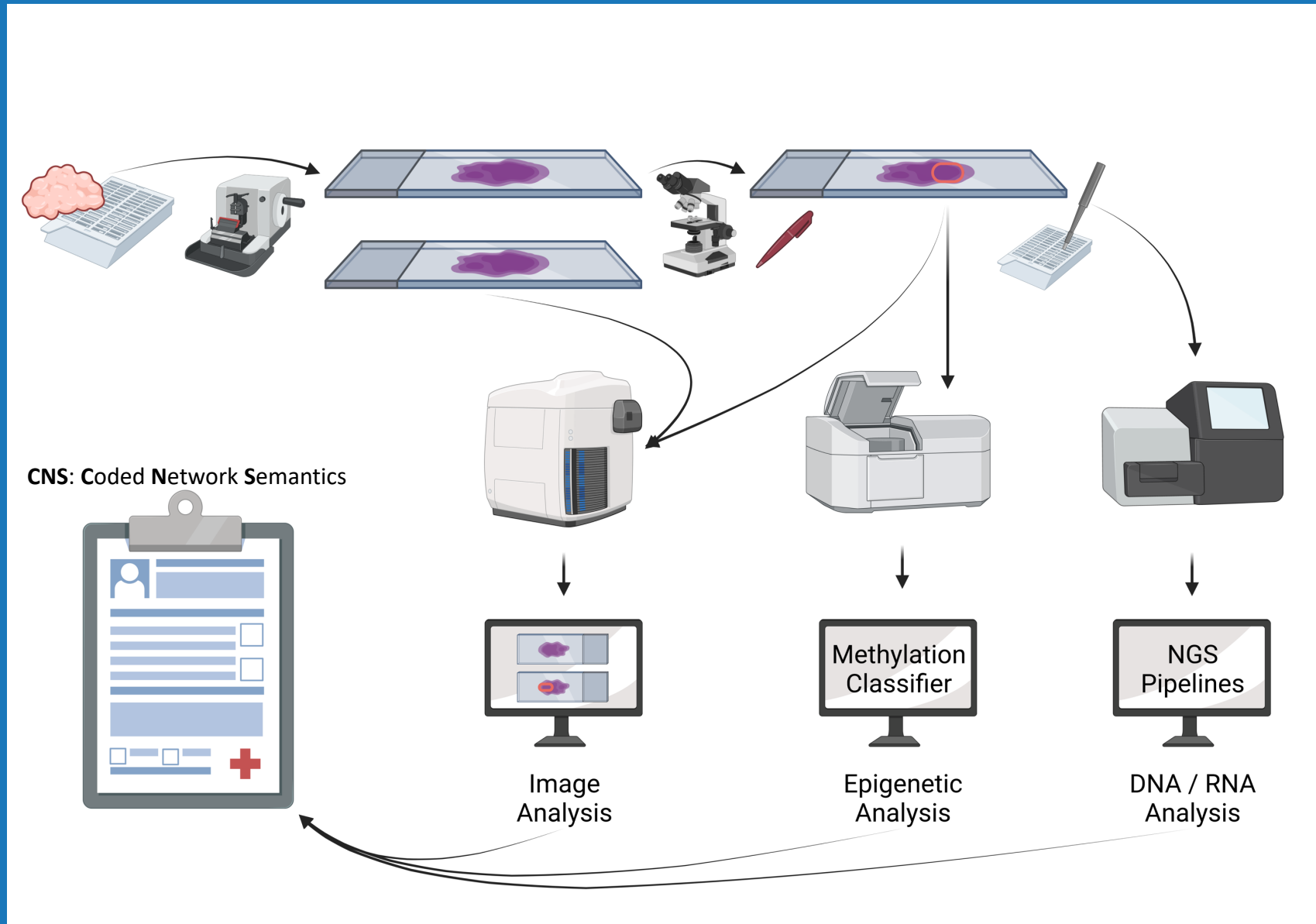
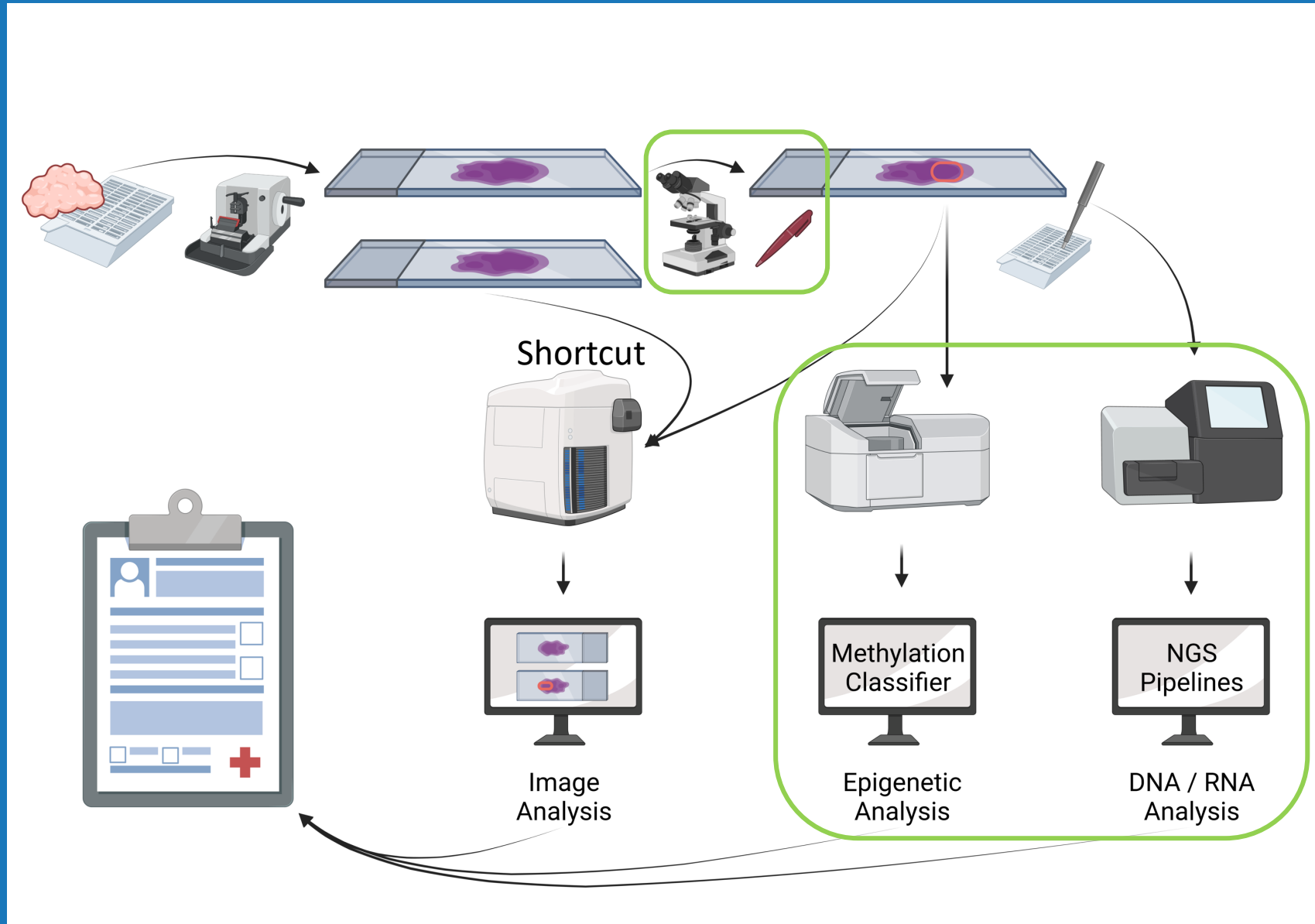


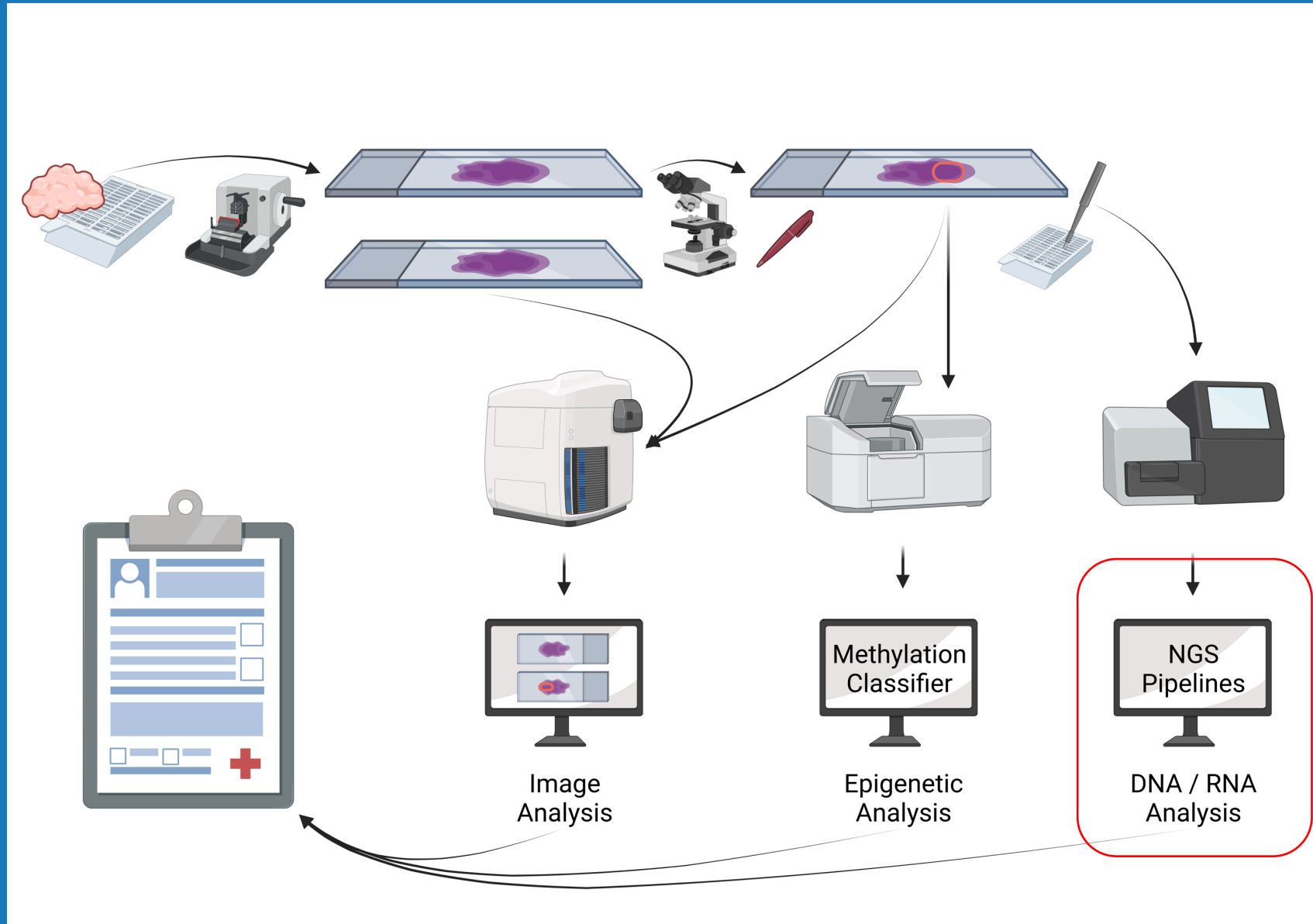
KI-gestützte morphologische Präzision- Medizin in der Neuroonkologie

Dr. rer. nat. Daniel Amsel
M.Sc. Bioinformatics

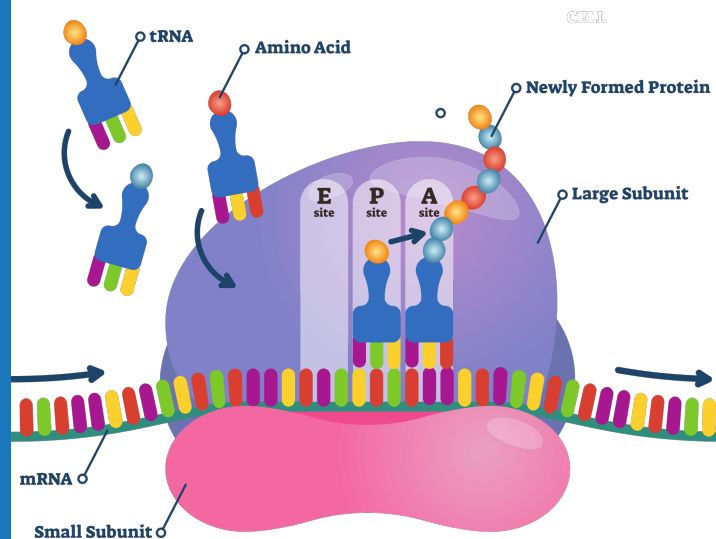
Junior Research Group Leader AI-RON
"AI-assisted morphomolecular Precision Medicine in Neurooncology"







DNA Analysis



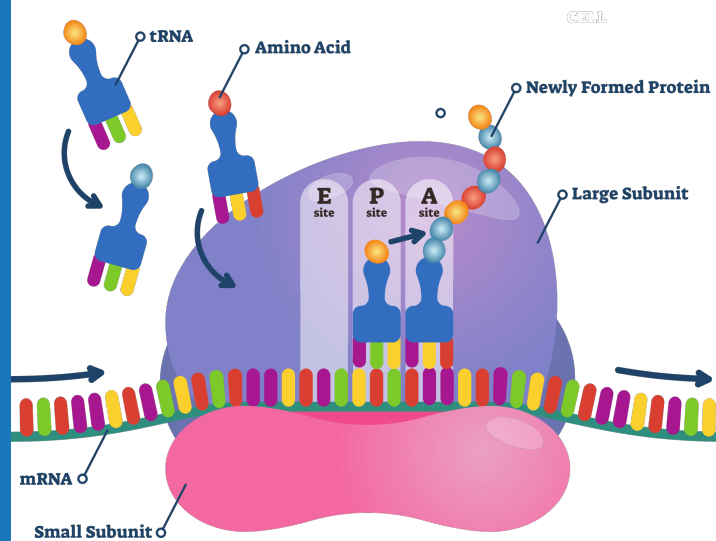
Source: <https://www.e-zyvec.com/wp-content/uploads/2020/01/Ribosome-1.png> 21.01.23

• Nucleotide Polymorphisms

Level	Alterations	Level-associated cancer types ①	Drugs	Citations
R1	F359V	Chronic Myelogenous Leukemia	Nilotinib	5
2	Y253H	Chronic Myelogenous Leukemia	Bosutinib	1
R1	G250E	Chronic Myelogenous Leukemia	Bosutinib	1
1	T315I	Chronic Myelogenous Leukemia	Ponatinib	3
R1	F359I	Chronic Myelogenous Leukemia	Nilotinib	5
2	F359C	Chronic Myelogenous Leukemia	Dasatinib	3
R1	G250E	Chronic Myelogenous Leukemia	Imatinib	5
R1	F359I	Chronic Myelogenous Leukemia	Imatinib	5
1	BCR-ABL1 Fusion	Chronic Myelogenous Leukemia	Asciminib	1
2	F317V	Chronic Myelogenous Leukemia	Bosutinib	1
R1	E255V	Chronic Myelogenous Leukemia	Nilotinib	5
R1	V299L	Chronic Myelogenous Leukemia	Bosutinib	1
R1	F359V	Chronic Myelogenous Leukemia	Imatinib	5
R1	T315A	Chronic Myelogenous Leukemia	Imatinib	5
1	BCR-ABL1 Fusion	Chronic Myelogenous Leukemia	Nilotinib	3
2	F317L	Chronic Myelogenous Leukemia	Nilotinib	3

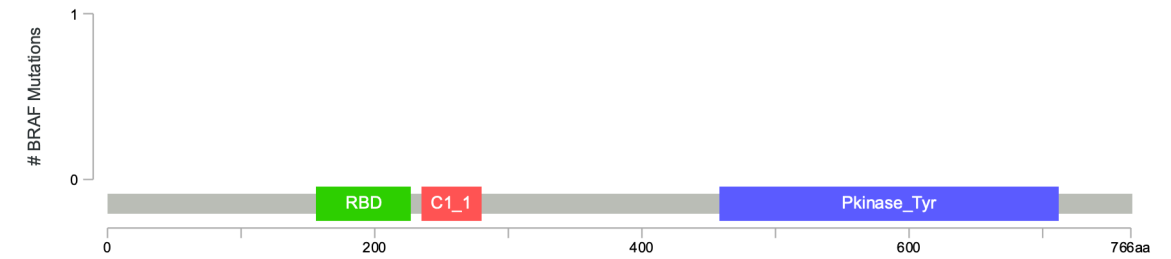
Source: <https://www.oncokb.org/gene/ABL1> 11.01.23

DNA Analysis

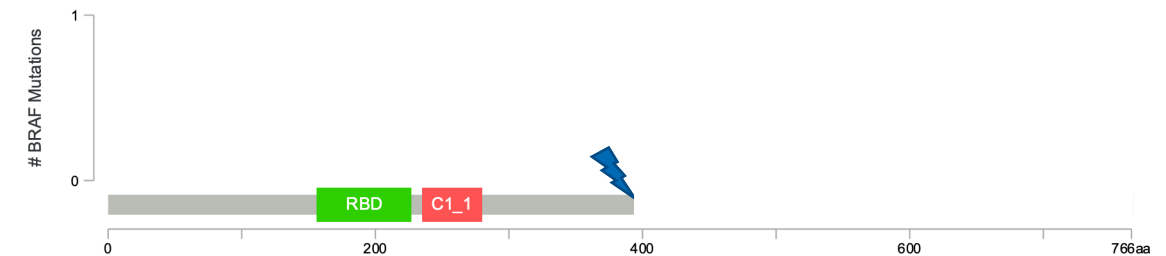


Source: <https://www.e-zylvec.com/wp-content/uploads/2020/01/Ribosome-1.png> 21.01.23

•small Insertions / Deletions

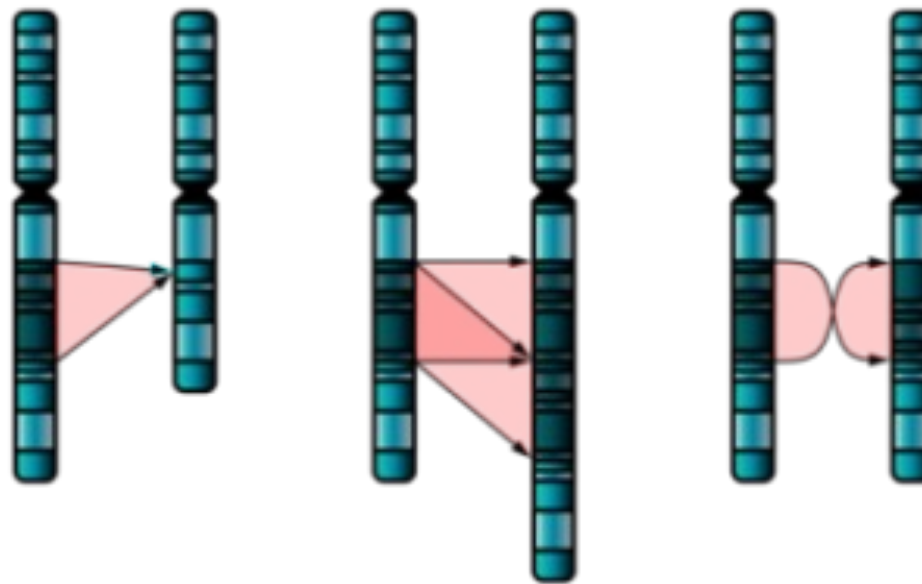


Source: <https://www.oncokb.org/gene/BRAF> 11.01.23



DNA Analysis

- Larger areas of the DNA can be deleted, duplicated or moved

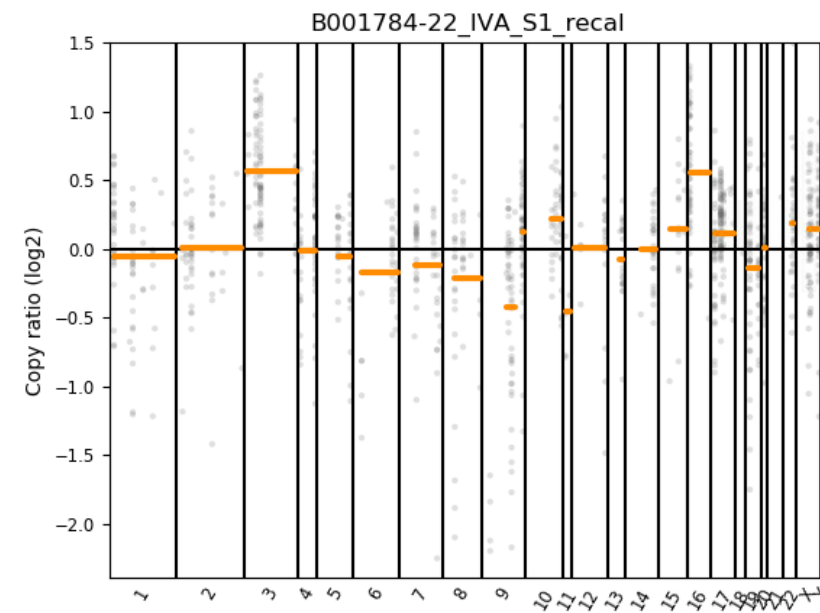
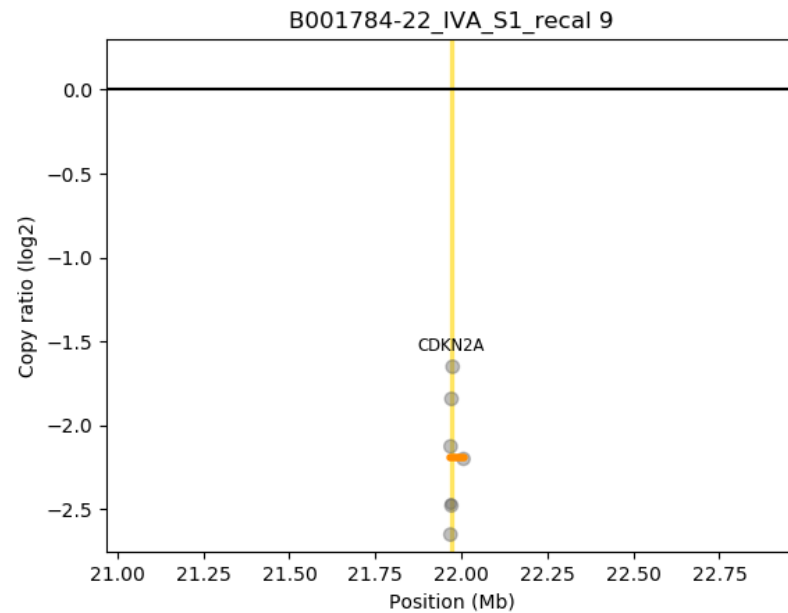


Source: https://bredagenetics.com/wp-content/uploads/2016/01/Single_Chromosome_Mutations.svg_-300x188.png 11.01.23

DNA Analysis

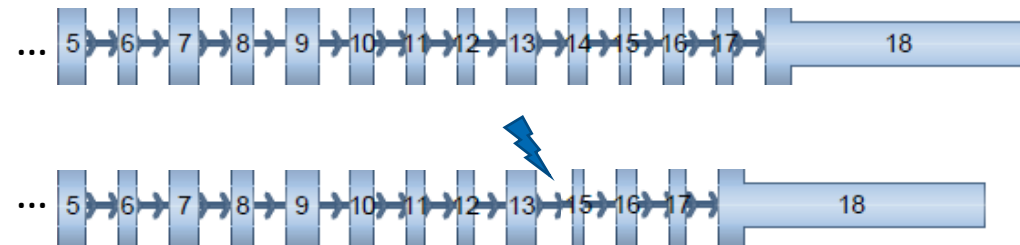
- CopyNumberVariation

e.g. CDKN2A/B Deletion = worse prognosis



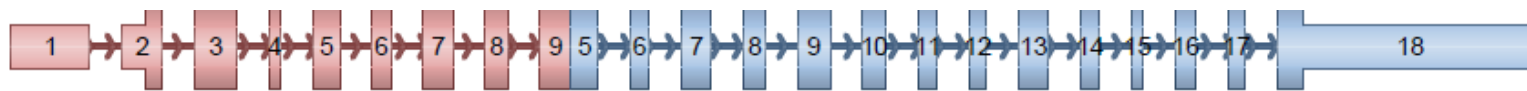
RNA Analysis

- Genefusions

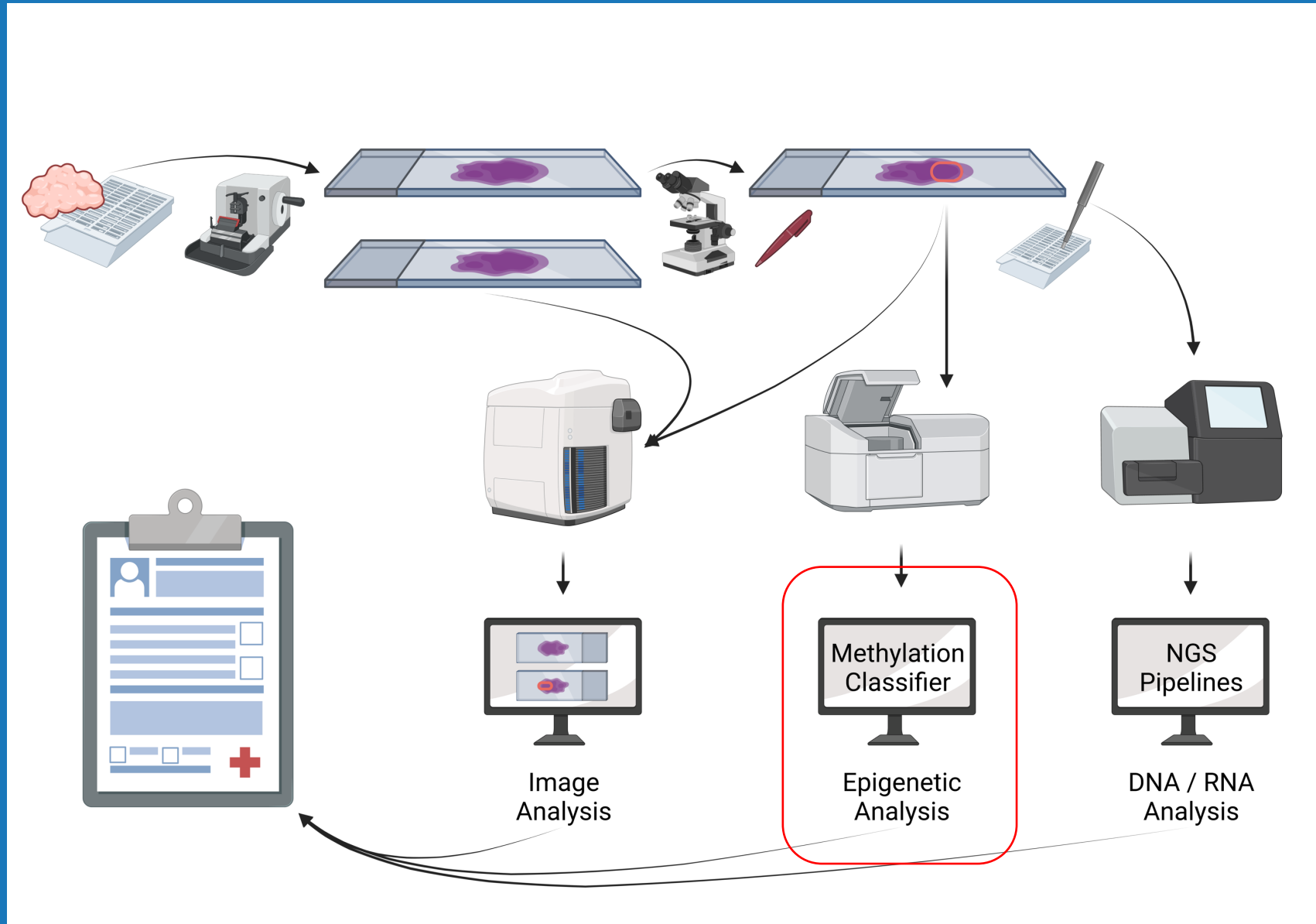


MET exon14 Skipping

e.g. Non-small-cell lung cancer



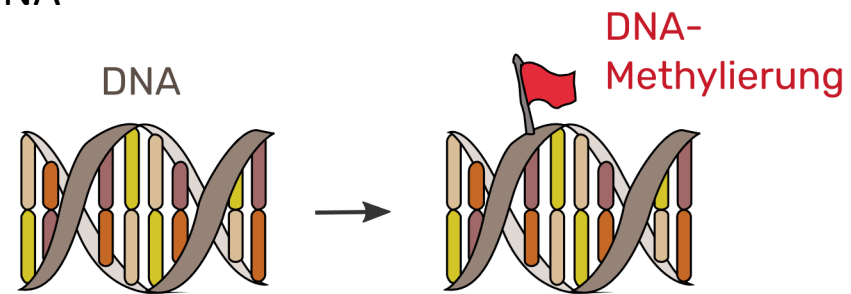
Internal genefusions
(e.g. Internal Tandem Duplication)
and
Gen1:Gen2 fusions
(e.g. BRAF::KIAA)



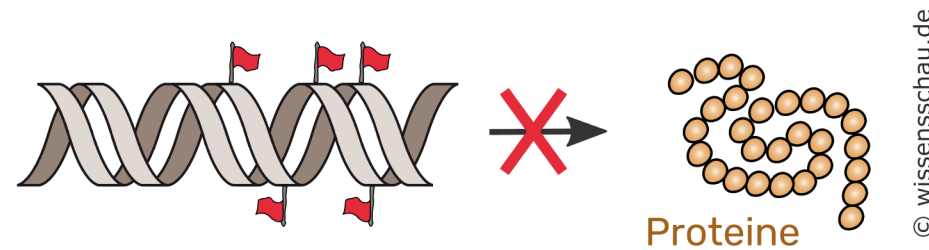
Epigenetic Analysis

- Epigenetics

Small molecules change the DNA

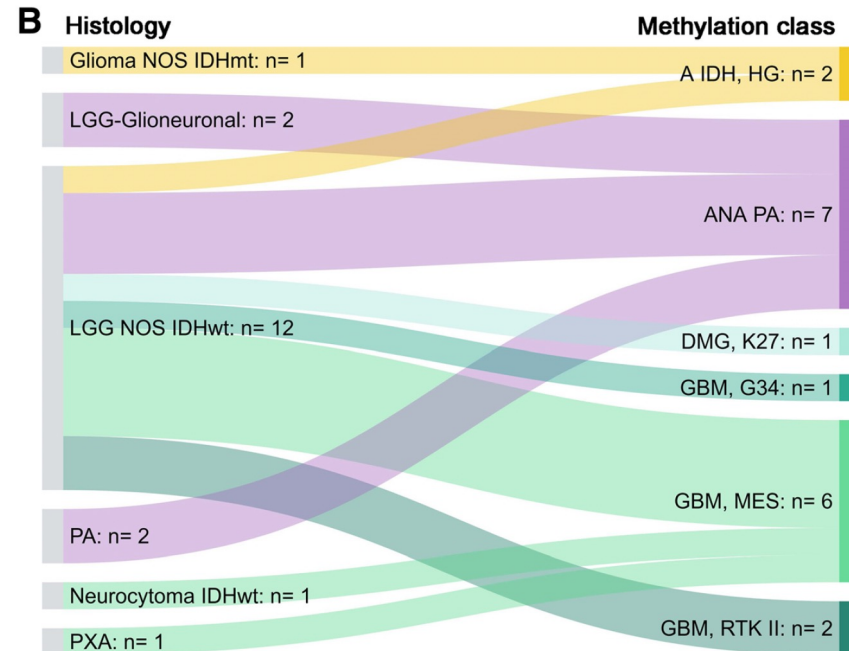


... and change the activity of the genes.



Source: https://www.wissenschau.de/genom/epigenetik_und_epigenom.php 08.01.23

Epigenetic Analysis



Jaunmuktane, Zane, et al. "Methylation array profiling of adult brain tumours: diagnostic outcomes in a large, single centre." *Acta neuropathologica communications* 7.1 (2019): 1-18.

Table 4 Clinical summary of cases with a significant methylation-mediated impact on patient care

Case no.	Initial pathology (*differential)	Initial treatment plan	Integrated diagnosis	New treatment plan	Methylation profiling impact
1	Glioma NOS -IDH1 (R132H)-neg, high-grade features	Offered FSRT/TMZ & adjuvant TMZ	DNET	Observation	1) Avoided unnecessary treatment 2) Resolved anxiety due to initial diagnosis/treatment
2	Anaplastic oligodendroglioma -IDH1 (R132H)-neg, 1p/19q-codeletion	1) Received FSRT 2) Planned for PCV	Anaplastic PXA	1) Hold PCV 2) Observe	Avoided unnecessary treatment
3	Glioma NOS -IDH1 (R132H)-neg, anaplastic features	Offered FSRT/TMZ and adjuvant TMZ	DLGNT	Observation	Avoided unnecessary treatment

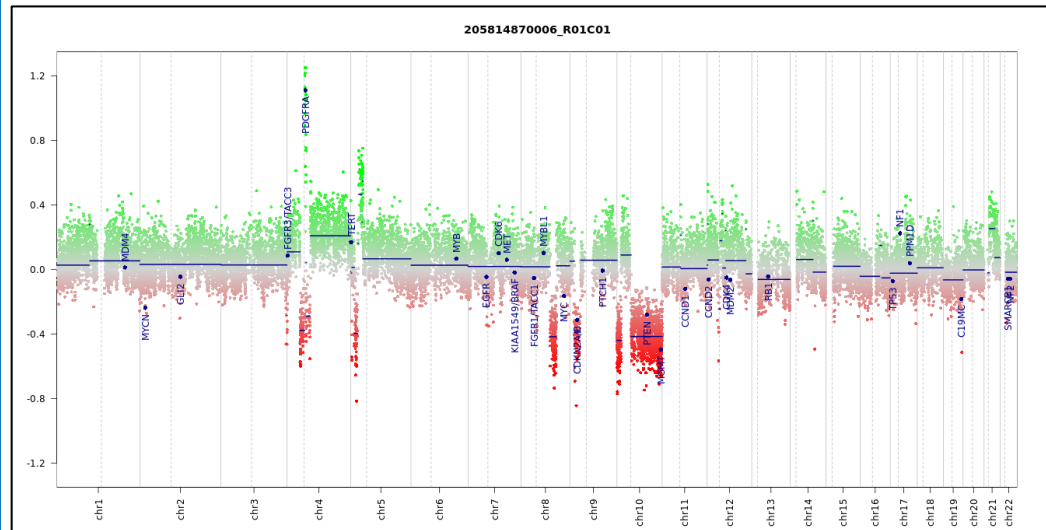
Current WHO: Methylation profiling is essential for diagnosis of Diffuse leptomeningeal glioneuronal tumor

6	1) PXA* 2) Other high-grade gliomas - IDH1 (R132H)-neg, BRAF (V600E)-neg	Considered reduced dosing for FSRT/TMZ & adjuvant TMZ	GBM, IDH wildtype	Treatment fully completed	Avoided possible insufficient initial treatment
7	Metastatic high-grade neuro-endocrine tumor -TTF1-pos, IDH1 (R132H)-neg, well demarcated	1) SRS post-op 2) FSRT and cisplatin/etoposide for 1st recurrence 3) Surgery and WBRT for second recurrence	GBM, IDH wildtype	Temozolomide provided after second recurrence	1) Received insufficient treatment and recurred 2) May have avoided unnecessary invasive biopsies

GBM glioblastoma, PXA pleomorphic xanthoastrocytoma, DLGNT diffuse leptomeningeal glioneuronal tumor, NOS not otherwise specified, DNET dysembryoplastic neuroepithelial tumor, SRS single-dose stereotactic radiosurgery, FSRT fractionated stereotactic radiotherapy, TMZ temozolomide, RT radiotherapy

Karimi, Shirin, et al. "The central nervous system tumor methylation classifier changes neuro-oncology practice for challenging brain tumor diagnoses and directly impacts patient care." *Clinical epigenetics* 11.1 (2019): 1-10.

Epigenetic Analysis

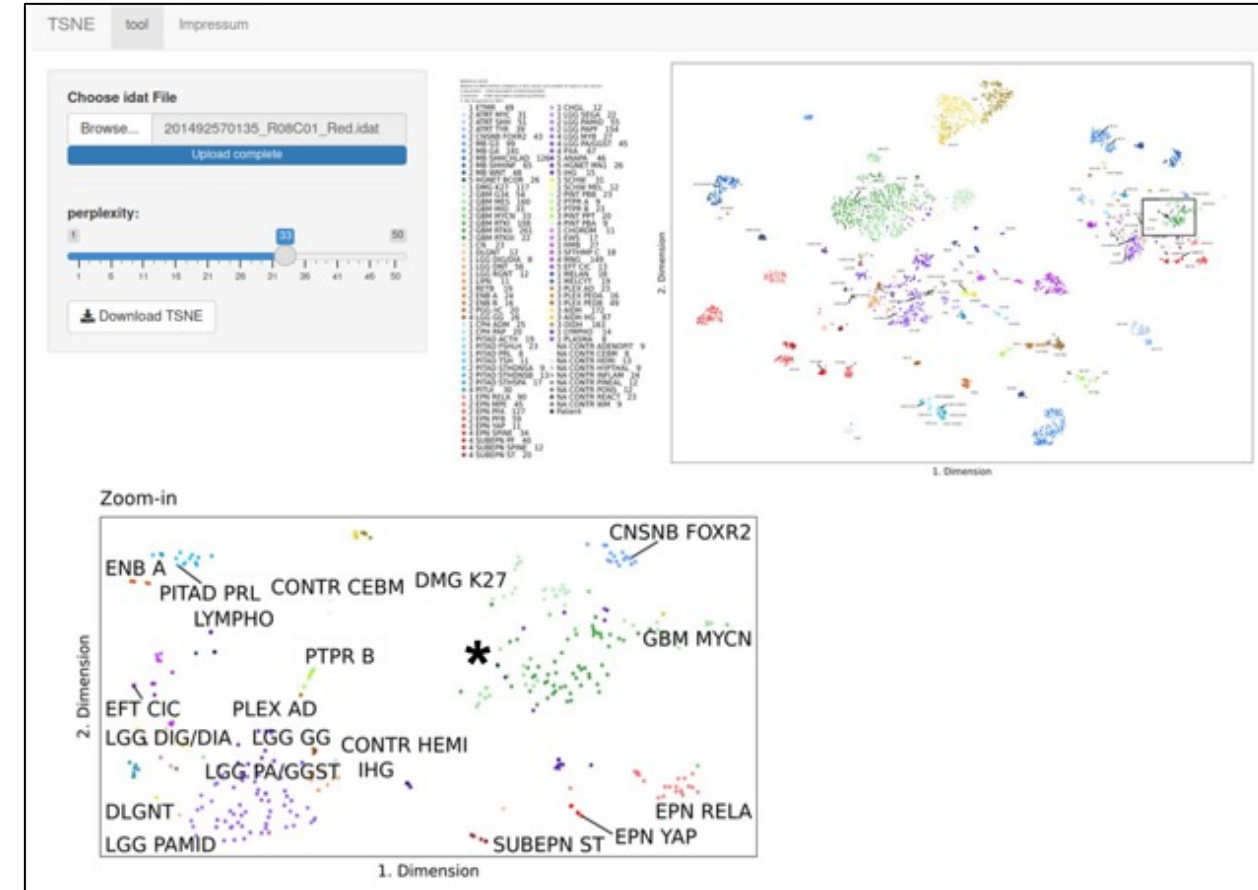


CopyNumberVariation (Array-based)

Classifier prediction (Brain tumor classifier; Version: 11b4)

Methylation classes (MCs with score >= 0.3)	Calibrated score	Interpretation
Methylation class family Glioblastoma, IDH wildtype	0.98715	match ✓
MC family members with score >= 0.1		
Methylation class glioblastoma, IDH wildtype, subclass midline	0.93045	●

Heidelberg-Classifier (<https://www.molecularneuropathology.org>)



t-SNE (own development)

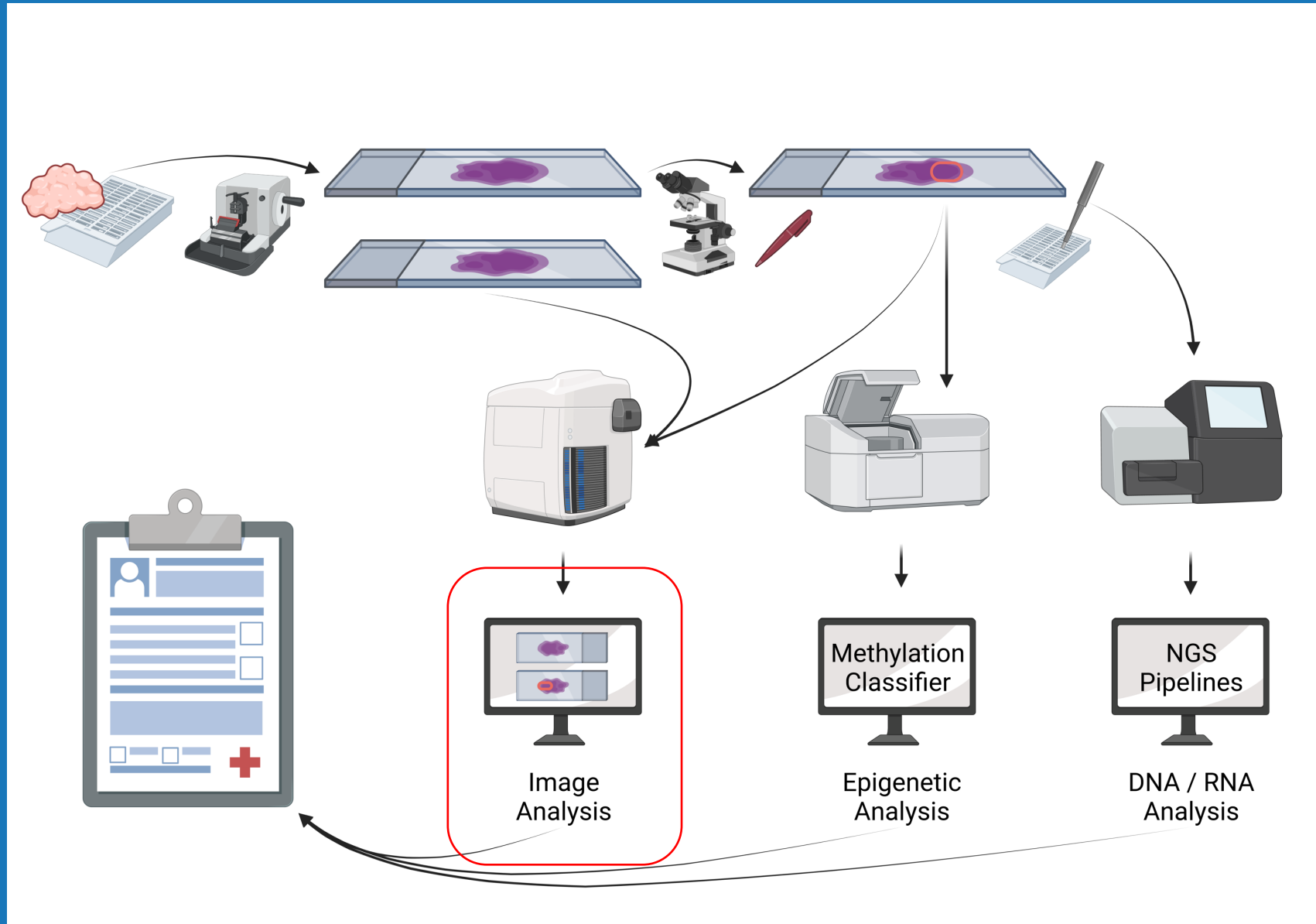
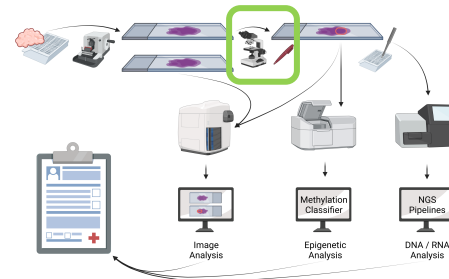


Image Analysis

Two goals:

- Support diagnostics by providing information, a trained human being can find as well



- Support diagnostics by providing information, no human being can see

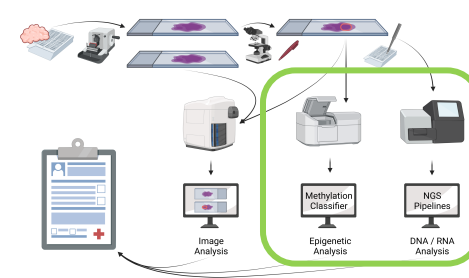


Image Analysis

Two goals:

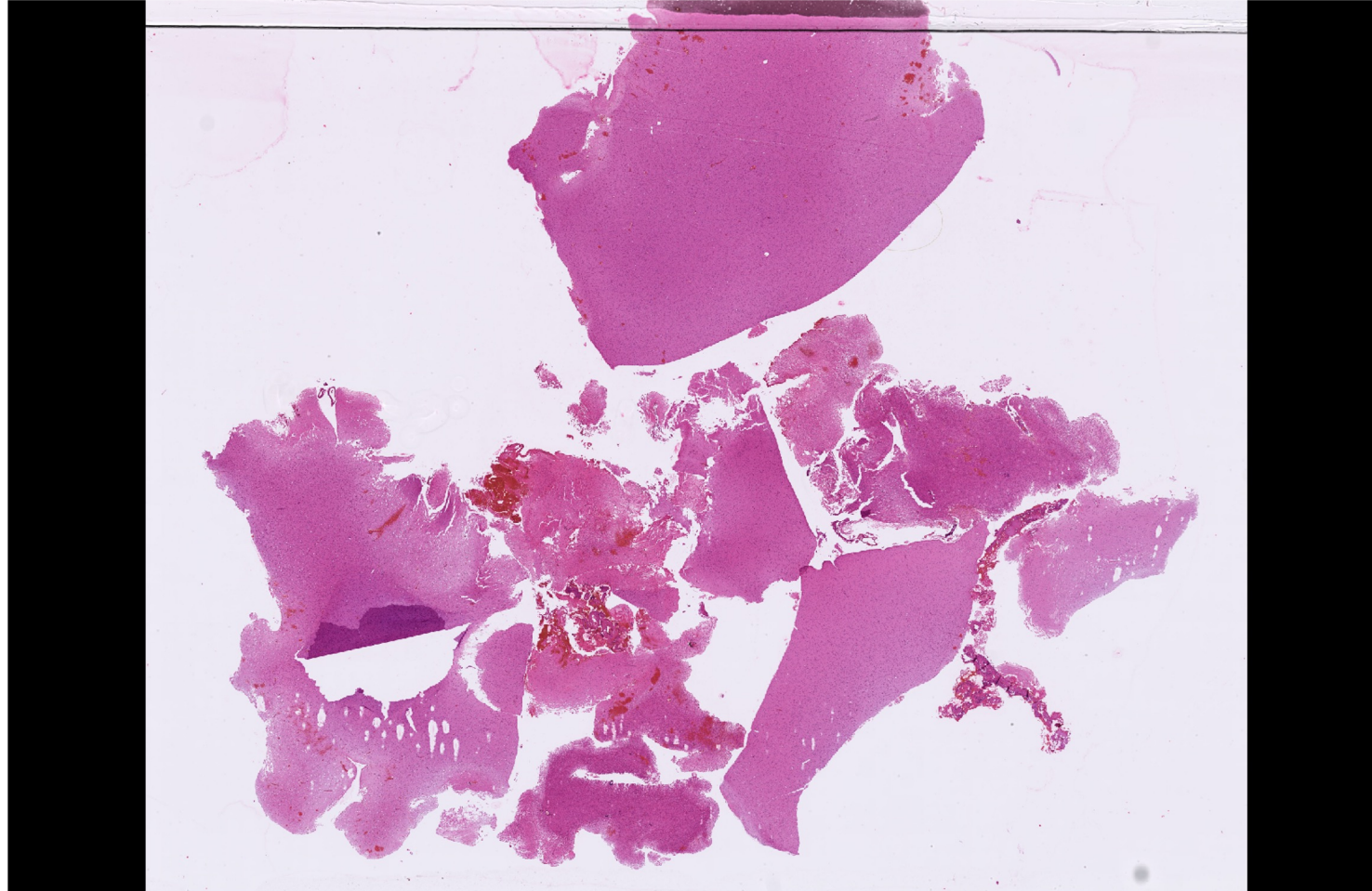
- Support diagnostics by providing information, a trained human being can find as well
 - Mitosis count
 - Highlight tumor area, necrosis, pseudopalisading,...
- Support diagnostics by providing information, no human being can see

Image Analysis

Two goals:

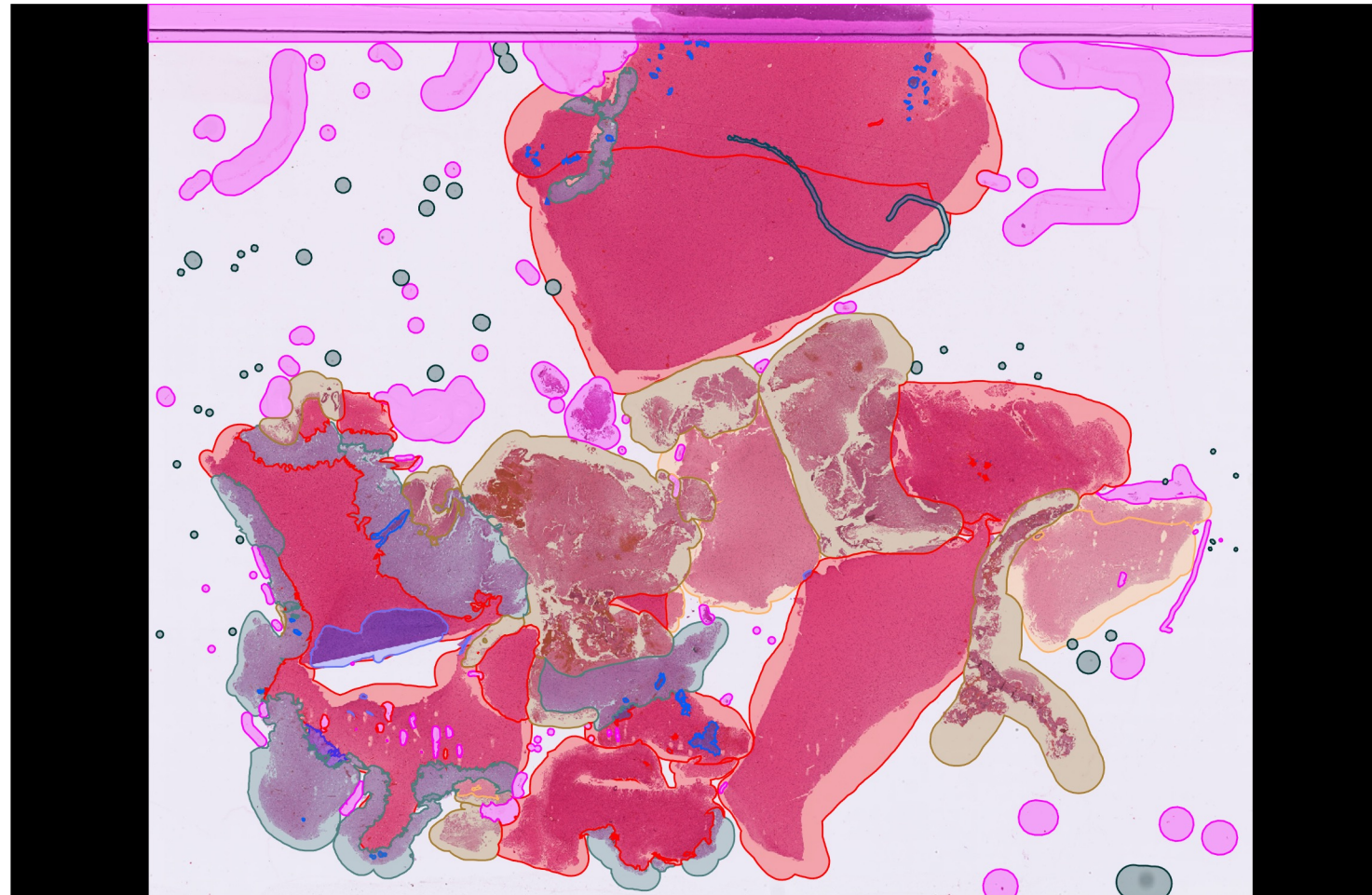
- Support diagnostics by providing information, a trained human being can find as well
 - Mitosis count
 - Highlight tumor area, necrosis, pseudopalisading,...
 - **Needs annotated data for AI training**
- Support diagnostics by providing information, no human being can see

QuPath - expert curation



QuPath - expert curation

- Tumor (13)
- Infiltrationszone (5)
- Hirnparenchym
- Blutung (30)
- Nekrosen
- Nekrose und Blutung (1)
- Pränekrose (16)
- artifiziell verändertes Gewebe (13)
- Pseudopalisaden
- Falten (6)
- Risse
- Artefakt (66)
- out of focus
- Luftblasen (19)
- Haare (1)
- Filzstift



brAIIn App – crowdsourcing and teaching

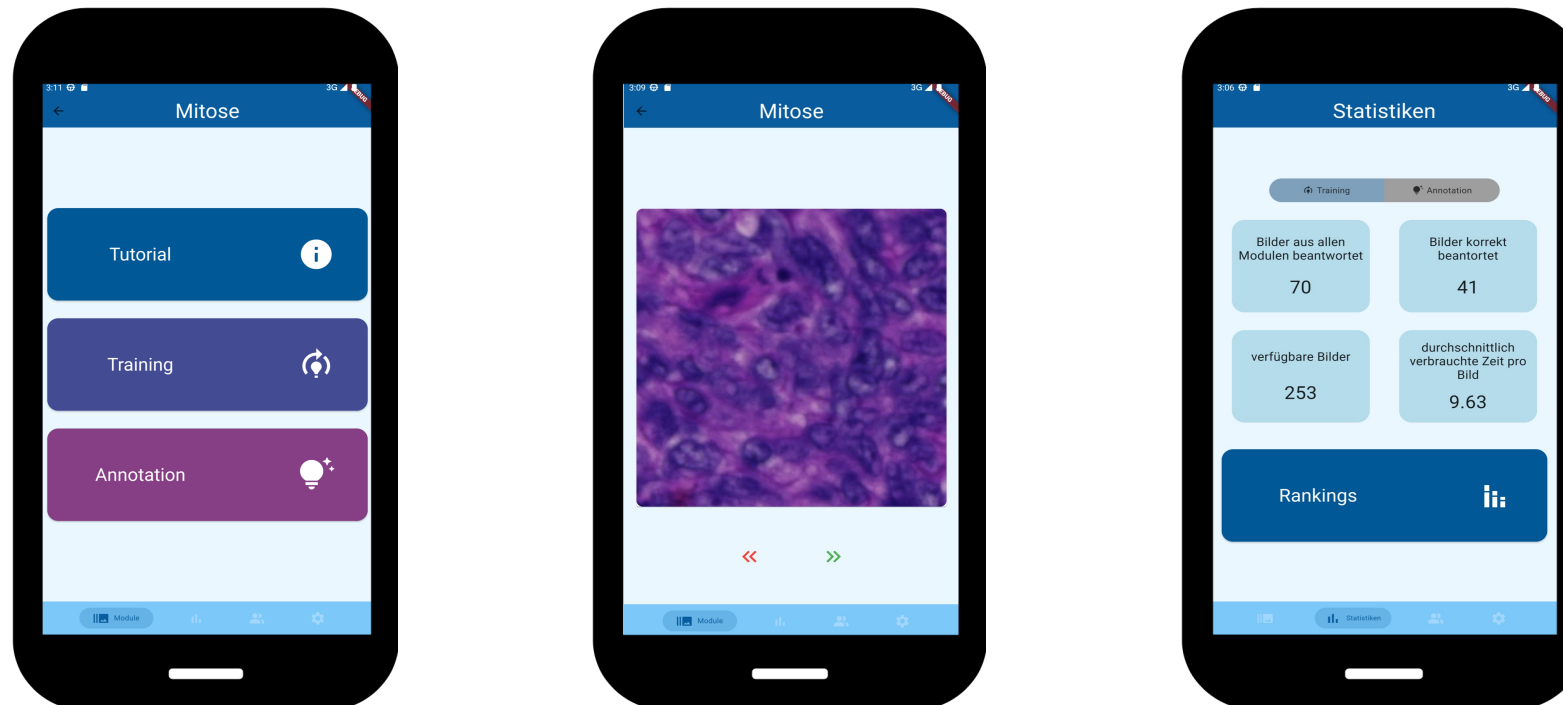


Image Analysis

Two goals:

- Support diagnostics by providing information, a trained human being can find as well
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Image Analysis

Two goals:

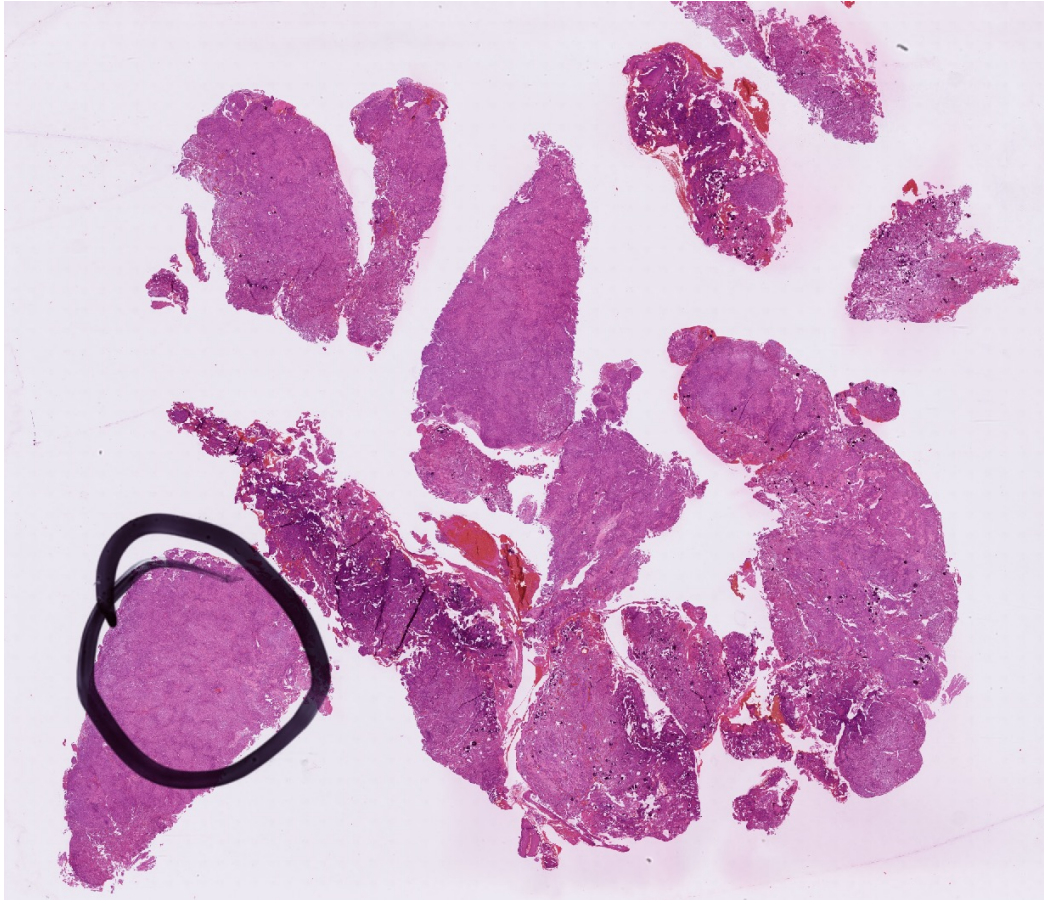
- Support diagnostics by providing information, a trained human being can find as well
 - Mitosis count
 - Highlight tumor area, necrosis, pseudopalisading,...
 - **Needs annotated data for AI training**
- Support diagnostics by providing information, no human being can see
 - Predict molecular genetic variants (IDH mutant,...)
 - Predict epigenetic type (methylation class diffuse midline glioma H3 K27M mutant,...)

Image Analysis

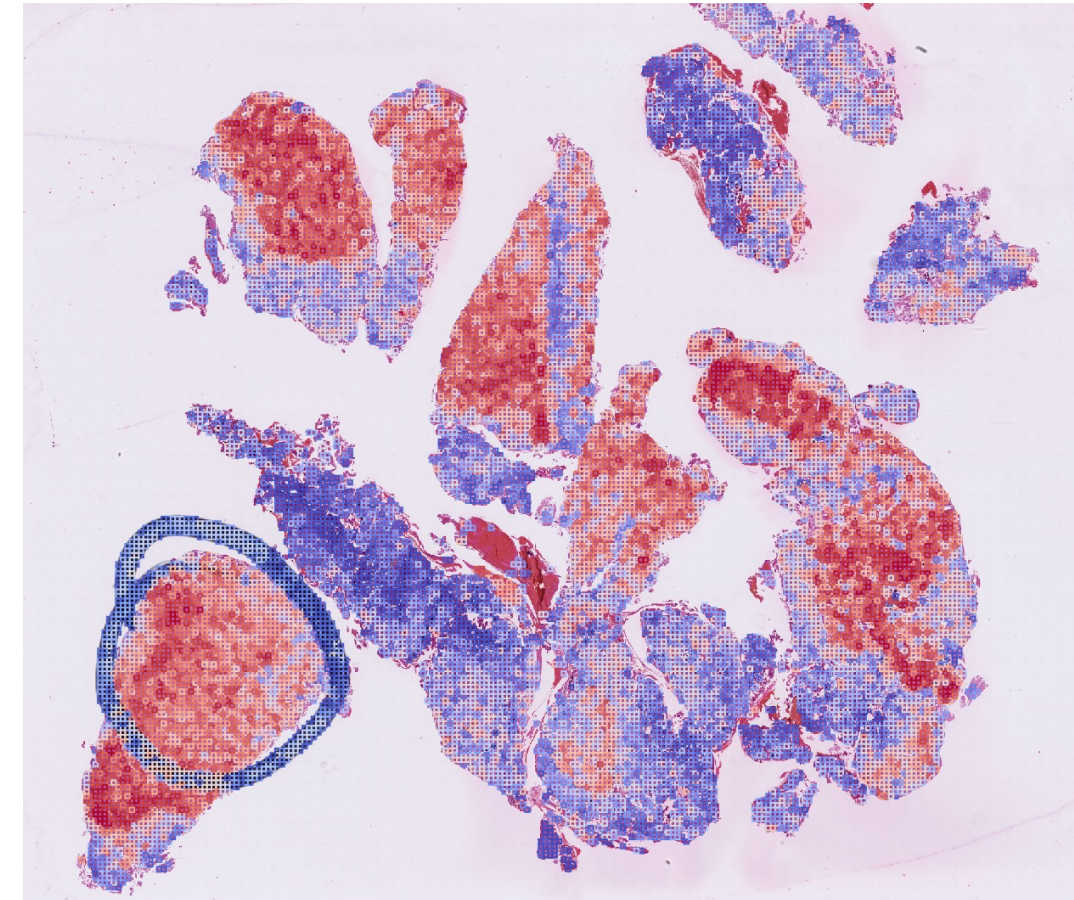
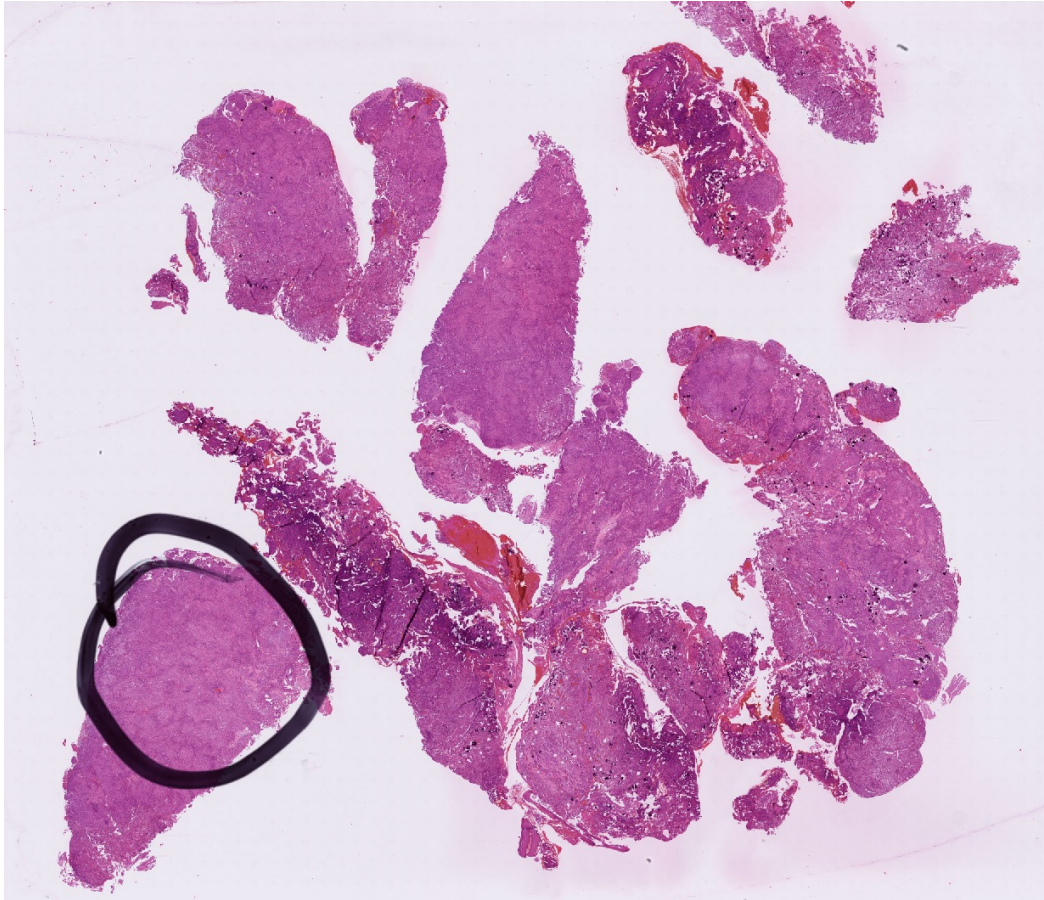
Two goals:

- Support diagnostics by providing information, a trained human being can find as well
 - Mitosis count
 - Highlight tumor area, necrosis, pseudopalisading,...
 - **Needs annotated data for AI training**
- Support diagnostics by providing information, no human being can see
 - Predict molecular genetic variants (IDH mutant,...)
 - Predict epigenetic type (methylation class diffuse midline glioma H3 K27M mutant,...)
 - **Weakly supervised AI training**

AI tumor classification



AI tumor classification



Low attention Attention Map High attention

MNG Benign-1 94%

Image Analysis Difficulties

Image Analysis Difficulties: Dataset size

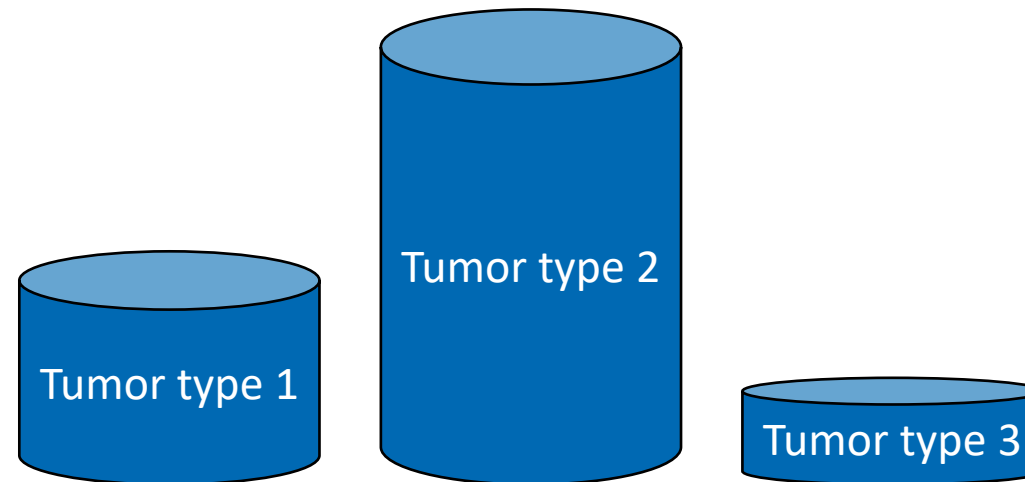


Image Analysis Difficulties: Dataset size

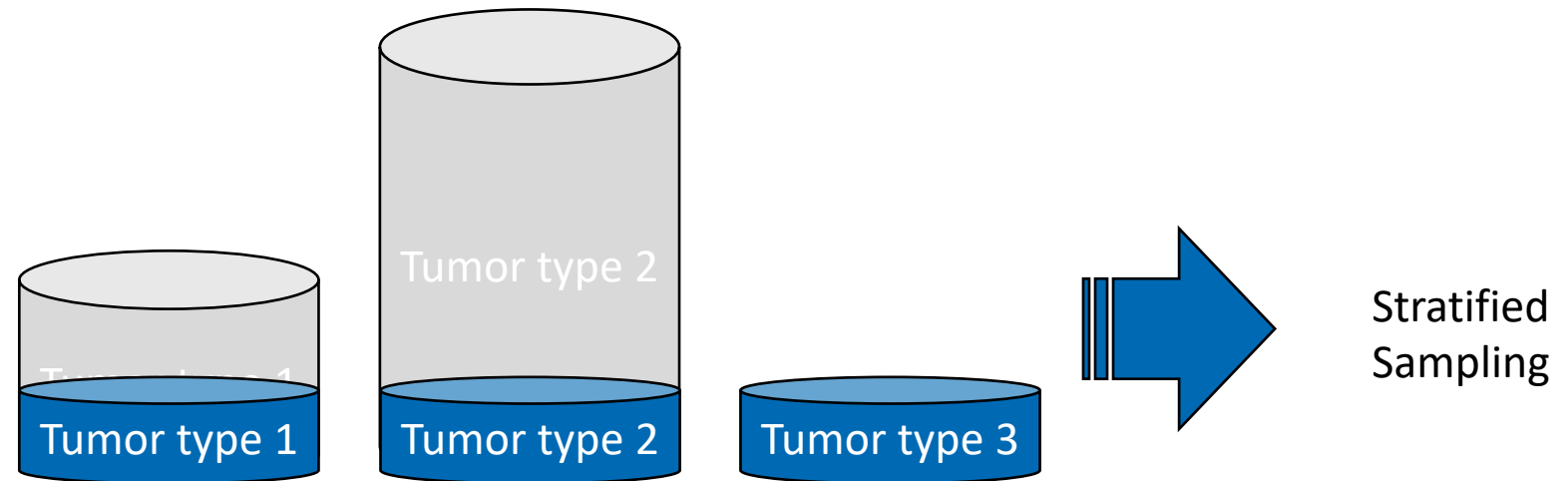
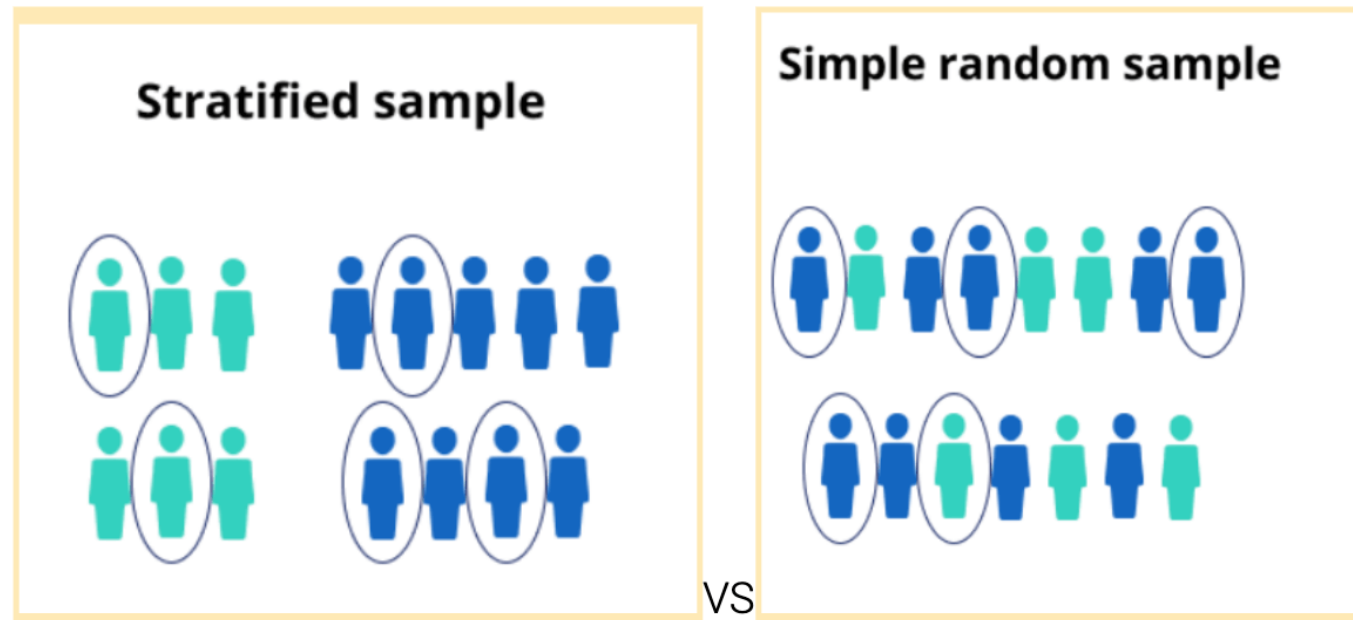


Image Analysis Difficulties: Dataset size



Source <https://www.qualtrics.com/m/assets/wp-content/uploads/2021/08/Screen-Shot-2021-08-31-at-10.17.31-AM.png> 14.02.2023

Image Analysis Difficulties: Dataset size

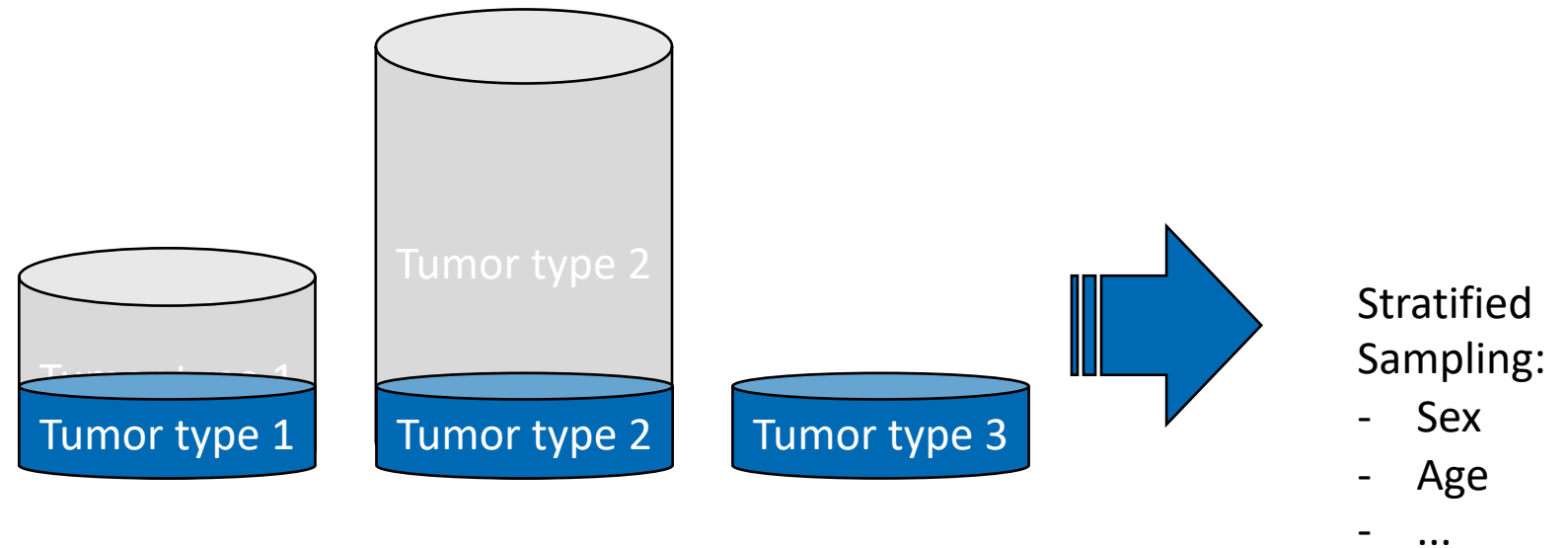


Image Analysis Difficulties: Artifacts

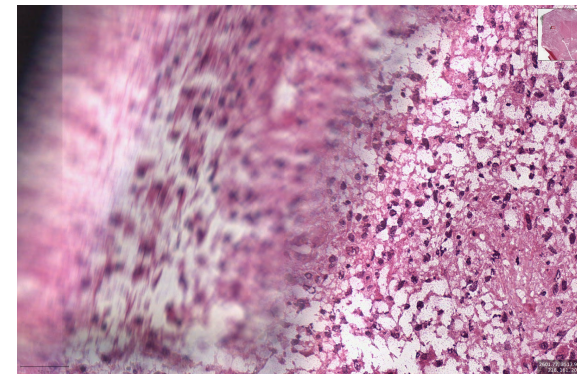
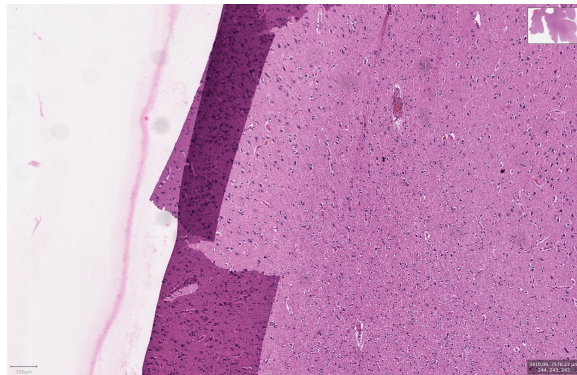
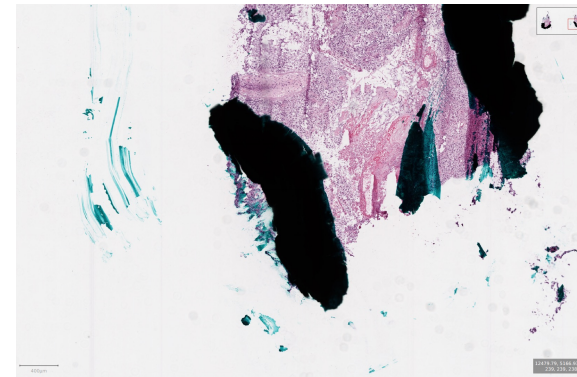
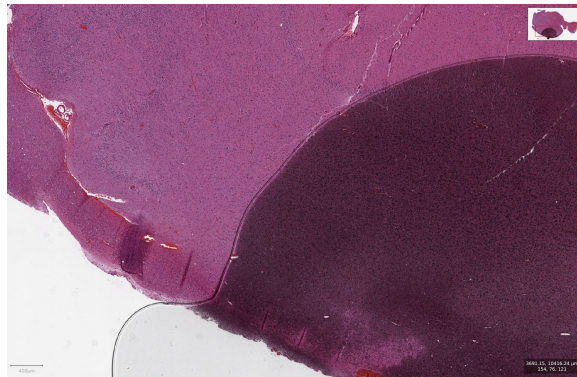
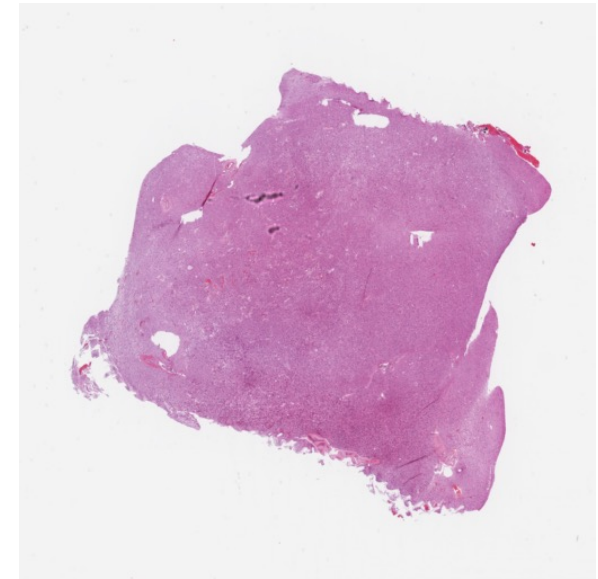
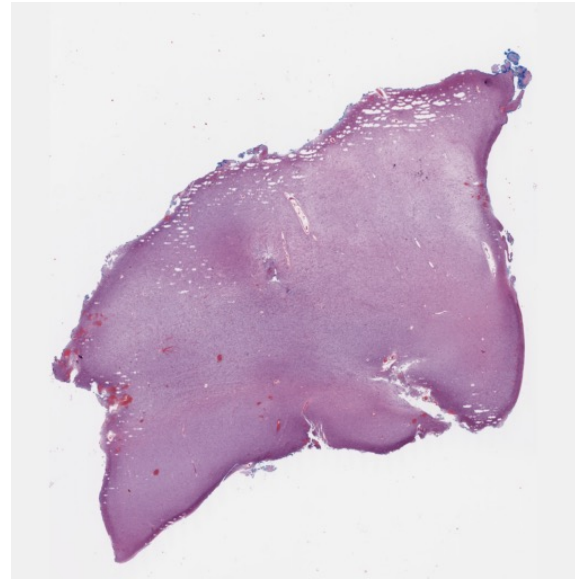
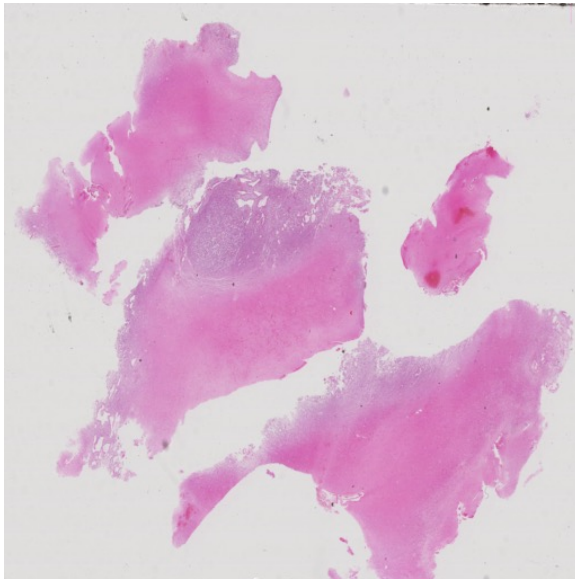
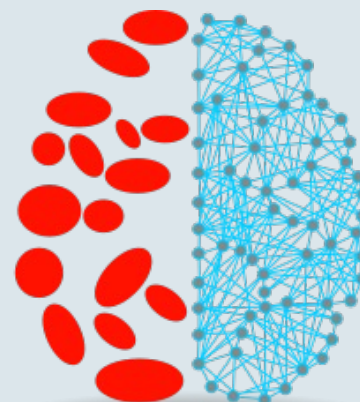


Image Analysis Difficulties: Domain shifts





Giessener Institut für
Neuropathologie



AI-RON

Thank you, for your attention!