FGAI4H-O-049

Berlin, 31 May – 2 June 2022

Source:	LMU Munich	
Title:	Workshop: TG-POC & TG-Histo - AI in morpho-molecular diagnostics and beyond	
Purpose:	Discussion | Information	
Contact:	Frederick Klauschen Dep. of Pathology, LMU Munich BIFOLD, Charité, Berlin Aignostics, Berlin	E-mail: Frederick.Klauschen@med.uni-muenchen.de
Abstract:	This PPT contains a presentation from the TG-POC & TG-Histo workshop on "Validation of annotations for AI models within the scope of point-of-care diagnostics (POC)"	

AI in morpho-molecular diagnostics and beyond

Frederick Klauschen
Dep. of Pathology, LMU Munich
BIFOLD, Charité, Berlin
Aignostics, Berlin

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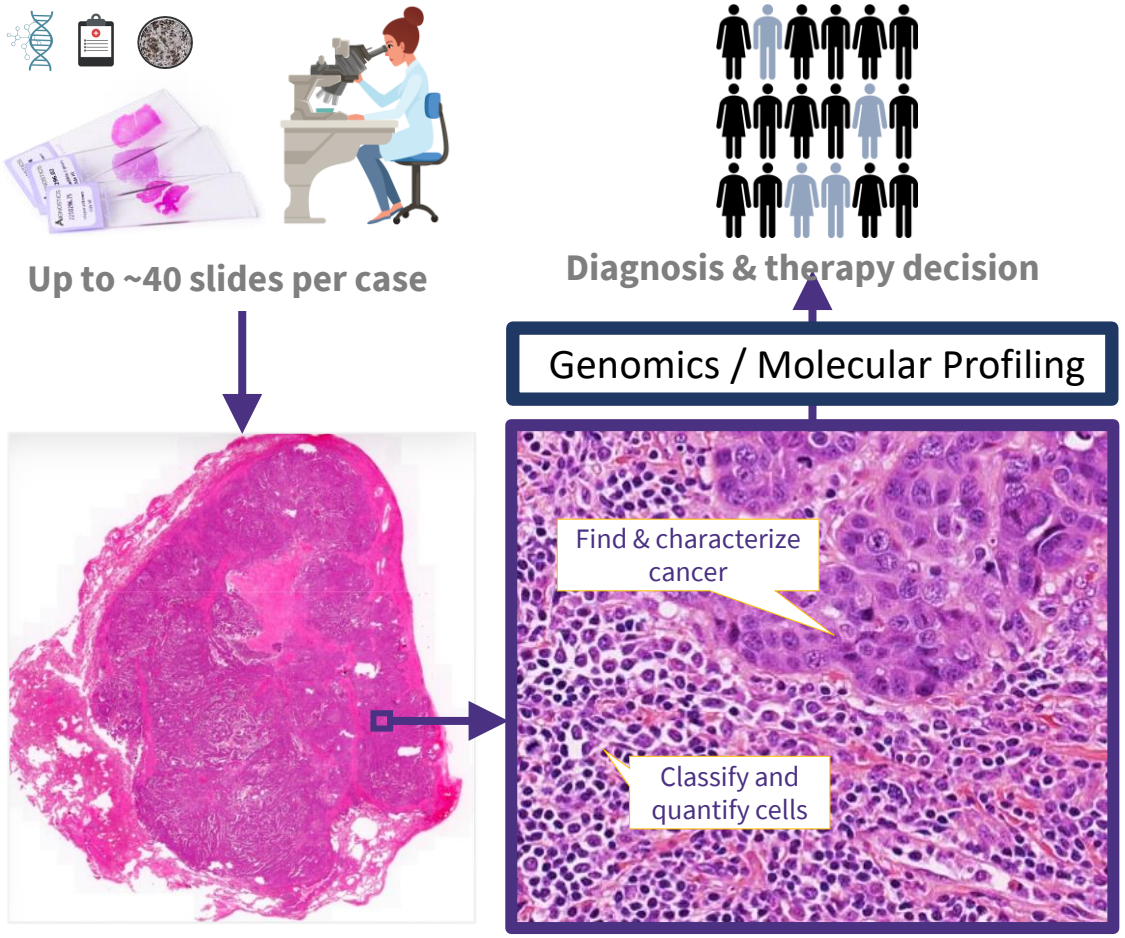
AIGNOSTICS

The problem: Today's pathology unfit for precision medicine

How pathologists work today

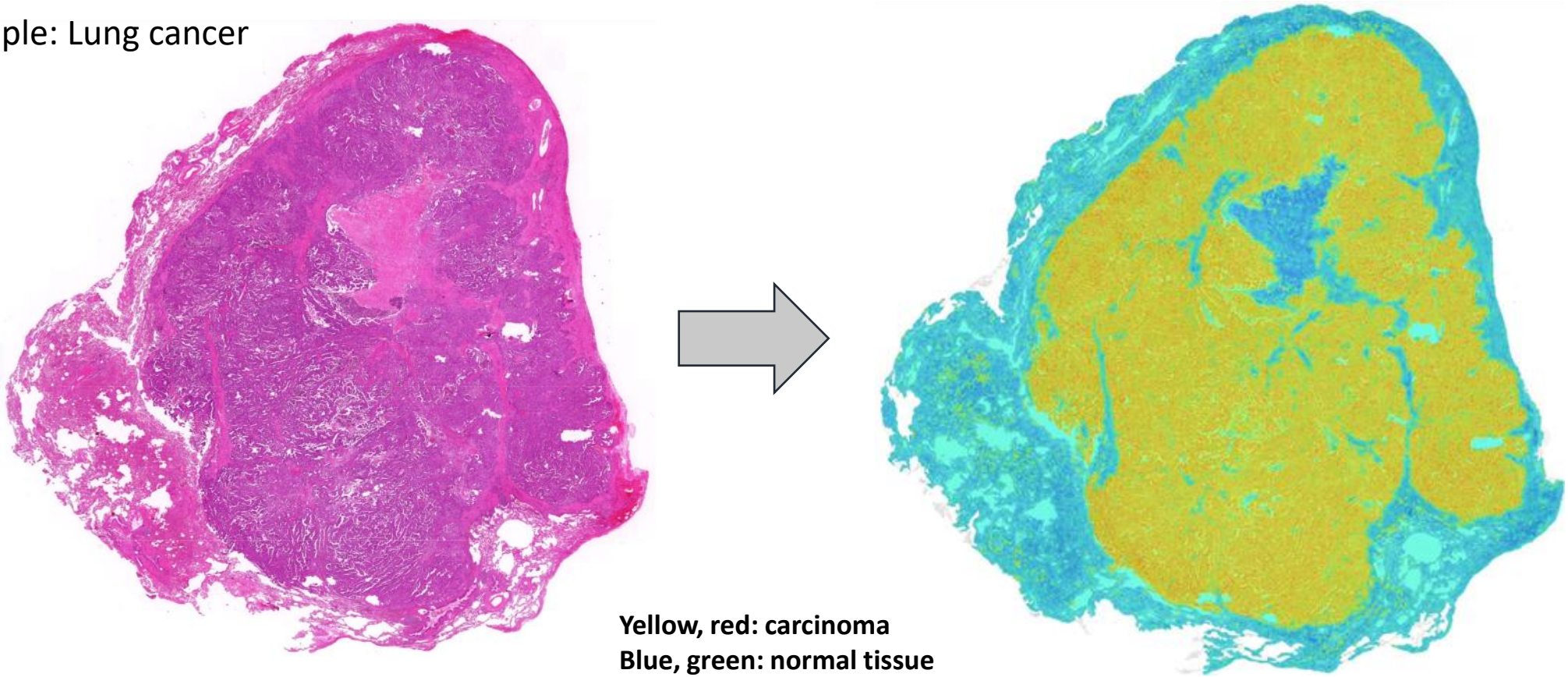


- Visual precision to characterize tissue quantitatively limited
- Human ability to integrate complex, multimodal data limited
- **Therefore, only simple biomarkers for patient stratification possible today**
- For example, only 12% of patients who receive immune checkpoint therapy will benefit [1]

1: Haslam A, Prasad V. Estimation of the Percentage of US Patients With Cancer Who Are Eligible for and Respond to Checkpoint Inhibitor Immunotherapy Drugs. JAMA Netw Open. 2019;2(5):e192535. Published 2019 May 3. doi:10.1001/jamanetworkopen.2019.2535

AI-supported pathology diagnostics

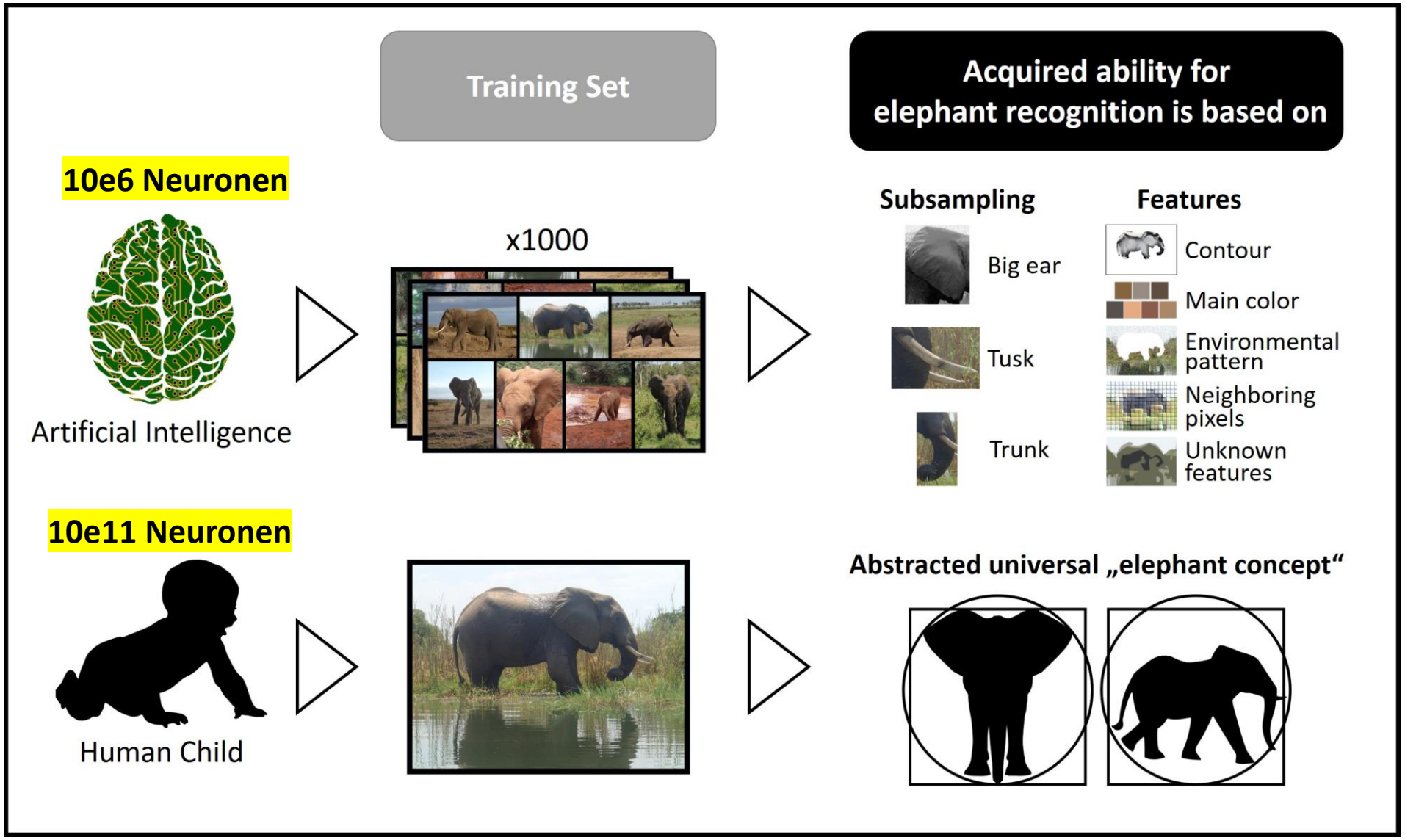
Example: Lung cancer



Yellow, red: carcinoma
Blue, green: normal tissue

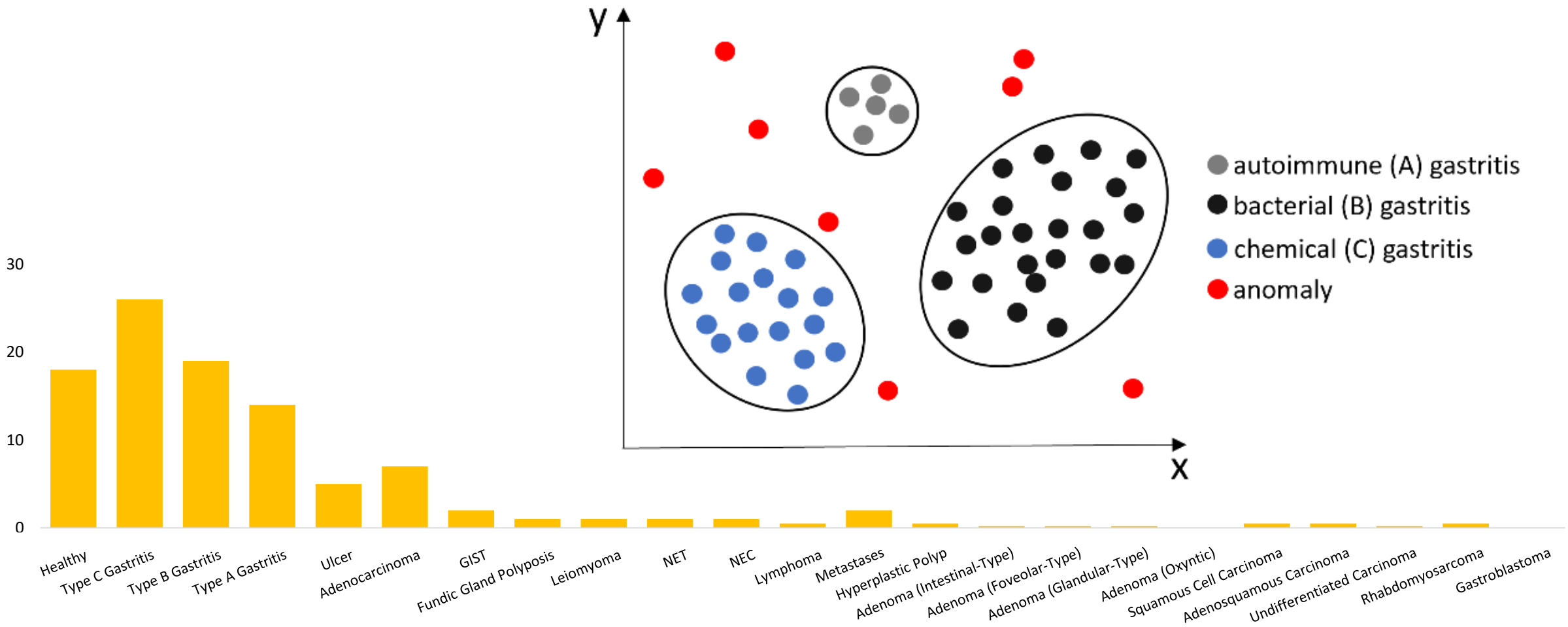
Numerous publications on simpler issues:
Cancer detection, classification of common tumour types, growth pattern, prediction of MSI, e.g.
1. Kather JN et al. *Nat Med*. 2019;25:1054–1056. 2. Coudray N et al. *Nat Med*. 2018;24:1559–1567.

Limits of current AI approaches



aus Stenzinger & Klauschen, Sem. Cancer Biol., Feb 2021

Challenge #1: many rare diagnoses "long tail"



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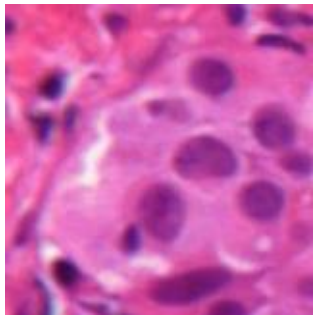
Challenge #2: Most AI are Black Boxes



Cancer?

Black Box

Yes/No

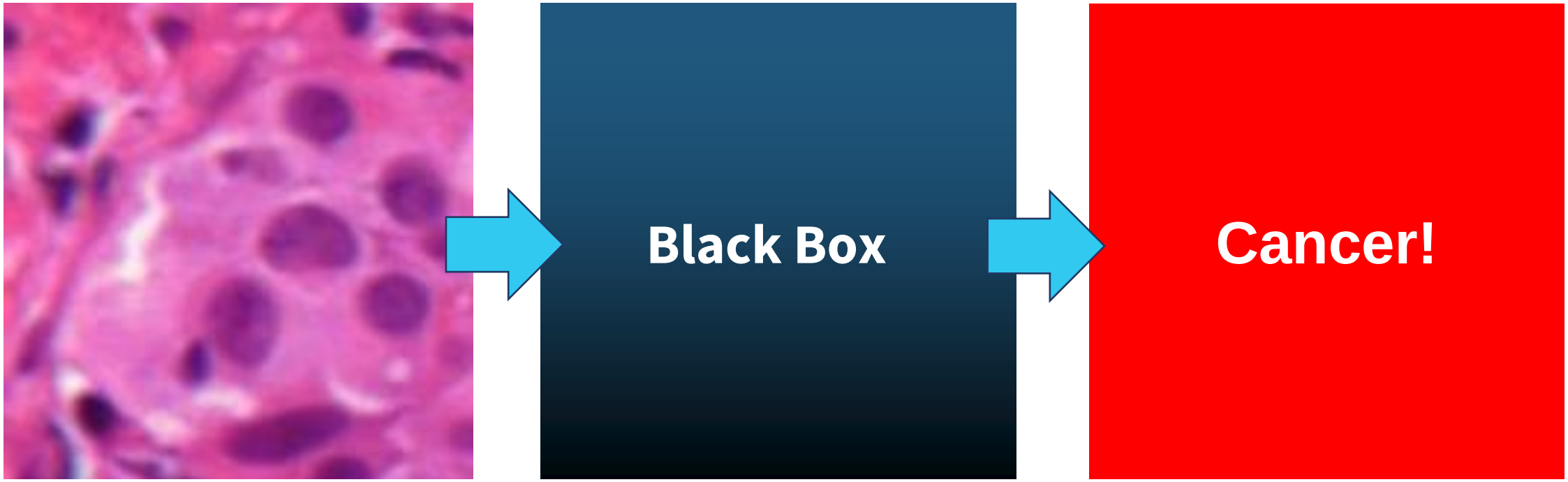
<u>Diagnostics:</u>

Problem of diagnostic result verification by pathologist!

<u>Research:</u>

Potential biomarkers hidden in black box!

Classical Black Box AI



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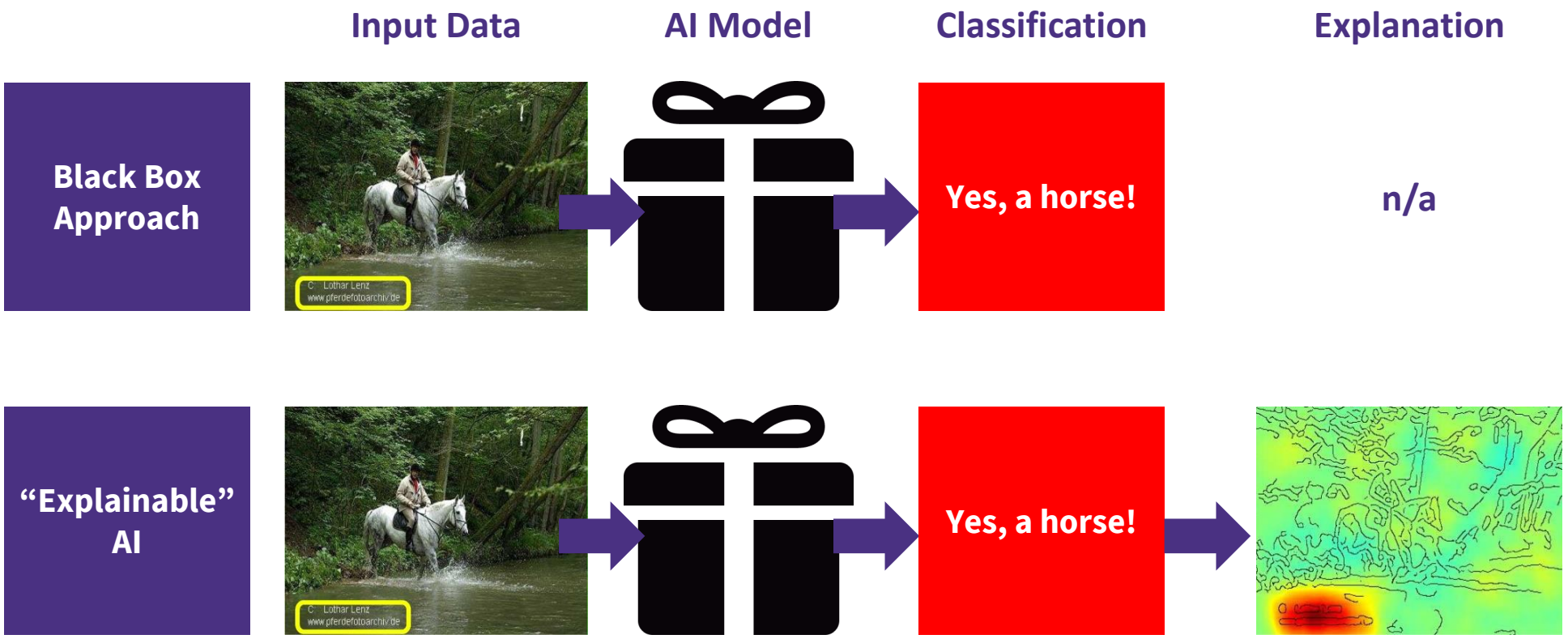
“Explainable” AI – Why does it matter?

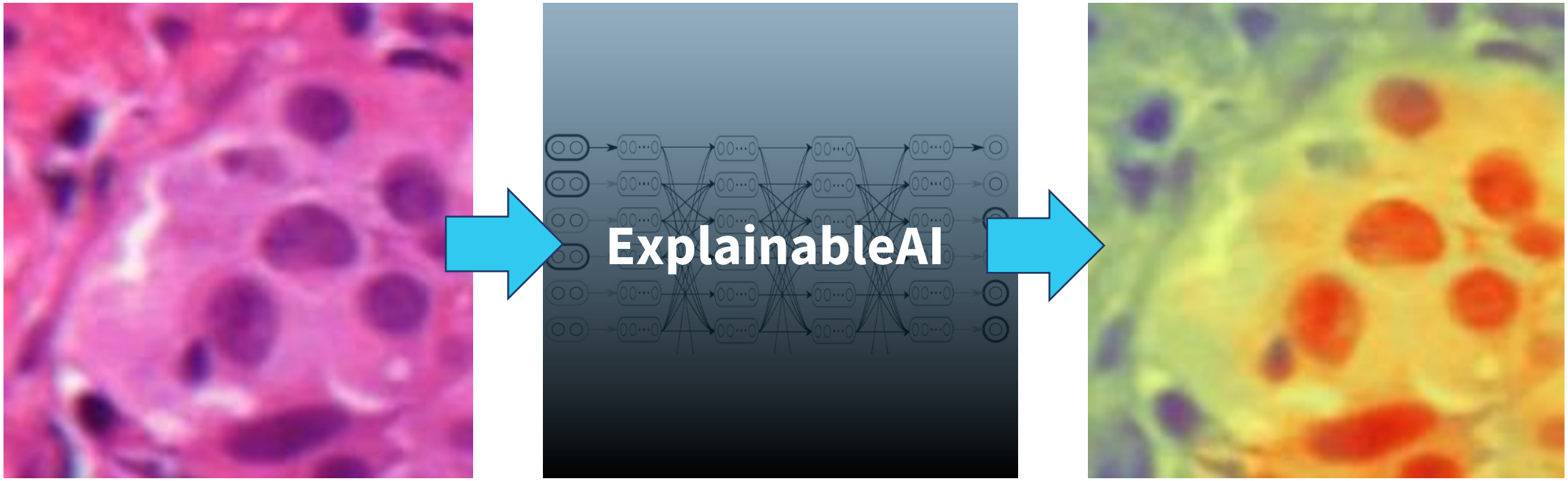


Source: https://www.nature.com/articles/s41467-019-08987-4

“Clever Hans” example: AI classifies the input as a horse due to the source tag in the picture.

This “source tag” could be an indicator of *insufficient training* or a *novel biomarker*.

Opening the Black Box with Explainable AI



Red: cancer cells

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Binder & Bockmayr, … Müller & Klauschen, Nature Machine Intelligence, 2021

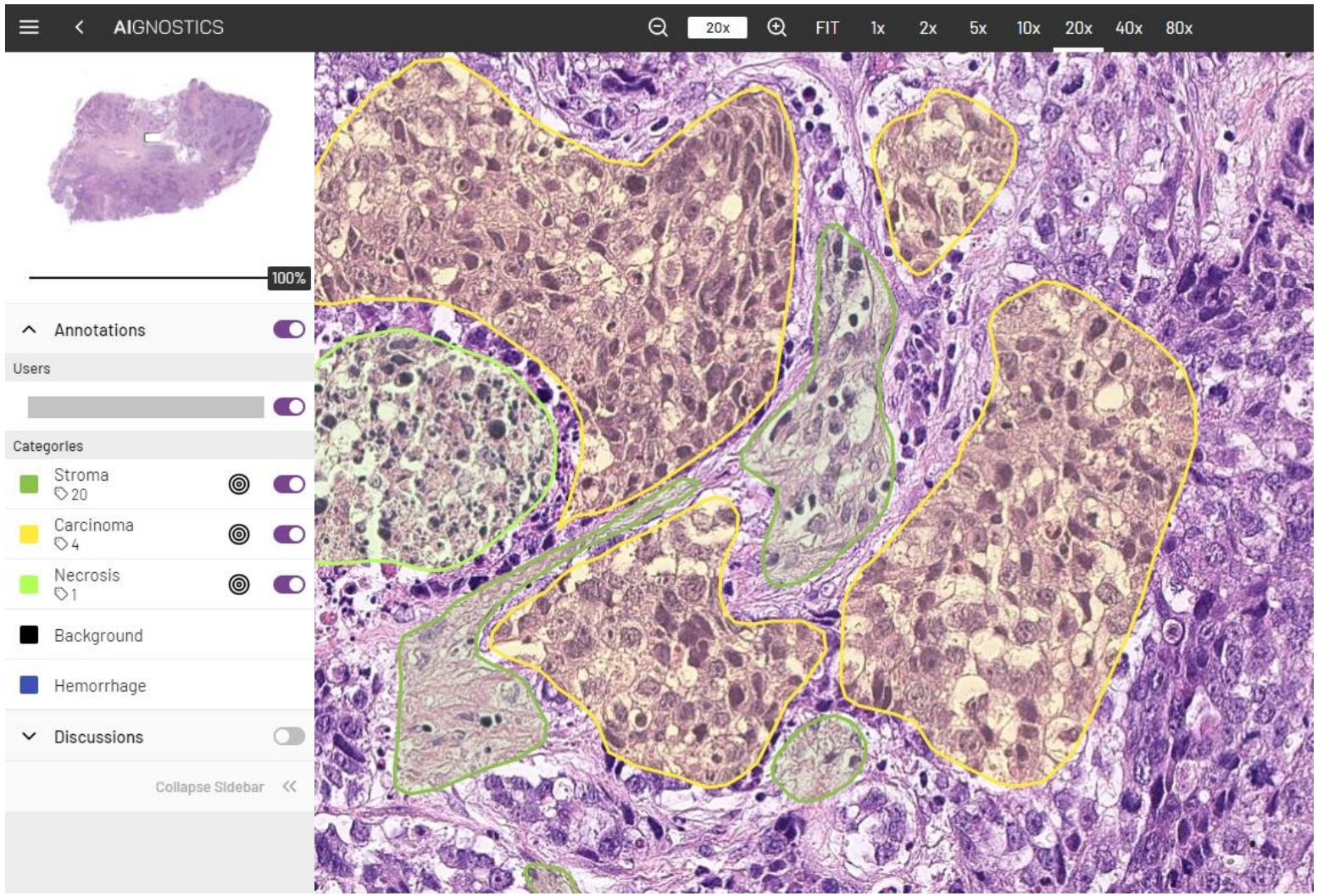
Challenge #3: „know your data“

training data access for generalizable model generation (in a complex regulatory environment)

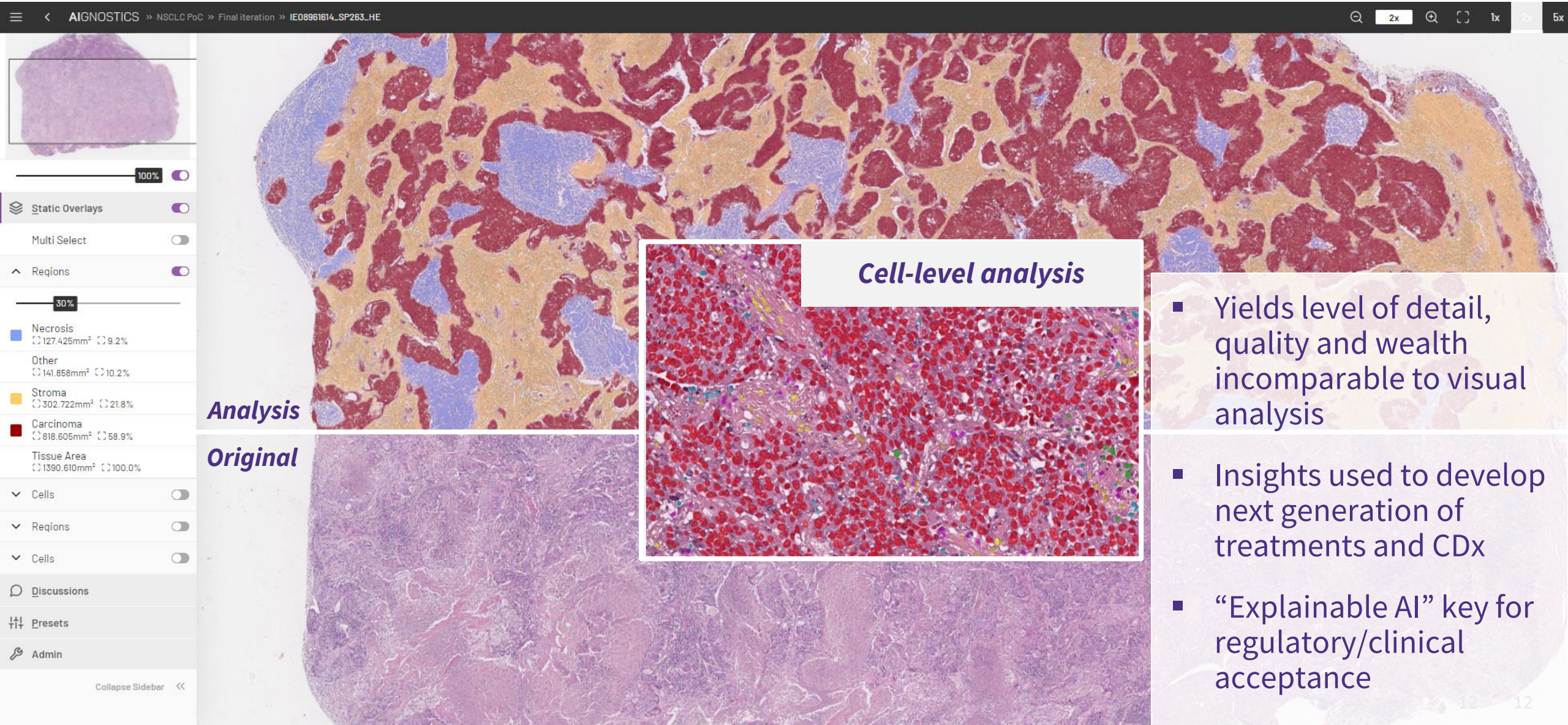
1 Data curation with multiple university hospital partners

2 Data processing on multiple platforms

3 Annotation by pathologist network



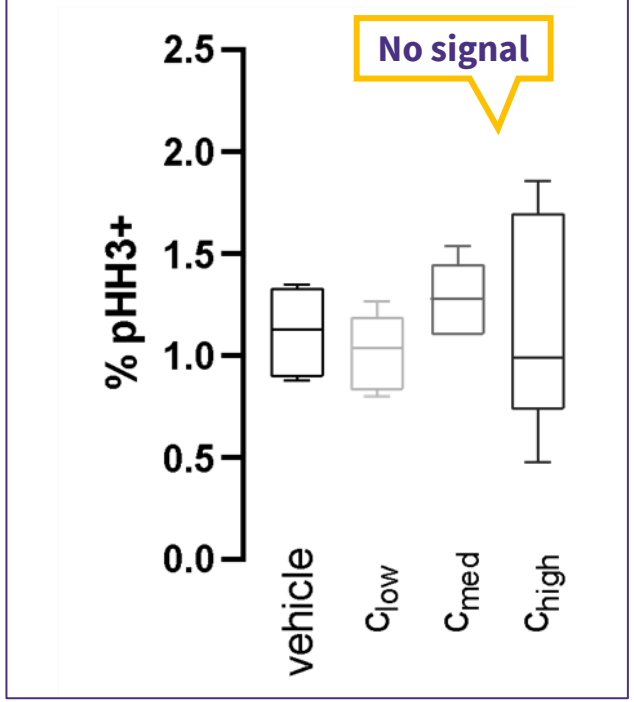
Multi-scale quantitative tissue analysis

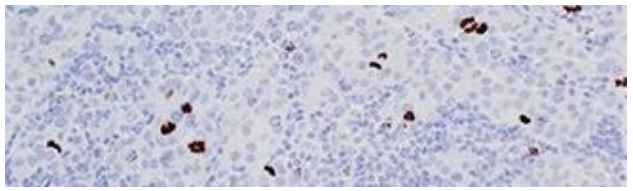


- Yields level of detail, quality and wealth incomparable to visual analysis
- Insights used to develop next generation of treatments and CDx
- “Explainable AI” key for regulatory/clinical acceptance

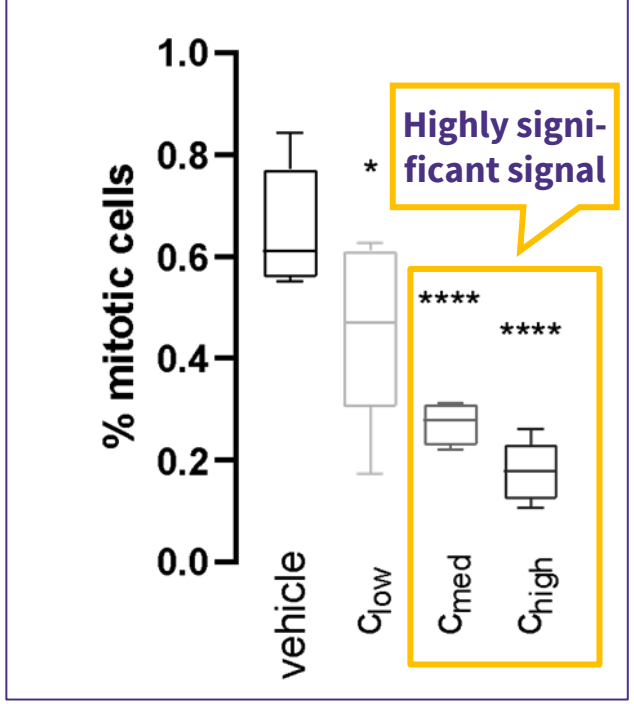
Example: Improved performance of AI over conventional Dx

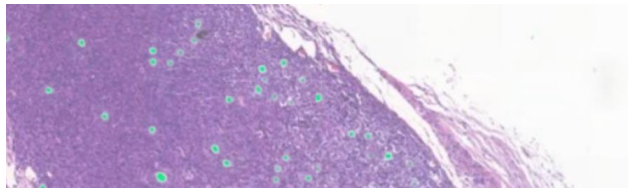
Pathologists + IHC





Aignostics' AI





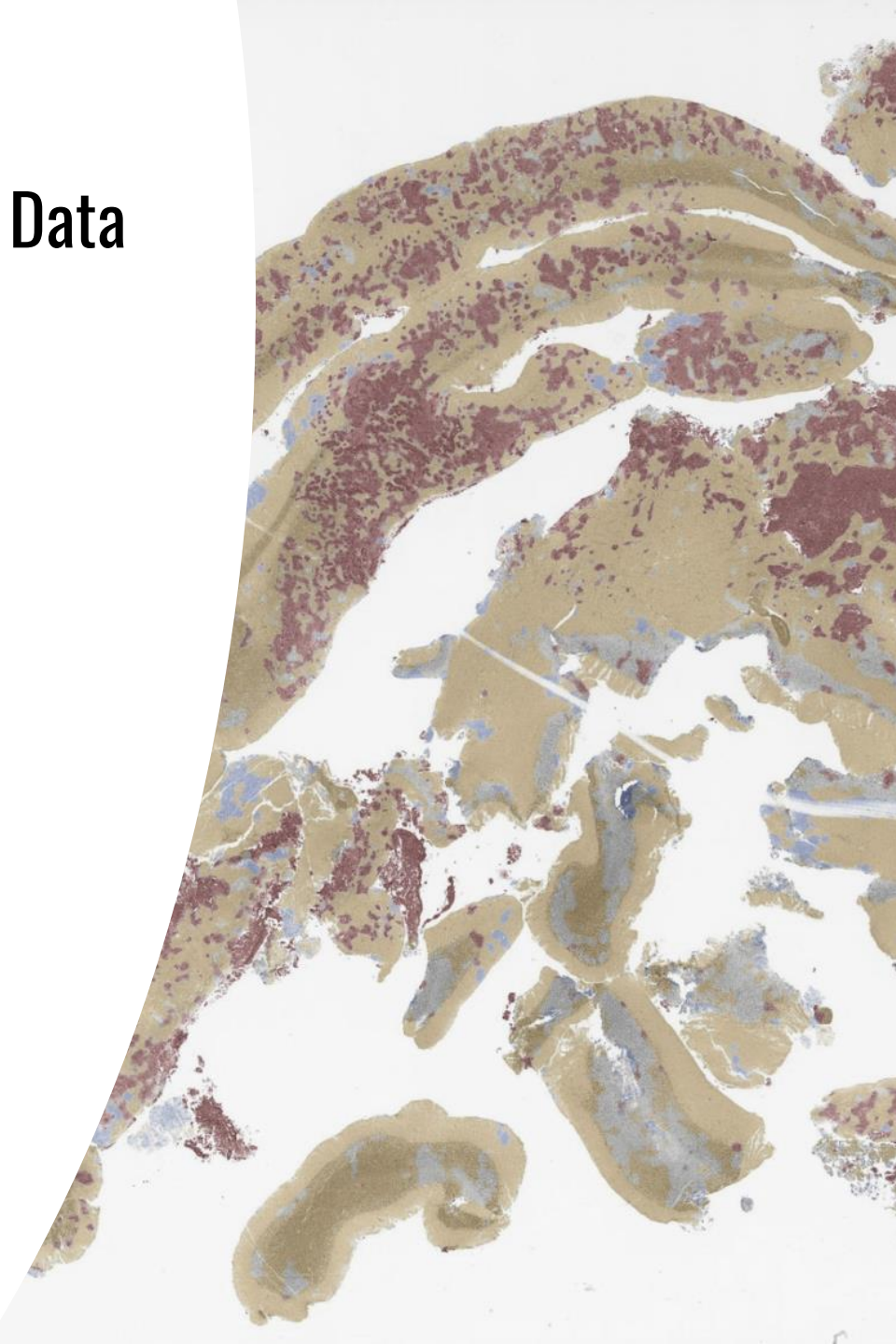
- In a preclinical biomarker study, AI "diagnosed" therapy efficacy after 24h based on mitotic count in H&E
- Conventional diagnostics was not able to detect changes accurately
- Mitotic count relevant for up to 80% of cancer cases
- **Next**: Application in clinical trials, potentially CDx

Machine-Learning-based Prediction of Immunotherapy-Response from Histology and Clinical Data in NSCLC

in cooperation with

Bristol Myers Squibb™

Data from clinical trials Checkmate 017, 026, 057
N ~ 1200 patients



Data preprocessing:

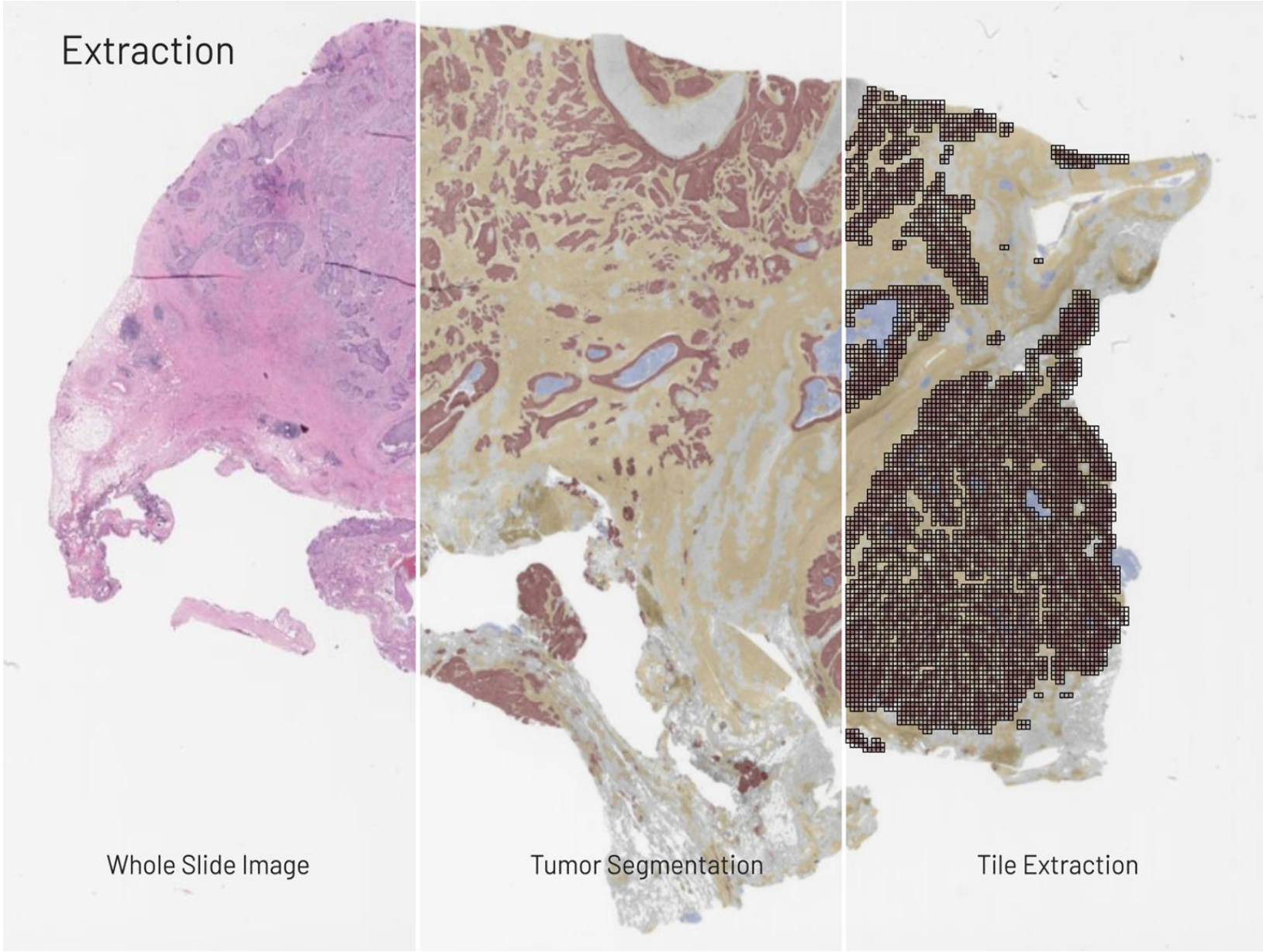
Assume relevant information lies in tumor histomorphology.
Extract tiles containing tumor.

Resulted in a dataset with 400k tiles.

Machine Learning:

Deep MIL neural network.

Extract feature encodings for tiles with CNN.
Aggregation networks in MIL framework.



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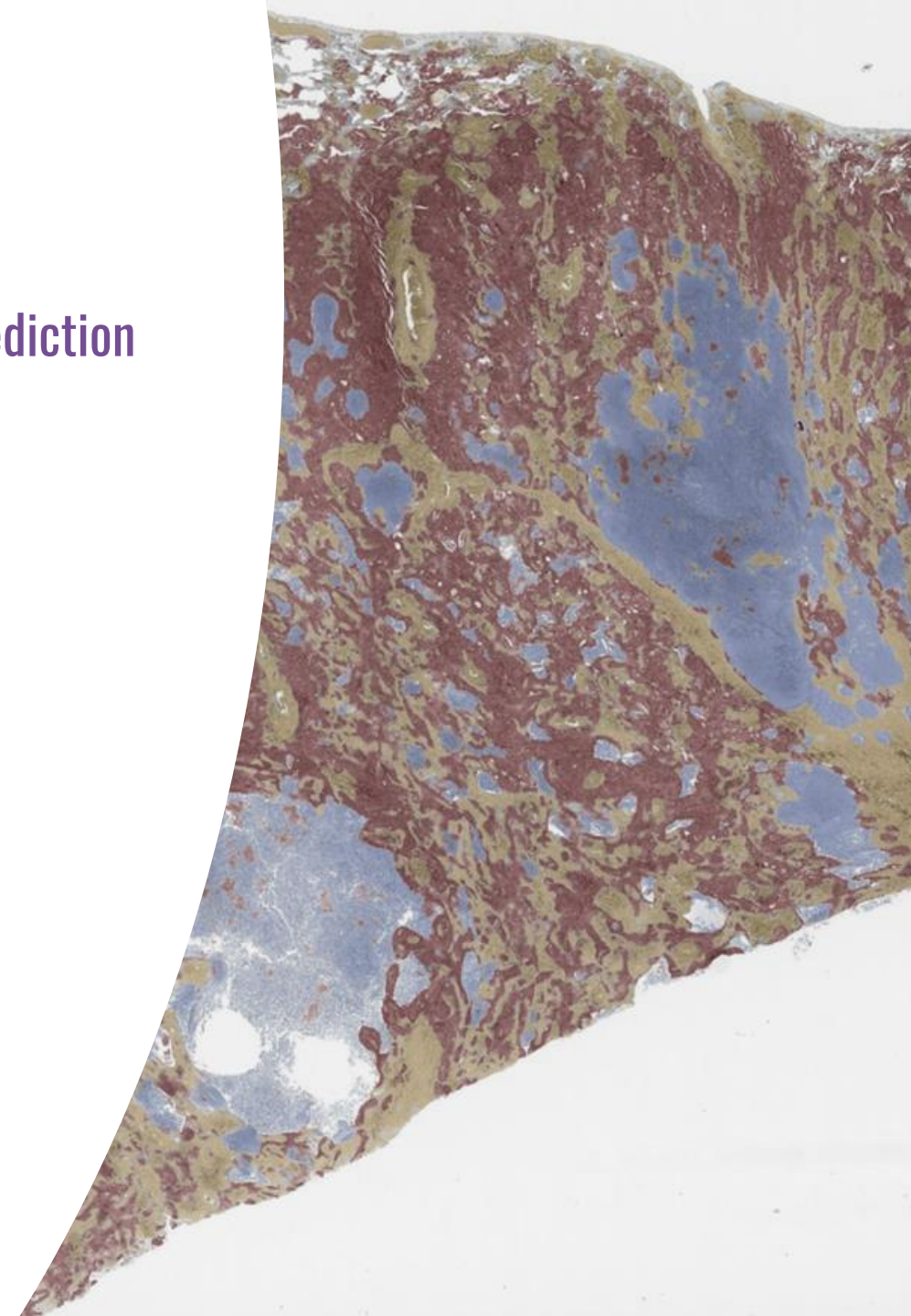
Comparison of “Clinical” and “Clinical+AI” outcome prediction

AUC in percent, 5-fold cross-validated		OS <10m vs. ⩾ 20m	PFS < 5m vs. ⩾ 7.5m	BOR PD vs. SD+PR+CR
“Clinical”	Treatment + PD-L1 *100% of cases*	61.0	50.5	67.0
	Treatment + PD-L1 *20% of cases with highest confidence predictions*	83.9	52.8	59.1
AI	H&E Image *100% of cases*			
	H&E Image + Treatment + PD-L1 *100% of cases*	67.5	56.9	65.7
	H&E Image + Treatment + PD-L1 *20% of cases with highest confidence predictions*	88.2	60.2	76.6

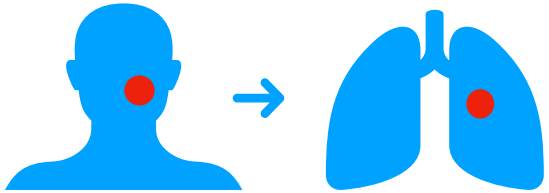
Improvement by AI:
+4 to 17 percentage pts.



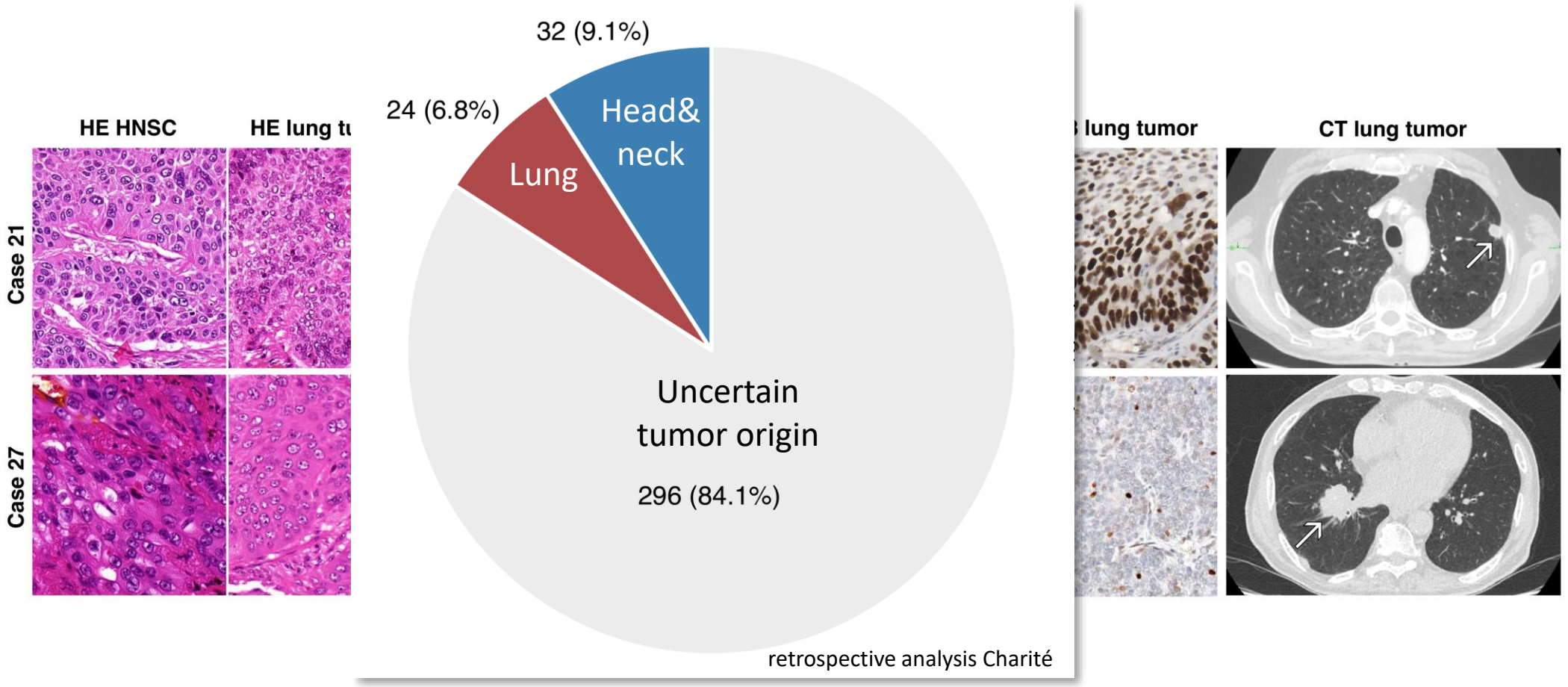
AI-based histology analysis complements conventional diagnostic and clinical parameters and yields better outcome predictions

in cooperation with Bristol Myers Squibb™

AI-supported molecular diagnostics



Primary lung cancer or metastasis from head&neck cancer?



Jurmeister P. and Bockmayr M., … Capper D. and Klauschen F., ***Science Transl. Med.**, 2019.*

AI analysis of DNA methylation profiling

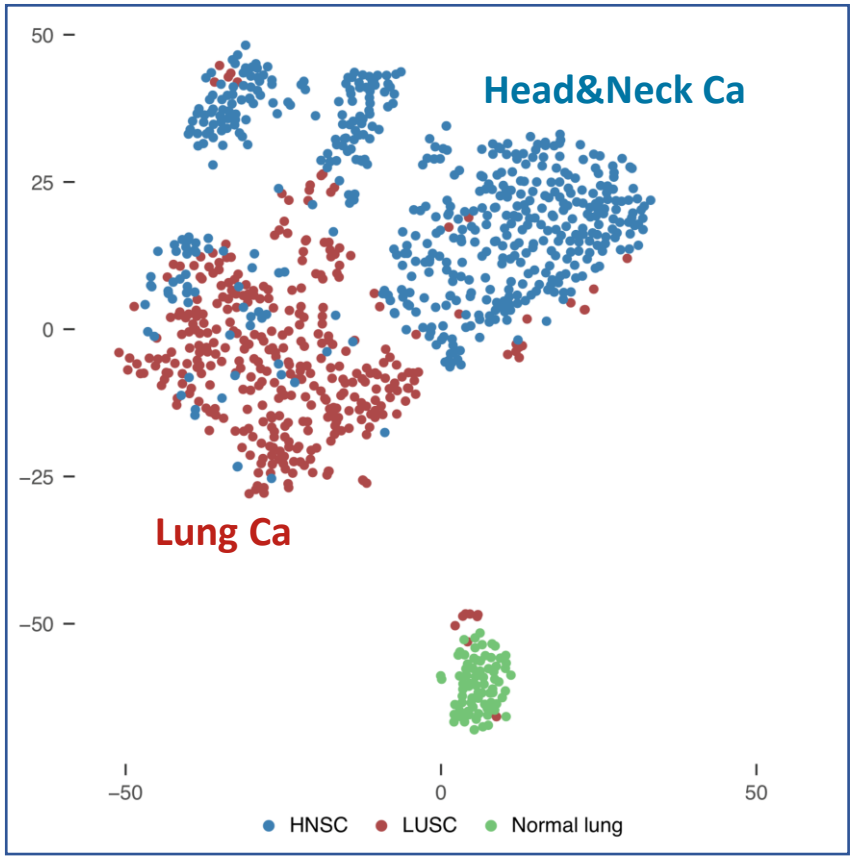
Primärtumor Trainingskohorte (n = 1087)

528 HNSC samples

370 LUSC samples

189 normal lung samples

EPIC 450k



classifier training

Validierungskohorte (n = 279)

110 HNSC samples

150 LUSC samples

19 normal lung samples

EPIC 450k

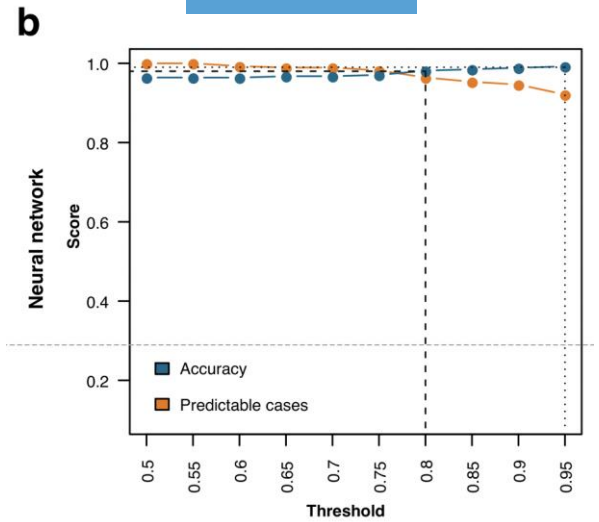
Validierung

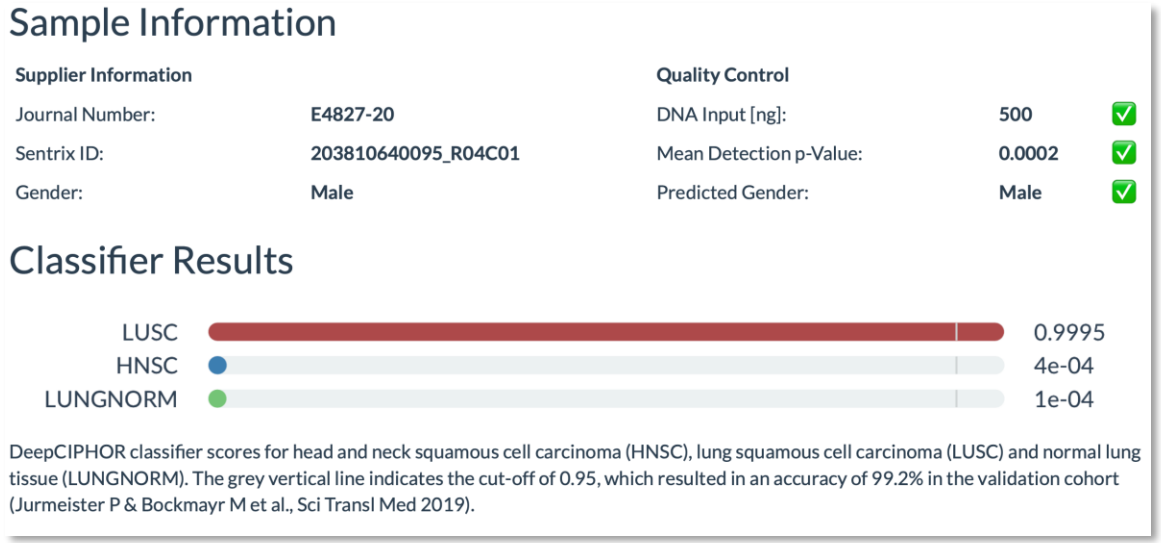
Jurmeister P. and Bockmayr M., … Capper D. and Klauschen F., ***Science Transl. Med.**, 2019.*

Standard RF classifier vs. Deep Learning

Neural network

Raw accuracy	96.4 %
Threshold accuracy	99.1 %
Predictable cases	92.1 %

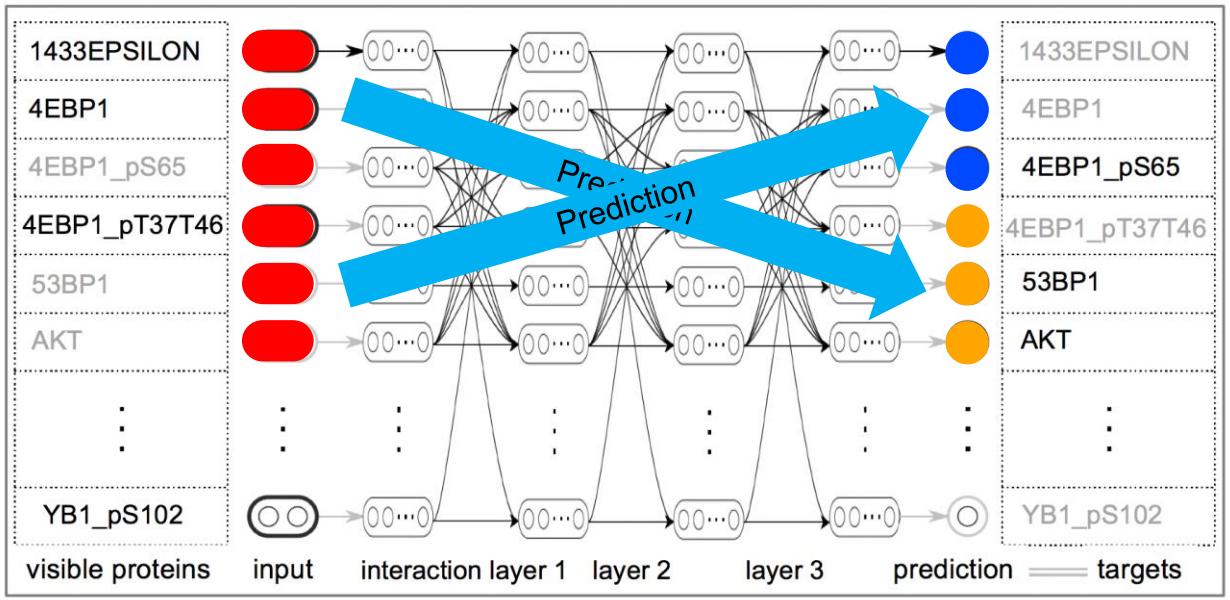




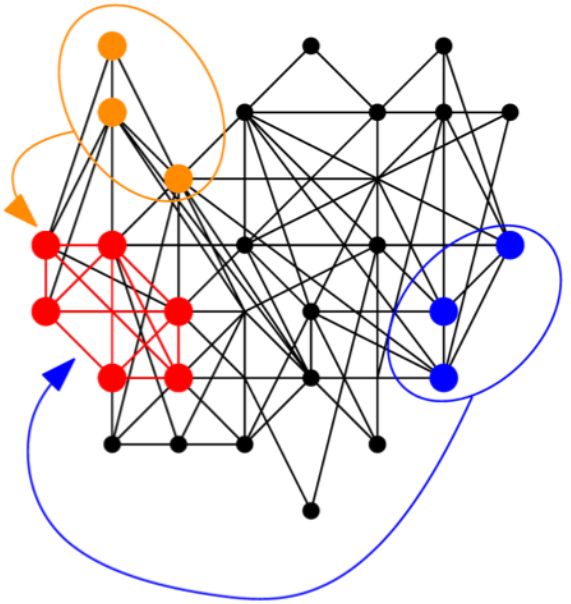
Combined AI – DNA-Methylation approach improved diagnostic accuracy from ”**chance**” to “**diagnostic grade**”.

Prediction of network topology from omics data with ExAI

Precondition: large numbers of samples for training!



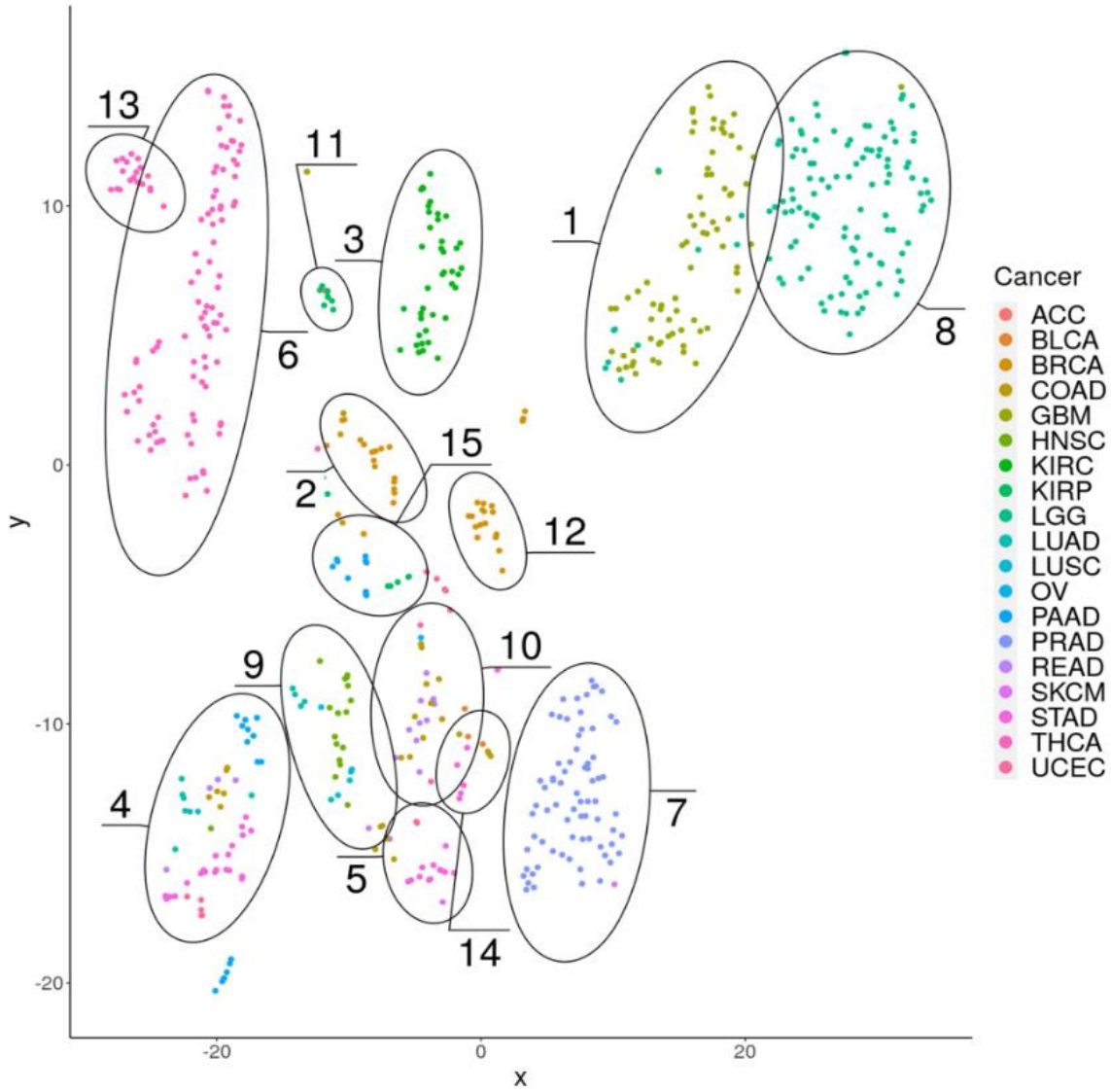
Interpretation

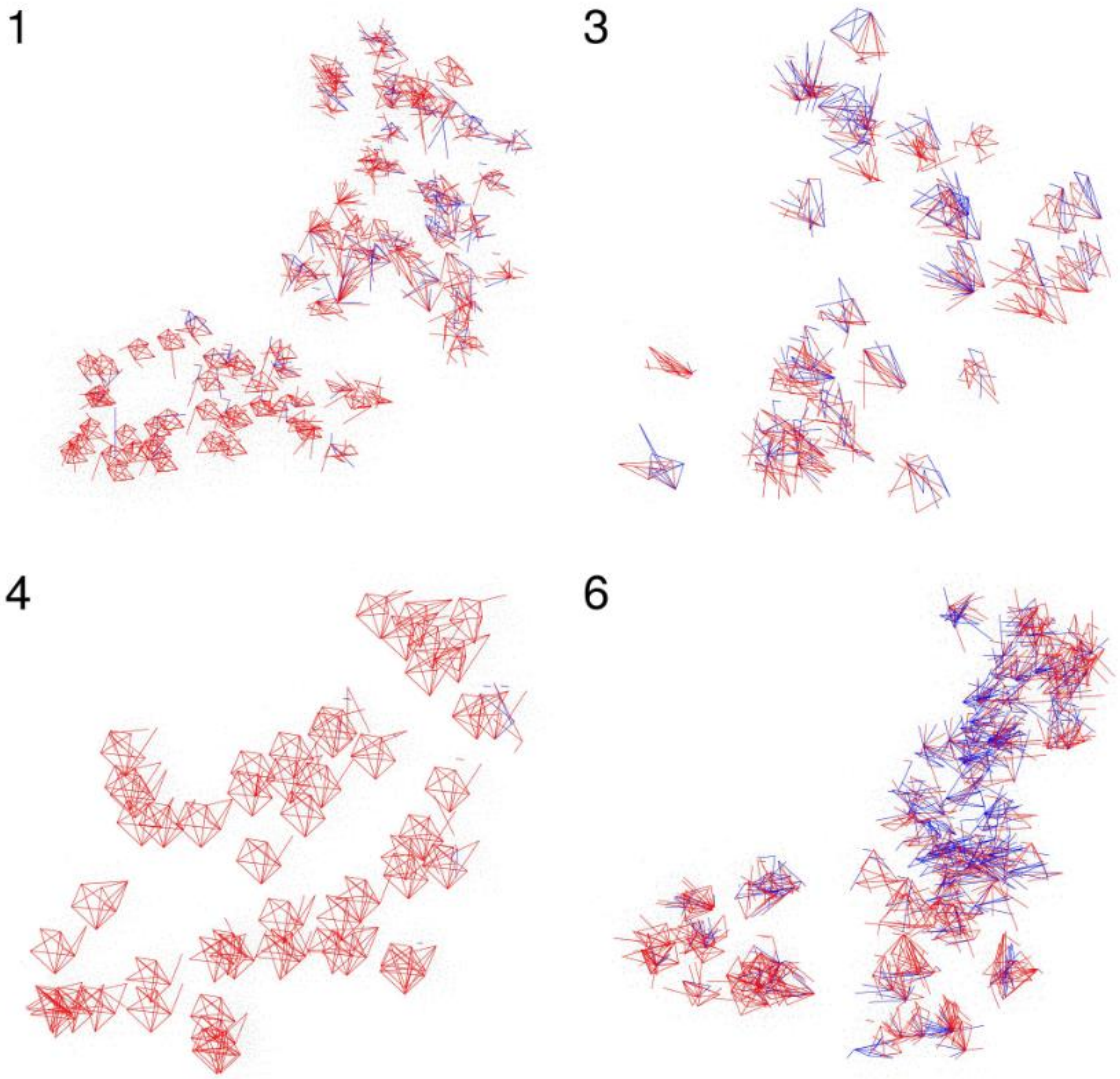


Interpretation with Layer-wise-relevance-propagation (LRP)
Bach,…,Klauschen, Müller, Samek, PLoS1, 2015

Modeling of Signaling Networks
Angermann*& Klauschen* et al., *Nature Methods*, 2012

ExAI-based analysis for individual patients

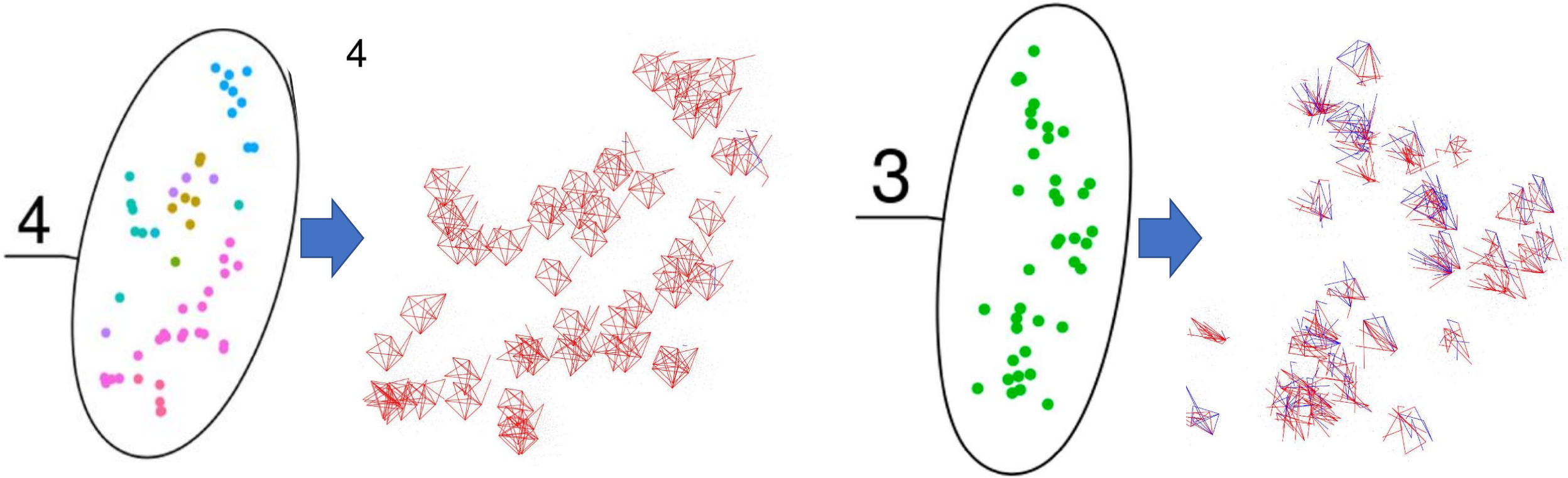




Many patients needed for training!

Keyl et al., Nature pj Precision Oncology, in print.

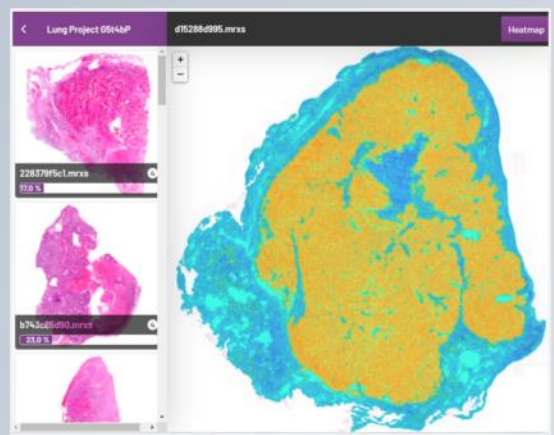
Similar network structures across tumor types vs. variable networks within a histotype



Keyl et al., Nature pj Precision Oncology, in print.

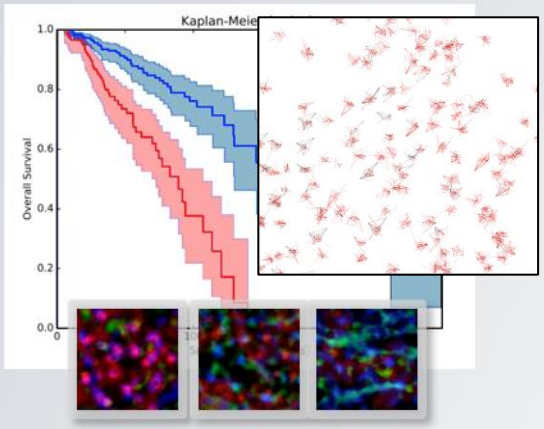
Pathology AI

Today
Improve Analysis



- Disease detection
- Feature quantification

Next
Improve Diagnosis

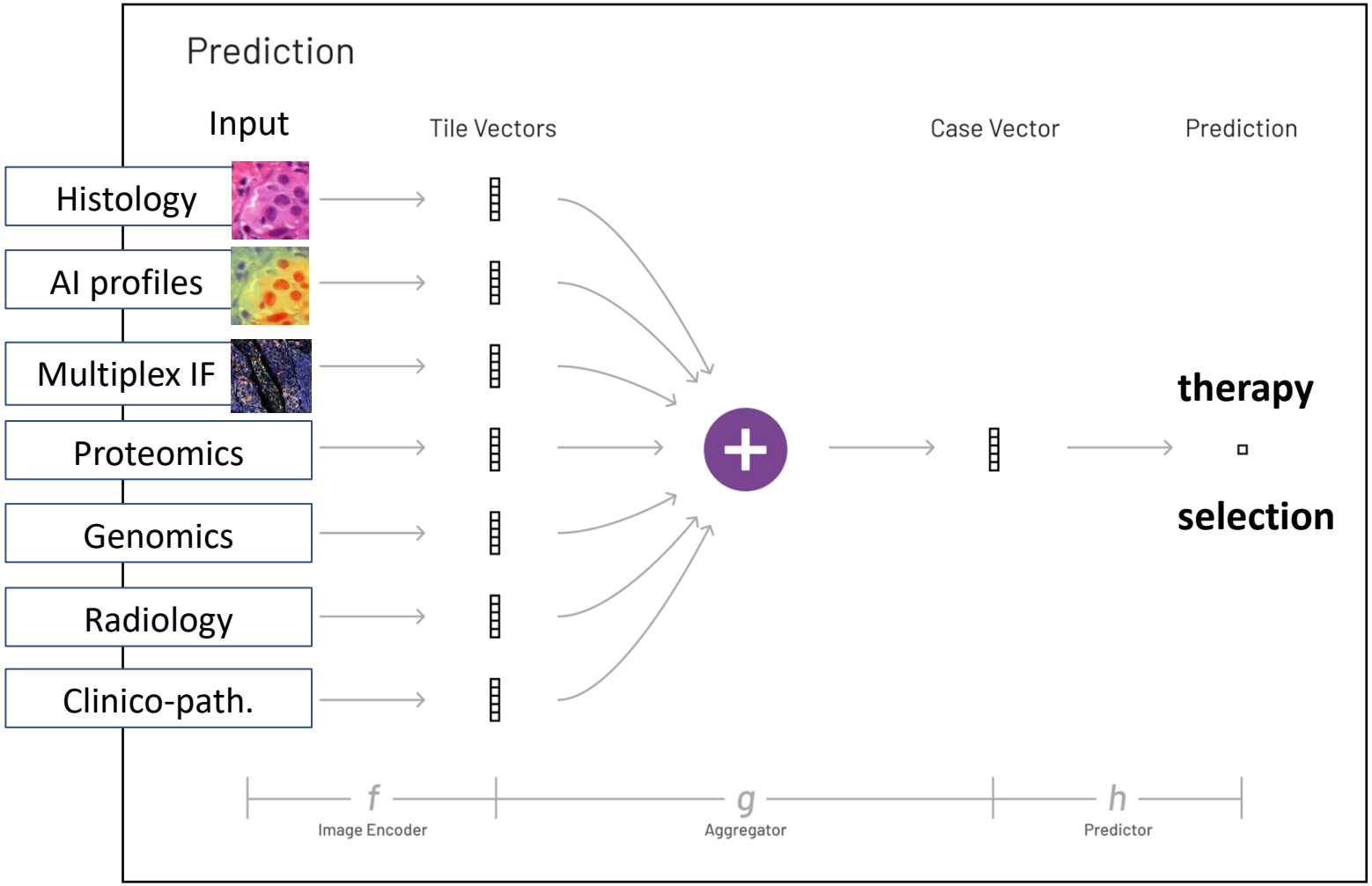


- (Differential) Diagnosis
- Outcome prediction
- Treatment suggestion

Future
Multi-modal data integration & clinical decision making

- AI-based precision medicine: integration of histological, molecular and clinical information
- AI diagnoses “easy” cases independently

AI will fundamentally change precision medicine through multi-modal prediction models



- Humans cannot process all data available per patient
- Pathology labs key to most data modalities and hence our starting point
- Successful projects are translated into Aignostics

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