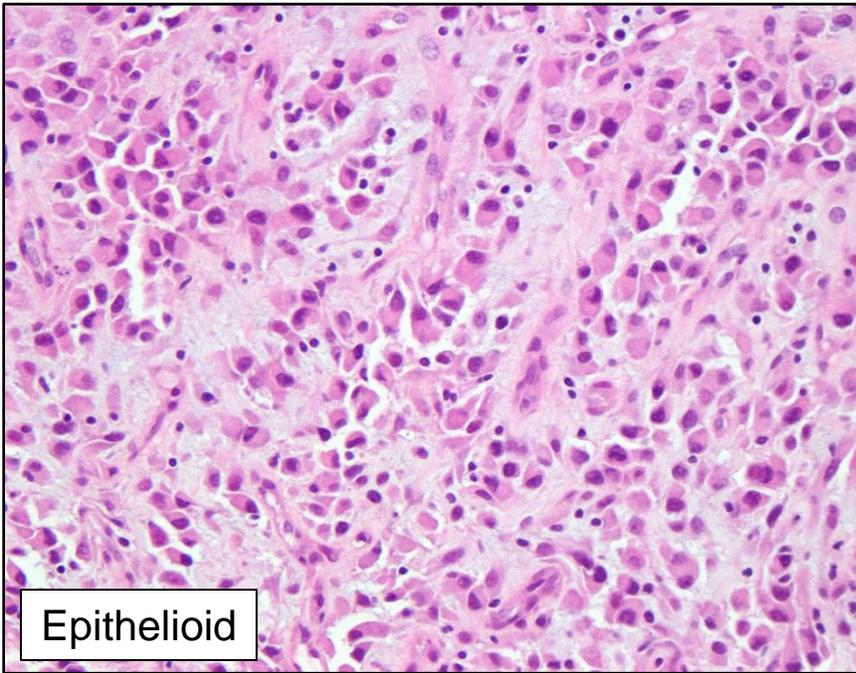
9p21 hemizygous deletion

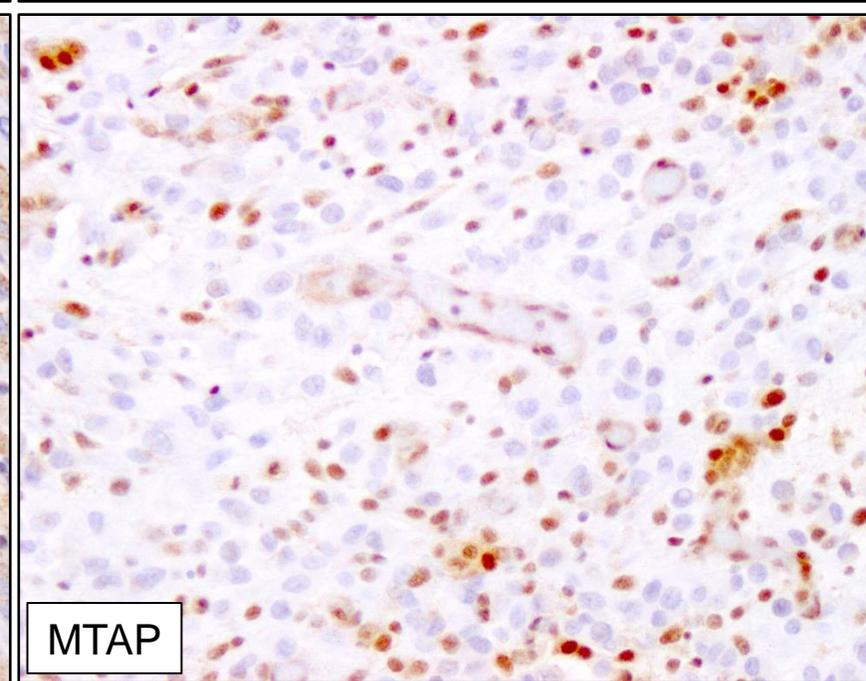
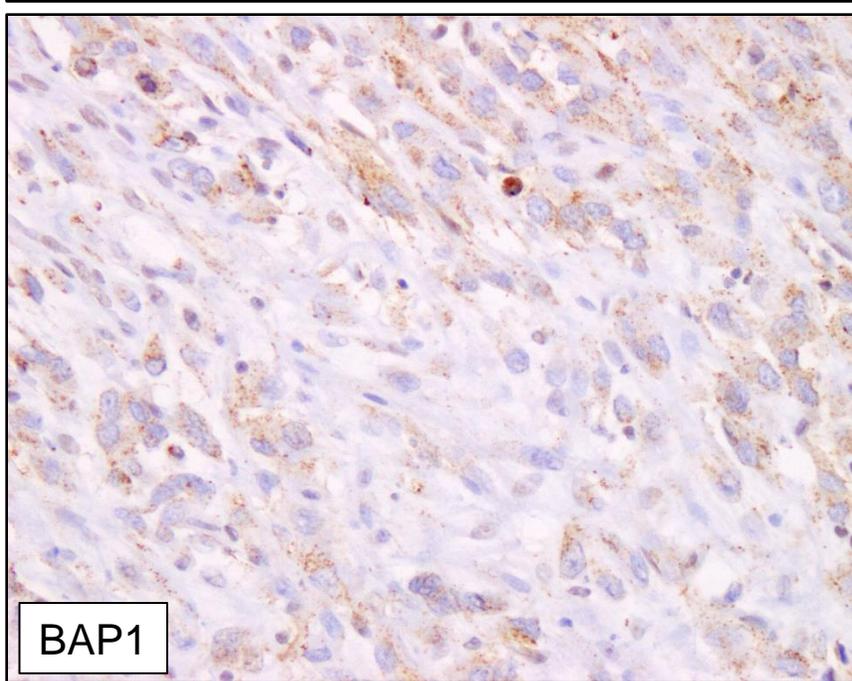
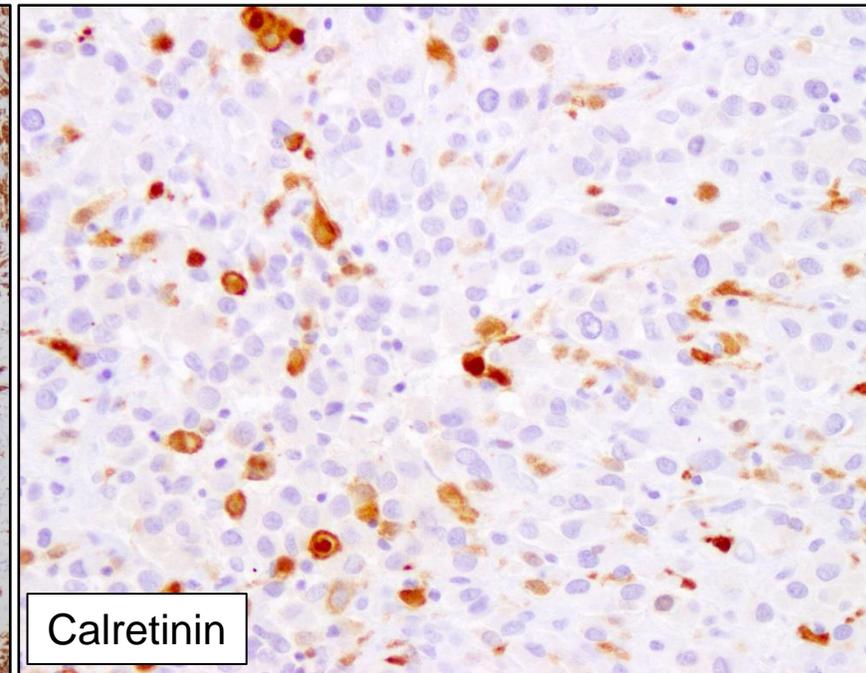
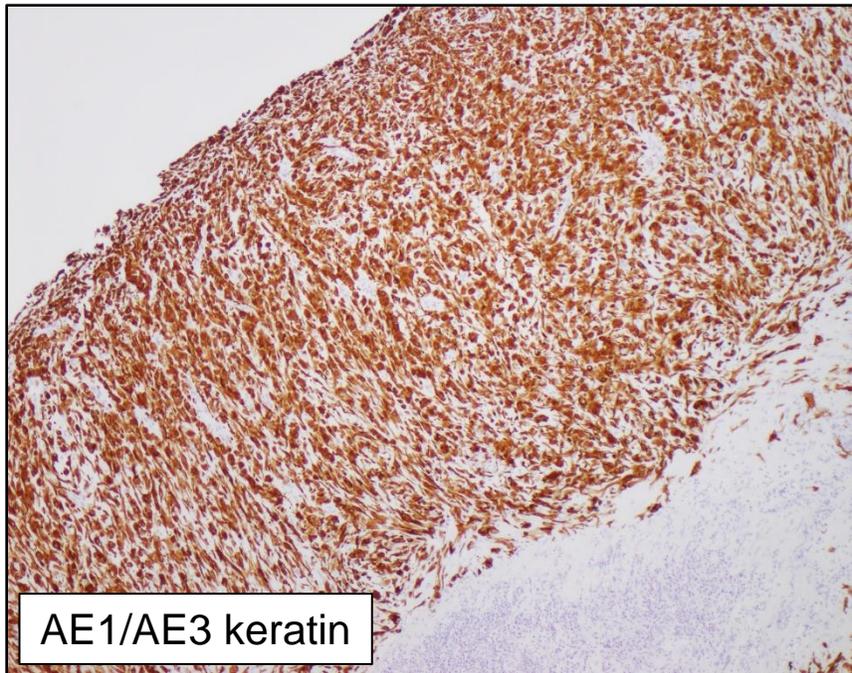


## **Recurrent Solitary Fibrous Tumor**

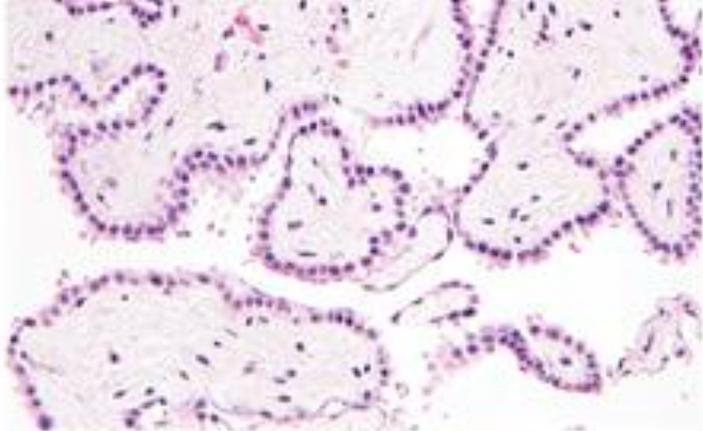
combined homozygous and hemizygous loss of 9p21



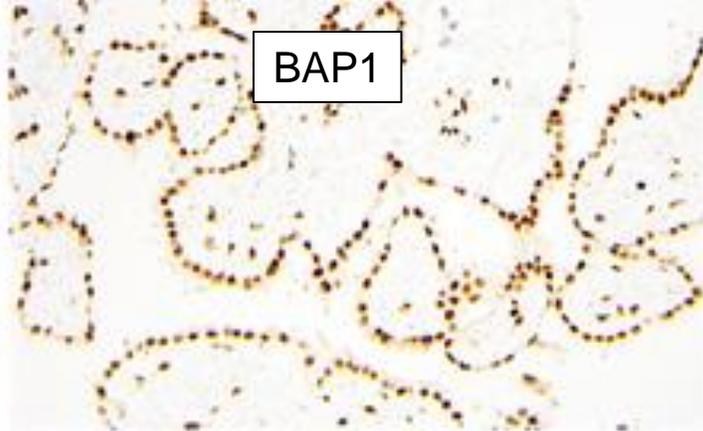




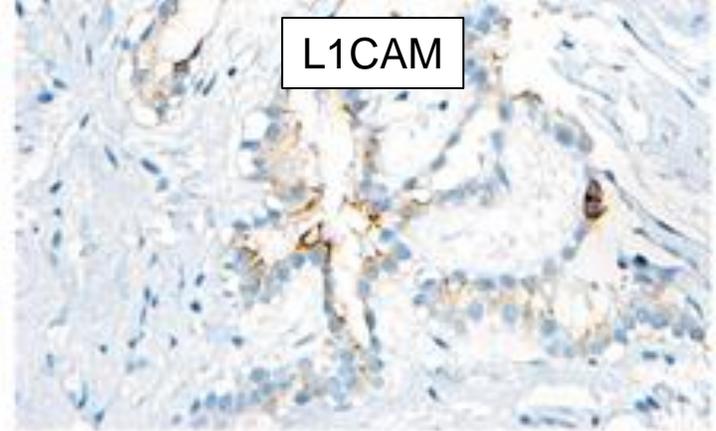
WDPM #3  
*TRAF7* mutant



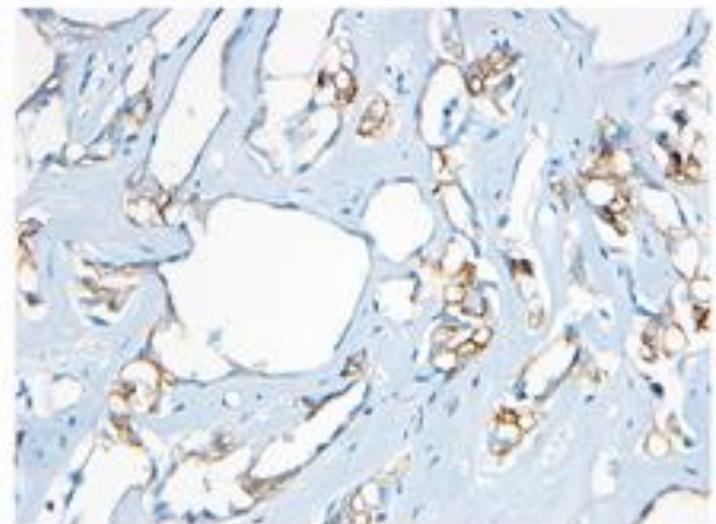
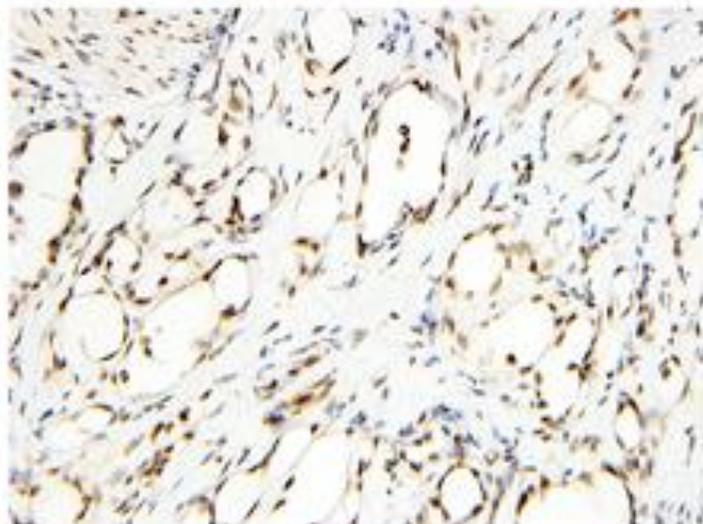
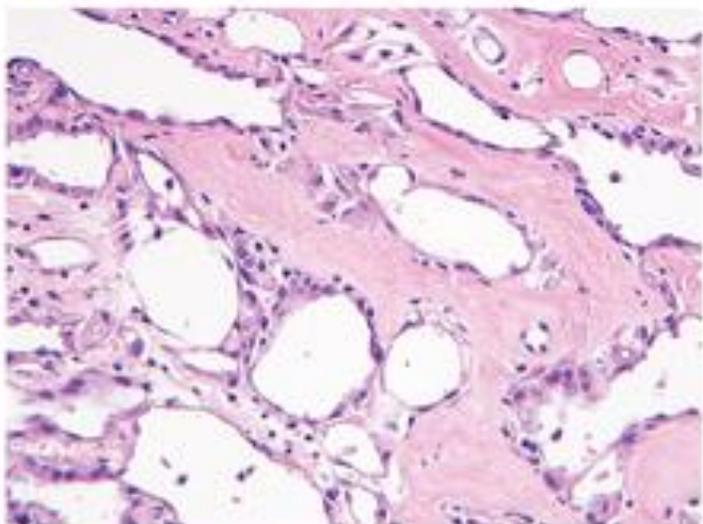
BAP1



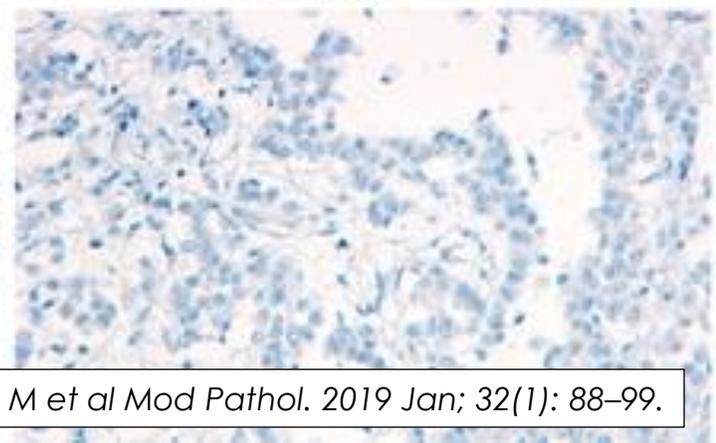
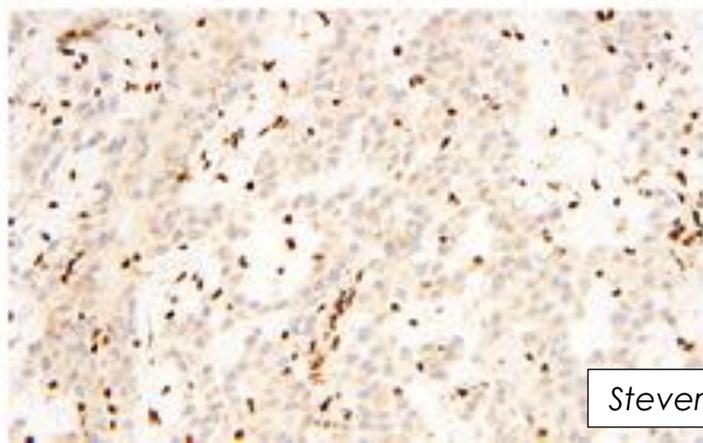
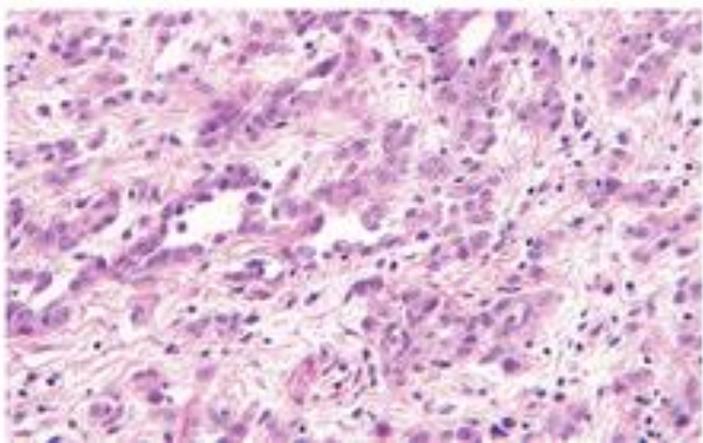
L1CAM

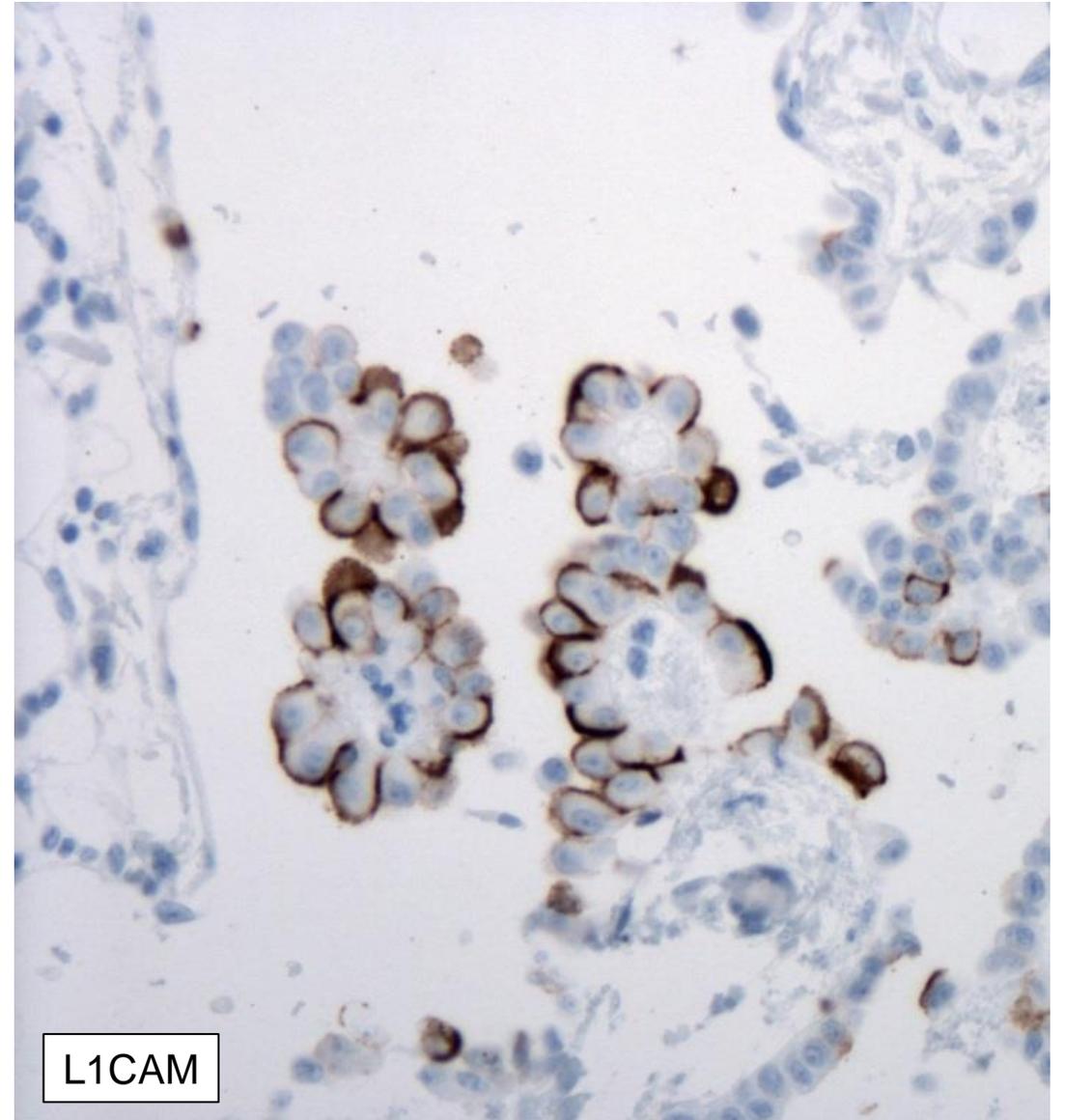
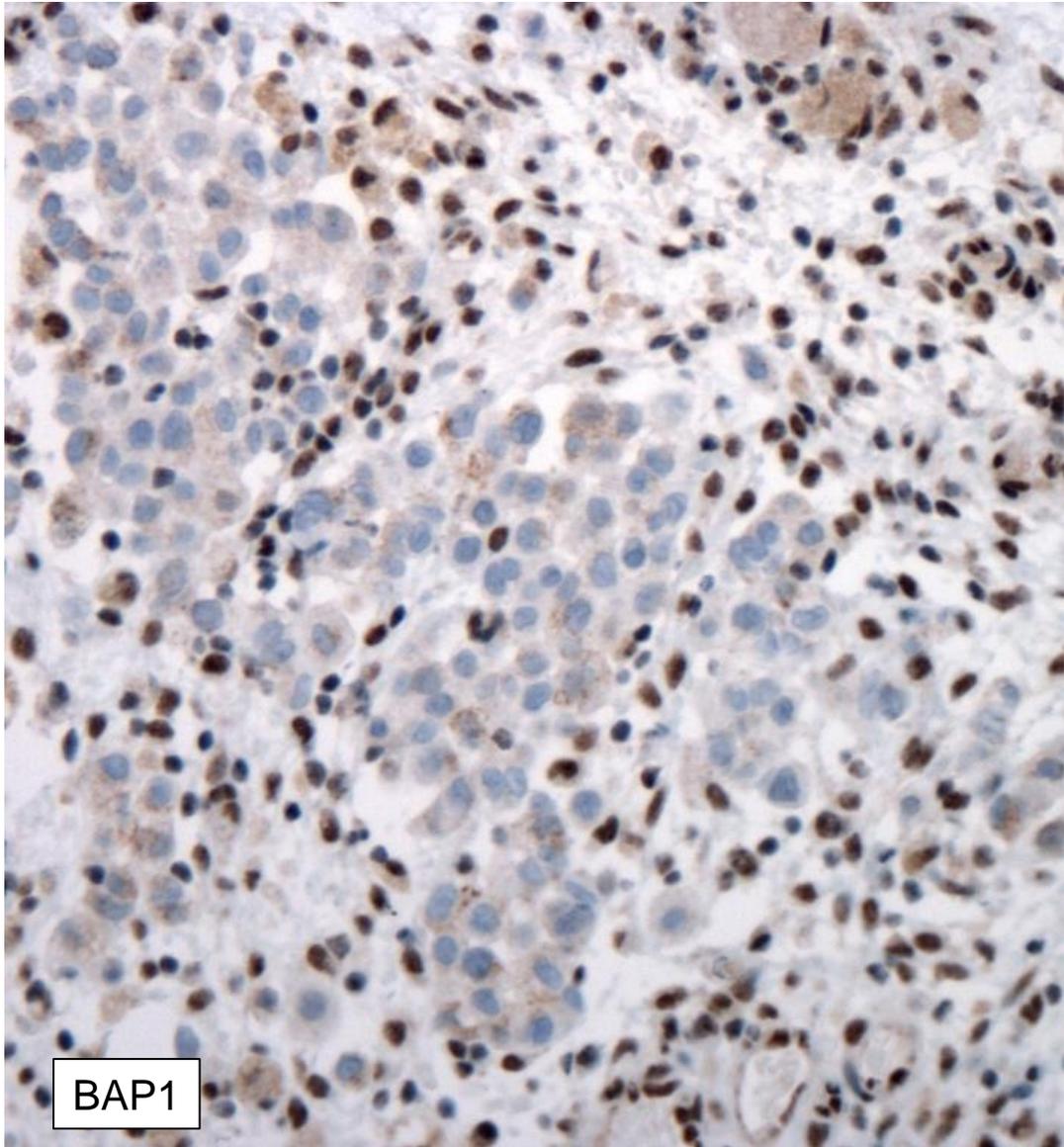


adenomatoid  
tumor of uterus  
*TRAF7* mutant



malignant  
mesothelioma  
*BAP1* mutant





# Genetics and Pathogenesis

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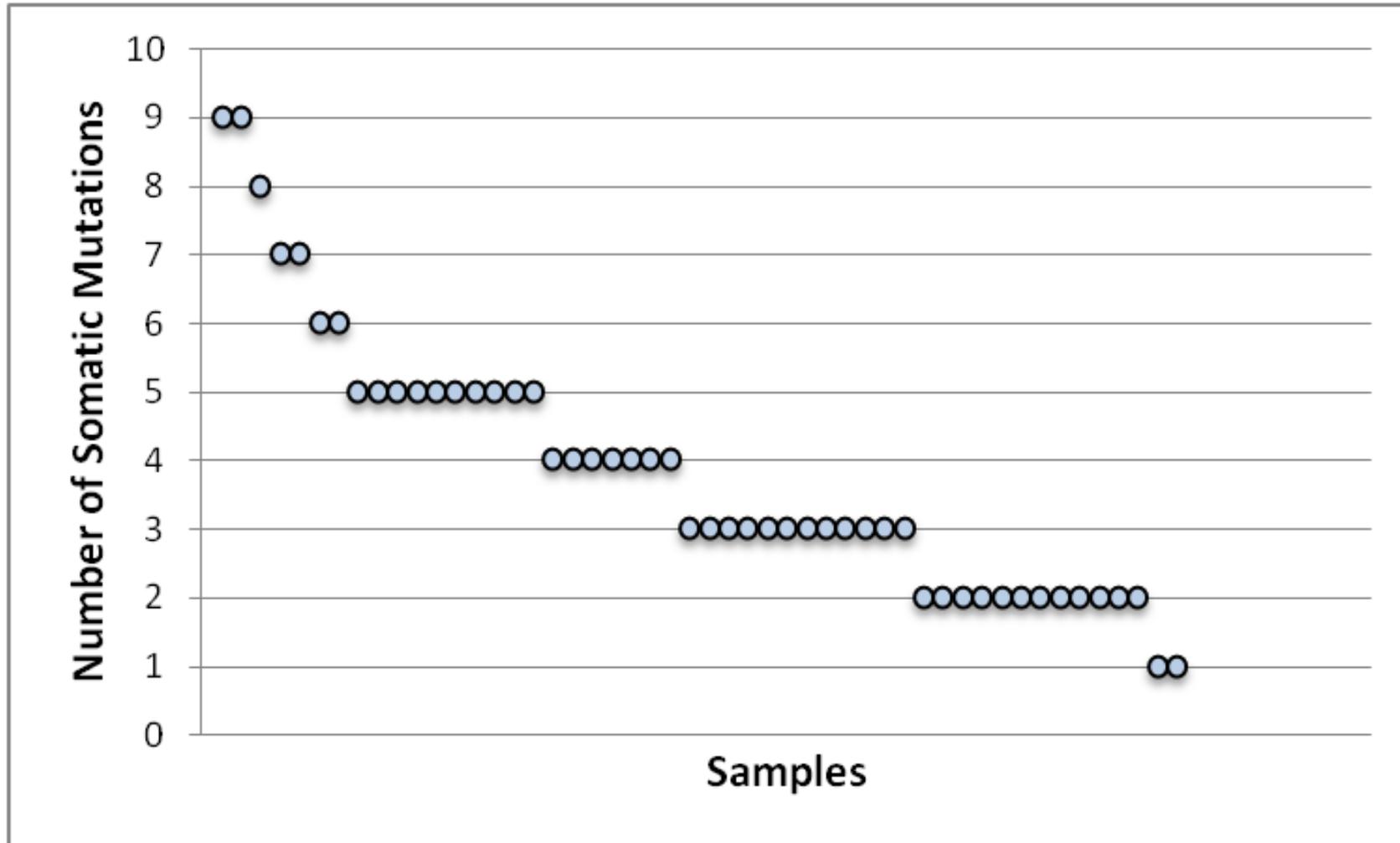
- **Understanding the molecular pathogenesis of genomic and epigenetic alterations for the development of mesothelioma has lagged behind of other common malignancies.**
- **Developments of novel methods for genetic and epigenetic analysis revealed fundamental molecular abnormalities of mesothelioma.**
- **Recent publications of mesothelioma describe a comprehensive lists of genetic, epigenetic and signaling alterations.**
  - Integrative Molecular Characterization of Malignant Pleural Mesothelioma. *Cancer Discov.* 2018 Oct 15 (TCGA Network, 74 samples)
  - Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. *Nat Genet.* 2016 Apr (BWH, 215 samples)

# **Molecular Abnormalities in Mesothelioma**

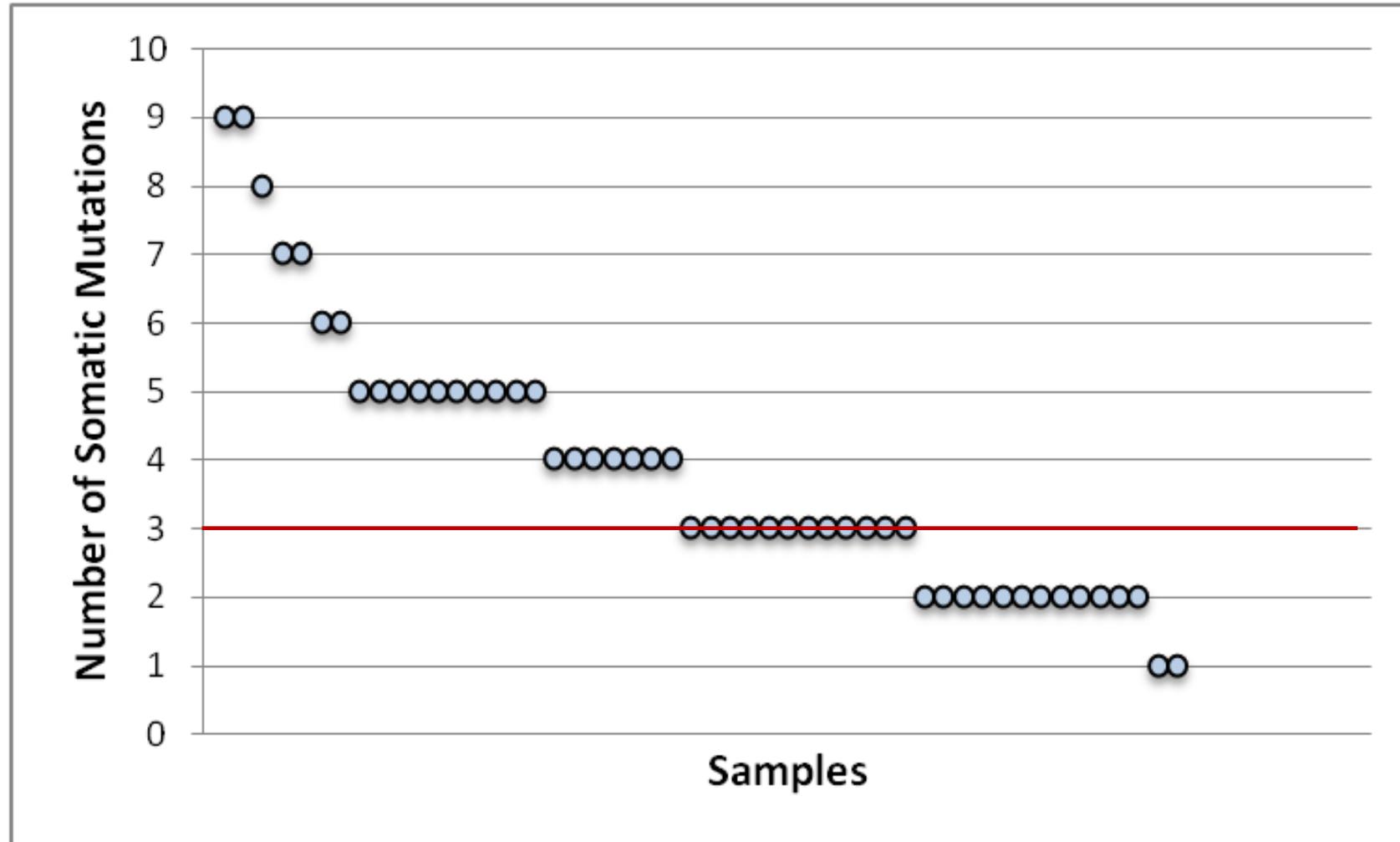
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- Targeted hybrid capture next generation sequencing (NGS) using an Illumina HiSeq 2500
  - Entire exon sequence of 275 genes
  - Selected intron coverage of 30 additional genes
- Overall number and type of mutations were determined.
- Copy number variation (CNV) analyses were performed.

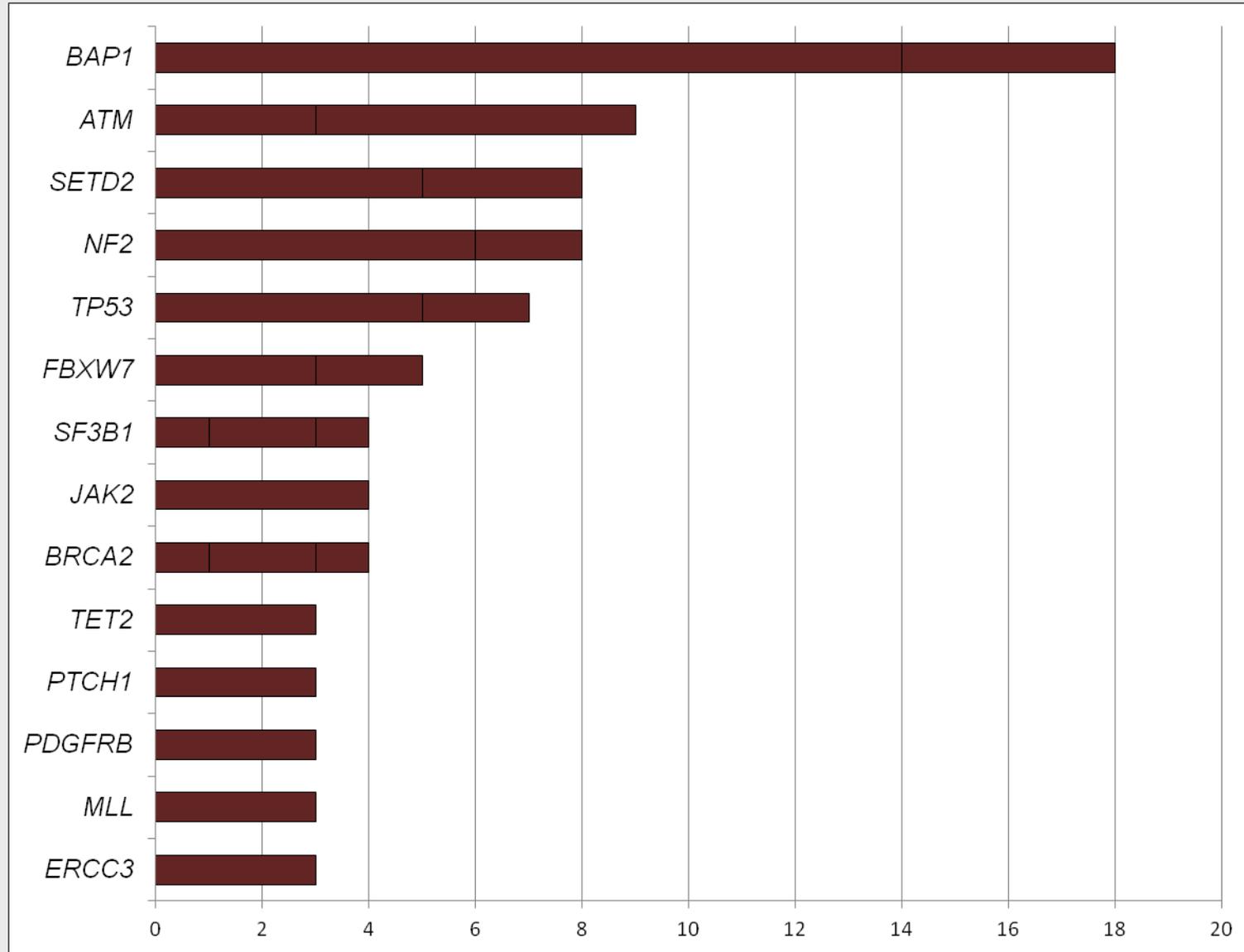
# Number of Mutations in Mesothelioma



# Number of Mutations in Mesothelioma

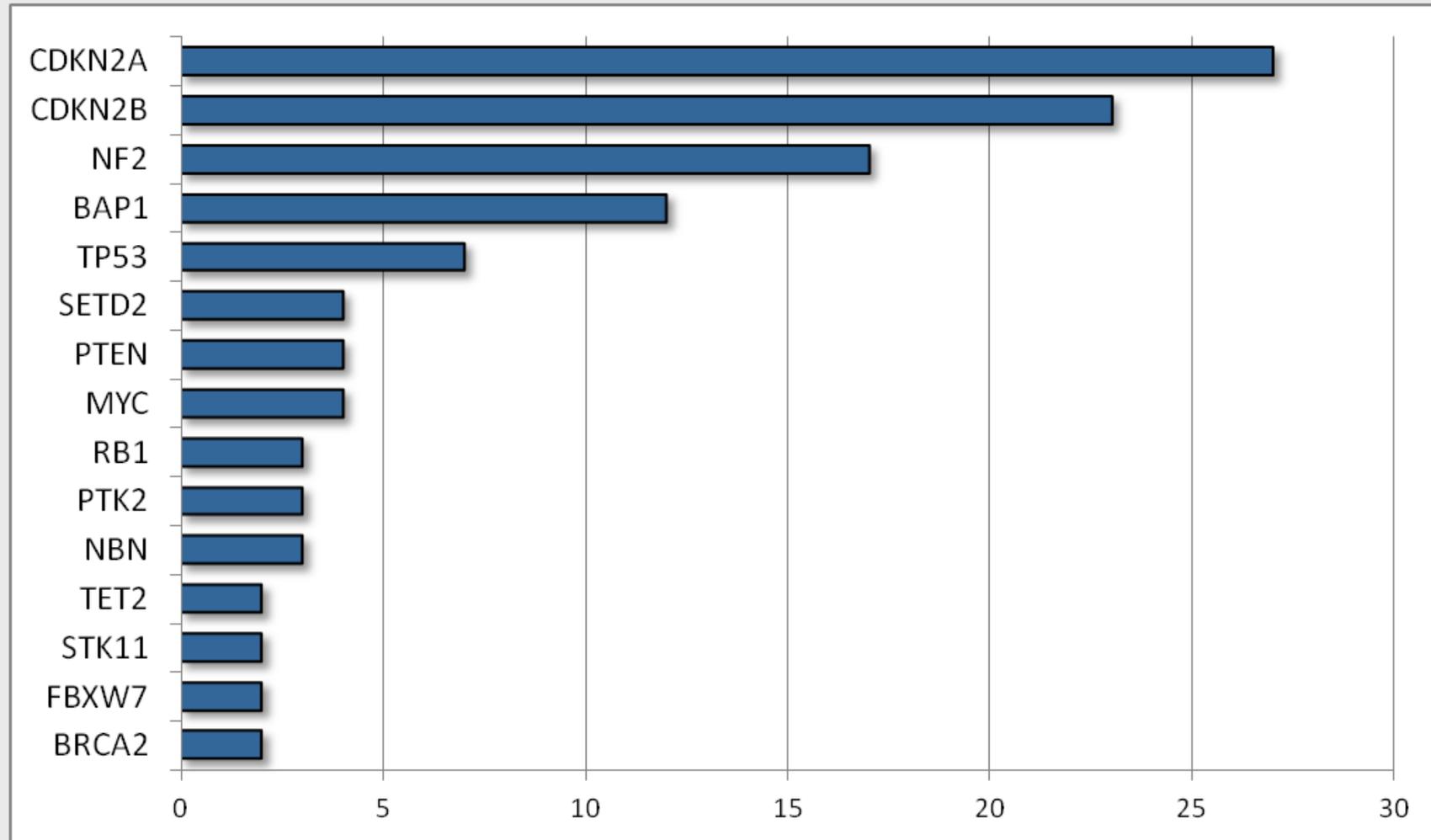


# Genes Mutated in Mesothelioma



*Racila et al. USCAP 2015*

# Copy Number Alterations in Mesothelioma



*Racila et al. USCAP 2015*

# Summary

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- The most common mutations in mesothelioma are in the *BAP1*, *ATM*, *SETD2*, and *NF2* genes, although some have unclear clinical significance.
- The most common copy number alterations were identified in *CDKN2A*, *CDKN2B*, *NF2*, and *BAP1*.

# Unusual Subgroups of Mesothelioma

- *BAP1* Tumor Predisposition Syndrome
- Pleural and peritoneal mesotheliomas with *EWSR1-ATF1* and *FUS-ATF1* gene fusions.
- Mesothelioma with *ALK* Rearrangements.

JAMA Oncology | Brief Report

# Identification of *ALK* Rearrangements in Malignant Peritoneal Mesothelioma

Yin P. Hung, MD, PhD; Fei Dong, MD; Jaclyn C. Watkins, MD; Valentina Nardi, MD; Raphael Bueno, MD;  
Paola Dal Cin, PhD; John J. Godleski, MD; Christopher P. Crum, MD; Lucian R. Chirieac, MD

## **Peritoneal Mesothelioma**

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**with *ALK* Rearrangements**

# Peritoneal Mesothelioma

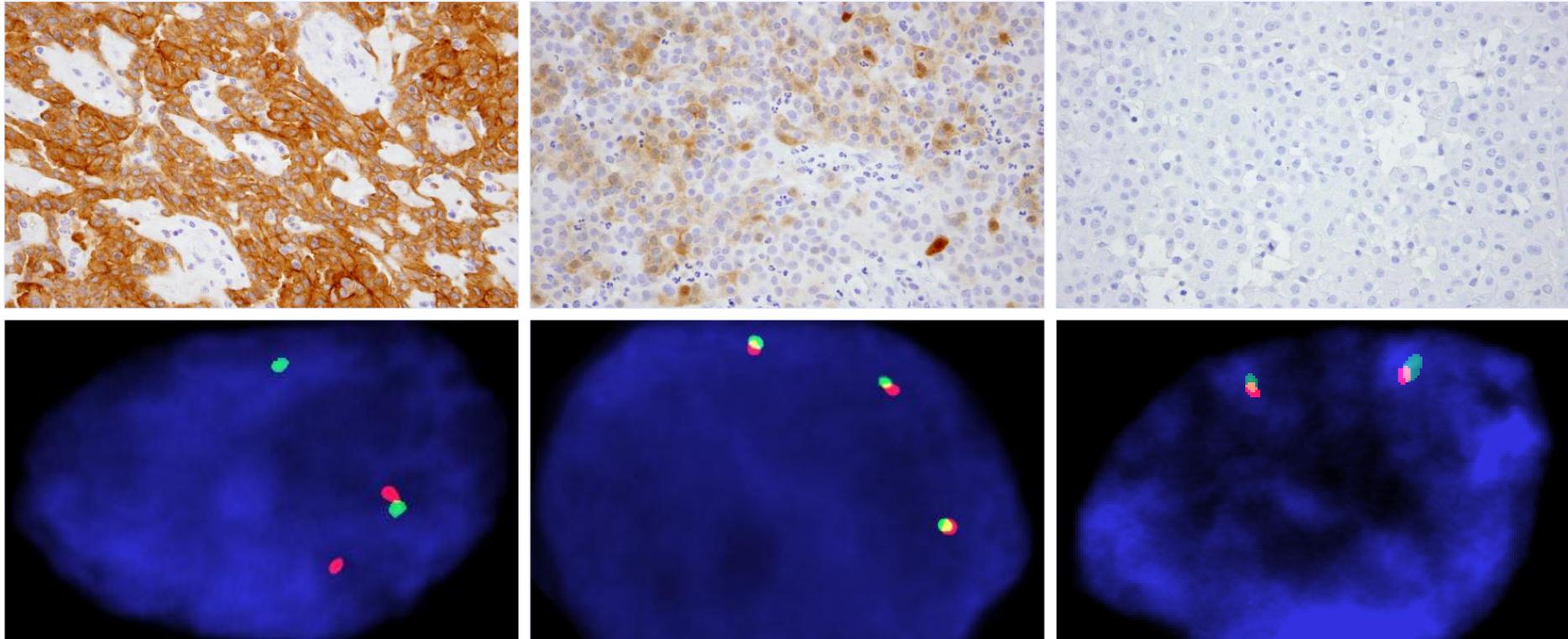
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## with *ALK* Rearrangements

In a large series of 88 consecutive patients with peritoneal mesothelioma, we identified *ALK* rearrangements in 3% of cases that:

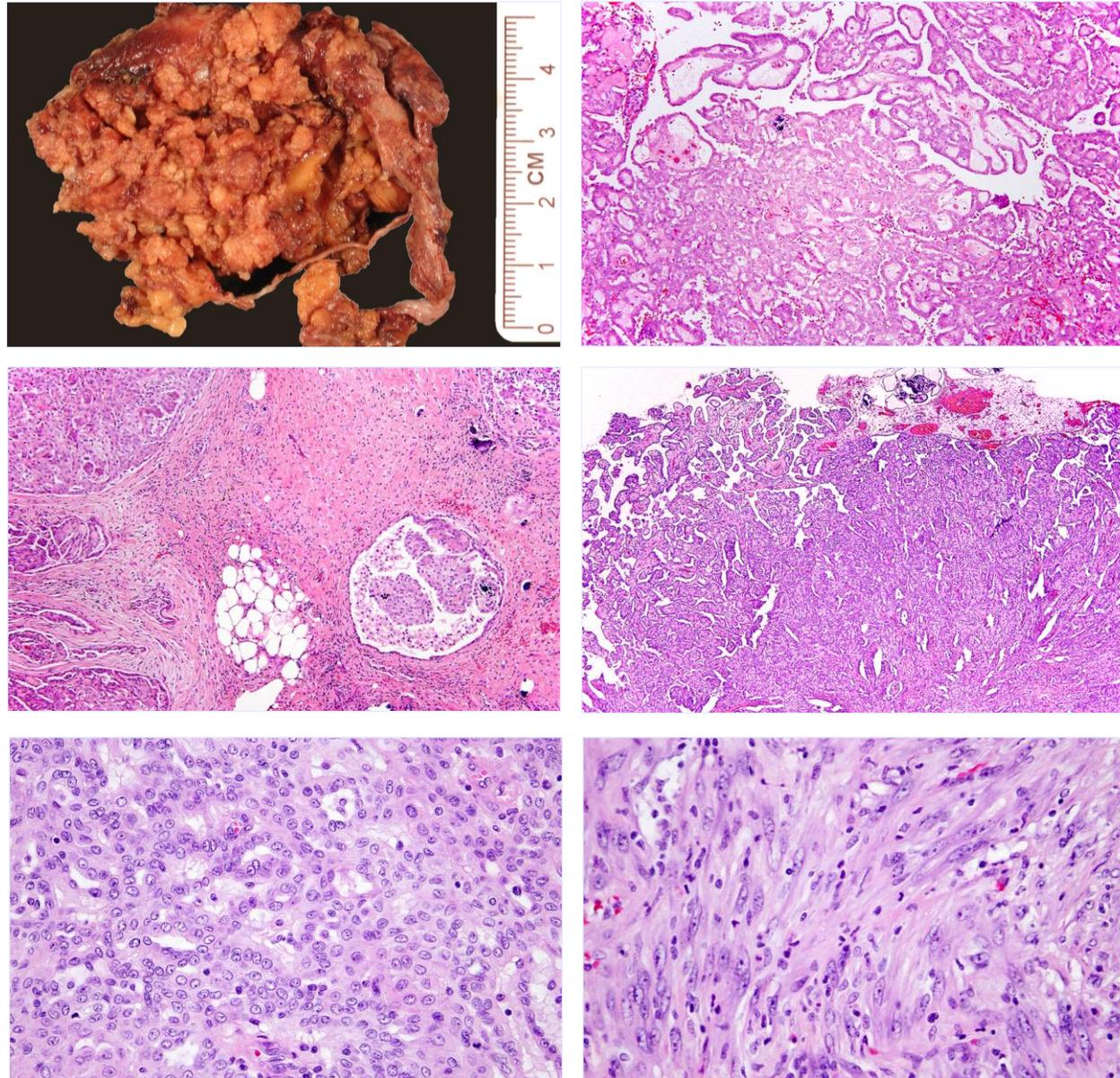
- Present in young women (25% in younger than 40 years of age)
- Lack asbestos fibers
- Have no history of therapeutic radiation
- Lack the typical cytogenetic and molecular abnormalities usually present in peritoneal mesothelioma

# ***ALK*-Rearrangements in Peritoneal Mesothelioma**



Yin P. Hung, MD, PhD et al. *JAMA Oncol.* 2018;4(2):235-238

# ALK-rearranged Peritoneal Mesothelioma



# ALK-rearranged Peritoneal Mesotheliomas

Case No.	1	2	3	4	5	6	7	8	9
Histology	E	E	B	E	E	E	E	E	B
ALK	■	■	■						
BAP1					■	■	■	■	■
SETD2						■	■	■	■
NF2				■					■

Molecular alterations

- Rearrangement
- Nonsense mutation
- Missense mutation
- Splice site mutation
- One-copy loss
- Two-copy loss

Yin P. Hung, MD, PhD et al. JAMA Oncol. 2018;4(2):235-238

# Peritoneal Mesothelioma

## with ALK Rearrangements

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### Summary

We identified unique ALK rearrangements in a subset of patients with peritoneal mesothelioma:

- No asbestos fibers
- No therapeutic radiation.
- No cytogenetic and molecular alterations typically found in these tumors
- Identification of clinically actionable *ALK* rearrangements reveals a novel mechanism of peritoneal mesothelioma with promise for targeted therapy.

# Pleural Mesothelioma and *BAP1* Inactivation Syndrome

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- *BAP1* is a tumor suppressor gene.
- Germline *BAP1* mutations are transmitted genetically in a dominant autosomal pattern.
- **BAP1 germline mutations confer increased susceptibility for the development of several tumors:**
  - Uveal melanomas
  - Epithelioid atypical Spitz tumors (ASTs) – **MBAIT** (**M**elanocytic **B**AP1-mutated **A**typical **I**ntradermal **T**umors)
  - Cutaneous Melanoma
  - Mesothelioma

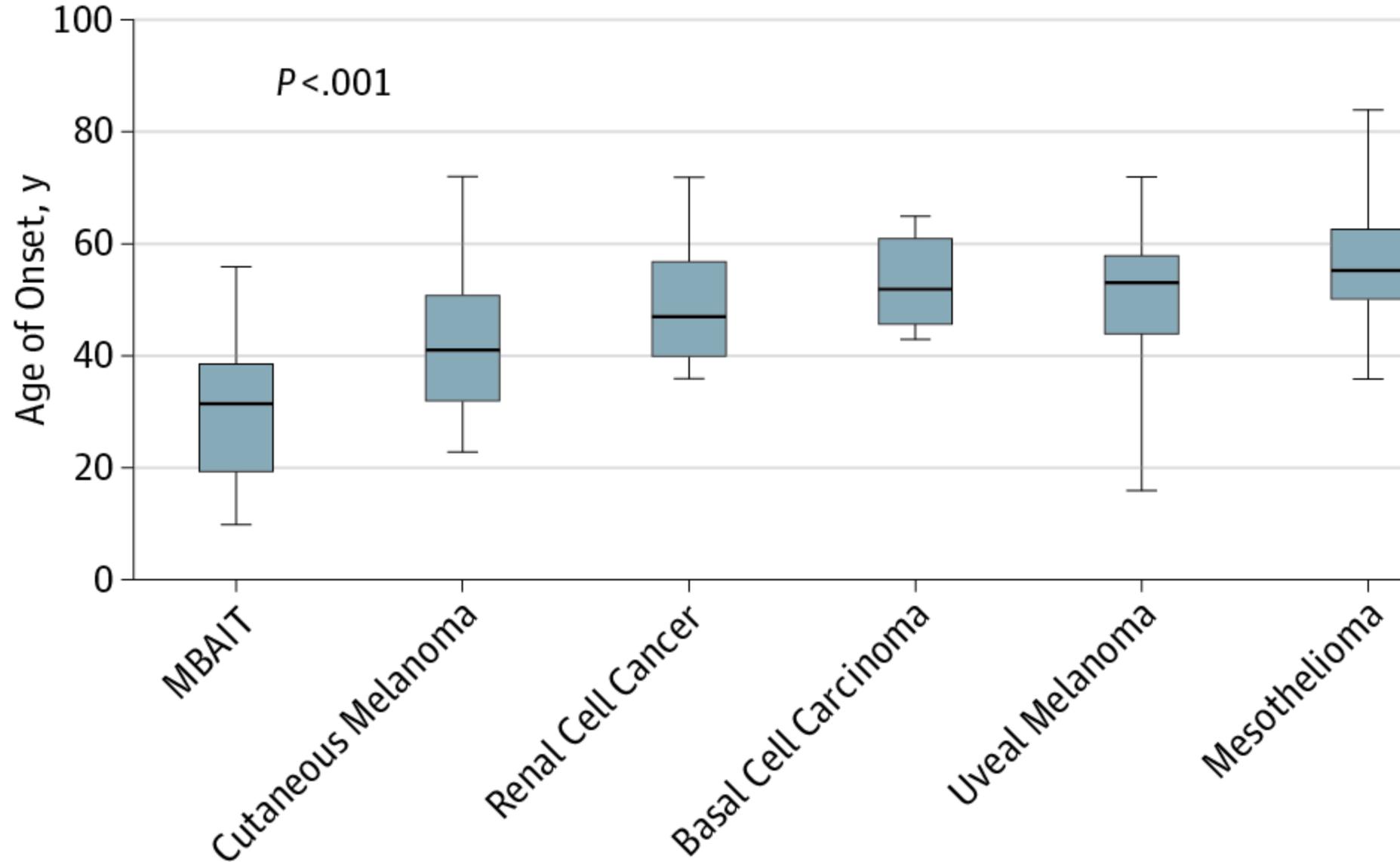
# Clinical Presentation of MBAITs



Carbone M et al, *J Transl Med.* 2012; 10: 179.

# BAP1 Inactivation Syndrome

Median Ages of Onset of Tumors



# **BAP1 Inactivation Syndrome**

## Median Ages of Onset and Prevalence of Tumors

**Table. Median Age of Onset and Prevalence of Characteristic Tumors in 215 Patients With BAP1 Syndrome**

<b>Tumor</b>	<b>Cases, No.</b>	<b>Estimated Penetrance, %<sup>a</sup></b>	<b>Median Age of Diagnosis in the Literature, y</b>	<b>Median Age of Diagnosis in Our Series, y</b>	<b>Median Age of Diagnosis in General Population, y</b>
Uveal melanoma	60	28.0	53	59	61 <sup>15</sup>
Mesothelioma	48	22.0	56	46	74 <sup>15</sup>
Cutaneous melanoma	38	18.0	41	43	61 <sup>15</sup>
MBAITs	36	17.0	32	31	24 <sup>16</sup>
Renal cell carcinoma	20	9.0	47	51	64 <sup>15</sup>
Basal cell carcinoma	14	6.5	52	41	75 <sup>17</sup>

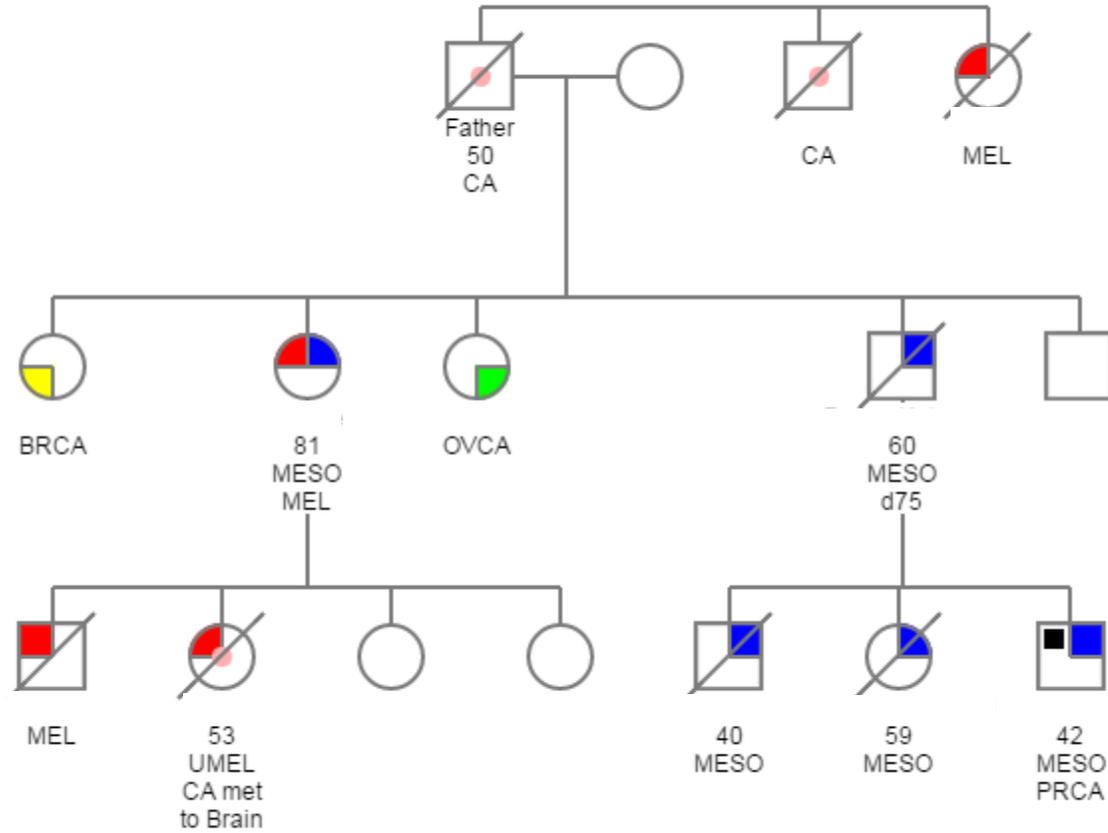
*Haugh, AM et al, JAMA Dermatol. 2017;153(10):999-1006*

# BAP1 Inactivation Syndrome

## Genetic Pedigree

### Legend

MESO=Mesothelioma  
 MEL Melanoma  
 UMEL Uveal Melanoma  
 CA Carcinoma of uncertain origin  
 OVCA Ovarian Carcinoma  
 PRCA Prostate Carcinoma  
 BRCA Brain Cancer



# Summary

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- Epithelioid mesothelioma with pleomorphic histology has a poorer prognosis, similar to Sarcomatoid mesothelioma.
- Transitional mesothelioma is a new subtype, classified under sarcomatoid mesothelioma type, with a poor prognosis.
- Sustained efforts and modern high throughput technologies have allowed to uncover novel genomic abnormalities in mesothelioma.
  - *ALK* rearrangements
  - *BAP1* Tumor Predisposition Syndrome
  - *EWSR1-ATF1* and *FUS-ATF1* gene fusions
- Investigation of BAP1 and MTAP IHC is helpful in the work up of patients with mesothelioma.