Implementazione e applicazione dell'IA nella ricerca preclinica e traslazionale

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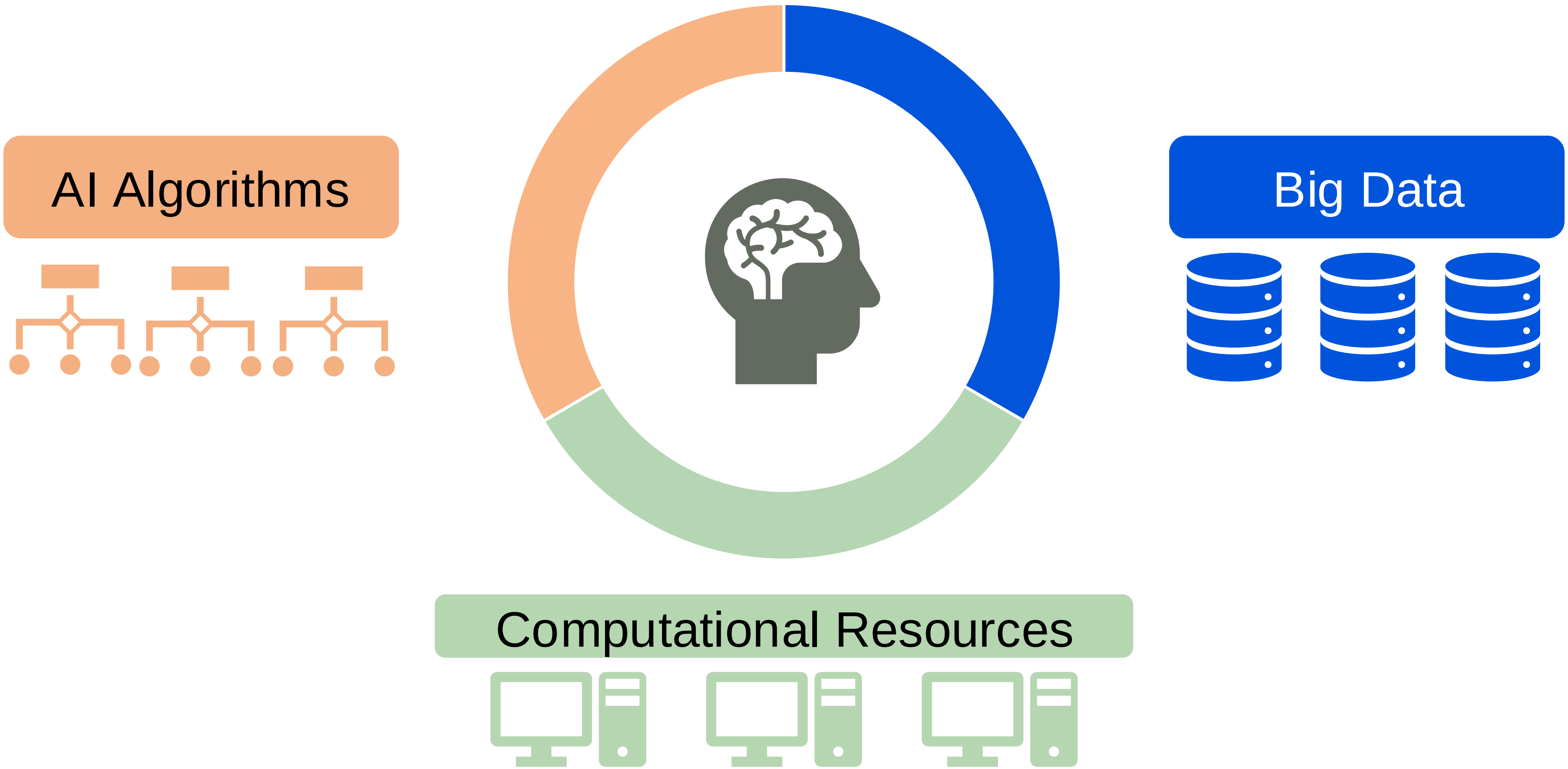
Disclosures

- **Honoraria as a consultant, advisor or speaker:** Roche, Menarini/Stemline.
- **Travel and accommodation support:** AstraZeneca.
- **Grant/Funding:** Merck

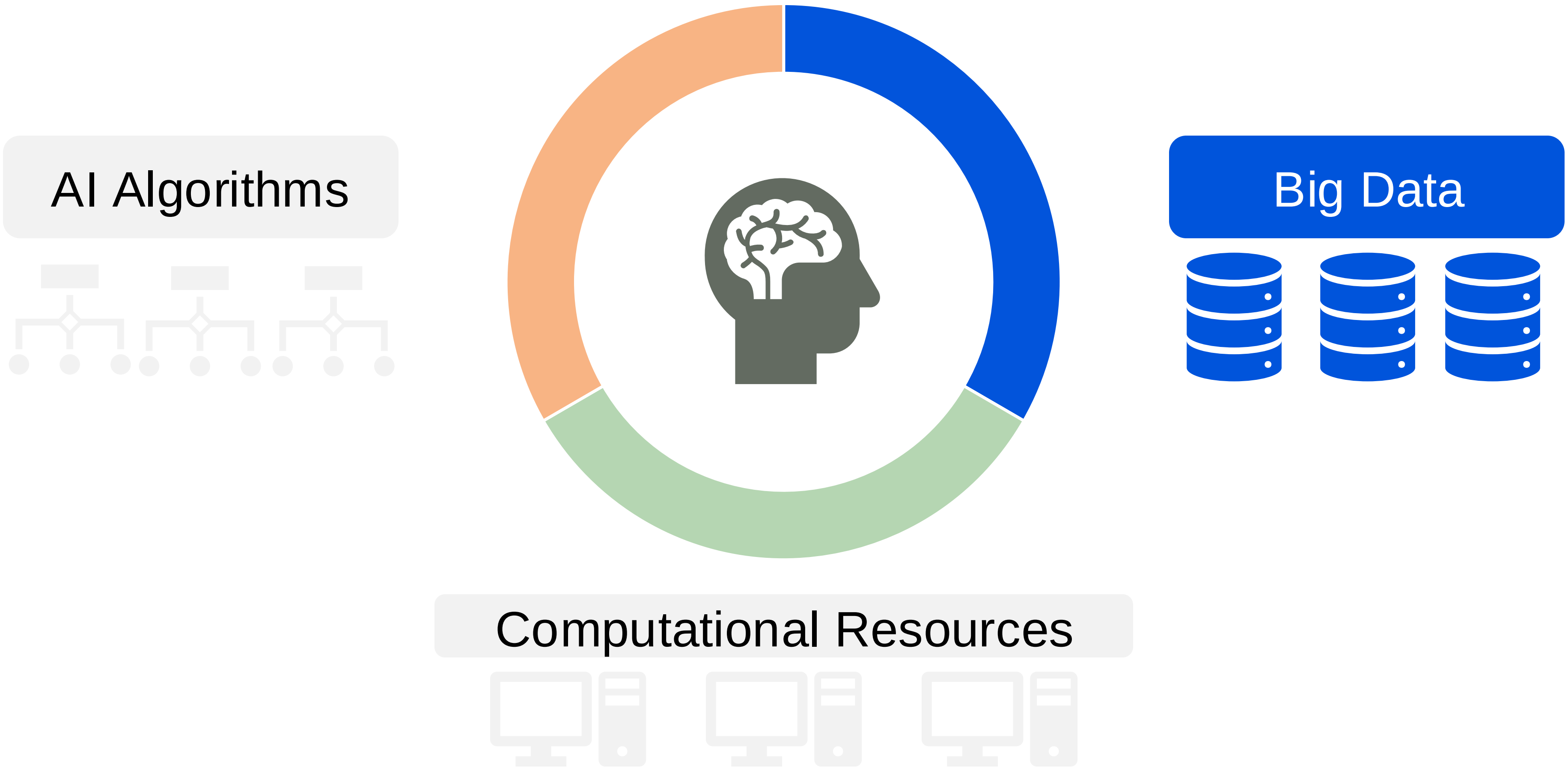
Agenda

- **Real-World Data (RWD) vs Real-World Evidence (RWE)**
- **Use of RWD to design external control arm(s)**
- **Use of AI in Oncology**
- **Multimodal integration of Big Data and AI in Oncology**
- **Take-home messages**

Big Data and Artificial Intelligence in Cancer Medicine



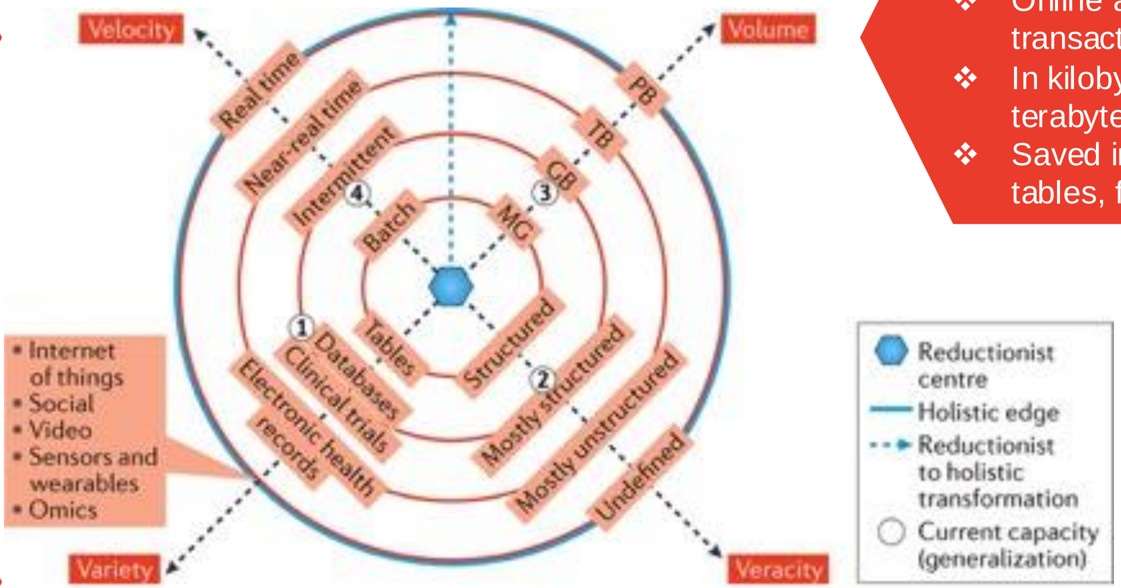
Big Data and Artificial Intelligence in Cancer Medicine



The 4 Vs of Biomedical Big Data

VELOCITY
- Speed of generating data
- Generated in real time
- Online and offline data
- In streams, batch or bits

VOLUME
- Amount of data generated
- Online and offline transactions
- In kilobytes or terabytes
- Saved in records, tables, files



VARIETY
- Structured and unstructured
- Online images and videos
- Human generated texts
- Machine generated readings

Adapted from Khozin, Nat Rev Drug Discov 2017

Real World Data vs Real World Evidence

Real World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources

- **Electronic health records (EHRs)**
- **Medical claims data**
- **Product and disease registries**
- **Patient-generated data, including in-home settings**
- **Data gathered from other sources, such as mobile devices, that can inform on health status**

Real World Evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD

Generated using different study designs, including but not limited to randomized trials (e.g., large simple trials, pragmatic trials), externally controlled trials, and observational studies

FDA Definitions

What is an externally controlled trial?

- An externally controlled trial is one in which the control group consists of patients who are not part of the same randomized study as the group receiving the investigational agent (i.e., there is no concurrently randomized control group).

- **Challenge**: Interpreting time to event endpoints in single arm trials

- **Potential solution**: use of well constructed external control designs

- **Methodological concern**: ensuring balance of factors for evaluation in the absence of randomization

Rivera, FDA Workshop 2021

External controls

Type

External control arm

Synthetic control arm

Temporality

Concurrent control:
Patient population treated during the same or similar period, reflecting a similar standard of care

Historical control:
Non contemporaneous patient population where retrospective or retrospectively analysed data is used as comparator

Rivera, FDA Workshop 2021

External control arms

External control designs

- Previously conducted clinical trial(s), including pooled trial data
- Historical real-world data (single source)
- Historical real-world data (pooled data)
- Prospective real-world data
- Hybrid prospective designs (e.g., concurrently randomized control as well as external control)

Uses of external controls

As benchmark or natural history study (**epidemiology**)

As individual patient level matched data for comparative study (**effectiveness**)

Use of external control arms

Rationale for lack of randomization

When randomized trials are:

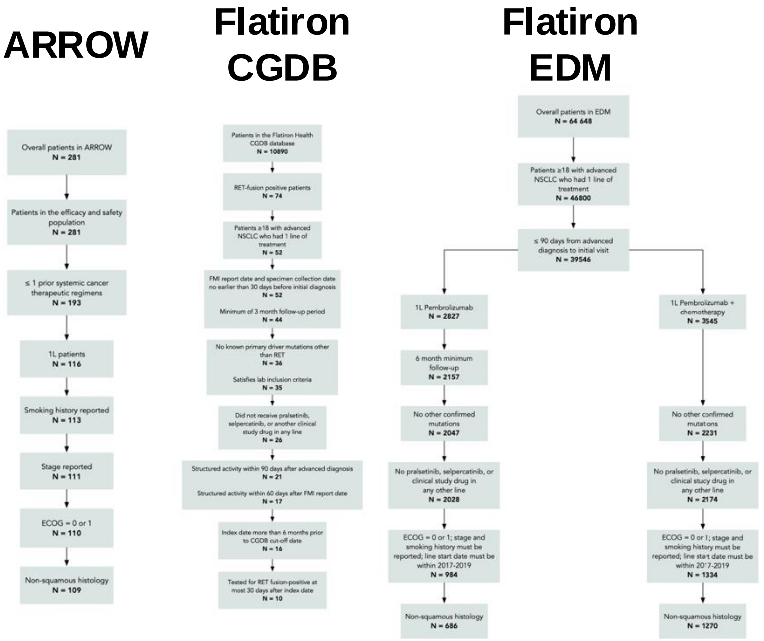
- ❖ Infeasible or impractical
- ❖ Unethical
- ❖ Lack of equipoise

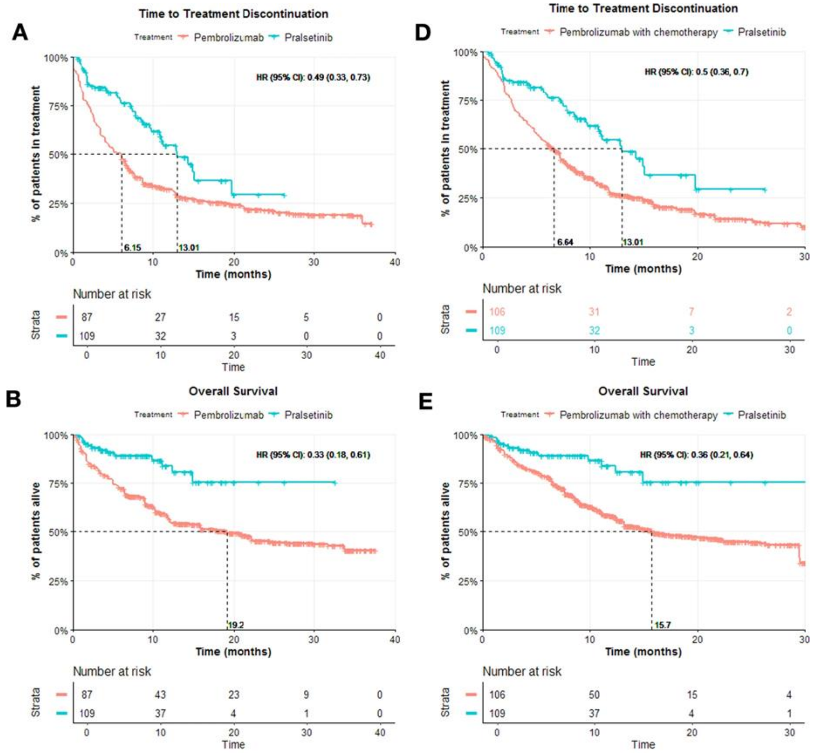
Applications

- Pediatrics
- Rare disease
- Significant unmet medical need (i.e., limited treatment options or standard of care)
- Molecular subgroups
- Under-represented populations

Rivera, FDA Workshop 2021

Real-world synthetic control arms to demonstrate the comparative effectiveness of pralsetinib in NSCLC





Popat, Nat Comm 2022

Other examples of the use of external RWD for drug evaluation by regulatory agencies

Table 1. Regulatory case studies

Drug	Disease setting	Source of external control data	Regulatory use of external control data
Selumetinib	Neurofibromatosis type 1 with inoperable plexiform neurofibromas (pediatric)	Previously conducted clinical trials	Establish natural history of disease
Erdafitinib	Unresectable urothelial cancer harboring select FGFR genetic alterations	Patient-level EHR data from US community-based cancer clinics	Establish natural history of disease
Pembrolizumab and lenvatinib	Advanced endometrial carcinoma that is not MSI-H or dMMR	Previously conducted clinical trials	Isolation of treatment effect
Several immunooncology combination therapies	Untreated, locally advanced or metastatic renal cell carcinoma	Previously conducted clinical trials	Isolation of treatment effect
Blinatumomab	Precursor B-cell ALL in complete remission with detectable MRD	Retrospective observational cohort study	Comparative efficacy analysis

ALL, acute lymphoblastic leukemia; dMMR, mismatch repair deficient; EHR, electronic health record; FGFR, fibroblast growth factor receptor; MRD, minimal residual disease; MSI-H, microsatellite instability-high.

Mishra-Kalyani, Ann Oncol 2022

Key methodological concerns

Data quality and metrics
(internal validity)

Cohort definition

RWD heterogeneity
(external validity)

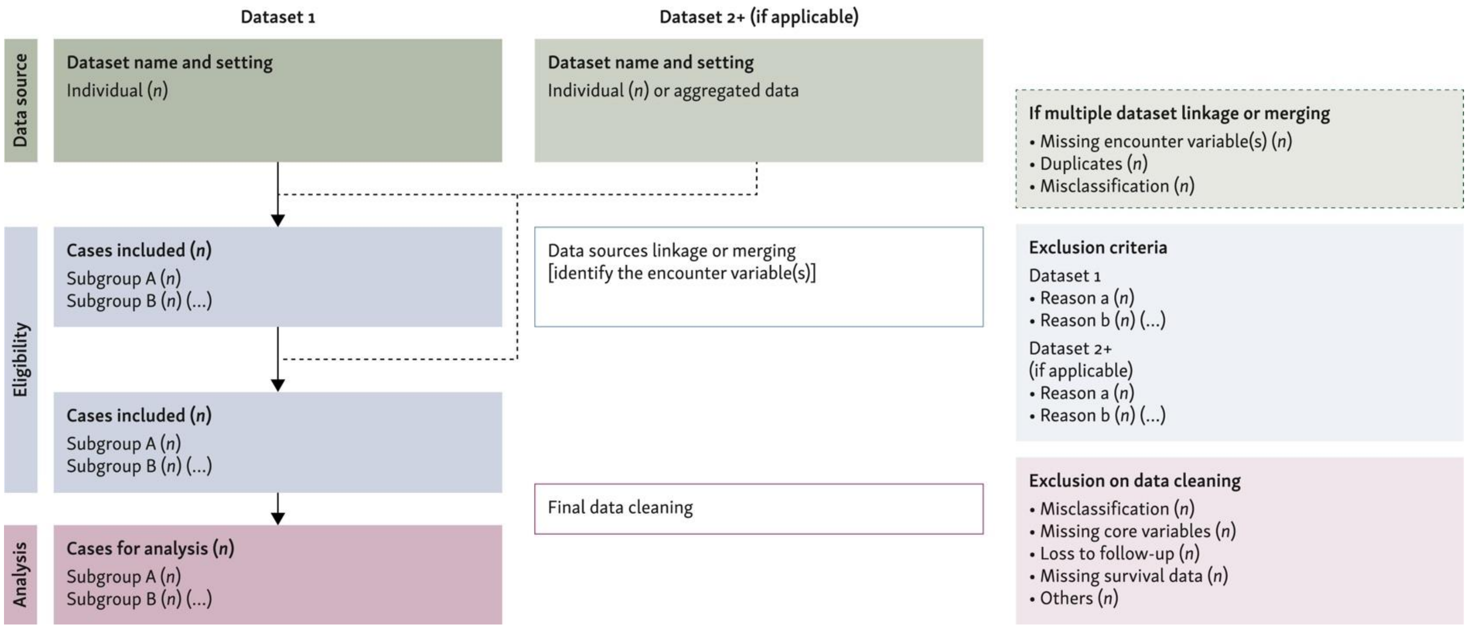
Endpoint validation
(response and time
to event)

Bias
(selection,
confounding
misclassification)

Fit for purpose:
is data complete,
consistent, accurate,
longitudinal?

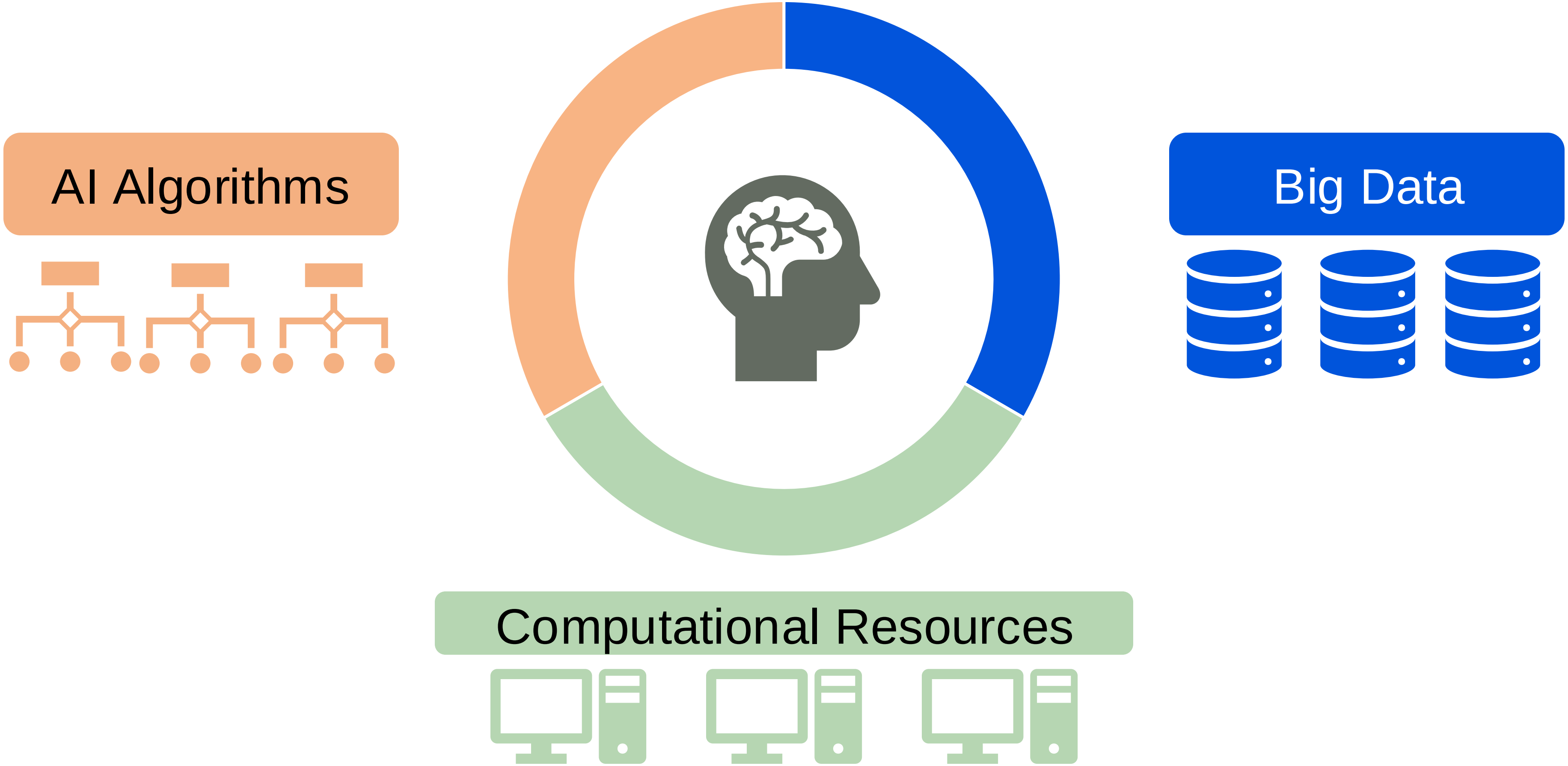
ESMO Guidance for Reporting Oncology Real-World Evidence

ESMO-GROW flowchart illustrating the process of case selection for analysis

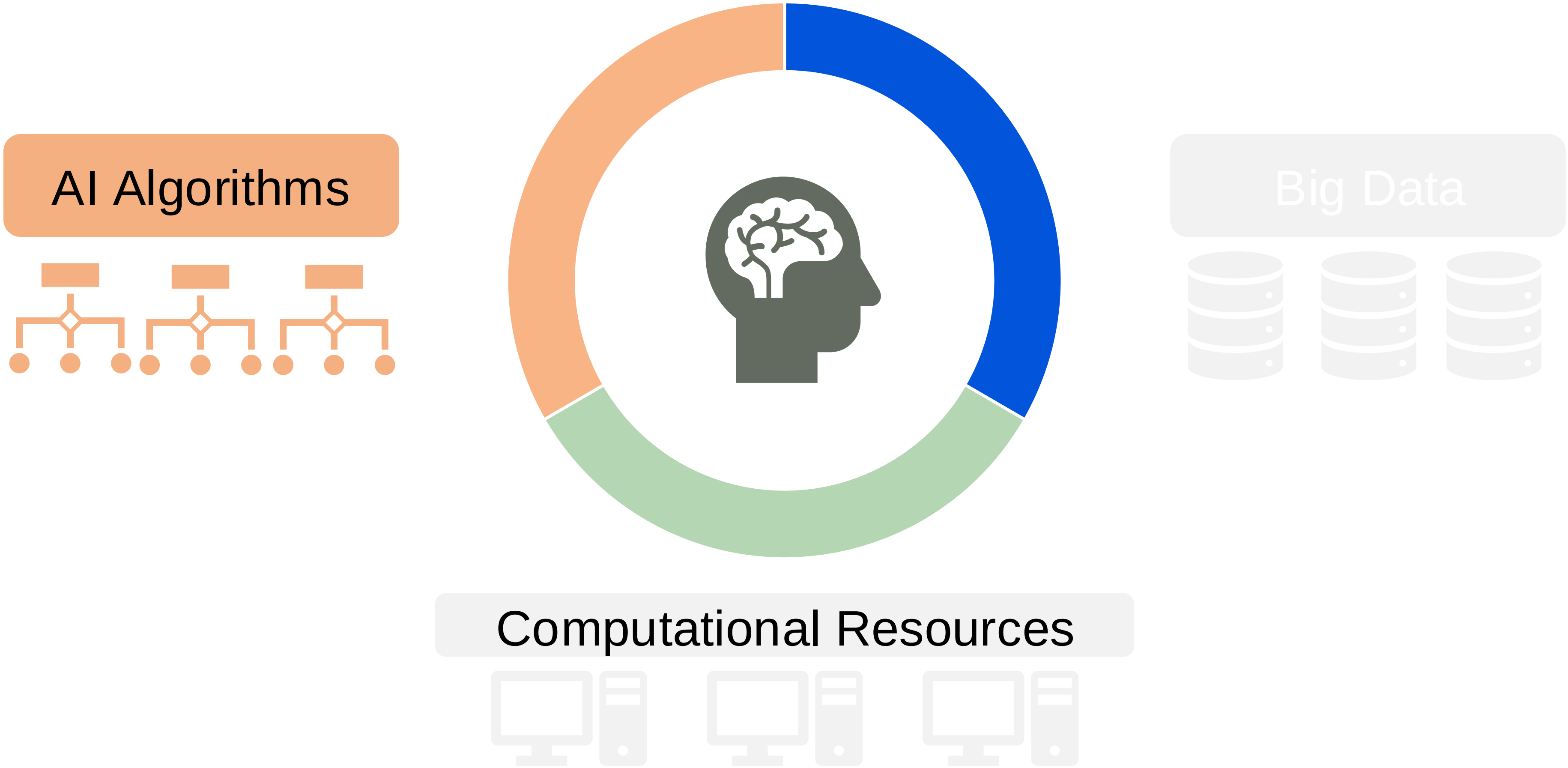


Castelo-Branco, Ann Oncol 2023

Big Data and Artificial Intelligence in Cancer Medicine

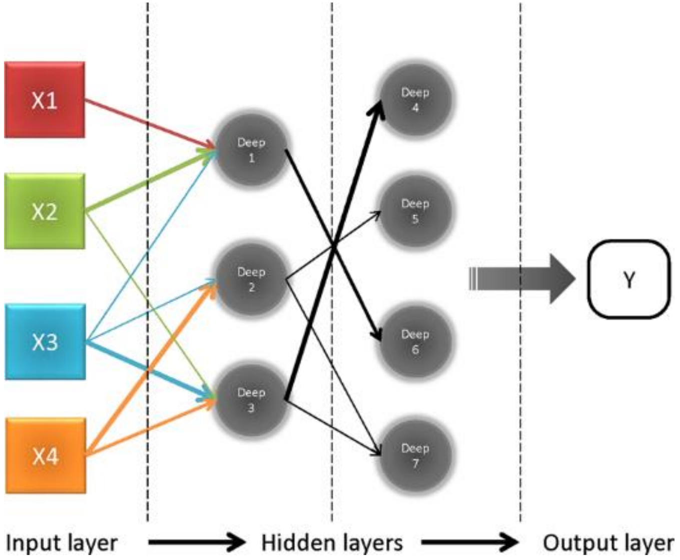


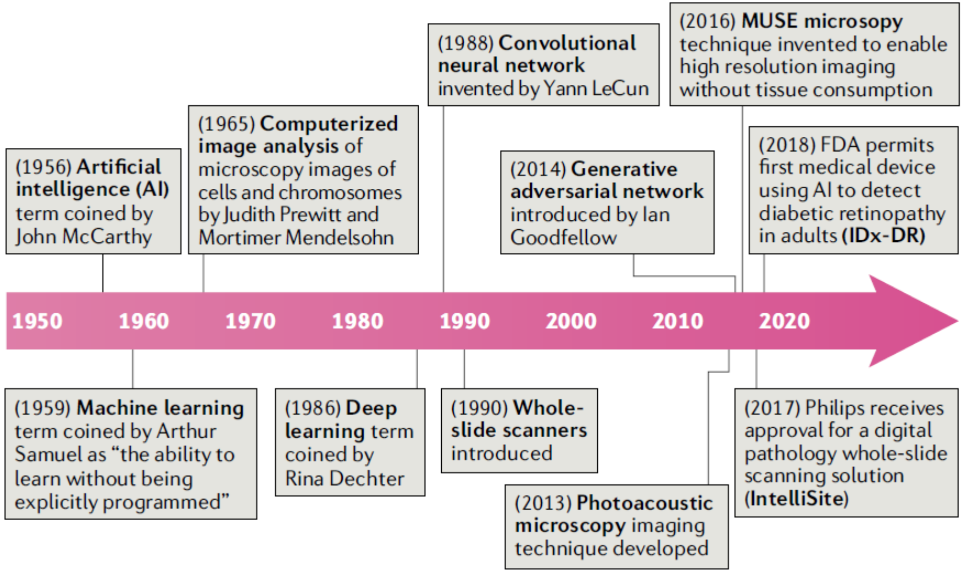
Big Data and Artificial Intelligence in Cancer Medicine



Introduction to Artificial Intelligence (AI)

The branch of computer science in which machine-based approaches are used to attempt to make a prediction — emulating what an intelligent human might do in the same situation.



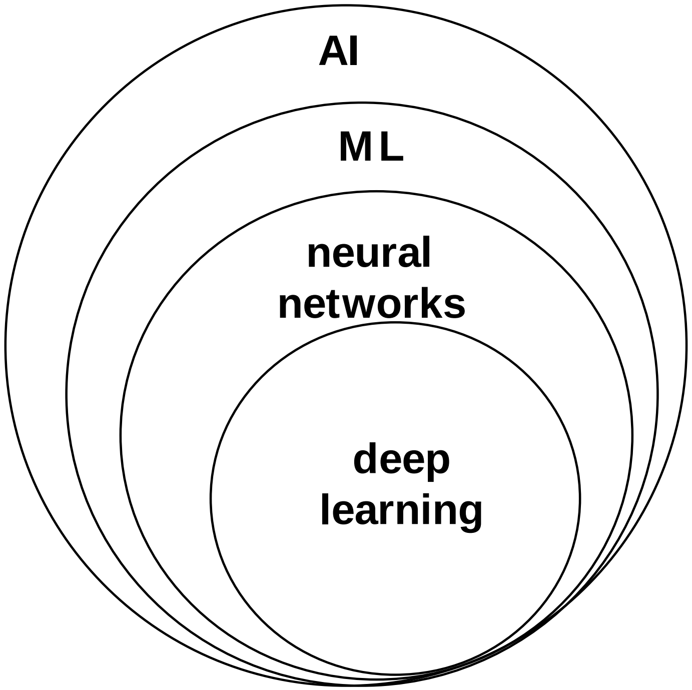


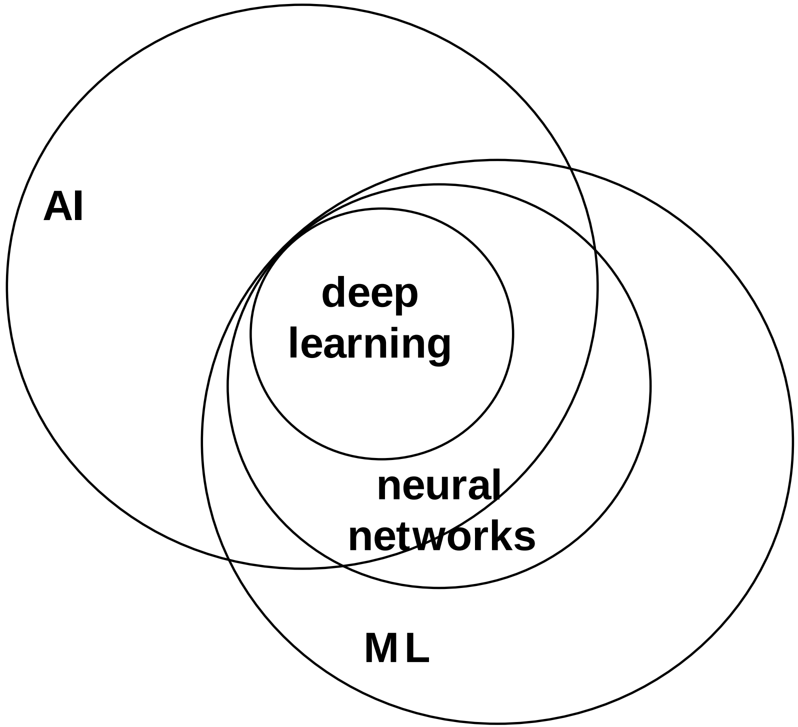
First FDA Breakthrough approval for an AI-based pathology solution was granted in 2019

Bera, Nat Rev Clin Oncol 2019

Taxonomy of Artificial Intelligence

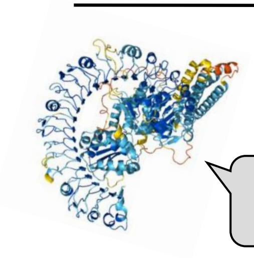
Debated





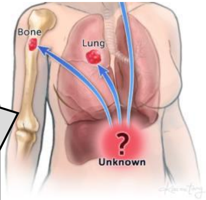
Examples of Artificial Intelligence

AI



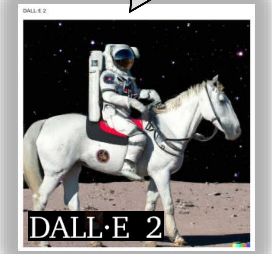
GPT3
Input: Text
Output: Continuation of text

Alpha Fold
Input: Amino acid sequence
Output: 3D structure of protein



TOAD
Input: Pathology image of CUP
Output: Probability of primary tumor site

DALLE 2 / Imagen
Input: Text
Output: Image

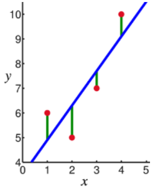



Article
Grandmaster level in StarCraft II using multi-agent reinforcement learning

AlphaStar
Input: game environment
Output: Beats humans at Starcraft II

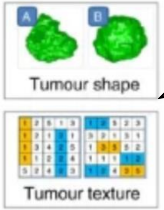
Vinyals et al., Nature 2019

not AI (?)



Linear regression

A phone book



Hand-crafted features for medical image analysis

image: Wikimedia Commons
Aerts et al., Nat Comms 2014

Courtesy of Jakob Kather

When AI should be used in Oncology?

Small datasets, tabular data

Classical statistics, classical machine learning

Image data

Free-text data

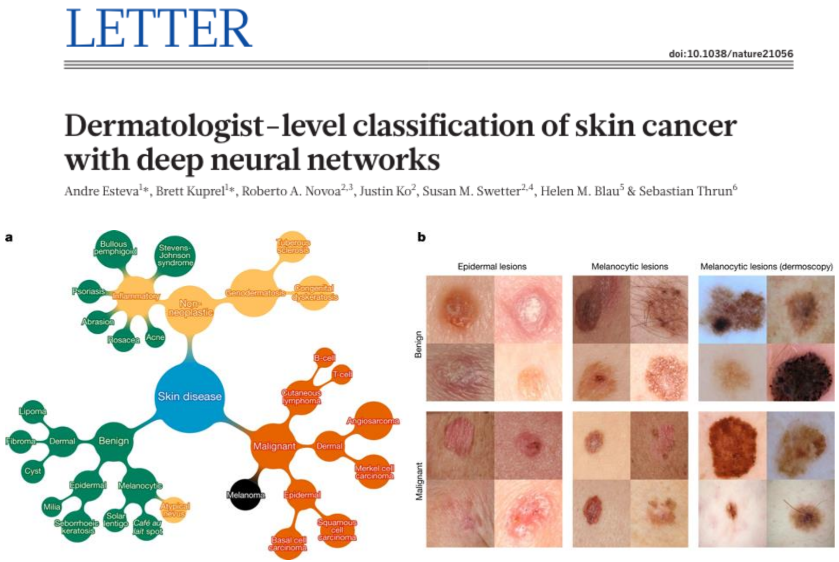
Convolutional Neural Networks or Transformers

Large Language Models (LLMs) (Transformers)

Deep Learning

Rosler, J Cancer Res Clin Oncol 2023

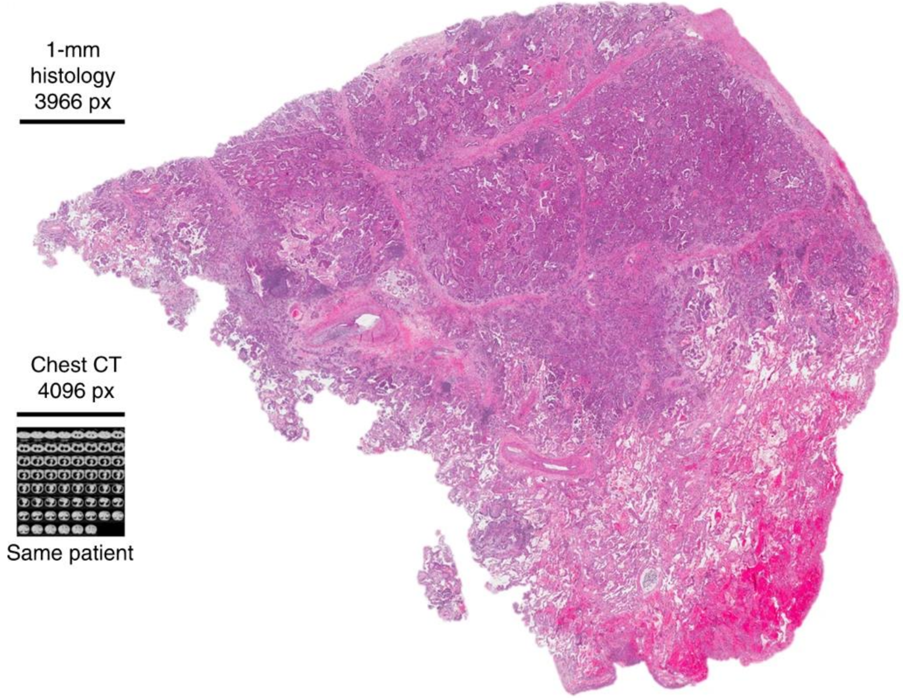
>90% of AI tools in Oncology use image data


LETTER

doi:10.1038/nature21056

Dermatologist-level classification of skin cancer with deep neural networks

Andre Esteva[1]*, Brett Kuprel[1]*, Roberto A. Novoa[2,3], Justin Ko[2], Susan M. Swetter[2,4], Helen M. Blau[5] & Sebastian Thrun[6]



Esteva, Nature 2017; Echle, Brit J Cancer 2021

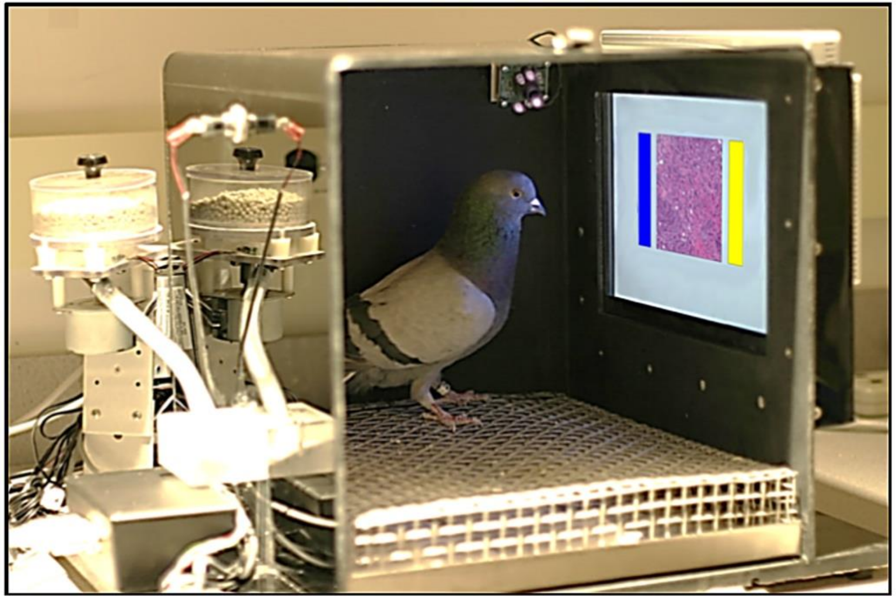
Image classification is easy (apparently)

PLOS | ONE

RESEARCH ARTICLE

Pigeons (*Columba livia*) as Trainable Observers of Pathology and Radiology Breast Cancer Images

Richard M. Levenson[1]*, Elizabeth A. Krupinski[3], Victor M. Navarro[2], Edward A. Wasserman[2]*

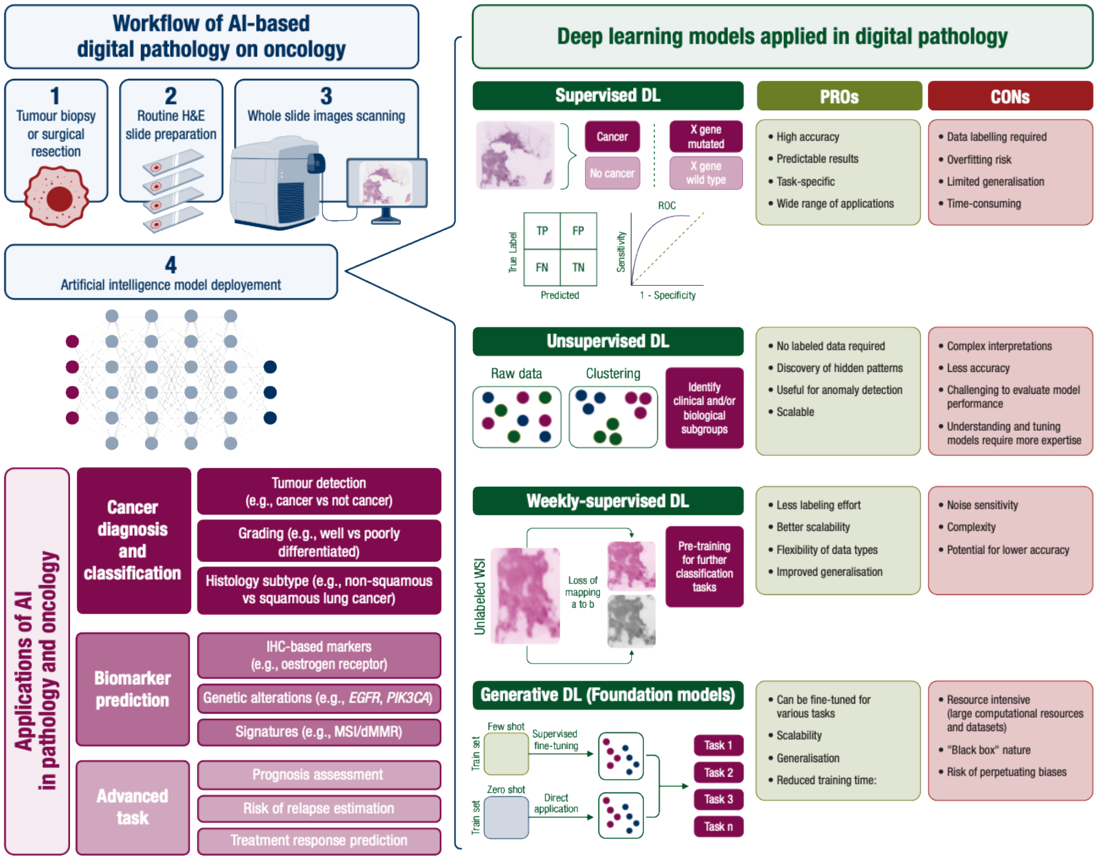


Levenson, PLoS ONE 2015

Supervised classification problems: Class A or Class B

Courtesy of Jakob Kather

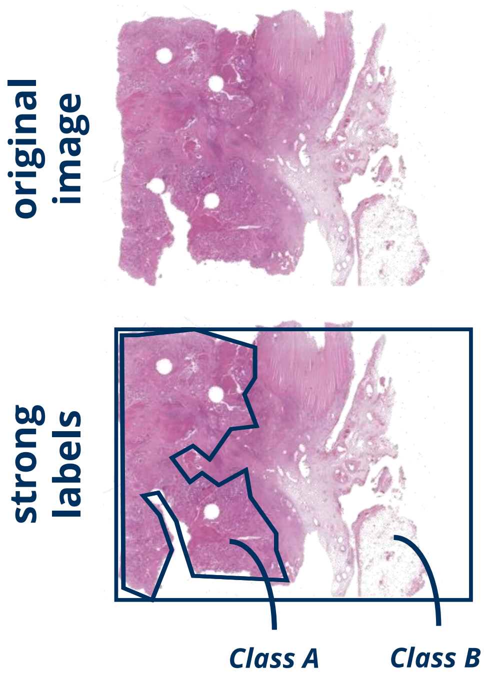
Current workflow, deep learning models and application of AI in pathology for oncology



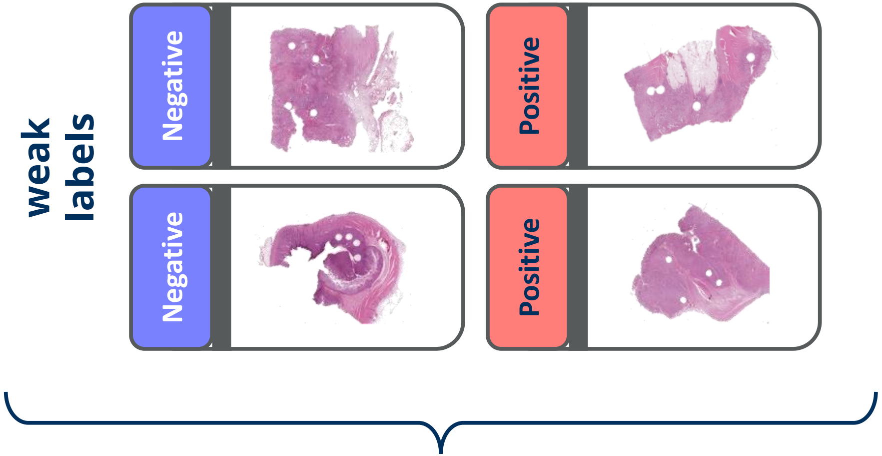
Marra, Ann Oncol. 2025, *in press*

Strong vs weak supervision

Strong supervision



Weak supervision



Deep Learning yields surprisingly good results when trained on weakly labeled data

Labels = Genetic alterations, survival, response, …

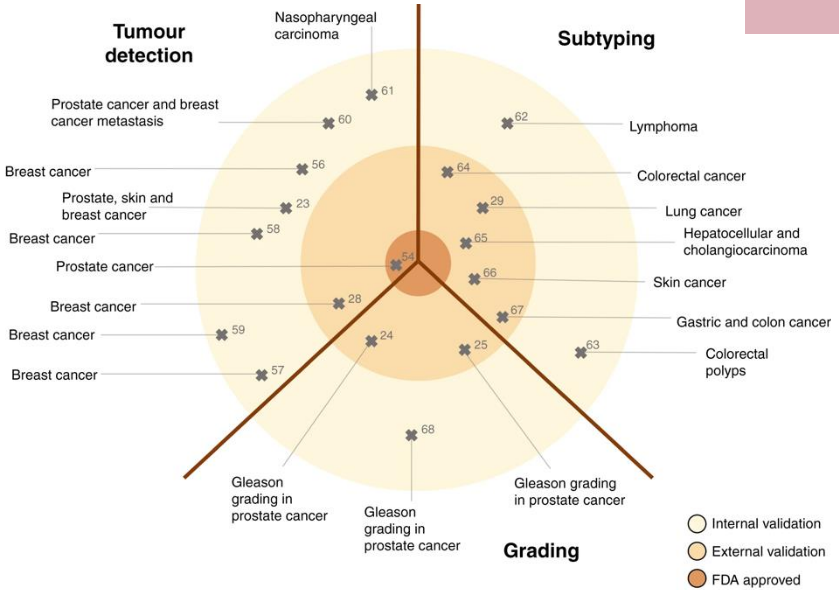
Courtesy of Jakob Kather

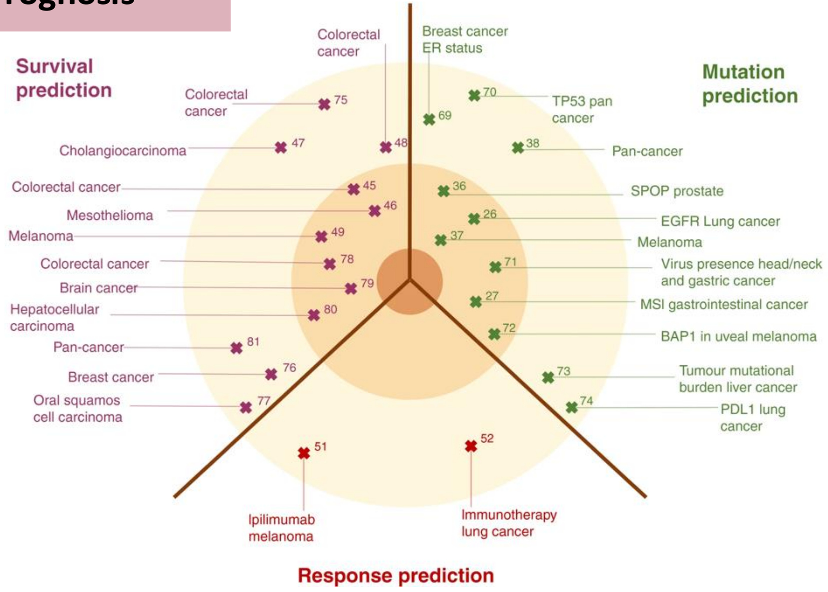
Which are the applications of AI in Oncology?

Tumor or not ?

Prognosis

Genotype



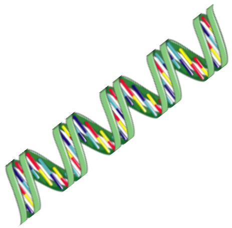


Treatment response

Echle, Br J Cancer. 2021

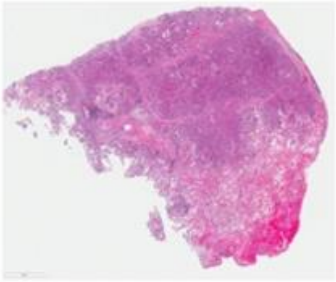
Central Assumption

Specific genetic alterations in cancer …



… elicit changes in the phenotype of …

1. Tumor cells
2. Tumor microenvironment



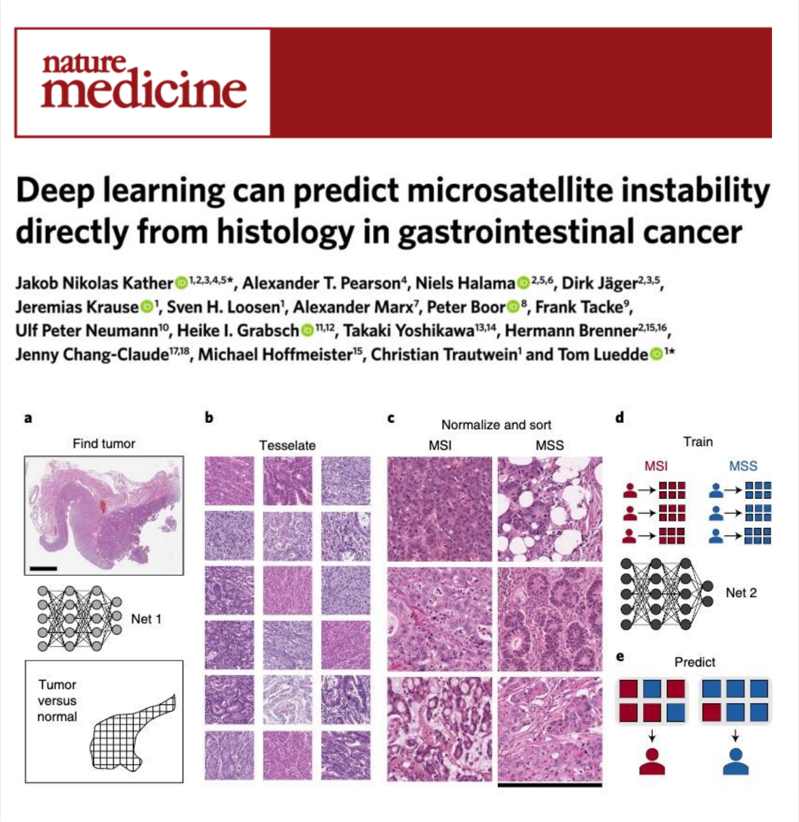
Deep learning can infer genotype from histology images

Courtesy of Jakob Kather

Weakly supervised Deep Learning can predict genetic alterations from H&E images

Genotype determines the phenotype

Deep Learning detects genotype from the phenotype



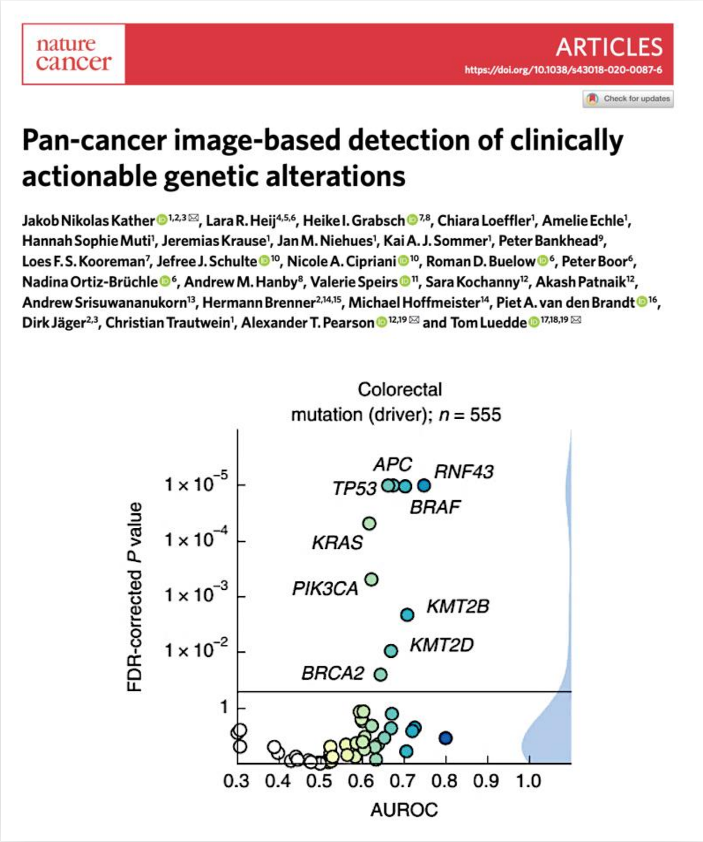
nature medicine

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

Jakob Nikolas Kather[1,2,3,4,5*], Alexander T. Pearson[4], Niels Halama[2,5,6], Dirk Jäger[2,3,5], Jeremias Krause[1], Sven H. Loosen[1], Alexander Marx[7], Peter Boor[8], Frank Tacke[9], Ulf Peter Neumann[10], Heike I. Grabsch[11,12], Takaki Yoshikawa[13,14], Hermann Brenner[2,15,16], Jenny Chang-Claude[17,18], Michael Hoffmeister[15], Christian Trautwein[1] and Tom Luedde[1*]

Kather, Nat Med 2019

Can we extend this to other genetic alterations?



nature cancer

ARTICLES

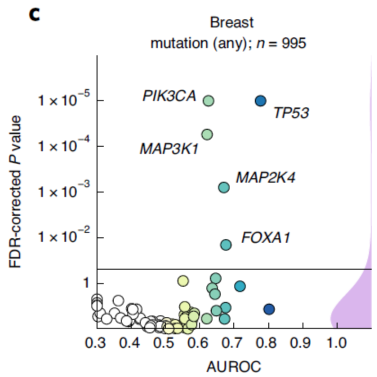
https://doi.org/10.1038/s43018-020-0087-6

Check for updates

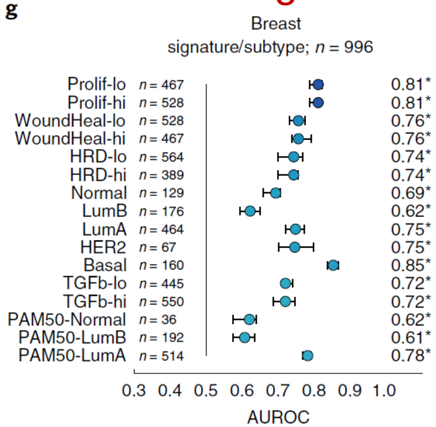
Pan-cancer image-based detection of clinically actionable genetic alterations

Jakob Nikolas Kather[1,2,3], Lara R. Heij[4,5,6], Heike I. Grabsch[7,8], Chiara Loeffler[1], Amelie Echle[1], Hannah Sophie Muti[1], Jeremias Krause[1], Jan M. Niehues[1], Kai A. J. Sommer[1], Peter Bankhead[9], Loes F. S. Kooreman[7], Jefree J. Schulte[10], Nicole A. Cipriani[10], Roman D. Buelow[6], Peter Boor[6], Nadina Ortiz-Brüchle[6], Andrew M. Hanby[8], Valerie Speirs[11], Sara Kochanny[12], Akash Patnaik[12], Andrew Srisuwananukorn[13], Hermann Brenner[2,14,15], Michael Hoffmeister[14], Piet A. van den Brandt[16], Dirk Jäger[2,3], Christian Trautwein[1], Alexander T. Pearson[12,19] and Tom Luedde[17,18,19]

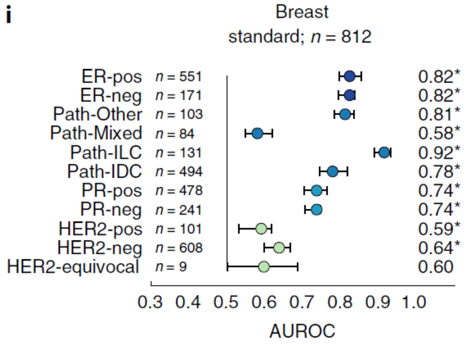
Detection of mutations



Detection of signatures

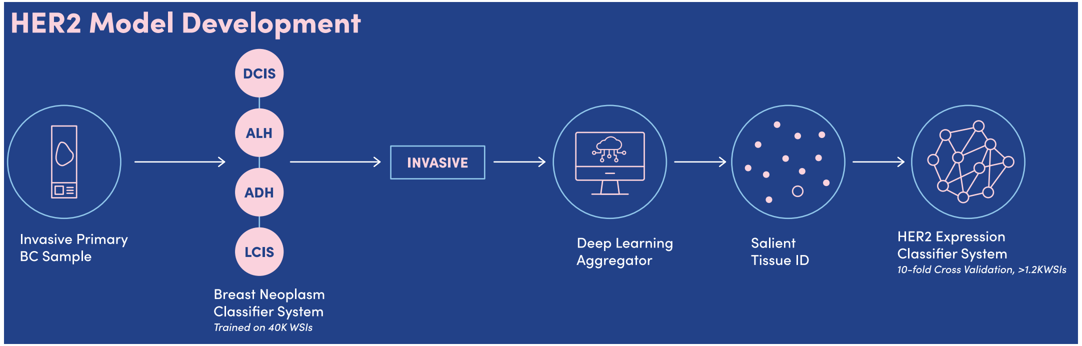


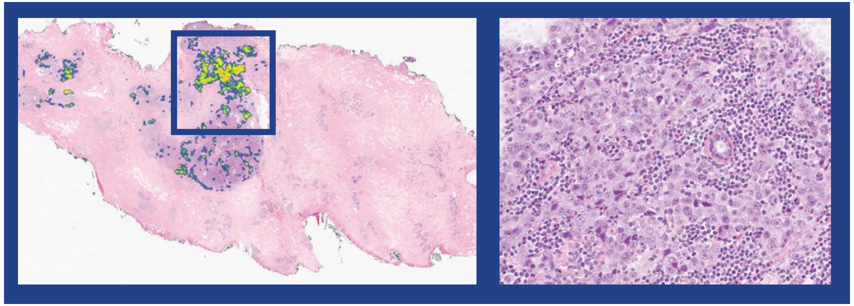
Histologic and clinical subtypes



Kather, Nature Cancer 2020

AI-driven model to recover cases with low levels of HER2 from IHC HER2-negative breast cancers

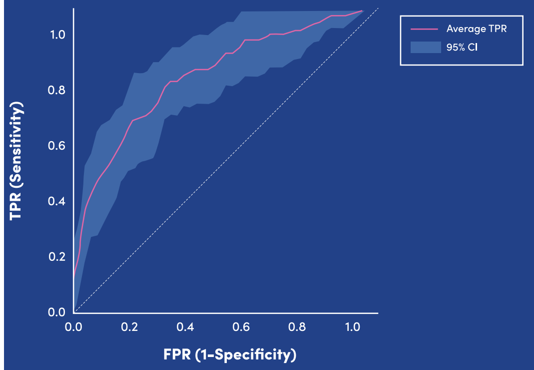




Slide Level Classification

AUC: 0.78 ±0.08

14.75 ± 4.2 +ve samples per fold. 172.12 ± 16.6 -ve



HER2 Model Performance

Metrics	Case Level	Slide Level
Sensitivity*	0.78	0.73
Specificity*	0.78	0.77
PPV*	0.23	0.21
NPV*	0.98	0.97

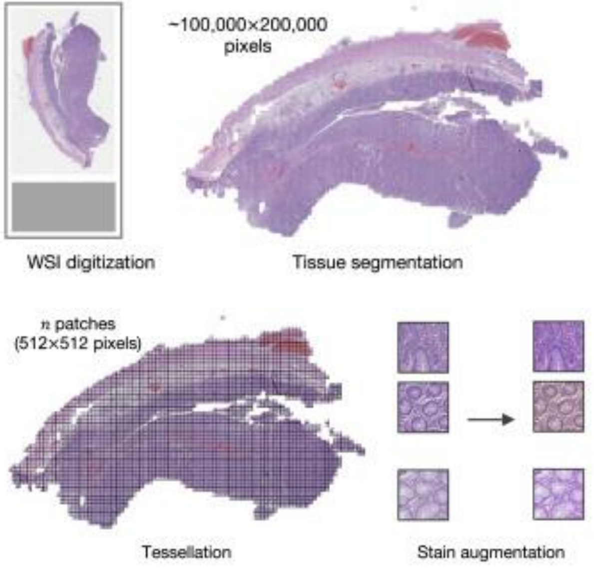
*Calculated on test set

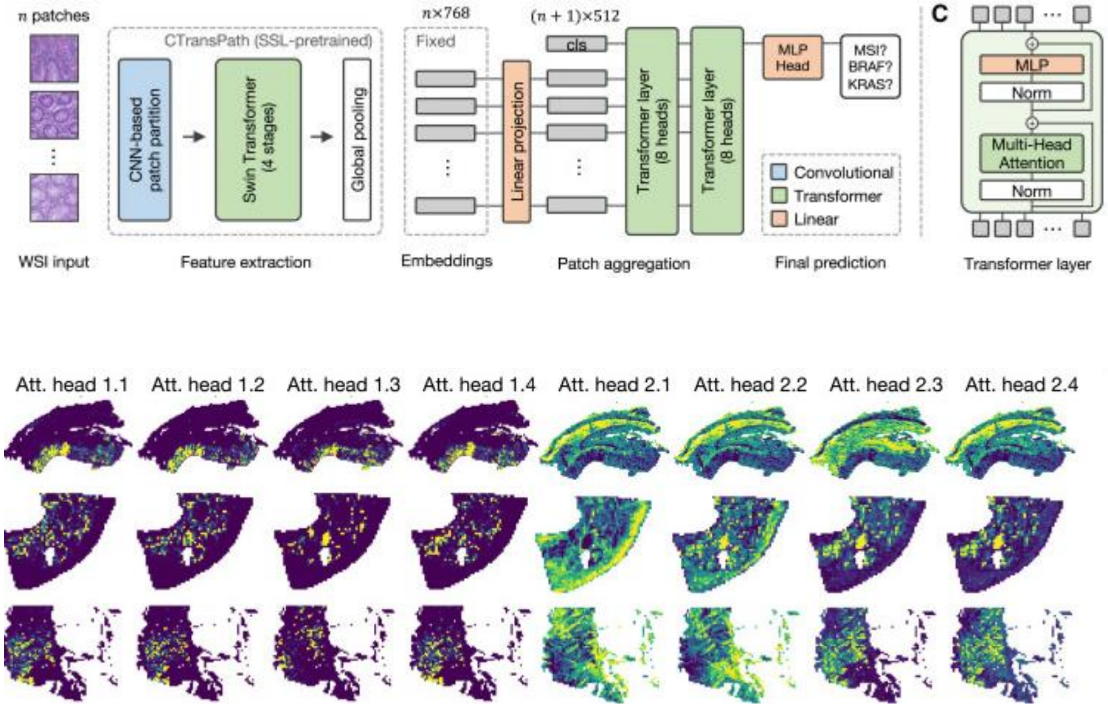
Sensitivity: # true positive / (# true positive + # false negative)
Specificity: # true negative / (# true negative + # false positive)
PPV: # true positive / (# true positive + # false positive)
NPV: # true negative / (# true negative + # false negative)

Paige®

Marra, ESMO 2022, manuscript in preparation

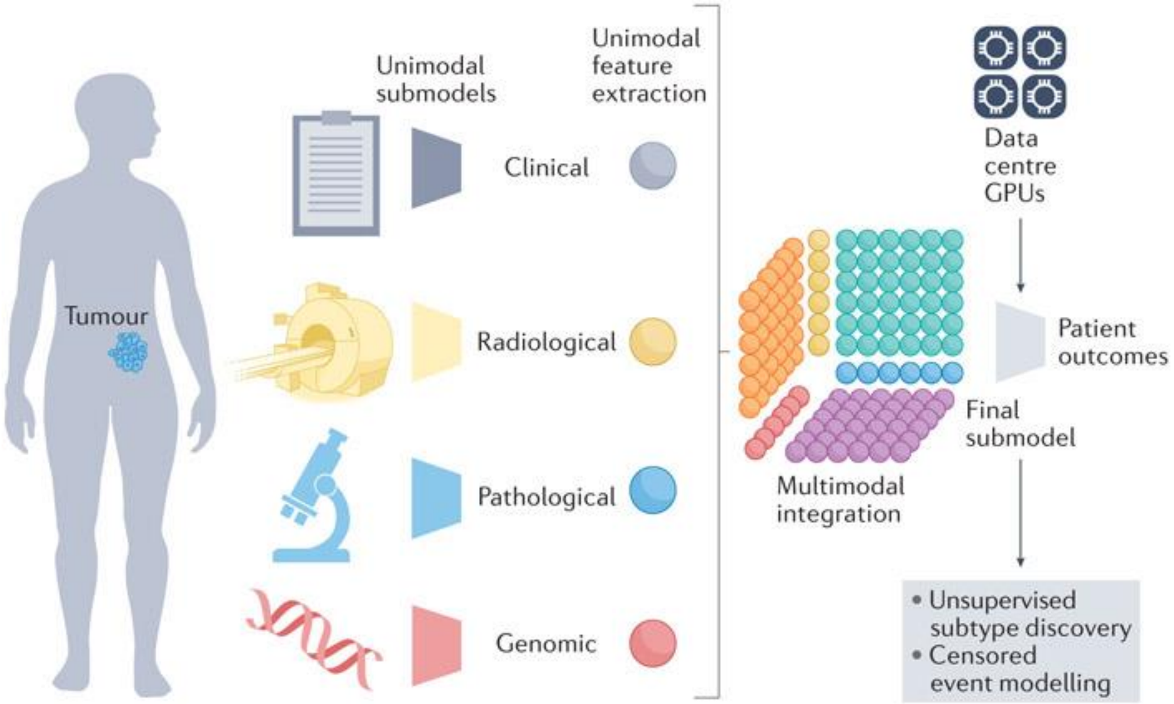
Transformers have multiple attention heads: more interpretability?





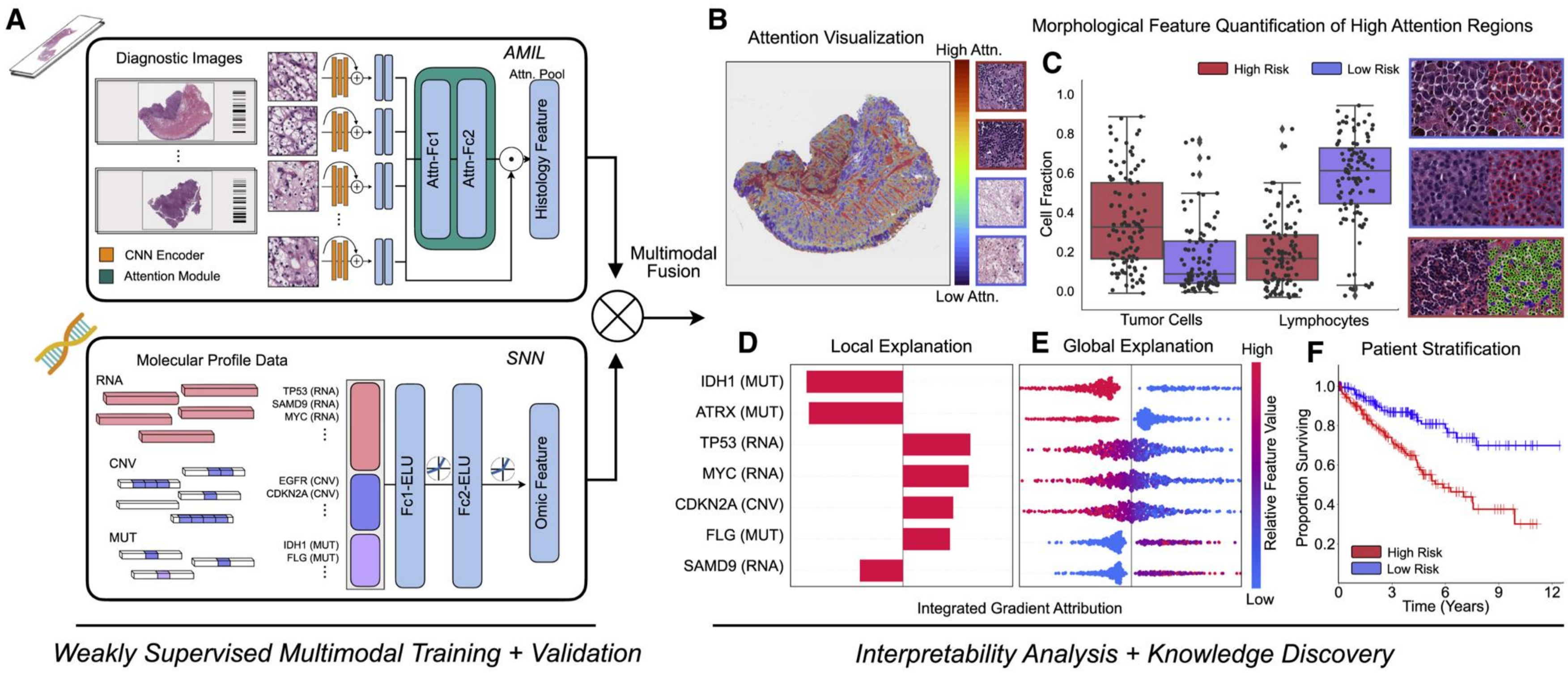
Wagner, Cancer Cell 2023

AI-driven multimodal data integration in Oncology



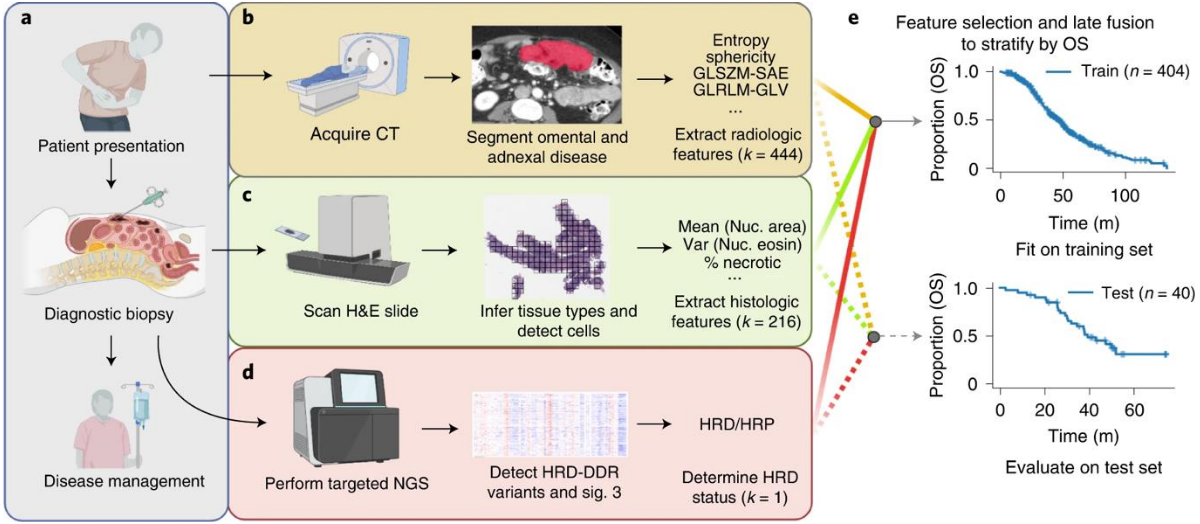
Acosta, Nat Med 2022; Boehm, Nat Rev Cancer 2022

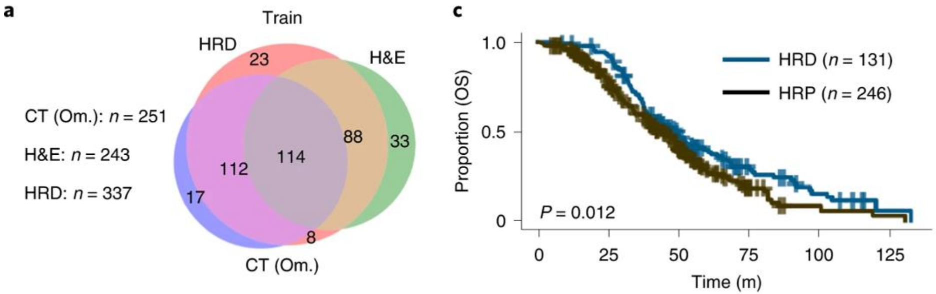
Multimodal integration of genetic data with image data



Chen, Cancer Cell 2022

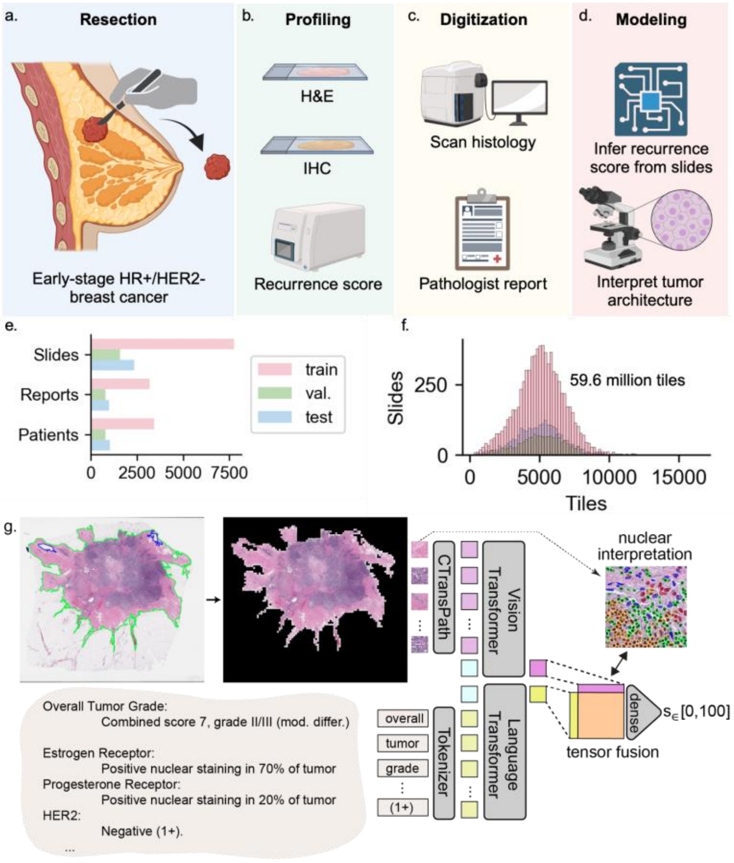
Multimodal integration of genetic data with image data

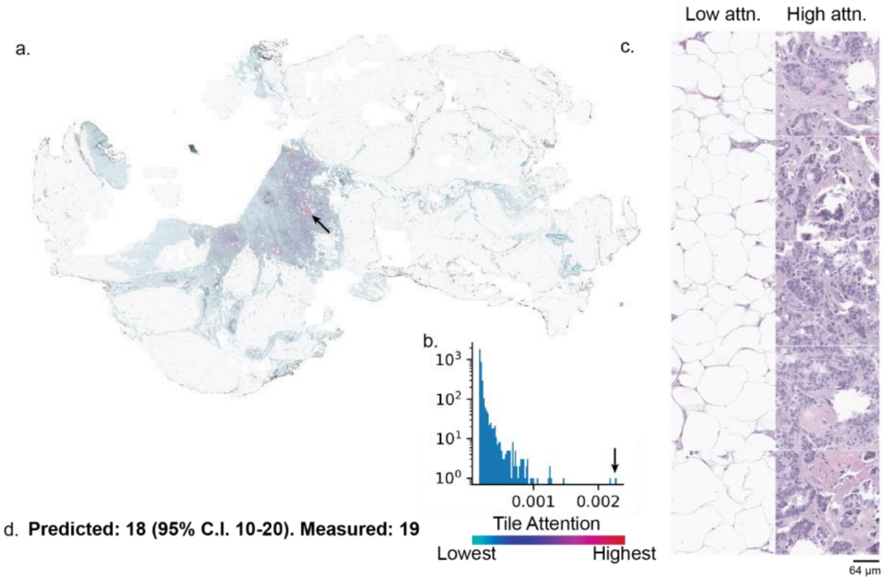




Boehm, Nat Cancer 2022

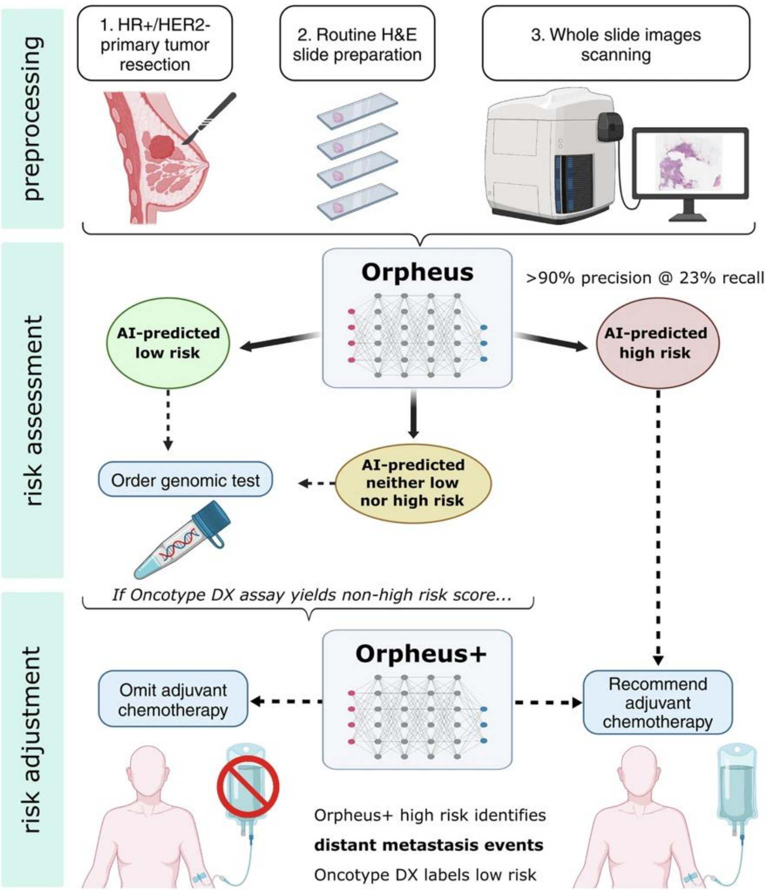
Developing a multimodal transformer model for breast cancer risk





Boehm, Marra et al., Nature Commun. 2025

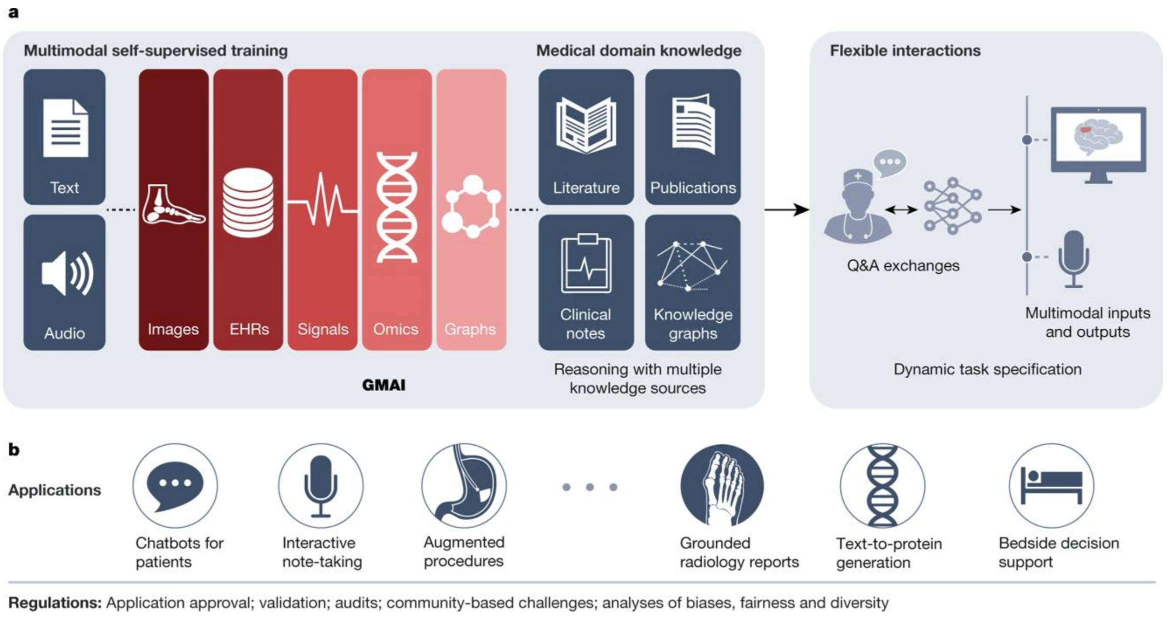
Developing a multimodal transformer model for breast cancer risk

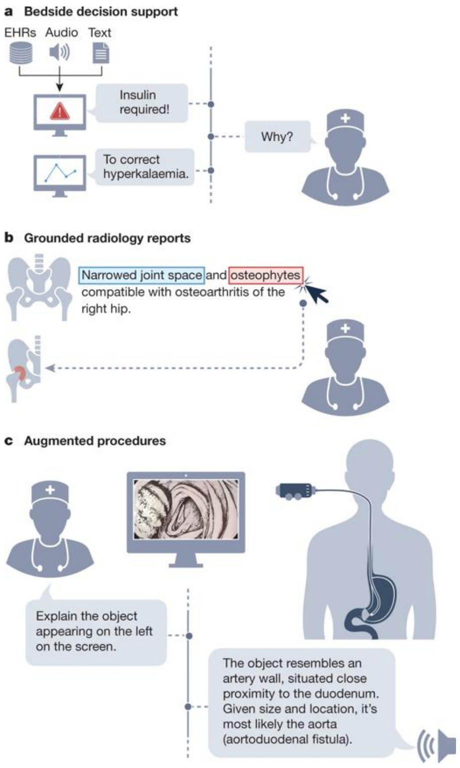


Potential clinical use case of the AI-based recurrence risk prediction model

Boehm, Marra et al., Nature Commun. 2025

Multimodal Foundation Models





Moor, Nature 2023

Take-Home Messages

- **Artificial Intelligence (AI)** has indisputable potential to enhance the care of patients with cancer from the the diagnosis to personalizing treatments
- The **multimodal integration of AI and Big Data** can further refine clinical subtyping to identify patient subsets for treatment escalation/de-escalation and testing new drugs
- From the clinical perspective, **building clinicians' trust in AI-assisted decision-making** is critical for the entry of AI in clinic

“AI won't replace humans, but humans using AI will”

Fei-Fei Li