Цифровая патология: примеры применения искусственных нейронных сетей в работе патоморфологов
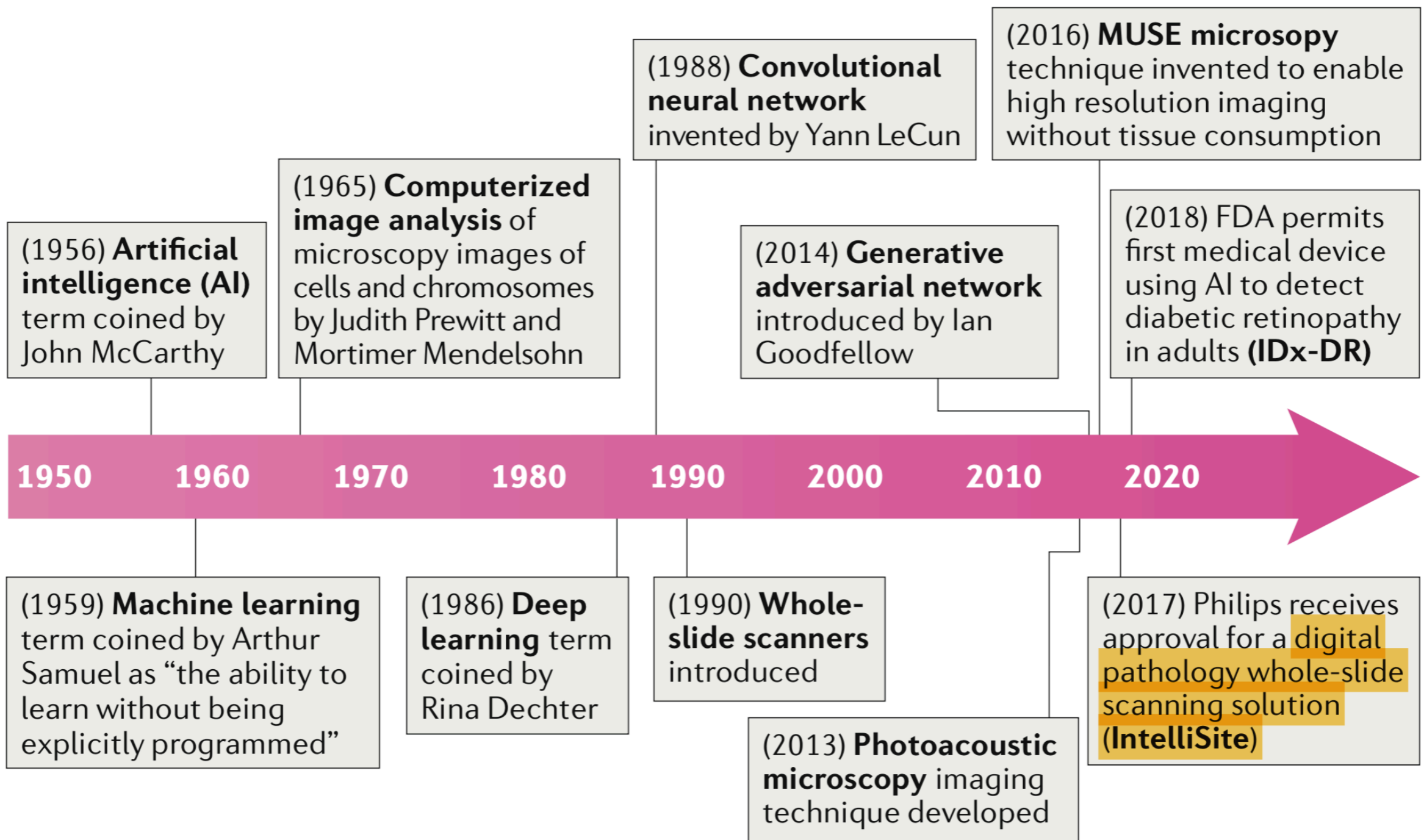
Лаборатория биоинформатики
НМИЦ АГП им. В.И. Кулакова
Наумов В.А.
Балашов И.С.

Digital pathology

Digital pathology includes the process of digitizing histopathology slides using whole-slide scanners as well as the analysis of these digitized whole-slide images (WSI) using computational approaches. Such

for precision oncology. Pathologists and oncologists are the primary end users of these image analysis approaches.

(1956) **Artificial intelligence (AI)** term coined by John McCarthy

(1965) **Computerized image analysis** of microscopy images of cells and chromosomes by Judith Prewitt and Mortimer Mendelsohn

(1988) **Convolutional neural network** invented by Yann LeCun

(2016) **MUSE microsopy** technique invented to enable high resolution imaging without tissue consumption

(2014) **Generative adversarial network** introduced by Ian Goodfellow

(2018) FDA permits first medical device using AI to detect diabetic retinopathy in adults **(IDx-DR)**

1950   1960   1970   1980   1990   2000   2010   2020

(1959) **Machine learning** term coined by Arthur Samuel as "the ability to learn without being explicitly programmed"

(1986) **Deep learning** term coined by Rina Dechter

(1990) **Whole-slide scanners** introduced

(2013) **Photoacoustic microscopy** imaging technique developed

(2017) Philips receives approval for a digital pathology whole-slide scanning solution **(IntelliSite)**

Most commonly, the result of this process is a histopathological diagnosis that is delivered in a written report to the treating physicians. While the systematic training

histopathology analysis is inherently limited by its subjective nature and the

widespread use of non-invasive or minimally invasive procedures to acquire diagnostic samples has considerably reduced the size and quality of specimens obtained, making the work of pathologists more challenging.
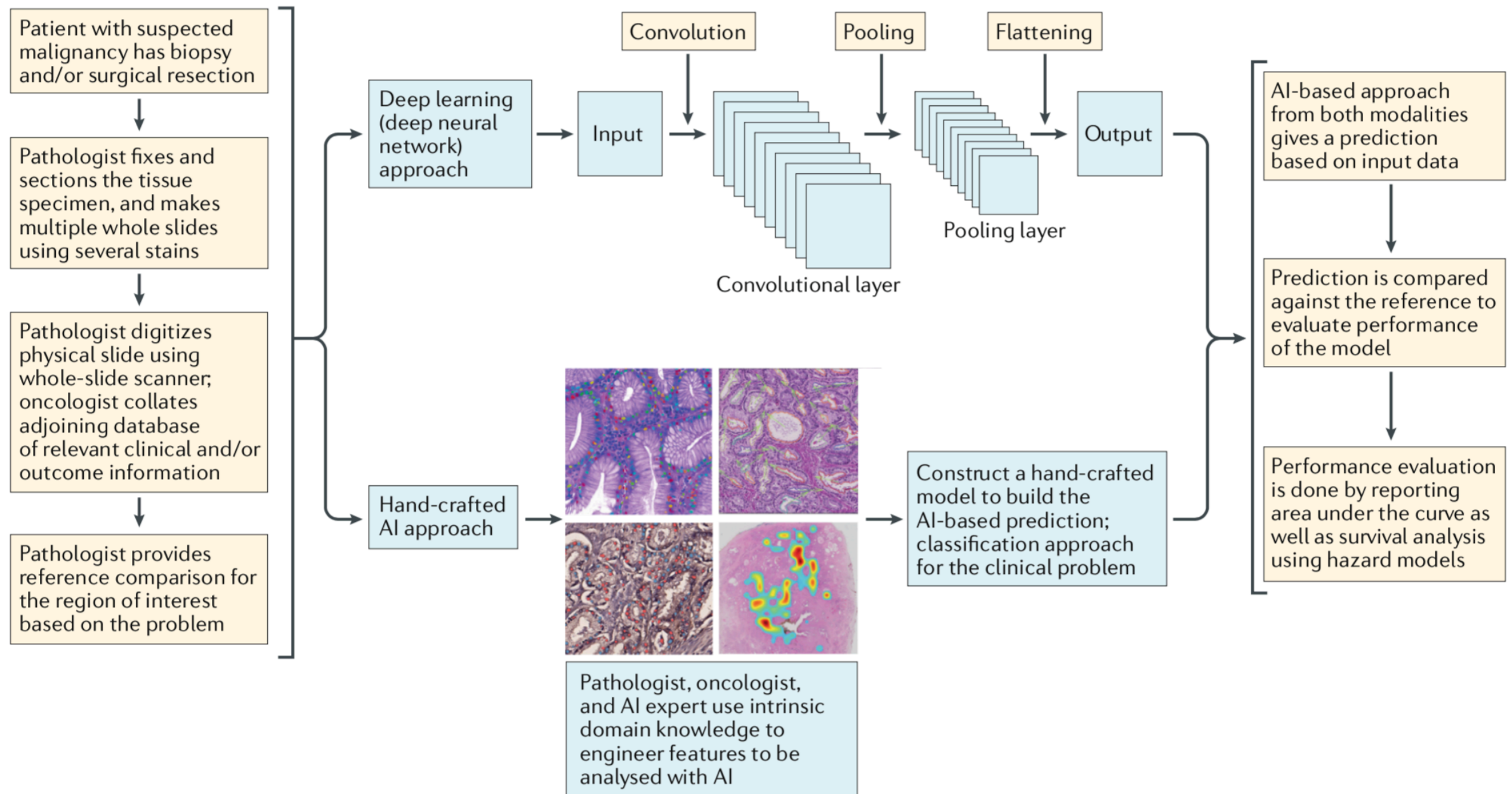
Два подхода к анализу

Patient with suspected malignancy has biopsy and/or surgical resection

Pathologist fixes and sections the tissue specimen, and makes multiple whole slides using several stains

Pathologist digitizes physical slide using whole-slide scanner; oncologist collates adjoining database of relevant clinical and/or outcome information

Pathologist provides reference comparison for the region of interest based on the problem

Deep learning (deep neural network) approach

Convolution

Pooling

Flattening

Input

Convolutional layer

Pooling layer

Output

Hand-crafted AI approach

Pathologist, oncologist, and AI expert use intrinsic domain knowledge to engineer features to be analysed with AI

Construct a hand-crafted model to build the AI-based prediction; classification approach for the clinical problem

AI-based approach from both modalities gives a prediction based on input data

Prediction is compared against the reference to evaluate performance of the model

Performance evaluation is done by reporting area under the curve as well as survival analysis using hazard models

Fig. 2 | **Workflow and general framework for artificial intelligence (AI) approaches in digital pathology.** Typical steps involved in the use of two popular categories of AI approaches: deep learning and hand-crafted feature engineering.

Два подхода к анализу
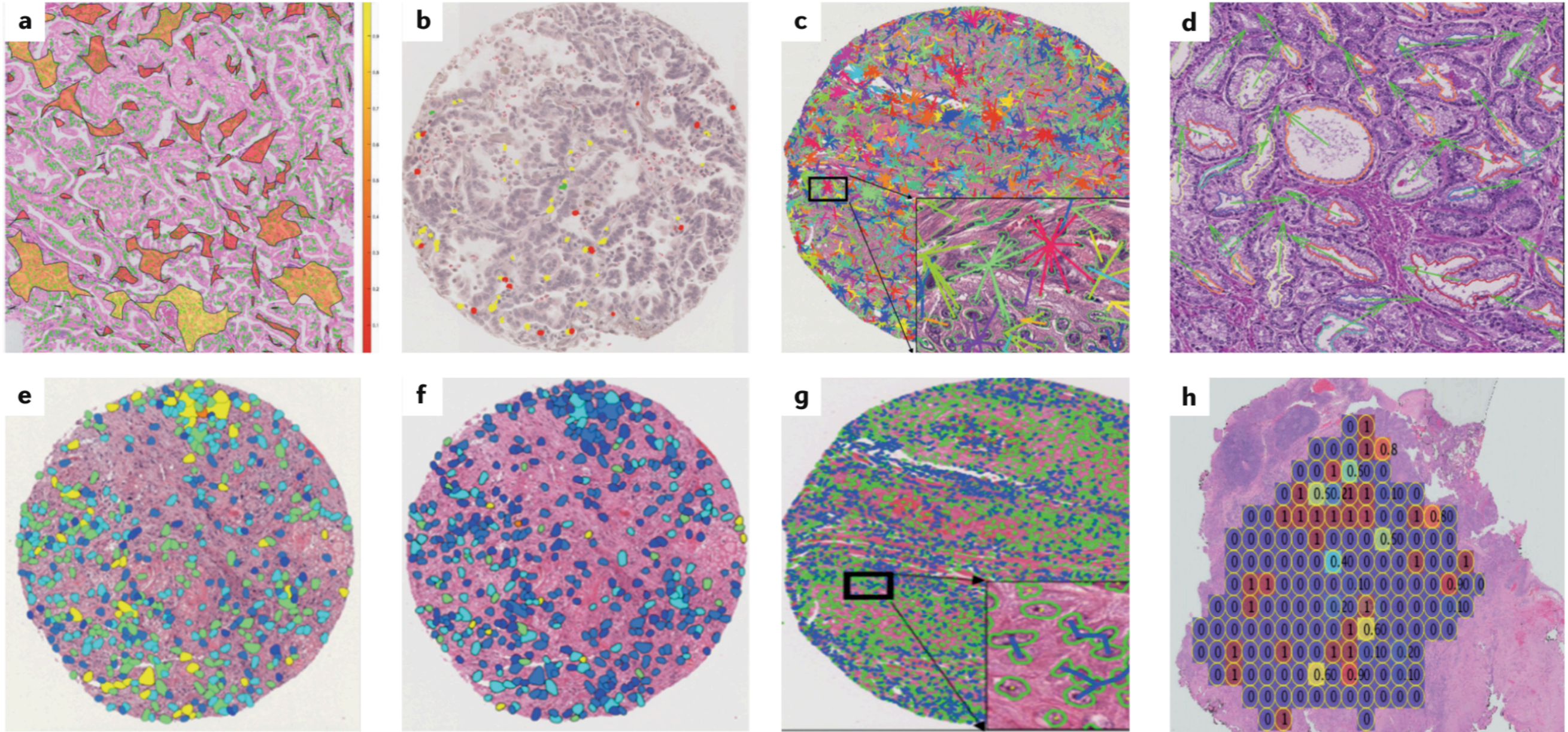
Fig. 3 | **Visual representations of hand-crafted features across cancer types. a** | Spatial arrangement of clusters of tissue-infiltrating lymphocytes in a non-small-cell lung carcinoma (NSCLC) whole-slide image. **b** | Features developed using quantitative immunofluorescence of tissue-infiltrating lymphocyte subpopulations (including detection of CD4+ and CD8+ T cells and CD20+ B cells) in NSCLC samples. **c** | Features reflecting the distribution and entropy of global cell cluster graphs constructed using NSCLC specimens. **d** | Features computing the relative orientation of the glands present in prostate cancer tissue. **e** | Diversity of texture of cancer cell nuclei in an oral cavity squamous cell carcinoma. **f** | Nuclear shape feature computed on cancer cell nuclei in a human papillomavirus-positive oropharyngeal carcinoma. **g** | Graph feature showing the spatial relationships of different cancer cell nuclei in an oral cavity carcinoma. **h** | Hand-crafted feature capturing cellular heterogeneity in an oestrogen receptor-positive breast cancer.

Искусственные нейронные сети

Convolutional neural networks
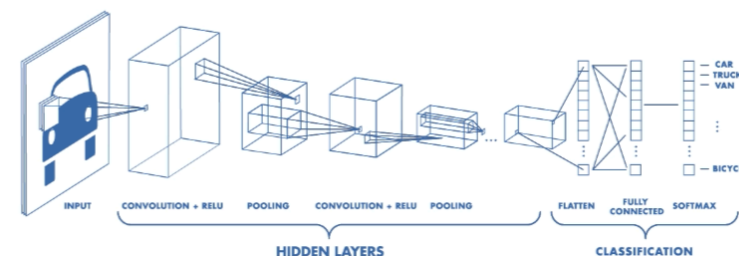
Fully convolutional networks
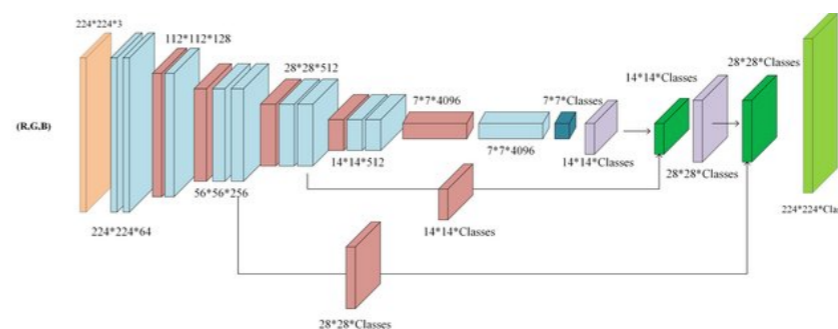
Recurrent neural networks
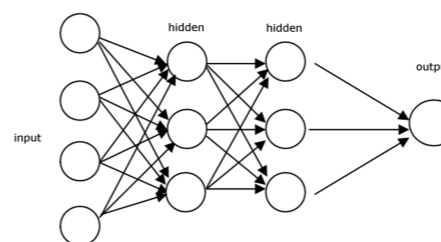
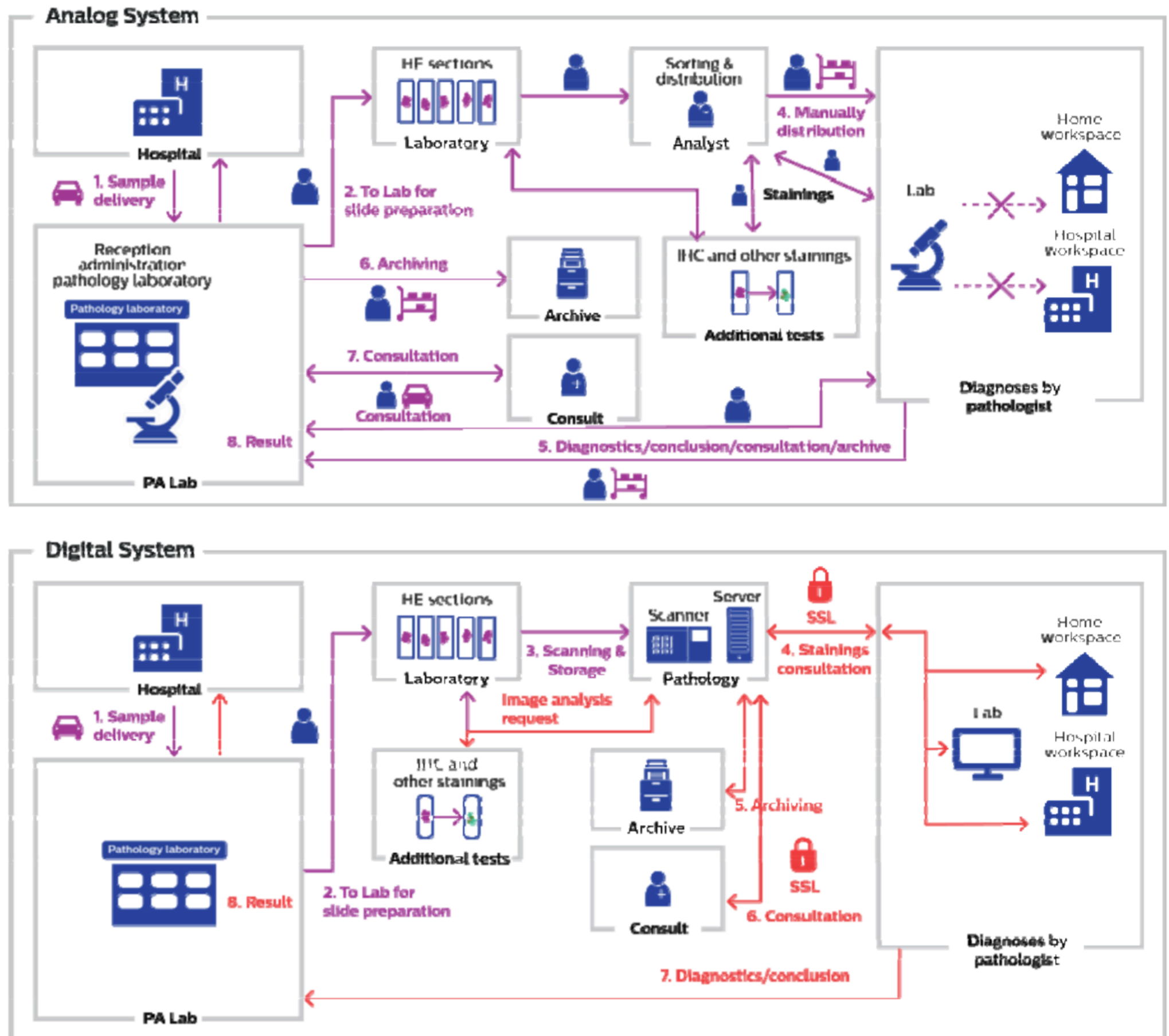Generative adversarial networks
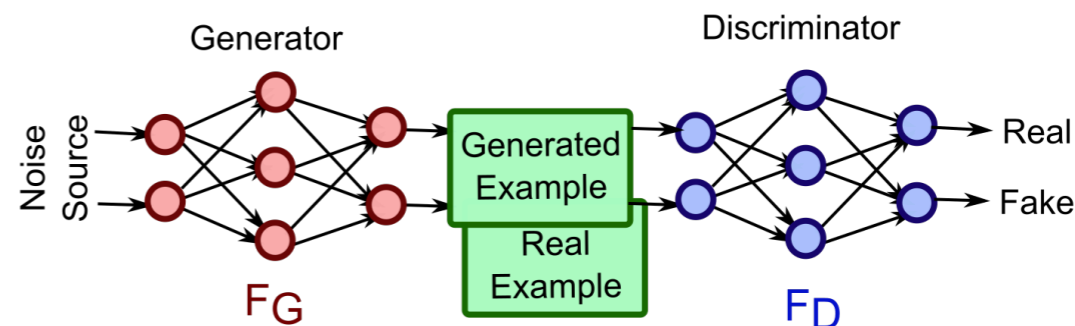
Что можно предсказывать?

- Диагностика
- Прогноз
- Выбор терапии

Что можно предсказывать?

Oncologist

Precision medicine approaches: treatment tailored to an individual patient

As a companion diagnostic assay to evaluate patient prognosis to determine optimum management plan

Identification of unique morphological features associated with gene alterations or signalling pathways

Detection of cells, cellular subtypes and histologic primitives (such as mitotic figures, tubules or nuclei)

Quantification of cells or objects (such as types of blood cells or haemoglobin)

Grading of the tissue according to severity of disease (for example, Gleason grading in prostate cancer)

Low risk   High risk

Early assessment of response to a specific drug or treatment

Detection of intratumoural heterogeneity by analyzing variance across the tissue block

Pathologist

Diagnosis of malignant from benign or inflammation and/or reactive changes

Delineation or annotation of which area is malignant or suspicious of pathology on a whole slide image

Identification of novel prognostic approaches beyond visual identification (such as spatial architecture or degree of multinucleation)

Stratification of patients on the basis of their risk of progression or recurrence to guide intensification or de-intensification therapy

Identification of patients who are more likely to respond to a particular therapeutic regimen or treatment

Сравнение процессов цифровой и аналоговой патологии

Сравнение процессов цифровой и аналоговой патологии
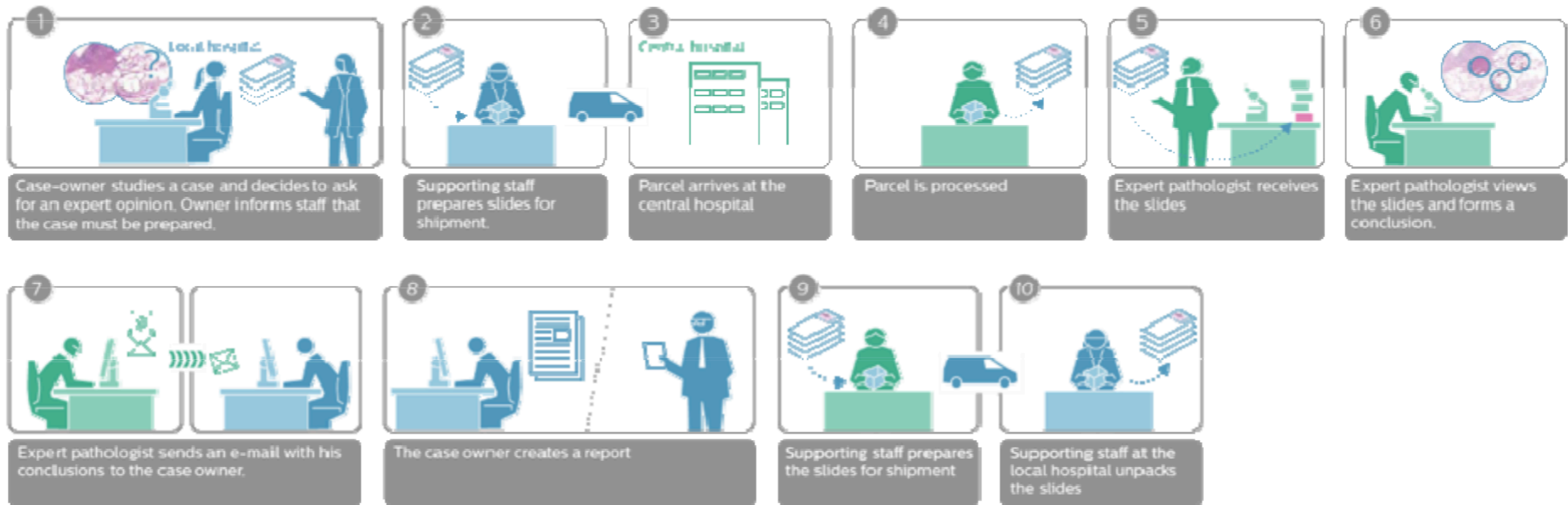
Consultation: analog versus digital workflow
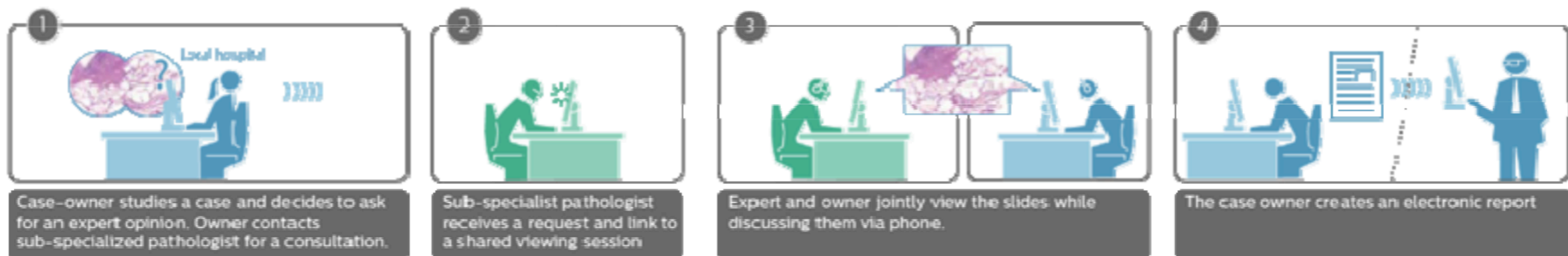
Сравнение процессов цифровой и аналоговой патологии

Figure 1. *Digital pathology suite. Whole slide scanners and computers are arranged ergonomically for digital pathology supervisors and technicians to manage scanning workflow.*

Fig. 6: Impact of the proposed decision support system on clinical practice.
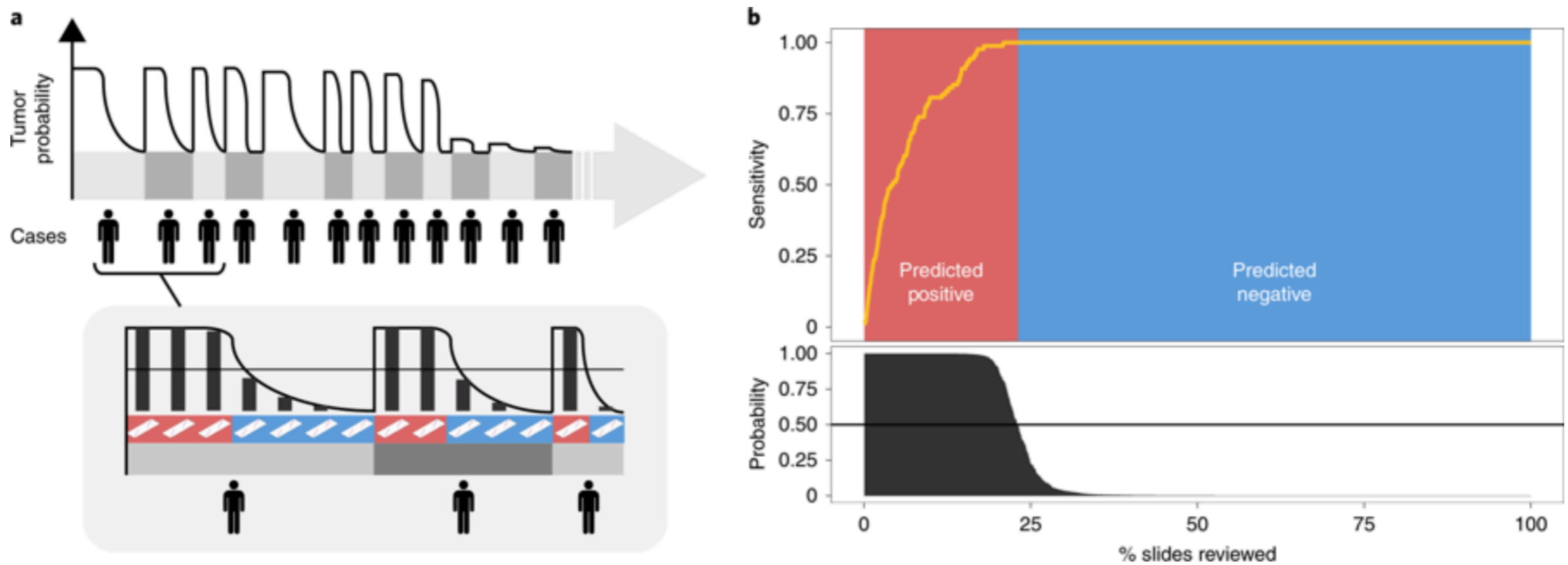
a, By ordering the cases, and slides within each case, based on their tumor probability, pathologists can focus their attention on slides that are probably positive for cancer. **b**, Following the algorithm's prediction would allow pathologists to potentially ignore more than 75% of the slides while retaining 100% sensitivity for prostate cancer at the case level ($n = 1,784$).

https://www.nature.com/articles/s41591-019-0508-1/figures/6

Dataset	Years	Slides	Patients	Positive slides	External slides	ImageNet
Prostate in house	2016	12,132	836	2,402	0	19.8×
Prostate external	2015–2017	12,727	6,323	12,413	12,727	29.0×
Skin	2016–2017	9,962	5,325	1,659	3,710	21.4×
Axillary lymph nodes	2013–2018	9,894	2,703	2,521	1,224	18.2×
Total		44,732	15,187			88.4×
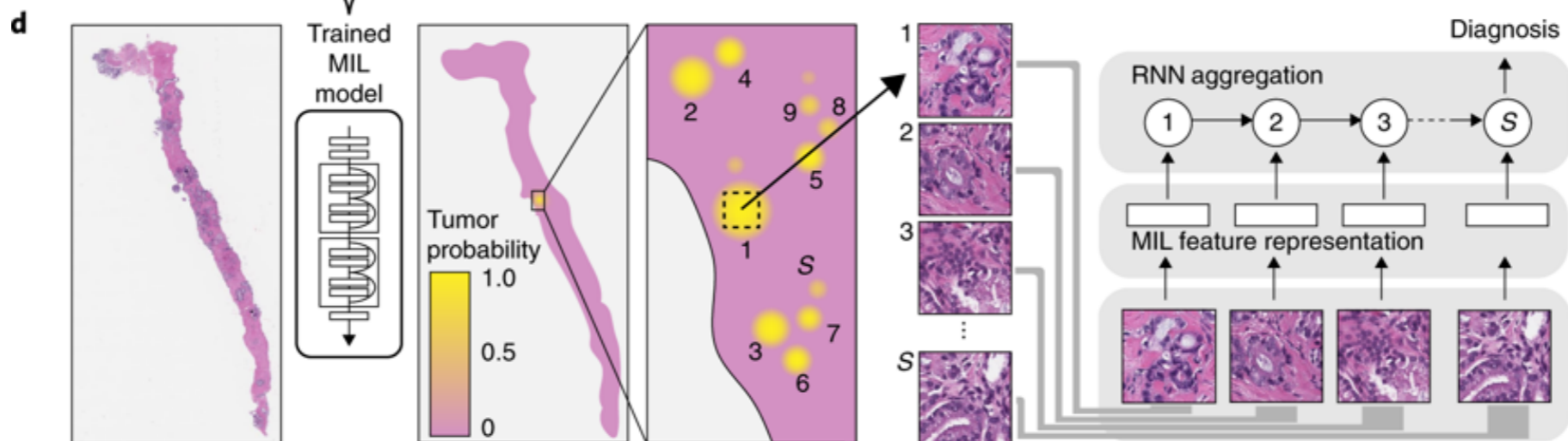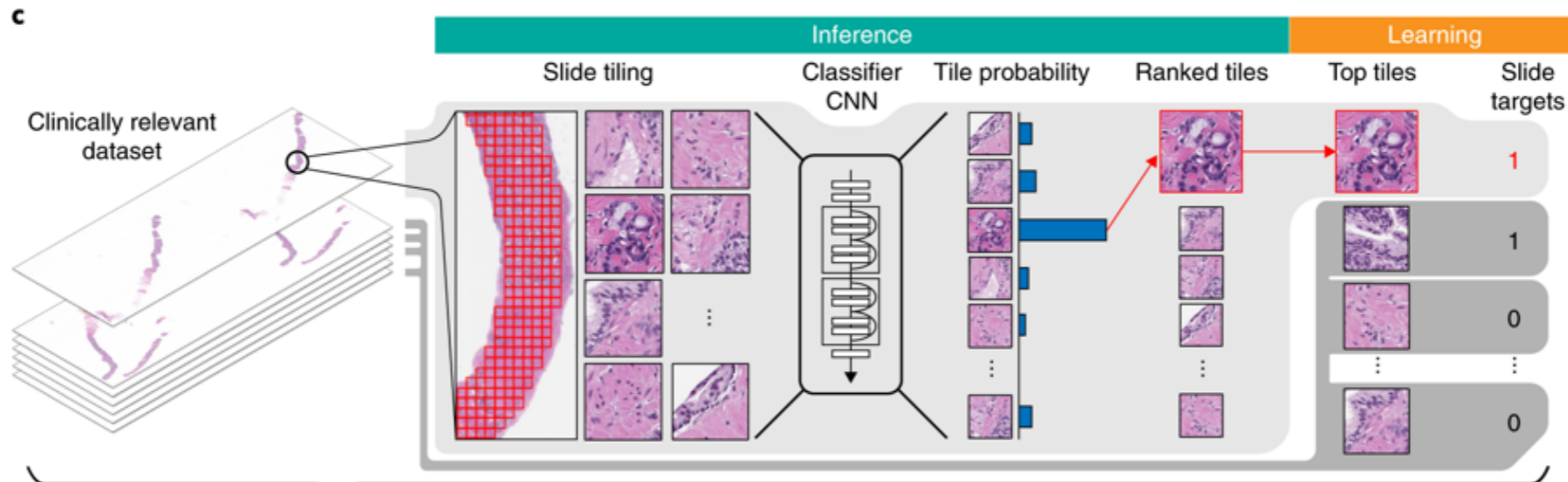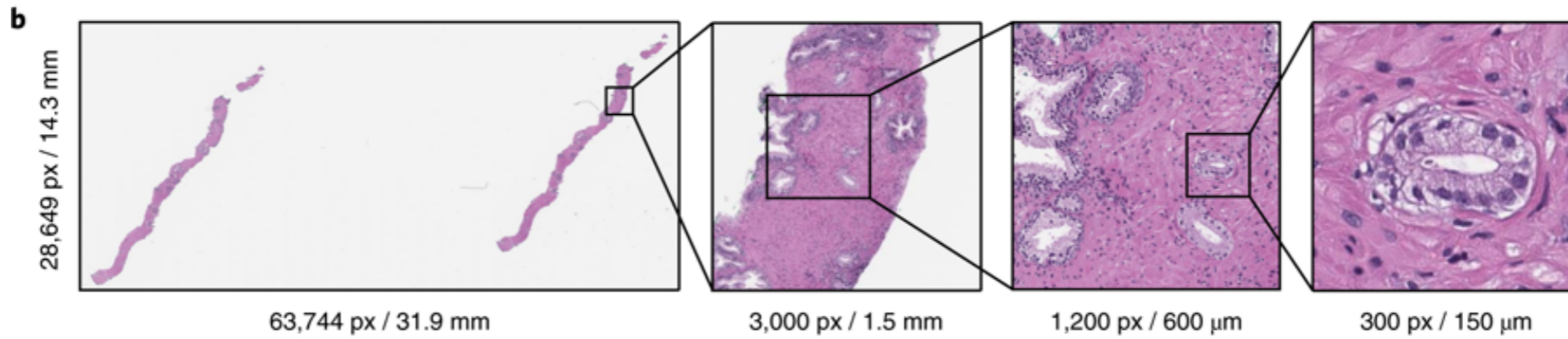
Разбор одной из работ

Deep learning can predict microsatellite instability directly from histology in gastrointestinal cancer

Jakob Nikolas Kather ✉, Alexander T. Pearson, Niels Halama, Dirk Jäger, Jeremias Krause, Sven H. Loosen, Alexander Marx, Peter Boor, Frank Tacke, Ulf Peter Neumann, Heike I. Grabsch, Takaki Yoshikawa, Hermann Brenner, Jenny Chang-Claude, Michael Hoffmeister, Christian Trautwein & Tom Luedde ✉

Статья о том что нейронная сеть смогла предсказать один из параметров опухоли желудка (микросателитная нестабильность) - опираясь только на микроскопические изображения. Обычно тот тест - дорогостоящая процедура, важная для диагностики, но назначаемая не всем из-за стоимость и сложности. Анализ изображений позволяет сделать этот тест всем, у кого берётся биопсия

Разбор одной из работ   **Выборка пациентов**

	TCGA-STAD	**TCGA-CRC-KR**	**TCGA-CRC-DX**	**TCGA-UCEC**	**DACHS**	**KCCH**
Material	FFPE	snap frozen	FFPE	FFPE	FFPE	FFPE
Staining	HE	HE	HE	HE	HE	HE
N patients	315	387	360	327	378	185
Median age [years]	67	67	67	63	68	65
% UICC stage 1	13%	17%	17%	69%	20%	0%
% UICC stage 2	31%	37%	37%	6 %	33%	39%
% UICC stage 3	44%	29%	30%	19%	33%	55%
% UICC stage 4	10%	12%	13%	4%	14%	6%

Supplementary Table 1: Clinico-pathological variables of all patient cohorts. STAD = stomach adenocarcinoma, CRC = colorectal cancer, KR = snap-frozen slides, DX = diagnostic slides with FFPE processing, FFPE = formalin-fixed and paraffin-embedded, HE = hematoxylin and eosin, UICC = Union internationale contre le cancer, UCEC = uterine corpus endometrial carcinoma, KCCH = Yokohama gastric cancer cohort, DACHS = German colorectal cancer cohort, MSI = microsatellite instable, NA = not applicable.

Разбор одной из работ

Выборка пациентов

b

biopsy

whole slide

AUC

number of blocks

c

patients
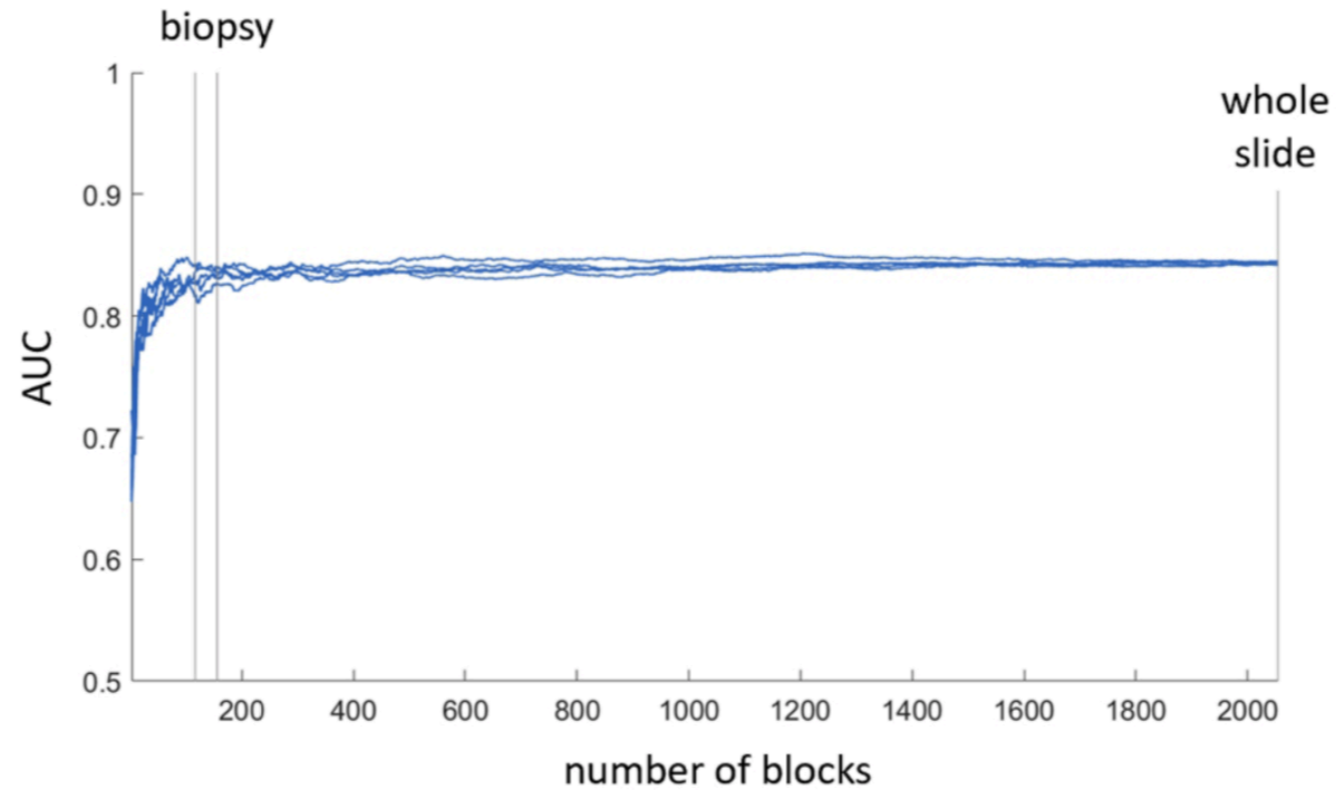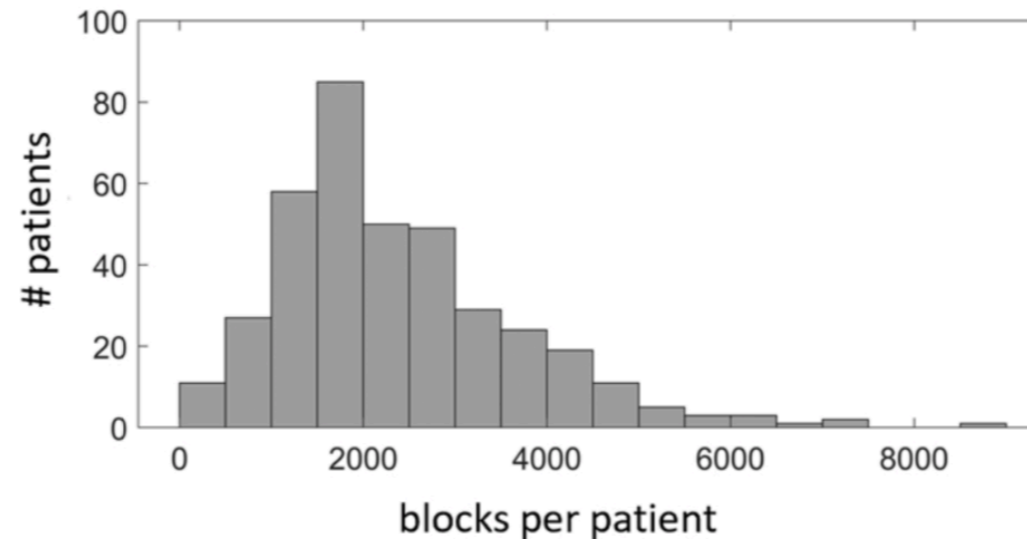
blocks per patient

(licensed under a CC-BY 4.0 license). **b**, Classification performance in virtual biopsies. We predicted MSI status in all patients in the DACHS cohort, varying the number of blocks (tiles) from 3 to 2,054, which was the median number of blocks per whole-slide image This experiment was repeated five times with different randomly picked blocks being used. As one block has an edge length of 256 μm, a 1-cm tissue cylinder with 100% tumor tissue from a standard 18G biopsy needle corresponds to 117 blocks and a 16G needle corresponds to 156 blocks. In clinical routine, usually only a part of each biopsy core contains tumor, but multiple biopsy cores are collected. With increasing tissue size, performance stabilizes at AUC = 0.84. This shows that a typical biopsy would be sufficient for MSI prediction. CI, confidence interval. **c**, Distribution of the numbers of blocks for all patients in DACHS (n = 378 patients).
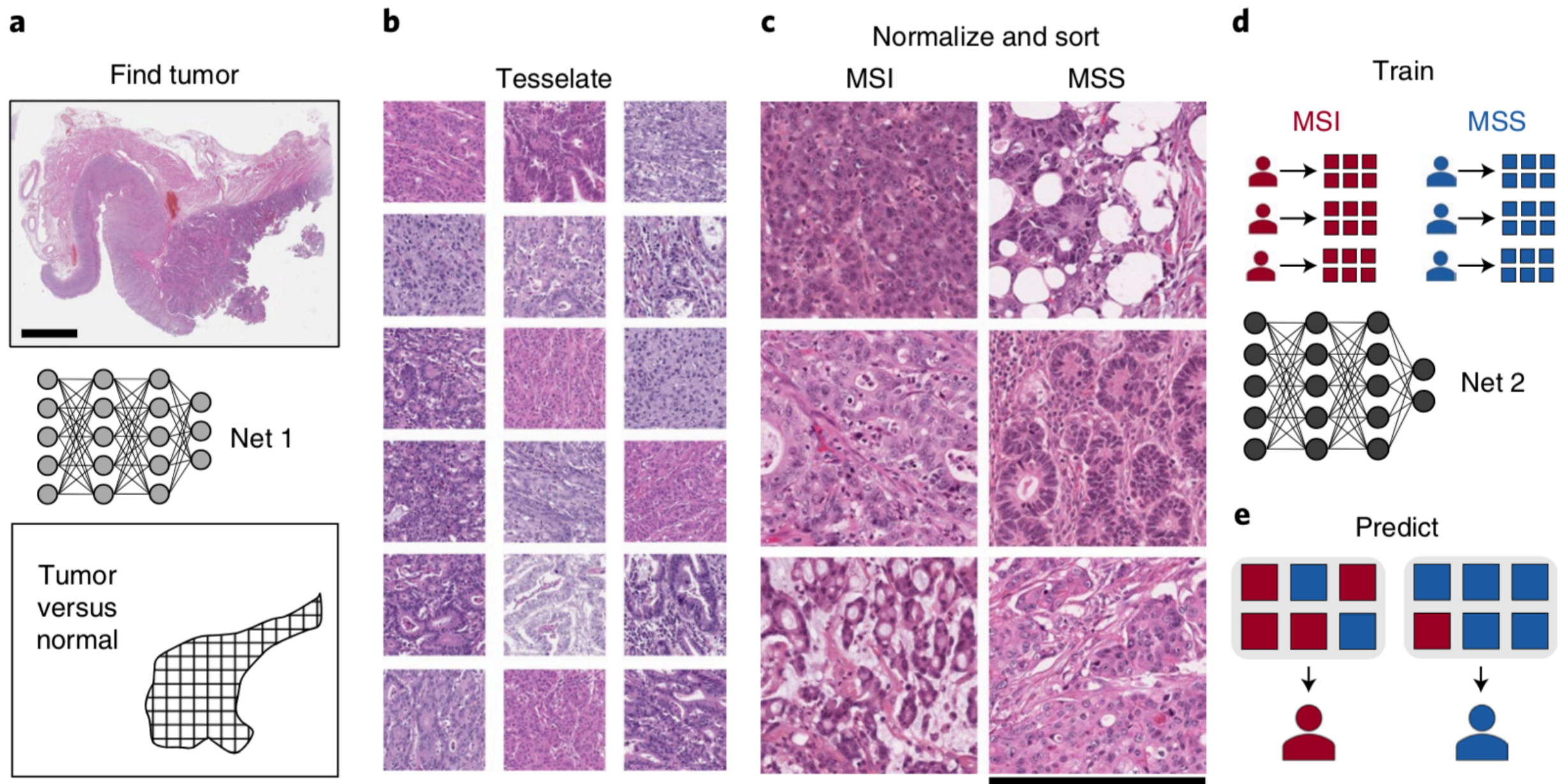
Fig. 1 | Tumor detection and MSI prediction in H&E histology. a, A convolutional neural network was trained as a tumor detector for STAD and CRC. Scale bar, 4 mm. **b,c**, Tumor regions were cut into square tiles (**b**), which were color-normalized and sorted into MSI and MSS (**c**). Scale bar, 256 μm. **d**, Another network was trained to classify MSI versus MSS. **e**, This automatic pipeline was applied to held-out patient sets.
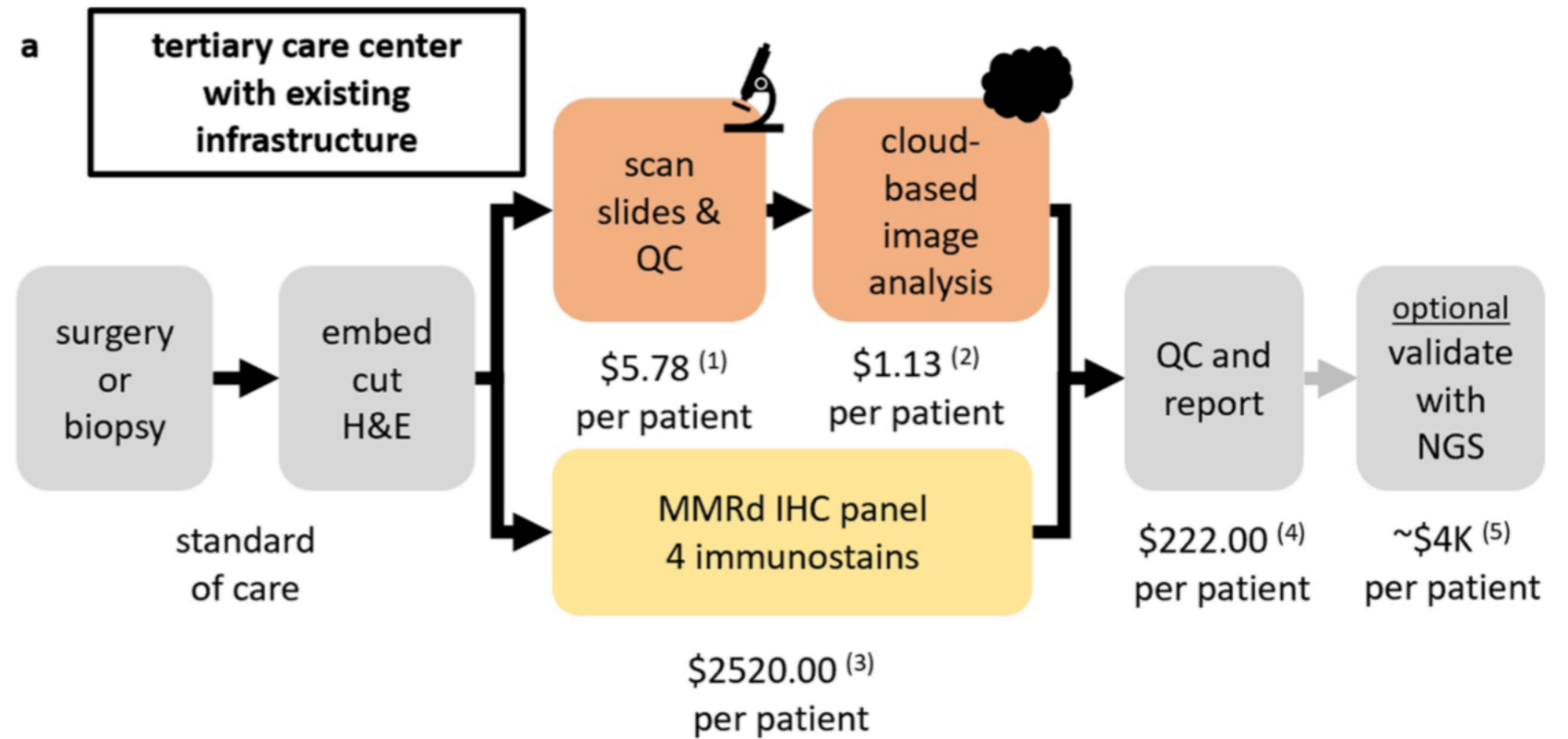
Разбор одной из работ   Результаты предсказания
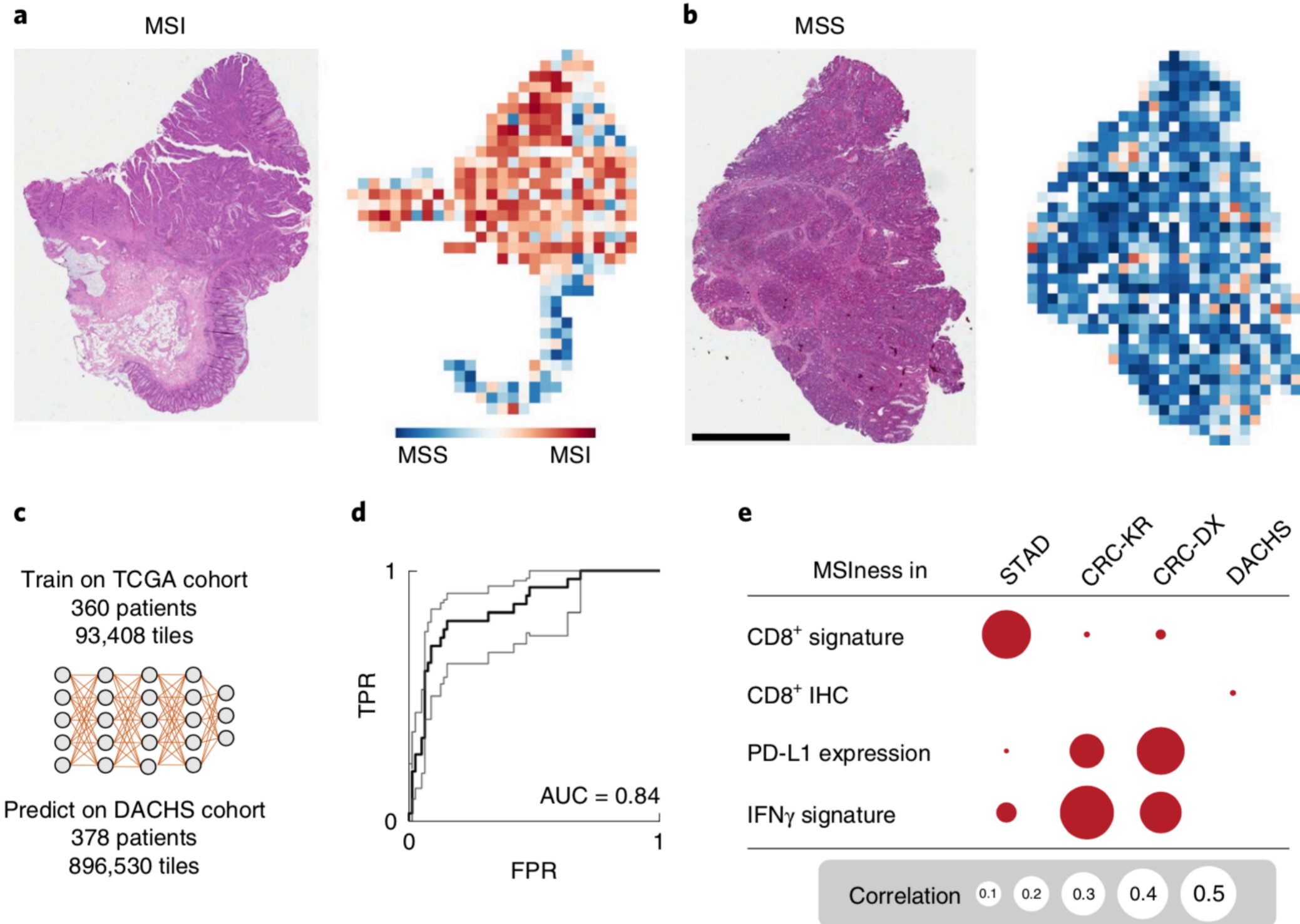
Fig. 2 | Classification performance in an external validation set. a,b, Tissue slides of patients with MSI and MSS tumors in the TCGA-CRC-DX test set show the spatial patterns of predicted MSI score (Extended Data Fig. 4). These images are representative of $n = 378$ patients. **c,** A network was trained on the TCGA-CRC-DX training cohort ($n = 260$ patients) and deployed on the DACHS cohort ($n = 378$ patients). **d,** Patient-level receiver operating characteristic curve with bootstrapped 95% CI in DACHS ($n = 378$ patients). FPR, false-positive rate ($1 -$ specificity); TPR, true-positive rate (sensitivity). **e,** Pearson correlation of predicted MSIness to transcriptomic and immunohistochemical (IHC) data across test sets. P values are listed in Supplementary Table 4. Sample sizes per cohort are: TCGA-STAD $n = 91$, TCGA-CRC-KR $n = 105$, TCGA-CRC-DX $n = 95$, DACHS $n = 134$ patients. No adjustments for multiple comparisons were made, and all statistical tests were two-sided.

Разбор одной из работ

Результаты предсказания
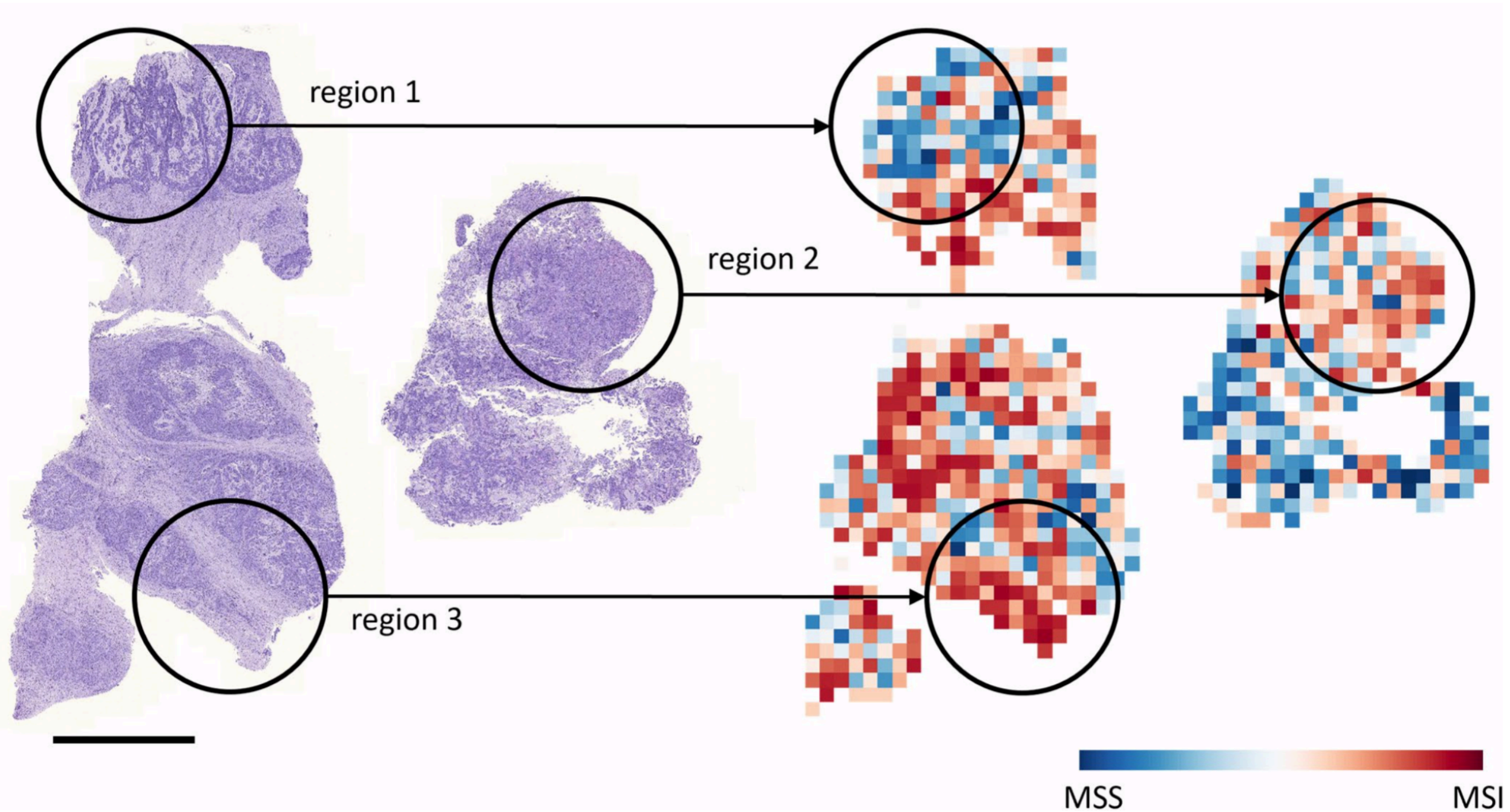
Extended Data Fig. 3 | Morphological correlates of intratumor heterogeneity of MSI. a, Histological image of a test set patient who was genetically determined as MSI. **b**, Corresponding predicted MSI map for the image shown in **a**. Three regions are highlighted. Region 1 is a glandular region with necrosis and extracellular mucus; this region was predominantly predicted to be MSS. Region 2 is a solid, dedifferentiated region, which was predicted to be MSI. Region 3 contained mostly budding tumor cells mixed with immune cells, this region was strongly predicted to be MSI. Together, these representative examples show that different morphologies elicit different predictions and that these predictions can be traced back to patterns that are understandable for humans. Scale bar, 2.5 mm. This figure is representative of $n = 378$ patients in the DACHS cohort.

Разбор одной из работ

Экономика

Наш опыт

Этапы работы с гистологическими срезами:

- автоматическая сегментация изображений на отдельные клетки

- кластеризация клеток на основе внешнего сходства

- присвоение кластерам наименований

- подсчёт соотношений различных кластеров и использование полученных соотношений в качестве весов для метода NMF

Спасибо за внимание!