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PEARLS OF LABORATORY MEDICINE

Classification and Genetics of Sarcomas

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Sarcomas

- Heterogeneous tumors of mesenchymal origin
- Two main classes
  - Bone sarcomas
  - Soft-tissue sarcomas
- More than 100 different histopathological subtypes defined
- About 50% of cases are associated with characteristic somatic molecular abnormalities, often gene fusions
- Many are associated with germline predisposition syndromes

Bone Sarcomas

- < 0.2% of human cancers
- ~3,000 cases a year; ~1,500 deaths a year
- Most often occur in children, adolescents and young adults
- Most common subtypes
  - Osteosarcoma (35%)
  - Chondrosarcoma (30%)
  - Ewing sarcoma (16%)
    - Associated with *EWS-FLI1* gene fusions

Soft-Tissue Sarcomas

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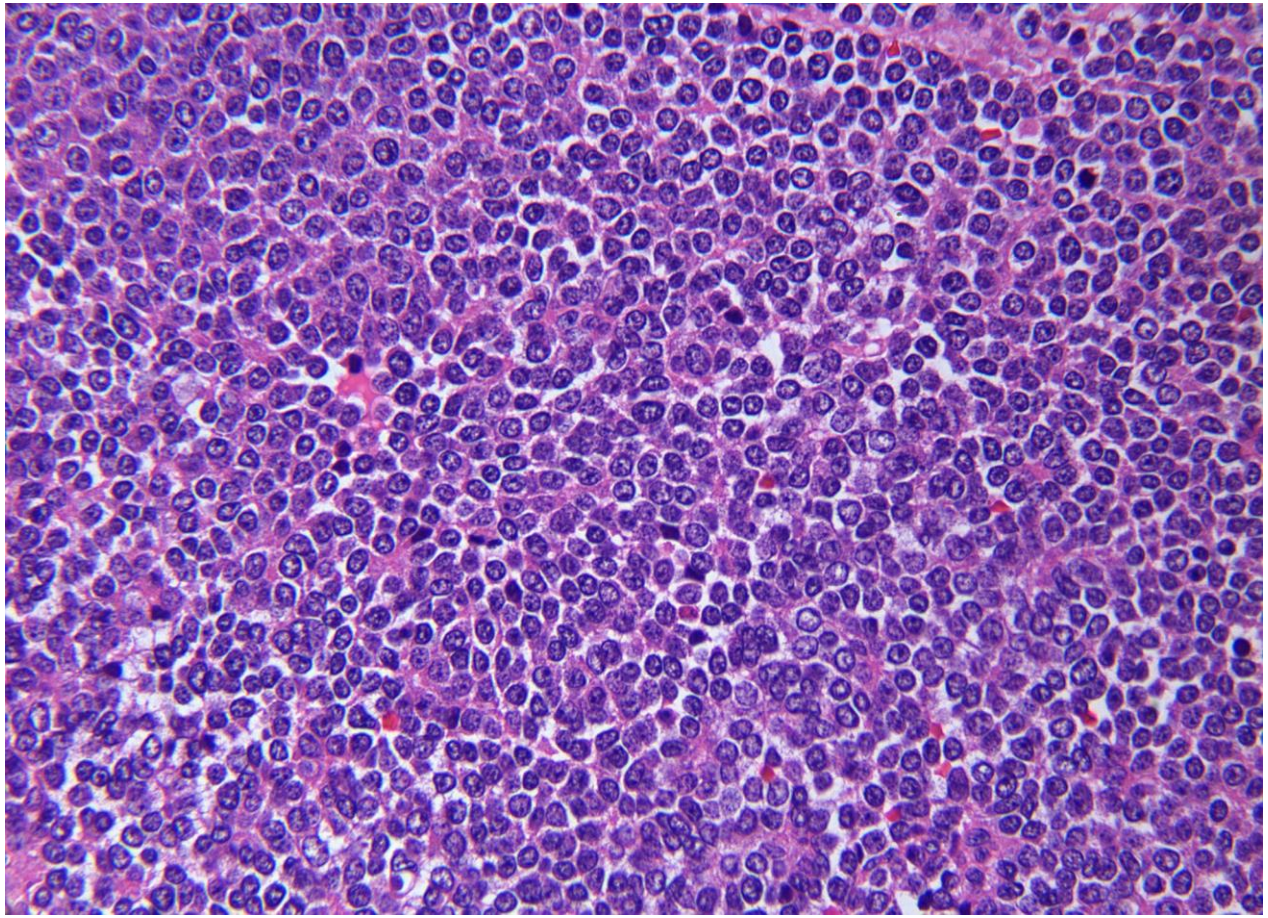
- <1% of human cancers
- ~12,000 cases a year; ~4,500 deaths a year
- ~45% of over 100 subtypes are associated with a recurrent molecular or cytogenetic abnormality
- Different types can occur in different age groups
- Some subtypes with the associated abnormality:
  - Desmoplastic small round cell tumors (*EWSR1-WT1* fusions)
  - Mixoid liposarcoma (gene fusions involving *DDIT3*)
  - Infantile fibrosarcoma (gene fusions involving *NTRK*)
  - Alveolar rhabdomyosarcoma (gene fusions involving *PAX* and/or *FOXO*)
  - Clear cell sarcoma (gene fusions involving *EWSR*)
  - Epithelioid sarcoma (fusions involving *SMARCB1*)

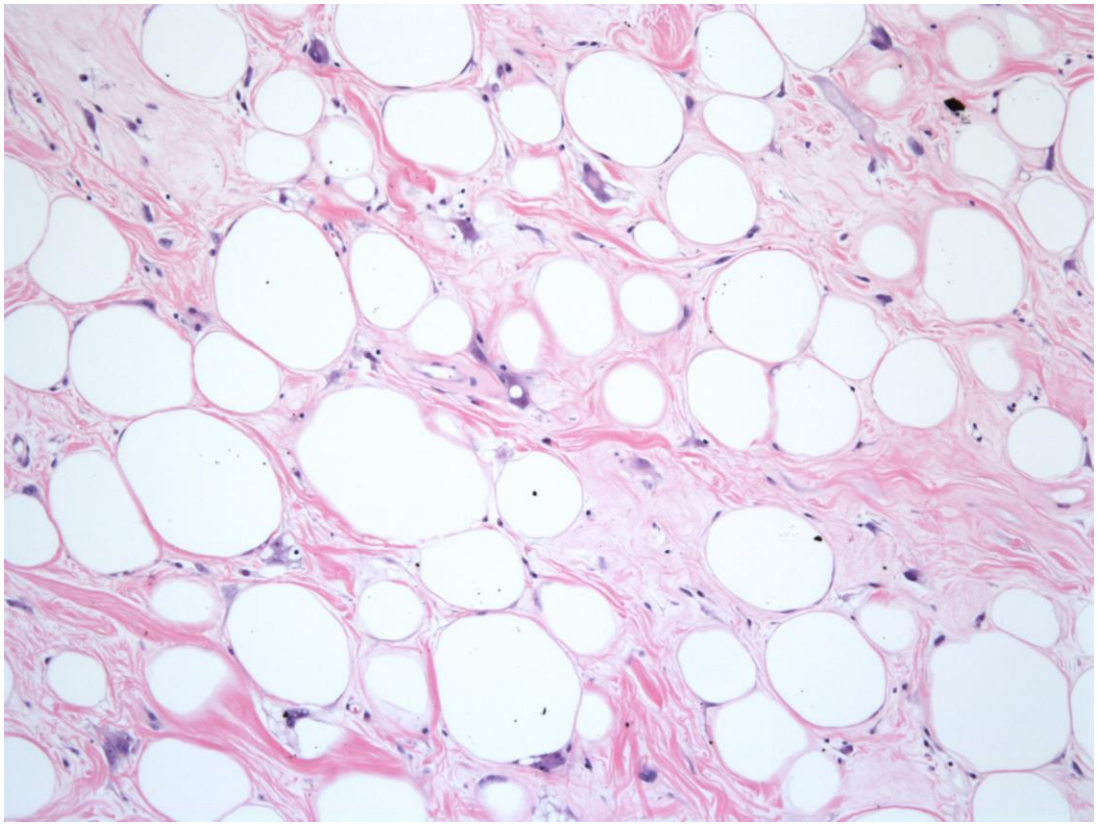
Ewing Sarcoma



H&E, 200X: this image demonstrates a monotonous population of small blue round cells in a soft tissue tumor

Images provided by Deepika Sirohi, MD, University of Utah

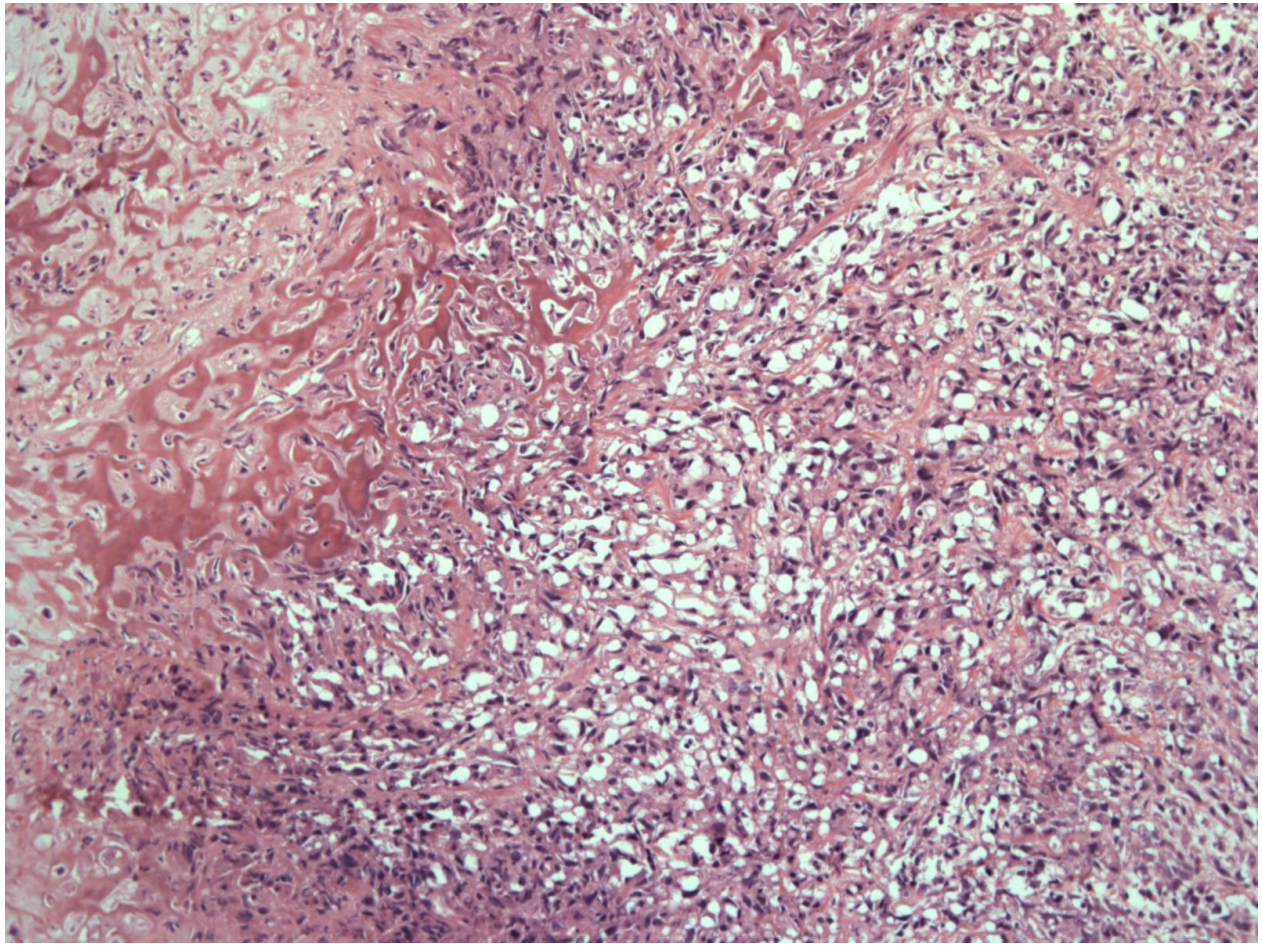
Liposarcoma



H&E, 200X: this image demonstrates a well-differentiated liposarcoma with variable-sized adipocytes with nuclear atypia

Images provided by Deepika Sirohi, MD, University of Utah

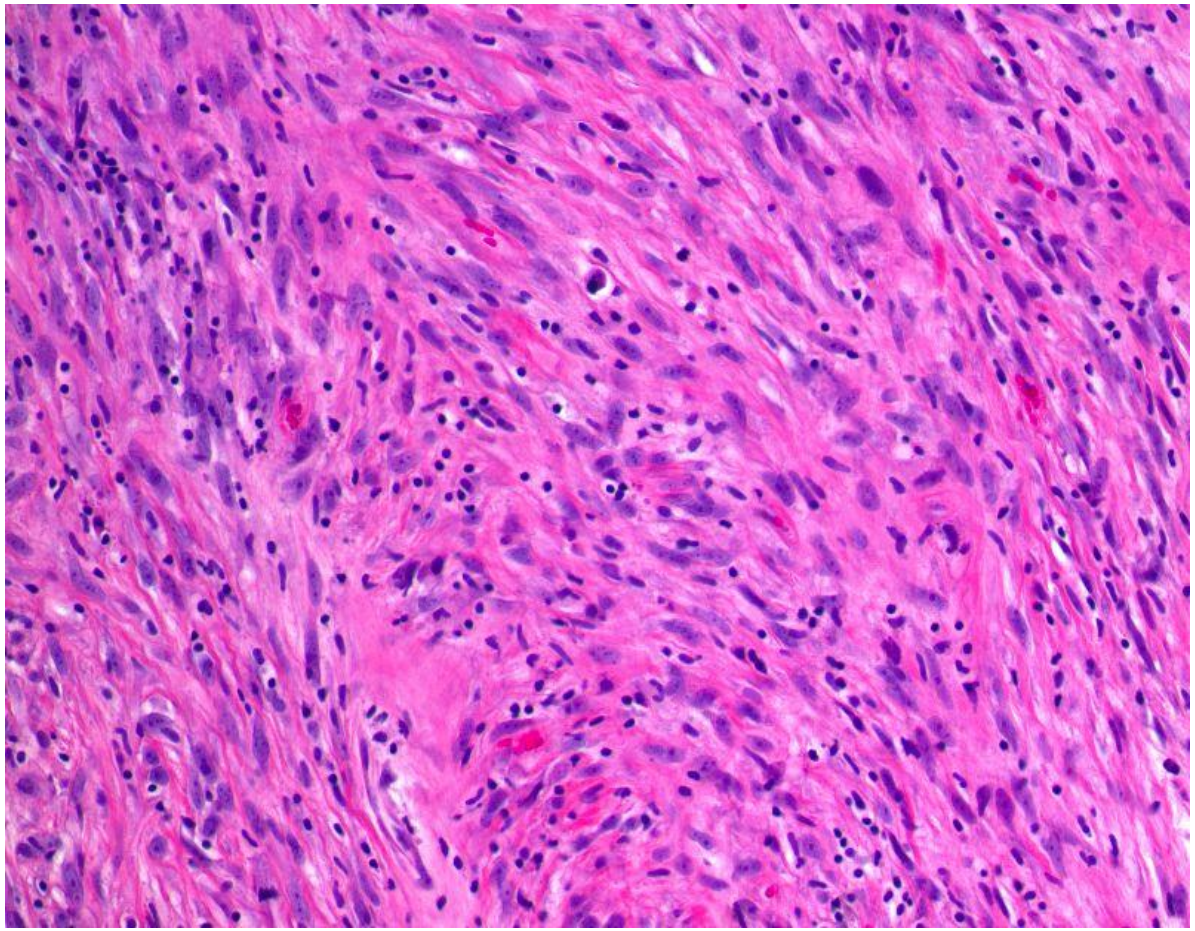
Osteosarcoma



H&E, 200X: this image demonstrates a proliferation of atypical spindle cells with laying down of malignant osteoid

Images provided by Deepika Sirohi, MD, University of Utah

Undifferentiated Pleomorphic Sarcoma (UPS)



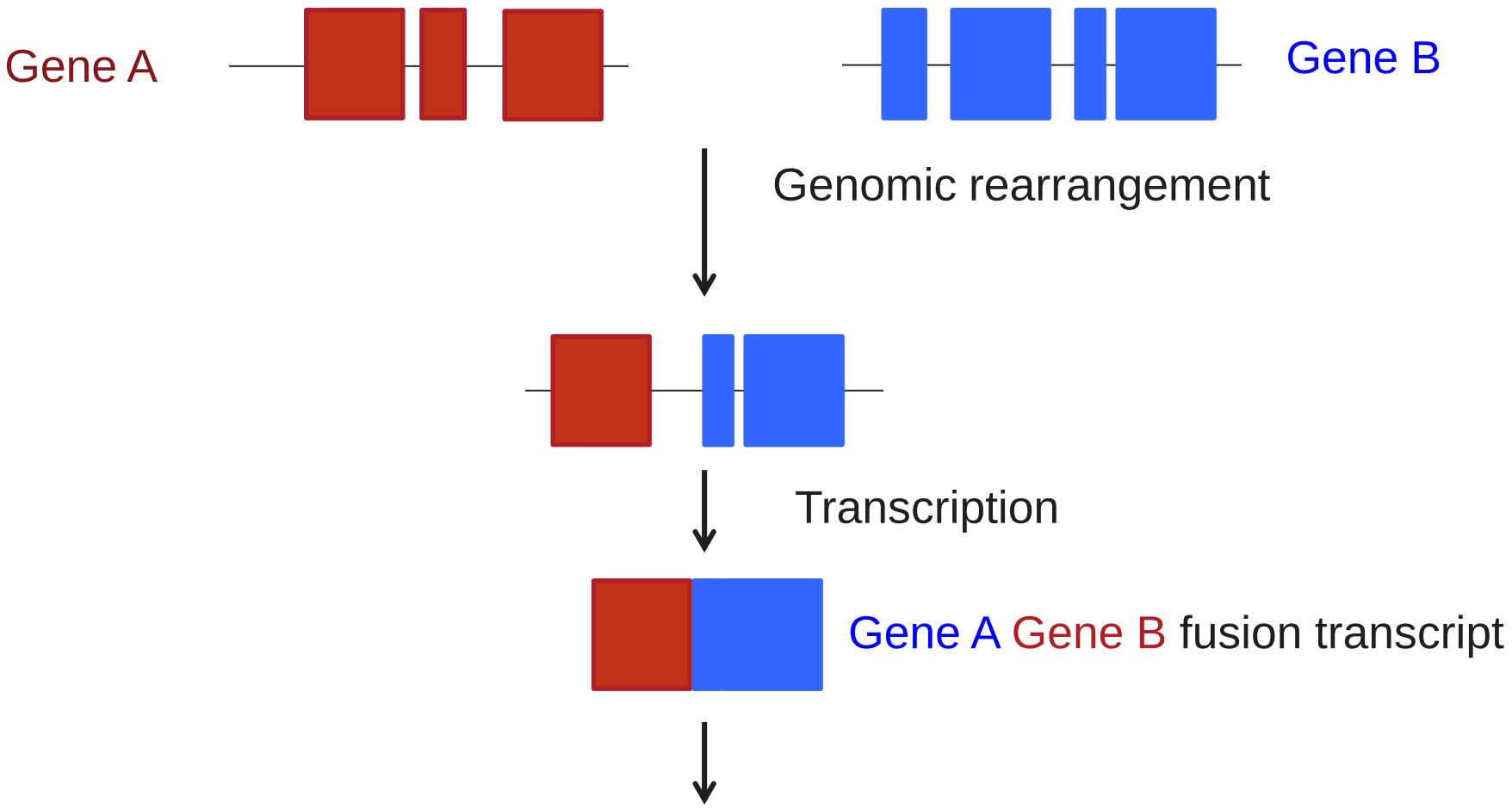
H&E, 200X: this image demonstrates an atypical fascicular proliferation of spindle cells with increased mitotic index

Images provided by Deepika Sirohi, MD, University of Utah

Three Classes of Sarcoma Genomes

- Simple karyotype with a defining translocation/gene fusion
- Simple or complex karyotype with a specific mutation
- Complex karyotype with multiple chromosomal rearrangements, duplications and deletions

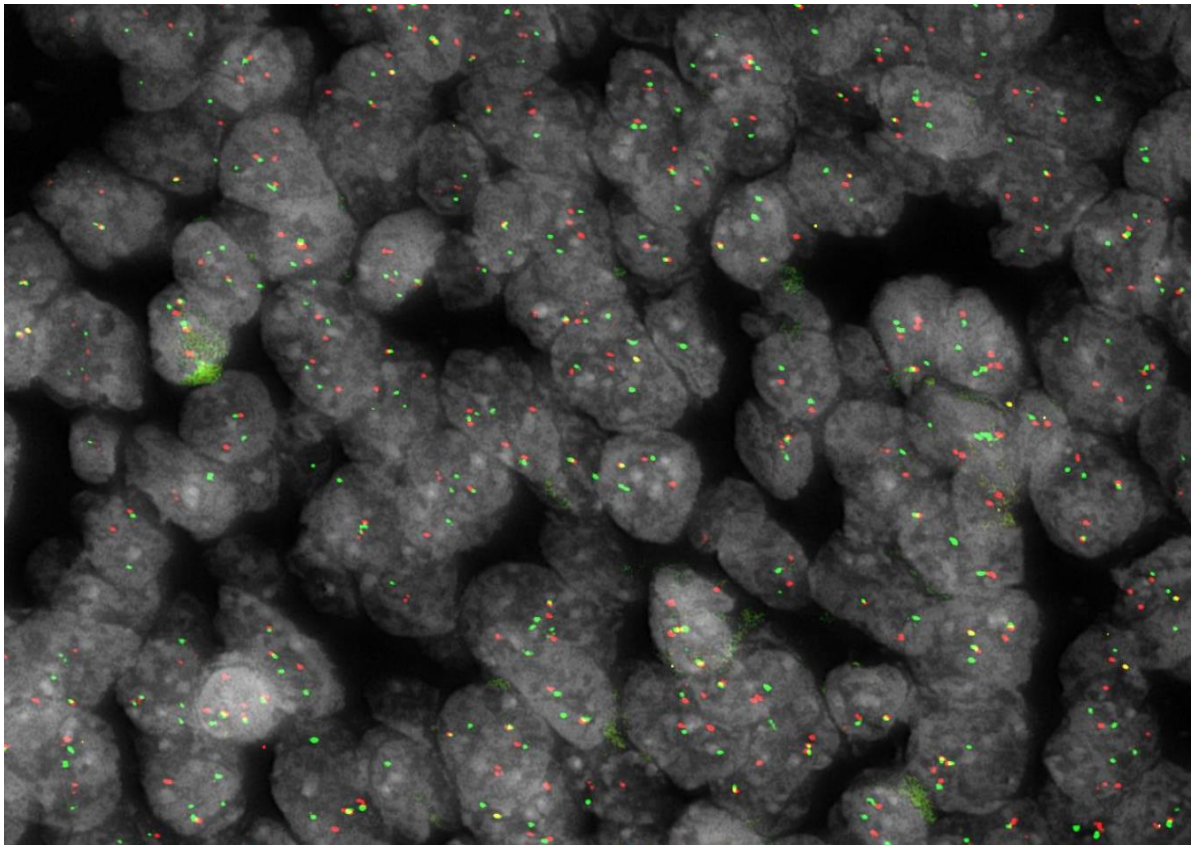
Gene Fusions are Common Molecular Events in Sarcomas



Gene Fusion Detection Methods

- Fluorescence in-situ hybridization (FISH)
  - Break-apart FISH is commonly used to detect gene fusions in sarcomas
- PCR with primers specific to the two fusion partners
- DNA sequencing
  - Gene panel
  - Whole genome
- RNA sequencing
  - Gene panel
  - Whole transcriptome

Gene Fusion Detection Using Break-Apart FISH



Green and red fluorescently labeled probes flank the *EWSR1* locus. Cells negative for an *EWSR1* gene fusion have two yellow signals (overlap of the green and red). Cells with split red and green signals are positive for an *EWSR1* gene fusion.

This image demonstrates a sarcoma positive for an *EWSR1* rearrangement (red and green split signals).

Images provided by Deepika Sirohi, MD, University of Utah

Gene Fusion Detection Using Next-Generation Sequencing

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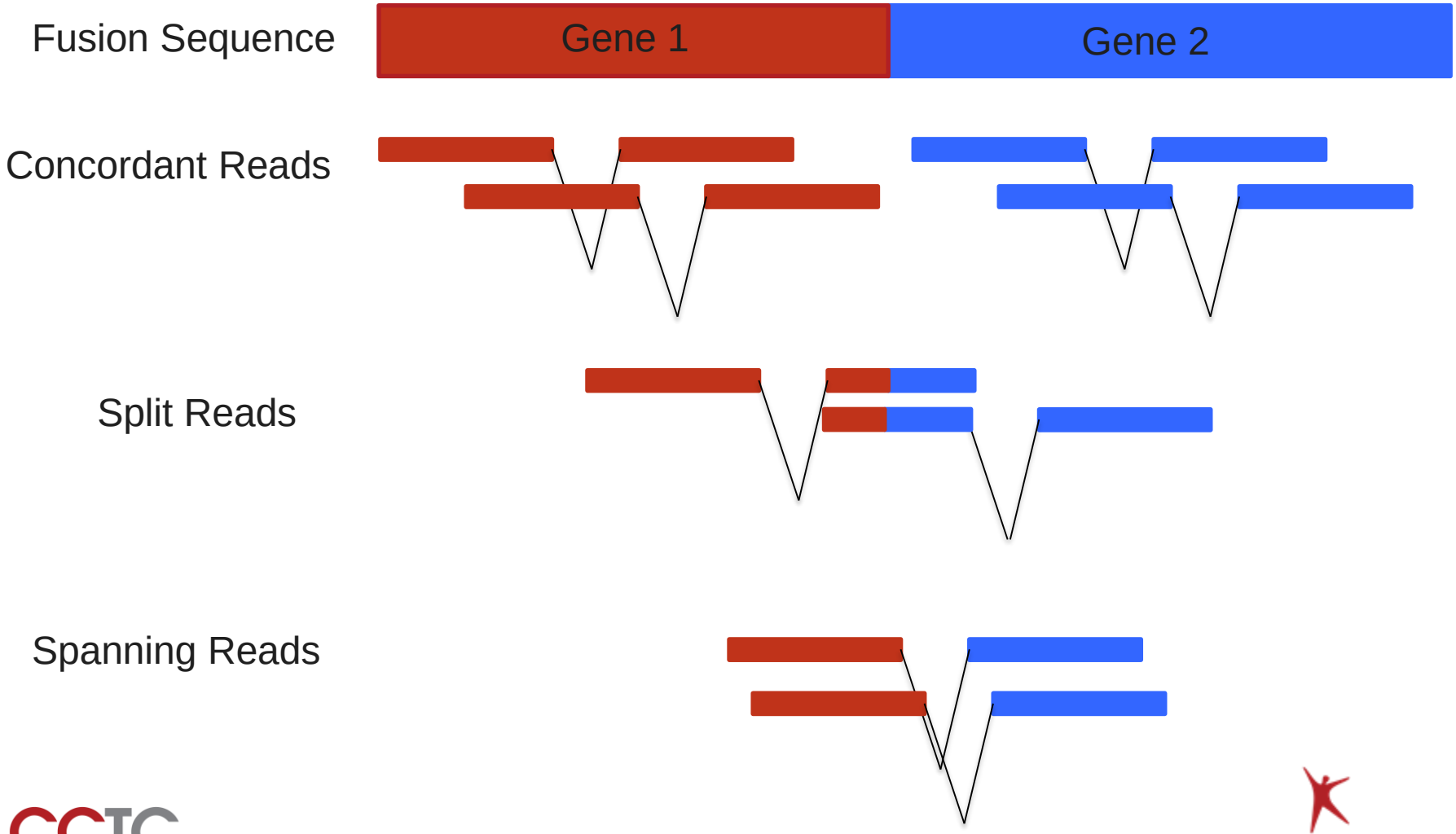

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Clinical Utility of Molecular Testing for Sarcomas

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- Arriving at diagnosis for cases with ambiguous histology
  - E.g. diagnosis of small round cell tumors
- Refining molecular subtype of disease
  - E.g. Alveolar subtype of rhabdomyosarcoma is associated with PAX-FOXO fusions
- Identifying treatment options
  - E.g. KIT and PDGFRA mutations in Gastro-Intestinal Stromal Tumors (GIST) are associated with response to Imatinib
- Confirmation of lesions with an unusual presentation (age, location, appearance)
  - E.g. Confirmation of a synovial sarcoma in a 76-year-old individual
- Aiding in diagnosis for cases with de-differentiated histology

Molecular Testing is Useful for Diagnosing Small Round Cell Tumors

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- Homogeneous light microscopic appearance of small round-cell neoplasms

- Ewing sarcoma, rhabdomyosarcoma, mesenchymal chondrosarcoma, desmoplastic small round cell tumor, round cell liposarcoma, poorly differentiated synovial sarcoma, and neuroblastoma may present in this way

- Identification of a characteristic gene fusion can help make the diagnosis (e.g. *EWS-FLI1* fusion in Ewing sarcoma)

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Cancer Predisposition Syndromes with Increased Risk of Sarcomas

- Li-Fraumeni syndrome
  - Germline heterozygous inactivating mutations in TP53
  - Childhood-onset sarcomas
- Retinoblastoma syndrome
  - Germline heterozygous inactivating mutations in RB1
  - Osteosarcomas
- Familial adenomatous polyposis (FAP)
  - Germline heterozygous inactivating mutations in APC
  - Desmoid tumors

Genetic Syndromes with Increased Risk of Sarcomas

Syndrome	Gene	Sarcoma
Rothmund-Thompson	*RECQLA*	Osteosarcoma
Neurofibromatosis, Type 1	*NF1*	Malignant peripheral nerve sheath tumor
Costello	*HRAS*	Rhabdomyosarcoma
Beckwith-Wiedemann	*CDKN1C*, *H19*, *IGF2*, *KCNQ1OT*1	Rhabdomyosarcoma

Take Home Messages

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- Sarcomas are a heterogeneous group of diseases with over 100 subtypes defined by histopathology
- Genetic testing can help with the diagnosis, molecular subtyping, and treatment selection
- A significant fraction of sarcomas are associated with either a germline cancer predisposition syndrome or a genetic syndrome with other phenotypic features

References

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3. Bridge J. The role of cytogenetics and molecular diagnostics in the diagnosis of soft-tissue tumors. Mod Pathol 2014;27: S80-S97
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