Molecular Diagnostics – Soft tissue and bone tumours

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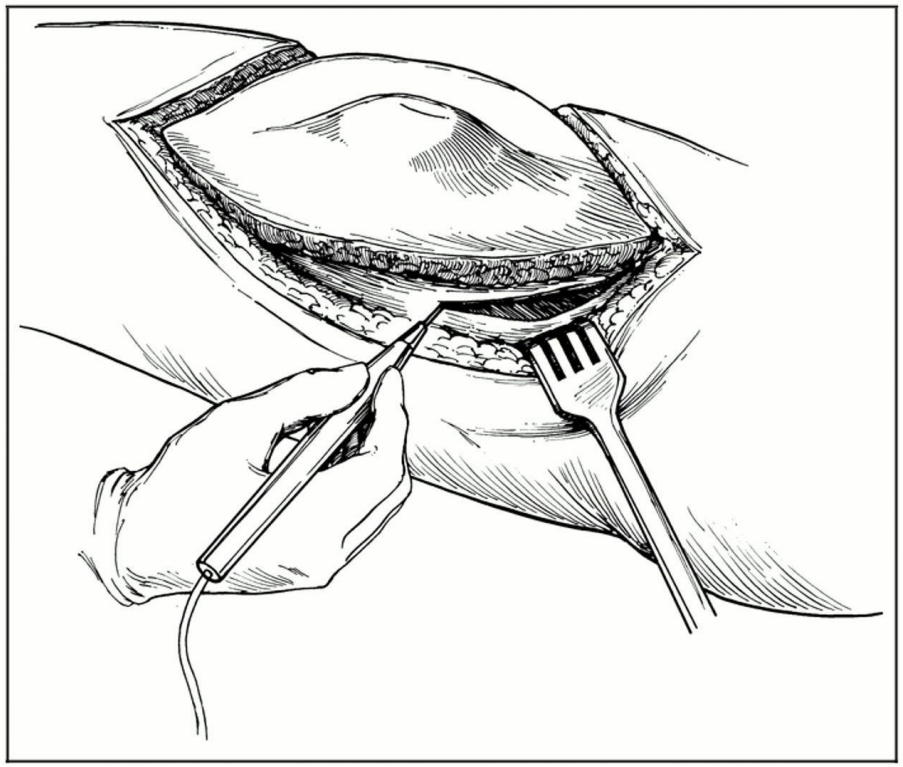
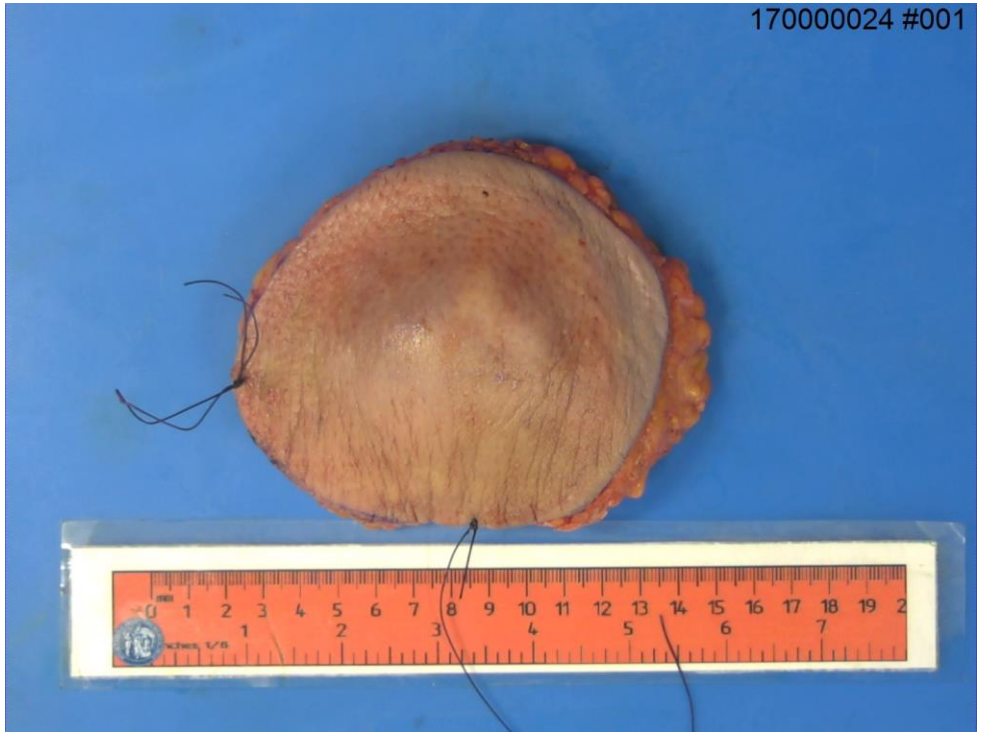
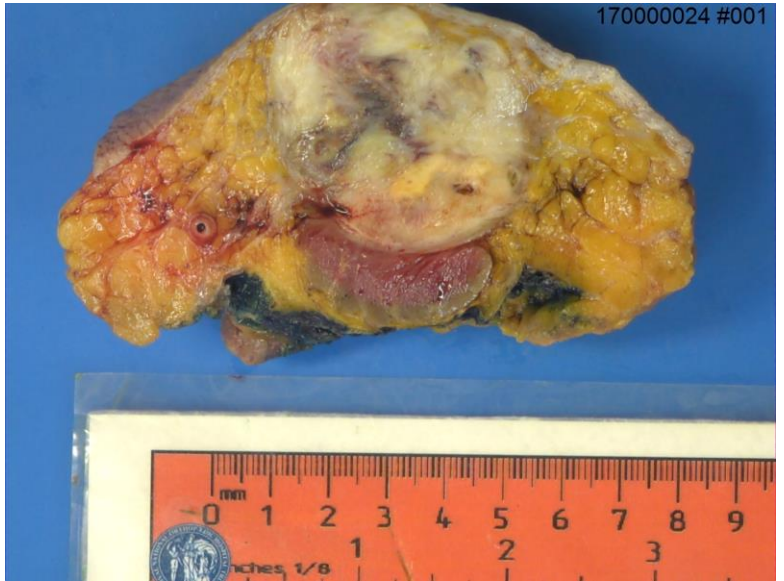
Royal National Orthopaedic Hospital NHS
NHS Trust

Outline

- Mesenchymal tumours– classification.
- Sarcomas and Molecular diagnostic assays (genetic).
- Recent developments in sarcoma diagnostics

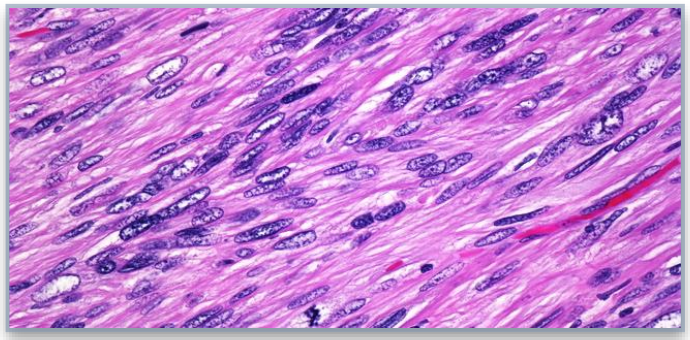






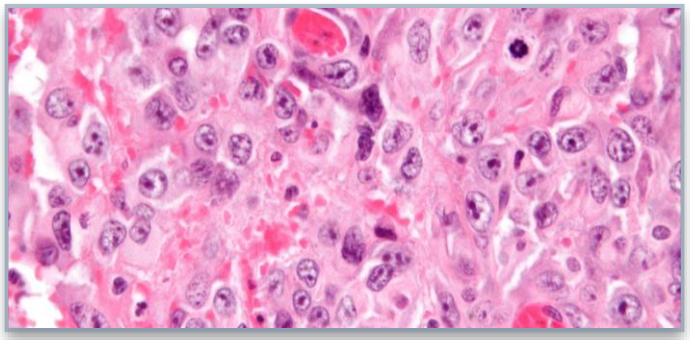
Oncological Outcomes of Operative Treatment of Subcutaneous Soft-Tissue Sarcomas of the Extremities*
J Bone Joint Surg Am, 1997 Jun; 79 (6): 888 -97 .

Classification of mesenchymal tumours



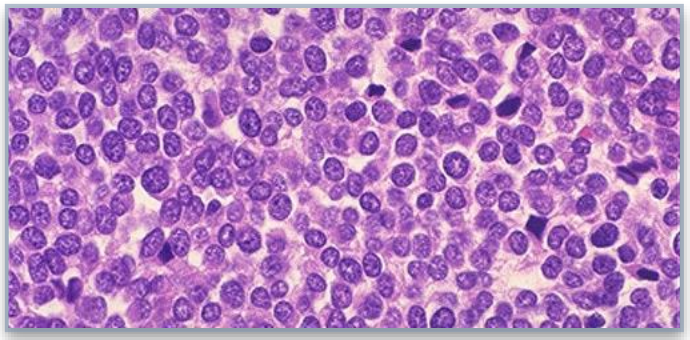
SPINDLE CELL

- Leiomyosarcoma
- Spindle cell rhabdomyosarcoma
- Fibrosarcoma
- Spindle cell sarcoma NOS



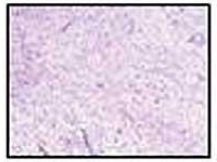
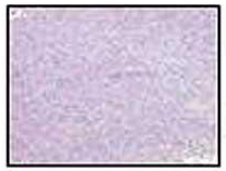
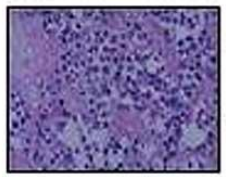
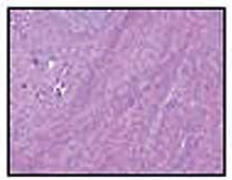
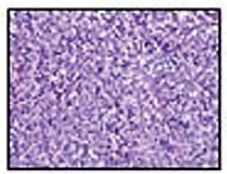
EPITHELIOID CELL

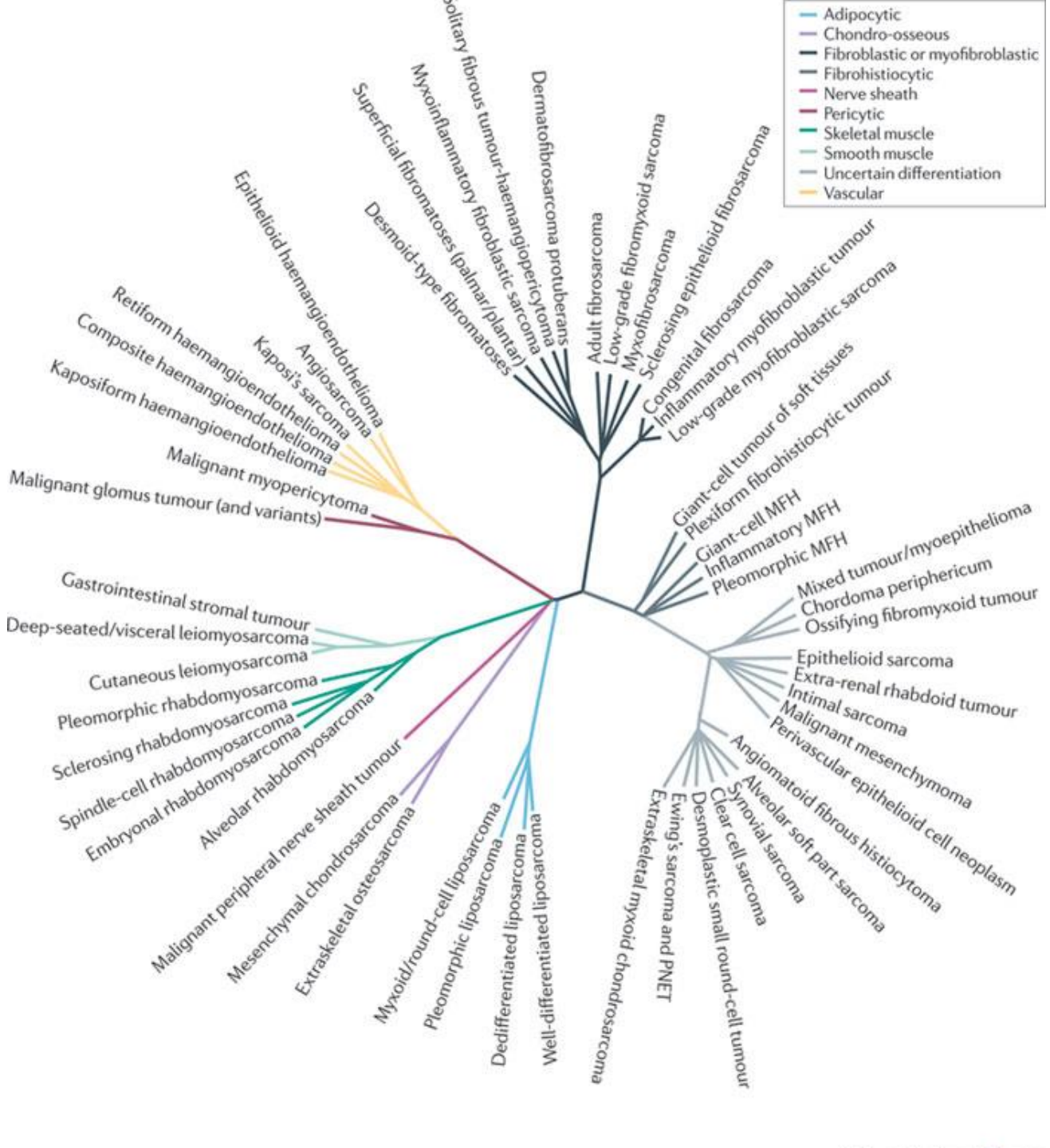
- Epithelioid sarcoma
- Epithelioid MPNST
- Epithelioid angiosarcoma
- Malignant rhabdoid tumour
- Metastatic Melanoma
- Metastatic carcinoma



ROUND CELL

- Ewing Sarcoma
- Desmoplastic round cell tumour
- Alveolar rhabdomyosarcoma
- Neuroblastoma
- Lymphoma
- Organ specific – Wilm's tumour, hepatoblastoma, pleuropulmonary blastoma

DIFFERENTATION	Subtypes	Chromosomal traslocations	Fusion trascripts
 ADIPOCYTIC TUMORS	*Lipoblastoma*:	t(7;8)(q31;q13); t(8;8)(q24;q13)	PLAG1-COL1A2;PLAG1-HAS2
	Myxoid liposarcoma	t(12;16)(q13;p11); t(12;22)(q13;q12)	CHOP-TLS; CHOP-EWS
 FRIBLOBLASTIC/ MYOFIBROBL.TUMORS	*Inflammatory myofibroblastic tumor*	t(1;2)(q25;p23); t(2;19)(p23;q13); t(2;17)(p23;q23)	TPM3-ALK; ALK-TPM4; ALK-CLTC
	Infantile fibrosarcoma	t(12;15)(p13;q25)	ETV6-NTRK3
	Dermatofibrosarcoma protuberans/ Giant cell fibroblastoma	t(17;22)(q22;q13)	COL1A1-PDGFB
 SKELETAL MUSCLE TUMORS	*Alveolar rhabdomyosarcoma*	t(2;13)(q35;q14); t(1;13)(p36;q14)	PAX3-FKHR; PAX7-FKHR
 TUMORS OF UNCERTAIN DIFFERENTIATION	*Angiomatoid fibrous histiocytoma*	t(12;22) (q13;q12); t(12;16) (q13;p11)	
	Synovial sarcoma	t(X;18)(p11.2;q11.2)	SYT-SSX1/2/4
	Alveolar soft part sarcoma	t(X;17)(p11;q25)	TFE3/ASPL
	Clear cell sarcoma	t(12;22)(q13;q12)	EWS-ATF1
	Extraskeletal myxoid chrondrosarcoma	t(9;22)(q22;q12); t(9;15)(q22;q21)	EWS-TEC; CHN-TFC12
	Desmoplastic small round cell tumor	t(11;22)(p13;q12)	EWS-WT1
 EWING SARCOMA		t(11;22)(q24;q12);t(21;22)(q22;q12); t(17;22)(q12;q12); t(7;22)(p22;q12);	FLI1-EWS; ERG-EWS E1AF-EWS; ETV1-EWS


Adipocytic
Chondro-osseous
Fibroblastic or myofibroblastic
Fibrohistiocytic
Nerve sheath
Pericytic
Skeletal muscle
Smooth muscle
Uncertain differentiation
Vascular
Solitary fibrous tumour-haemangiopericytoma
Dermatofibrosarcoma protuberans
Myxoinflammatory fibroblastic sarcoma
Superficial fibromatoses (palmar/plantar)
Desmoid-type fibromatoses
Epithelioid haemangioendothelioma
Angiosarcoma
Kaposi's sarcoma
Retiform haemangioendothelioma
Composite haemangioendothelioma
Kaposiform haemangioendothelioma
Malignant myopericytoma
Malignant glomus tumour (and variants)
Adult fibrosarcoma
Low-grade fibromyxoid sarcoma
Myxofibrosarcoma
Sclerosing epithelioid fibrosarcoma
Congenital fibrosarcoma
Inflammatory myofibroblastic tumour
Low-grade myofibroblastic sarcoma
Giant-cell tumour of soft tissues
Plexiform fibrohistiocytic tumour
Giant-cell MFH
Inflammatory MFH
Pleomorphic MFH
Mixed tumour/myoepithelioma
Chordoma periphericum
Ossifying fibromyxoid tumour
Epithelioid sarcoma
Extra-renal rhabdoid tumour
Intimal sarcoma
Malignant mesenchymoma
Perivascular epithelioid cell neoplasm
Angiomatoid fibrous histiocytoma
Alveolar soft part sarcoma
Synovial sarcoma
Clear cell sarcoma
Desmoplastic small round-cell tumour
Ewing's sarcoma and PNET
Extraskeletal myxoid chondrosarcoma
Gastrointestinal stromal tumour
Deep-seated/visceral leiomyosarcoma
Cutaneous leiomyosarcoma
Pleomorphic rhabdomyosarcoma
Sclerosing rhabdomyosarcoma
Spindle-cell rhabdomyosarcoma
Embryonal rhabdomyosarcoma
Alveolar rhabdomyosarcoma
Malignant peripheral nerve sheath tumour
Mesenchymal chondrosarcoma
Extraskeletal osteosarcoma
Myxoid/round-cell liposarcoma
Pleomorphic liposarcoma
Dedifferentiated liposarcoma
Well-differentiated liposarcoma

Survival Rates

Figure 6b: Bone sarcoma 5-year rolling 5-year relative survival rates in males and females (UK: 1996-2010)

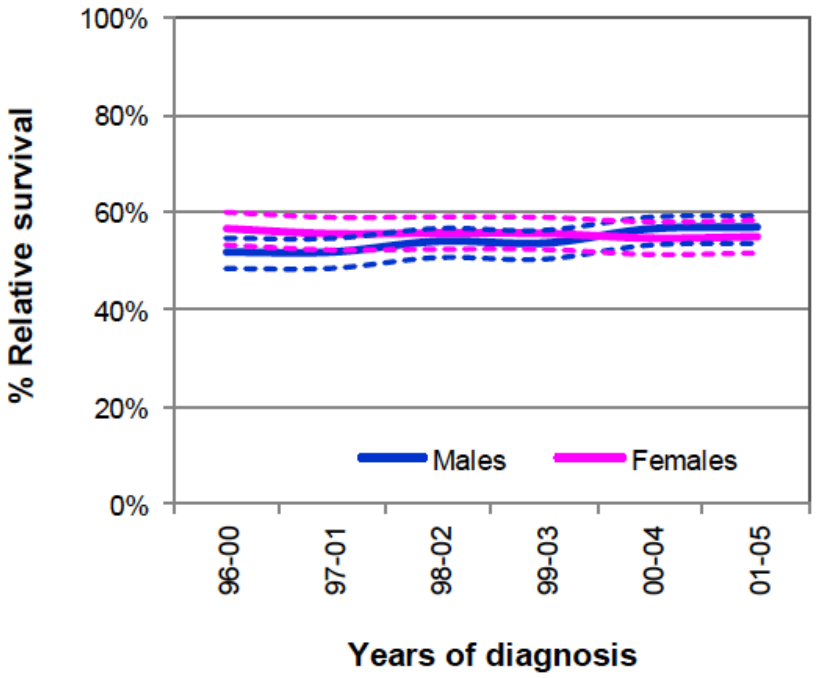
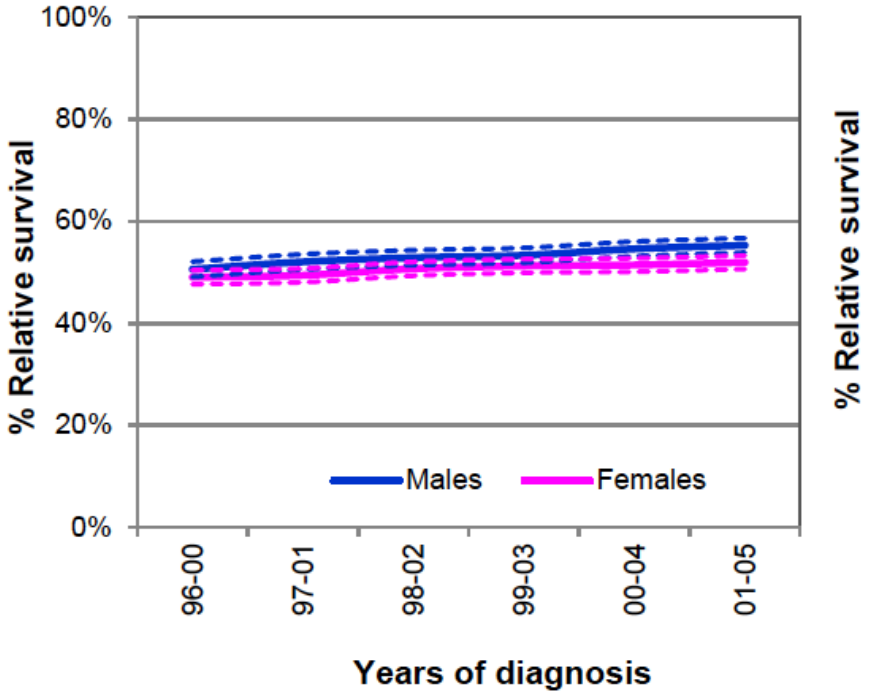
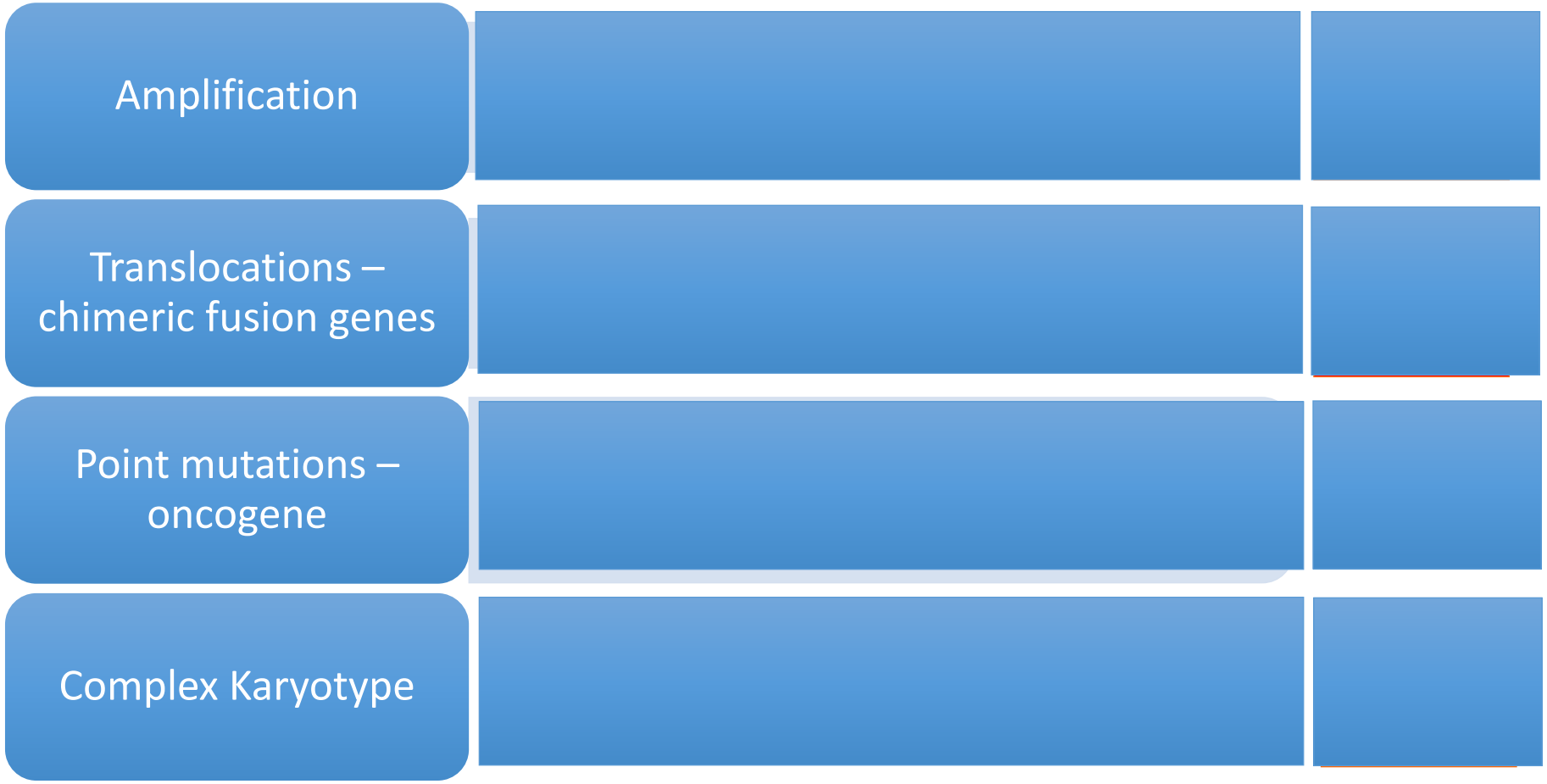


Figure 6a: Soft tissue sarcoma (excluding skin) 5-year rolling 5-year relative survival rates in males and females (UK: 1996-2010)



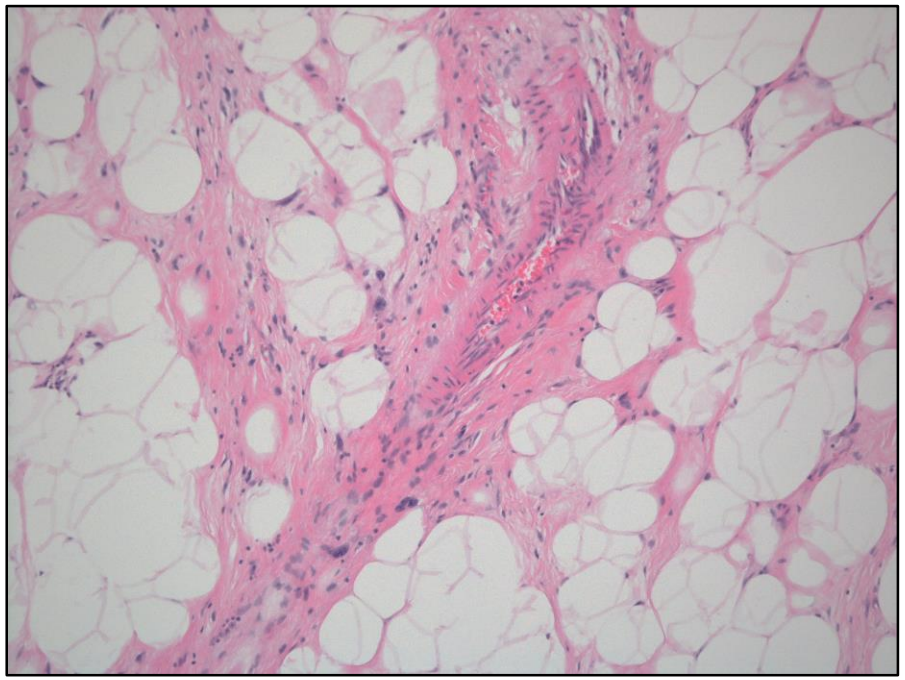
NCIN national cancer intelligence network
Using information to improve quality & choice

Molecular classification of mesenchymal tumours

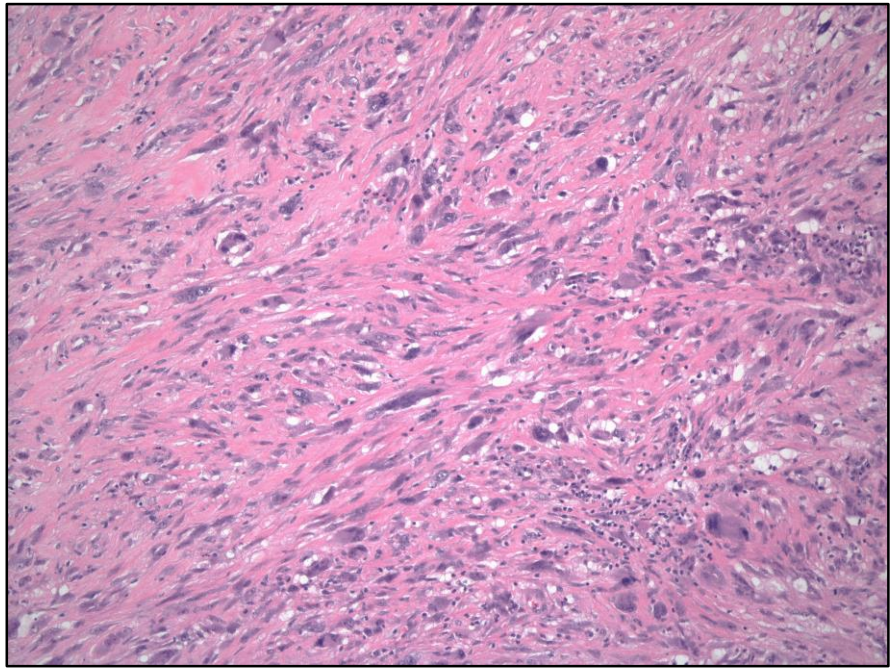


Atypical lipomatous tumour
Well differentiated Liposarcoma
Dedifferentiated liposarcoma

Well-differentiated –
slow growing, does not metastasize, multiply recurrent, no response to chemotherapy



Dedifferentiated–
aggressive, can metastasize, limited and transient benefit to chemotherapy, median survival about 12 months



Gene Amplification – diagnostic tests

MDM2 amplification

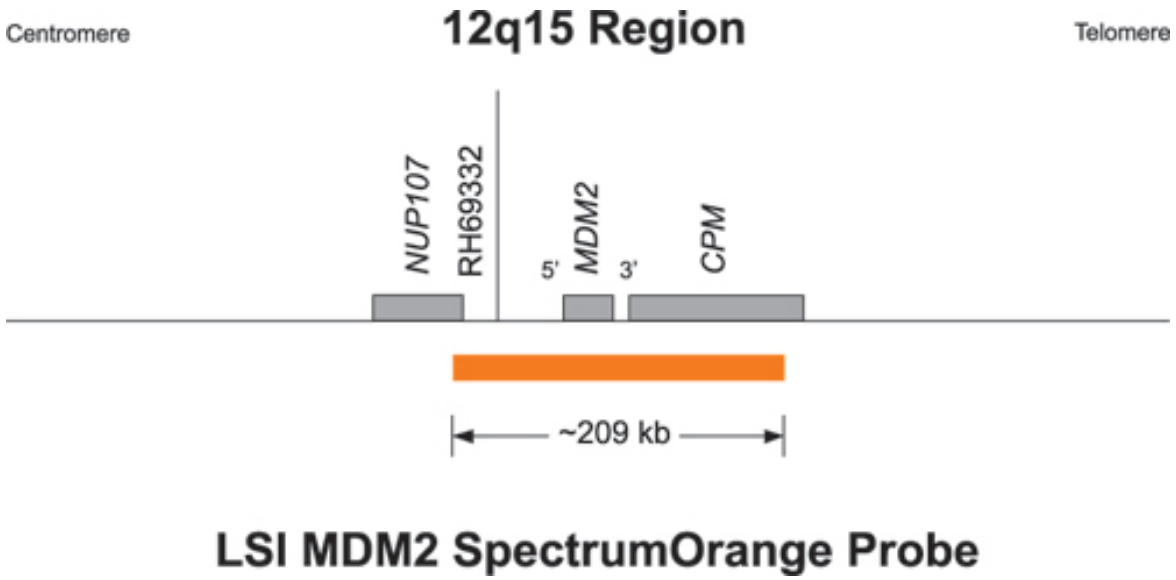
- Atypical lipomatous tumour/ dedifferentiated liposarcoma
- Low grade osteosarcoma / parosteal osteosarcoma

MDM2/CDK4 amplification – medical treatment options

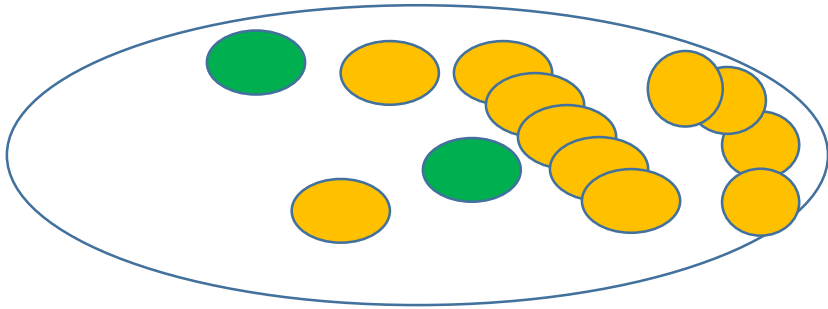
- RG7112
- Oral – inhibitor of *MDM2*
- Good response to well – dedifferentiated liposarocma

Interphase FISH
(Design for amplification)

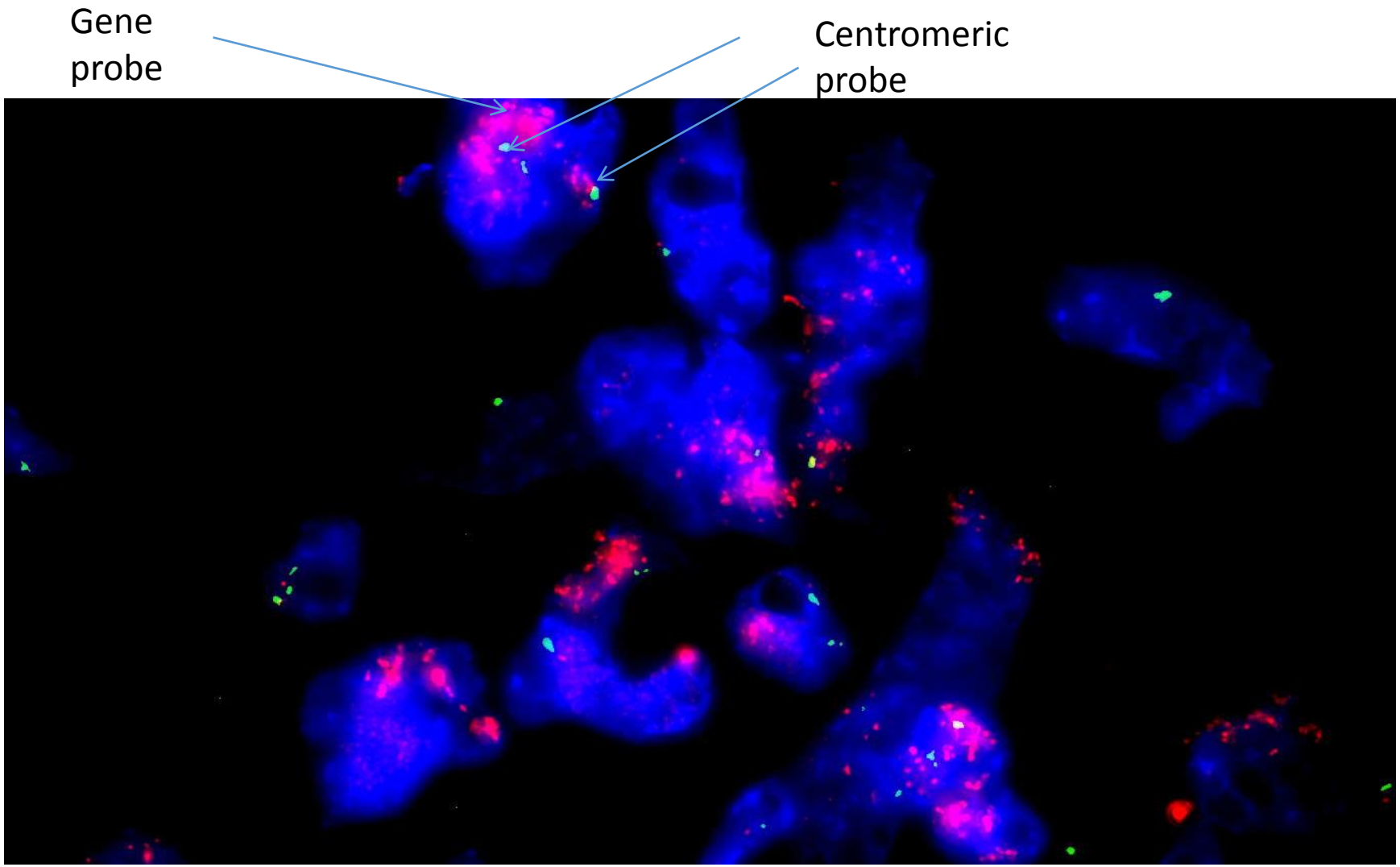
- Assay design –
- centromeric probe (enumerate the chromosomes)
- gene probe (enumerate the gene copy number)



- Addition of centromeric probe for the chromosome of interest– enables one to count number of chromosomes present.
- Diploid,
- aneuploid,polysomy
- low level copy gain,
- high level amplification



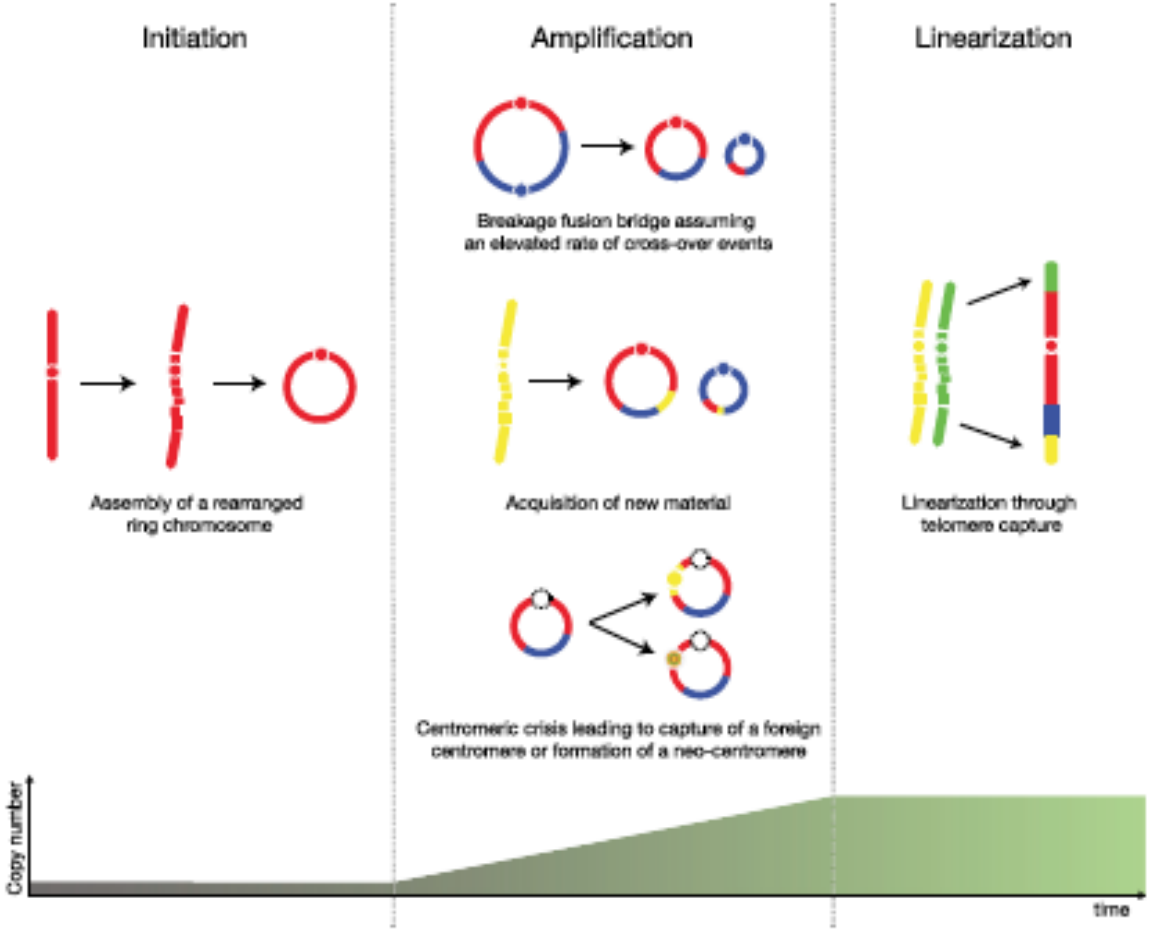
MDM2 amplification – Well differentiated liposarcoma

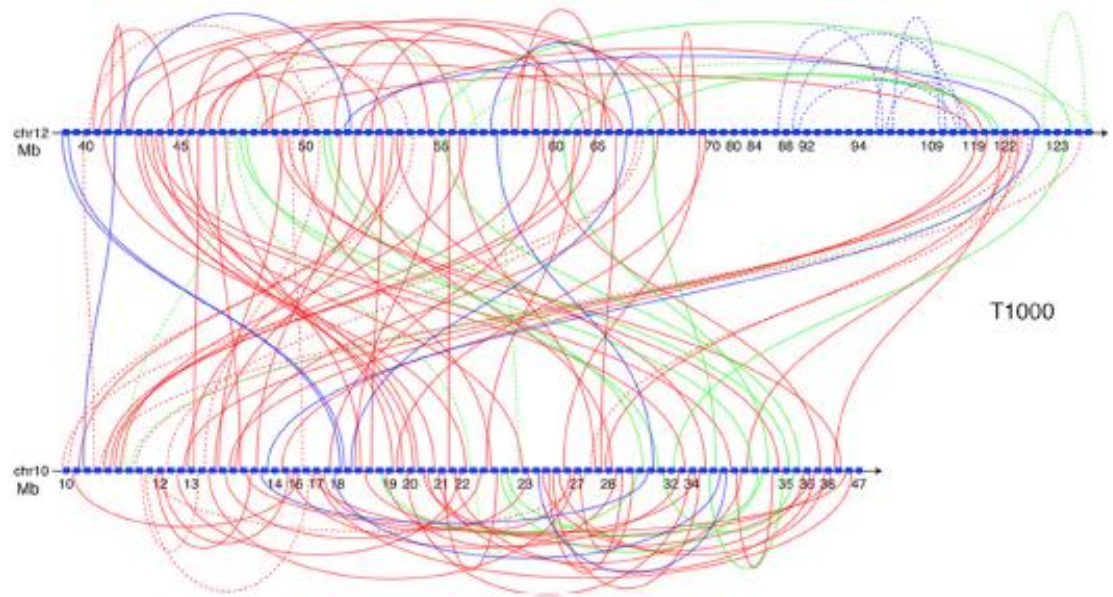


Cancer Cell
Article

The Architecture and Evolution of Cancer Neochromosomes

Dale W. Garsed,[1,8,9,15] Owen J. Marshall,[5,15,17] Vincent D.A. Corbin,[2,3,13,15] Arthur Hsu,[2,15] Leon Di Stefano,[2] Jan Schröder,[2,3] Jason Li,[1] Zhi-Ping Feng,[2,3] Bo W. Kim,[5] Mark Kowarsky,[2] Ben Lansdell,[2] Ross Brookwell,[6] Ola Myklebost,[10] Leonardo Meza-Zepeda,[10] Andrew J. Holloway,[1] Florence Pedeutour,[7] K.H. Andy Choo,[5] Michael A. Damore,[11] Andrew J. Deans,[12] Anthony T. Papenfuss,[2,3,4,8,13,16,*] and David M. Thomas[1,8,14,16,*]





FISH as an aetiological adjunct

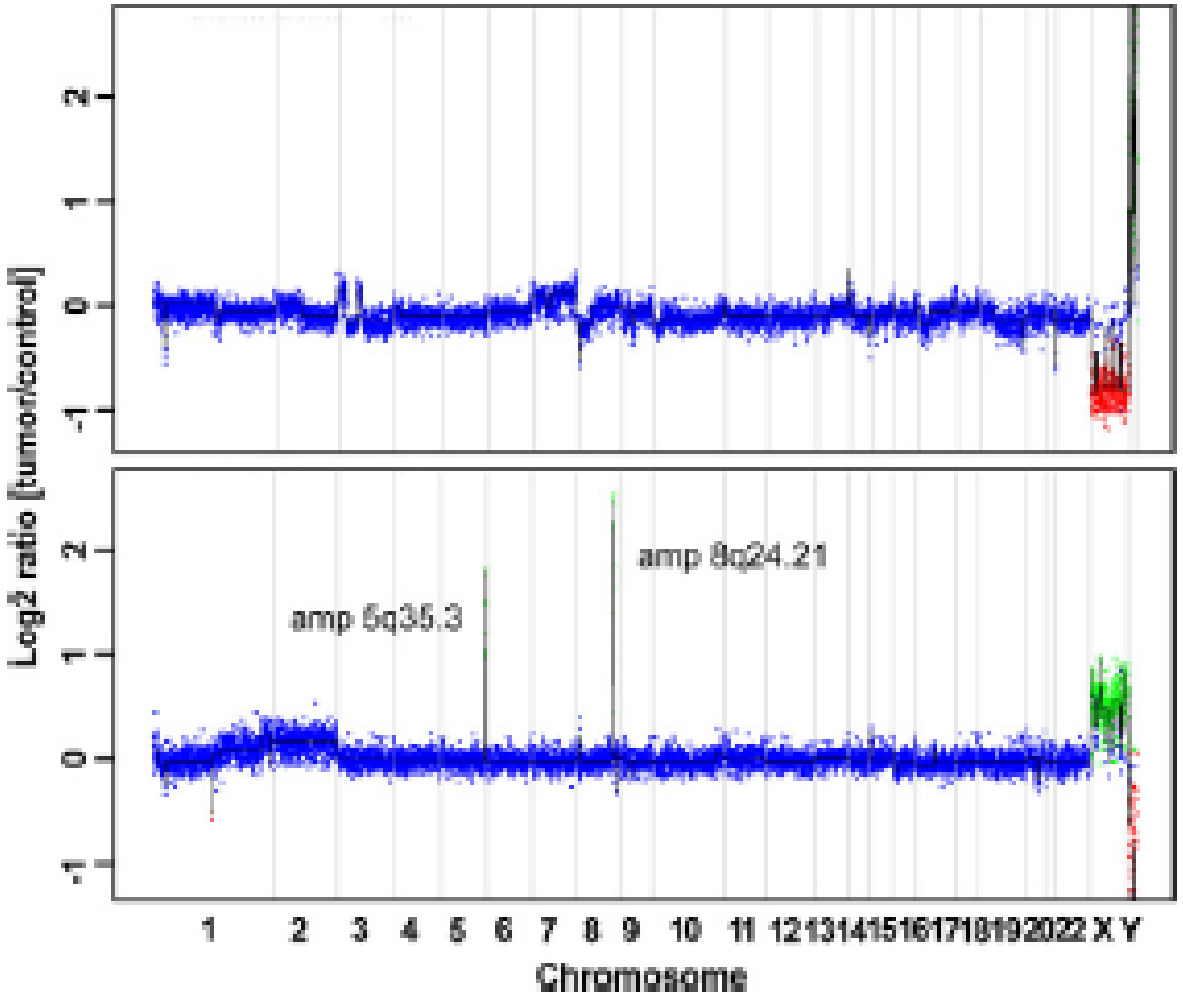
MYC – radiation induced angiosarcoma

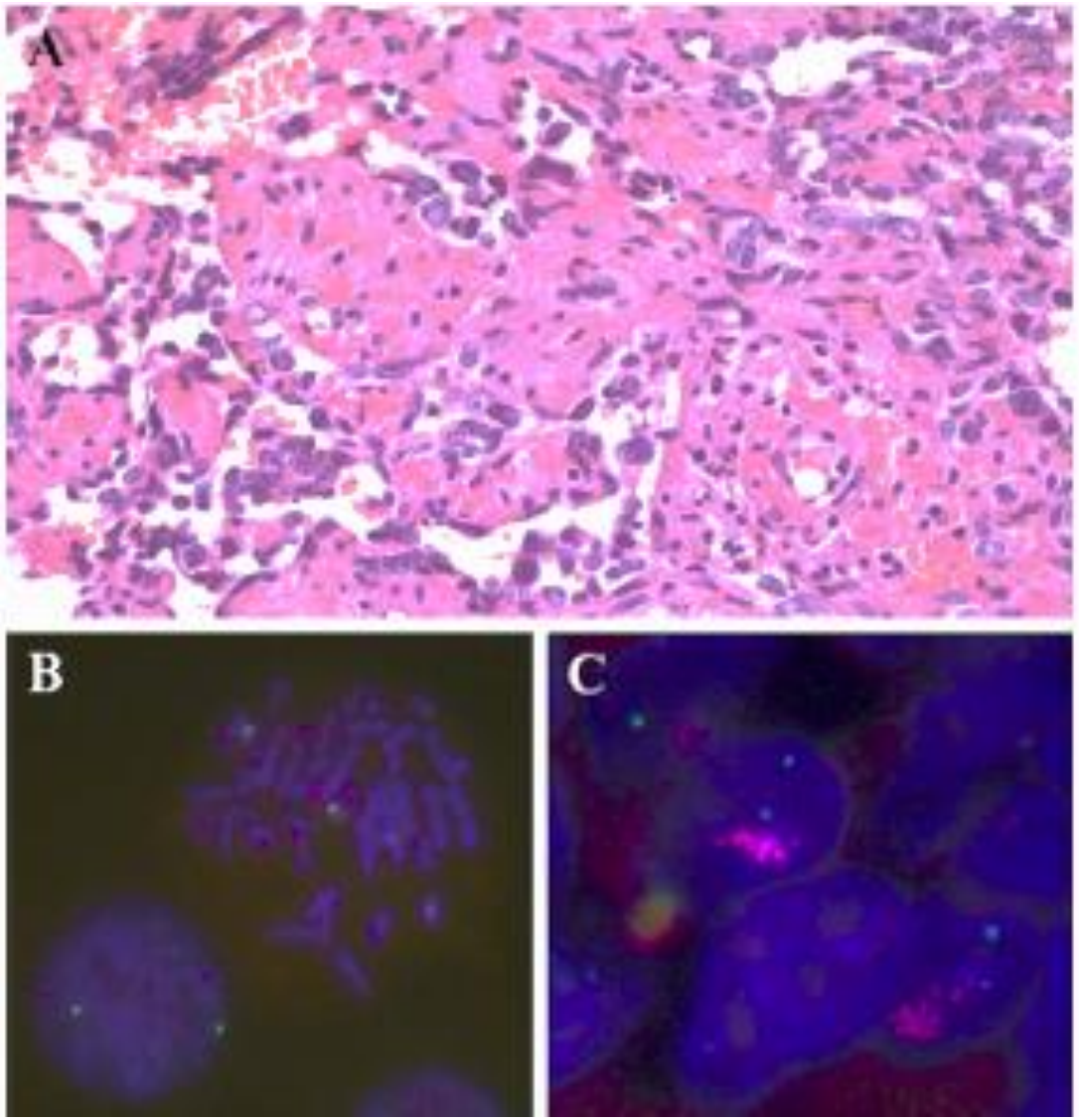
The American Journal of Pathology, Vol. 176, No. 1, January 2010

DOI: 10.2353/ajpath.2010.090637

Short Communication

MYC High Level Gene Amplification Is a Distinctive Feature of Angiosarcomas after Irradiation or Chronic Lymphedema


Log2 ratio [tumor/control]
amp 5q35.3
amp 9q24.21
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 22 X Y
Chromosome


A
B
C

FISH – predictive and prognostic

ARTICLE

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DOI: 10.1038/ncomms15936 OPEN

Recurrent mutation of IGF signalling genes and distinct patterns of genomic rearrangement in osteosarcoma

Sam Behjati[1,2,3,*], Patrick S. Tarpey[1,*], Kerstin Haase[4], Hongtao Ye[5], Matthew D. Young[1], Ludmil B. Alexandrov[6], Sarah J. Farndon[1,7], Grace Collord[1], David C. Wedge[8], Inigo Martincorena[1], Susanna L. Cooke[1], Helen Davies[1], William Mifsud[7], Mathias Lidgren[1], Sancha Martin[1], Calli Latimer[1], Mark Maddison[1], Adam P. Butler[1], Jon W. Teague[1], Nischalan Pillay[5,9], Adam Shlien[10], Ultan McDermott[1], P. Andrew Futreal[1,11], Daniel Baumhoer[12], Olga Zaikova[13], Bodil Bjerkehagen[13], Ola Myklebost[13,14], M. Fernanda Amary[5], Roberto Tirabosco[5], Peter Van Loo[4,15], Michael R. Stratton[1], Adrienne M. Flanagan[5,9,**] & Peter J. Campbell[1,16,**]

OSTEOSARCOMA

Cancer Medicine

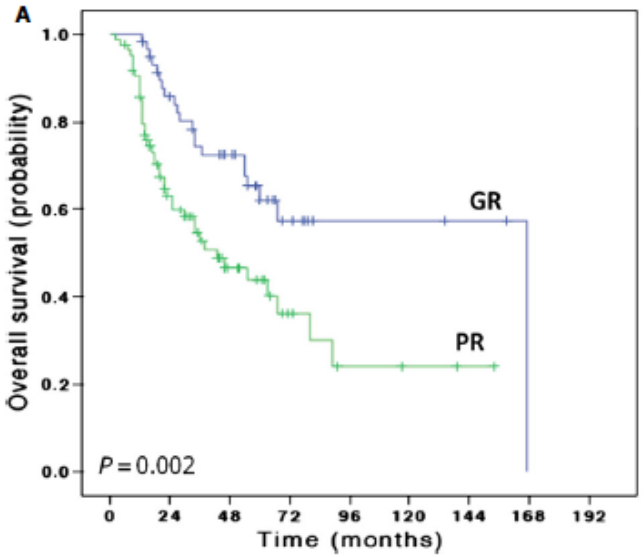
Open Access

ORIGINAL RESEARCH

Fibroblastic growth factor receptor 1 amplification in osteosarcoma is associated with poor response to neo-adjuvant chemotherapy

M. Fernanda Amary[1,2], Hongtao Ye[1], Fitim Berisha[1], Bhavisha Khatri[1], Georgina Forbes[1], Katie Lehovsky[1], Anna M. Frezza[2,3], Sam Behjati[4], Patrick Tarpey[4], Nischalan Pillay[1,2], Peter J. Campbell[4], Roberto Tirabosco[1], Nadège Presneau[2], Sandra J. Strauss[2,3] & Adrienne M. Flanagan[1,2]

[1]Histopathology, London Sarcoma Service, Royal National Orthopaedic Hospital NHS Trust, Stanmore, Middlesex, HA7 4LP, U.K.
[2]UCL Cancer Institute, Huntley Street, London, WC1E 6BT, U.K.
[3]University College London Hospitals Foundation Trust, London Sarcoma Service, 250 Euston Road, London, NW1 2PG, U.K.
[4]Cancer Genome Project, Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridgeshire, CB10 1SA, U.K.



Gene amplification

- Diagnostic test – Atypical lipomatous tumour / Dedifferentiated liposarcoma

➢MDM2 amplification

- Predictive and prognostic utility – osteosarcoma

➢FGFR1 amplification / IGF amplification

- Biology of disease

Molecular classification of sarcomas

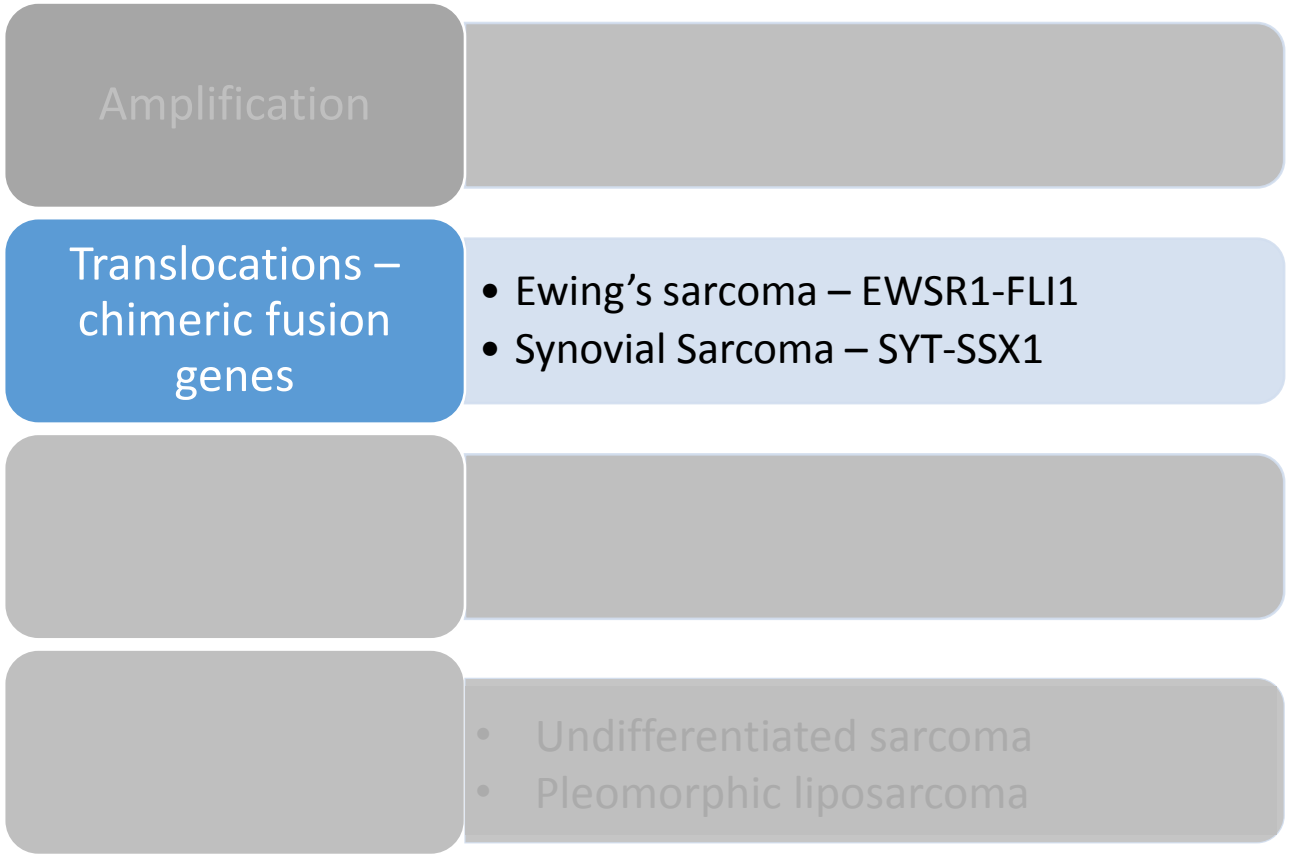


Table 3: *Selected chromosomal translocations in sarcomas*

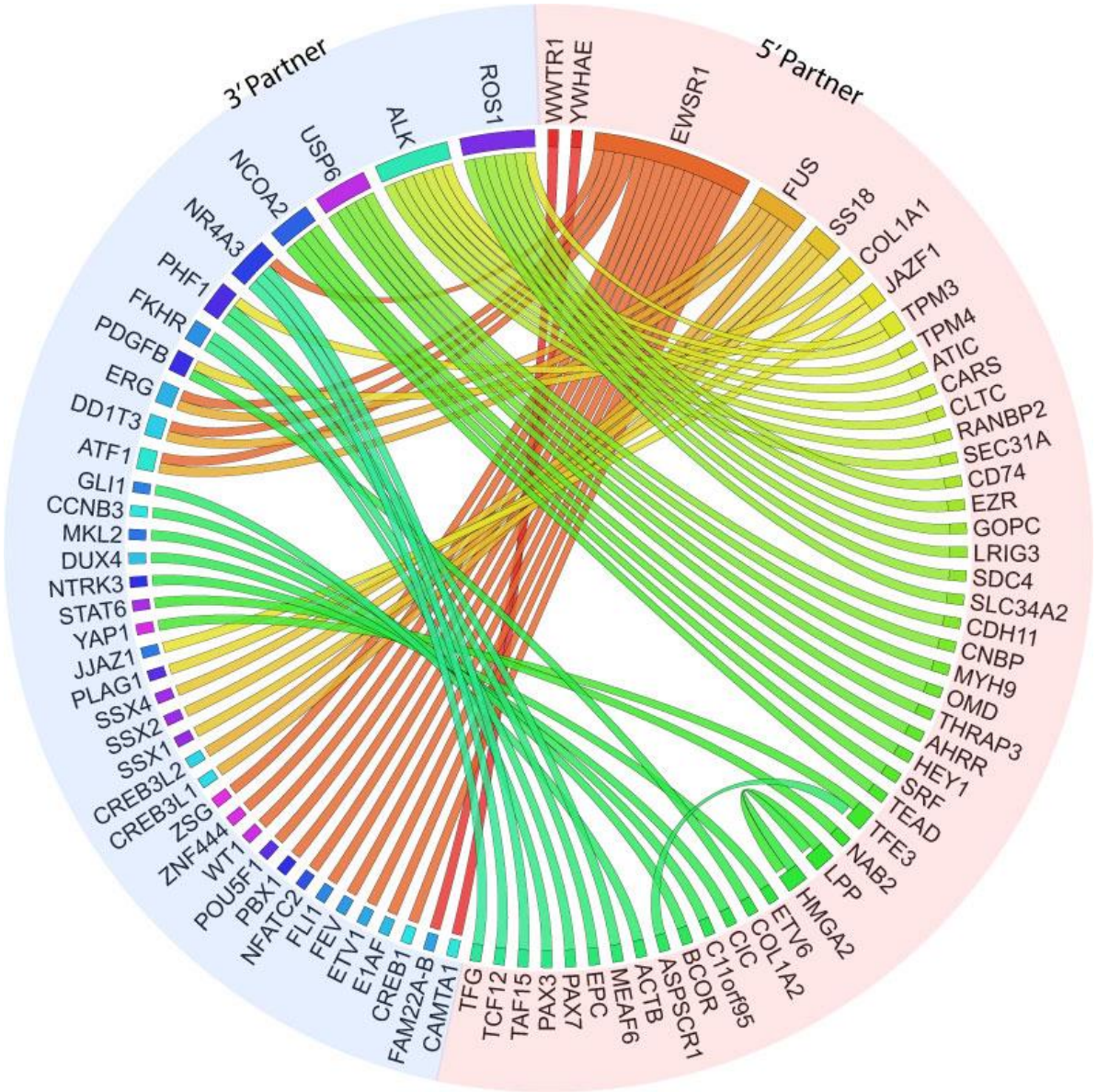
Sarcoma type	Translocation	Effect of translocation
Ewing's/PNET	t(11;22) (80-85%) t(21;22) t(7;22) t(2;22) t(17;22)	EWS-FL1 translocation: some variants associated with more favourable prognosis. FL1 acts as transcription factor.
Rhabdomyosarcoma (alveolar)	t(2;13) t(1;13)	PAX-FOX01a gene fusion. Encodes chimeric transcription factor. Fusion status correlates with clinical outcome.
DFSP	t(17;22)	Fusion of collagen 1 type 1α and PDGFβ.
Synovial sarcoma	t(X;18)	Biology of fusion product not well known –?transcription co-factor.
Clear cell sarcoma	t(12;22)	EWS-ATF1
Myxoid liposarcoma	t(12;16) t(12;22)	CHOP-EWS/CHOP-TLS fusion product.
Desmoplastic small round-cell tumour	t(11;22)	EWS-WT1

Fusion gene detection – diagnostic assays

- RT-PCR
- FISH
- Immunohistochemistry – e.g. *NAB2—STAT6* fusion in Solitary Fibrous Tumour.

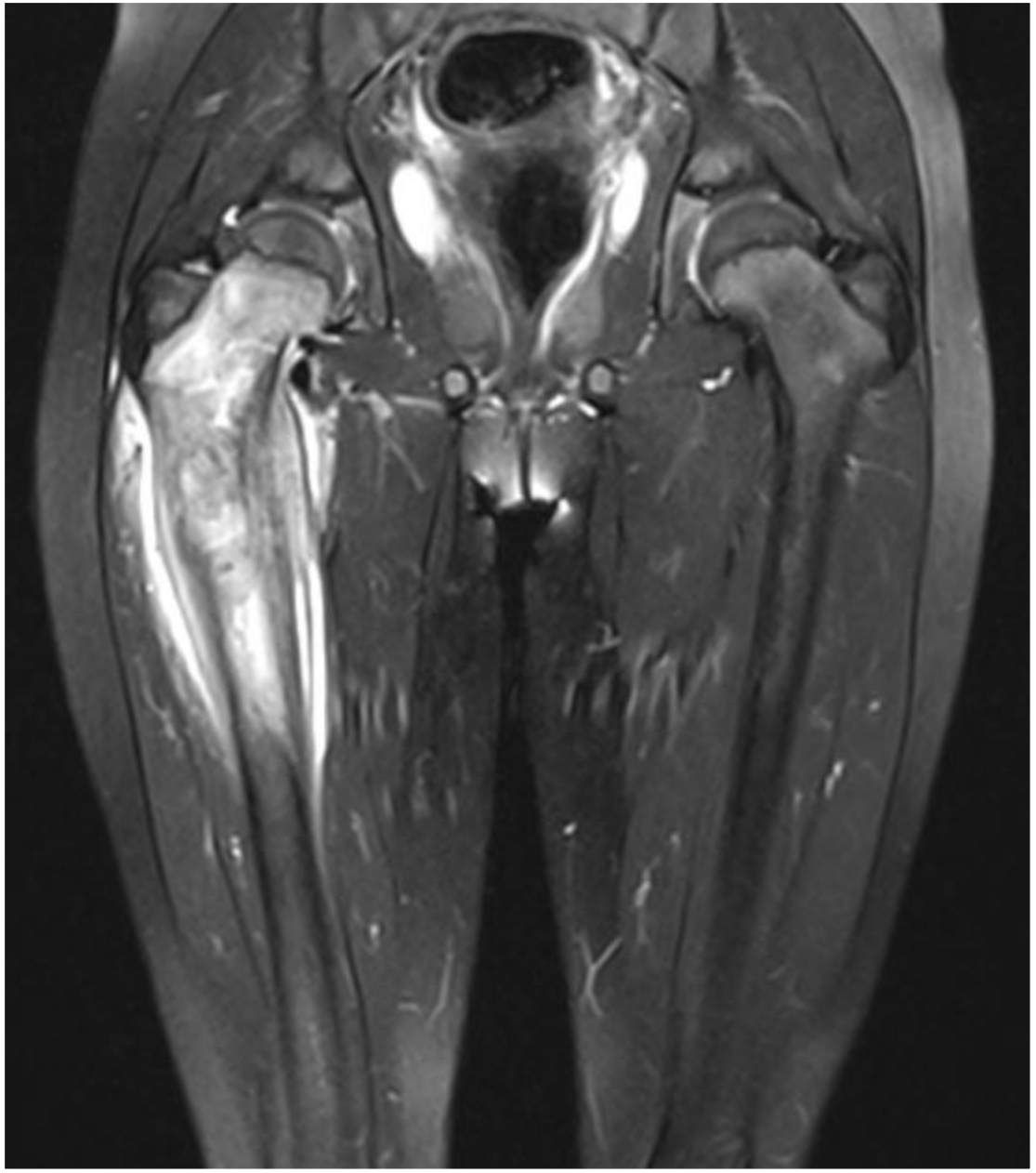
- RNA – in situ hybridisation (RNAscope)
- RNA-seq

Archer® FusionPlex® Sarcoma Kit



ARCHER AMP™ Sequencing Assays

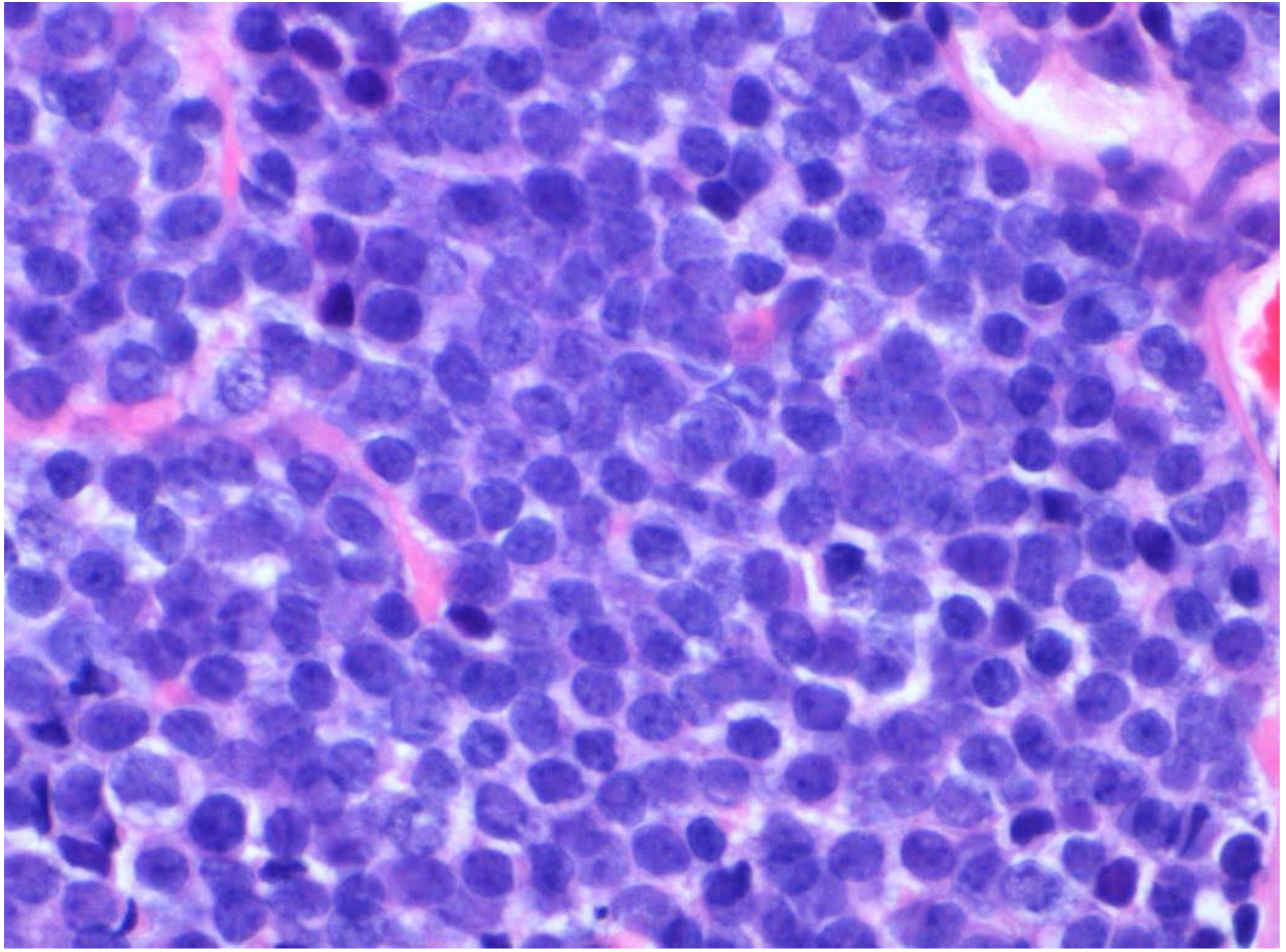
1	Whole Genome Sample	Archer's Anchored Multiplex PCR AMP™ technology simultaneously isolates RNA and DNA sequences of interest from whole transcriptomes or genomes and prepares them for next generation sequencing
2	Captured Targets	The process yields a high enriched NGS-ready library of the targeted sequences of interest
3	Ion Torrent™ AND Illumina®	The captured targets can be sequenced on Ion Torrent™ and Illumina® sequencers
4		Proprietary software generates a report of genetic mutations in a straightforward format that doesn't require programming expertise and can be viewed to the single nucleotide level



16yr old. Proximal femur fracture.

Radiological Differential diagnosis:

-**Infection**
-**Langerhan's cell histiocytosis**
-**Osteosarcoma**
-**Ewing sarcoma**



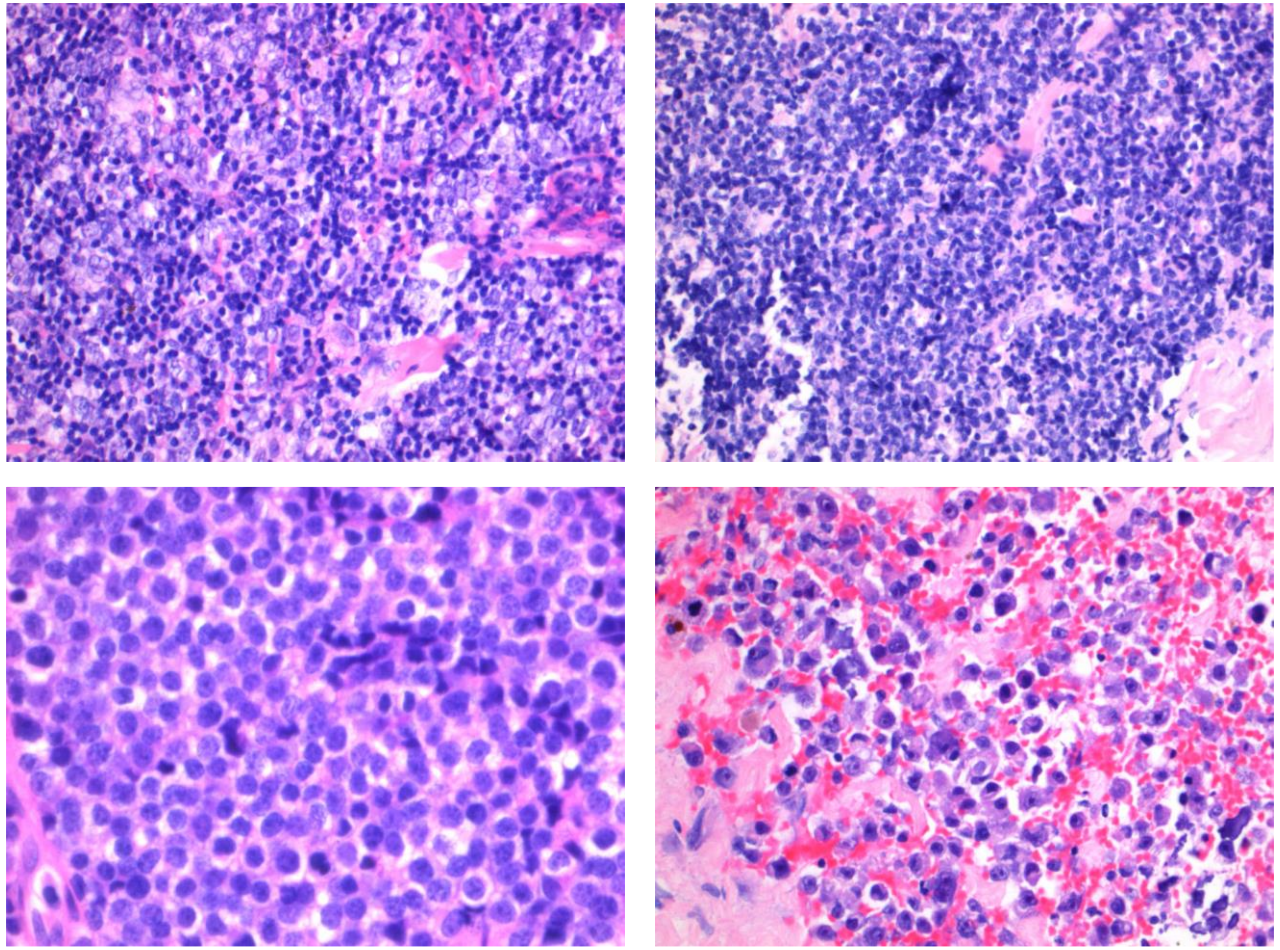
Differential Diagnosis

- Ewing’s sarcoma
- Ewing’s-like Round Cell Sarcomas
- Small Cell Osteosarcoma
- Lymphoma
- Alveolar Rhabdomyosarcoma
- Desmoplastic Small Round Cell Tumour
- Round Cell Liposarcoma (HG Myxoid LPS, WHO 2013)
- Mesenchymal Chondrosarcoma
- Neuroblastoma
- Metastatic Melanoma

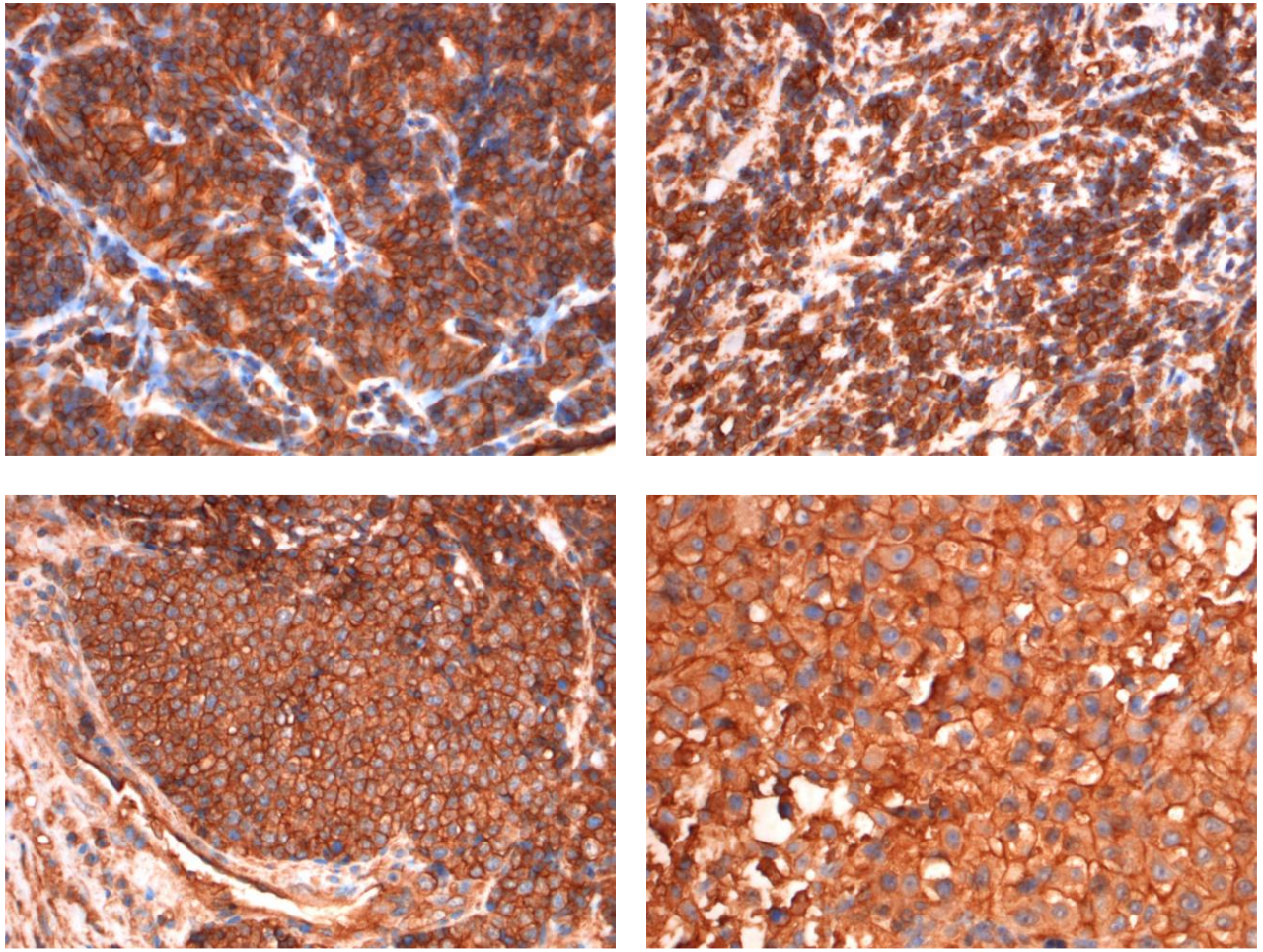
Immunohistochemistry

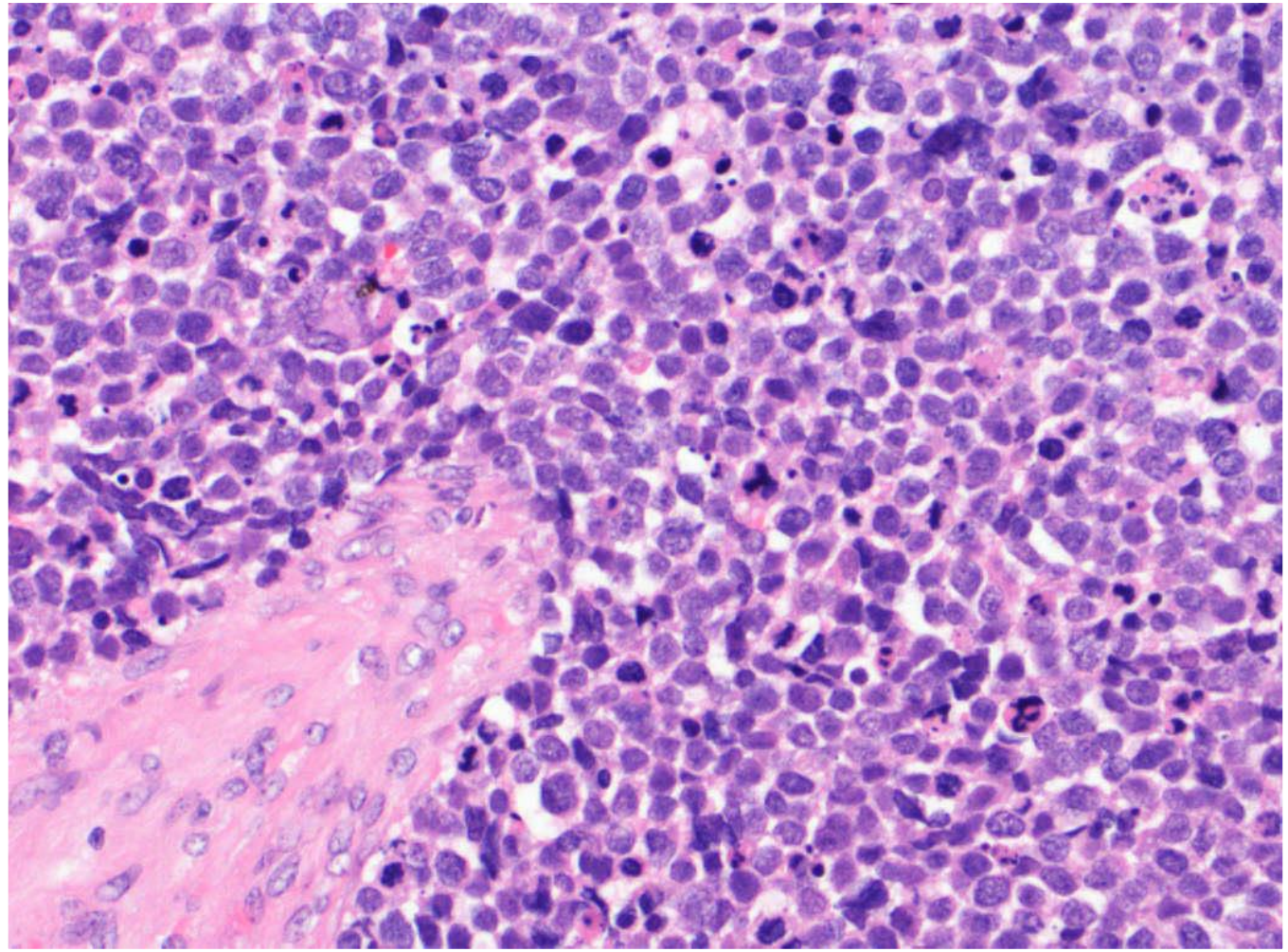
- CD99
- CD45
- TdT
- S100
- Desmin
- Pan cytokeratin

The value of CD99



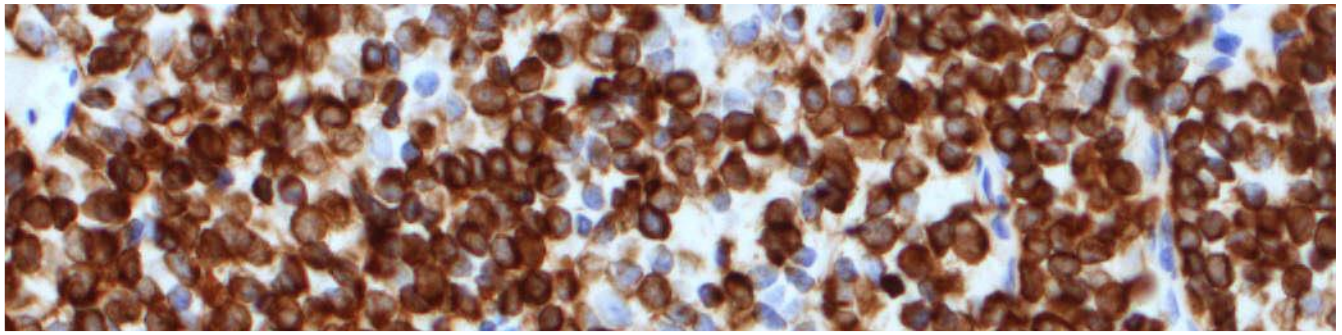
The value of CD99



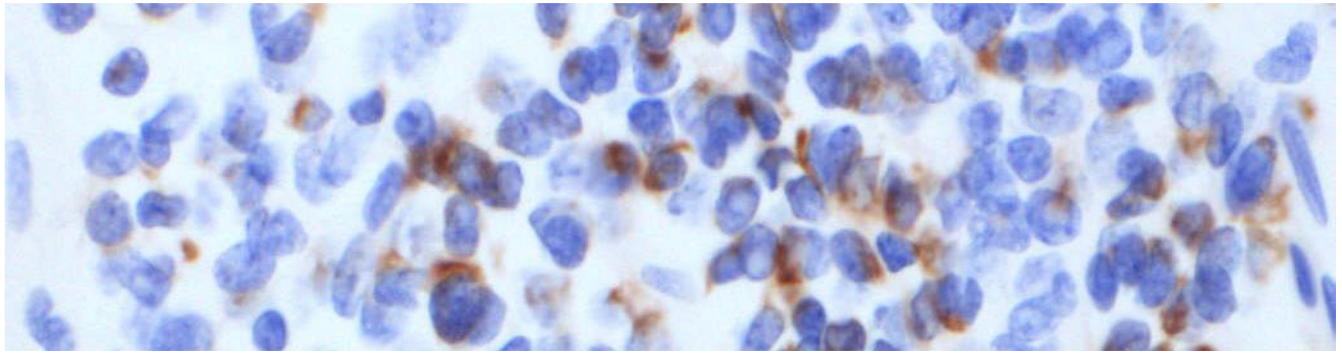


The common immunophenotype

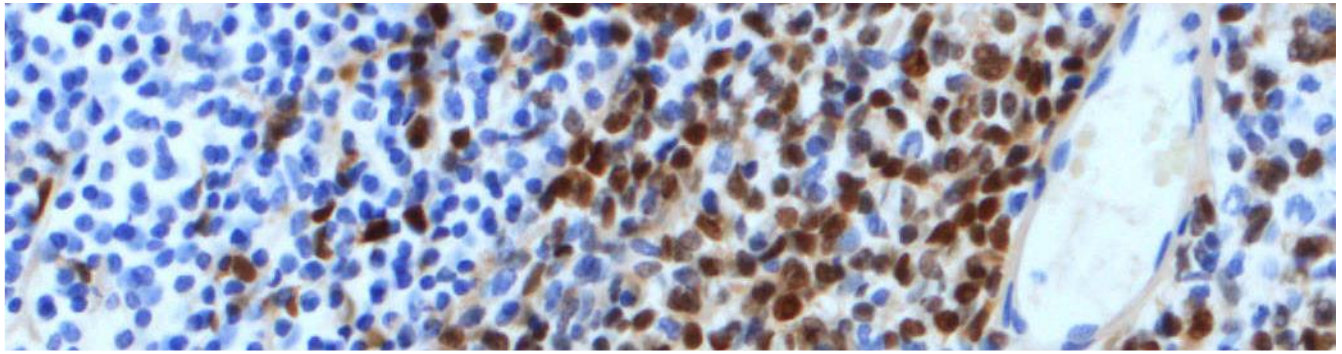
• CD99	+++
• CD45	Neg.
• TdT	Neg.
• S100	Neg.
• Desmin	Neg.
• Pankeratin	Neg.



MNF116
(~10%)



CK20



S100

The uncommon immunophenotype

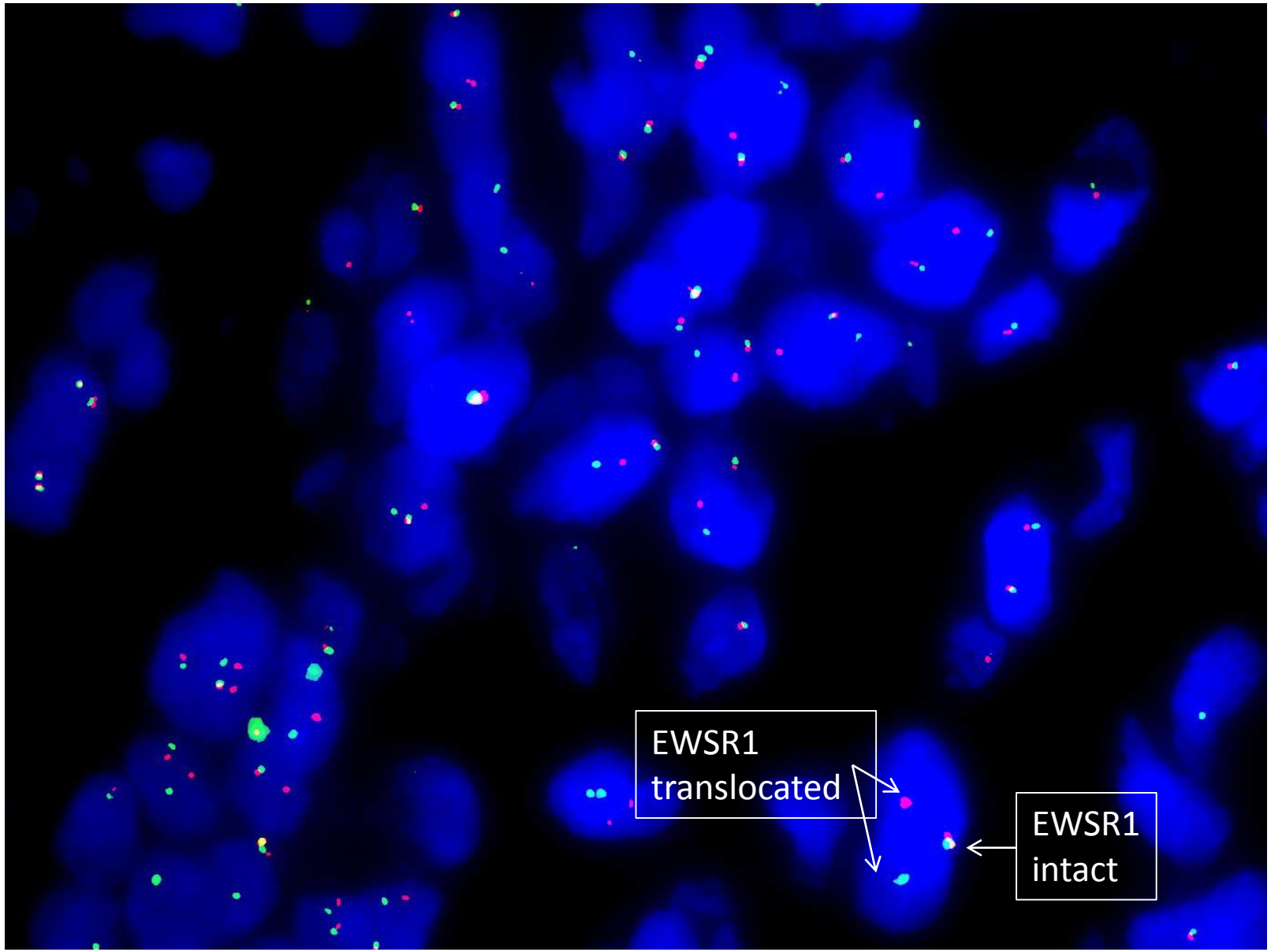
Molecular confirmation needed

Break-apart FISH

- Fusion detection: break-apart probe corresponding to the most commonly rearranged partner.
- E.g. FISH for Ewing sarcoma
- EWSR1 – FLI1

EWSR1 BREAK APART DESIGN – DUAL COLOUR

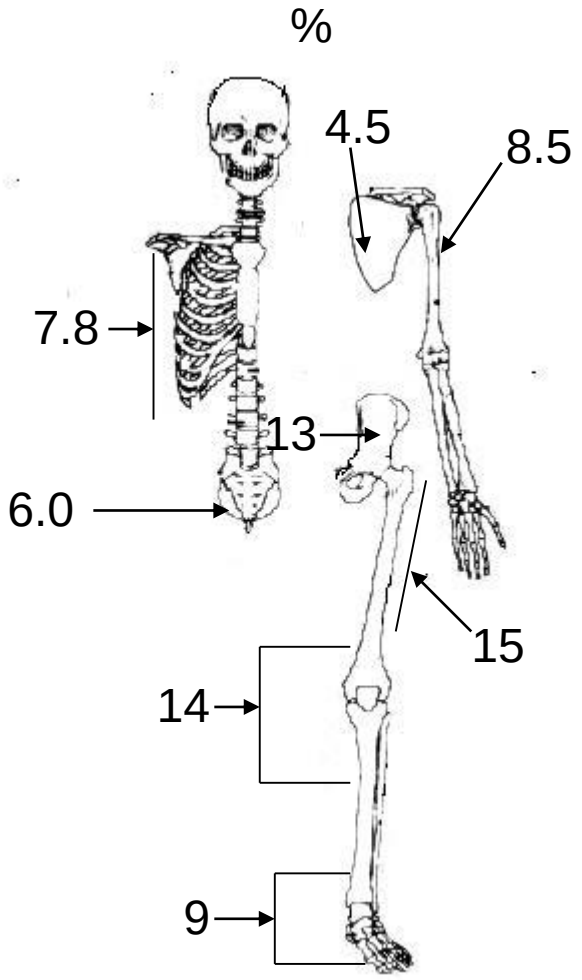
LSI EWSR1 Dual Color, Break Apart Rearrangement Probe

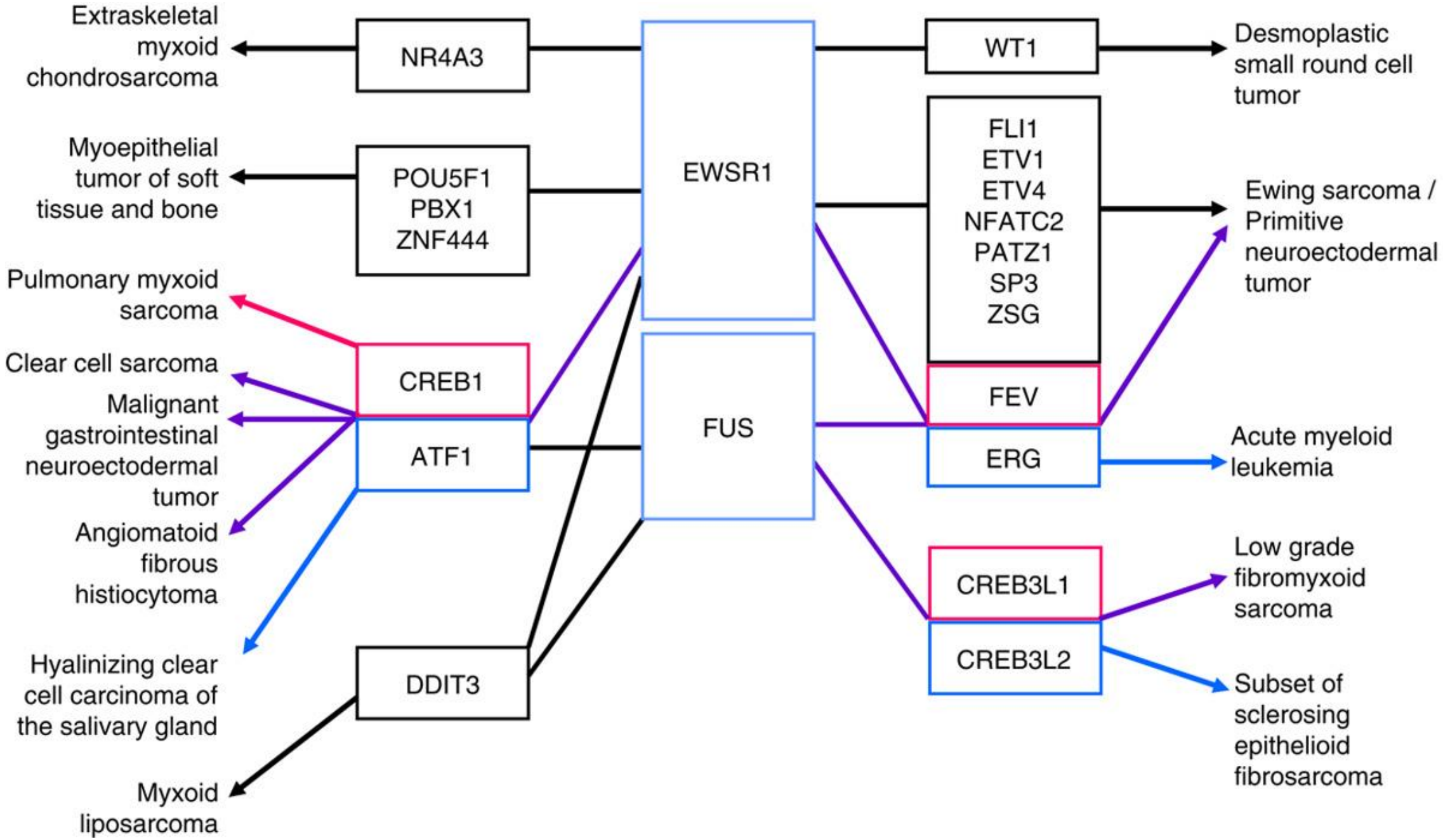

EWSR1
translocated
EWSR1
intact

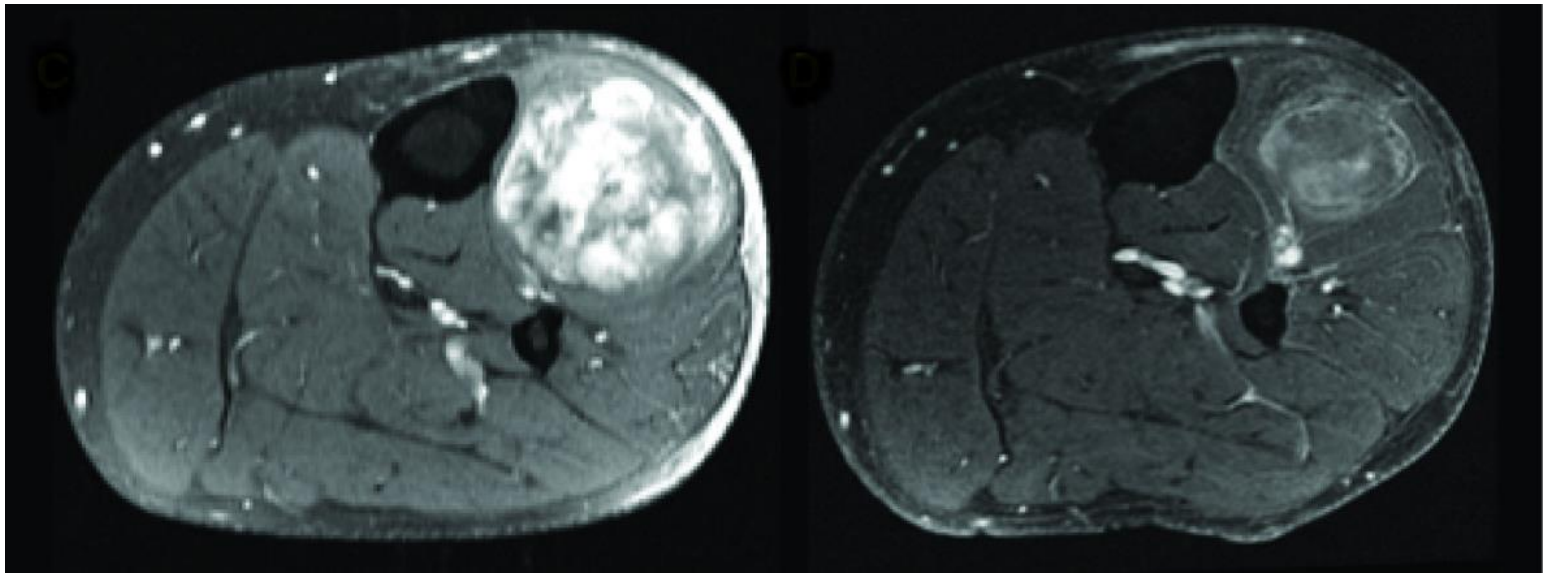
Codman’s triangle

EWING'S SARCOMA

* **Peak incidence : II decade**
* **Male predilection**
* **Pain is the main symptom**
* **70% bone; 30% soft tissue**
* ***EWSR1* gene rearrangement (~95%)**
* **Chemosensitive tumour**

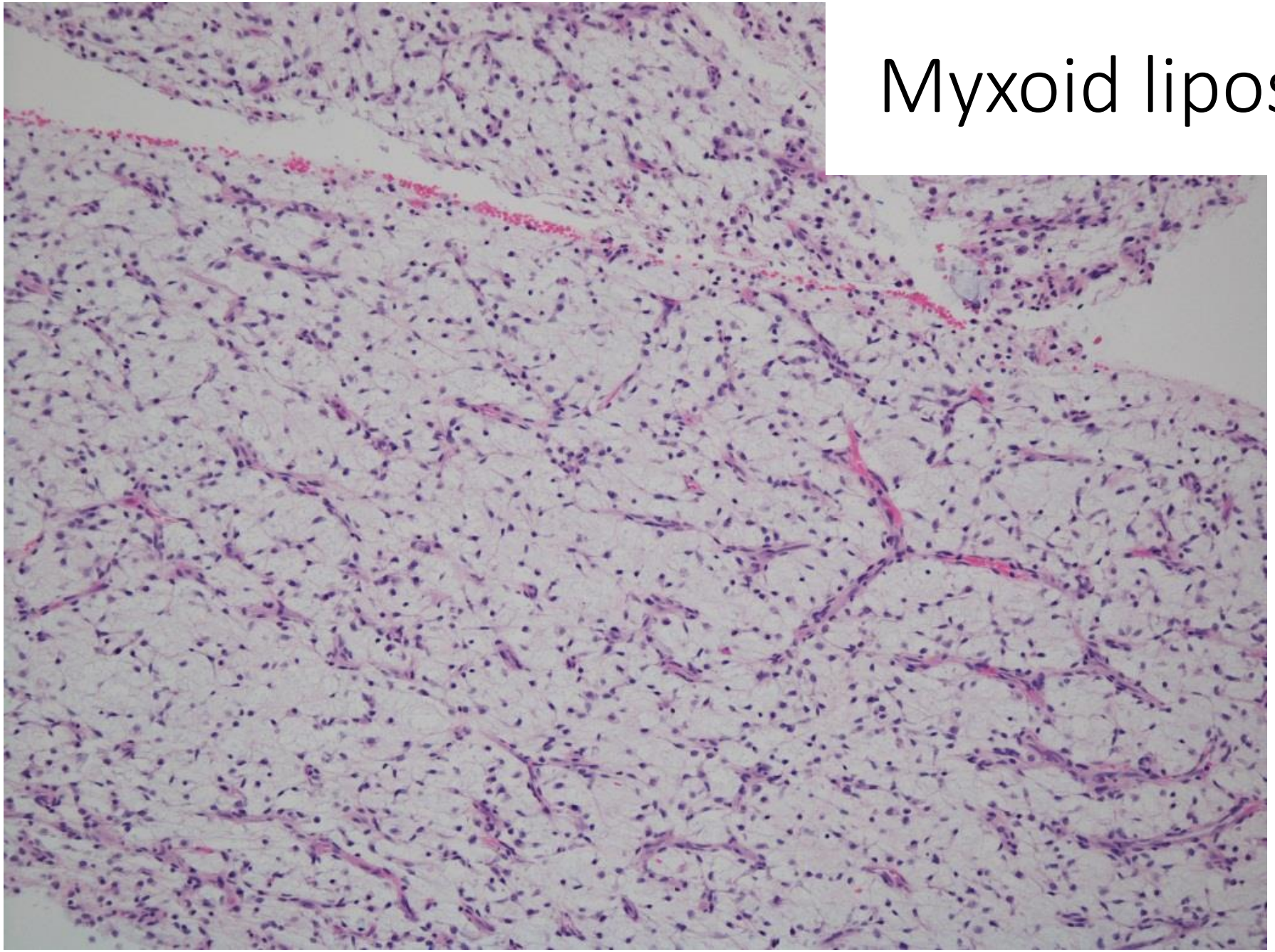



Extraskeletal myxoid chondrosarcoma
NR4A3
Myoepithelial tumor of soft tissue and bone
POU5F1
PBX1
ZNF444
Pulmonary myxoid sarcoma
Clear cell sarcoma
Malignant gastrointestinal neuroectodermal tumor
Angiomatoid fibrous histiocytoma
CREB1
ATF1
Hyalinizing clear cell carcinoma of the salivary gland
Myxoid liposarcoma
DDIT3
EWSR1
FUS
WT1
FLI1
ETV1
ETV4
NFATC2
PATZ1
SP3
ZSG
FEV
ERG
CREB3L1
CREB3L2
Desmoplastic small round cell tumor
Ewing sarcoma / Primitive neuroectodermal tumor
Acute myeloid leukemia
Low grade fibromyxoid sarcoma
Subset of sclerosing epithelioid fibrosarcoma



45yr old male – lump in the leg

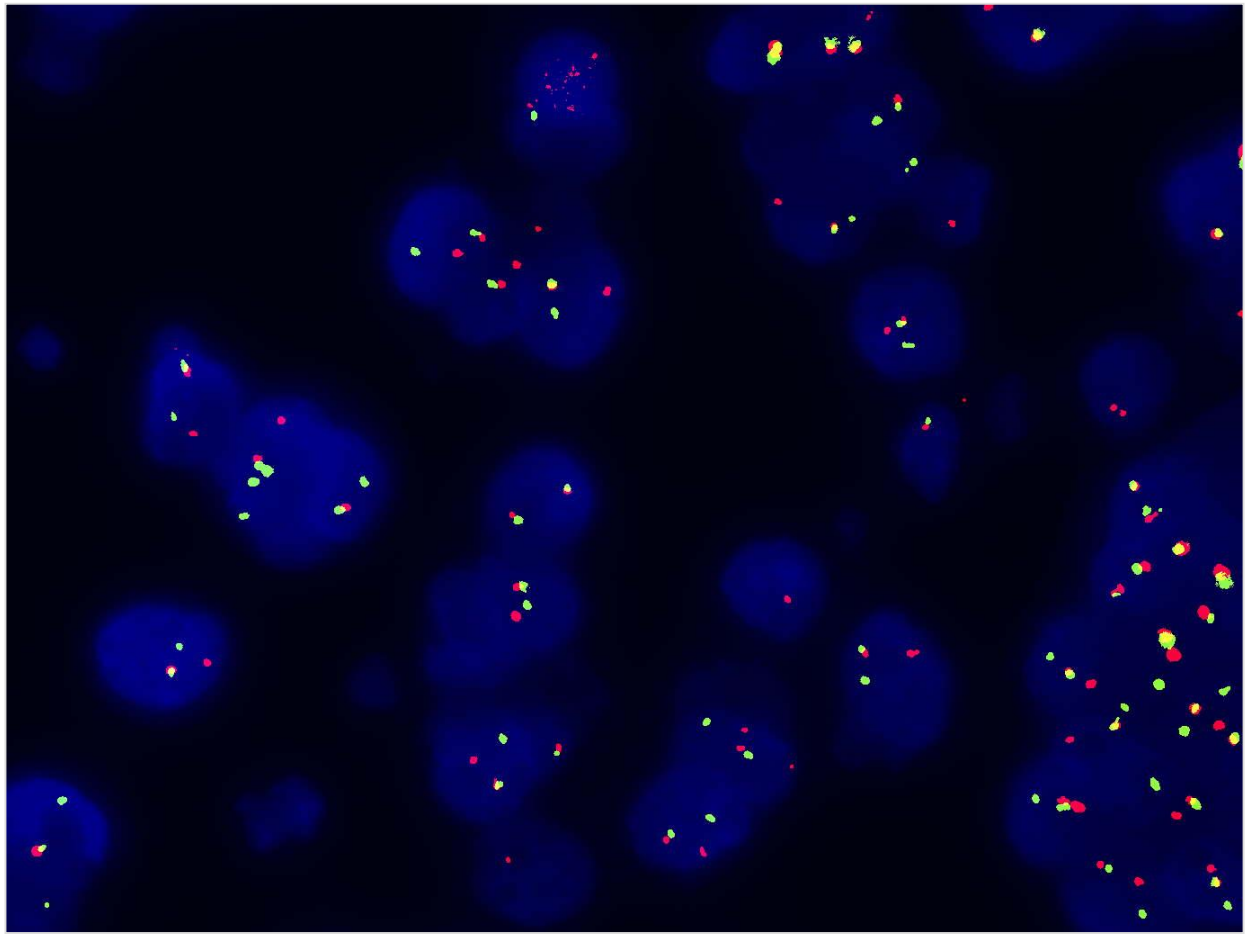
Myxoid liposarcoma

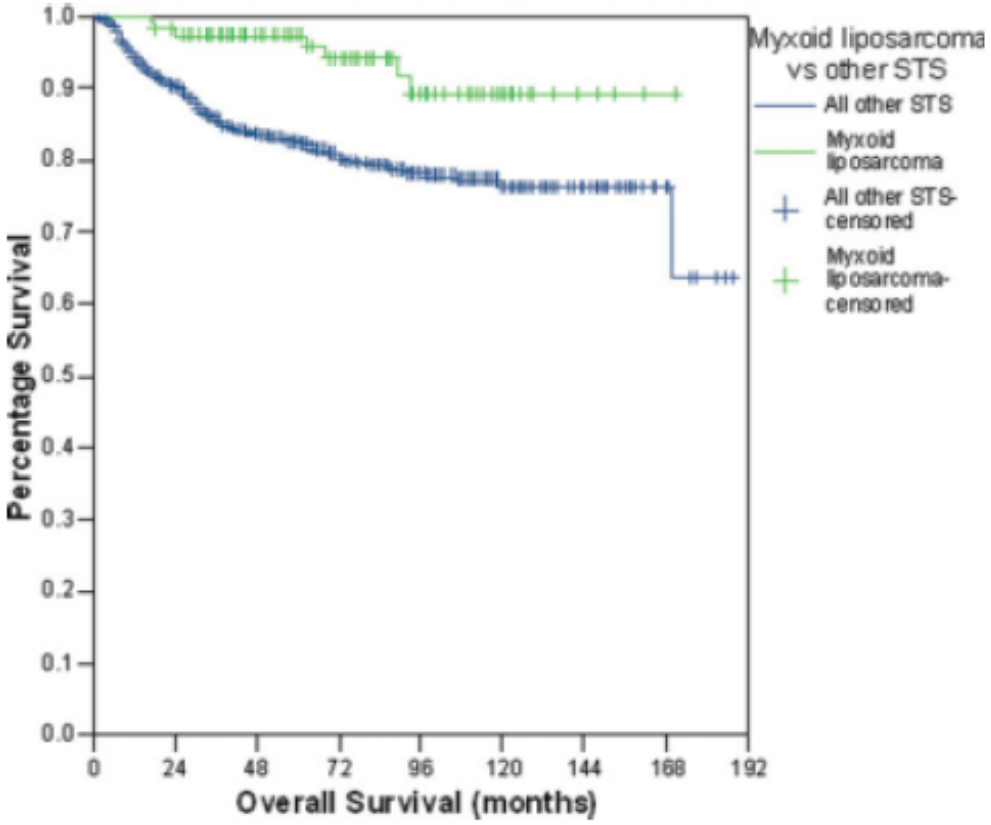


Myxoid/round cell liposarcoma

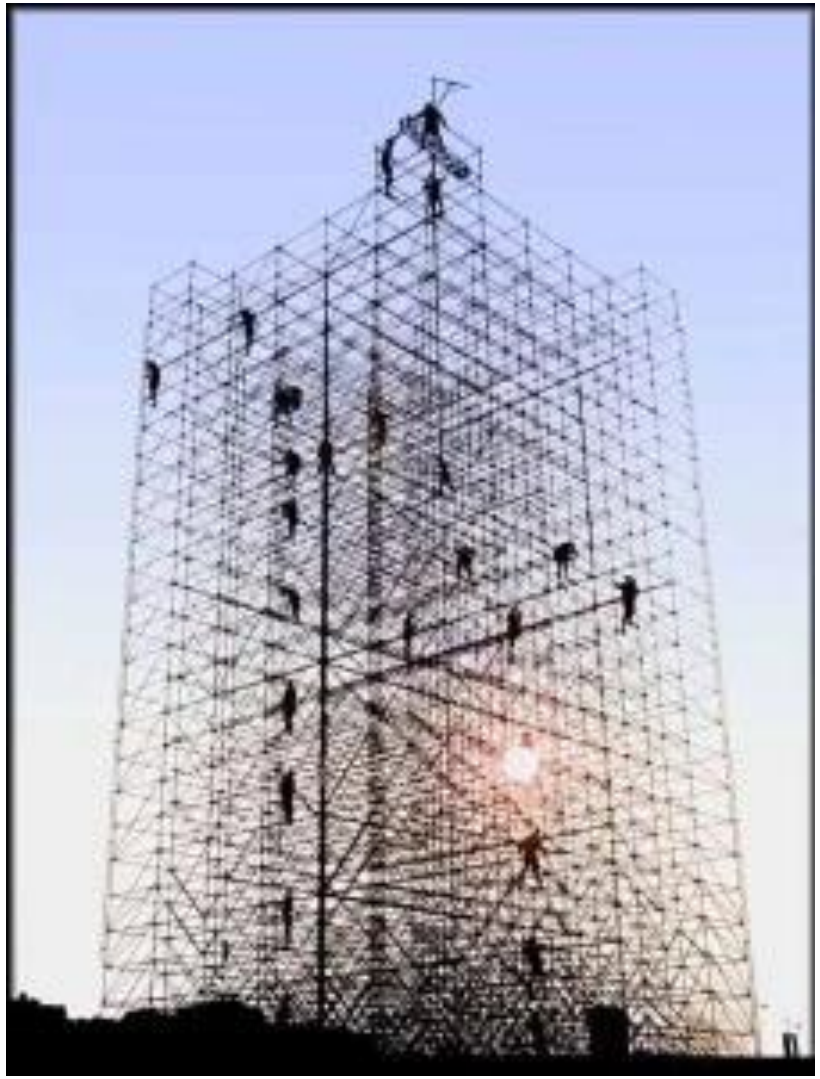
Break apart FISH – *DDIT3*

EWSR1-DDIT3 / FUS-DDIT3





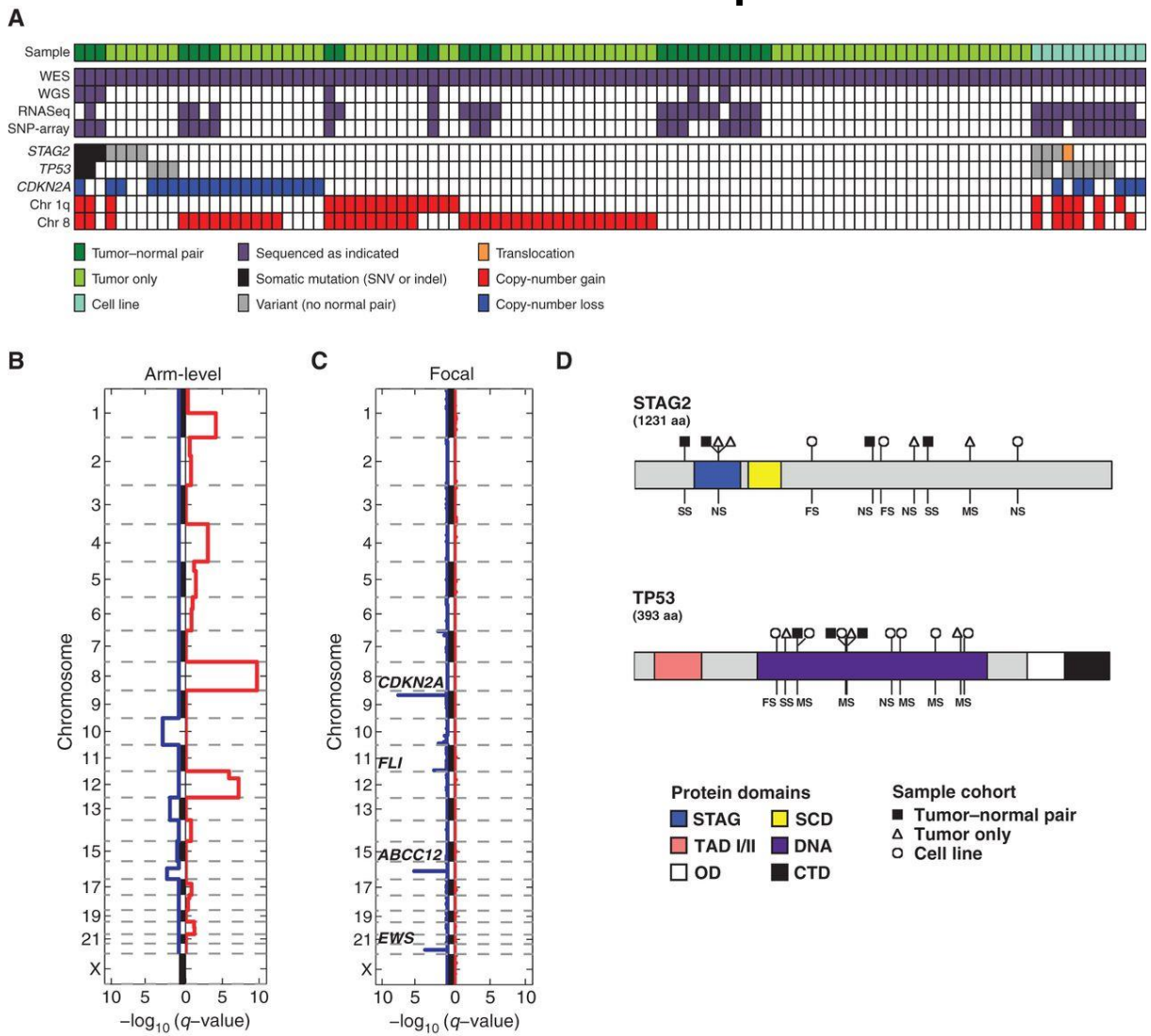
International Cancer Genome consortium/ TCGA



- Bone tumours:

1. Chondrosarcoma: *IDH1/IDH2*
2. Giant cell tumours of bone – *H3F3A* (G34W)
3. Chondroblastoma: *H3F3B* (K36M)
4. Osteosarcoma: IGF signalling
5. Chordoma:
6. Ewing's sarcoma – *STAG2*, *TP53*, *CDKN2A*

Genomic landscape of Ewing sarcoma

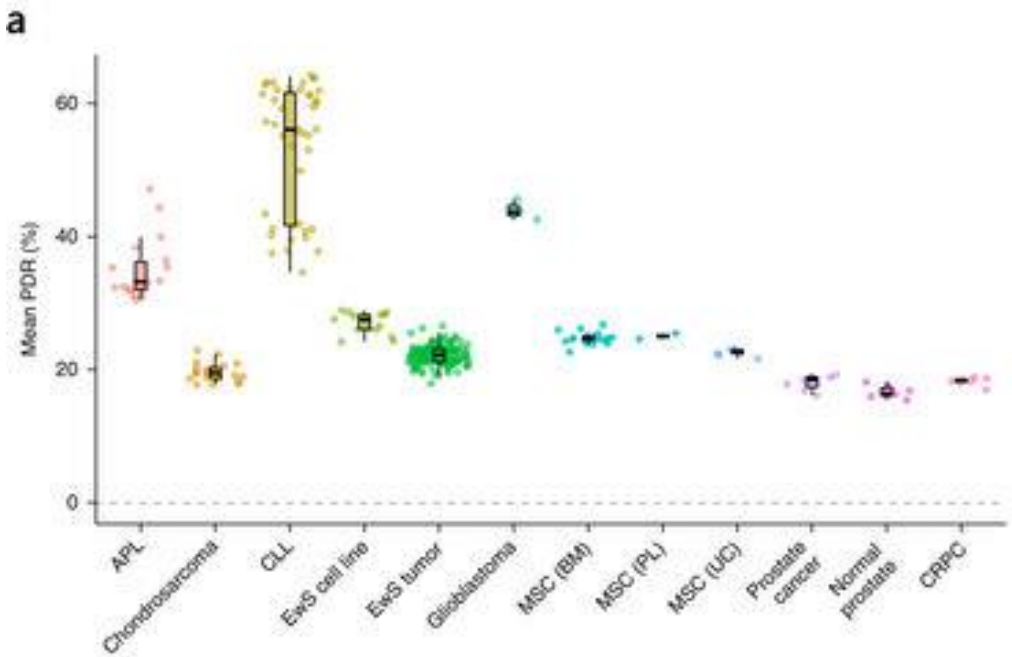


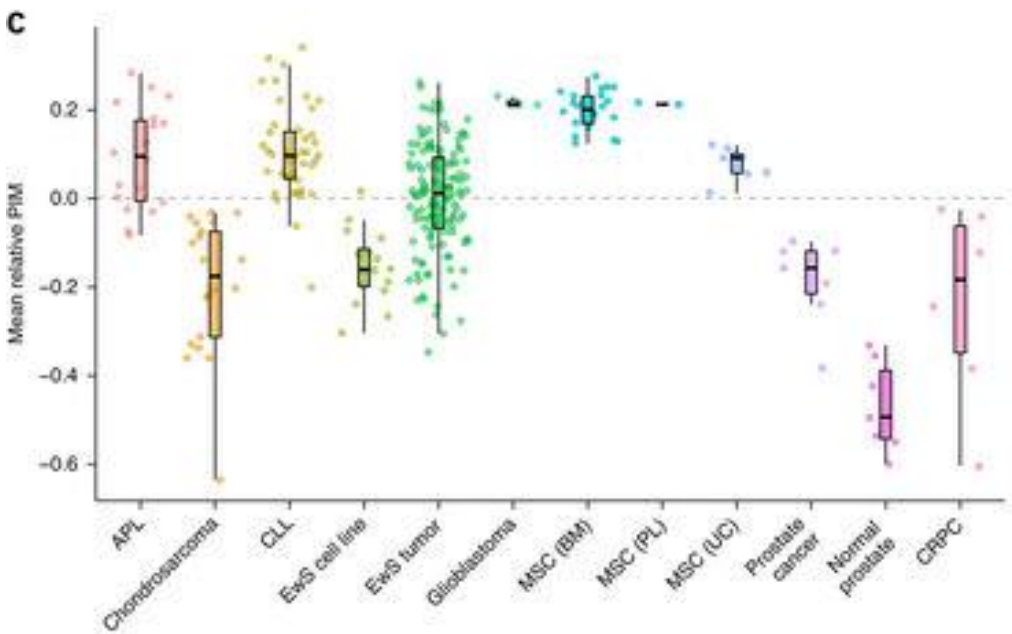
Cancer Discovery
Nov 2014, Vol4,
Issue 1

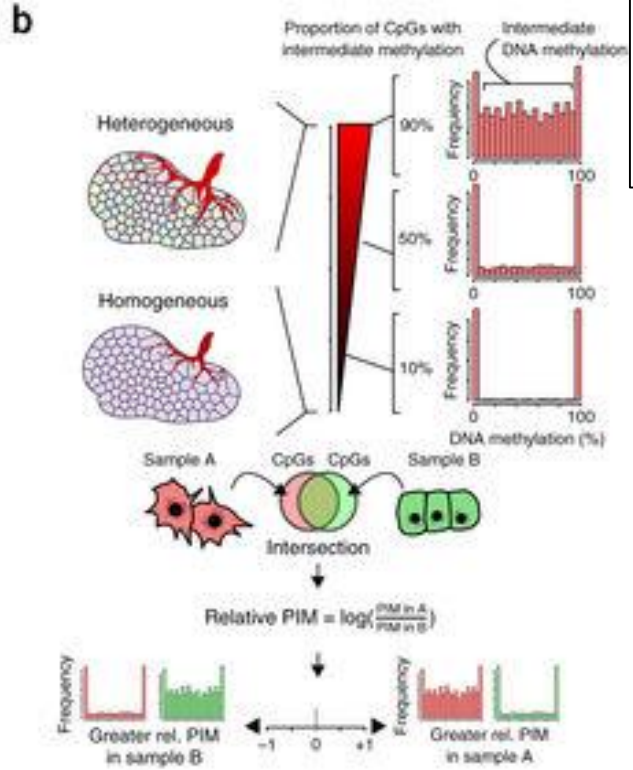
RESOURCE

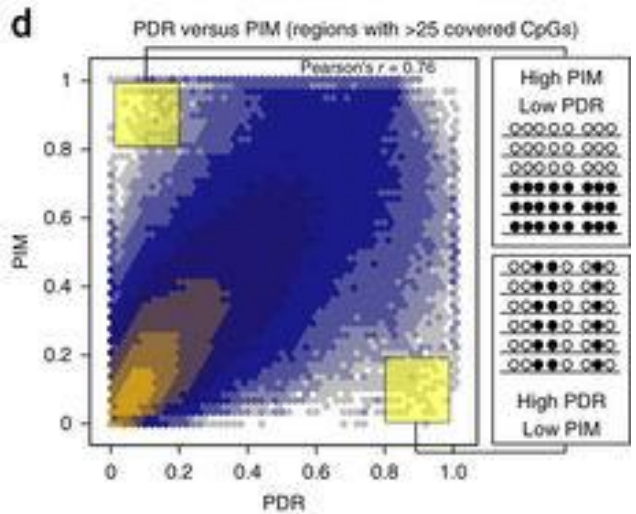
nature medicine

DNA methylation heterogeneity defines a disease spectrum in Ewing sarcoma

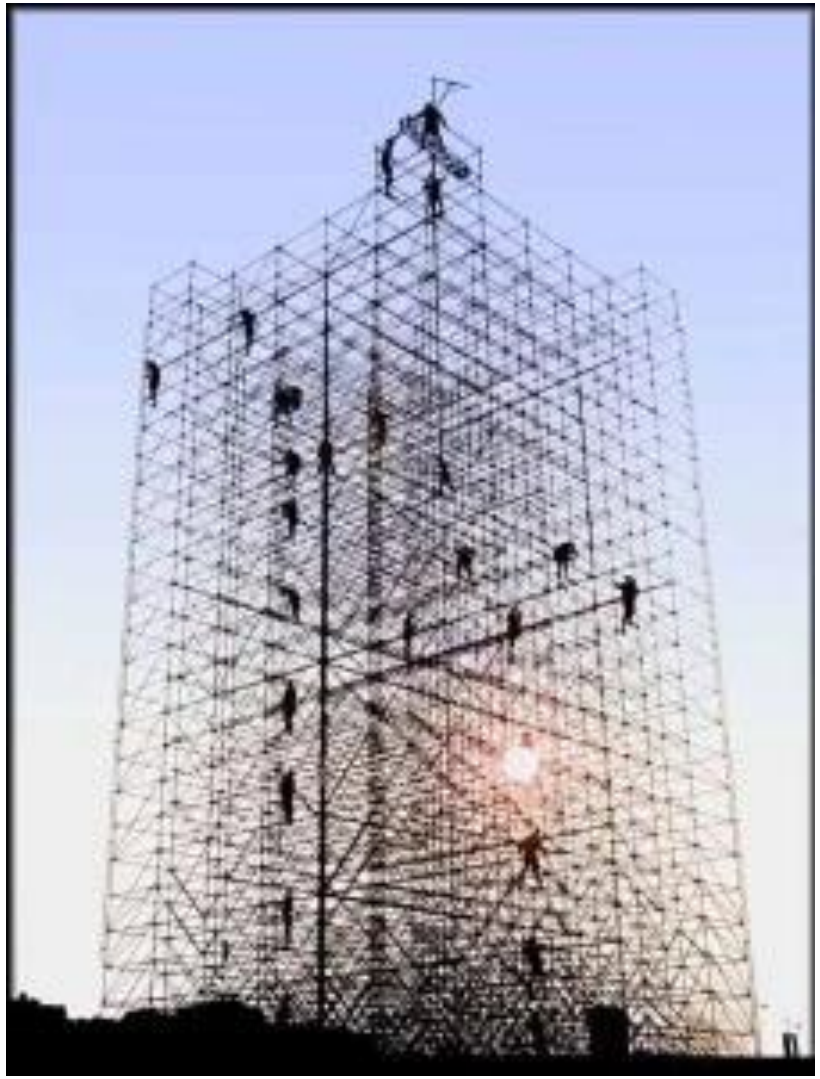








The post TCGA, ICGC era



Output from genome sequencing studies

- Biological processes implicated in cancer development.
- Tumour heterogeneity.
- Evolution of metastasis.
- Mutational processes involved in carcinogenesis.
- Identification of drug targets.
- Outcome and response to therapy.
- Identification of new cancer genes.

Dramatic increase in our understanding of genomic events that characterise cancer but…

1) Clinical implementation of this knowledge to inform decision making is a major challenge.

1) Do not fully understand the interaction between molecular therapeutic agents and the genetic mutations they target…

Recurrent BRAF Gene Fusions in a Subset of Pediatric Spindle Cell Sarcomas: Expanding the Genetic Spectrum of Tumors With Overlapping Features With Infantile Fibrosarcoma.
Kao YC, Fletcher CDM, Alaggio R, Wexler L, Zhang L, Sung YS, Orhan D, Chang WC, Swanson D, Dickson BC, Antonescu CR.
Am J Surg Pathol. 2017 Sep 4. doi: 10.1097/PAS.0000000000000938. [Epub ahead of print]

Recurrent BRAF Gene Rearrangements in Myxoinflammatory Fibroblastic Sarcomas, but Not Hemosiderotic Fibrolipomatous Tumors.
Kao YC, Ranucci V, Zhang L, Sung YS, Athanasian EA, Swanson D, Dickson BC, Antonescu CR.
Am J Surg Pathol. 2017 Jul 7. doi: 10.1097/PAS.0000000000000899. [Epub ahead of print]

Expanding the molecular signature of ossifying fibromyxoid tumors with two novel gene fusions: CREBBP-BCORL1 and KDM2A-WWTR1.
Kao YC, Sung YS, Zhang L, Chen CL, Huang SC, Antonescu CR.
Genes Chromosomes Cancer. 2017 Jan;56(1):42-50. doi: 10.1002/gcc.22400. Epub 2016 Aug 26.

Myopericytomatosis: Clinicopathologic Analysis of 11 Cases With Molecular Identification of Recurrent PDGFRB Alterations in Myopericytomatosis and Myopericytoma.
Hung YP, Fletcher CDM.
Am J Surg Pathol. 2017 Aug;41(8):1034-1044. doi: 10.1097/PAS.0000000000000862.

nature genetics

PRC2 is recurrently inactivated through *EED* or *SUZ12* loss in malignant peripheral nerve sheath tumors

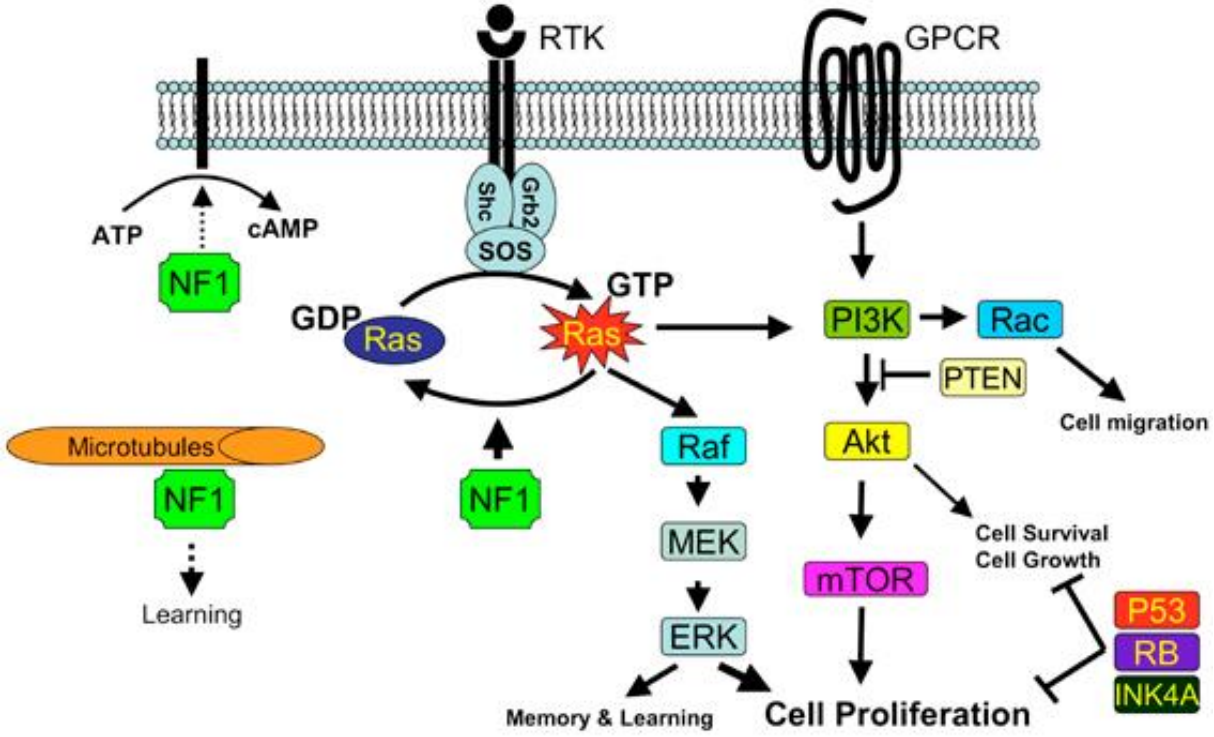
William Lee[1,2,17], Sewit Teckie[2,3,17], Thomas Wiesner[3,17], Leili Ran[3,17], Carlos N Prieto Granada[4], Mingyan Lin[5], Sinan Zhu[3], Zhen Cao[3], Yupu Liang[3], Andrea Sboner[6–8], William D Tap[9,10], Jonathan A Fletcher[11], Kety H Huberman[12], Li-Xuan Qin[13], Agnes Viale[12], Samuel Singer[14], Deyou Zheng[5,15,16], Michael F Berger[3,4], Yu Chen[3,9,10], Cristina R Antonescu[4] & Ping Chi[3,9,10]

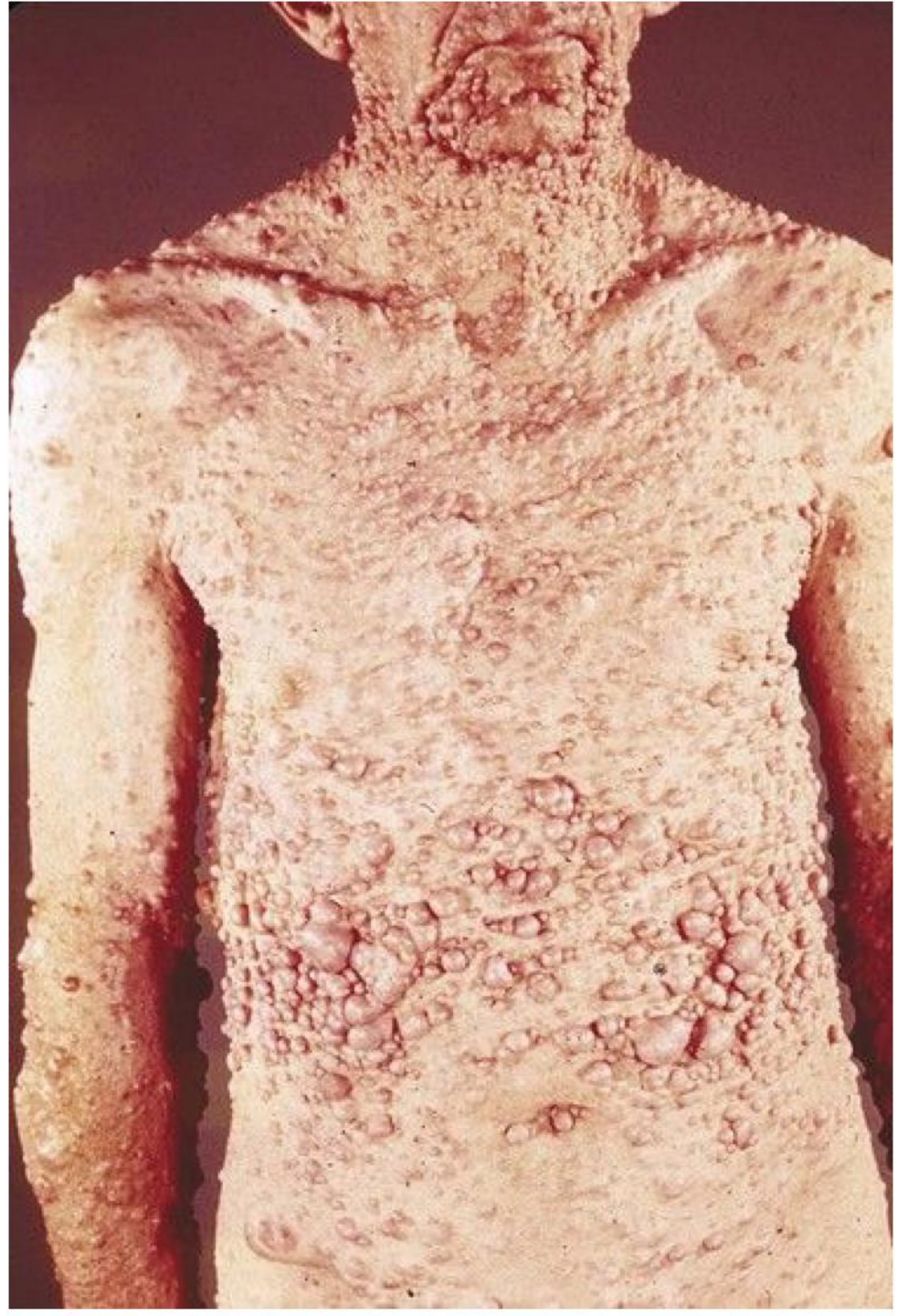
Somatic mutations of *SUZ12* in malignant peripheral nerve sheath tumors

Ming Zhang[1,2], Yuxuan Wang[1,2], Sian Jones[3], Mark Sausen[3], Kevin McMahon[1,2], Rajni Sharma[4], Qing Wang[1,2], Allan J Belzberg[5], Kaisorn Chaichana[5], Gary L Gallia[5], Ziya L Gokaslan[5], Greg J Riggins[5], Jean-Paul Wolinksy[5], Laura D Wood[4], Elizabeth A Montgomery[4], Ralph H Hruban[4], Kenneth W Kinzler[1,2], Nickolas Papadopoulos[1,2], Bert Vogelstein[1,2] & Chetan Bettegowda[1,2,5]

Neurofibromatosis Type I

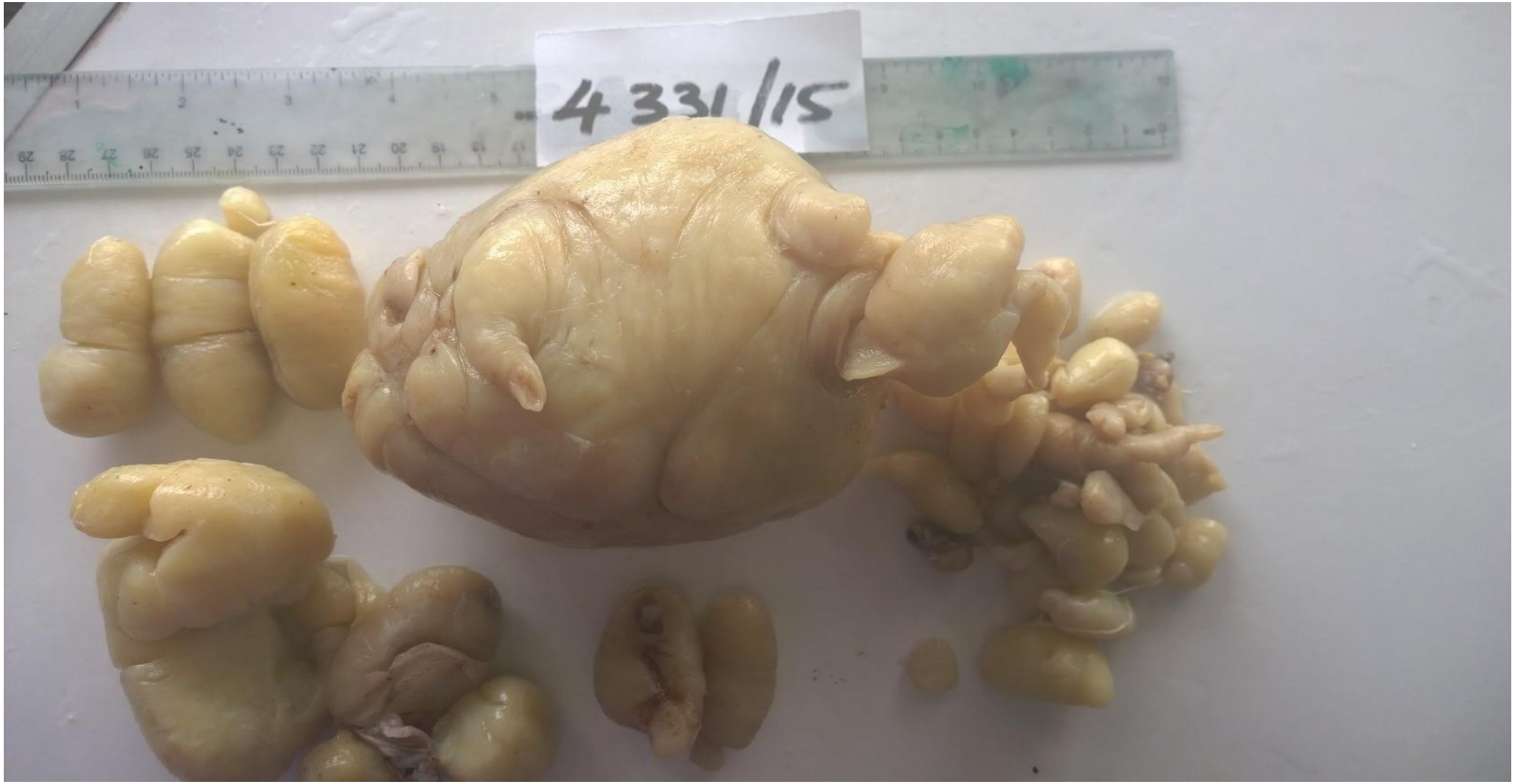
- Common genetic disease.
- 1 in 3500 people. AD with high penetrance.
- NF1 – deletions, insertions, splice site mutations, mis-sense, non-sense mutations

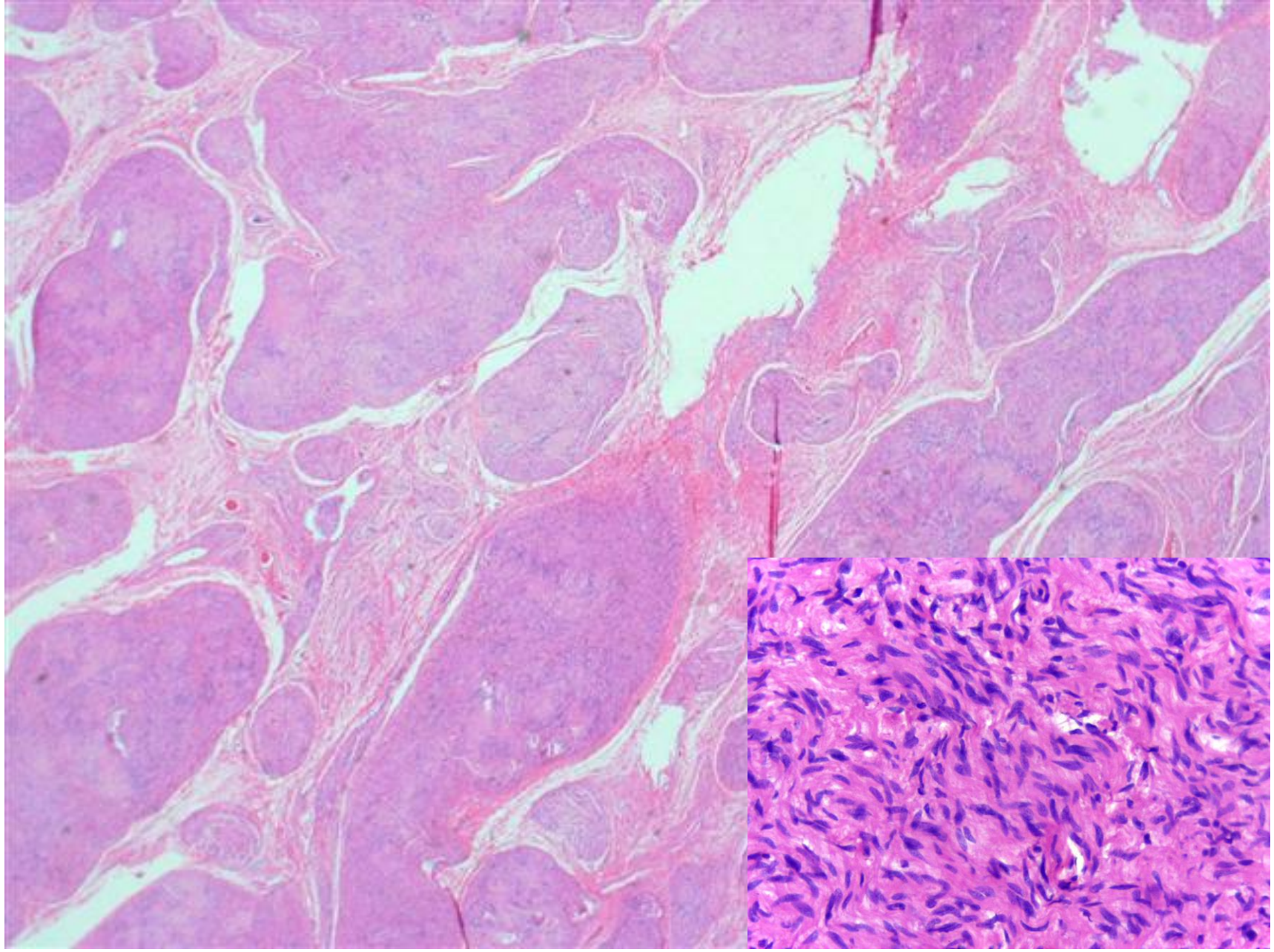




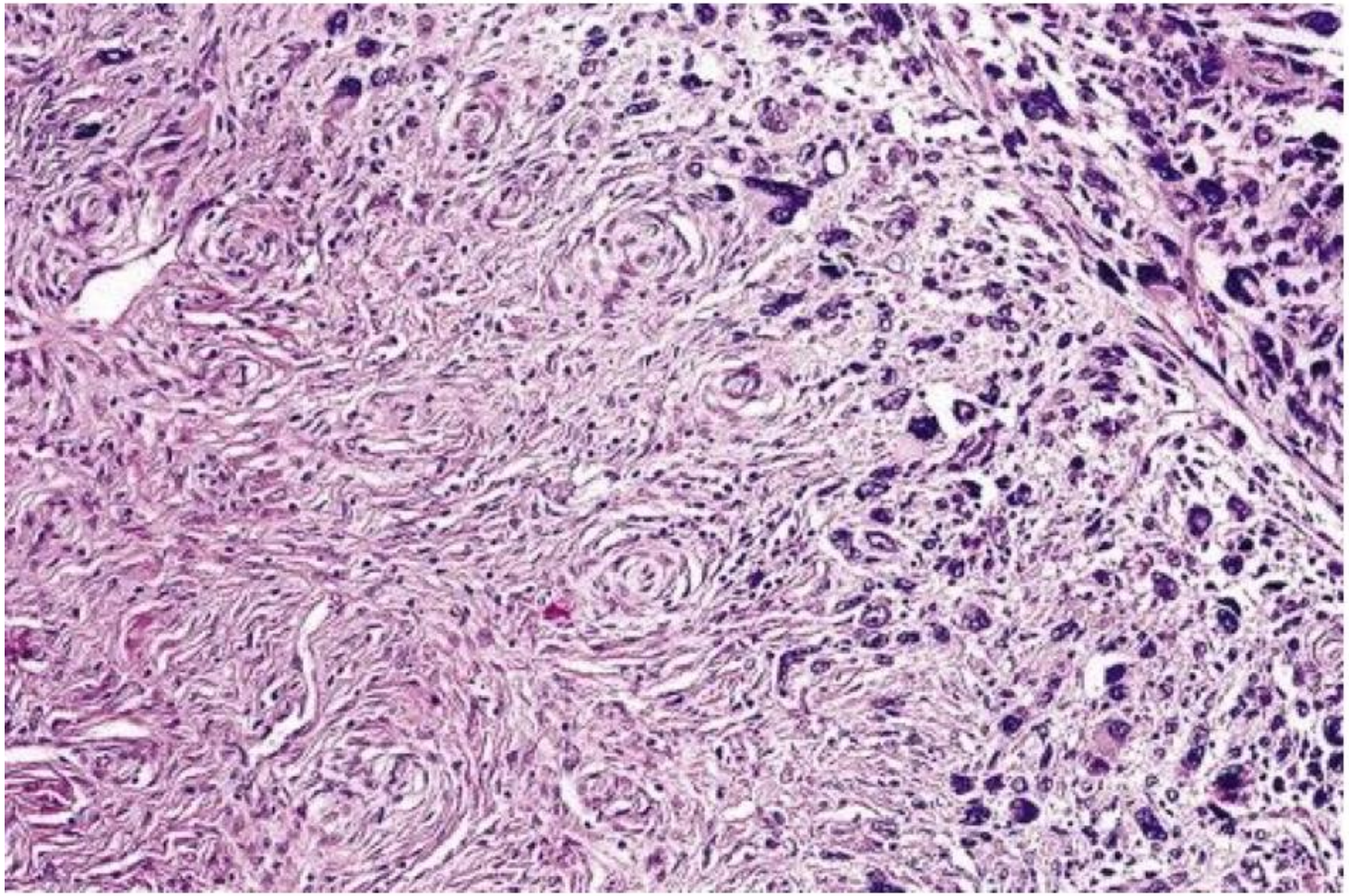
Enzinger and Weiss's Soft Tissue Tumors, 6th Edition

PLEXIFORM NEUROFIBROMA

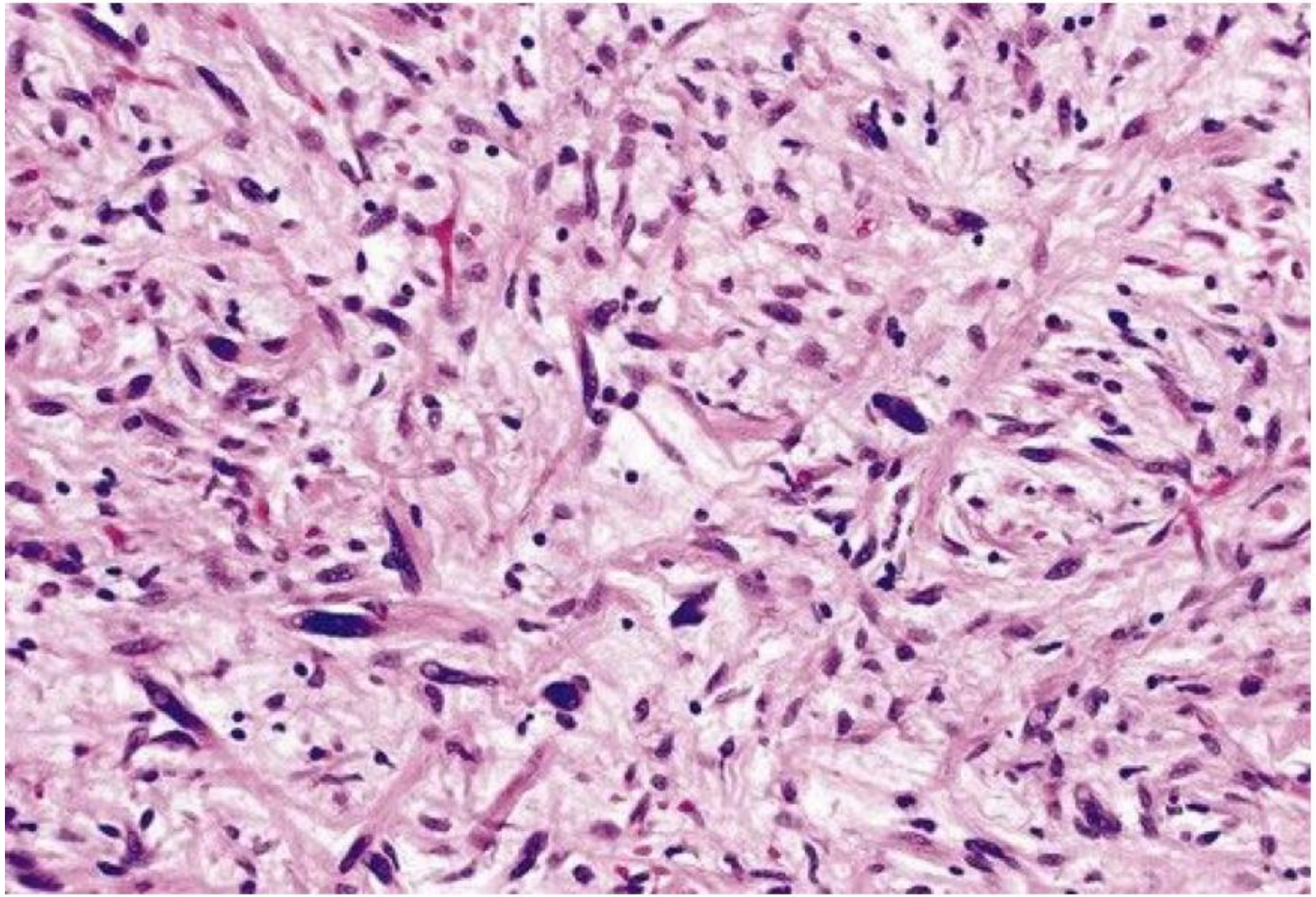




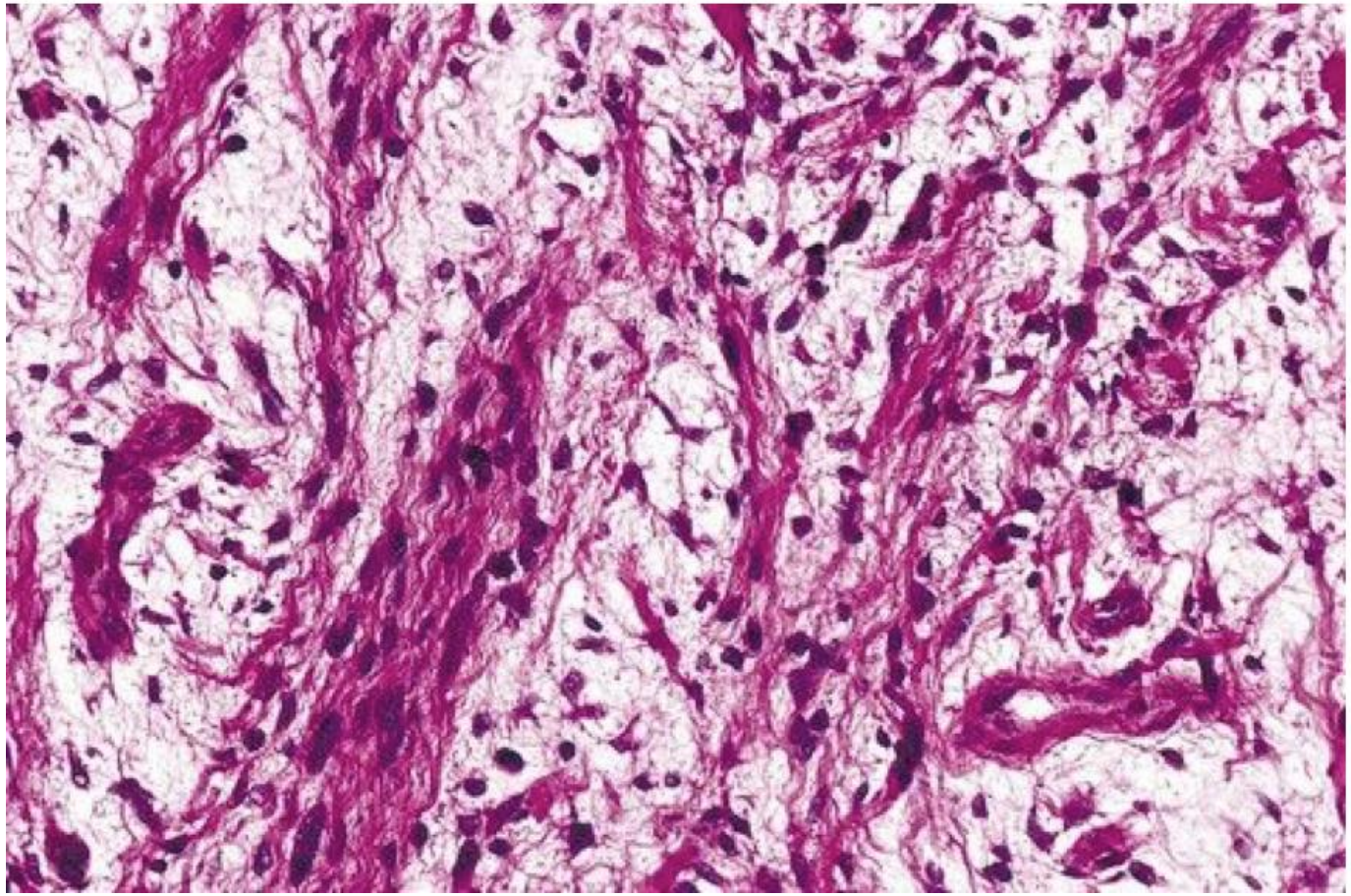
- Distinction between a neurofibroma with atypical features and MPNST Grade 1 is one of the most difficult – histological continuum.



“Atypical” neurofibroma

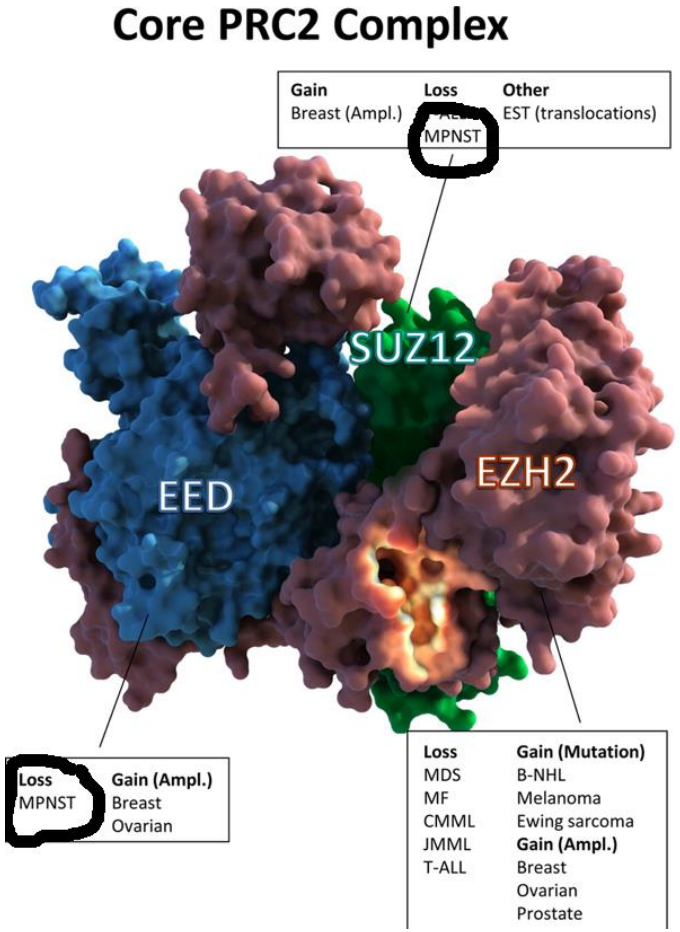


Low grade MPNST



Enzinger and Weiss's Soft Tissue Tumors, 6th Edition

MPNST have mutations in the PRC2 complex



- H3K27me3
- Transcriptional repression
-

Published in: Cigall Kadoch; Robert A. Copeland; Heike Keilhack; *Biochemistry* **2016,** 55, 1600-1614.
DOI: 10.1021/acs.biochem.5b01191

Loss of H3K27me3 Expression Is a Highly Sensitive Marker for Sporadic and Radiation-induced MPNST

Carlos N. Prieto-Granada, MD,† Thomas Wiesner, PhD,‡ Jane L. Messina, MD,† Achim A. Jungbluth, MD,* Ping Chi, MD, PhD,‡§‖ and Cristina R. Antonescu, MD**

Am J Surg Pathol • Volume 40, Number 4, April 2016

TABLE 2. H3K27me3 Monoclonal Antibody IHC Results of the Different Entities Included in the MPNST Differential Diagnosis and Miscellaneous Tumors

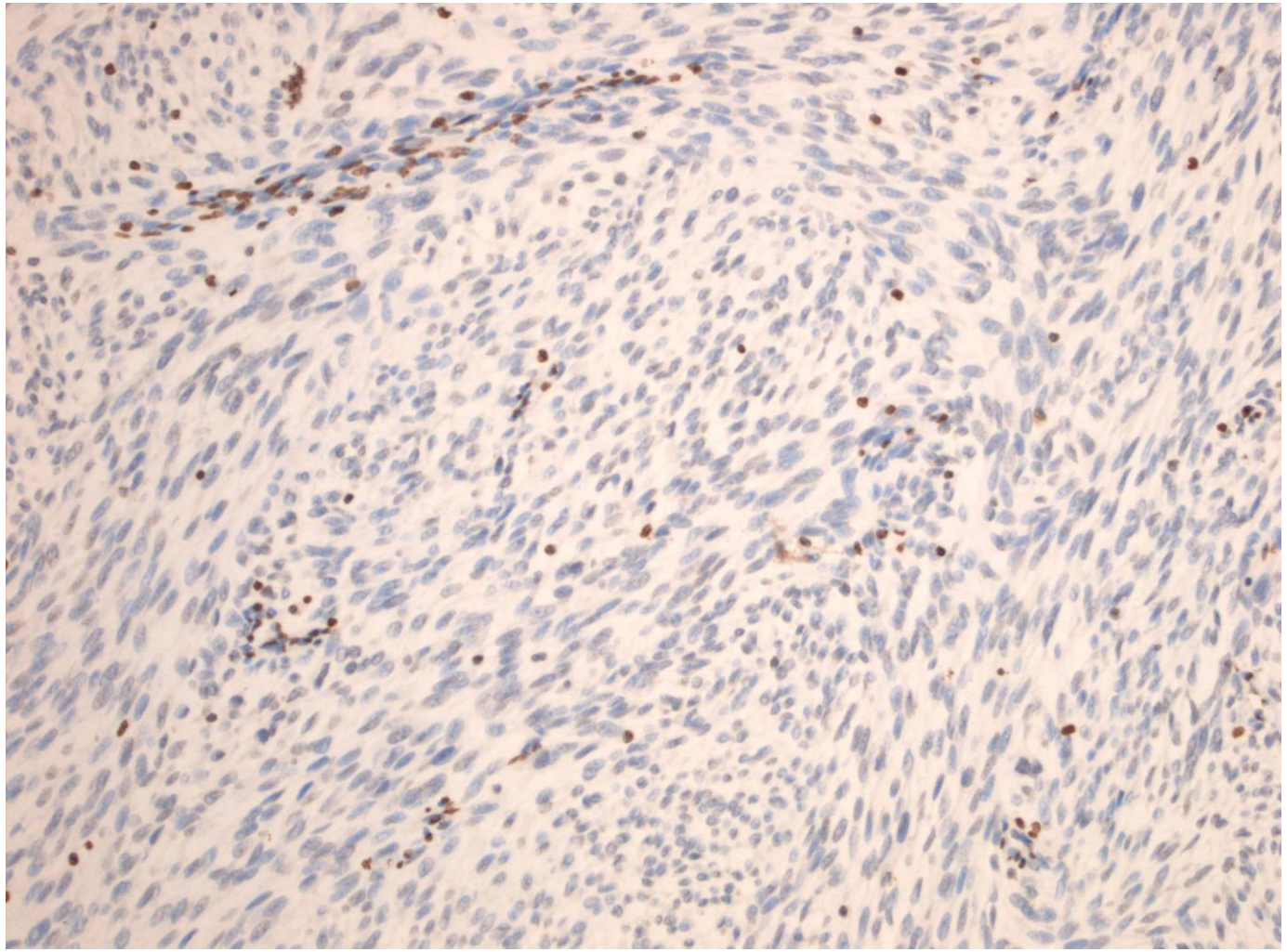
Diagnosis	H3K27me3 IHC Loss/Total Cases
Cutaneous melanoma	
Pure desmoplastic melanoma	0/37
Mixed desmoplastic melanoma	0/11
Spindle cell melanoma	0/5
Synovial sarcoma (MF, BF, and PD)	0/113
GIST	
KIT/*PDGFRA* mutant	0/109
SDHB-deficient WT pediatric and adult	0/13
WT dedifferentiated GIST	0/1
Liposarcoma	
Well differentiated	0/31
Dedifferentiated	0/44
Ossifying fibromyxoid tumor	0/6
Soft tissue myoepithelial carcinomas	0/6
MFS	0/63

In the case of GIST, *KIT* and *PDGFRA* were WT.
BF indicates biphasic; MF, monophasic; PD, poorly differentiated.

H3K27Me3 loss in >90% of MPNST

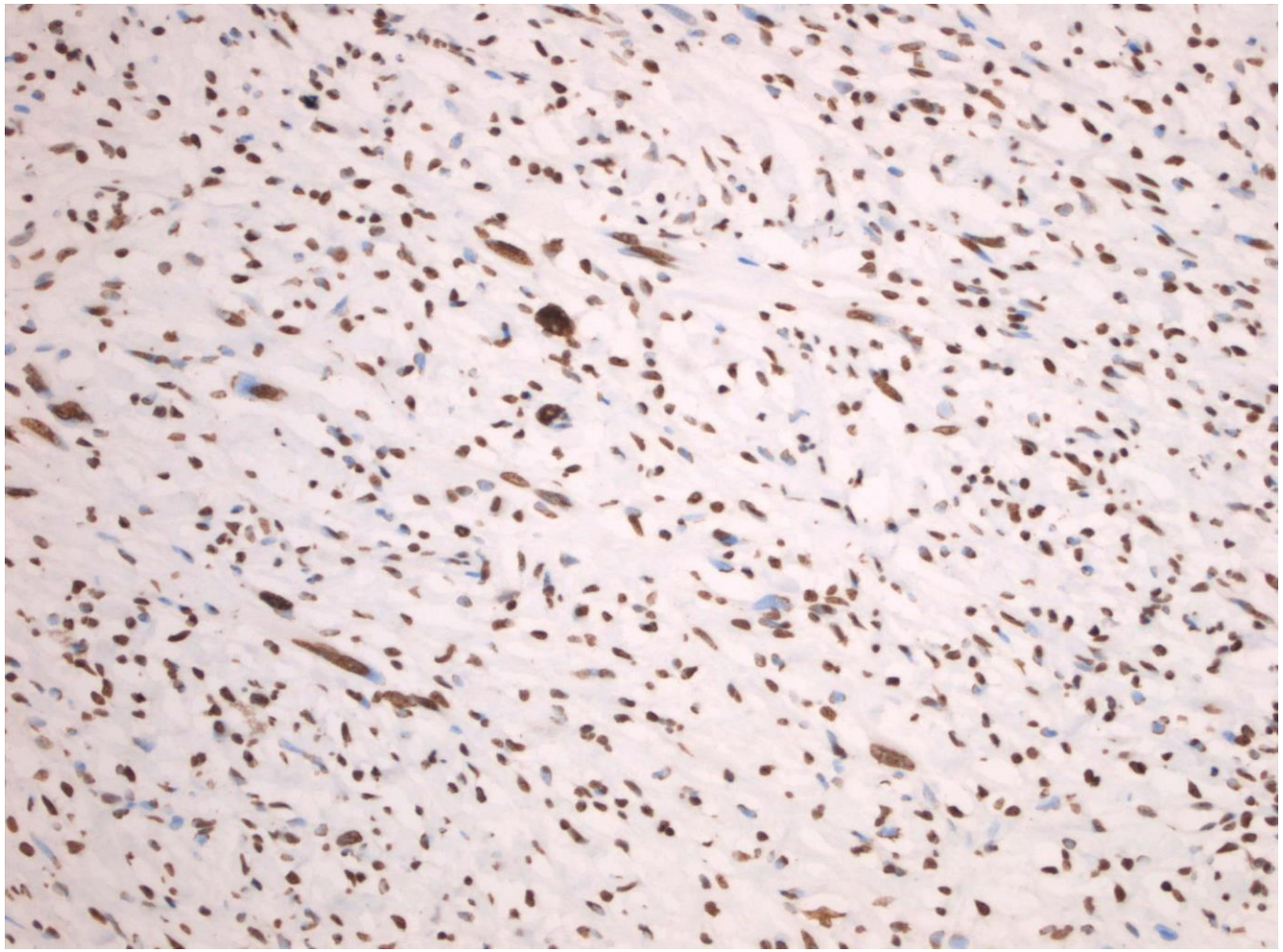
MPNST Grade 3

H3K27me3 - immunohistochemistry



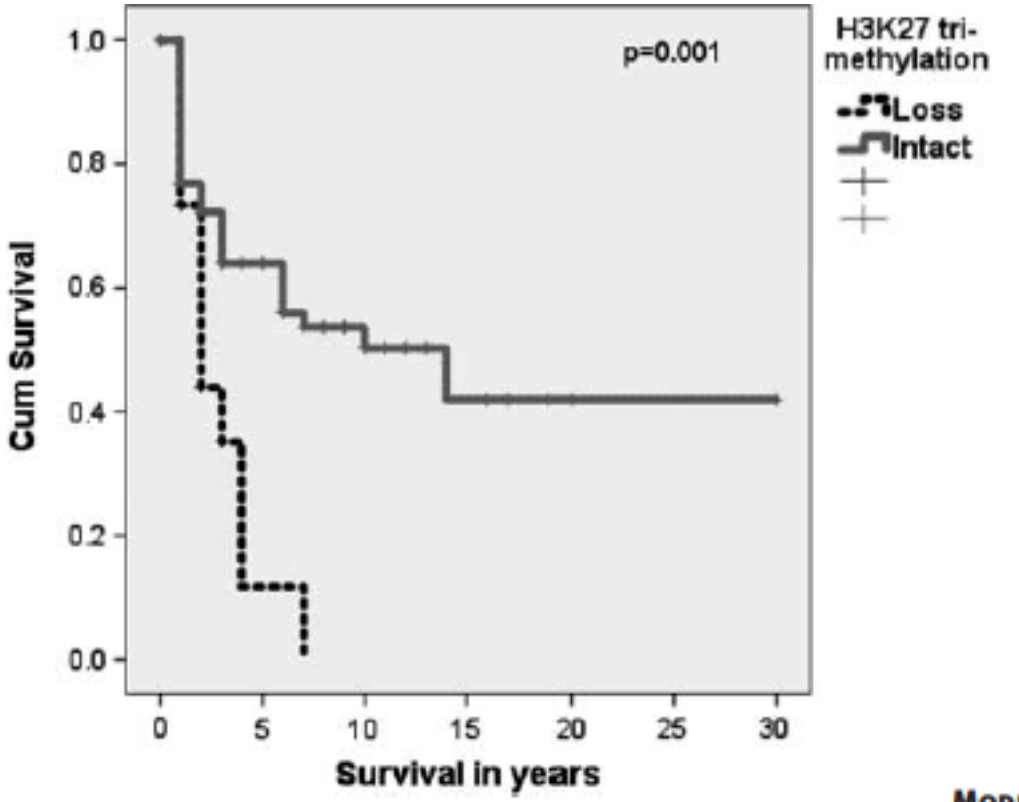
Atypical Neurofibroma

H3K27me3 - immunohistochemistry



H3K27me3

- Prognostic utility



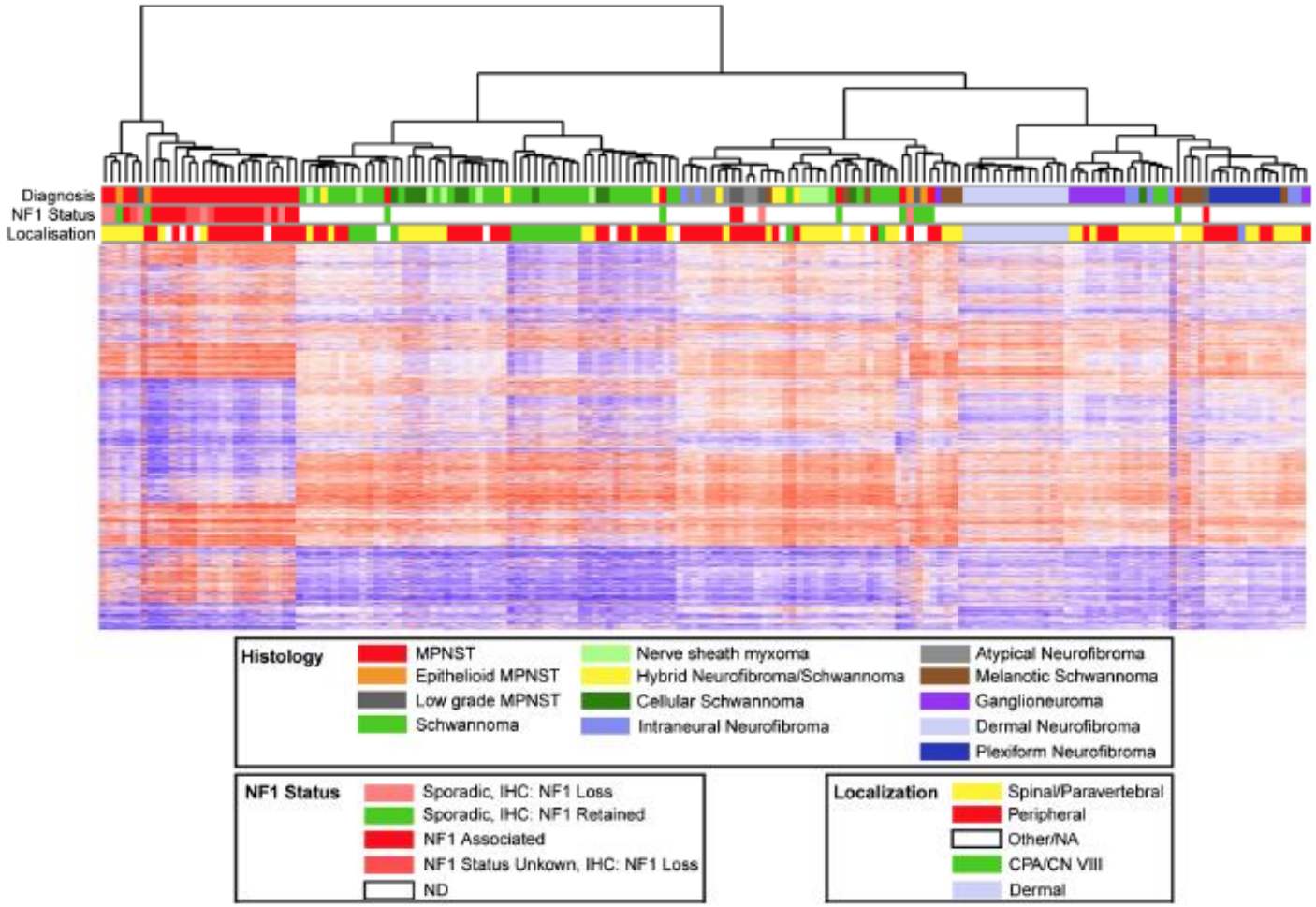
MODERN PATHOLOGY (2016) 29, 582–590

Acta Neuropathol (2016) 131:877–887
DOI 10.1007/s00401-016-1540-6

ORIGINAL PAPER

Methylation-based classification of benign and malignant peripheral nerve sheath tumors

Manuel Röhrich[1,2] · Christian Koelsche[1,2] · Daniel Schrimpf[1,2] · David Capper[1,2] · Felix Sahm[1,2] · Annekathrin Kratz[1,2] · Jana Reuss[2] · Volker Hovestadt[3] · David T. W. Jones[4] · Melanie Bewerunge-Hudler[5] · Albert Becker[6] · Joachim Weis[7] · Christian Mawrin[8] · Michel Mittelbronn[9,10] · Arie Perry[11] · Victor-Felix Mautner[12] · Gunhild Mechtersheimer[13] · Christian Hartmann[14] · Ali Fuat Okuducu[15] · Mirko Arp[16] · Marcel Seiz-Rosenhagen[16] · Daniel Hänggi[16] · Stefanie Heim[17] · Werner Paulus[17] · Jens Schittenhelm[18] · Rezvan Ahmadi[19] · Christel Herold-Mende[19] · Andreas Unterberg[19] · Stefan M. Pfister[4,20] · Andreas von Deimling[1,2] · David E. Reuss[1,2]



MPNST

Machine learning and diagnostics

Train / Test Split		
Sarcoma Types	Train	Test
Synovial Sarcoma	7	3
Undifferentiated Sarcoma	35	15
Dedifferentiated Liposarcoma	44	19
Leiomyosarcoma(lms)	72	31
MPNST	6	3
Myxifibrosarcoma	15	7
Total	179	78

4.6 Summary of Classifier performances

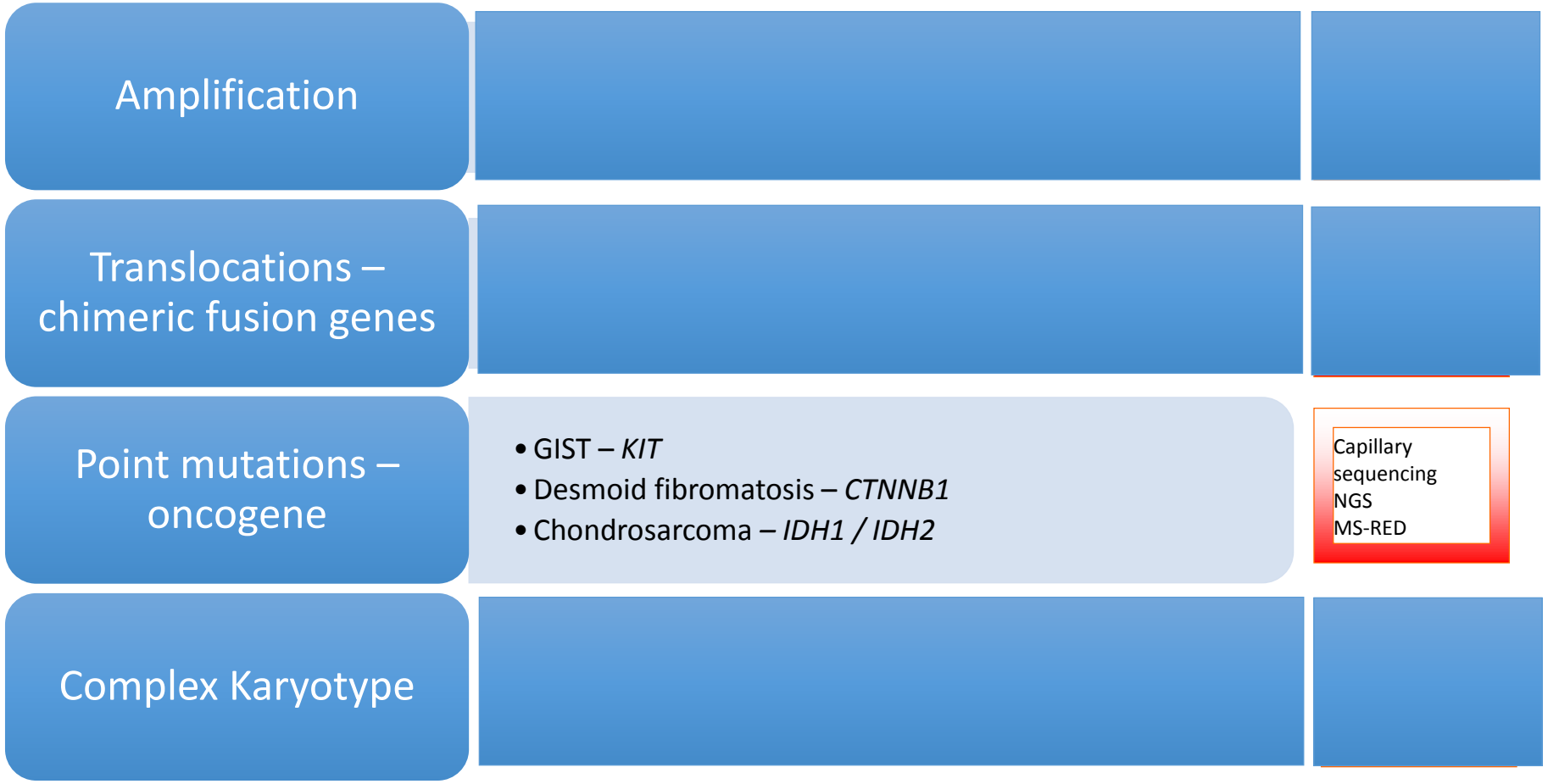
Type of Feature Reduction	Principal Component Feature Extraction	HighVariance Feature Selection	Chi Square	Chi Square	High Dimensional Data			MeDeCom		
Type of Classifier	Logistic Regression	Logistic Regression	Logistic Regression	Support Vector Classifier	Support Vector Classifier	XGBoost	Random Forest	Support Vector Classifier	XGBoost	Random Forest
Classifier Performance Comparison	61.5	66.66	70.51	74.35	71.79	71.79	69.23	72.5	72.5	77.5

Figure 4.14: Summary of classification performance

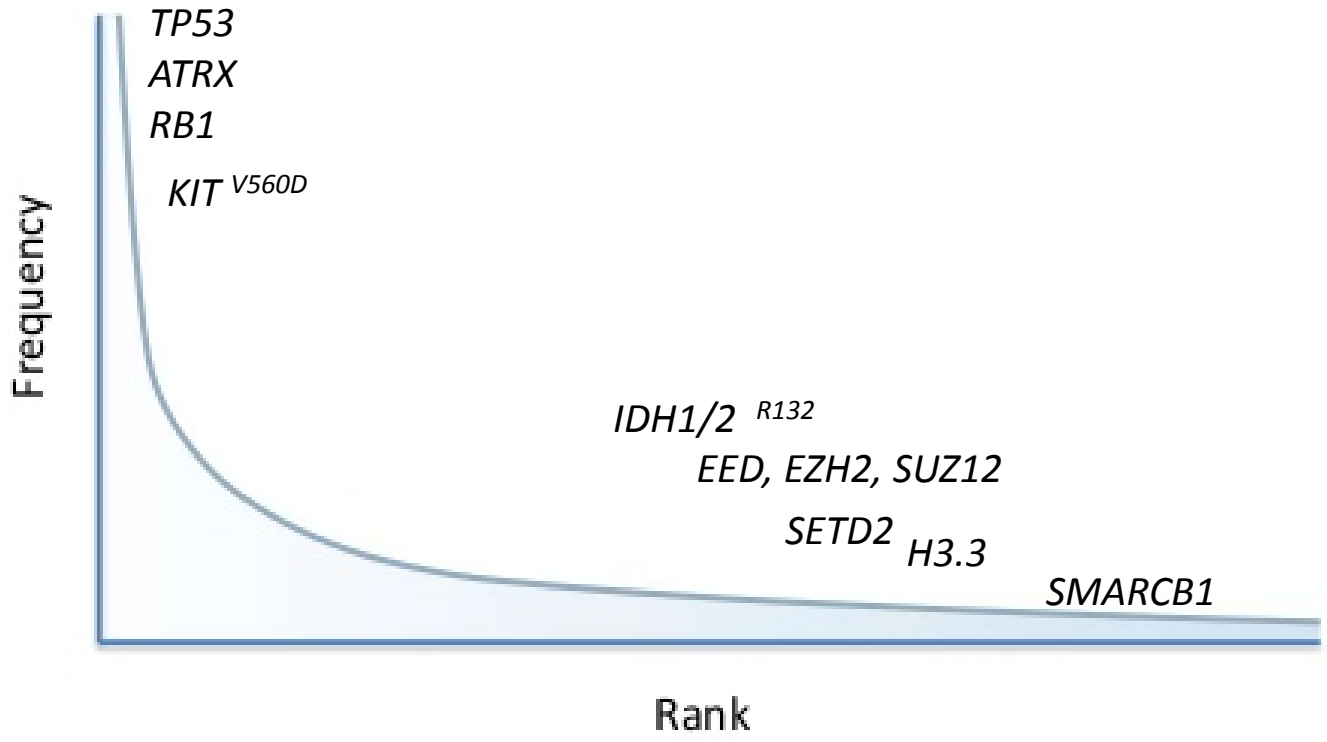
UCL MSc study – computer science

Manmohan Nair
Chris Steele

Molecular classification of mesenchymal tumours



Sarcoma hotspot mutations



Long tail distribution of cancer hotspots

Applications of molecular techniques

- Lipomatous tumours – ALT, Myxoid liposarcoma
- Small round blue cell tumours – Ewing sarcoma
- MPNST

- FISH
- Next generation sequencing
- Methylation profiling

Pathologist's role – beyond single gene mutations

- Era of immuno-oncology – need for biomarkers of response to checkpoint inhibition.
- - PD1/PDL1 expression, CTLA4
- Mutational burden

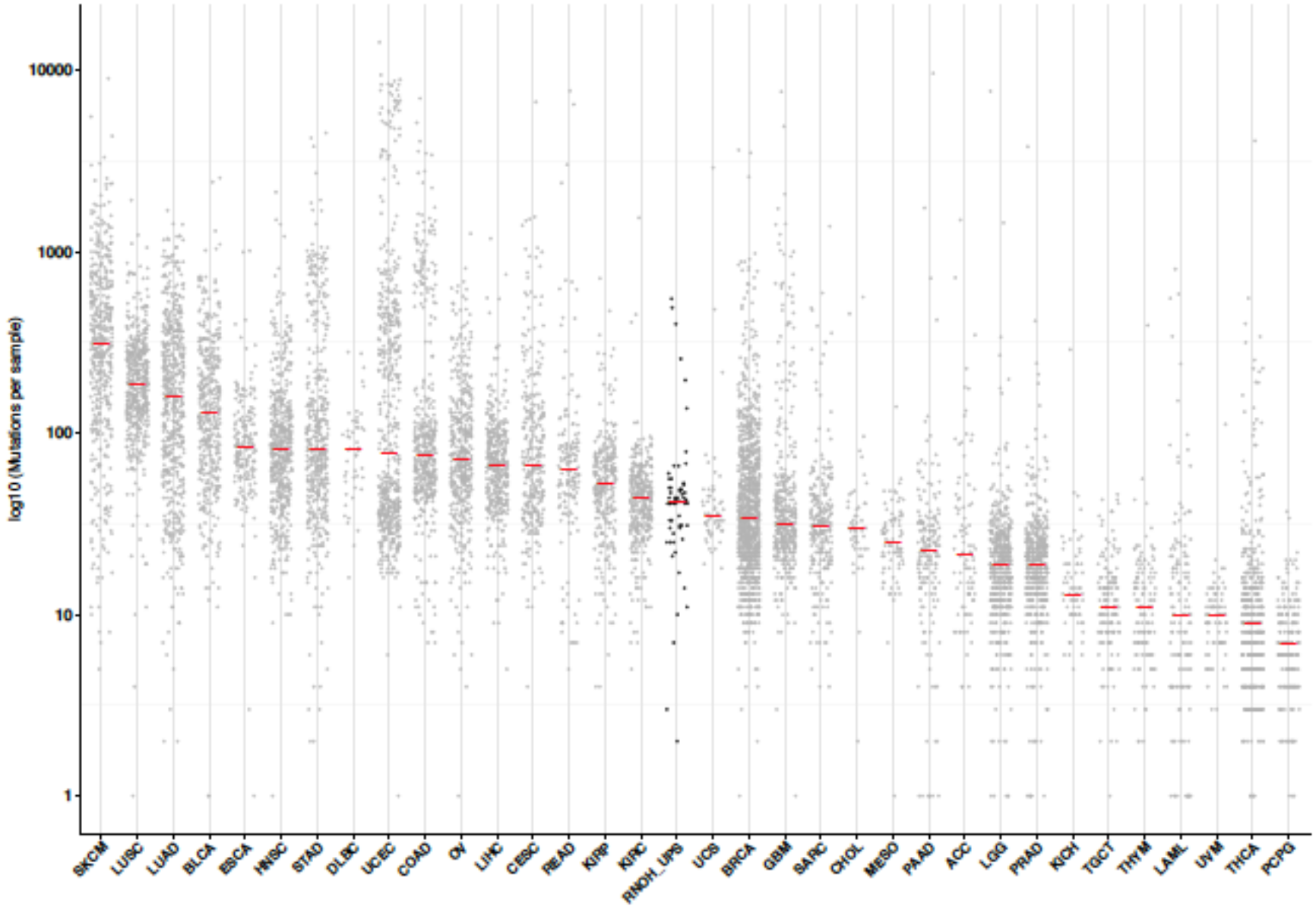
Chalmers et al. Genome Medicine (2017) 9:34
DOI 10.1186/s13073-017-0424-2

Genome Medicine

RESEARCH Open Access

Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden

Mutational burden



Thanks for your attention.