



The role of Pathologists in the diagnosis of SARCOMA and GIST

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CCC_Subunit_Sarcoma

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What can the “best” pathologist tell

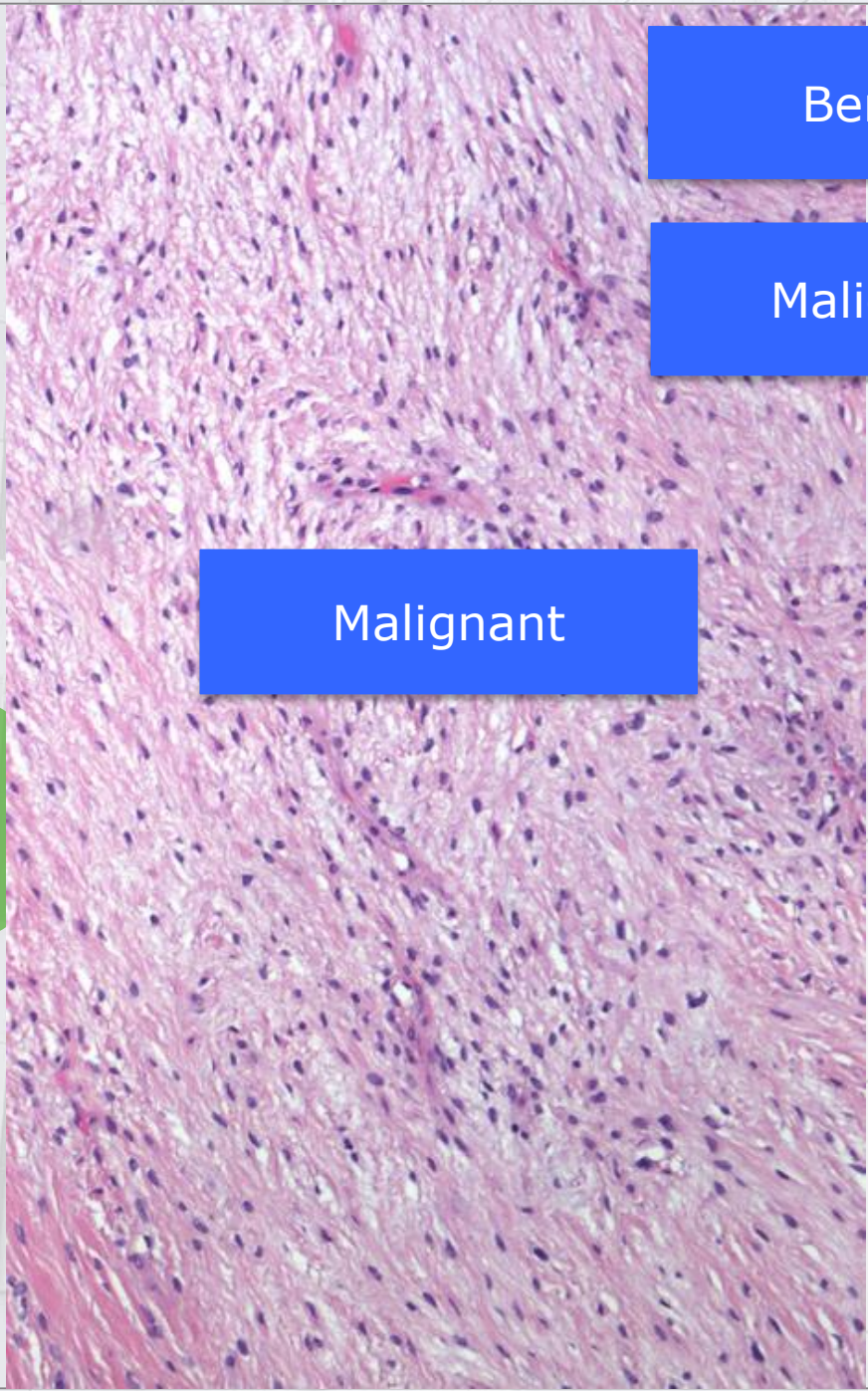
- ▶▶ The exact diagnosis – Grading
- ▶▶ That the resection margins are adequate
- ▶▶ Provide results of molecular testing

YES WE CAN

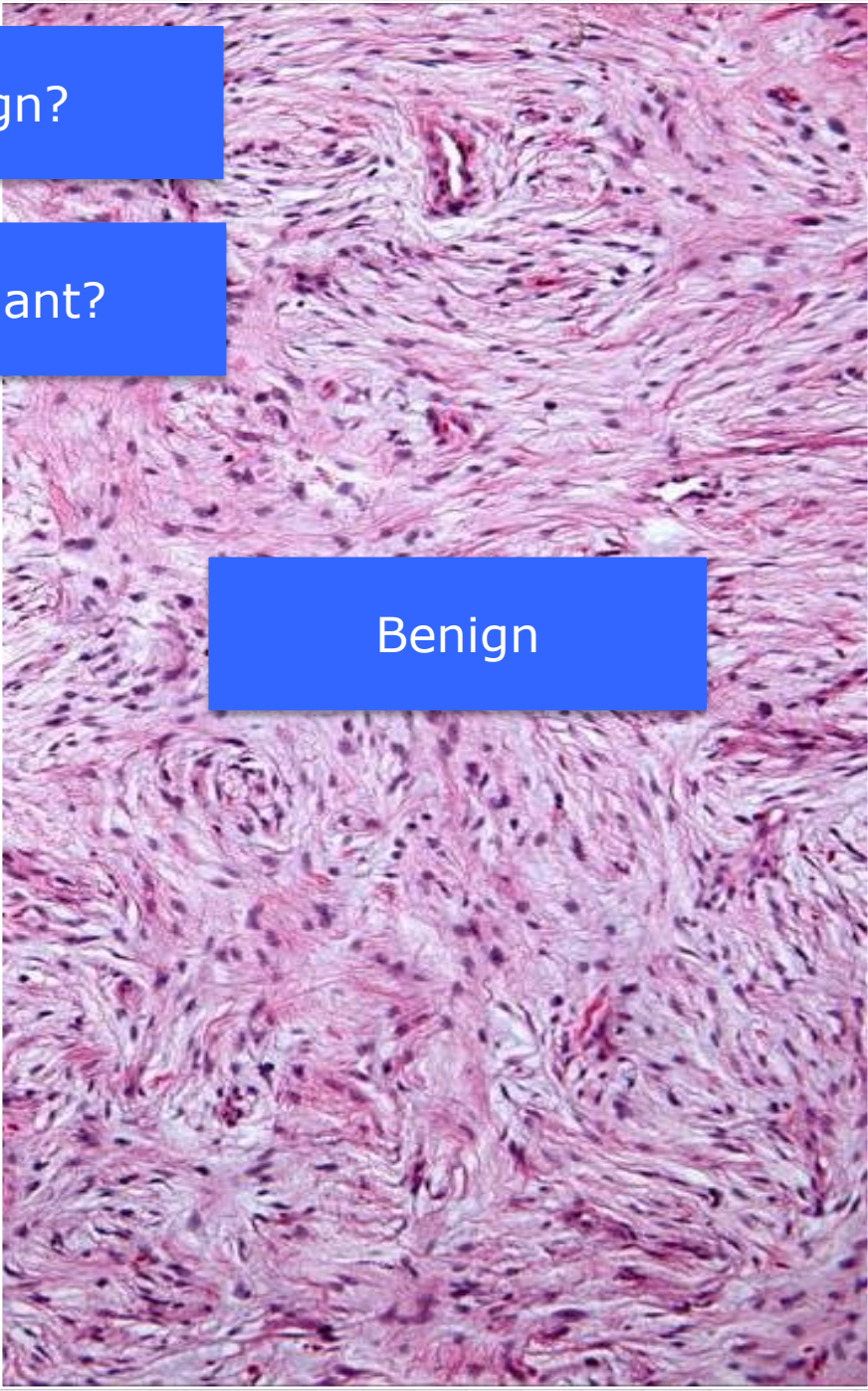
But there are limitations

Main ISSUES in sarcoma pathology:

- 1. Sarcomas are rare**
- 2. Many (117+) benigne and malignant tumors with significant morphologic overlap**
- 3. Significant intertumoral heterogeneity**
- 4. Limited material for diagnosis**
- 5. Experience of a single pathologist is limited based on the limited number of cases one can see in a general pathology service**



Malignant



Benign

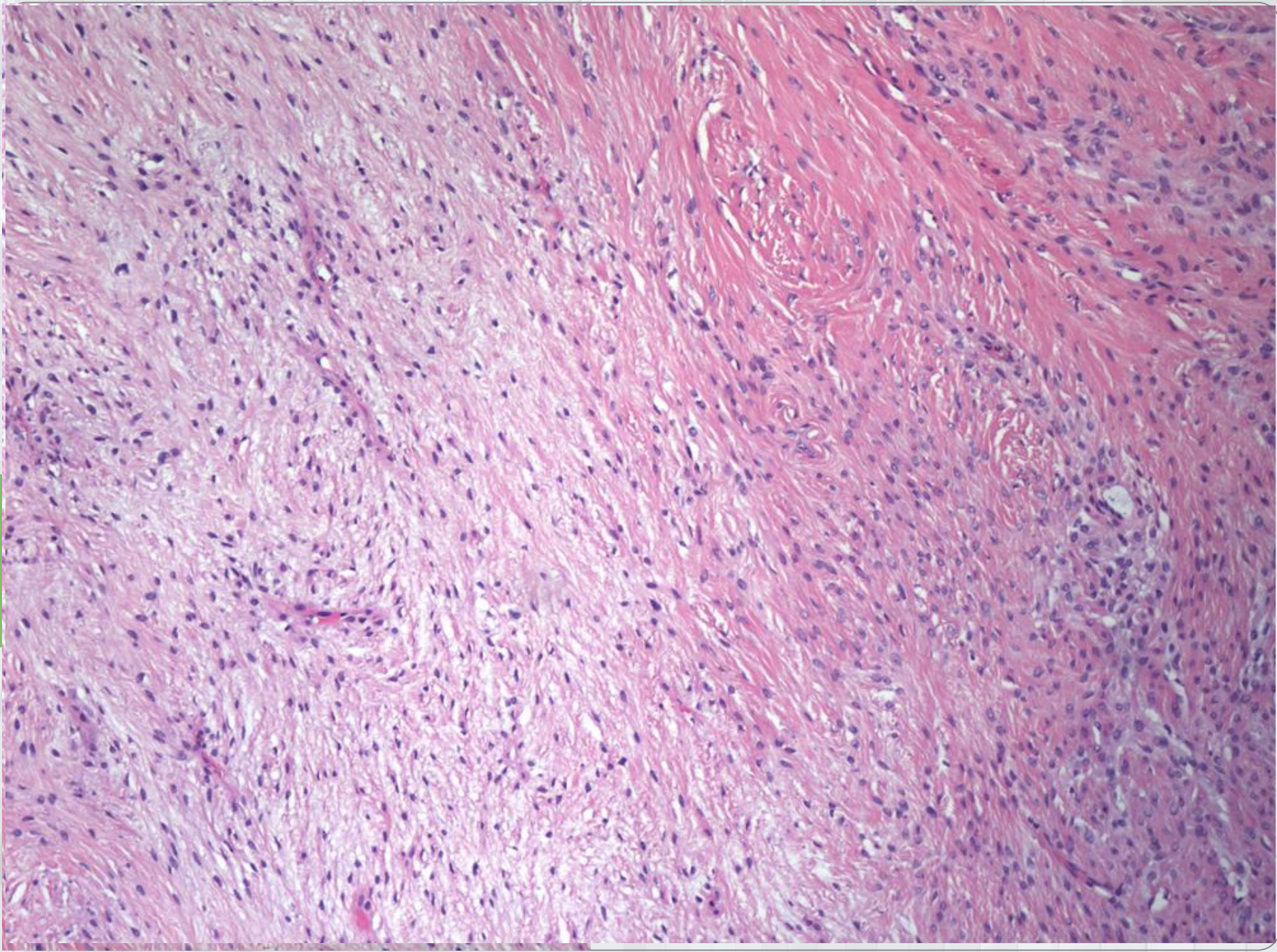
Benign?

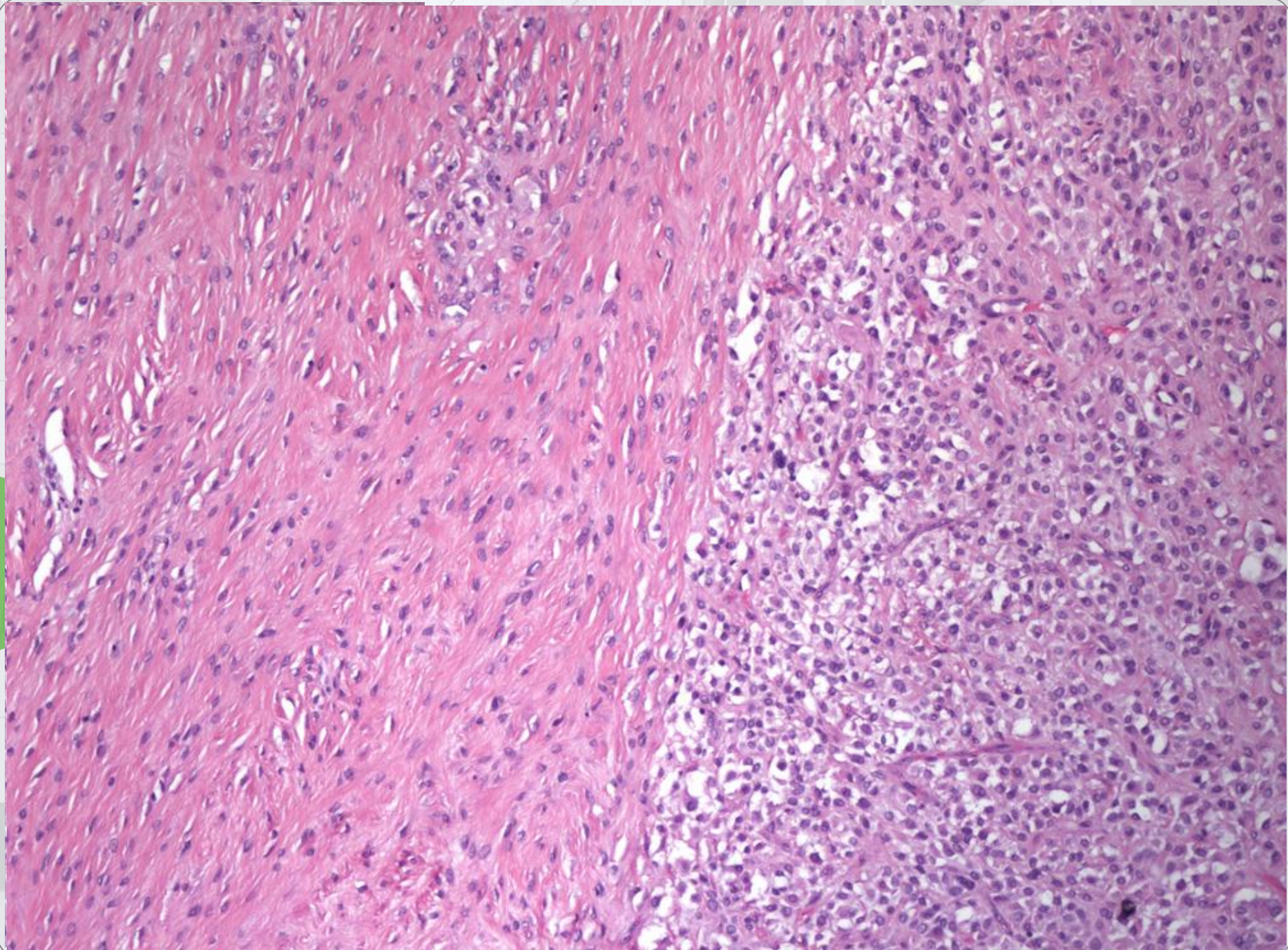
Malignant?

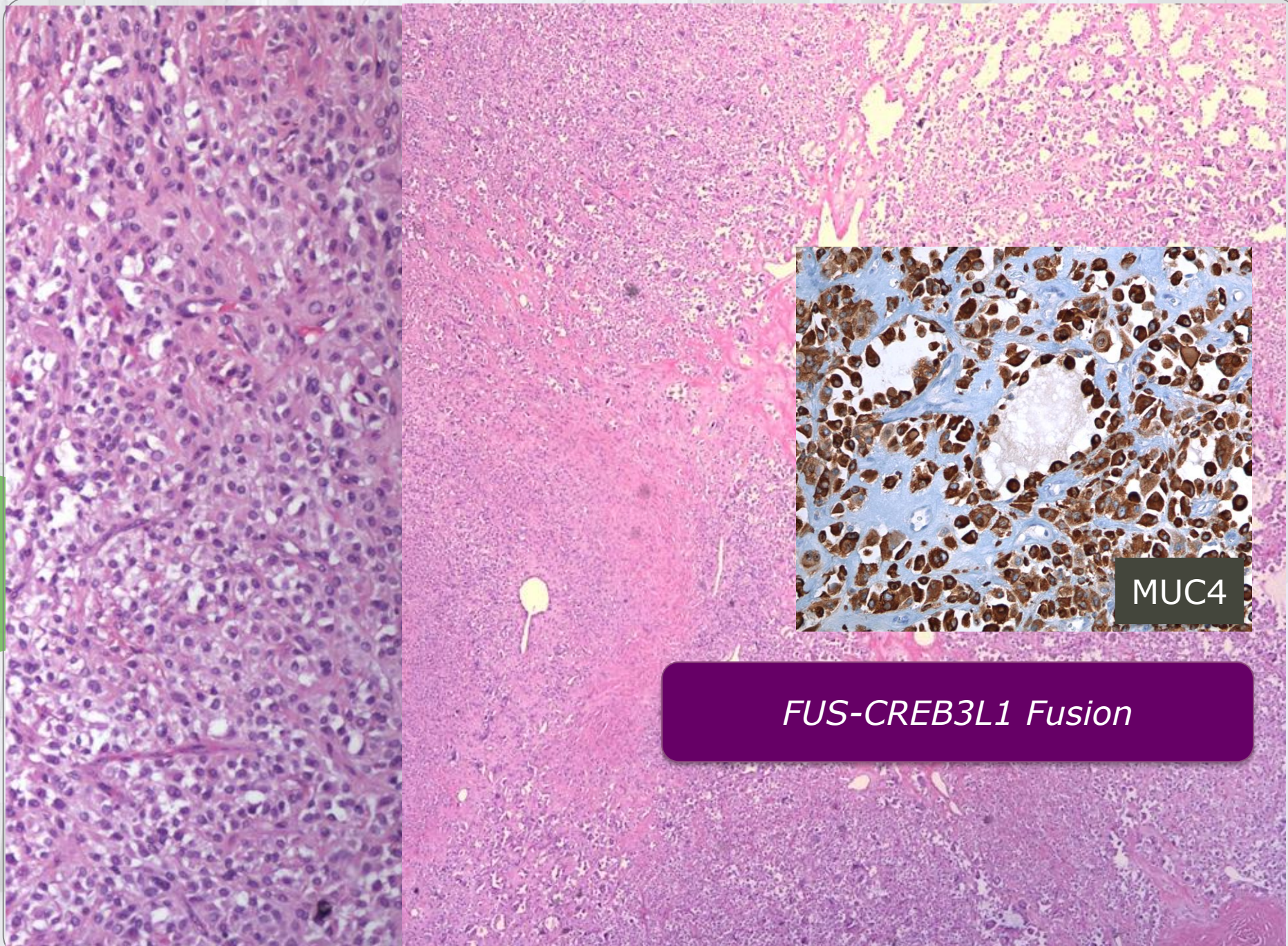
Soft tissue sarcomas

Main ISSUES in sarcoma pathology:

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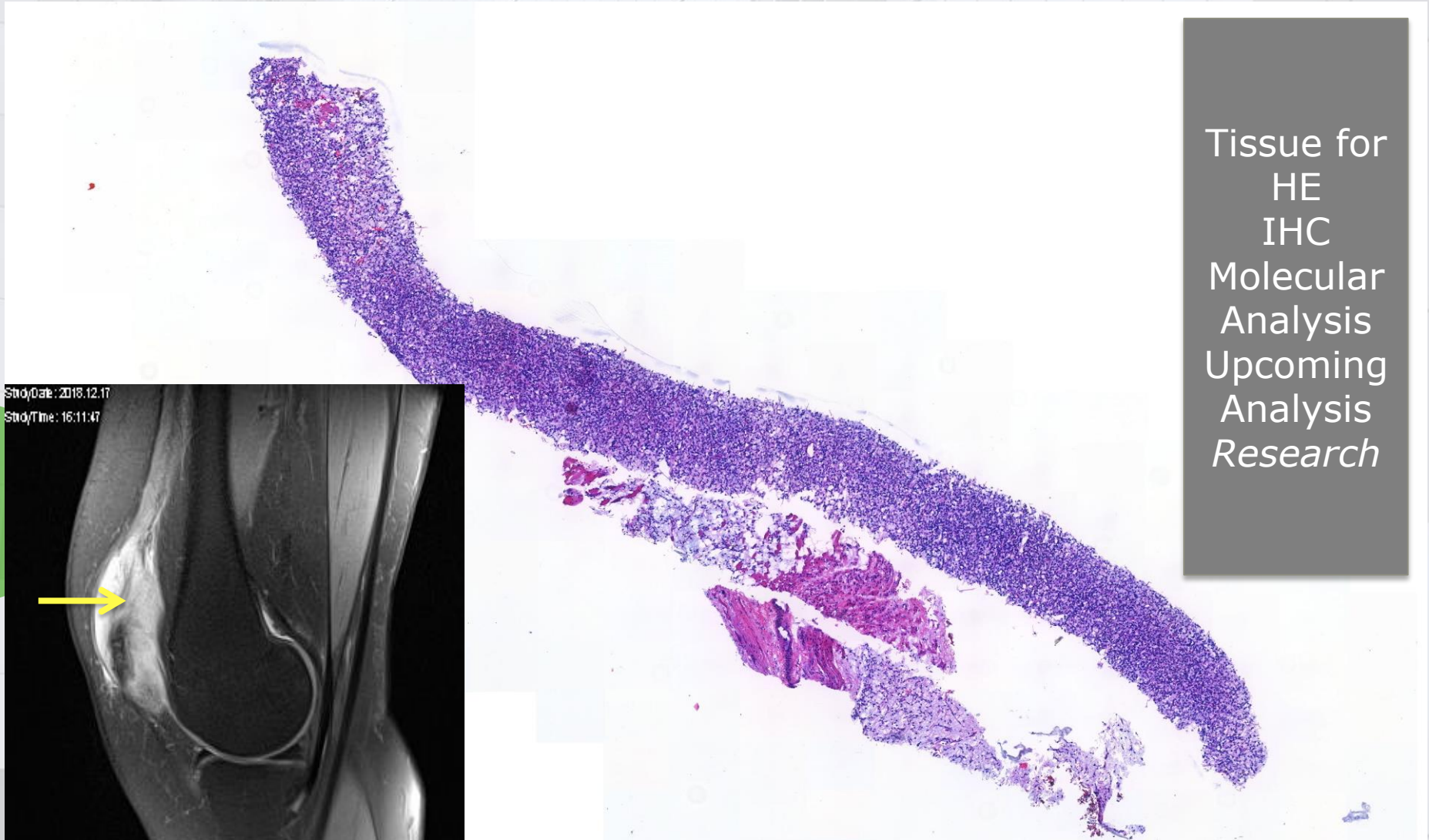
MUC4

FUS-CREB3L1 Fusion

Main ISSUES in sarcoma pathology:

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Tissue for
HE
IHC
Molecular
Analysis
Upcoming
Analysis
Research



Main ISSUES in sarcoma pathology:

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Role of Pathology 2019

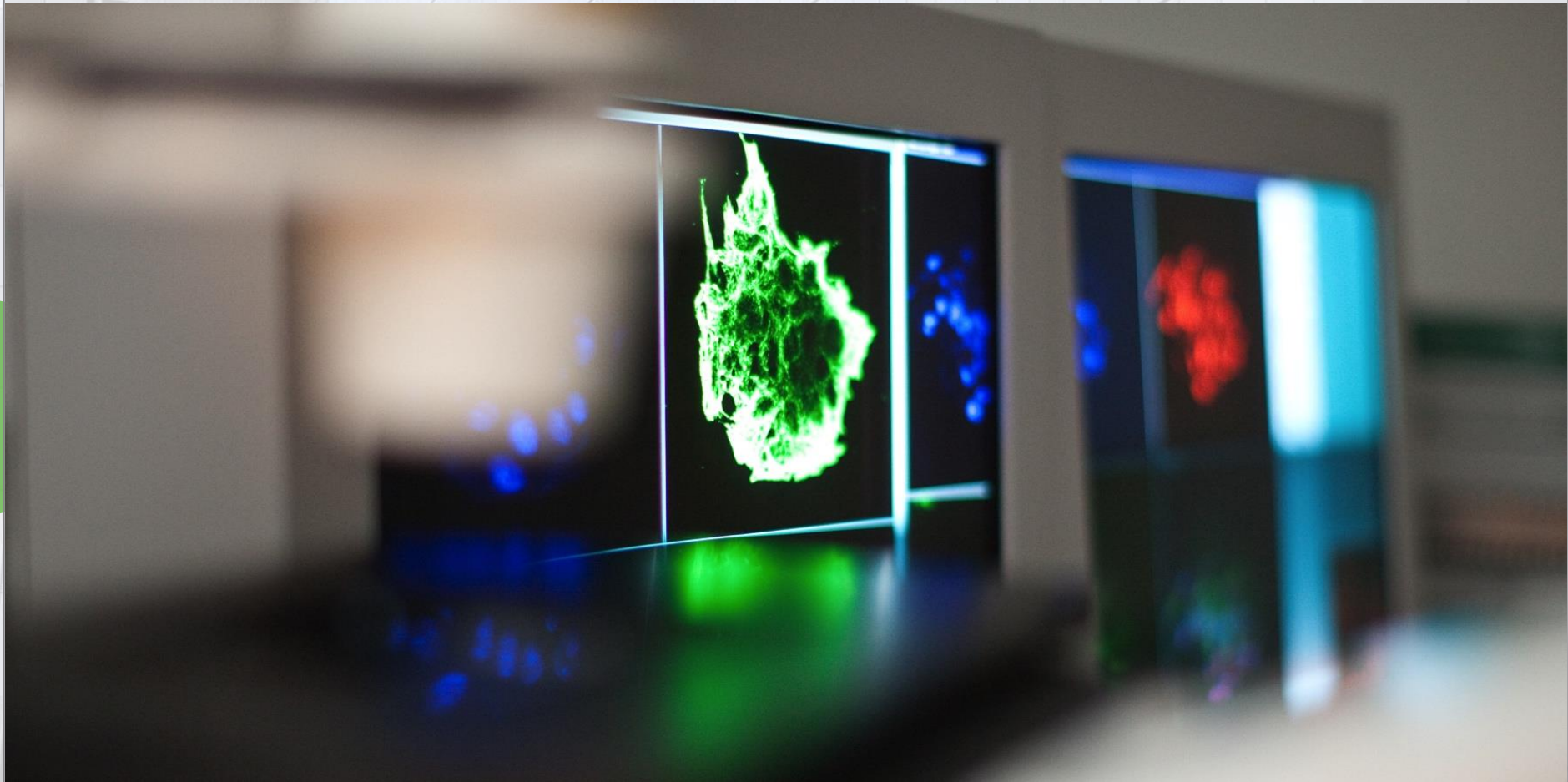
NEW TECHNOLOGIES

NGS

**Deep Learning
Computational
Pathology**

Ther

Diagnosis







**Ion Gene Studio
5S Prime**

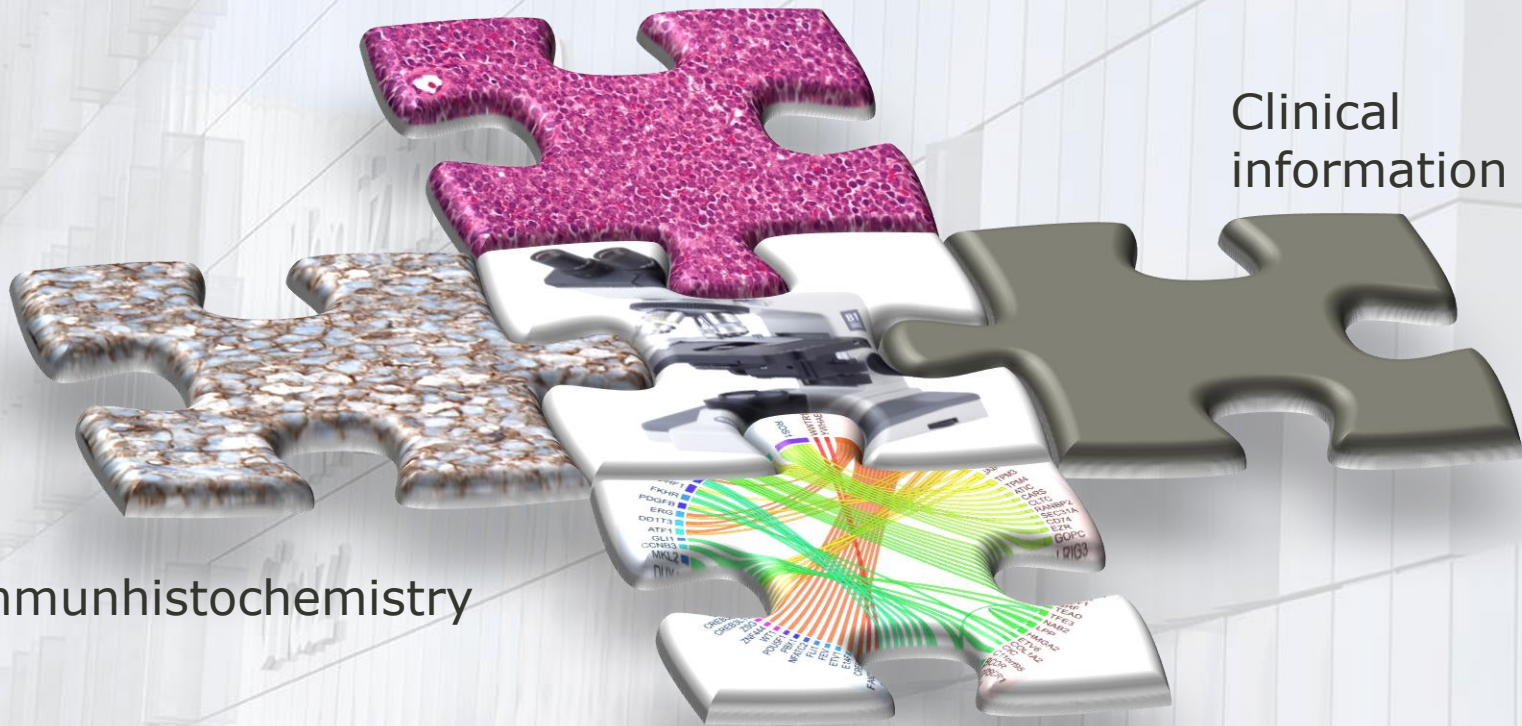
Morphology

Clinical
information

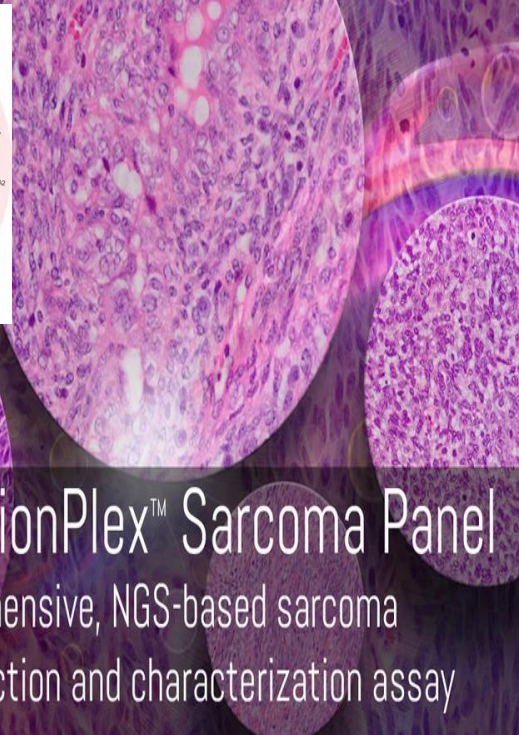
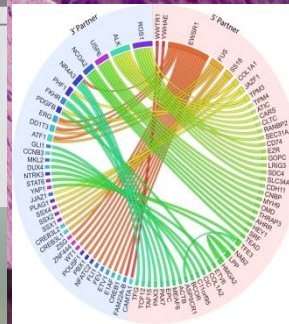
Immunohistochemistry

Molecular
Diagnostic

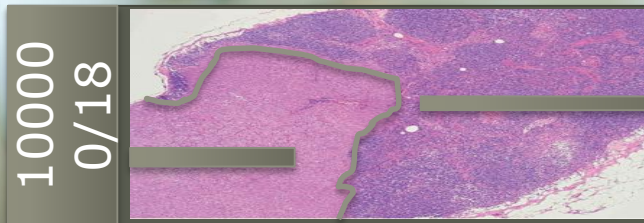
Diagnostic process – step by step



Pathology changed



Archer™ FusionPlex™ Sarcoma Panel
The first comprehensive, NGS-based sarcoma gene fusion detection and characterization assay



1997



World Health Organization
International Histological
Classification of Tumours

Histological Typing of Soft Tissue Tumours

S. W. Weiss
In Collaboration with L. H. Sobin
and Pathologists in 9 Countries

Second Edition



Springer-Verlag

2000

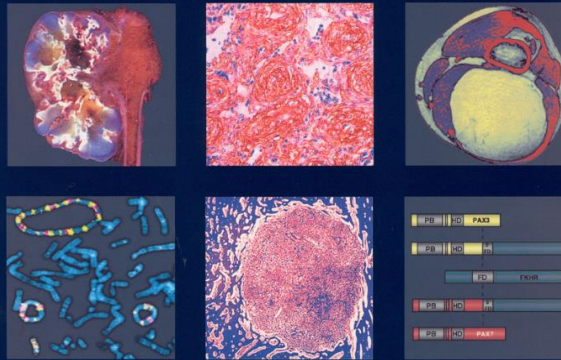
World Health Organization Classification of Tumours



Pathology & Genetics

Tumours of Soft Tissue and Bone

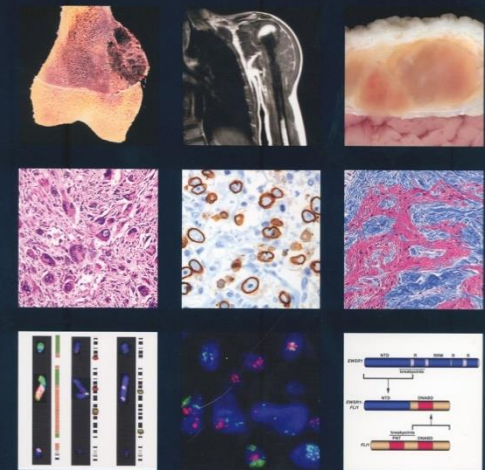
Edited by Christopher D.M. Fletcher, K. Krishnan Unni, Fredrik Mertens



2013

WHO Classification of Tumours of Soft Tissue and Bone

Edited by Christopher D.M. Fletcher, Julia A. Bridge, Pancras C.W. Hogendoorn, Fredrik Mertens



2019

Genetics

Genetics/molecular
Classification
New Entities

1997



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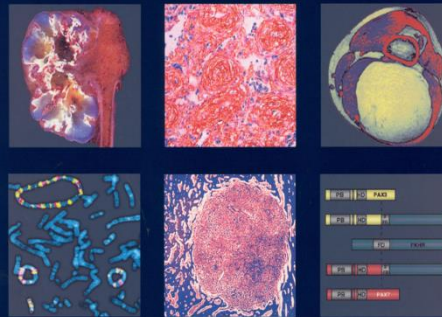
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Pathology & Genetics

Tumours of Soft Tissue and Bone

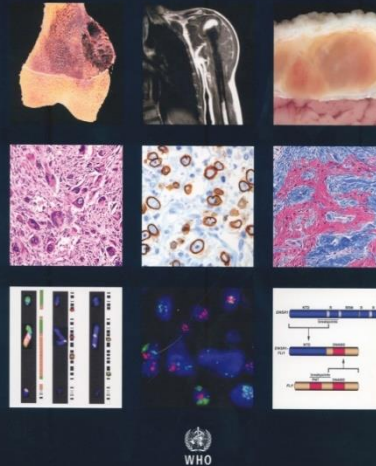
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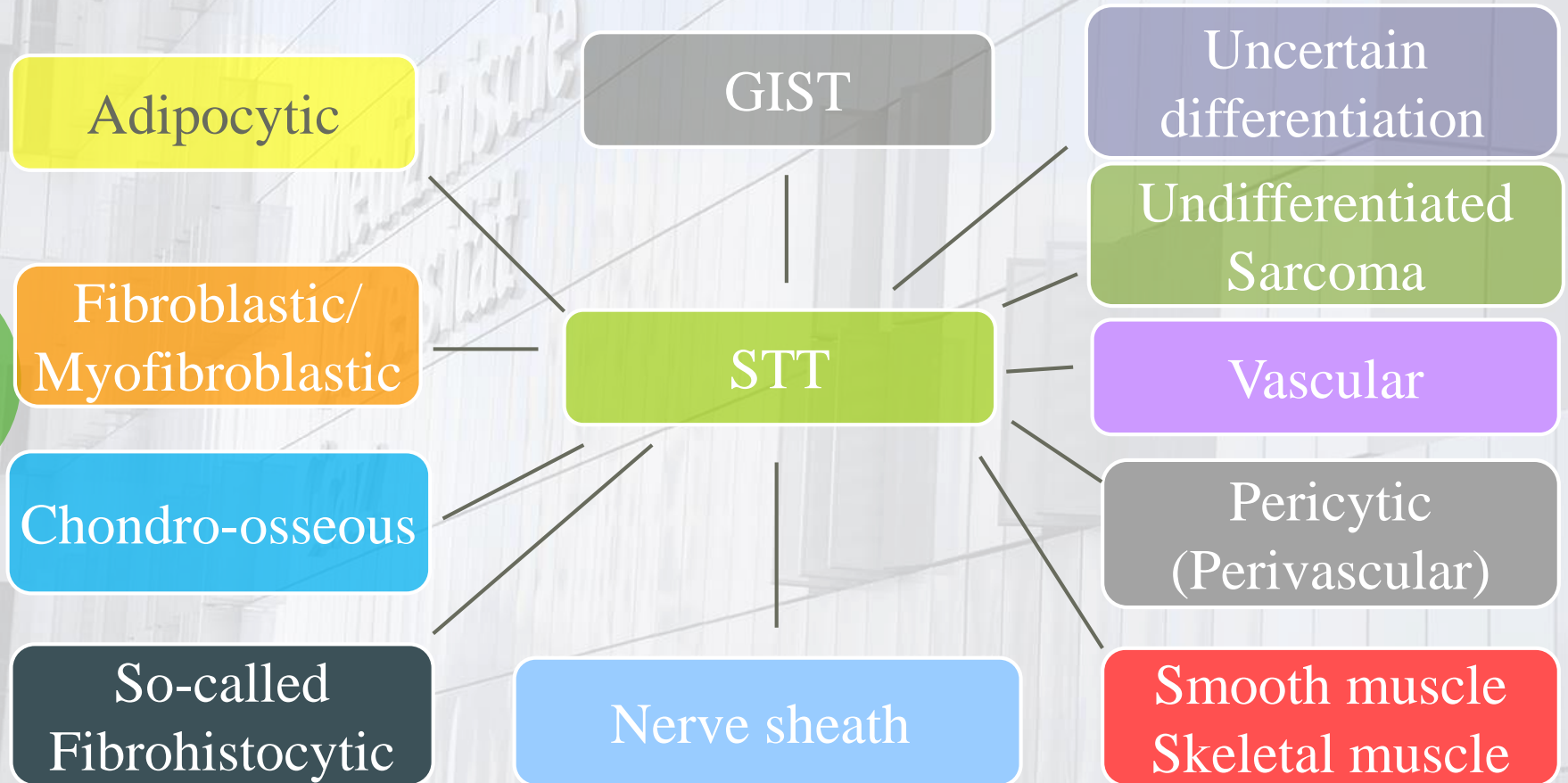
2019/20

NEW
WHO
Tumours of
Soft Tissue
and Bone

Genetics/molecular
Classification
New Entities

Classification of STT (line of differentiation)

WHO 2013 -> *new upcoming WHO....2019/2020*



Diagnostic of soft tissue tumors



Diagnostic workflow


Clinical Presentation

Gross/Histology

Immunohistochemistry

Molecular Diagnostics

CLINICAL INFORMATIONS

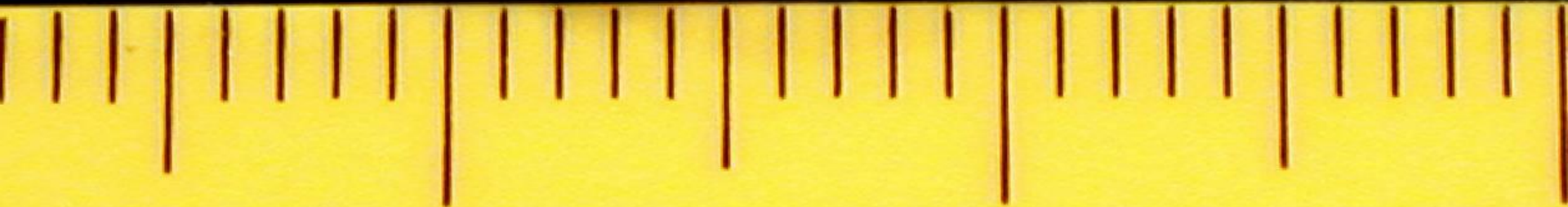
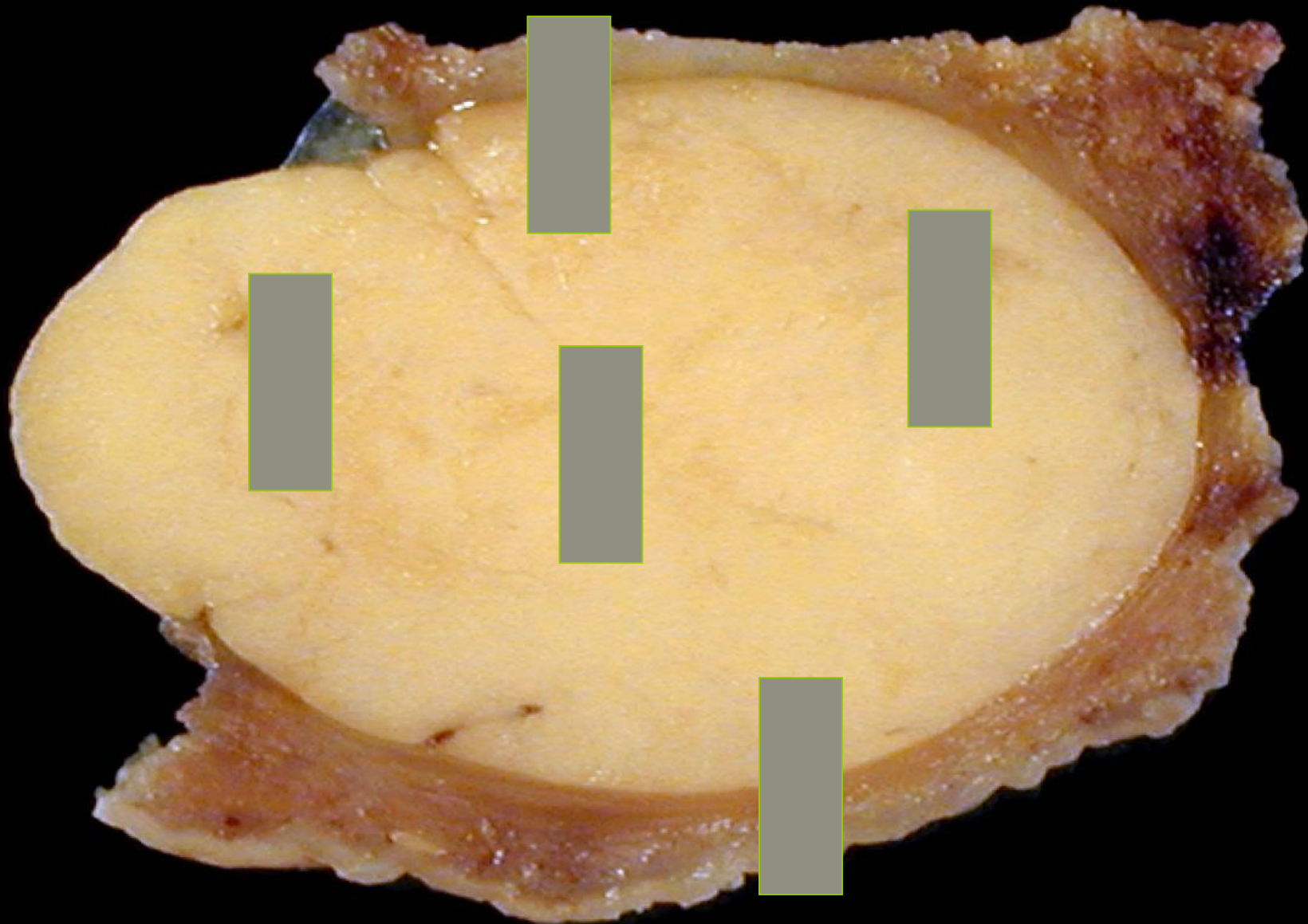


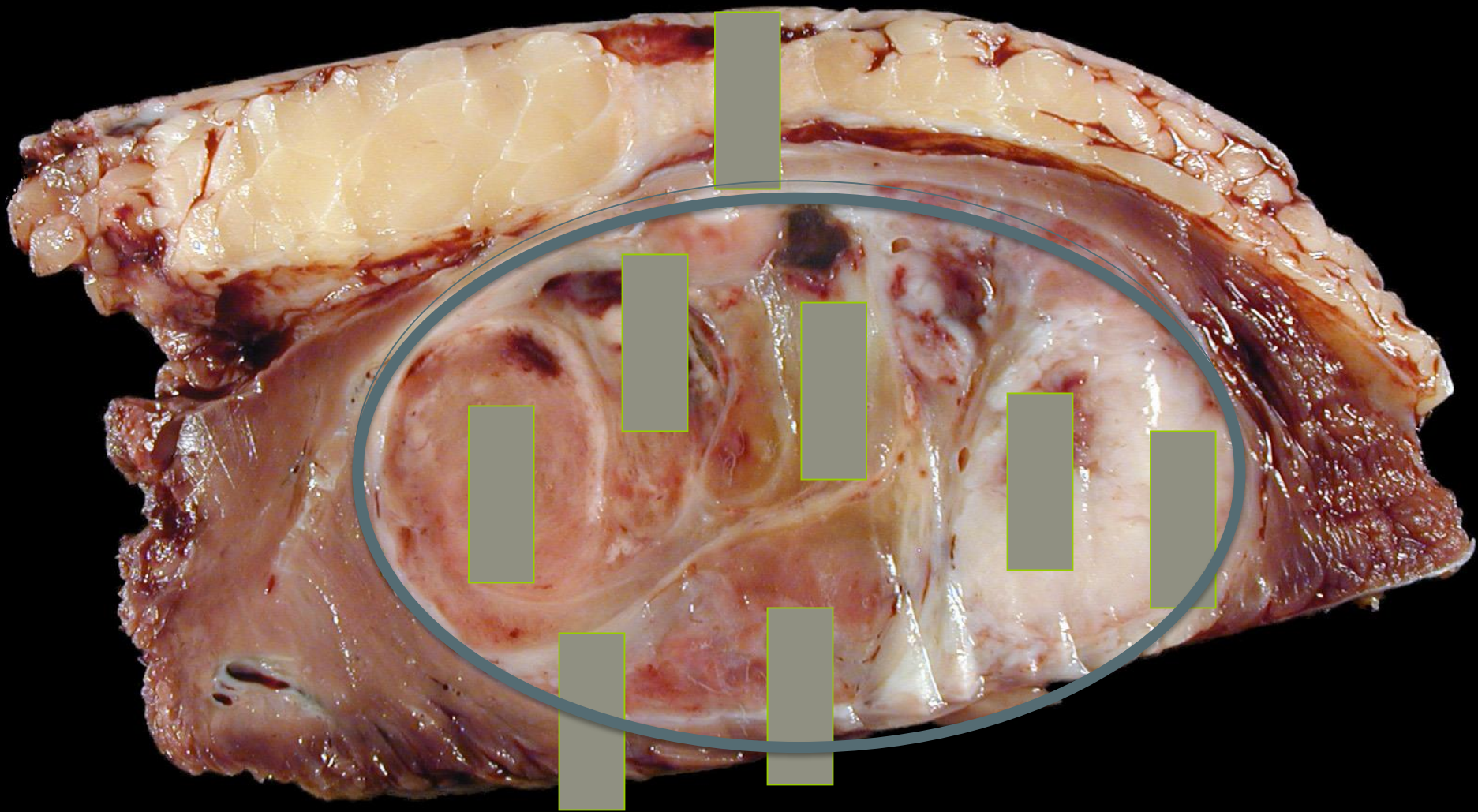
Look holistically at your patient
Age/Sex
Size
Location
Association with organs/structures
Duration
CT/MRI

Gross Description

- ▶▶ Location (superficial or deep)
- ▶▶ Size
- ▶▶ Resection margins
- ▶▶ Association with other structures (nerves, vessels, bone..)
- ▶▶ Evaluation of the cut surface

Unfixed material -> cryo samples (documentation)
-> adequate fixation (documentation)





0

14

Morphologic Pattern Recognition

117 different malignant and benigne STT

▶▶ Cell Type:

- Spindle-cell-morphology
- Epithelioid-cell-morphology
- Pleomorphic –cell-morphology
- Round-cell-morphology

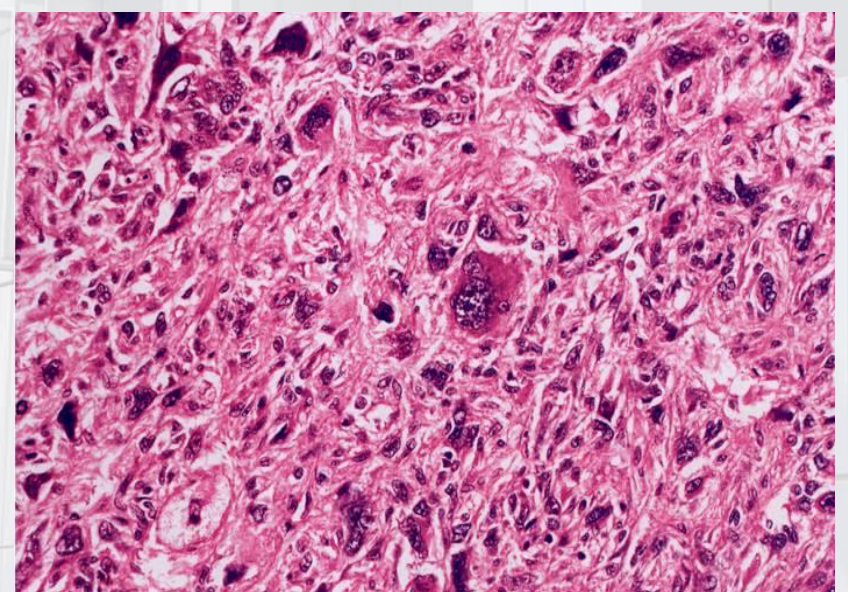
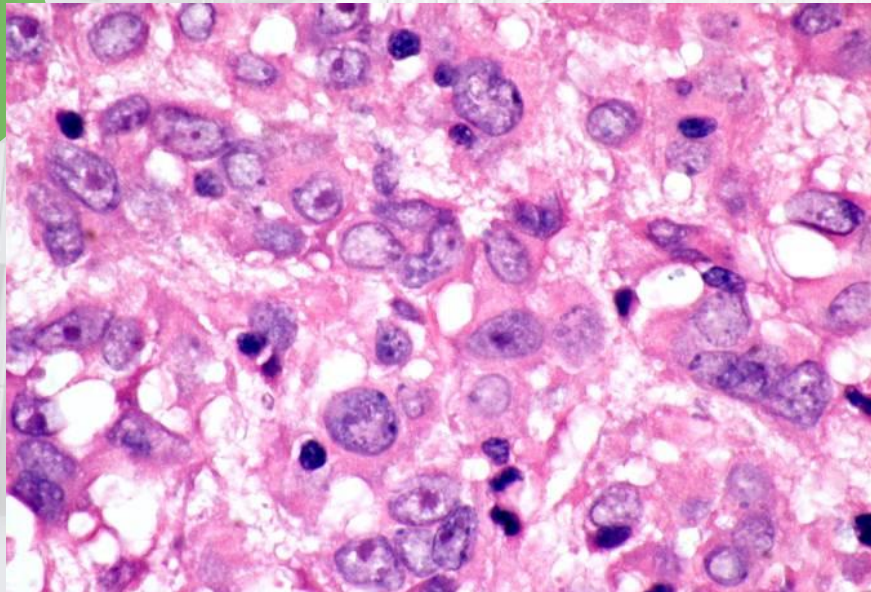
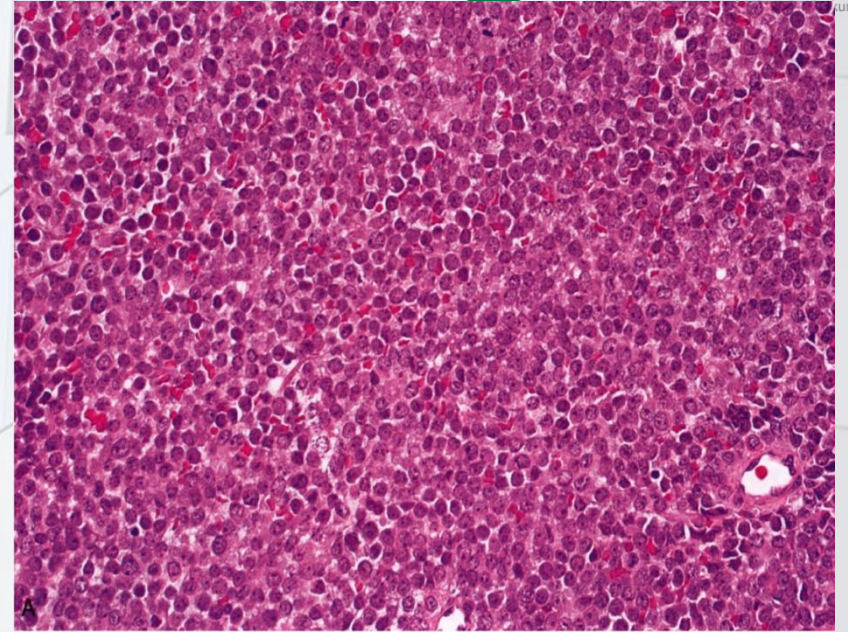
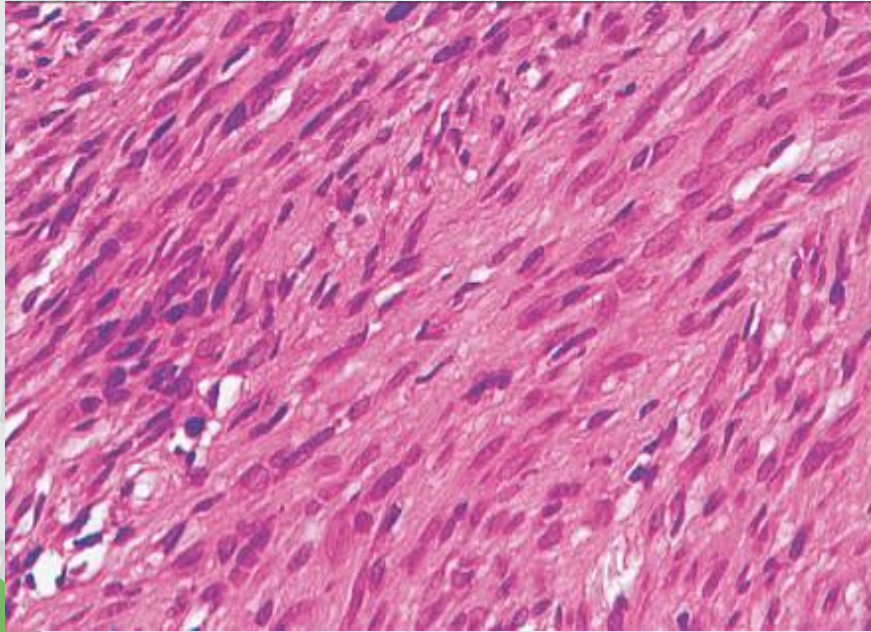
▶▶ Matrix:

- Myxoid
- Fibrous
- Bone, Cartilage, Calcification.....

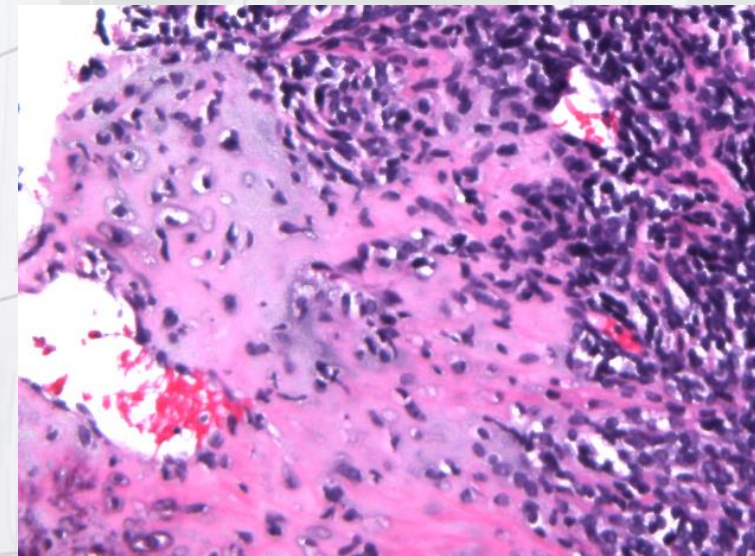
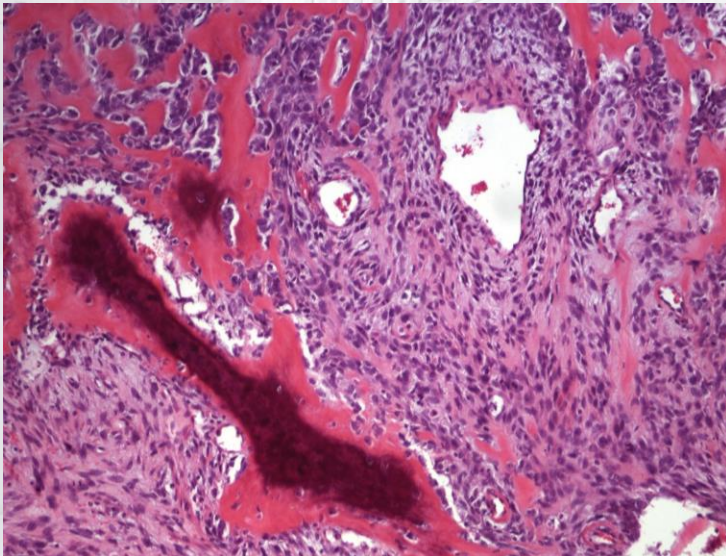
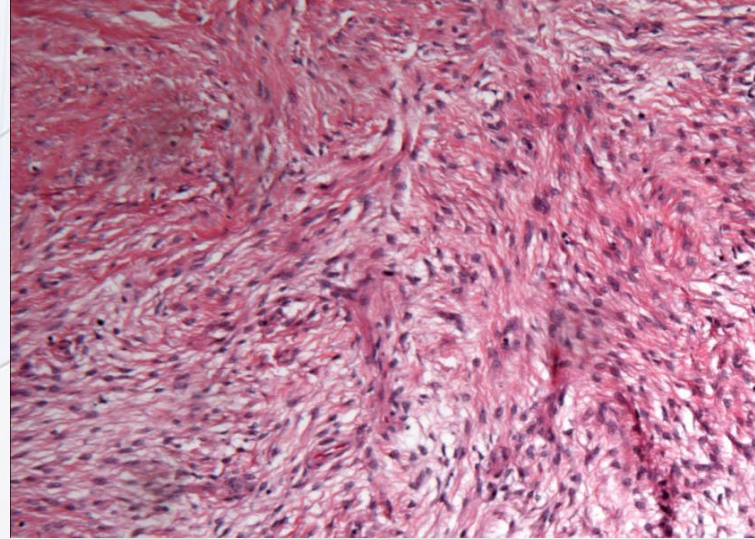
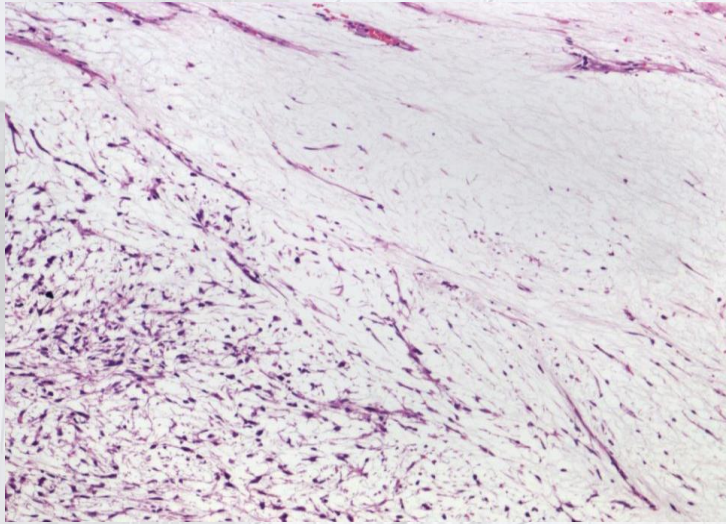
▶▶ Vascular Pattern:

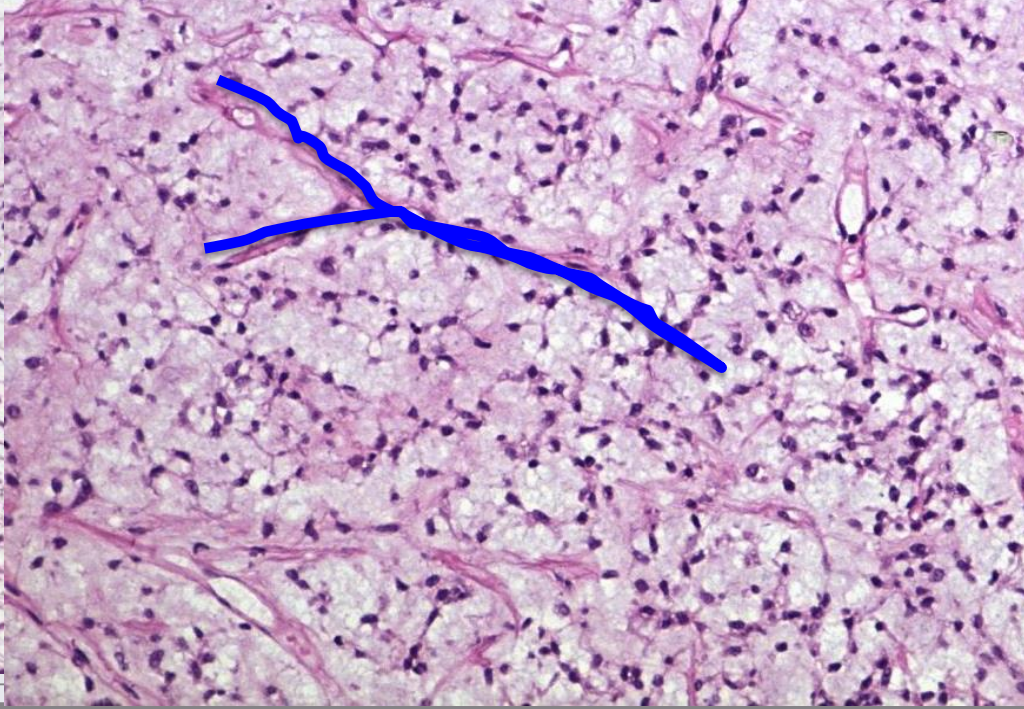
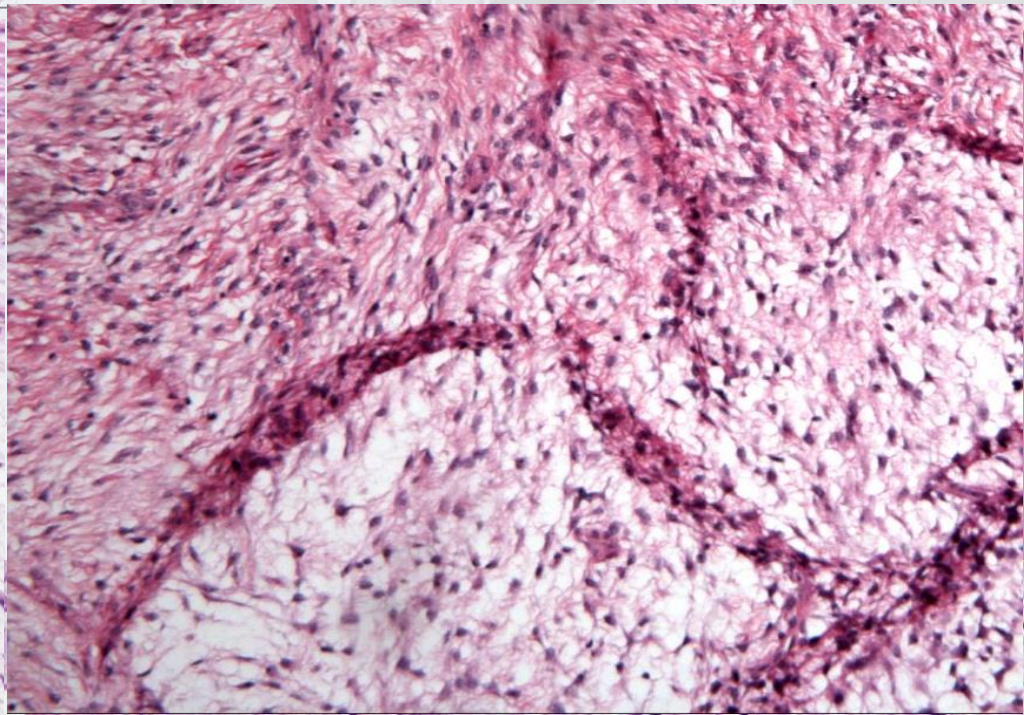
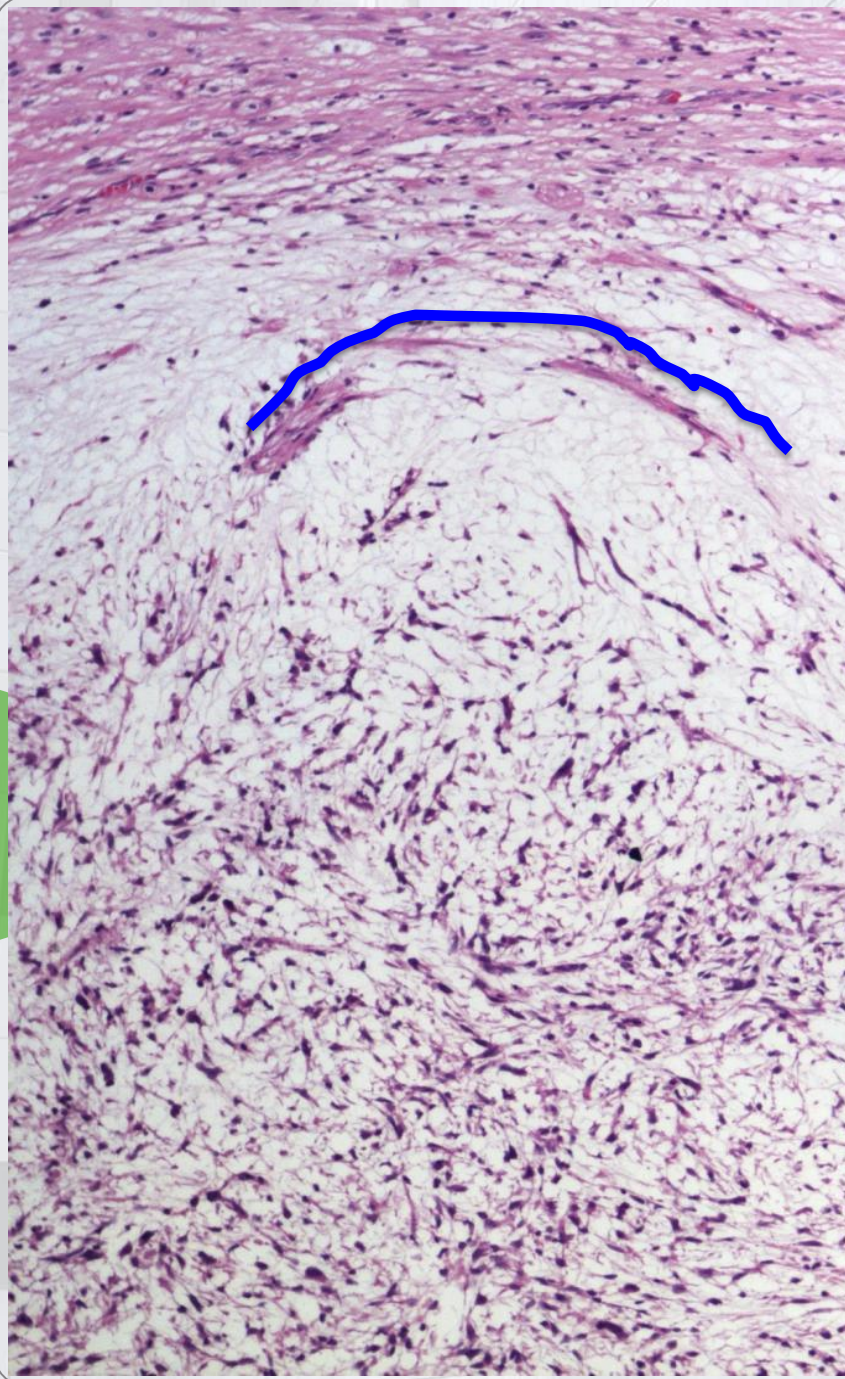
▶▶ Location:

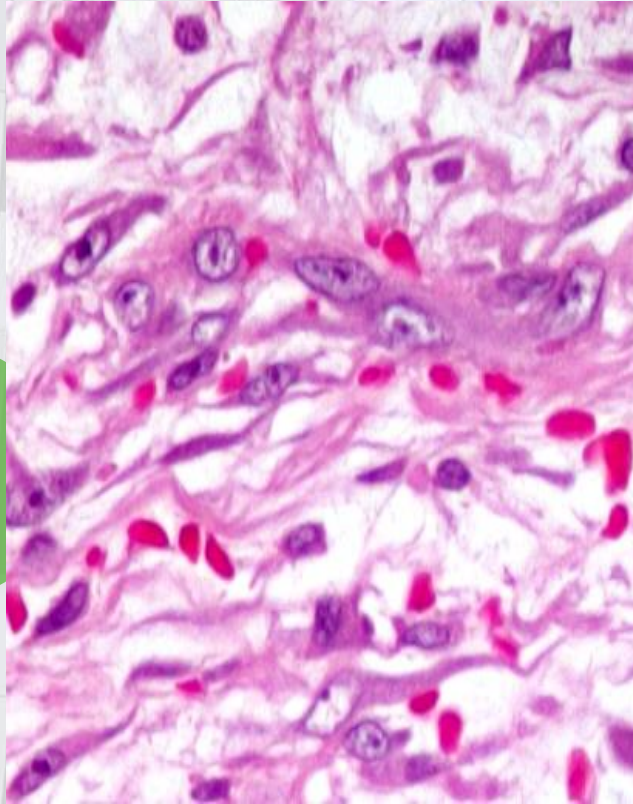
Cell shape



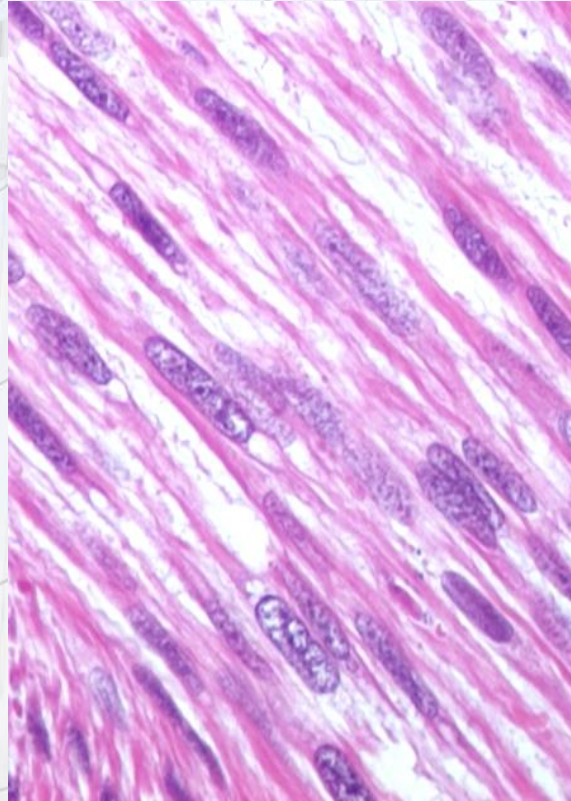
Stroma



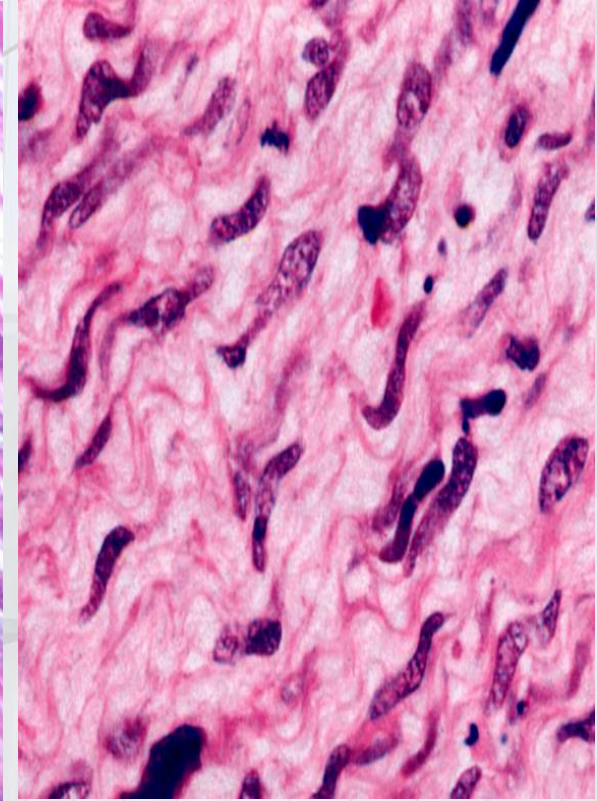




Fibroblasts/Myofibroblasts

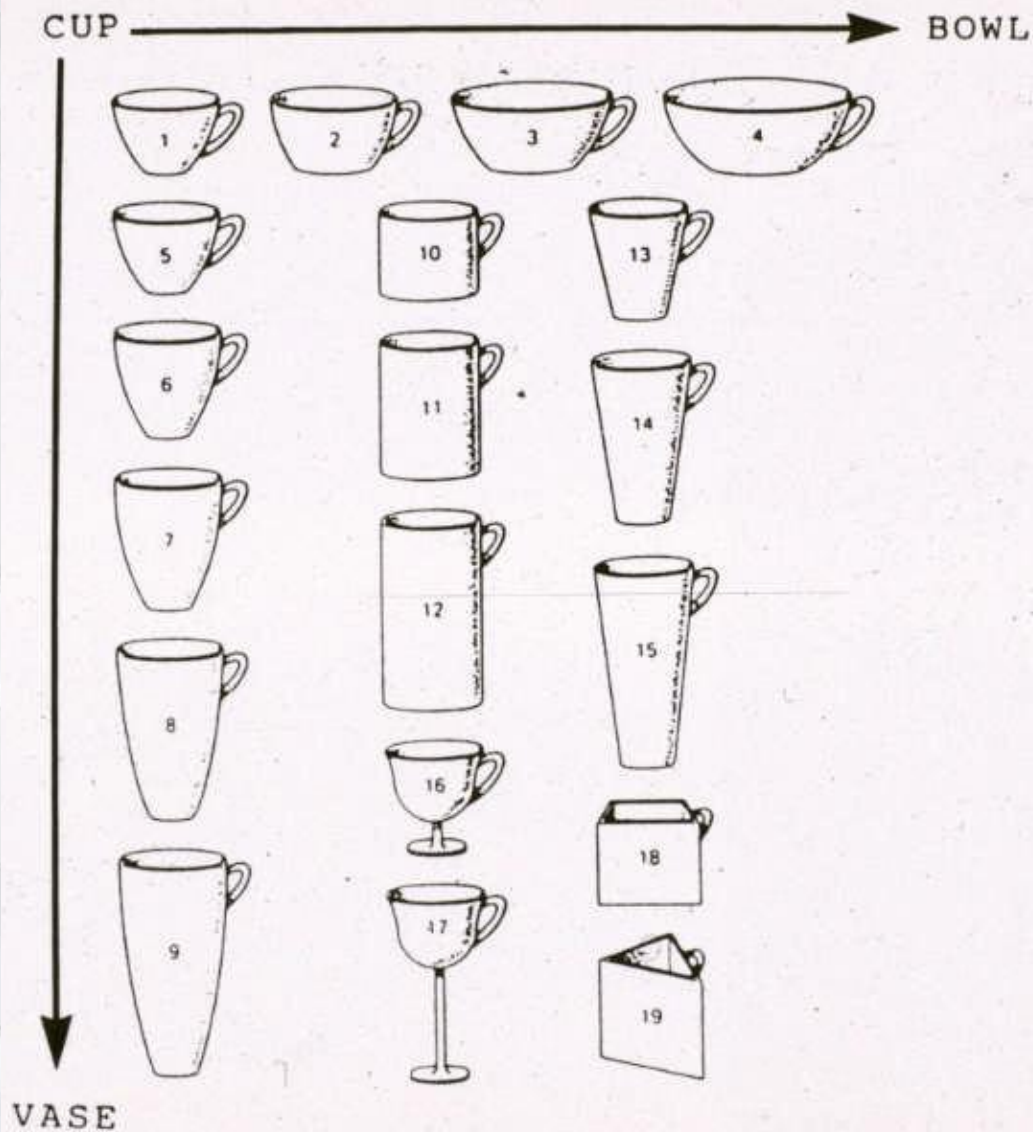
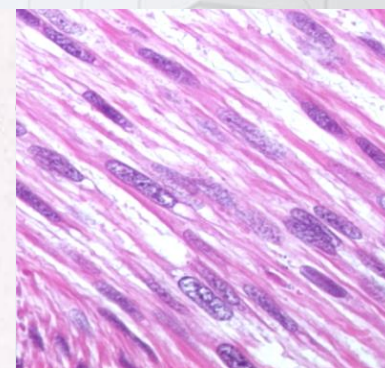
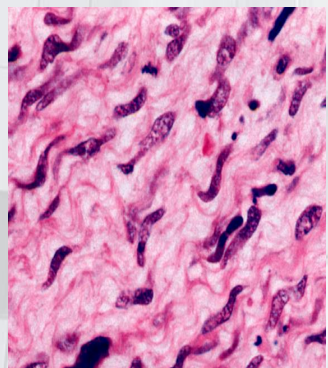
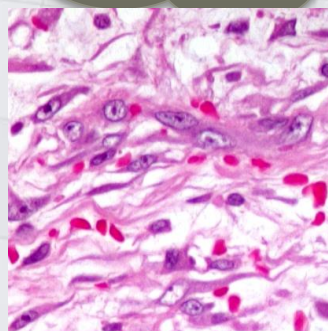


Smooth muscle cells



Neural cells

Spindle-cell tumor/sarcoma





DIFFERENCES SHOWN



SPARKLING WINE FLUTE



WHITE WINE GLASS (RECOMMENDED)



STANDARD WINE GLASS

Spindle Sarcophagus

SYRAH / SHIRAZ	BORDEAUX / CABERNET	TEMPRANILLO / RIOJA	BURGUNDY / PINOT NOIR	ZINFANDEL / CHIANTI
SAUVIGNON BLANC	RIESLING (SWEET)	CHABLIS / CHARDONNAY	MONTRACHET	RIESLING (DRY) / PINOT GRIGIO
CHAMPAGNE	VINTAGE CHAMPAGNE	SAUTERNES	ROSE / BLUSH	VINTAGE PORT



IHC



Immunohistochemistry:

To **confirm/ identify** the line of differentiation

- **Epithelial Tumors**
- **Mesenchymal Tumors** (hematopoetic, melanocytic..)
- **Germline Tumors**

To confirm a diagnosis made on HE

To identify the proliferation activity

To identify biomarkers

IHC Panel

The Hot „6“

„Helpers“

IHC Panel to diagnose STT

EMA

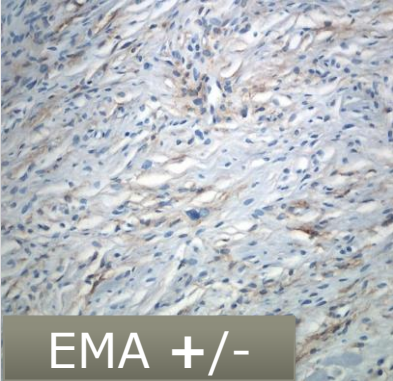
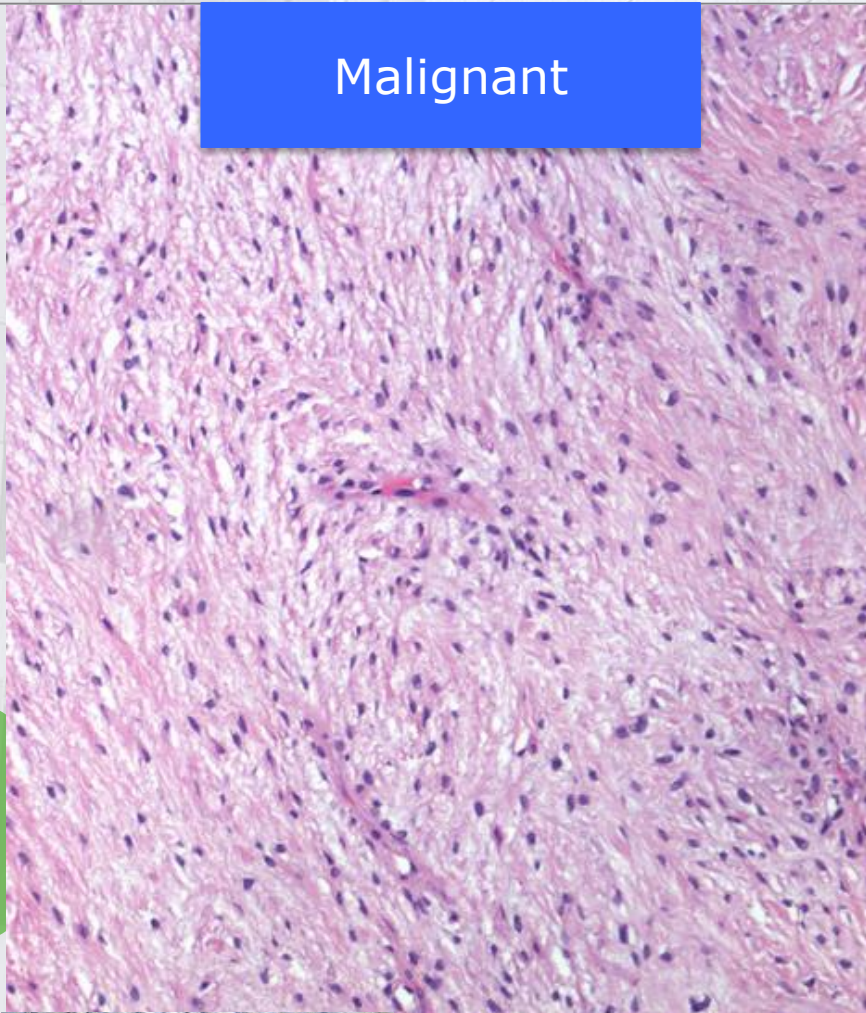
AE1/AE3

S100

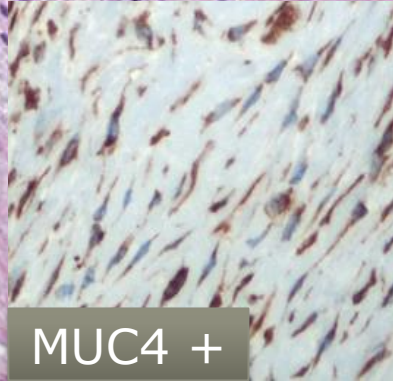
STAT6, MYOD1, MUC4, TLE1,
H3K27me, BCOR, SMARCA4, INI1,
SATB1...

GIST: KIT, DOG1, SDHB, SDHA

Malignant



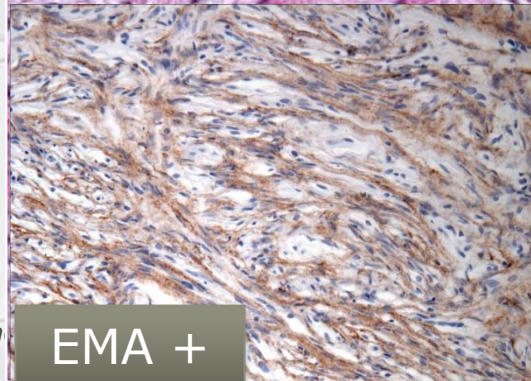
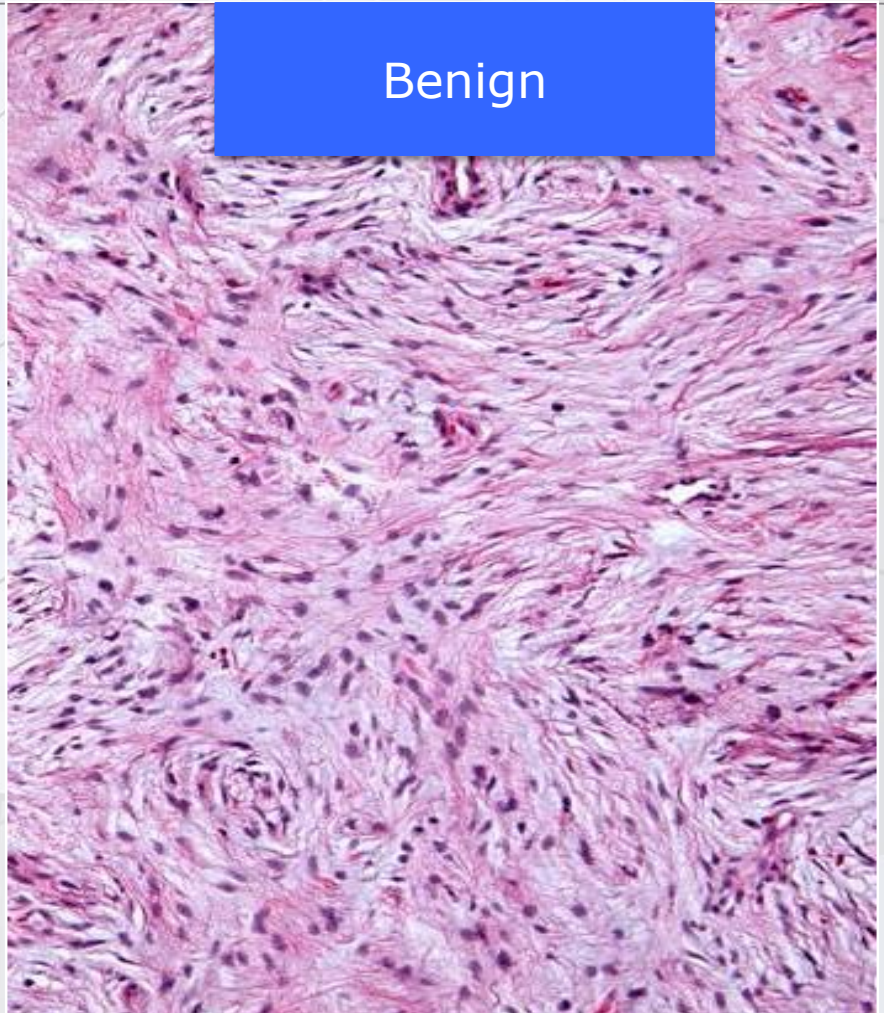
EMA +/-



MUC4 +

Can

Benign



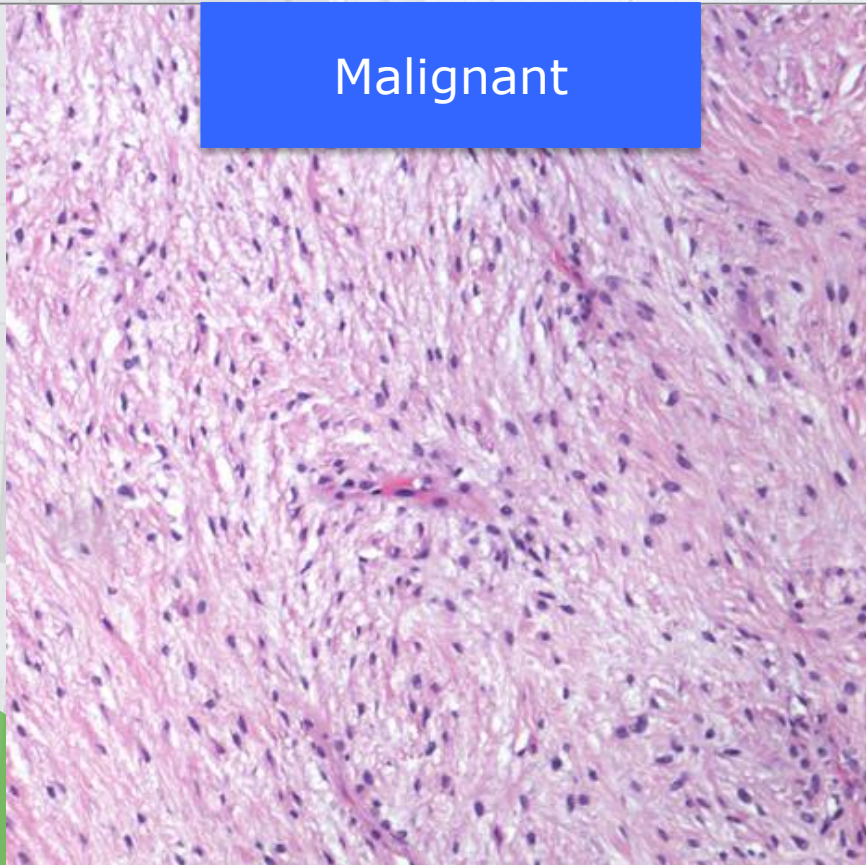
EMA +

MUC4 -

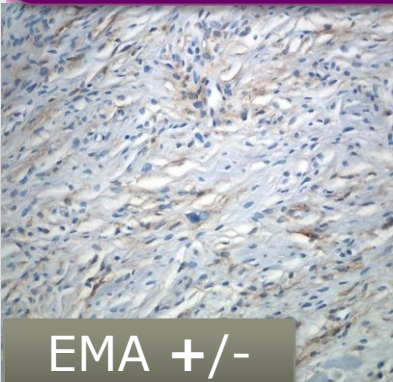
Method	Advantages	Disadvantages
Cytogenetics DNA	Global view Primary and secondary abnormalities identified Does not require knowledge of abnormality or diagnosis May detect abnormalities not seen by FISH or PCR	Requires fresh tissue (dividing cells) Low resolution Cryptic rearrangements Lower sensitivity Slower TAT
FISH DNA or RNA	More targeted view Requires prior knowledge of abnormality or diagnosis Diagnostically specific and sensitive Moderate resolution Moderate analytic sensitivity Multiple tissue types can be used FFPE, frozen, cytology or cultured cells (FISH or iFISH) Can localize abnormality to specific cells Faster TAT	Need for fluorescence microscope Signals fade Does not work on decal tissue
RT-PCR (reverse transcriptase) RNA	High resolution (very targeted view) High sensitivity and specificity, and quantifiable (MRD) Multiplexing possible Can use FFPE, frozen sections, cytology, or fresh Faster TAT	Requires knowledge of abnormality Does not work on decal tissue FFPE may have degraded RNA PCR inhibitors
IHC Protein	Can use FFPE, frozen sections or cytology Morphologic correlation Rapid TAT Relatively inexpensive Mutation specific antibodies available	Interlab variability
NGS DNA or RNA	High throughput (huge multiplex capability) High resolution (individual nucleotide level)	Cost of equipment (decreasing) Need and cost of bioinformatics



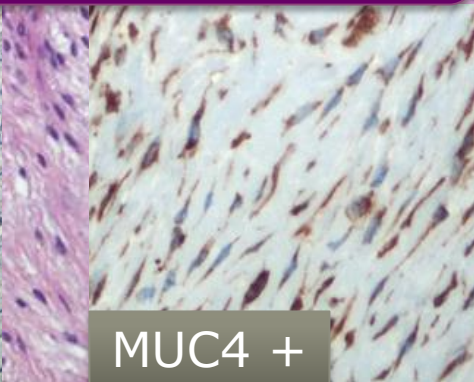
Malignant



FUS-CREB3L1 Fusion



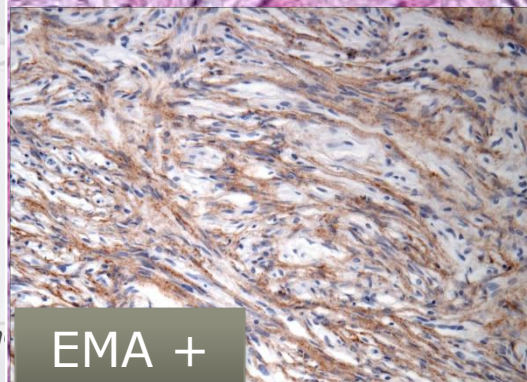
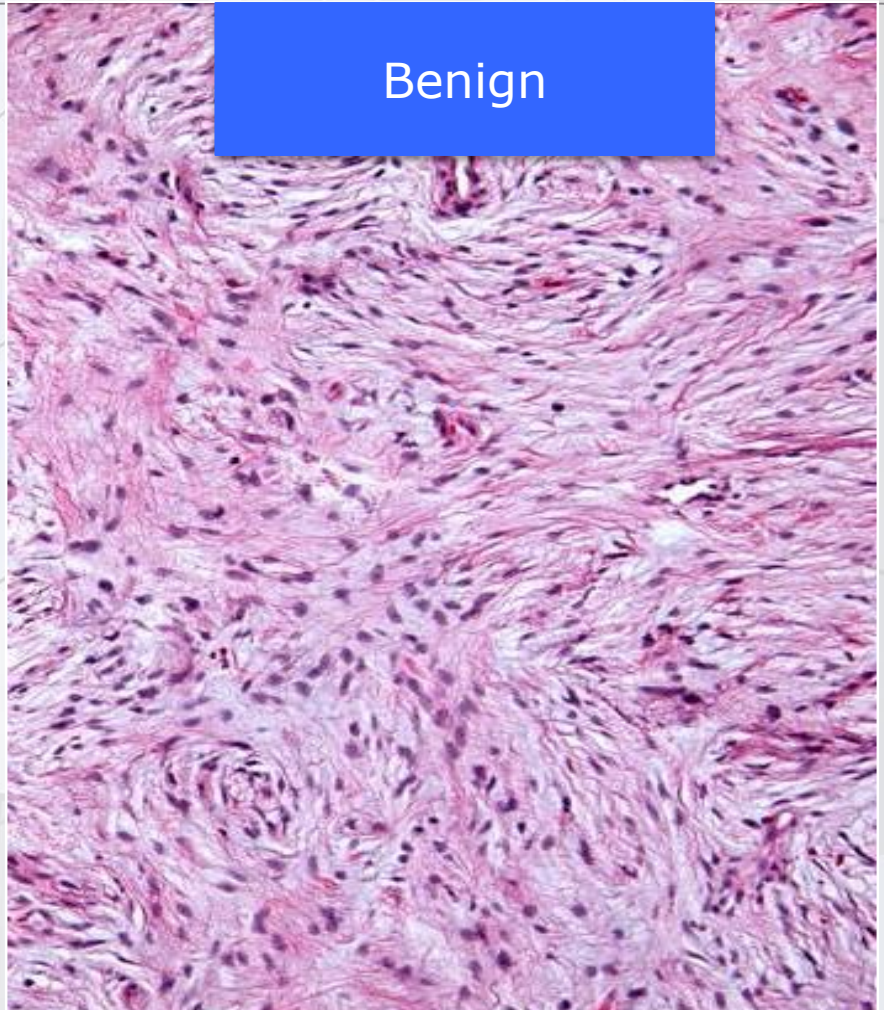
EMA +/-



MUC4 +

Can

Benign



EMA +



MUC4 -

Molecular Classification of Soft Tissue Tumors

Molecular view of sarcoma

- 1 simple genetic changes
 - Translocations
 - Amplifications
 - Mutations
- 2 complex genetic changes; most common (LMS, MPNST, UPS)

Table 1. Gene fusions in soft tissue tumours*

Tumour	Gene fusion	Chromosome aberration
Adipocytic tumours Lipoma	<i>EBF1-LOC204010</i>	t(5;12)(q33;q14)
	<i>HMGA2-CXCR7</i>	t(2;12)(q37;q14)
	<i>HMGA2-EBF1</i>	t(5;12)(q33;q14)
	<i>HMGA2-LHFP</i>	t(12;13)(q14;q13)
	<i>HMGA2-LPP</i>	t(3;12)(q28;q14)
	<i>HMGA2-NFIB</i>	t(9;12)(p22;q14)
	<i>HMGA2-PPAP2B</i>	t(1;12)(p32;q14)
	<i>LPP-C12orf9</i>	t(3;12)(q28;q14)
Lipoblastoma	<i>COL1A2-PLAG1</i>	t(7;8)(q21;q12)
	<i>HAS2-PLAG1</i>	del(8)(q12q24)
Chondroid lipoma	<i>C11orf95-MKL2</i>	t(11;16)(q13;p13)
Myxoid/round cell liposarcoma	<i>FUS-DDIT3</i>	t(12;16)(q13;p11)
	<i>EWSR1-DDIT3</i>	t(12;22)(q13;q12)
Dedifferentiated liposarcoma	<i>CNOT2-ASTN2</i>	t(9;12)(q33;q15)
	<i>CTDSP2-FAM19A2</i>	?t(12)(q14q14)
	<i>NR6A1-TRHDE</i>	t(9;12)(q33;q21)
	<i>NUP107-LGR5</i>	?t(12)(q15q21)
	<i>NUP107-PAPPA</i>	t(9;12)(q33;q15)
	<i>RCOR1-WDR70</i>	t(5;14)(p13;q32)
Fibroblastic/Myofibroblastic tumours Soft tissue angiofibroma	<i>AHRR-NCOA2</i>	t(5;8)(p15;q13)
	<i>GTF2I-NCOA2</i>	t(7;8;14)(q11;q13;q31)
Dermatofibrosarcoma protuberans	<i>COL1A1-PDGFB</i>	t(17;22)(q21;q13)
Solitary fibrous tumour	<i>NAB2-STAT6</i>	inv(12)(q13q13)
Infantile fibrosarcoma	<i>ETV6-NTRK3</i>	t(12;15)(p13;q25)
Low-grade fibromyxoid sarcoma	<i>FUS-CREB3L2</i>	t(7;16)(q34;p11)
	<i>FUS-CREB3L1</i>	t(11;16)(p11;p11)
Sclerosing epithelioid fibrosarcoma	<i>FUS-CREB3L2</i>	t(7;16)(q34;p11)

Lipofibromatosis like
neural tumor
NTRK1-related
fusions

Table 1. (Continued)

Tumour	Gene fusion	Chromosome aberration
Inflammatory myofibroblastic tumour	<i>AT1C-ALK</i>	inv(2)(p23q35)
	<i>CARS-ALK</i>	t(2;11)(p23;p15)
	<i>CLTC-ALK</i>	t(2;17)(p23;q23)
	<i>PPF1BP1-ALK</i>	t(2;12)(p23;p11)
	<i>RANBP2-ALK</i>	t(2;2)(p23;q13)
	<i>RREB1-TFE3</i>	t(X;6)(p11;p24)
	<i>SEC31A-ALK</i>	t(2;4)(p23;q21)
	<i>TPM3-ALK</i>	t(1;2)(q21;p23)
	<i>TPM4-ALK</i>	t(2;19)(p23;p13)
So-called fibrohistiocytic tumours Tenosynovial giant cell tumour	<i>COL6A3-CSF1</i>	t(1;2)(p13;q37)
Smooth muscle tumours Leiomyoma of the uterus	<i>CUX1-AGR3</i>	inv(7)(p21q22)
	<i>HMGA2-CCNB1IP1</i>	t(12;14)(q14;q11)
	<i>HMGA2-COG5</i>	t(7;12)(q31;q14)
	<i>HMGA2-COX6C</i>	t(8;12)(q22;q14)
	<i>HMGA2-RAD51L1</i>	t(12;14)(q14;q24)
Pericytic (perivascular) tumours Pericytoma with t(7;12)	<i>ACTB-GLI1</i>	t(7;12)(p22;q13)
Skeletal muscle tumours Alveolar rhabdomyosarcoma	<i>FOXO1-FGFR1</i>	t(8;13;9)(p11;q14;q32)
	<i>PAX3-FOXO1</i>	t(2;13)(q36;q14)
	<i>PAX3-FOXO4</i>	t(X;2)(q13;q36)
	<i>PAX3-NCOA1</i>	t(2;2)(p23;q36)
	<i>PAX3-NCOA2</i>	t(2;8)(q36;q13)
	<i>PAX7-FOXO1</i>	t(1;13)(p36;q14)
Spindle cell rhabdomyosarcoma	<i>SRF-NCOA2</i>	t(6;8)(p21;q13)
	<i>TEAD1-NCOA2</i>	t(8;11)(q13;p15)
Vascular tumours Epithelioid hemangioendothelioma	<i>WWTR1-CAMTA1</i>	t(1;3)(p36;q25)
	<i>YAP1-TFE3</i>	t(X;11)(p11;q22)

Vascular Tumors

- FOS and FOSB-related fusions in epithelioid hemangiomas (benigne)
- SERPINE1-FOSB in pseudomyogenic hemangioendothelioma (intermediate)

Spindelcell and sclerosing Rhabdomyosarcoma with MYOD1 mutations poor prognosis; VGLL2/NCOA2 fusion in congenital/infantile-good prognosis)

Table 1. (Continued)

Tumour	Gene fusion	Chromosome aberration
Tumours of uncertain differentiation Angiomatoid fibrous histiocytoma	<i>EWSR1-CREB1</i>	t(2;22)(q33;q12)
	<i>FUS-ATF1</i>	t(12;16)(q13;p11)
	<i>EWSR1-ATF1</i>	t(12;22)(q13;q12)
Ossifying fibromyxoid tumour	<i>EP400-PHF1</i>	t(6;12)(p21;q24)
Myoepithelioma/mixed tumour	<i>EWSR1-ATF1</i>	t(12;22)(q13;q12)
	<i>EWSR1-PBX1</i>	t(1;22)(q23;q12)
	<i>EWSR1-POU5F1</i>	t(6;22)(p21;q12)
	<i>EWSR1-ZNF444</i>	t(19;22)(q13;q12)
Synovial sarcoma	<i>SS18-SSX1, SS18-SSX2 or SS18-SSX4</i>	t(X;18)(p11;q11)
	<i>SS18L1-SSX1</i>	t(X;20)(p11;q13)
Alveolar soft part sarcoma	<i>ASPSCR1-TFE3</i>	t(X;17)(p11;q25)
Clear cell sarcoma	<i>EWSR1-CREB1</i>	t(2;22)(q33;q12)
	<i>EWSR1-ATF1</i>	t(12;22)(q13;q12)
Extraskeletal myxoid chondrosarcoma	<i>TAF15-NR4A3</i>	t(9;17)(q31;q12)
	<i>TFG-NR4A3</i>	t(3;9)(q12;q31)
	<i>TCF12-NR4A3</i>	t(9;15)(q31;q21)
	<i>EWSR1-NR4A3</i>	t(9;22)(q31;q12)
Desmoplastic small round cell tumour	<i>EWSR1-WT1</i>	t(11;22)(p13;q12)
	<i>EWSR1-ERG</i>	t(21;22)(q22;q12)
Ewing sarcoma	<i>EWSR1-ERG</i>	t(21;22)(q22;q12)
	<i>EWSR1-ETV1</i>	t(7;22)(p21;q12)
	<i>EWSR1-ETV4</i>	t(17;22)(q21;q12)
	<i>EWSR1-FEV</i>	t(2;22)(q35;q12)
	<i>EWSR1-FLI1</i>	t(11;22)(q24;q12)
	<i>EWSR1-NFATC2</i>	r(20;22)(q13;q12)
EWSR1 fusion with non ETS transcription factor EWSR1-NFATc2 EWSR1-SMARCA5 EWSR1-SP3	<i>EWSR1-PATZ1</i>	inv(22)(q12q12)
	<i>EWSR1-SMARCA5</i>	t(4;22)(q31;q12)
	<i>SFPQ-TFE3</i>	t(X;1)(p11;p34)

PAX3 Fusion Positive
Biphenotypic Sinonasal
Sarcoma:
PAX3-MAML3
PAX3-NCOA1
PAX3-FOXO1

PECOMAS:
PSF-TFE3, DVL-TFE3, TFE3-unknown
partner.
RAD51B-PRAGB/OPHN1 uterine
Pecomias.
Alternative TSC2 and TSC3 mutations.
TFE3 Pecomias may have a better
prognosis...

Table 1. (Continued)

Tumour	Gene fusion	Chromosome aberration
Undifferentiated/unclassified sarcomas		
Undifferentiated/unclassified sarcomas	<i>BCOR-CCNB3</i>	inv(X)(p11p11)
	<i>CIC-DUX4</i>	t(4;19)(q35;q13)
	<i>CIC-DUX4L10</i>	t(10;19)(q26;q13)
	<i>EWSR1-POU5F1</i>	t(6;22)(p21;q12)
	<i>EWSR1-SP3</i>	t(2;22)(q31;q12)
Chondro-osseous tumours		
Soft tissue chondroma	<i>HMGA2-LPP</i>	t(3;12)(q28;q14)
Mesenchymal chondrosarcoma	<i>HEY1-NCOA2</i>	t(8;8)(q13;q21 or del(8)(q13q21))

**BCOR-MAML3
BCOR-ITD**

No month without a new described fusion 😊

	<i>YWHAЕ-FAM22B</i>	t(10;17)(q22;p13)
	<i>ZC3H7B-BCOR</i>	t(X;22)(p11;q13)
Epithelioid sarcoma of the ovary	<i>CMKLR1-HNF1A</i>	?t(12;12)(q23;q24)
	<i>ERBB3-CRADD</i>	?t(12;12)(q13;q22)
	<i>SMARCB1-WASF2</i>	t(1;22)(p36;q11)
Primary pulmonary myxoid sarcoma	<i>EWSR1-CREB1</i>	t(2;22)(q33;q12)

*Gene fusions were retrieved from Mitelman *et al.*,¹⁰ Queried on April 30, 2013. Gene fusions in black were identified using the classical route (chromosome banding and FISH), gene fusions in blue were identified through global gene expression profiling and gene fusions in red were found using next-generation sequencing data.

Why do we want to use molecular testing in STT?

- ▶▶ **Diagnostic:** Aid in rendering a morphologic diagnosis
- ▶▶ **Prognostic:** Educated guess at a tumour's behavior without the influence of treatment
- ▶▶ **Predictive:** Response of tumour to therapy
- ▶▶ **Personalized Treatment:**

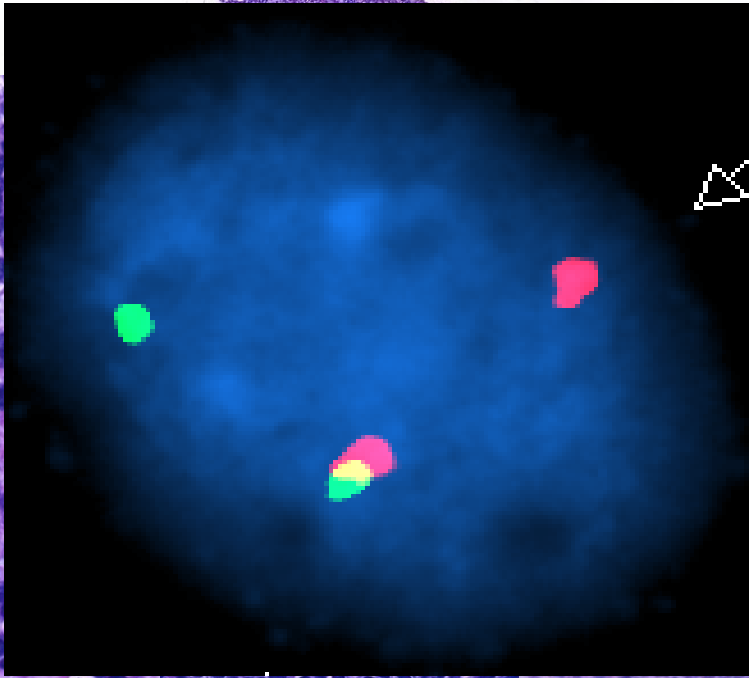
Agent	Tumour types	Known alteration or recognized or proposed target	Approximate response rate	Refs
Imatinib	GIST*	KIT and PDGFR α mutations	~80%	126
	Dermatofibrosarcoma protuberans	COL1A1–PDGFR α fusions	High	132,133
	Tenosynovial giant cell tumour and pigmented villonodular synovitis	COL6A3–CSF1 fusions	High	200
Sunitinib	Imatinib-resistant GIST	KIT mutations	~8%	201
	Desmoid tumour and deep fibromatosis	Unknown	Unknown	202
	Alveolar soft-part sarcoma	ASPL–TFE3 fusion	Unknown	145
Sorafenib	Angiosarcoma	VEGFR2 mutations, VEGF or its receptors	~15%	129
	Desmoid tumour and deep fibromatosis	Unknown	High	203
Denosumab	Giant-cell tumour of bone	RANK ligand	Moderate	204
Crizotinib	Inflammatory myofibroblastic tumour	ALK fusions	Unknown	205
MET inhibitor	Alveolar soft-part sarcoma	ASPL–TFE3 fusion	Unknown	38,206
	Clear-cell sarcoma	EWS–ATF1 fusions	Unknown	134,135,206
IGF1R antibody	Solitary fibrous tumour-haemangiopericytoma	IGF1R and VEGFR, and IGF2 overexpression	Unknown	207,208
	Ewing's sarcoma	EWS–FLI1 or EWS–ERG	10–15%	137–139
Bevacizumab	Angiosarcoma	VEGFR2 mutations, VEGF or its receptors	~15%	73,129, 143,209
Cediranib	Alveolar soft-part sarcoma	ASPL–TFE3 fusion	Unknown	144
Pazopanib	Synovial sarcoma	Unknown	~15%	130
mTOR inhibitors	PEComas and related conditions lymphangioma, leiomyomatosis and angiomyolipoma	mTOR	High	146–148

ALK, anaplastic lymphoma kinase; COL6A3, collagen type VI alpha 3 chain; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor; PEComa, perivascular epithelioid cell tumour; TFE3, transcription factor binding to 101 kDa protein; CSF1, colony-stimulating factor 1 receptor. *Dasatinib and sorafenib are also indicated for KIT-mutant GIST.

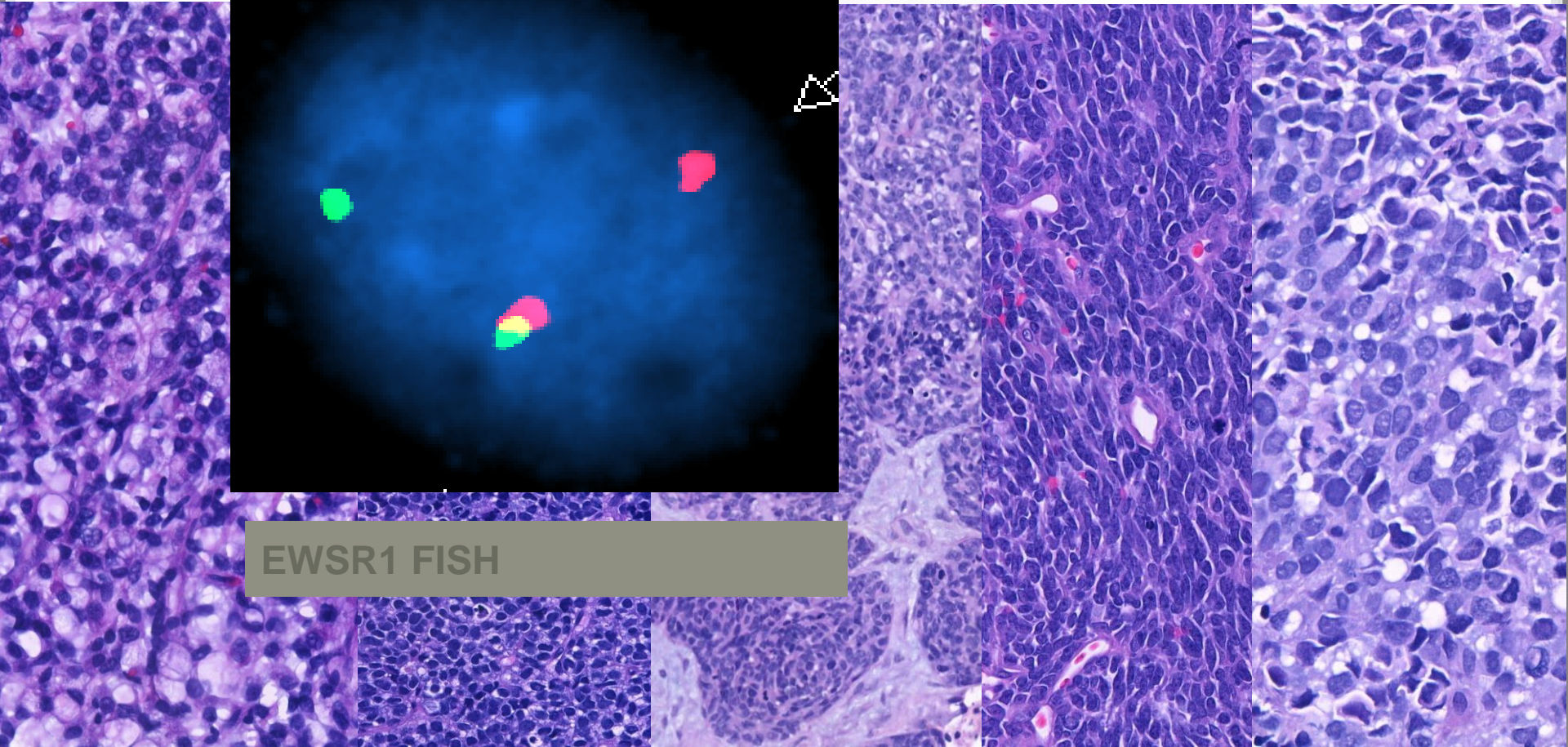
Tumors with NTRK1-3 fusions

Personalized Treatment:

Options to get treatment based on the underlying molecular profile „basket trials“



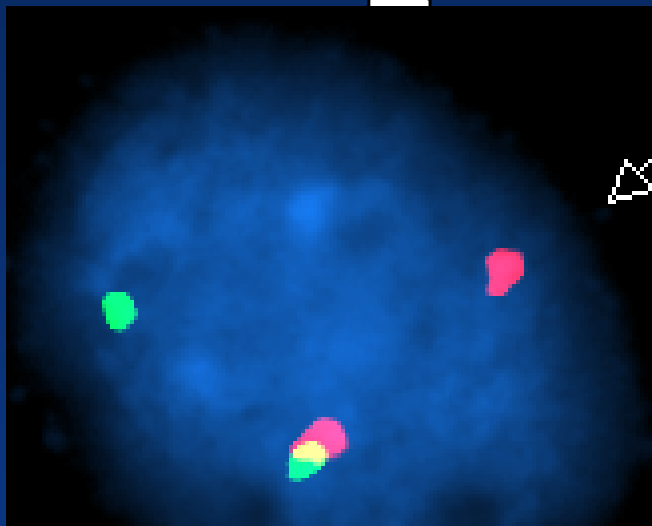
EWSR1 FISH



Chromosome

22

p



PBX1 (1q23)

MET

SP3 (2q31)

Other

CREB1 (2q34)

CCS/AFH

FEV (2q36)

ES/PNET

DUX4 (4q35)

RMS

EWSR1 (22q12)

(6p21)

noma

ner

(7p22)

ES/PNET

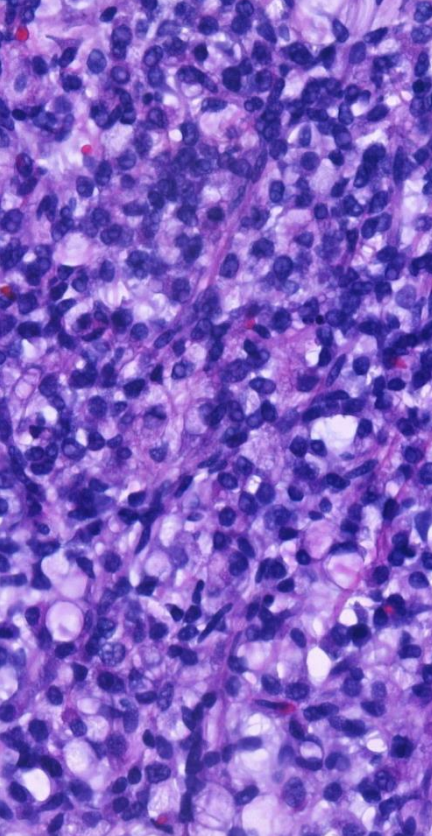
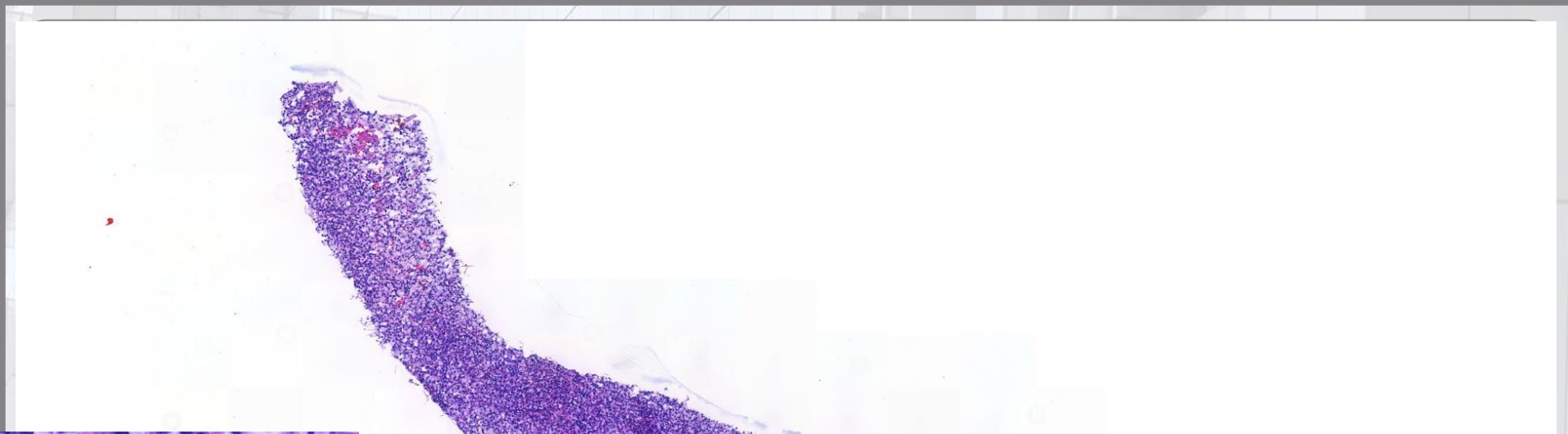
- AFH: Angiomatoid fibrous histiocytoma
- AL: Acute leukemia
- CCS: Clear cell sarcoma
- DSRCT: Desmoplastic small round cell tumor
- EMCS: Extraskelatal myxoid chondrosarcoma
- ES/PNET: Ewing sarcoma/PNET
- MET: Myoepithelial cell tumor
- M/RCLS: Myxoid/round cell liposarcoma
- RMS: Rhabdomyosarcoma
- Undiff ES-like: Undifferentiated Ewing sarcoma-like



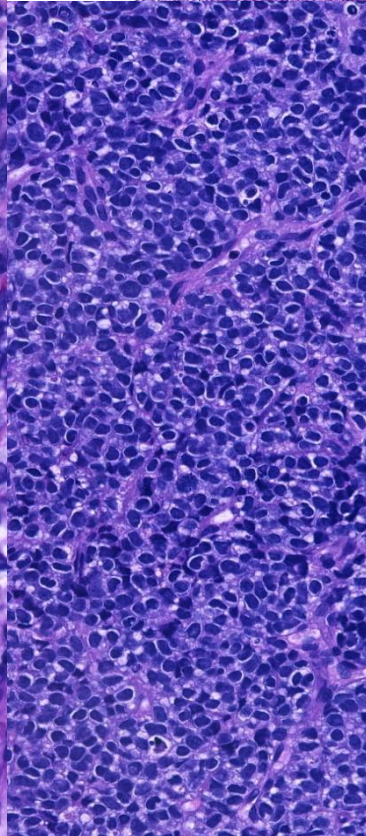
EWSR1 break apart = Ewing Diagnosis?

Translocation associated sarcomas

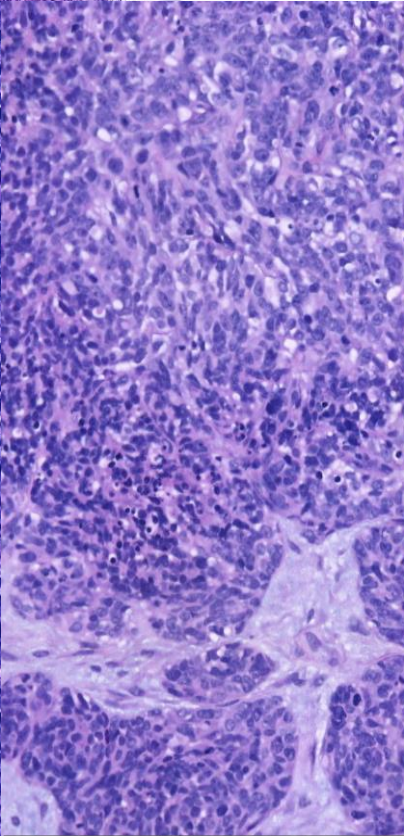
- ▶▶ Growing number of tumor types with known translocations
- ▶▶ Multiple fusion partner in same disease
- ▶▶ One fusion partner that participates in different fusions
- ▶▶ „Promiscuous“ gene fusions that occur in several tumor types



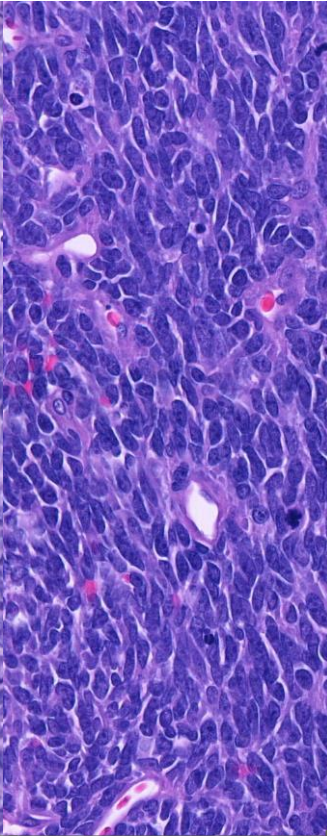
MLS EWSR1-DDIT3



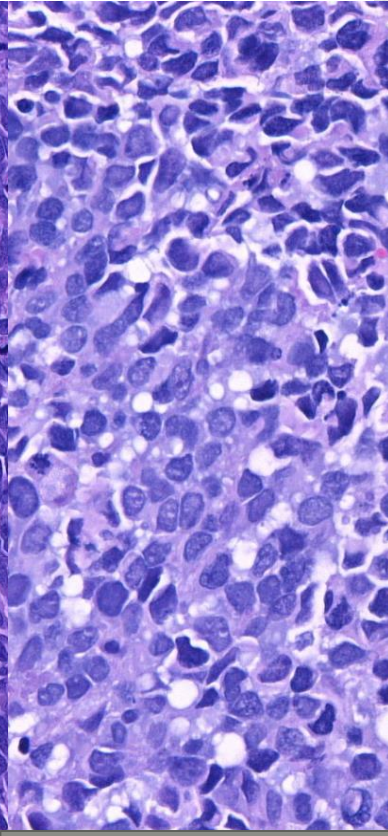
Ewing EWSR1-FLI1



DSCT EWSR1-WT1



SS SYT-SSX



ARMS PAX3-FOXO1A



Archer™ FusionPlex™ Sarcoma Panel

The first comprehensive, NGS-based sarcoma
gene fusion detection and characterization assay

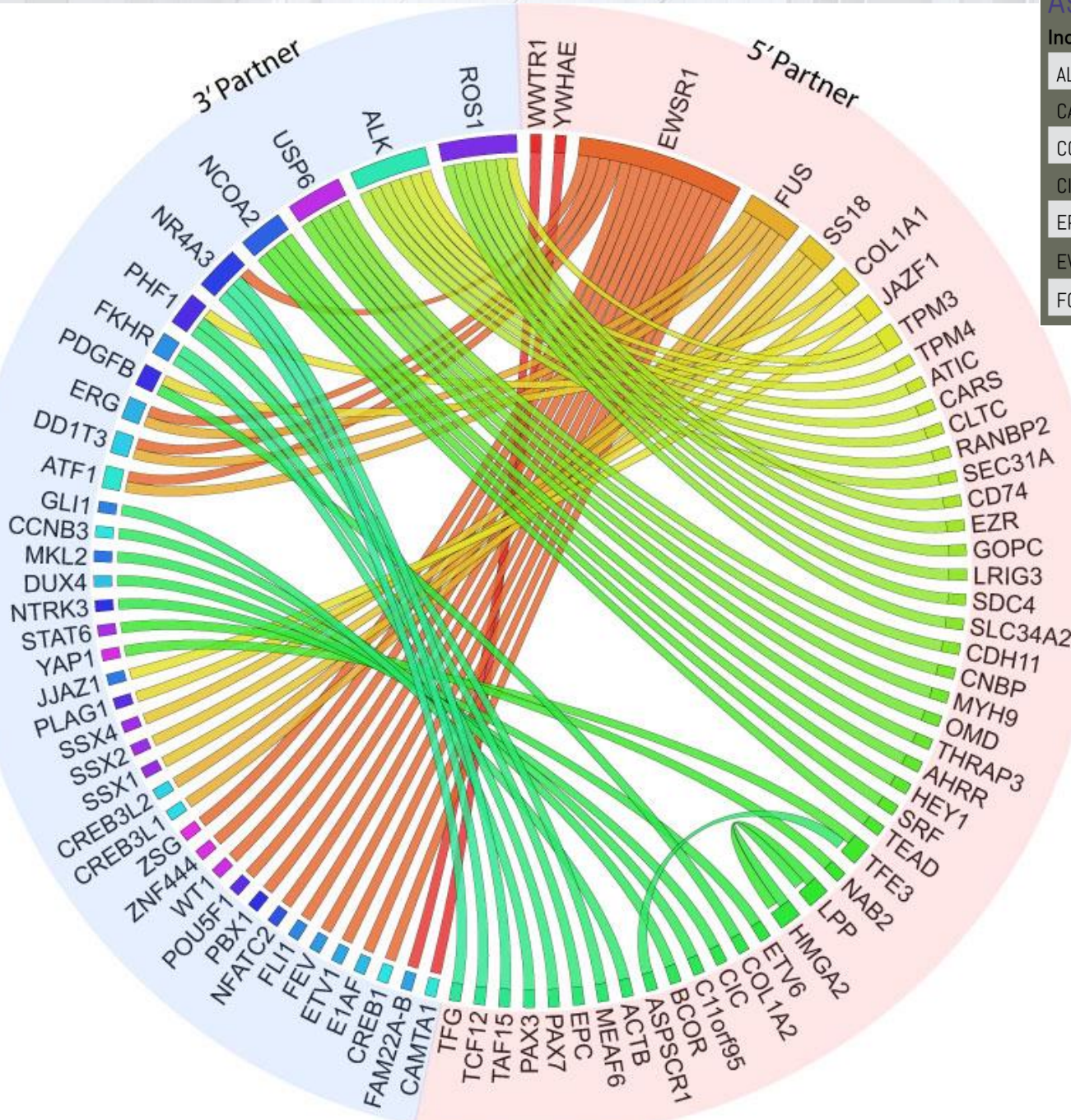
**Is a targeted sequencing assay that simultaneously detects and identifies fusions of
35 genes associated with soft tissue cancers.**

Assay Targets

Includes the following genes and their fusion partners:

ALK	FUS	NTRK3	TCF12
CAMTA1	GLI1	PDGFB	TFE3
CCNB3	HMGA2	PLAG1	TFG
CIC	JAZF1	ROS1	USP6
EPC1	MEAF6	SS18	YWHAE
EWSR1	MKL2	STAT6	
FOXO1	NCOA2	TAF15	

BCOR, NTRK1,2,3....

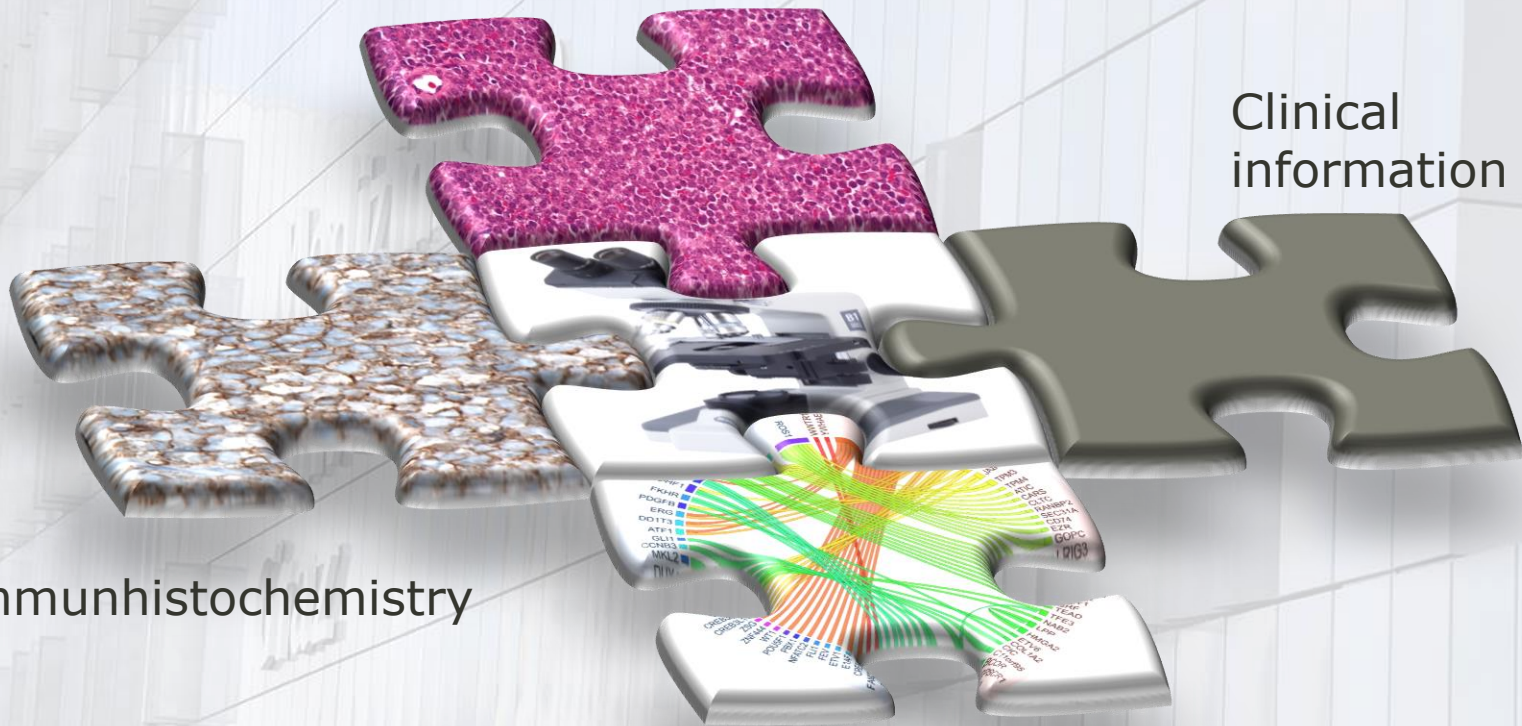


Morphology

Clinical
information

Immunohistochemistry

Molecular
Diagnostic



Pathology report

- ▶▶ Diagnosis
- ▶▶ *Grading*
- ▶▶ Resection margins
- ▶▶ Comment on LVI
- ▶▶ *Molecular diagnostic*

Second opinion in a Sarcoma Center

GIST - Pathology

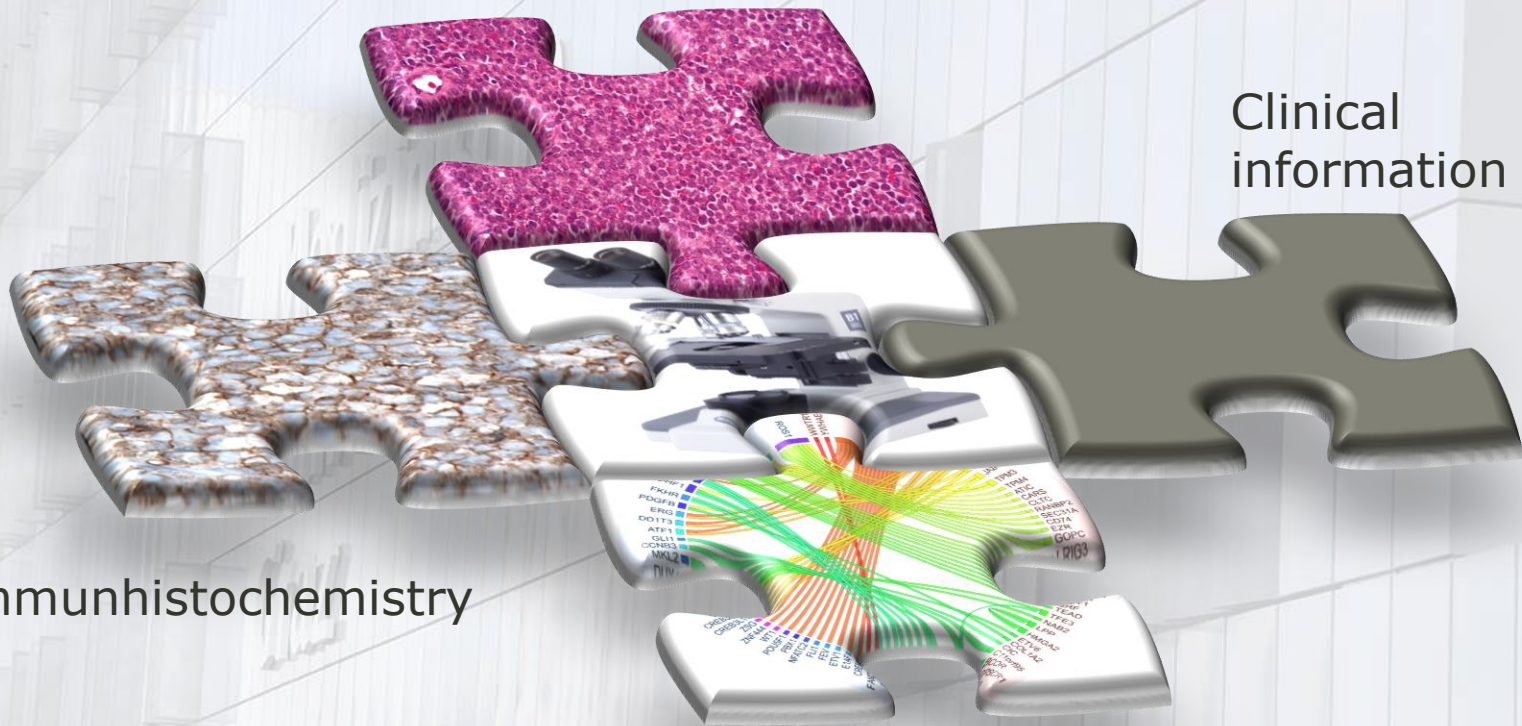
- Most common mesenchymal tumors of the GI-Tract (-> top on the list in the DDX of pathologists)
 - GIST is a well defined tumor entity
- For Gist we have well established IHC (KIT, DOG1, SDHB, *SDHA*)
 - Well established and defined risk stratification
 - Well known molecular profile

Morphology

Clinical
information

Immunohistochemistry

Molecular
Diagnostic



Clinical Information:

- Age
- Location
- Solitary or multiple lesion(s)
- Size
- Relevant clinical history

Diagnosis

Pathology

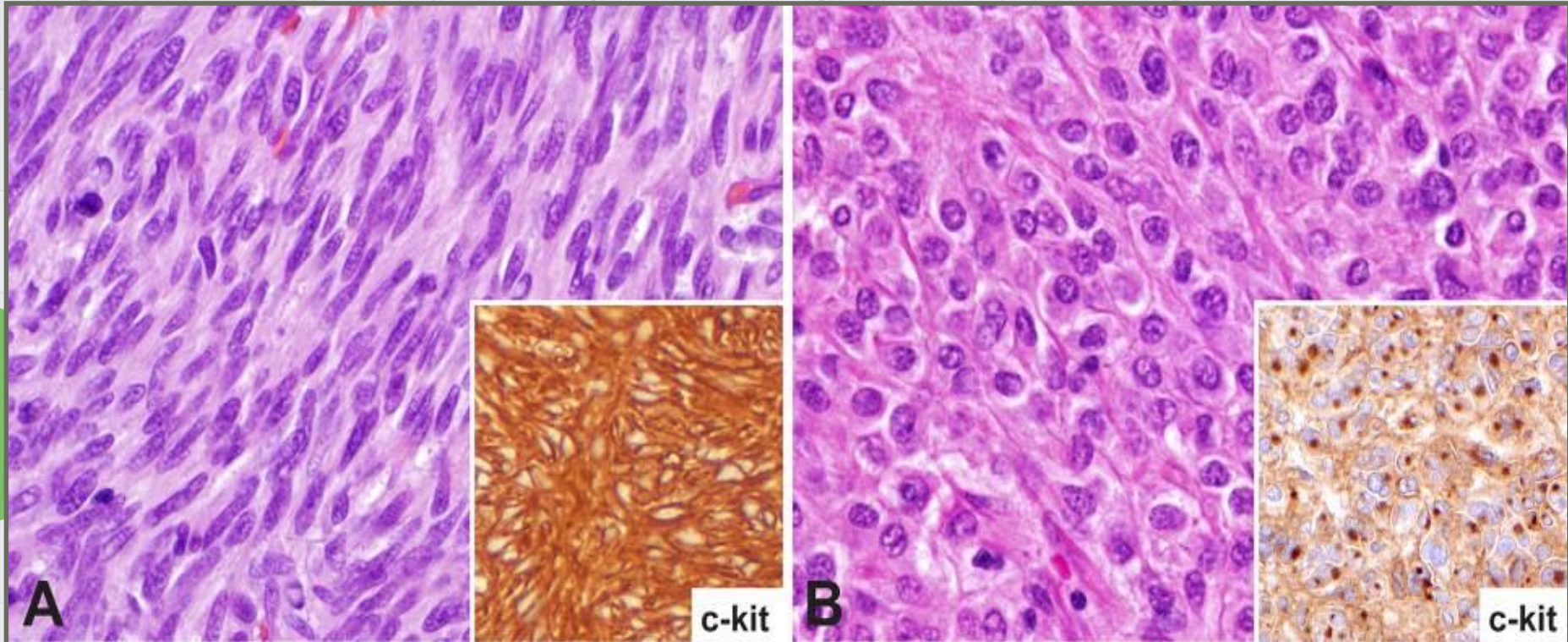
- Morphology
- IHC
- DDx
- Mitotic Activity 5mm²
- Molecular Diagnostics

Predictive Pathology

Therapy

Prognosis

Morphology

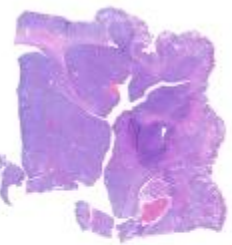








Spindel 70%

Epitheloid 10%

Mixed 10%

IMMUNOHISTOCHEMISTRY

H&E	CD117 DOG 1	CD34	Smooth muscle actin	S100 protein	Desmin	Pan- keratin
	95%	70%	30%	5%	2%	<1%
NO GIST DIAGNOSIS WITHOUT IHC						
						
	+	+	+	+	+	+

Differential Diagnosis: Gist with spindle cell morphology

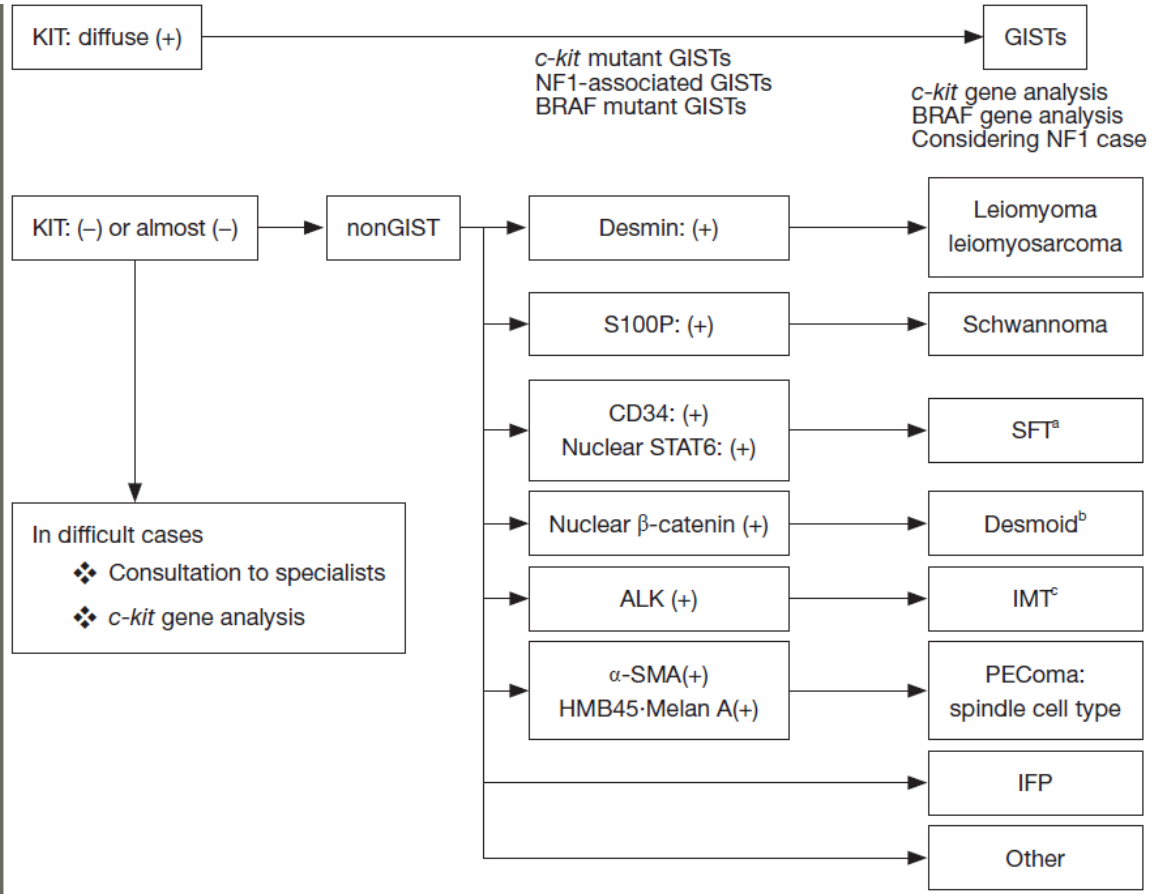
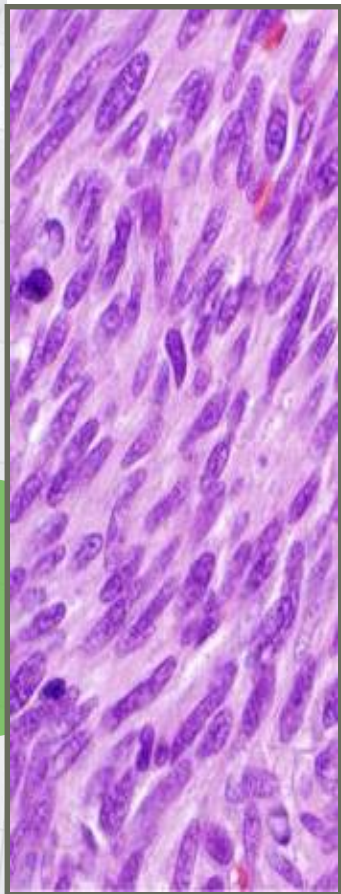


Figure 1 Flow chart of differential diagnoses of spindle cell mesenchymal tumors. ^a, NAB2-STAT6 fusion gene analysis is useful; ^b, β-catenin gene analysis is useful; ^c, ALK FISH is useful. GIST, gastrointestinal stromal tumor; SFT, solitary fibrous tumor; IMT, inflammatory myofibroblastic tumor; IFP, inflammatory fibroid polyp; ALK, anaplastic lymphoma kinase; FISH, fluorescent in situ hybridization; STAT, signal transducer and activator of transcription; NAB2, NGFI-A binding protein-2; α-SMA, α-smooth muscle actin.

Differential Diagnosis: Gist with epithelioid or mixed morphology

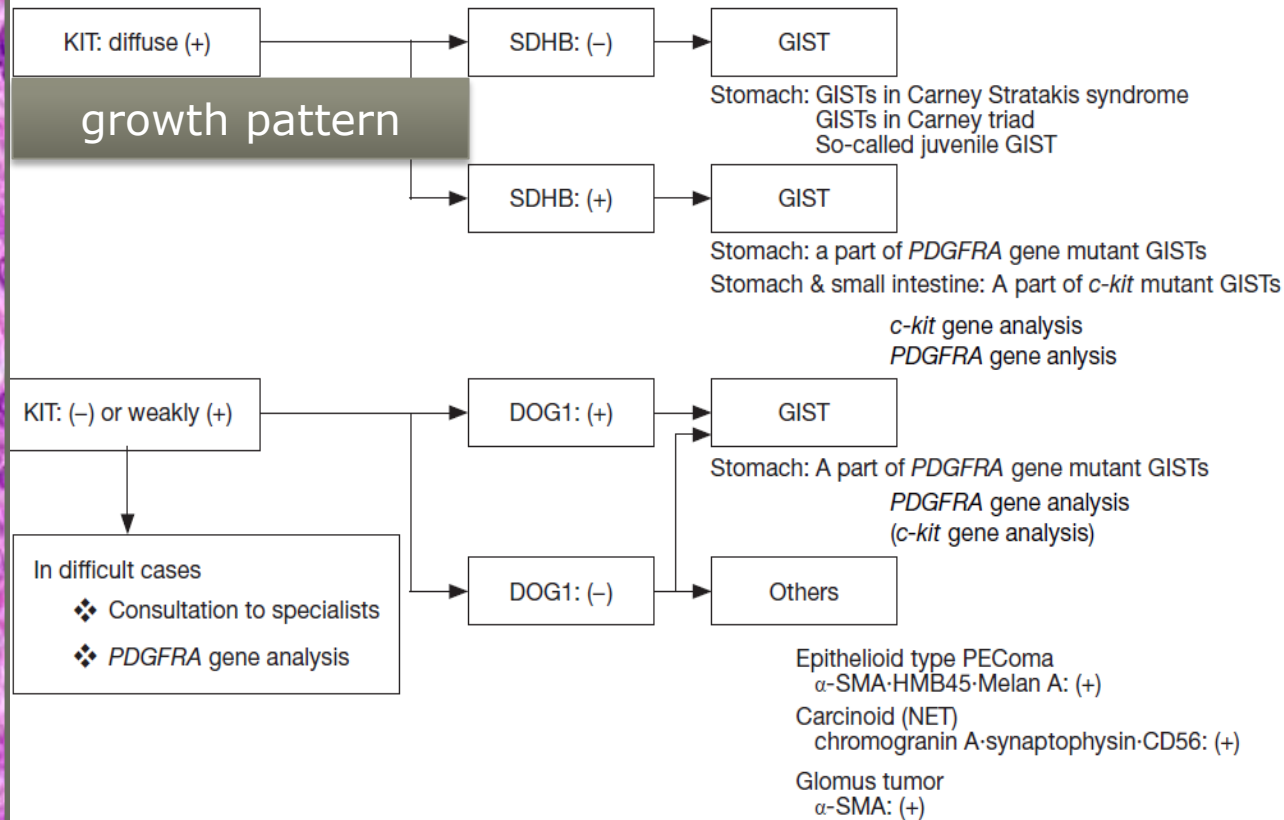
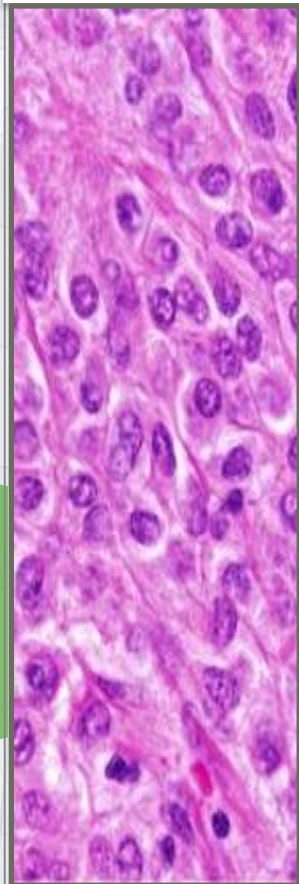


Figure 2 Flow chart of differential diagnosis of epithelioid cell mesenchymal tumors. SDHB, succinate dehydrogenase subunit B; GIST, gastrointestinal stromal tumor; PDGFRA, platelet-derived growth factor receptor alpha; NET, neuroendocrine tumor; α -SMA, α -smooth muscle actin; PEComa, perivascular epithelioid cell tumor.

Transl Gastroenterol Hepatol 2018;3:27

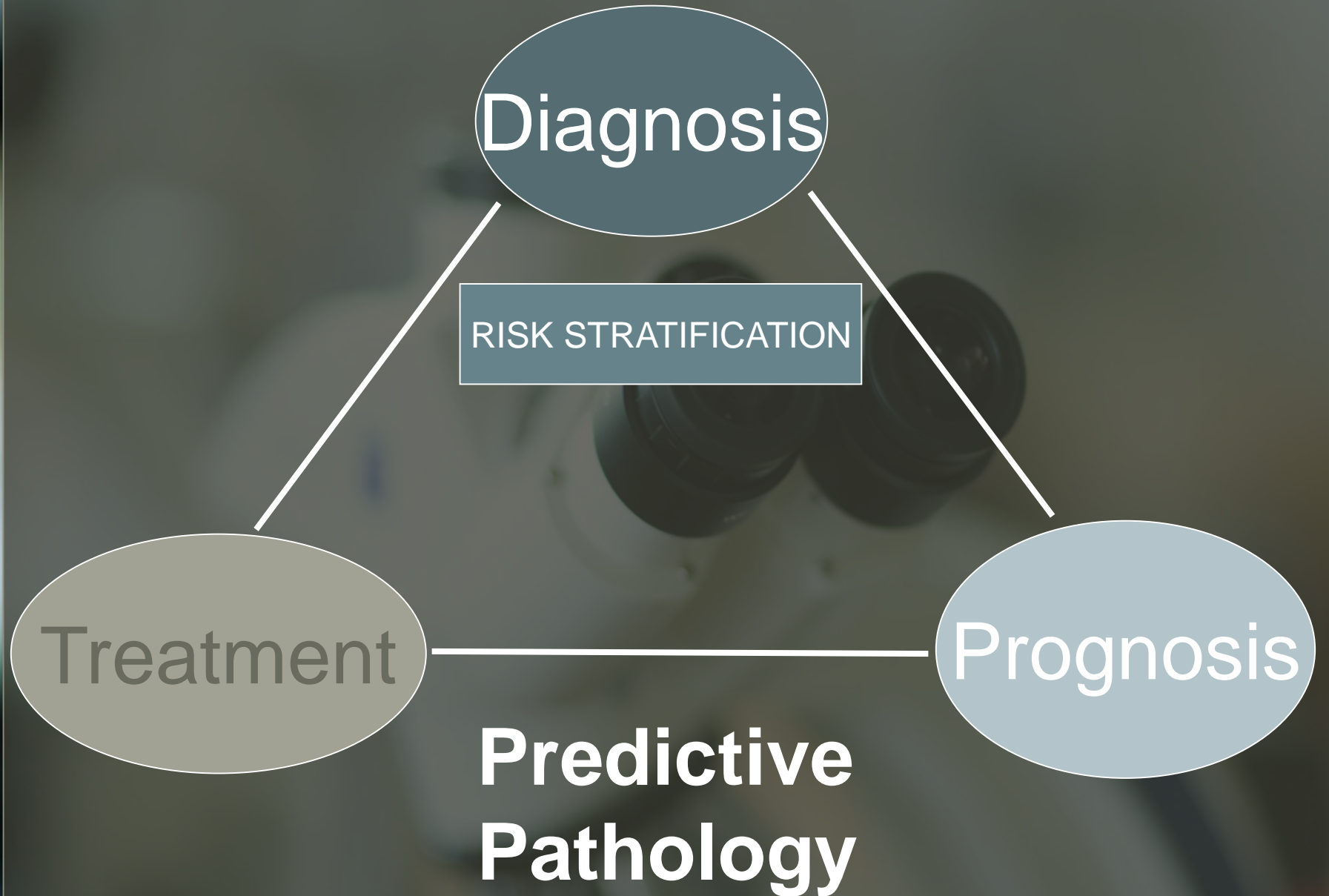
Diagnosis

RISK STRATIFICATION

Treatment

Prognosis

**Predictive
Pathology**



5mm²

Table 1: Risk stratification of primary GIST

	Site	Risk of progressive disease [+]			
Mitotic index	Size	Gastric	Duodenum	Jejunum/Ileum	Rectum
H&E	≤2cm	None	none	None	none
	>2≤5cm	very low (1.9%)	low (8.3%)	low (4.3%)	Low (8.5%)
	>5≤10cm	low (3.6%)	#	Moderate (24%)	#
	>10cm	moderate (10%)	high (34%)	high (52%)	high (57%)
20-25 HPF	≤2cm	none*	#	high*	high (54%)
	>2≤5cm	moderate (16%)	high (50%)	high (73%)	high (52%)
	>5≤10cm	high (55%)	#	high (85%)	#
	>10cm	high (86%)	high (86%)	high (90%)	high (71%)



as metastasis

Tumour rupture is an additional adverse prognostic factor and should be recorded

Table based on Miettinen et al, Semin Diagn Pathol, 2006.
Data based on long-term follow-up of 1055 gastric,
629 small intestinal, 144 duodenal and 111 rectal GISTs. Modified NCCN guidelines.

- Metastatic GIST
- Before adjuvant treatment
 - Children and young adults
 - Diagnostic challenging cases

Mutational analysis has a predictive value for sensitivity to molecular-targeted therapy and to prognostic value. Its inclusion in the diagnostic work-up of all GISTs should be considered standard practice (with the possible exclusion of < 2 cm non-rectal GISTs, which are very unlikely ever to be candidates for medical treatment)

ESMO 2018

CLINICAL PRACTICE GUIDELINES

Gastrointestinal stromal tumour Clinical Practice Guidelines for diagnosis and follow-up[†]

Table 1. Personalised medicine synopsis table

Biomarker	Method	Use	LoE	GoR
Mitotic index	Pathology	Disease classification Prognostic relevance Used for medical treatment decisions	IV	A
<i>KIT/PDGFRα/</i> <i>BRAF</i>	Sanger sequencing or NGS	Disease classification Prognostic relevance Predictive relevance Used for medical treatment decisions Currently actionable/targetable	I	A
SDH	IHC	Disease classification Prognostic relevance Predictive relevance Used for medical treatment decisions	III	A

Area of 5mm²

GoR, grade of recommendation; IHC, immunohistochemistry; LoE, level of evidence; NGS, next generation sequencing; PDGFR α , platelet-derived growth factor receptor alpha; SDH, succinate dehydrogenase.

Diagnosis

Treatment
Yes/NO

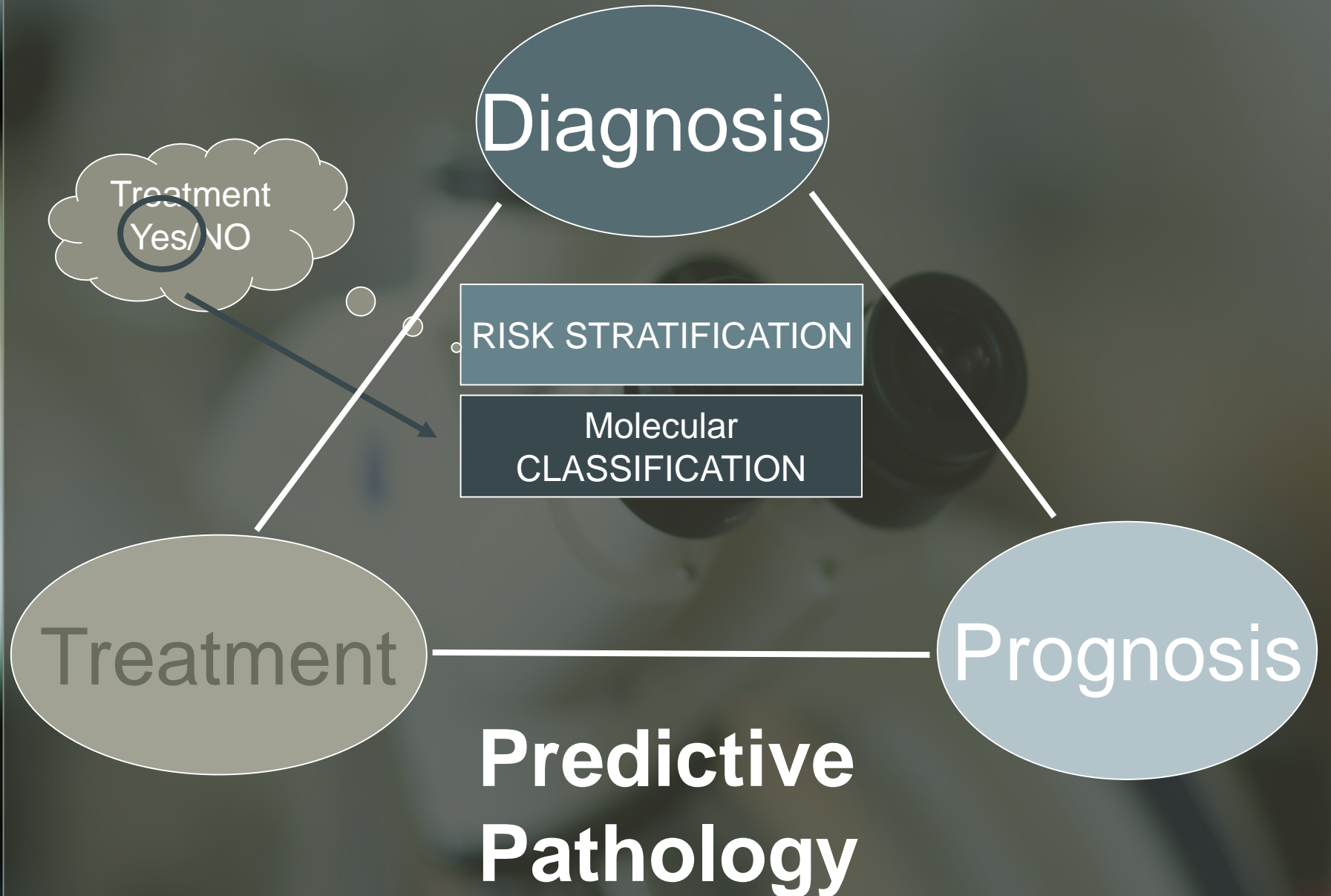
RISK STRATIFICATION

Molecular
CLASSIFICATION

Treatment

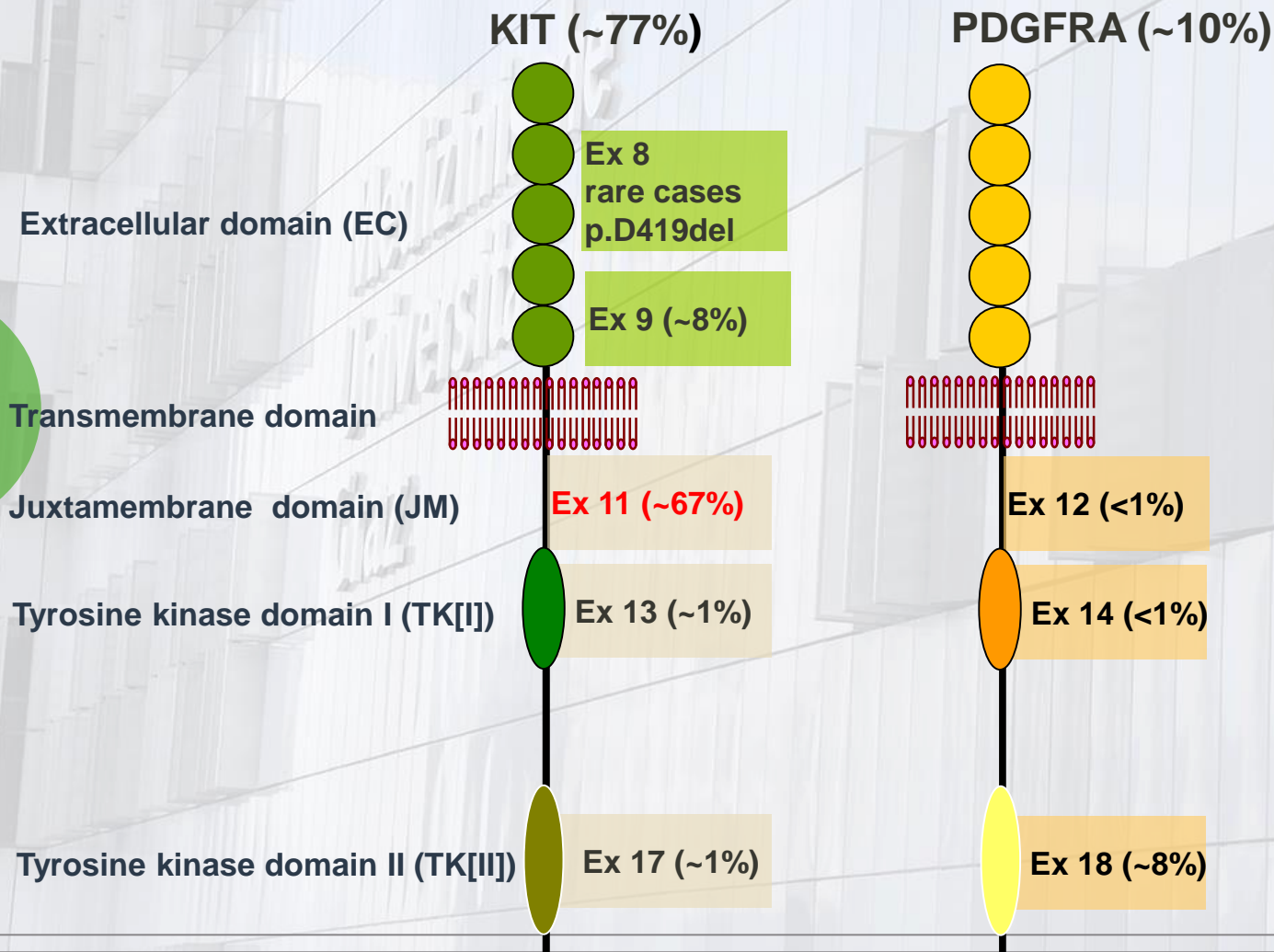
Prognosis

Predictive
Pathology



Mutations in GIST

**Gist Panel: KIT- Exons 8, 9,11,13,17
 PDGFRA-Exons 12,14,18, BRAF, HRAS,
 NRAS, KRAS, NF-1, SDHA, B ,C ,D, p16,
 PT53, RB1**



**Wildtype
 GISTs
 (~13%)**



**Mutations
 SDH
 BRAF
 RAS....**

Diagnosis

Treatment
Yes/NO

Imatinib
400 mg
800 mg

RISK STRATIFICATION

Molecular
CLASSIFICATION

Treatment

Prognosis

**Predictive
Pathology**



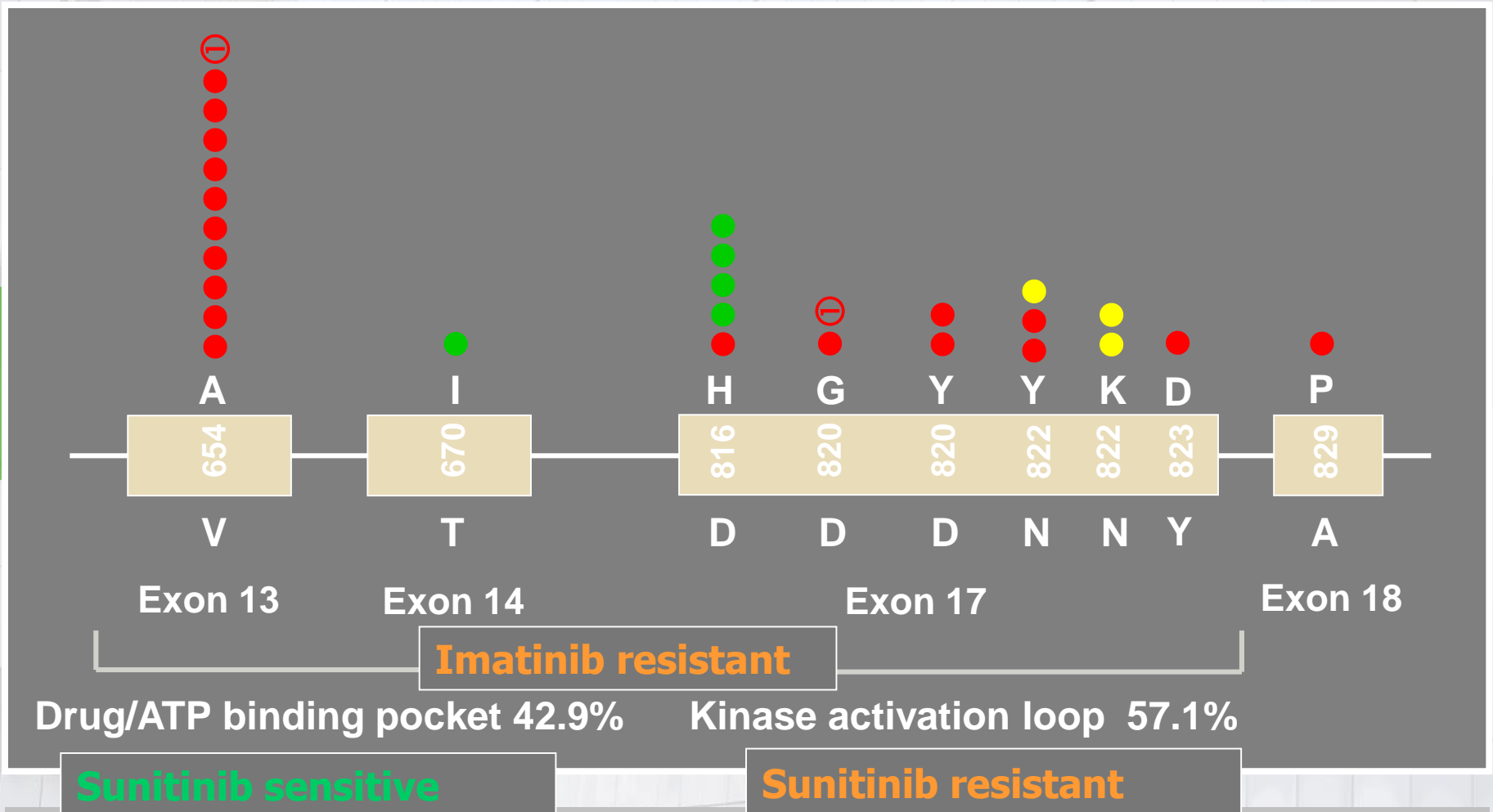
Personalized Therapy available!



Resistance mechanisms in GIST

- ❖ 2/3 secondary acquired mutations
 - ❖ In 73-86% of pt. with *KIT* exon 11 primary mutations
 - ❖ In 19-33% of pt. with *KIT* exon 9 primary mutations
- ❖ 1/3 reactivation of *KIT* oncoprotein by other mechanisms

Secondary Mutations



● Exon 11

● Exon 9

● Exon 13

Diagnostic Challenge

Morphologic variability

- Pleomorphic GIST*
- Dedifferentiated GIST* („sarcomatous“)
- GIST heterologous differentiation
- „Uncommon“ morphology („rhabdoid“)*
- KIT negative GIST*

*occur before and after treatment



-wild-type [WT] GIST-

- Lack *KIT* and *PDGFRA* mutations
- 85% of GISTs in children
 - 10% to 15% of GISTs in adults

KIT and *PDGFRA* WT Gist Heterogenous Group

Sporadic WT

- Pat. 6LD
- NCCN Risk Strat.
- No LN metastasis
- Location (*)
- Presentation(*)
- Morphology(*)
- (*)identical to mutated GIST

WT Gist in young adults
Similar Clinical features as the pediatric WT GIST

NF1

- Commonly small intestine
- Multifocal
- Small
- Low mitotic rate
- Good prognosis
- IGF1R neg./ IHC
- Loss of 14q and 22q

BRAF-mut. GIST

- First described in 2008
- (in one case as a secondary mutation in a *PDGFRA*-mutant GIST)
- Approx. 20-30 cases reported
- Mean age 58 a
- Female=Male
- Commonly in the small bowel
- Commonly spindle cell morphology
- Clinical behaviour variable

Pediatric WT

CT

CSS

- Stomach
- Female Predominance
- Commonly epithelioid morphology
- Multifocal Gist (synchronous or metachronous)
- Risk Stratification not useful to predict clinical behavior
- LN metastases common
- Indolent clinical course in metastatic setting
- Do not response to imatinib
- IGFR1 pos./IHC

Molecular Classification of

Group A

SDHB retained by IHC

Mutations

KIT

PDGFR α

BRAF

HRAS

NRAS

NF-1.....

No alteration in Methylation

Group B

SDHB lost by IHC

Molecular analysis -> WT GIST

Think of SDHB deficient GIST

In all GISTS in patients <30a

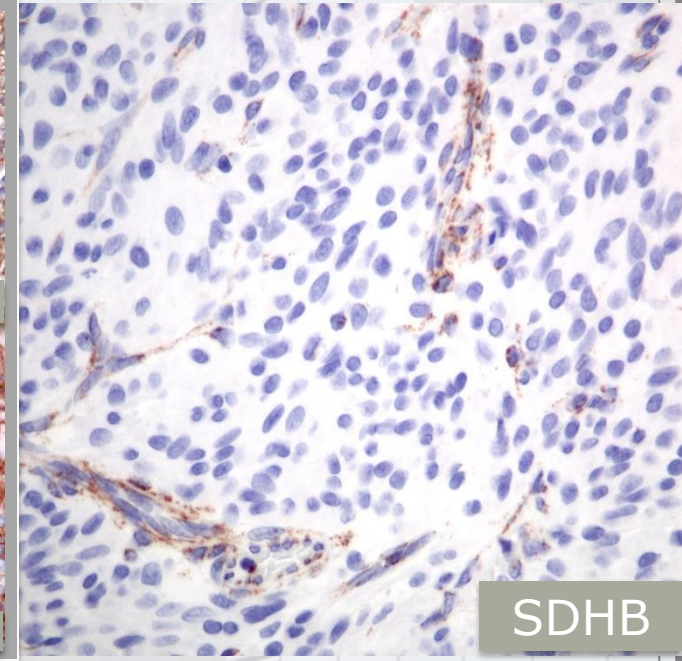
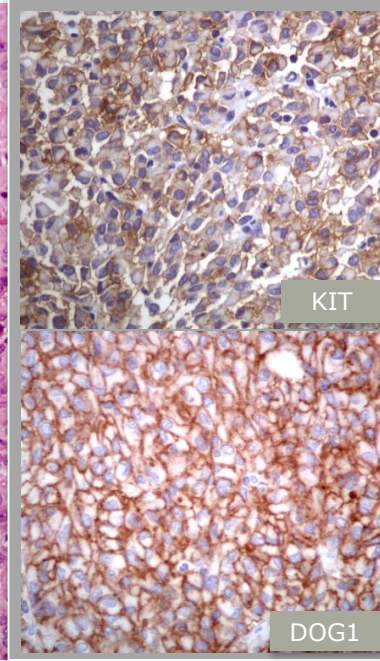
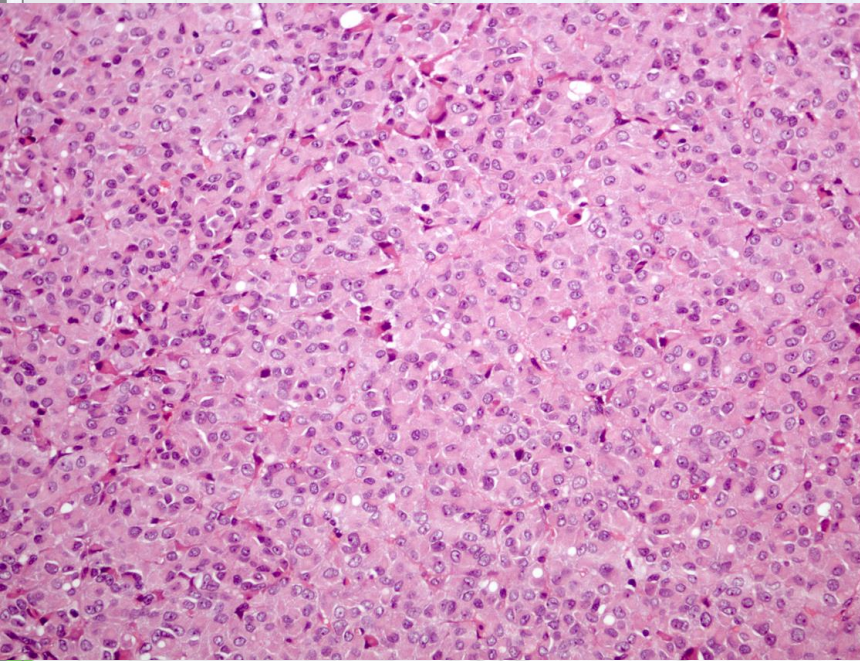
All GISTS with distinctive multinodular/plexiform morphology irrespectively of age

-> Risk Stratification not working

-> LN metastases

-> Imatinib not working.....

Global tumor hypermethylation



Commonly epithelioid morphology

Molecular Classification of

Group A

SDHB retained by IHC

Mutations

KIT

PDGFRA

BRAF

HRAS

NRAS

NF-1.....

Group B

SDHB lost by IHC

SDHA,B,C,D
mutant
Gist

SDHC

epimutant Gist
(Promoter hypermethylation)

Carney Triad

Carney-Stratakis Syndrome

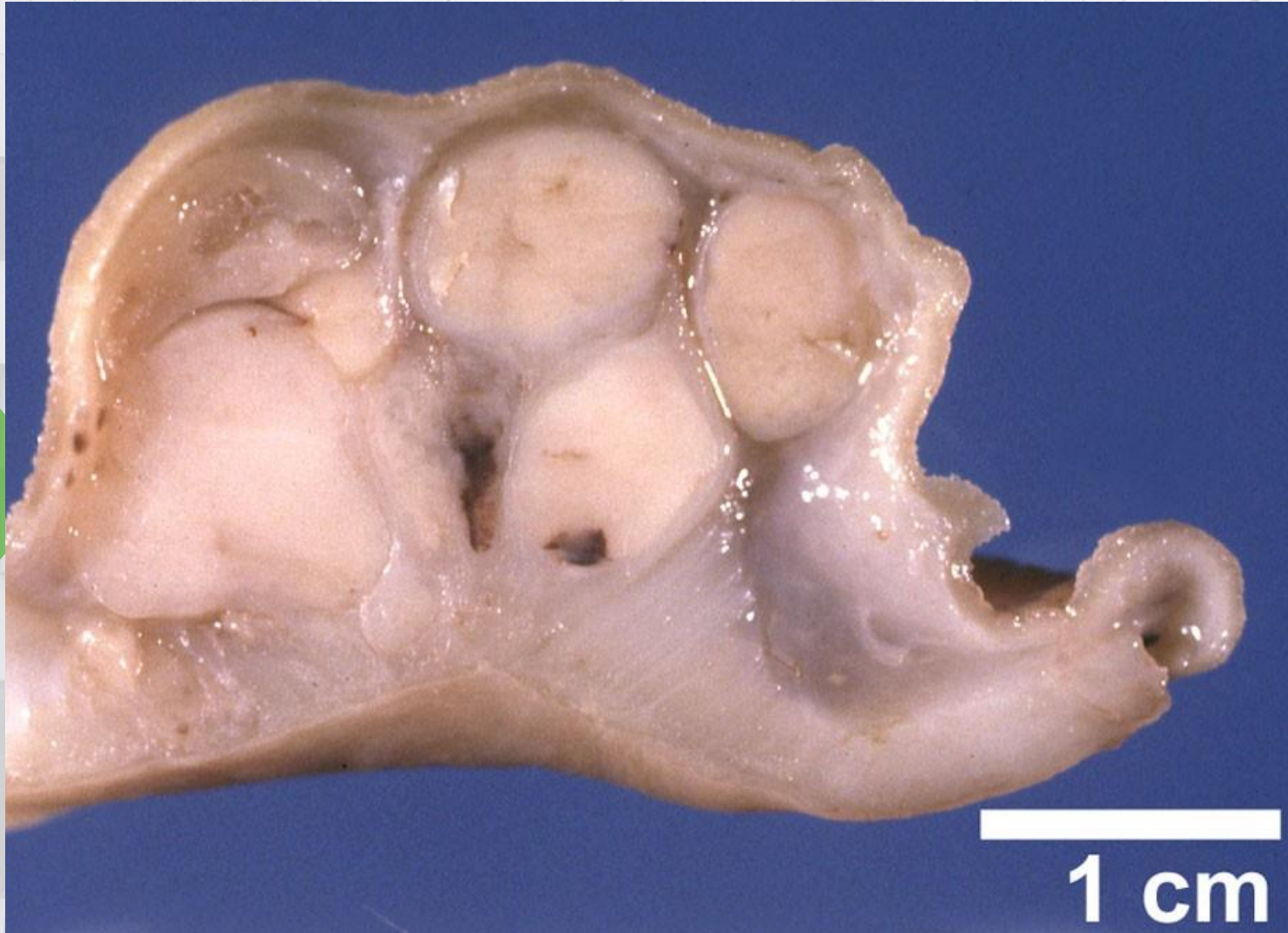
Mutations: ARID1B, ATR, FGFR1, LTK, SUFU, PARK2, ZNF217, EGFR

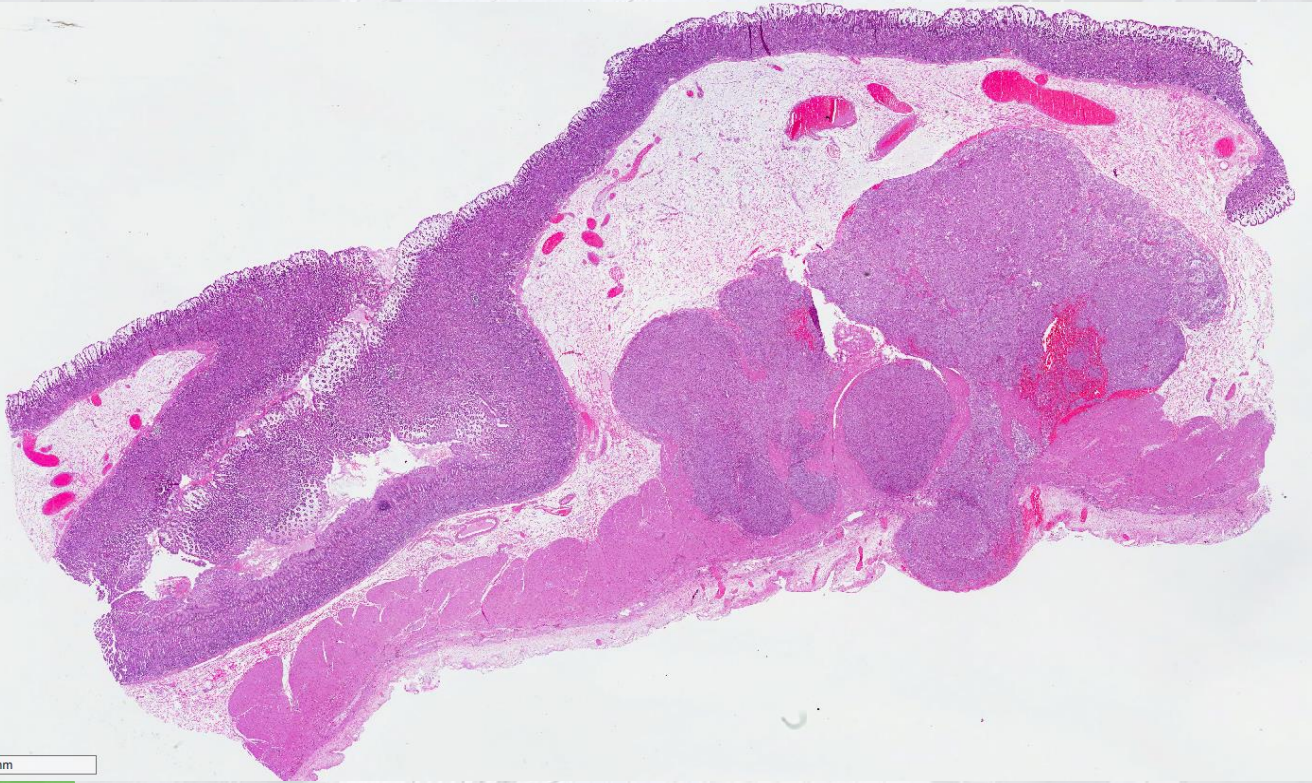
Fusions: FGFR1-HOOK3 ,FGFR1-TACC1, ETV6-NTRK3, KIT-PDGFA

Global tumor hypermethylation

Morphology of SDHB deficient Gist

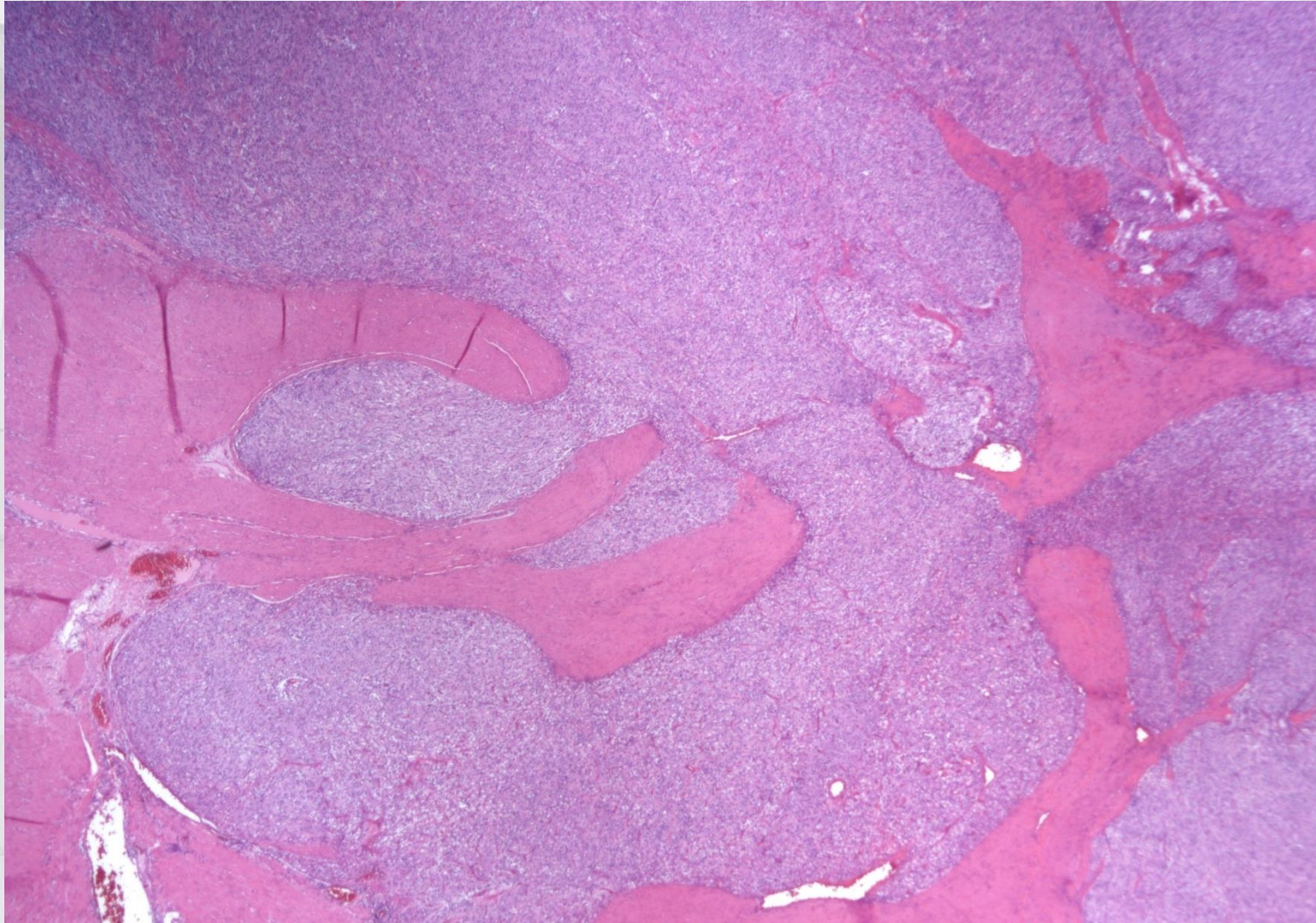
Plexiform/multinodular
growth pattern

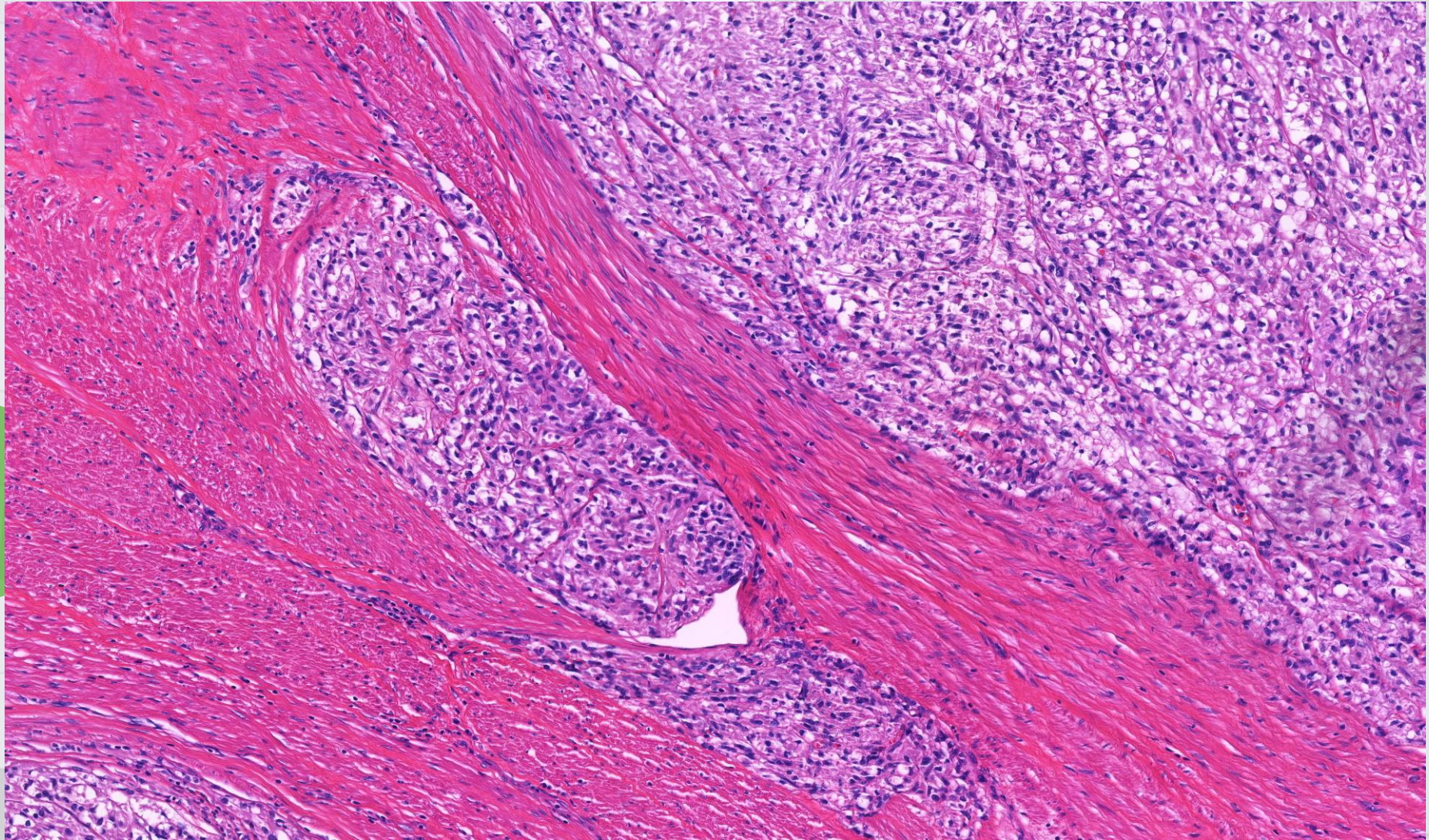


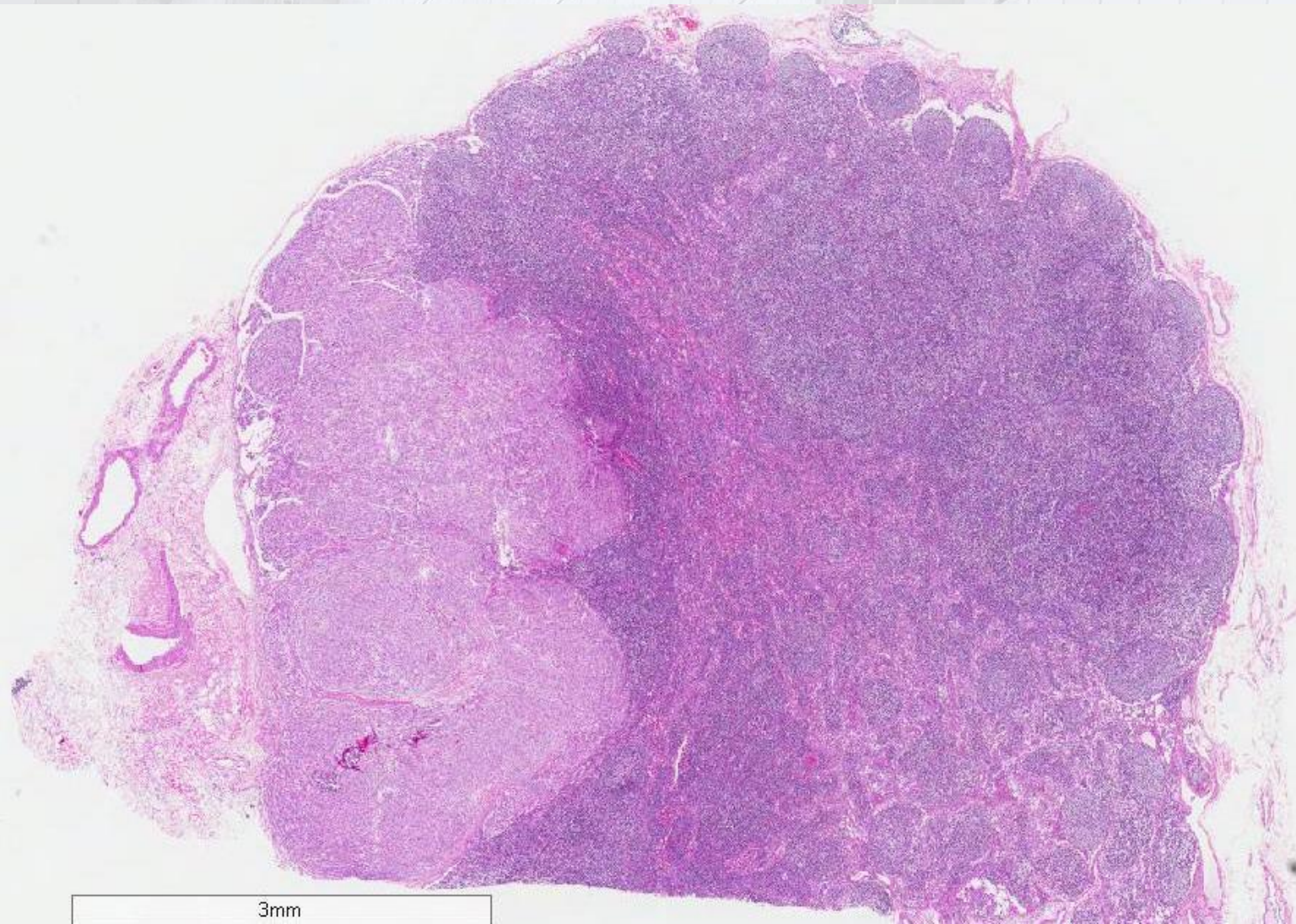


Gist with a distinctive plexiform or multinodular growth pattern located in the stomach!

SDHB deficient 54 a female







Consider SDHB deficient GIST

- ▶▶ In the stomach
- ▶▶ Predominantly in children and young adults – unifocal and multifocal
- ▶▶ SDHB IHC in all GIST (irrespective of age) with multinodular/plexiform growth



Treatment

DIAGNOSIS

Clinic

HE

IHC

MOL
PATH

GOLDEN STANDARD



Communication with the patient
Good communication within the sarcoma team

Perspectives

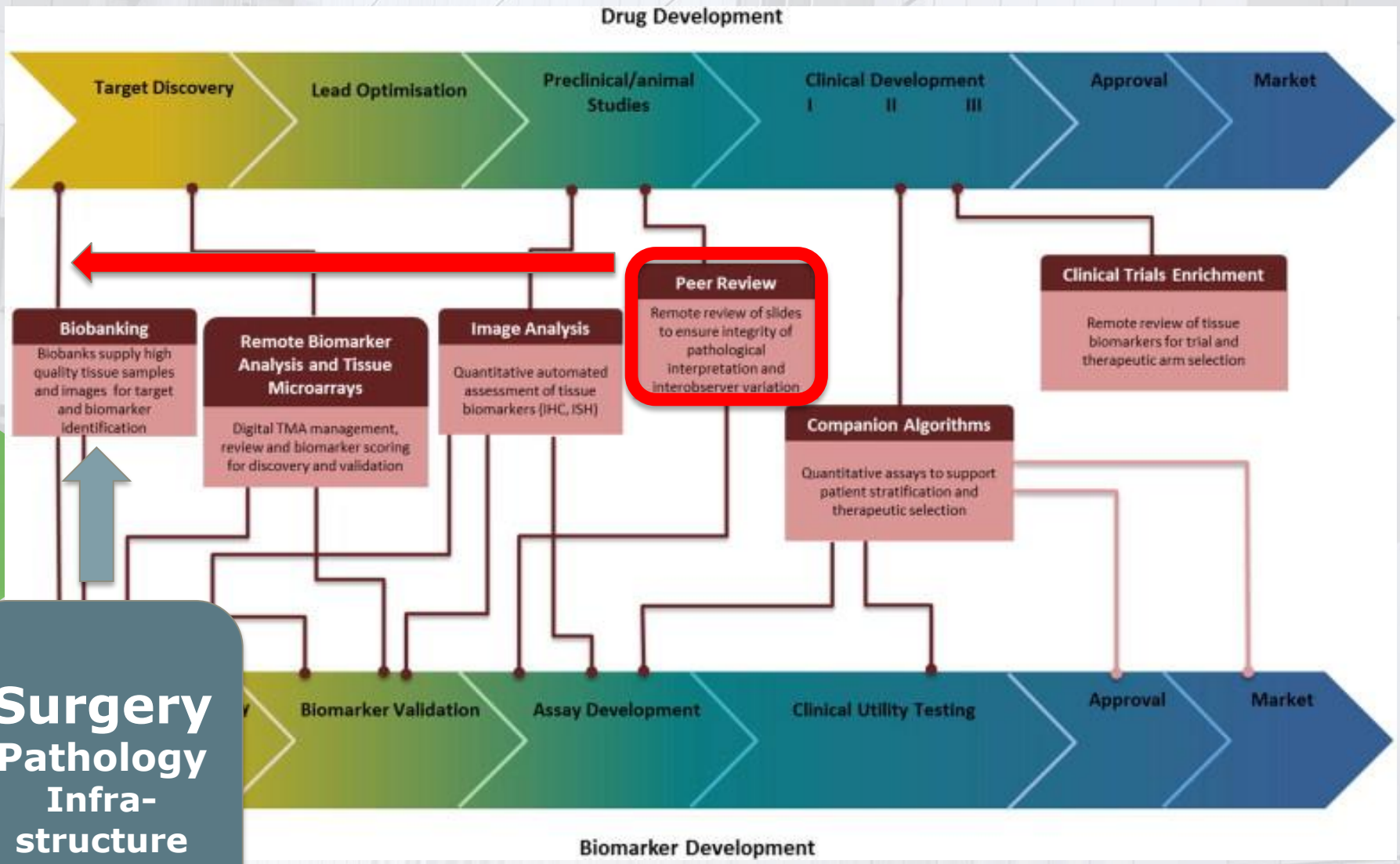
- Precise
- Predictive
- Preventive
- Personalised



TALK about very orphan disease

Sarcoma Centers need

- 1. to cooperate with patients advocacy groups**
- 2. the support/understanding of all physicians that patients with orphan disease need to be treated at specialized centers**



FUTURE CHALLENGES
Especially for research

**DATABASE available for the sarcoma
research community**

**COMPUTATIONAL
MEDICINE**

Sarcomas need to be further defined

Role of Pathology:

Tissue is the ISSUE

Well defined tissue collections for research

FFPE samples

Cryosamples

- Diagnosis
- IHC-Profile
- Molecular Pathology
- Clinic
- Treatment

FUTURE CHALLENGES

Privacy data protection

One informant consent to use tissue for research

- ▶▶ **very individual from institution to institution**
- ▶▶ **very individual between countries**
- ▶▶ **individual approaches of ethics committee**

NEED TO SHARE DATA



COMPREHENSIVE CANCER CENTER Krebszentrum **GRAZ**

**Der Mensch im Mittelpunkt
Auf höchstem Niveau betreut**

CCC-Subzentrum Sarkome

