Publieksdag Hersentumoren

Hersentumoren publieksdag 2023: Moleculaire aspecten van hersentumoren/diagnostiek

Zaterdag 18 maart 2023
De Landgoederij, Bunnik

Naam : **Angelika Mühlebner**
Functie : *neuropatholoog, UMCU*

In samenwerking met: hersentumor.nl LWNO hersentumor contactgroep hersenletsel.nl

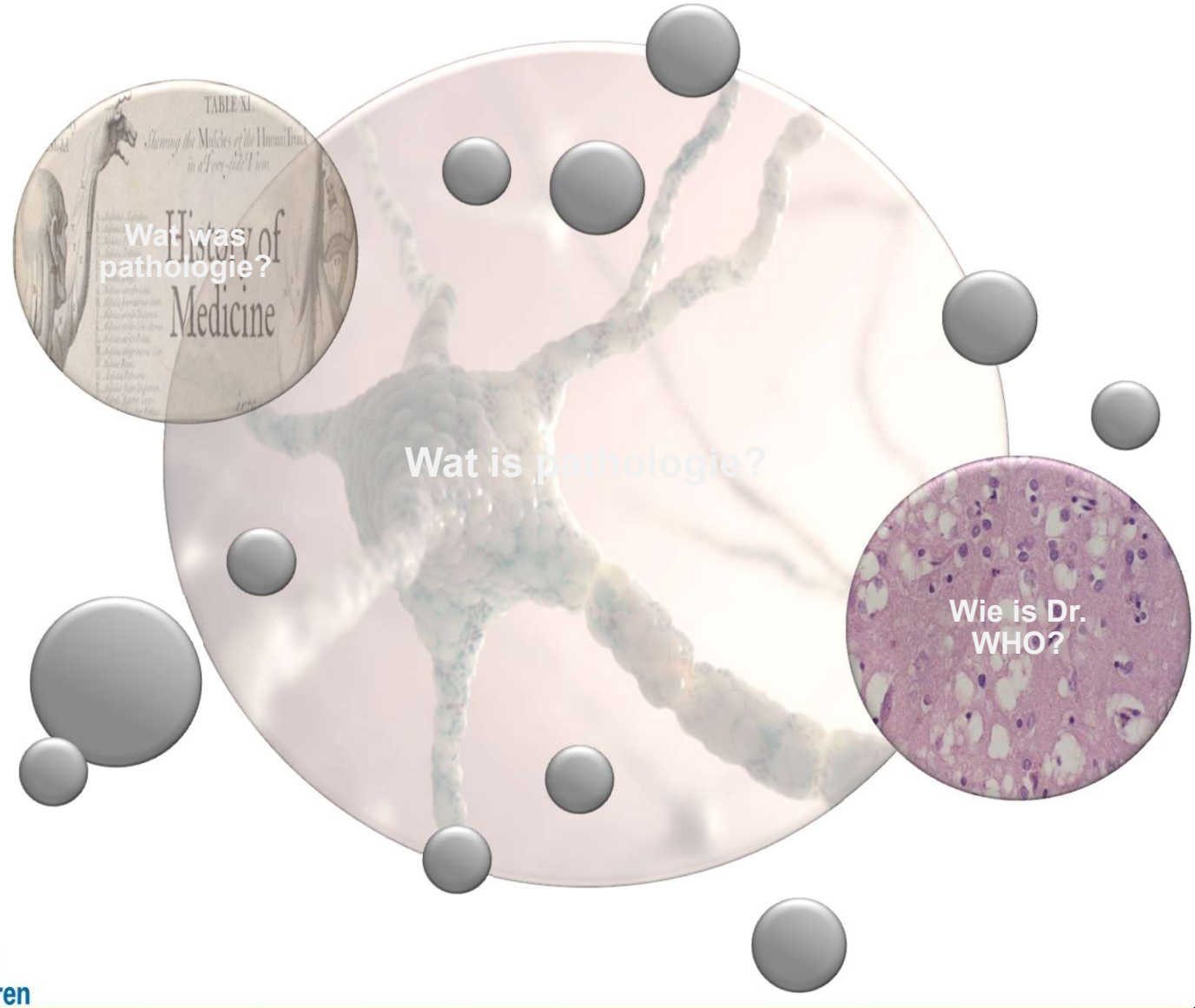
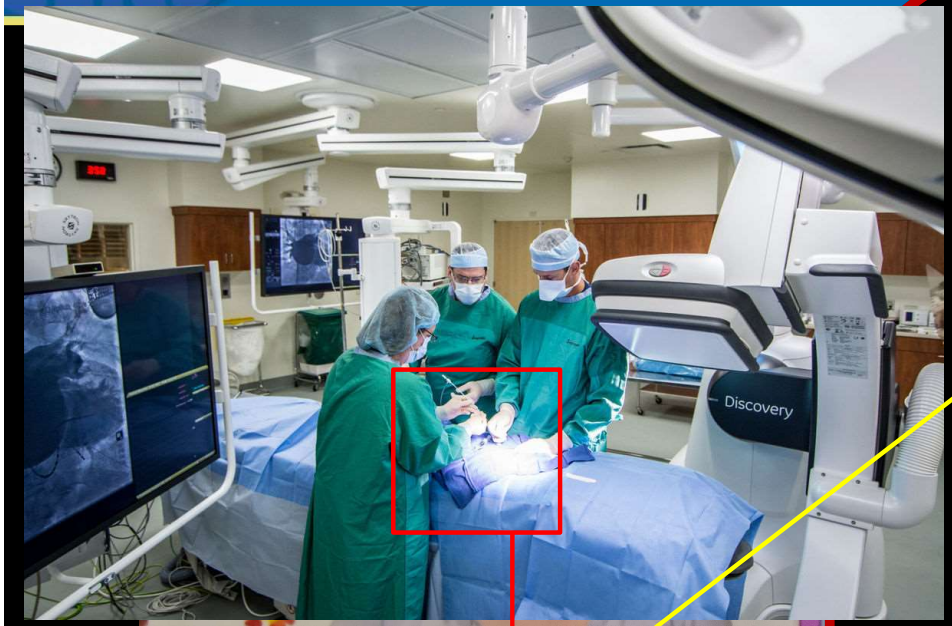
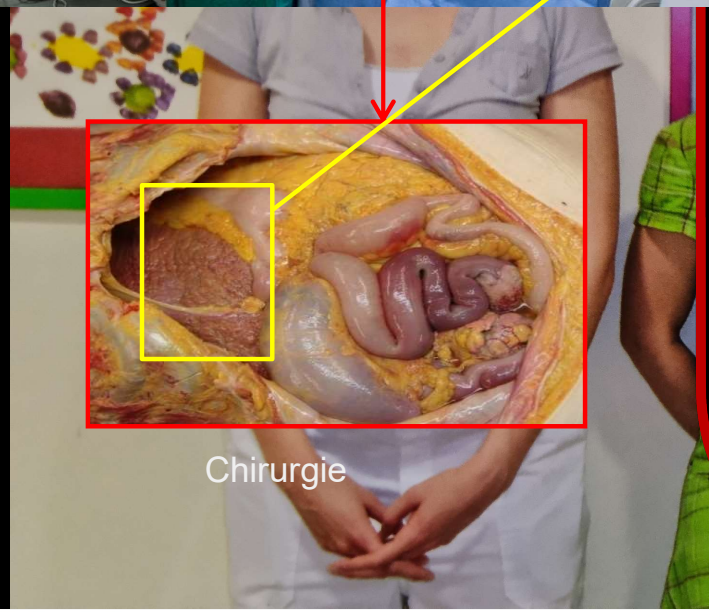
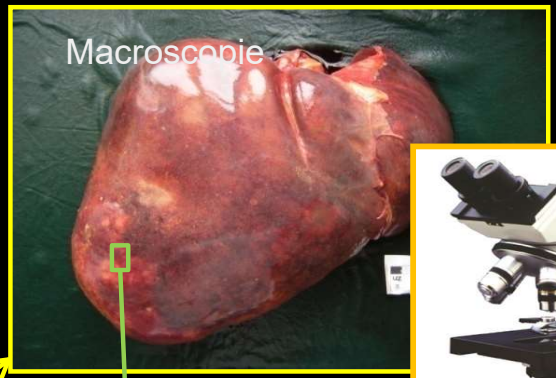
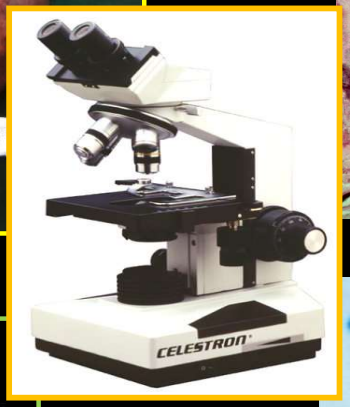


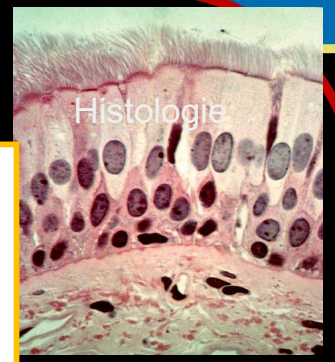
TABLE XI.
History of Medicine
Wat was pathologie?
Wat is pathologie?
Wie is Dr. WHO?


Discovery

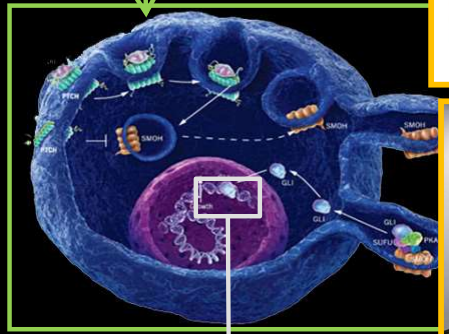

Chirurgie


Macroscopie


CELESTRON


Histologie

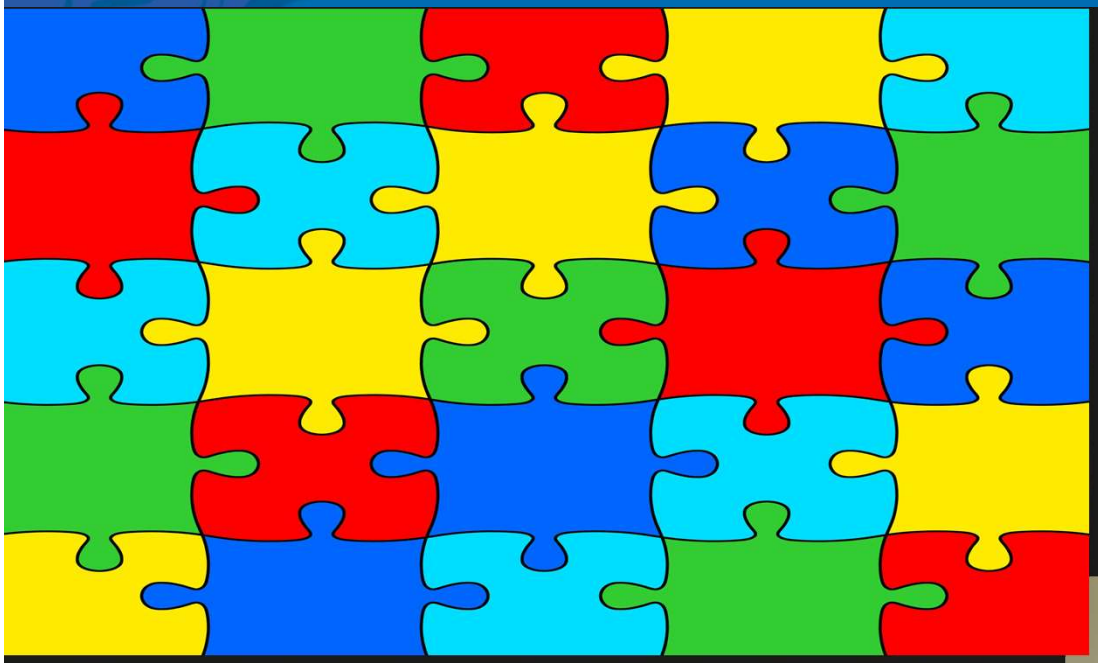

Cytologie



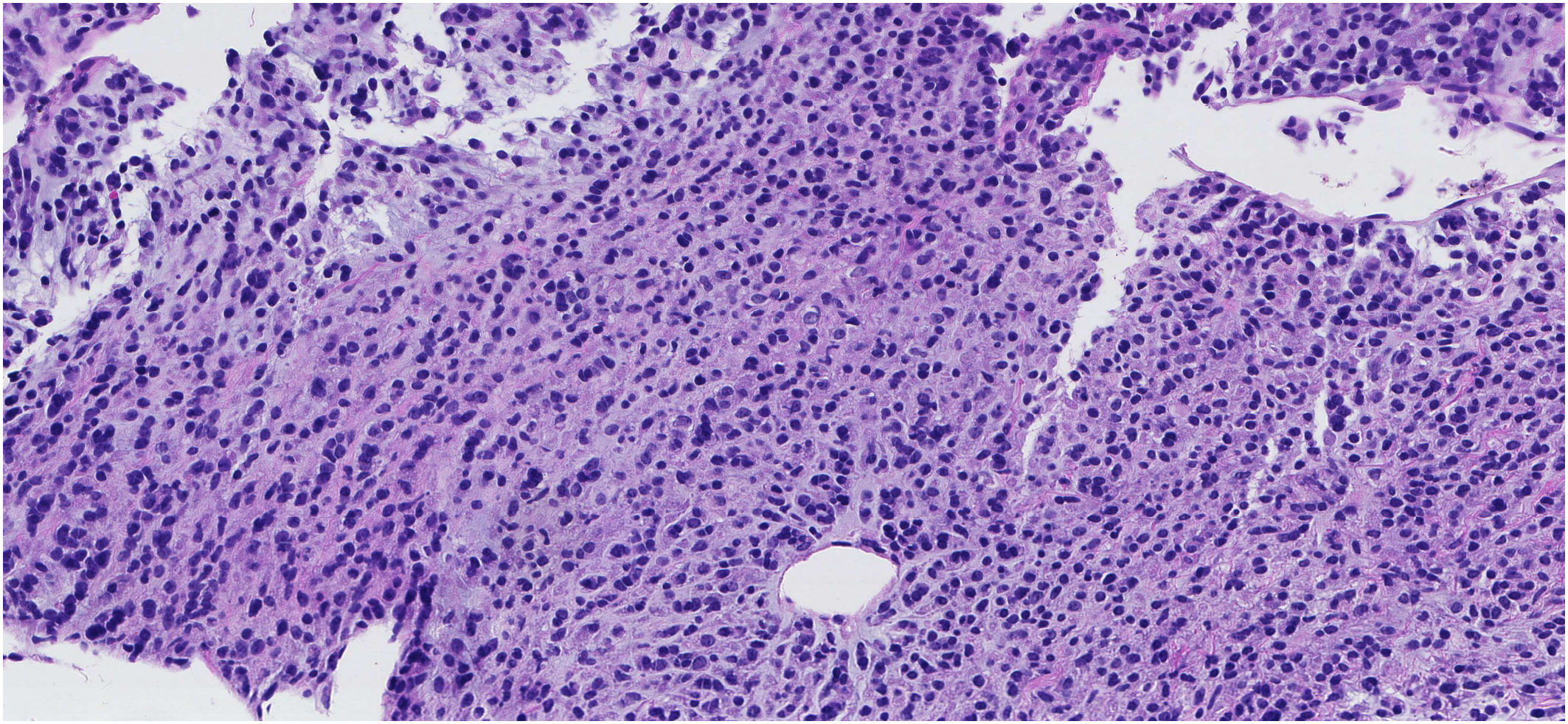

Elektronen
Microscopie


Moleculaire
Biologie

Lilith 1983 -2011



In elkaar puzzelen van de diagnose



Brain Pathology **19** (2009) 551–564

HISTORICAL PERSPECTIVE

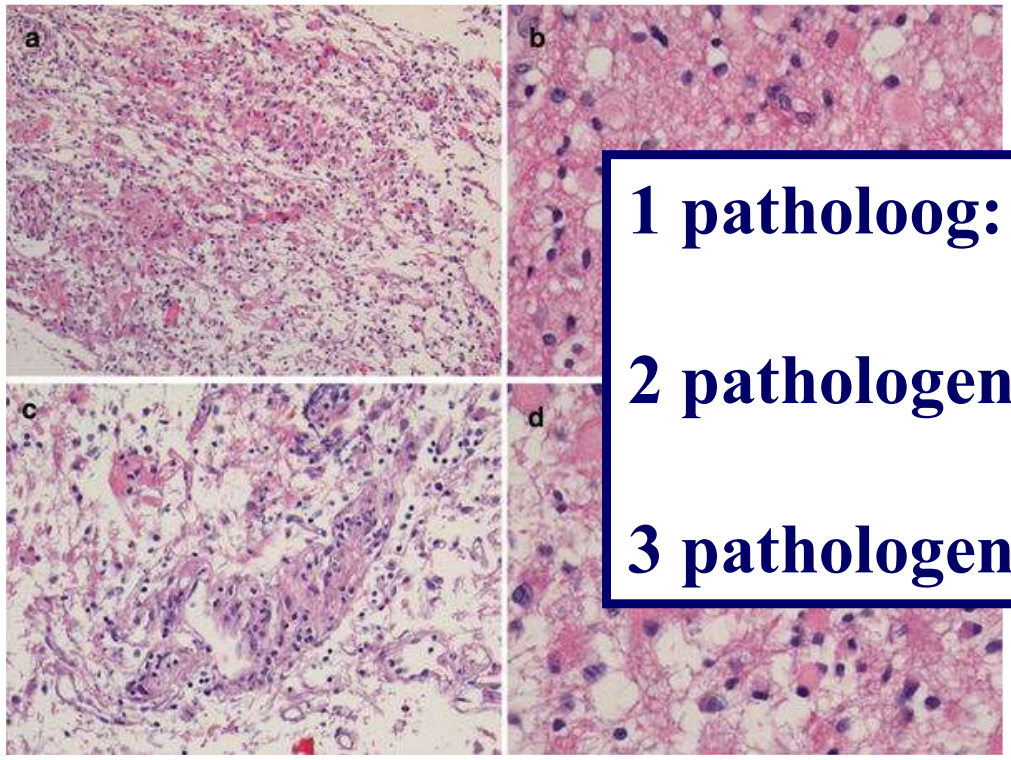
Development of the WHO Classification of Tumors of the Central Nervous System: A Historical Perspective

Bernd W. Scheithauer, MD

Department of Pathology and Laboratory Medicine, Mayo Clinic, Rochester, Mi.

Interobserver variation of the histopathological diagnosis in clinical trials on glioma: a clinician's perspective

Martin J. van den Bent



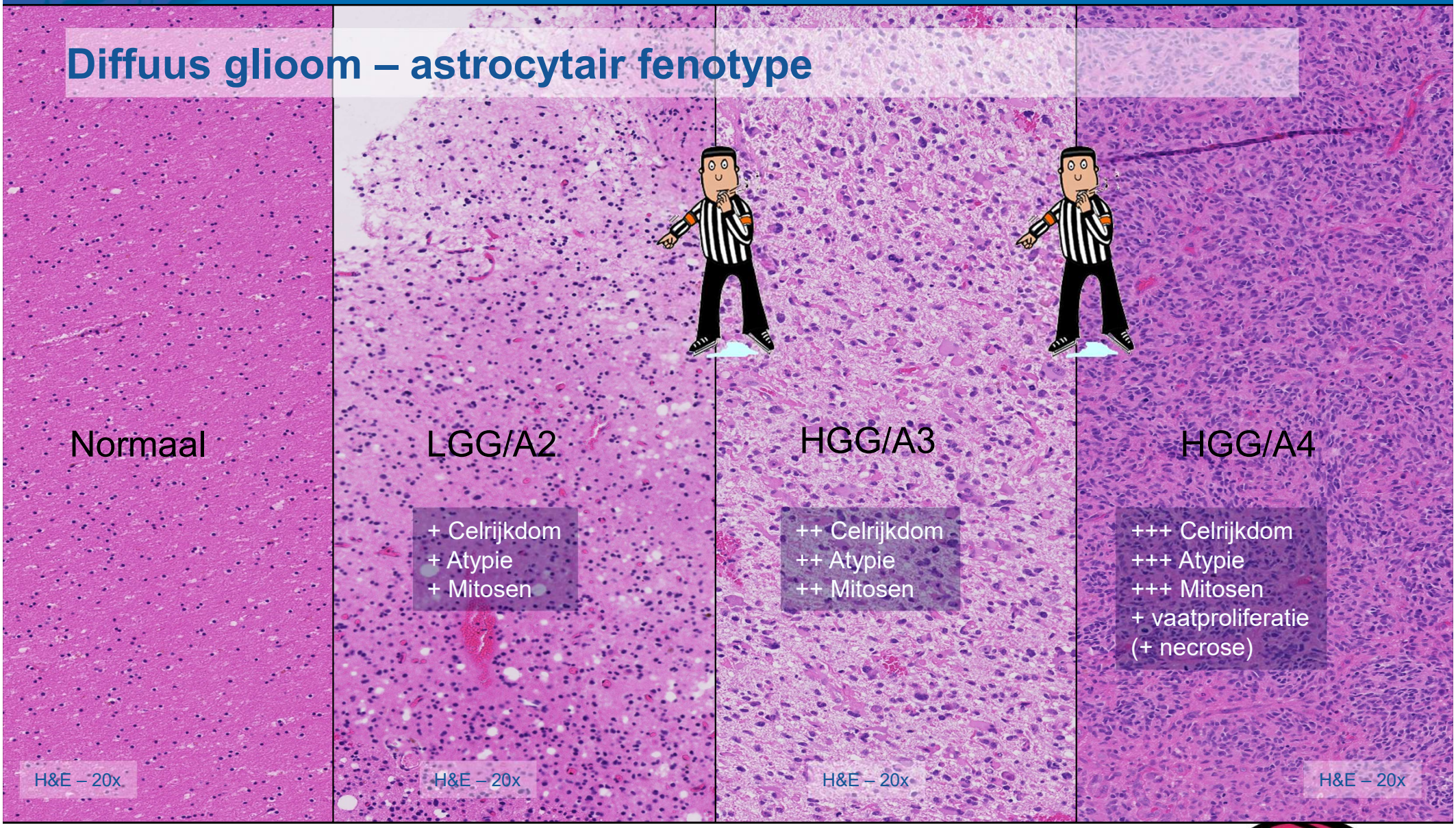
1 patholoog: diagnose

2 pathologen: discussie

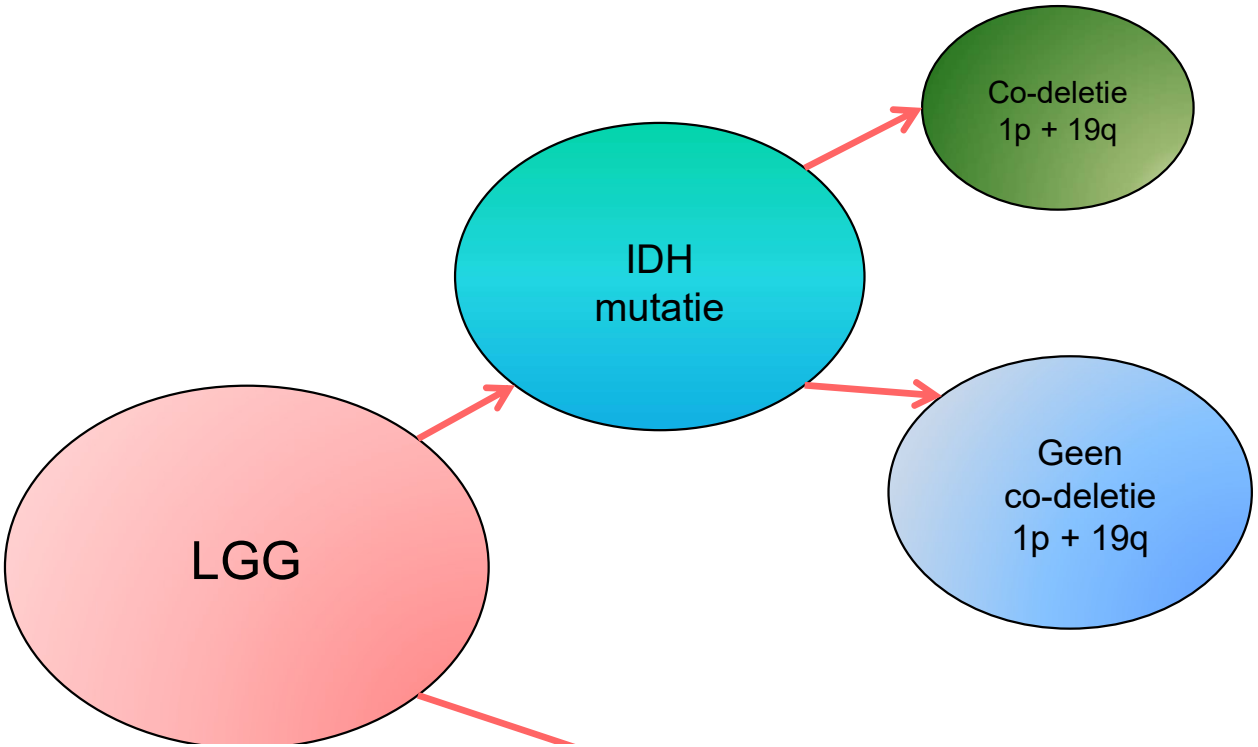
3 pathologen: chaos

histopathological diagn
linician's perspective

Diffuus glioom – astrocytair fenotype



Gliomen: moleculair profiel

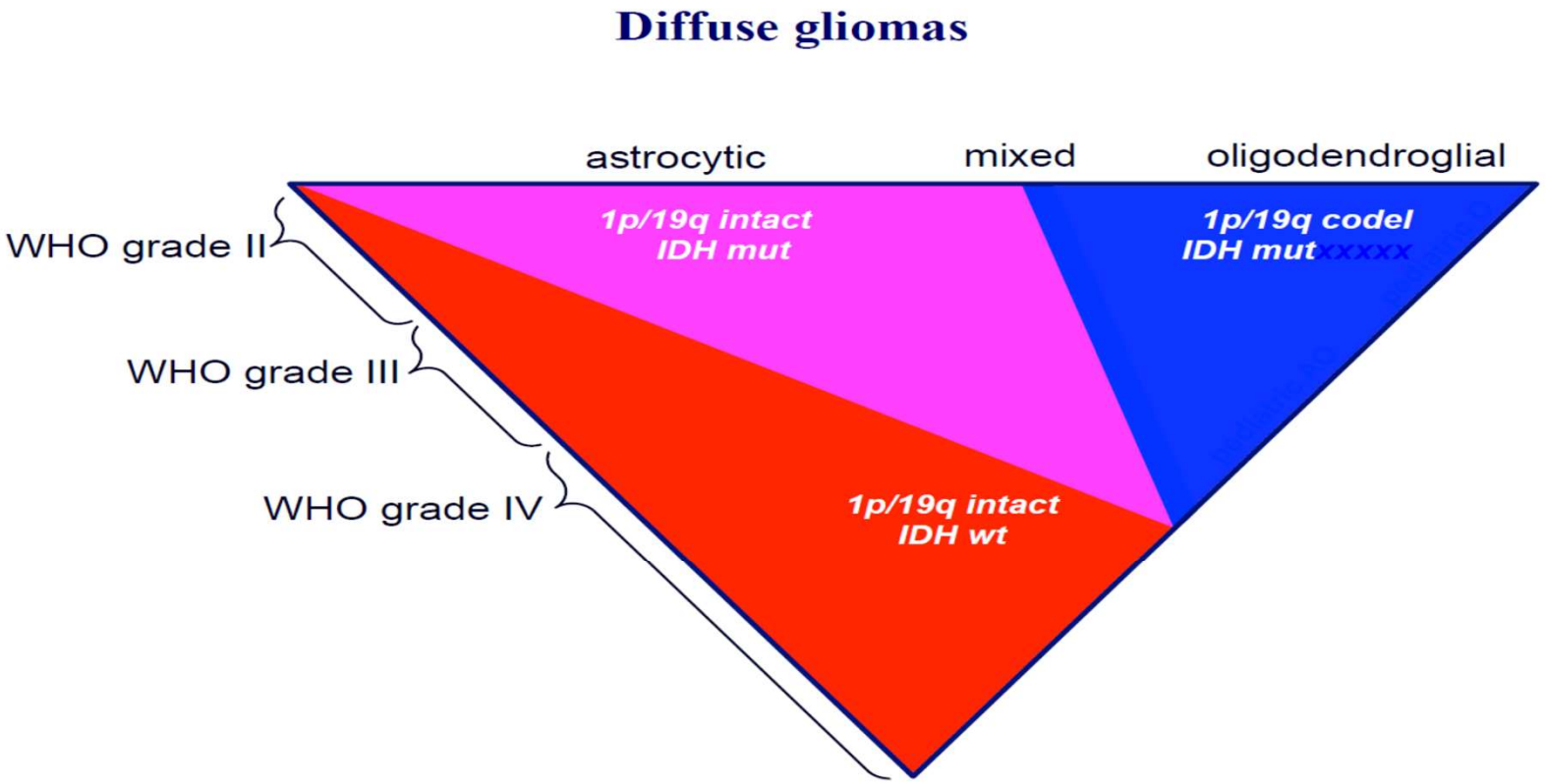


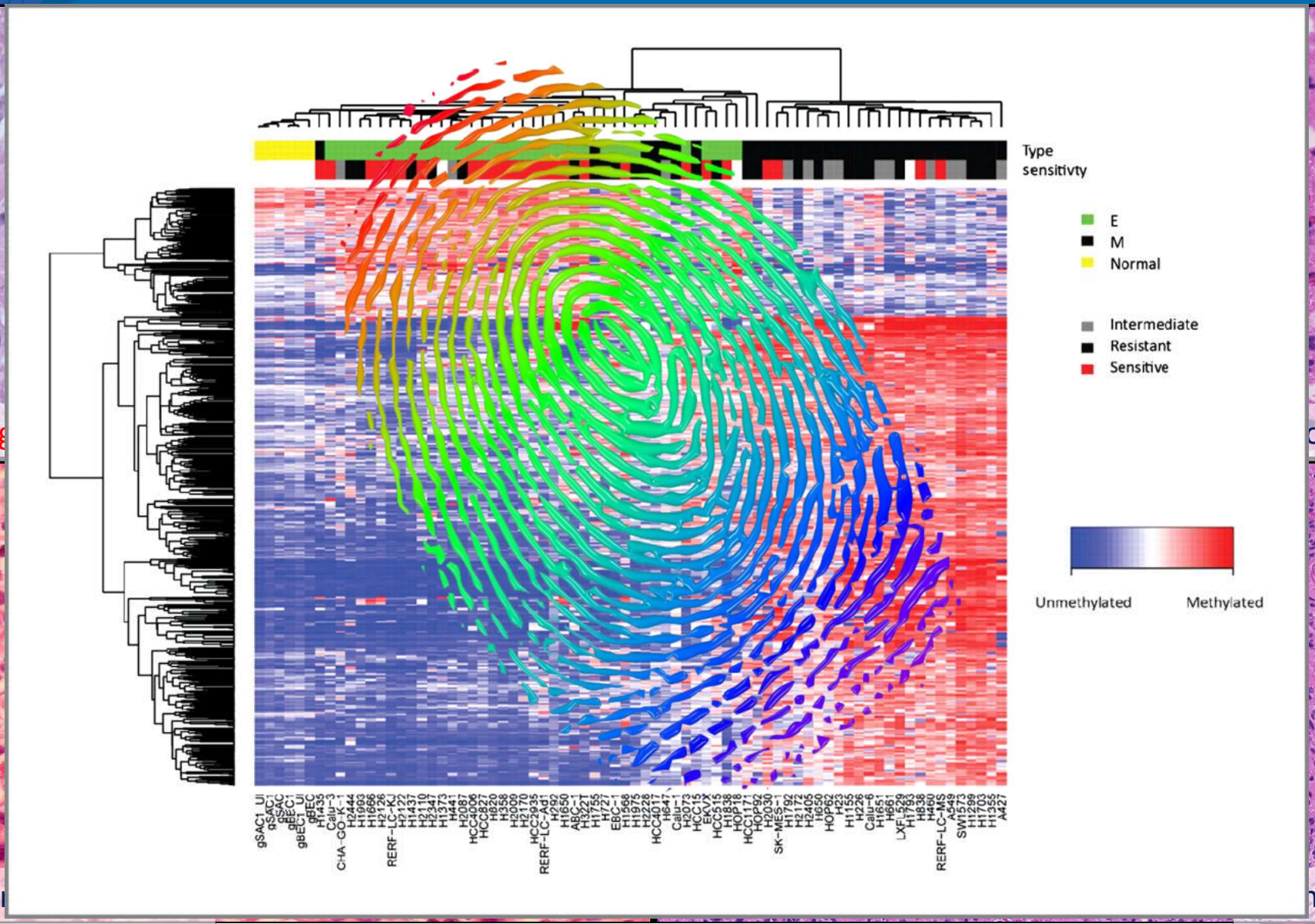
Moleculaire wijzigingen		Klinisch beloop
Inactivatie	Activatie	
CIC FUBP1 NOTCH1	PIK3CA TERT IDH1 IDH2	LGG
TP53 ATRX	MYC IDH1 IDH2	LGG ((GBM))
PTEN CDKN2A NF1	EGFR MDM4 TERT	((LGG)) GBM

Co-deletie 1p/19q

Gunstige prognostische factor
Voorspelt gevoeligheid voor alkylerend chemotherapeuticum (PCV)
Verbeterde overleving

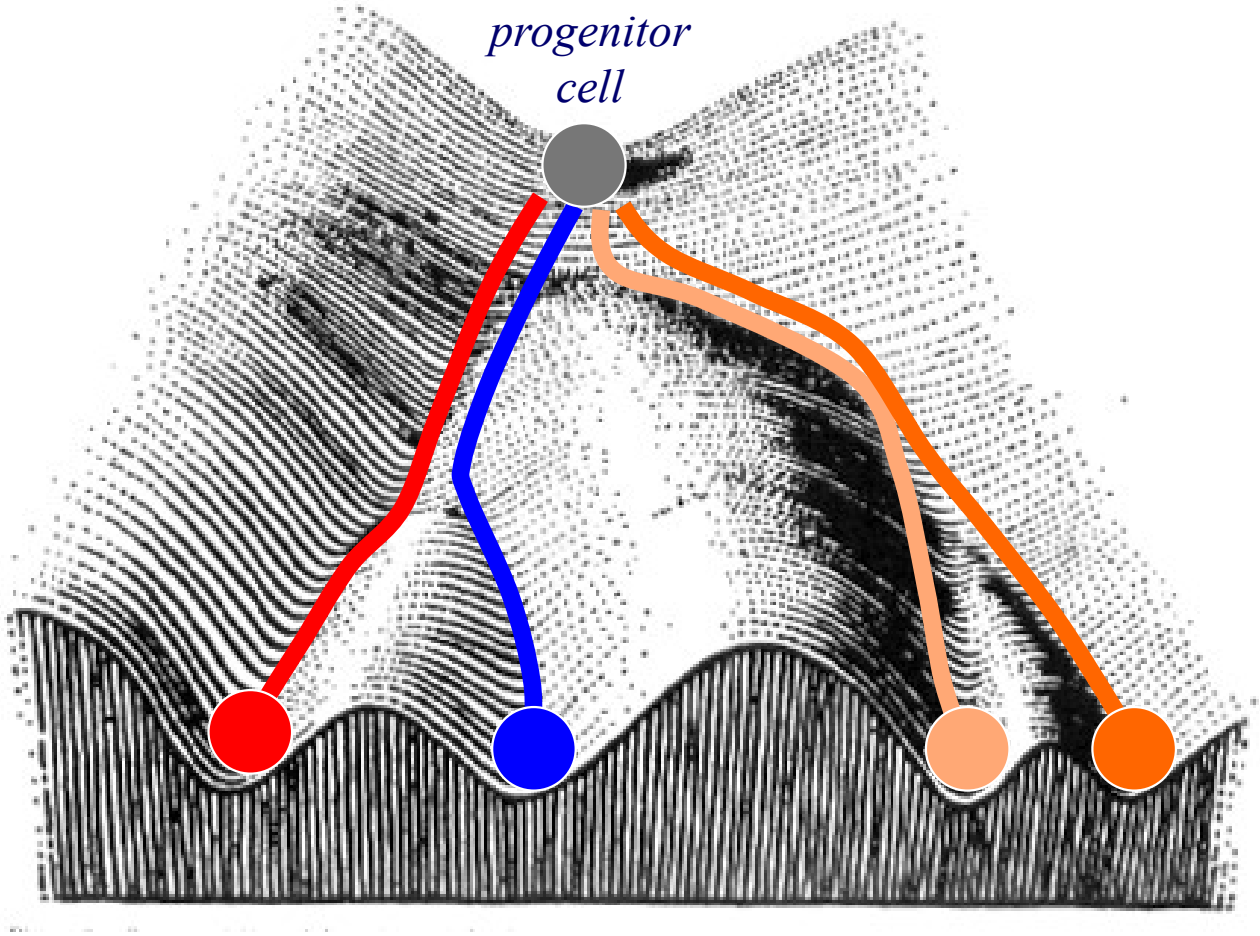
Gliomen: moleculair profiel





Publieksdag
Hersentumoren

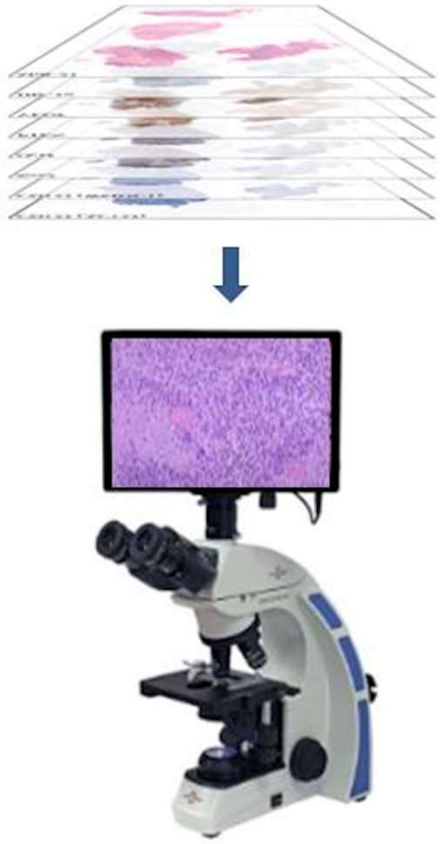
Het principe van de methylatie…



Courtesy of Dr. David Capper, DKFZ/Heidelberg, Germany

Moderne diagnostiek van hersentumoren

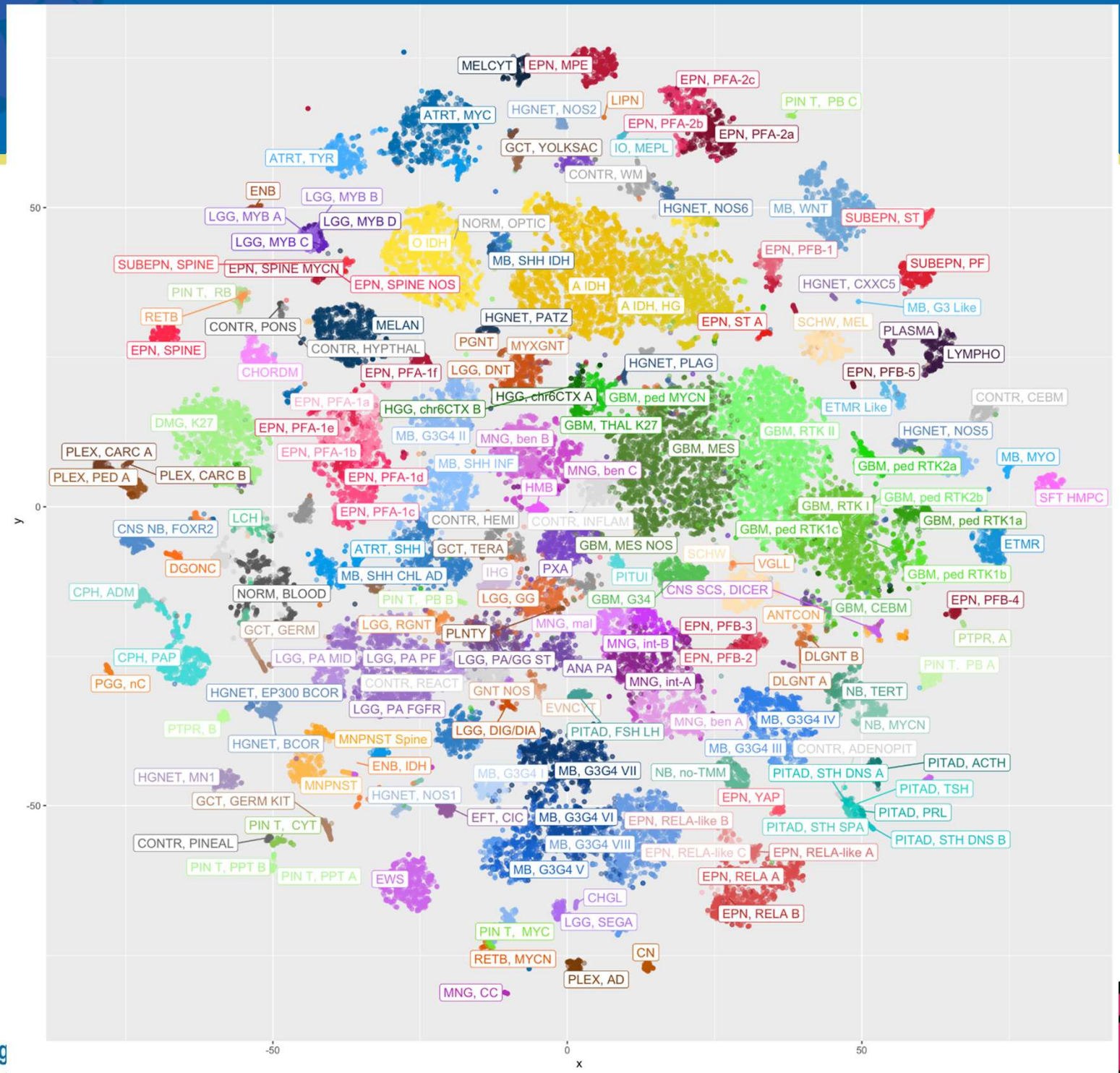
Microscopie



DNA analyse

Methylome profiel

Kristensen BW, Priesterbach-Ackley LP, Petersen JK, Wesseling P.
Molecular Pathology of CNS Tumors
Ann Oncol 2019;30:1265-1278



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WHO classificatie van hersentumoren

International Agency for Research on Cancer

World Health Organization

WHO classification of CNS tumour types, 5th edition (2021)

GLIOMAS, GLIONEURONAL TUMOURS & NEURONAL TUMOURS

Adult-type diffuse gliomas
- Astrocytoma, IDH-mutant
- Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
- Glioblastoma, IDH-wildtype

Paediatric-type diffuse low-grade gliomas
- Diffuse astrocytoma, *MYB*- or *MYBL1*-altered
- Angiocentric glioma
- Polymorphous low-grade neuroepithelial tumour of the young
- Diffuse low-grade glioma, MAPK pathway-altered

Paediatric-type diffuse high-grade gliomas
- Diffuse midline glioma, H3K27-altered
- Diffuse hemispheric glioma, H3G34-mutant
- Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wild type
- Infant-type hemispheric glioma

Circumscribed astrocytic gliomas
- Pilocytic astrocytoma
- High-grade astrocytoma with piloid features
- Pleomorphic xanthoastrocytoma
- Subependymal giant cell astrocytoma
- Chordoid glioma
- Astroblastoma, *MN1*-altered

Glioneuronal and neuronal tumours
- Ganglioglioma
- Gangliocytoma
- Desmoplastic infantile ganglioglioma
- Desmoplastic infantile astrocytoma
- Dysembryoplastic neuroepithelial tumour
- Diffuse glioneuronal tumour with oligodendroglioma-like features and nuclear clusters *
- Papillary glioneuronal tumour
- Rosette-forming glioneuronal tumour
- Myxoid glioneuronal tumour
- Diffuse leptomeningeal glioneuronal tumour
- Multinodular and vacuolating neuronal tumour
- Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)
- Central neurocytoma
- Extraventricular neurocytoma
- Cerebellar liponeurocytoma

Ependymal tumours
- Supratentorial ependymoma
- Supratentorial ependymoma, *ZFTA* fusion-positive
- Supratentorial ependymoma, *YAP1* fusion-positive
- Posterior fossa ependymoma
- Posterior fossa group A (PFA) ependymoma
- Posterior fossa group B (PFB) ependymoma
- Spinal ependymoma
- Spinal ependymoma, *MYCN*-amplified
- Myxopapillary ependymoma
- Subependymoma

CHOROID PLEXUS TUMOURS
- Choroid plexus papilloma
- Atypical choroid plexus papilloma
- Choroid plexus carcinoma

EMBRYONAL TUMOURS

Medulloblastomas, molecularly defined
- Medulloblastoma, WNT-activated
- Medulloblastoma, SHH-activated and *TP53*-wildtype
- Medulloblastoma, SHH-activated and *TP53*-mutant
- Medulloblastoma, non-WNT/non-SHH

Medulloblastomas, histologically defined
- Medulloblastomas

Other CNS embryonal tumours
- Atypical teratoid/rhabdoid tumour
- Cribriform neuroepithelial tumour *
- Embryonal tumour with multilayered rosettes
- CNS neuroblastoma, *FOXR2*-activated
- CNS tumour with *BCOR* internal tandem duplication
- CNS embryonal tumour, NEC/NOS

PINEAL TUMOURS
- Pineocytoma
- Pineal parenchymal tumour of intermediate differentiation
- Pineoblastoma
- Papillary tumour of the pineal region
- Desmoplastic myxoid tumour of the pineal region, *SMARCB1*-mutant *

CRANIAL & SPINAL NERVE TUMOURS
- Schwannoma
- Neurofibroma
- Perineurioma
- Hybrid nerve sheath tumours
- Malignant melanotic nerve sheath tumour
- Malignant peripheral nerve sheath tumour
- Cauda equina neuroendocrine tumour (previously paraganglioma)

MENINGIOMA
- Meningioma

OTHER MESENCHYMAL TUMOURS

Fibroblastic and myofibroblastic tumours
- Solitary fibrous tumour

Vascular tumours
- Cavernous haemangioma
- Capillary haemangioma
- Arteriovenous malformation
- Haemangioblastoma

Skeletal muscle tumours
- Embryonal rhabdomyosarcoma
- Alveolar rhabdomyosarcoma
- Rhabdomyosarcoma, pleomorphic-type
- Spindle cell rhabdomyosarcoma

Tumours of uncertain differentiation
- Intracranial mesenchymal tumour, FET::CREB fusion-positive *
- *CIC*-rearranged sarcoma
- Primary intracranial sarcoma, *DICER1*-mutant
- Ewing sarcoma

Chondrogenic tumours
- Mesenchymal chondrosarcoma
- Chondrosarcoma
- Dedifferentiated chondrosarcoma

OTHER MESENCHYMAL TUMOURS (continued)

Notochordal tumours
- Chordoma

MELANOCYTIC TUMOURS

Diffuse meningeal melanocytic neoplasms
- Meningeal melanocytosis
- Meningeal melanomatosis

Circumscribed meningeal melanocytic neoplasms
- Meningeal melanocytoma
- Meningeal melanoma

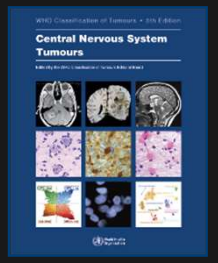
HAEMATOLYMPHOID TUMOURS

CNS lymphomas
- Primary diffuse large B-cell lymphoma of the CNS
- Lymphomatoid granulomatosis
- Intravascular large B-cell lymphoma
- MALT lymphoma of the dura
- Follicular lymphoma
- Anaplastic large cell lymphoma (ALK+/ALK-)
- T-cell lymphoma
- NK/T-cell lymphoma

Histiocytic tumours
- Erdheim-Chester disease
- Rosai-Dorfman disease
- Juvenile xanthogranuloma
- Langerhans cell histiocytosis
- Histiocytic sarcoma

GERM CELL TUMOURS
- Mature teratoma
- Immature teratoma
- Teratoma with somatic-type malignancy
- Germinoma
- Embryonal carcinoma
- Yolk sac tumour
- Choriocarcinoma
- Mixed germ cell tumour

TUMOURS OF THE SELLAR REGION
- Adamantinomatous craniopharyngioma
- Papillary craniopharyngioma
- Pituicytoma
- Granular cell tumor of the sellar region
- Spindle cell oncocytoma
- Pituitary adenoma/pituitary neuroendocrine tumour
- Pituitary blastoma



CATEGORY
Family
Type

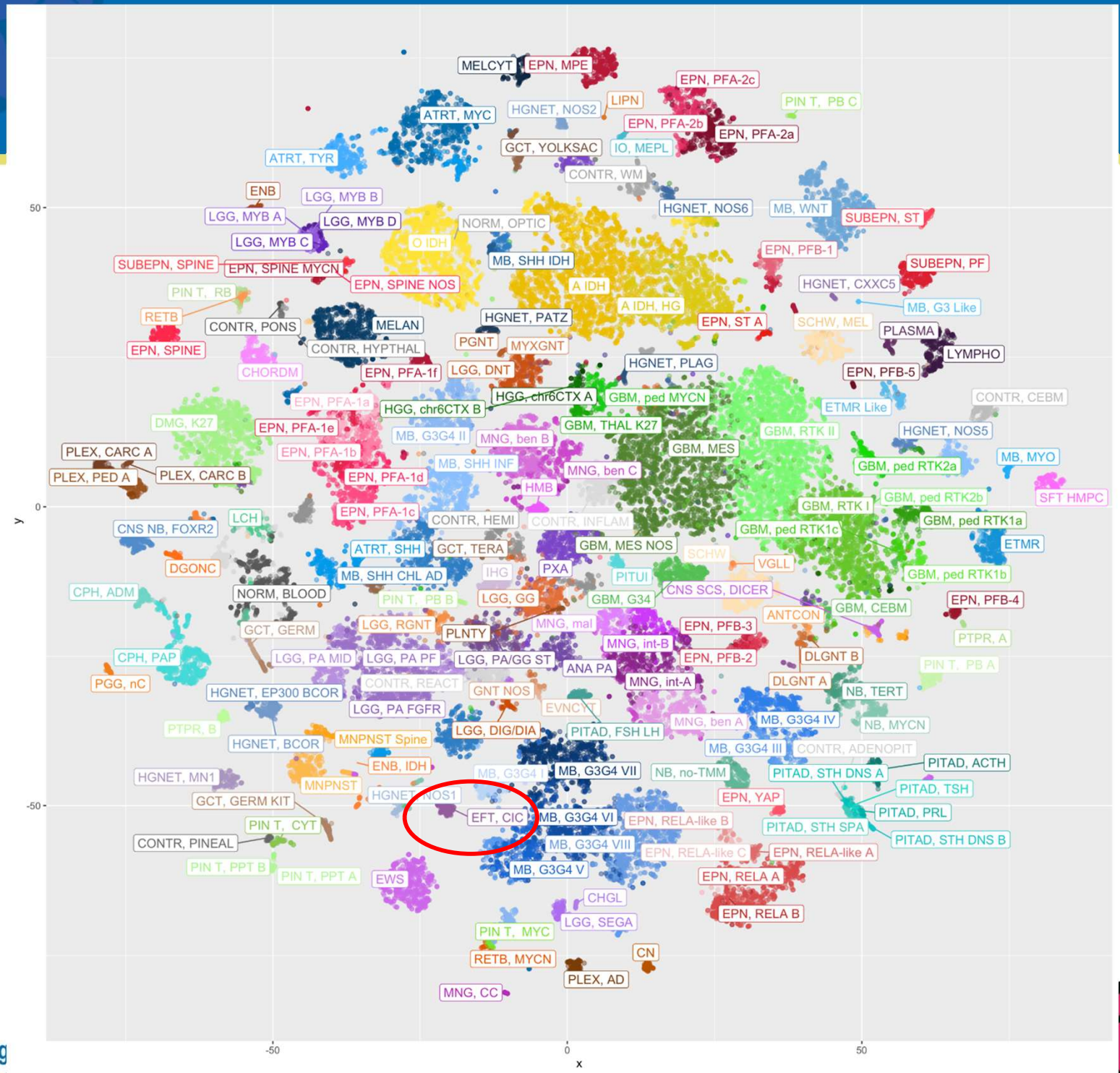
* provisional type

Lilith re-visited in 2018

Brain tumor methylation classifier results (v11b4)

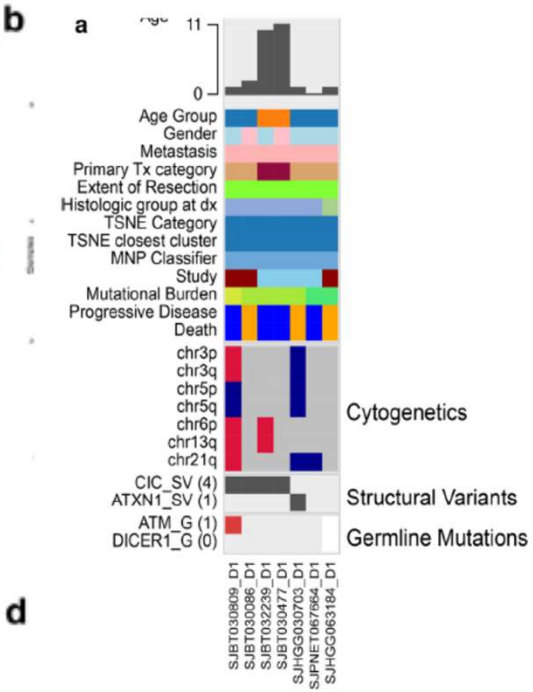
Methylation classes (MCs with score >= 0.3)	Calibrated score	Interpretation	
methylation class CNS Ewing sarcoma family tumor with CIC alteration	0.76	no match	✗

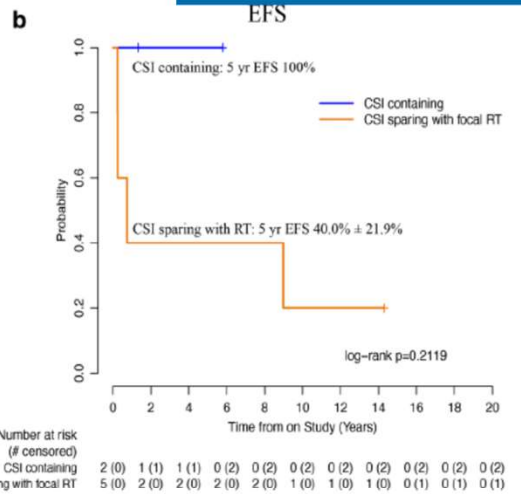
Legend: ✓ Match (score >= 0.9) ✗ No match (score < 0.9): possibly still relevant for low tumor content and low DNA quality cases. ● Match to MC family member (score >= 0.5)

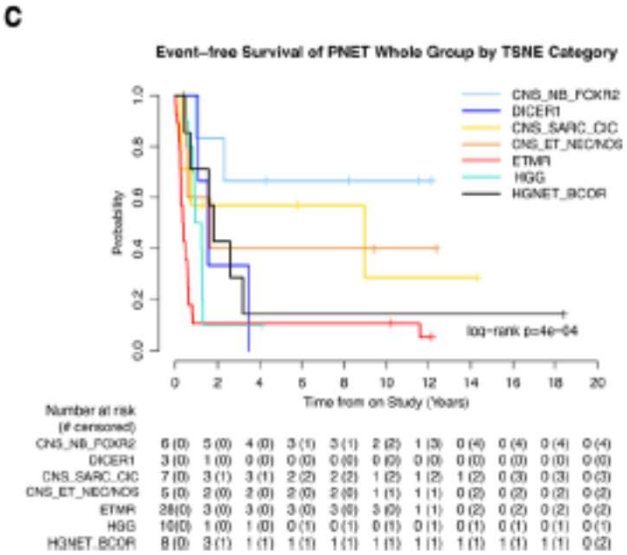


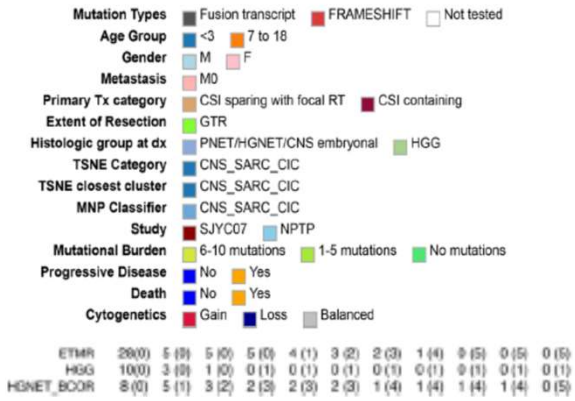
Publieksdag Hersentumoren

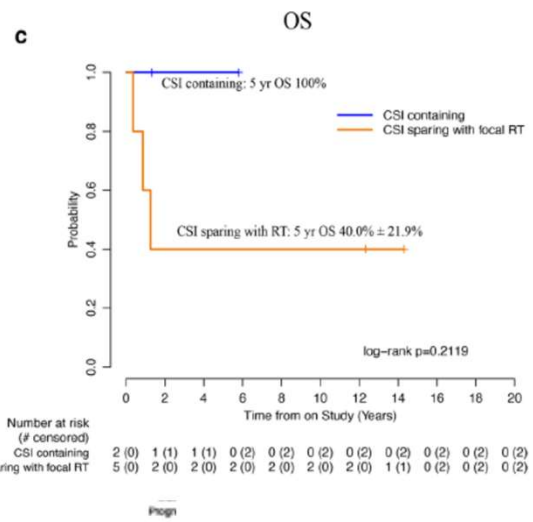

a
HGG


b
a
11
0
Age Group
Gender
Metastasis
Primary Tx category
Extent of Resection
Histologic group at dx
TSNE Category
TSNE closest cluster
MNP Classifier
Study
Mutational Burden
Progressive Disease
Death
chr3p
chr3q
chr5p
chr5q
chr6p
chr13q
chr21q
Cytogenetics
CIC_SV (4)
ATXN1_SV (1)
Structural Variants
ATM_G (1)
DICER1_G (0)
Germline Mutations
SJBT030809_D1
SJBT030086_D1
SJBT032239_D1
SJBT030477_D1
SJHGG030703_D1
SJPNET067664_D1
SJHGG063184_D1


b
EFS
CSI containing: 5 yr EFS 100%
CSI containing
CSI sparing with focal RT
CSI sparing with RT: 5 yr EFS 40.0% ± 21.9%
log-rank p=0.2119
Probability
Time from on Study (Years)
Number at risk
(# censored)
CSI containing 2 (0) 1 (1) 1 (1) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2)
CSI sparing with focal RT 5 (0) 2 (0) 2 (0) 2 (0) 2 (0) 1 (0) 1 (0) 1 (0) 0 (1) 0 (1) 0 (1)


c
Event-free Survival of PNET Whole Group by TSNE Category
CNS_NB_FOXR2
DICER1
CNS_SARC_CIC
CNS_ET_NEC/NOS
ETMR
HGG
HGNET_BCOR
Probability
log-rank p=4e-04
Time from on Study (Years)
Number at risk
(# censored)
CNS_NB_FOXR2 6 (0) 5 (0) 4 (0) 3 (1) 3 (1) 2 (2) 1 (3) 0 (4) 0 (4) 0 (4) 0 (4)
DICER1 3 (0) 1 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0)
CNS_SARC_CIC 7 (0) 3 (1) 3 (1) 2 (2) 2 (2) 1 (2) 1 (2) 1 (2) 0 (3) 0 (3) 0 (3)
CNS_ET_NEC/NOS 5 (0) 2 (0) 2 (0) 2 (0) 2 (0) 1 (1) 1 (1) 0 (2) 0 (2) 0 (2) 0 (2)
ETMR 28(0) 3 (0) 3 (0) 3 (0) 3 (0) 3 (0) 1 (1) 0 (2) 0 (2) 0 (2) 0 (2)
HGG 10(0) 1 (0) 1 (0) 0 (1) 0 (1) 0 (1) 0 (1) 0 (1) 0 (1) 0 (1) 0 (1)
HGNET_BCOR 8 (0) 3 (1) 1 (1) 1 (1) 1 (1) 1 (1) 1 (1) 1 (1) 1 (1) 1 (1) 0 (2)


d
Mutation Types Fusion transcript FRAMESHIFT Not tested
Age Group <3 7 to 18
Gender M F
Metastasis M0
Primary Tx category CSI sparing with focal RT CSI containing
Extent of Resection GTR
Histologic group at dx PNET/HGNET/CNS embryonal HGG
TSNE Category CNS_SARC_CIC
TSNE closest cluster CNS_SARC_CIC
MNP Classifier CNS_SARC_CIC
Study SJYC07 NPTP
Mutational Burden 6-10 mutations 1-5 mutations No mutations
Progressive Disease No Yes
Death No Yes
Cytogenetics Gain Loss Balanced
ETMR 28(0) 5 (0) 5 (0) 5 (0) 4 (1) 3 (2) 2 (3) 1 (4) 0 (5) 0 (5) 0 (5)
HGG 10(0) 3 (0) 1 (0) 0 (1) 0 (1) 0 (1) 0 (1) 0 (1) 0 (1) 0 (1) 0 (1)
HGNET_BCOR 8 (0) 5 (1) 3 (2) 2 (3) 2 (3) 2 (3) 1 (4) 1 (4) 1 (4) 1 (4) 0 (5)


c
OS
CSI containing: 5 yr OS 100%
CSI containing
CSI sparing with focal RT
CSI sparing with RT: 5 yr OS 40.0% ± 21.9%
log-rank p=0.2119
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CSI containing 2 (0) 1 (1) 1 (1) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2)
CSI sparing with focal RT 5 (0) 2 (0) 2 (0) 2 (0) 2 (0) 2 (0) 2 (0) 1 (1) 0 (2) 0 (2) 0 (2)

Samenvattend

- De landschap van de hersentumor diagnostiek is behoorlijk veranderd!
- Het is een complex plaatje met meer puzzelsteentjes in verschillende kleuren!
- Er moet nog minimum een generatie overheen gaan om alle gegevens wat beter te kunnen begrijpen.

Hersentumoren