Epignostix Sarcoma Methylation Classifier

Version 13.1

Released: June 2025

- **120 subclasses,** 93 classes
- Training set: **4,377 methylation profiles**
- **94%** subclass-level accuracy
- Two tier hierarchical output structure
- Proposed evidence level annotation
- **150,000+ patient cases** analyzed
- 500+ institutions worldwide use the classifier

Sample Collection
(Fresh Frozen / FFPE)
Tumor assesment (>= 50%)

↓

Pre-analytical procedure
(DNA extraction)

↓

Raw data generation
(idat file)

↓

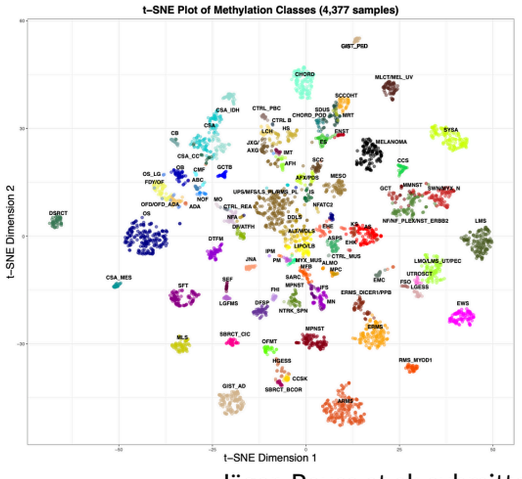
Epignostix Sarcoma Tumor Methylation Classifier
(QC, Tumor classification, CNV analysis)

↓

PDF and html Report

List of Sarcoma Classes Version 13.1

- aneurysmal bone cyst
- adamantinoma
- angiomatoid fibrous histiocytoma
- atypical fibroxanthoma / pleomorphic dermal sarcoma
- angioleiomyoma
- atypical lipomatous tumor/well differentiated liposarcoma
- alveolar rhabdomyosarcoma
- angiosarcoma
- alveolar soft part sarcoma
- chondroblastoma
- clear cell sarcoma of soft parts
- clear cell sarcoma of the kidney
- chordoma
- chondromyxoid fibroma
- chondrosarcoma (clear cell, IDH, mesenchymal)
- dedifferentiated liposarcoma
- dermatofibroma/(atypical) fibrous histiocytoma
- dermatofibrosarcoma protuberans
- desmoplastic small round cell tumour
- desmoid-type fibromatosis
- haemangioendothelioma epithelioid
- haemangioendothelioma kaposiform
- extraskeletal myxoid chondrosarcoma
- epithelial nerve sheath tumor
- embryonal rhabdomyosarcoma
- embryonal rhabdomyosarcoma DICER1-mutant
- epithelioid sarcoma
- Ewings sarcoma
- Ewings sarcoma EWSR_NFATC2 fused
- fibrous dysplasia/osteofibrous dysplasia
- fibrous hamartoma of infancy
- fibrosarcoma ovary
- granular cell tumor (peripheral type)
- giant cell tumour of bone
- histiocytic sarcoma
- infantile fibrosarcoma
- inflammatory myofibroblastic tumour
- intranodal palisaded myofibroblastoma
- intimal sarcoma
- juvenile nasopharyngeal angiofibroma
- juvenile xanthogranuloma / adult xanthogranuloma
- Kaposi sarcoma
- low-grade fibromyxoid sarcoma
- lipoma / lipoblastoma
- leiomyoma / leiomyosarcoma (uterine type) / PEComa
- leiomyosarcoma
- myofibroma
- myxoid liposarcoma
- myositis ossificans
- myopericytoma
- malignant peripheral nerve sheath tumour
- myxoma intramuscular
- neurofibroma / neurofibroma plexiform
- nodular fasciitis
- non-ossifying fibroma
- NTRK-rearranged spindle cell neoplasm
- osteoblastoma
- osteofibrous dysplasia / osteofibrous dysplasia like adamantinoma
- ossifying fibromyxoid tumour
- osteosarcoma
- low grade osteosarcoma
- proliferative myositis
- spindle cell sclerosing rhabdomyosarcoma
- sarcoma MPNST-like
- sarcoma with BCOR genetic alterations
- CIC-rearranged sarcoma
- uterine sarcoma, SMARCA4-deficient
- sclerosing epithelioid fibrosarcoma
- solitary fibrous tumor (CNS type)
- schwannoma / myxoma nerve sheath
- synovial sarcoma
- undifferentiated pleomorphic sarcoma
- myxofibrosarcoma
- pleomorphic liposarcoma
- pleomorphic rhabdomyosarcoma



Jäger, Reuss et al; submitted

- On-premise version for routine use
- Compatible with standard laptops
  An installation guide is included.
- RUO Platform freely accessible for academic research and scientific use
- Register here:
  https://app.epignostix.com/
- Contact for more information
  info@epignostix.com

Publications connected to the Epignostix SarcomaMethylation Classifier

Advancing sarcoma diagnostics with expanded DNA methylation-based classification

Jaeger, N. et al., submitted

Purpose

Sarcomas pose a severe diagnostic challenge. A wide variety of these distinct entities need to be distinguished from each other and from less aggressive types of mesenchymal tumors. A machine learning based classifier for sarcomas utilizing DNA methylation data from 1077 tumors recognizing 62 sarcoma types has already been developed and termed the sarcoma classifier, which we had published in 2021. Here we present a major advancement of the initial sarcoma classifier.

Methods

DNA methylation profiles and histologic data from an unprecedented multi-institutional cohort of mesenchymal tumors were collected and analyzed. Utilizing a random forest-based methodology, the classifier was rigorously validated through five-fold nested cross-validation, achieving a 98% class-level accuracy and a Brier score of 0.017, indicative of well-calibrated probability estimates. The hierarchical output structure facilitates comprehensive interpretation, allowing clinicians to assess tumor subclass and aggregate class-level probabilities for informed decision-making.

Results

The new sarcoma classifier v13.1 was developed based on a training set of 4377 methylation profiles from sarcomas and less aggressive mesenchymal tumors comprising 116 tumor and 4 control groups forming 93 distinct methylation classes, and was validated using four independent sarcoma cohorts, comprising a total of 1547 mesenchymal tumors. A diagnostic prediction was obtained in 73% in the validations sets with matching predictions observed in 91% of the diagnostic predictions.

Conclusions

Adding new sarcoma types and expanding tumor sample numbers in each methylation class in the new sarcoma classifier decisively increased the percentage of diagnostic predictions and improved match with histologic evaluation. This substantial advancement will promote clinical implementation of the tool for the diagnosis of mesenchymal tumor lesions.

Sarcoma classification by DNA methylation profiling in clinical everyday life: the Charité experience

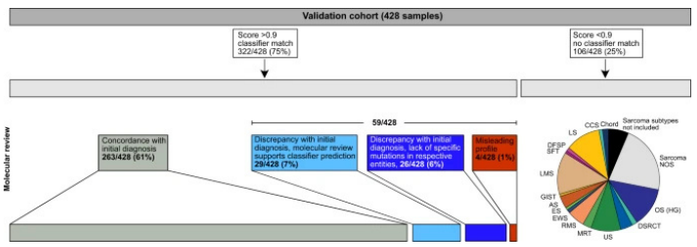
Roohani S. et al., Clinical Epigenetics 14, 149 (2022)

Accurate sarcoma diagnosis remains a challenge in clinical practice due to overlapping histological features and the rarity of many subtypes. This study reports the implementation of DNA methylation profiling for sarcoma classification in a routine diagnostic setting at Charité – Universitätsmedizin Berlin. Over a two-year period, 107 clinical cases were analyzed using a reference methylation classifier. The results led to a refinement of the initial diagnosis in 47% of cases and a complete change in 12%, often with direct therapeutic implications. The study confirms the practical value of DNA methylation profiling in real-world clinical workflows, demonstrating its role in improving diagnostic precision and guiding patient management in complex sarcoma cases.

Sarcoma classification by DNA methylation profiling

Koelsche C. et al., Nature Communications 12, 498 (2021)

Sarcomas are malignant soft tissue and bone tumours affecting adults, adolescents and children. They represent a morphologically heterogeneous class of tumours and some entities lack defining histopathological features. Therefore, the diagnosis of sarcomas is burdened with a high inter-observer variability and misclassification rate. Here, we demonstrate classification of soft tissue and bone tumours using a machine learning classifier algorithm based on array-generated DNA methylation data. This sarcoma classifier is trained using a dataset of 1077 methylation profiles from comprehensively pre-characterized cases comprising 62 tumour methylation classes constituting a broad range of soft tissue and bone sarcoma subtypes across the entire age spectrum. The performance is validated in a cohort of 428 sarcomatous tumours, of which 322 cases were classified by the sarcoma classifier. Our results demonstrate the potential of the DNA methylation-based sarcoma classification for research and future diagnostic applications.



Assessment of the utility of the sarcoma DNA methylation classifier in surgical pathology

Miettinen M. et al., American Journal of Surgical Pathology 48, 112–122 (2024)

Diagnostic classification of soft tissue tumors is based on histology, immunohistochemistry, genetic findings, and radiologic and clinical correlations. Recently, a sarcoma DNA methylation classifier was developed, covering 62 soft tissue and bone tumor entities. The classifier is based on large-scale analysis of methylation sites across the genome. It includes DNA copy number analysis and determines O 6 methylguanine DNA methyl-transferase methylation status. In this study, we evaluated 619 well-studied soft tissue and bone tumors with the sarcoma classifier. Problem cases and typical examples of different entities were included. The classifier had high sensitivity and specificity for fusion sarcomas: Ewing, synovial, CIC -rearranged, and BCOR -rearranged. It also performed well for leiomyosarcoma, malignant peripheral nerve sheath tumors (MPNST), and malignant vascular tumors. There was low sensitivity for diagnoses of desmoid fibromatosis, neurofibroma, and schwannoma. Low specificity of matches was observed for angiomatoid fibrous histiocytoma, inflammatory myofibroblastic tumor, Langerhans histiocytosis, schwannoma, undifferentiated sarcoma, and well-differentiated/dedifferentiated liposarcoma. Diagnosis of lipomatous tumors was greatly assisted by the detection of MDM2 amplification and RB1 loss in the copy plot. The classifier helped to establish diagnoses for KIT-negative gastrointestinal stromal tumors, MPNSTs with unusual immunophenotypes, and undifferentiated melanomas. O 6 methylguanine DNA methyl-transferase methylation was infrequent and most common in melanomas (35%), MPNSTs (11%), and undifferentiated sarcomas (11%). The Sarcoma Methylation Classifier will likely evolve with the addition of new entities and refinement of the present methylation classes. The classifier may also help to define new entities and give new insight into the interrelationships of sarcomas.

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