Artificial Intelligence and Computational Oncology

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Disclosures

- Consulting fees from Novartis

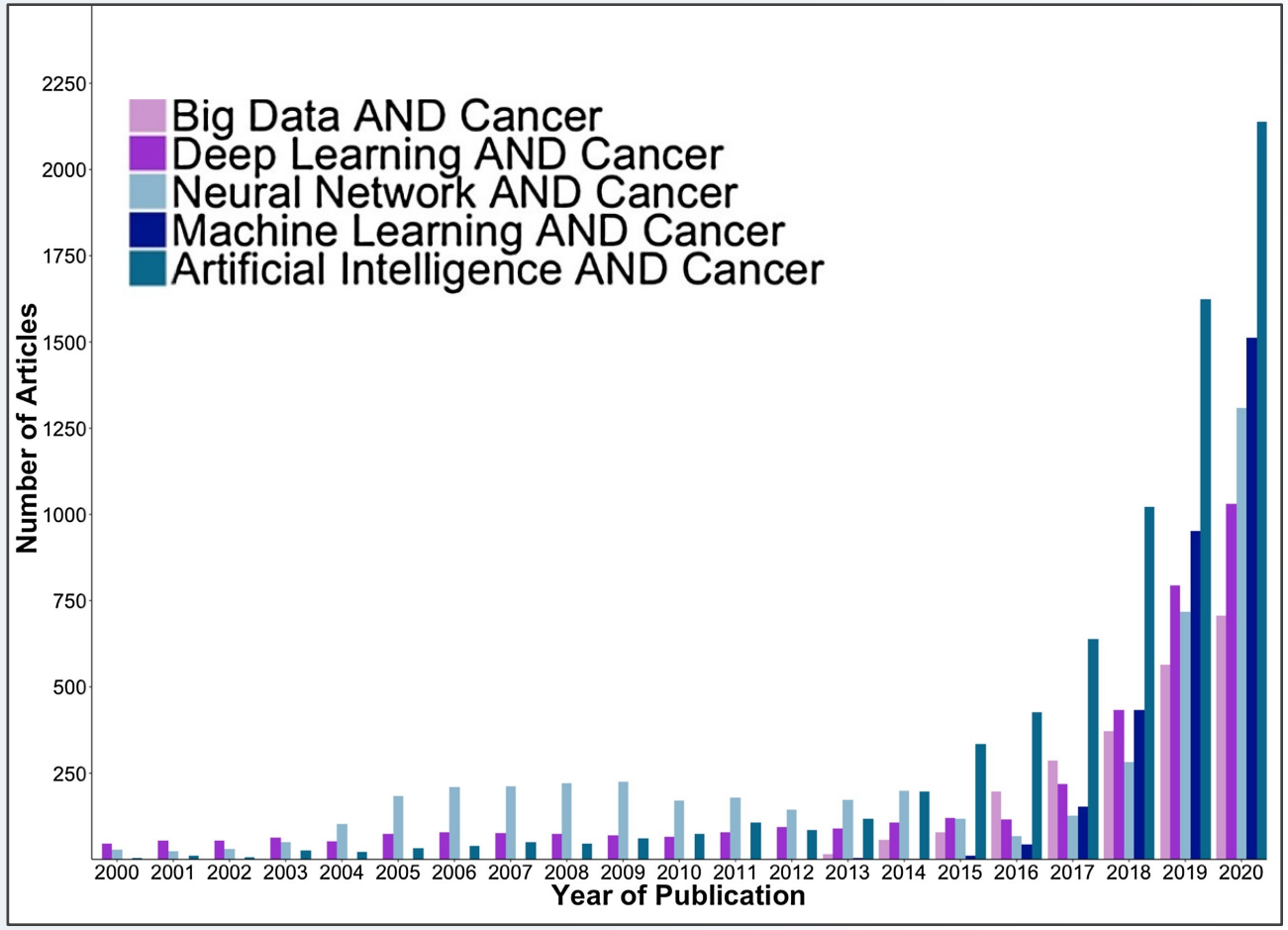
Learning Objectives

- Describe common terminology used in artificial intelligence / machine learning studies
- Review the current use of artificial intelligence and computational models in oncology, with a focus on lymphoma
- Discuss strengths and limitations of artificial intelligence models

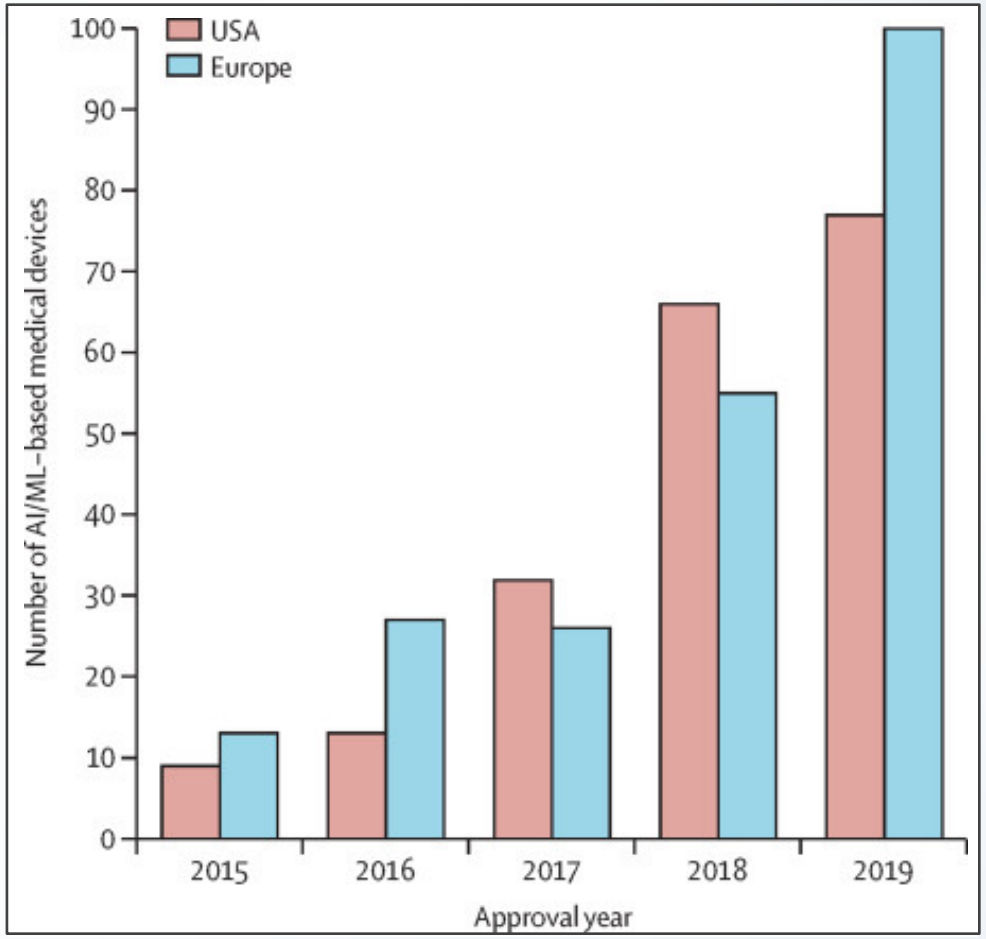
Background and Terminology

Growing Importance of Artificial Intelligence in Oncology

Publications on AI in Oncology

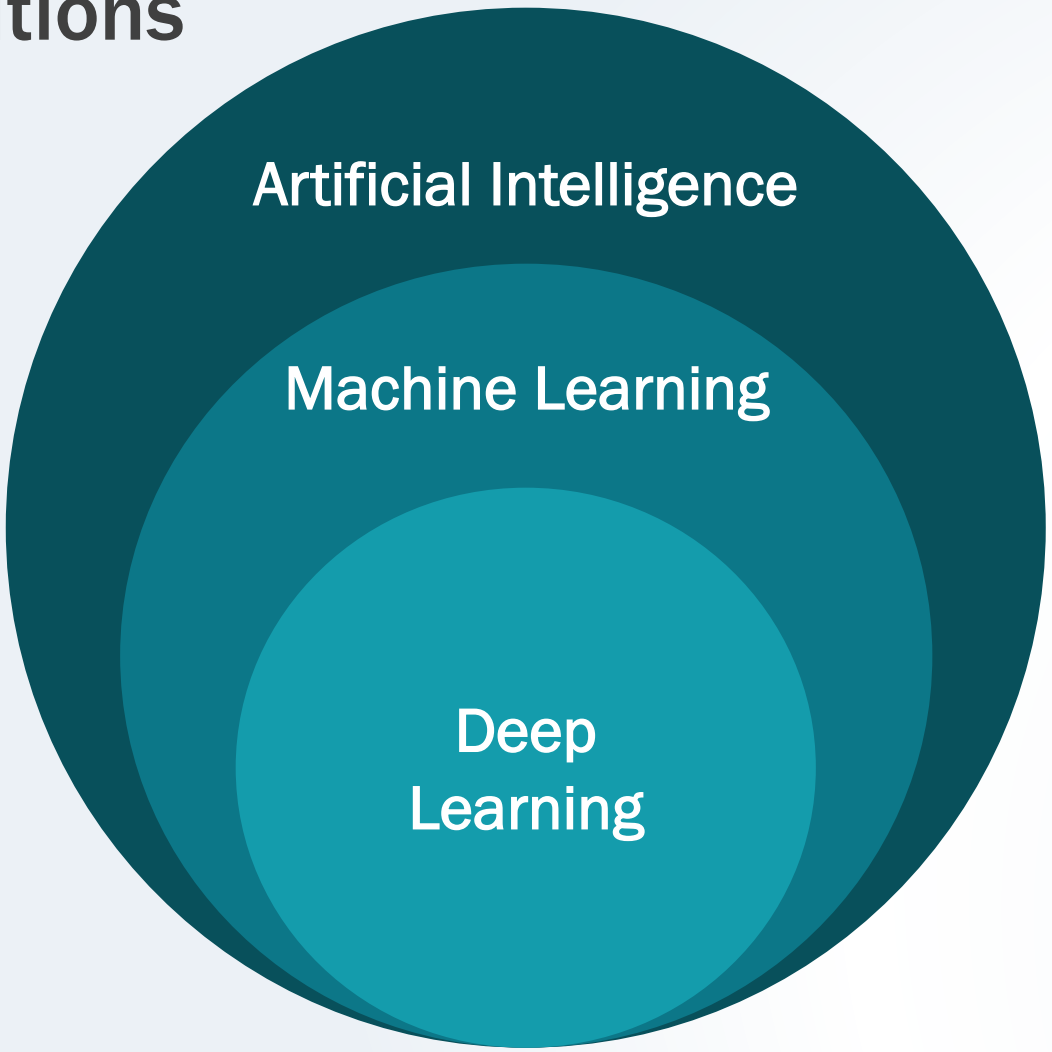


Rise in Approval of AI-based Devices



Elkhader, Seminars in Cancer Biology 2021, Muehlematter, Lancet Digital Health 2021

Definitions



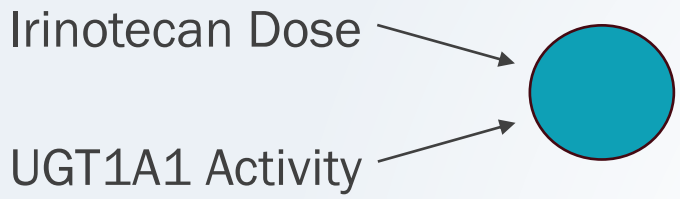
Artificial intelligence: Machine imitation of human cognition

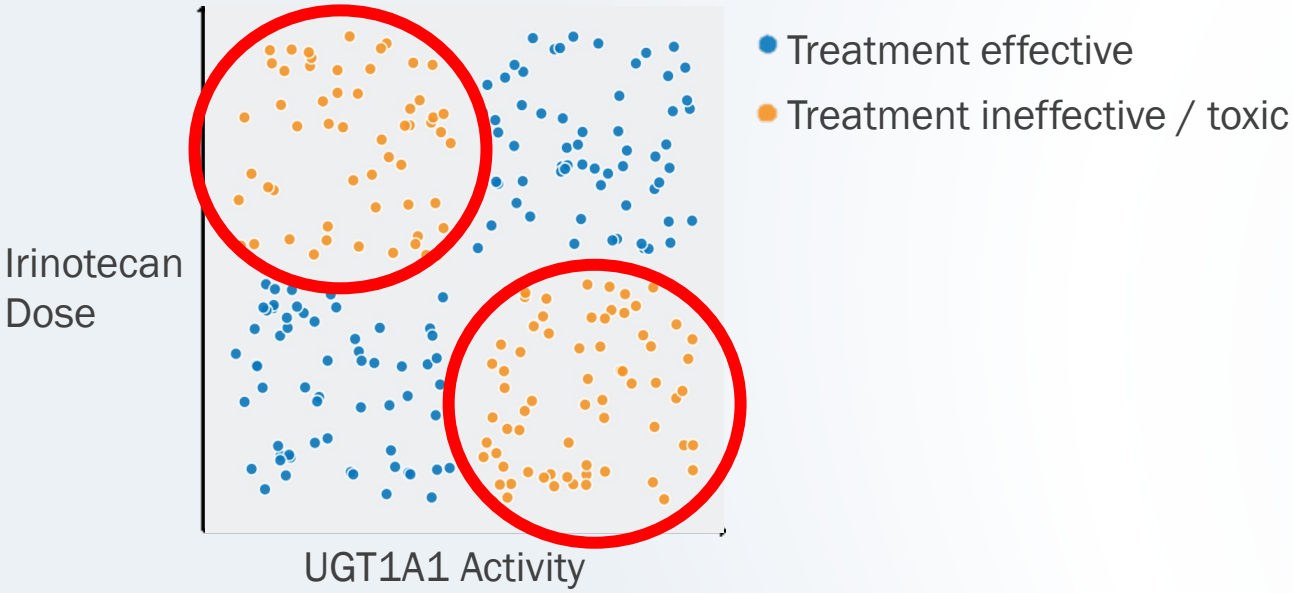
Machine learning: Algorithms that improve in accuracy as they are exposed to additional data

Deep Learning: Identifying complex features with multilayered neural networks

‘Deep’ Networks can Uncover Nonlinear Relationships in Data

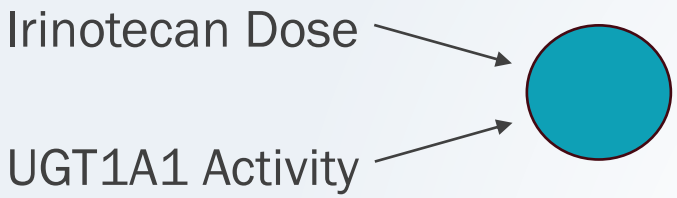
Challenging to Identify Nonlinear Relationships With a Shallow Model

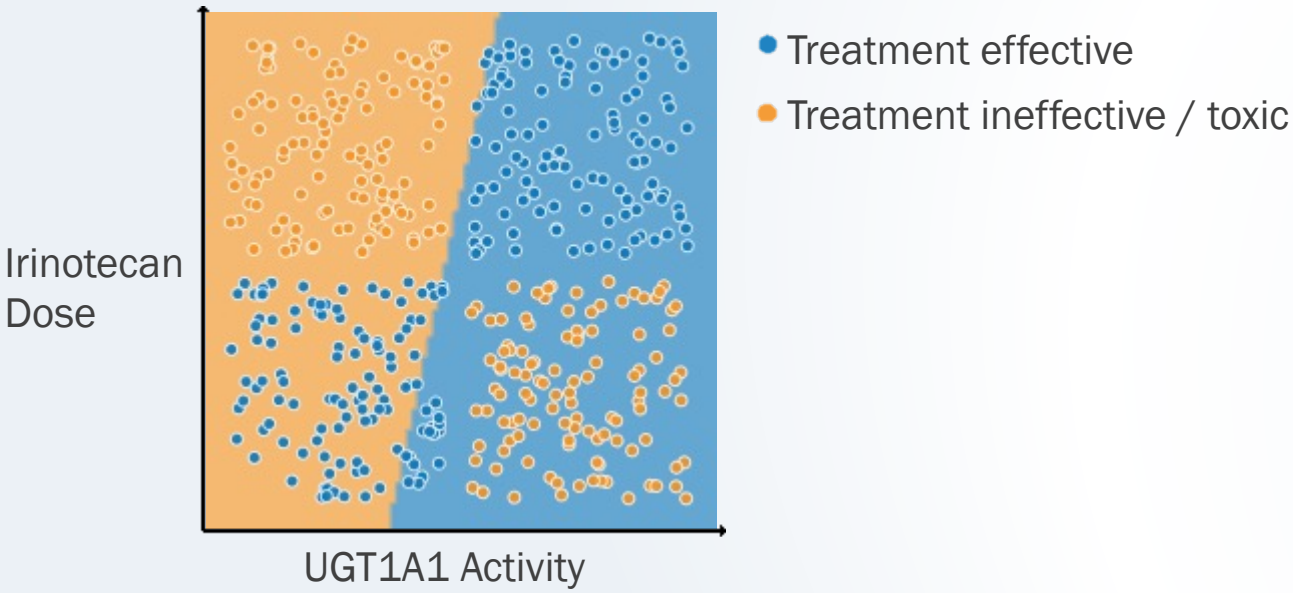




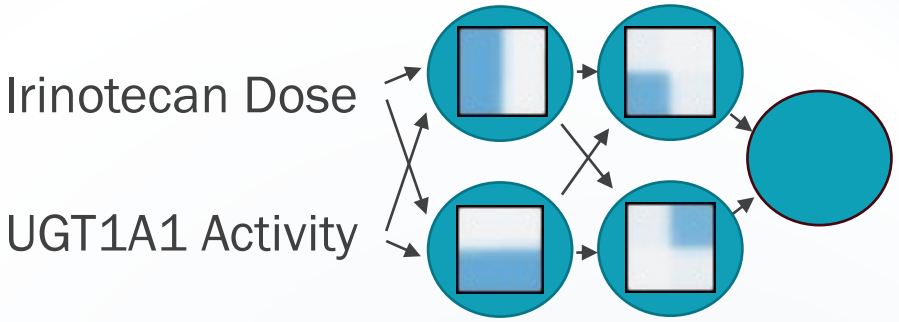
‘Deep’ Networks can Uncover Nonlinear Relationships in Data

Challenging to Identify Nonlinear Relationships With a Shallow Model





‘Deep’ Networks Use Combinations of Simple Features to Identify Complex Relationships



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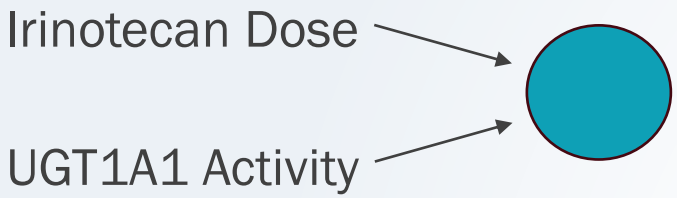

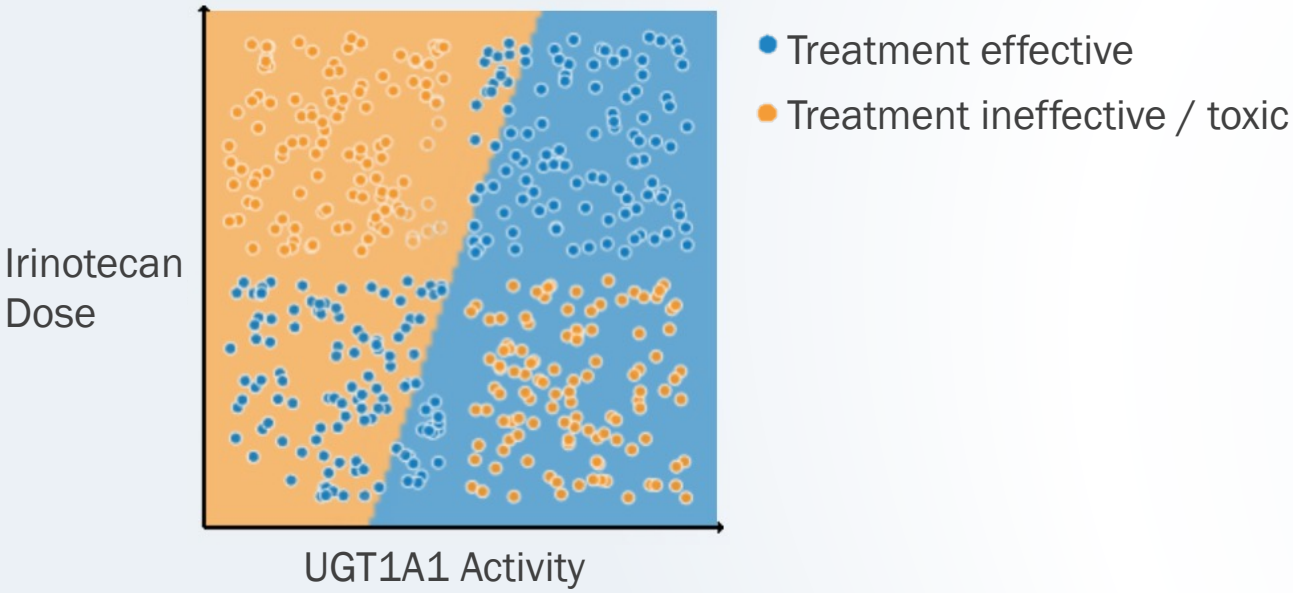

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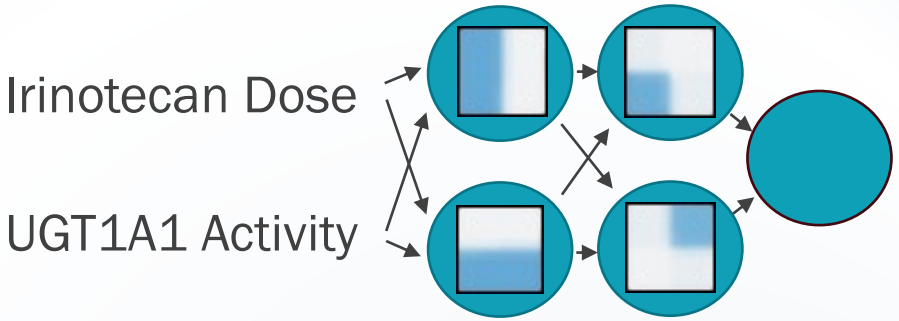
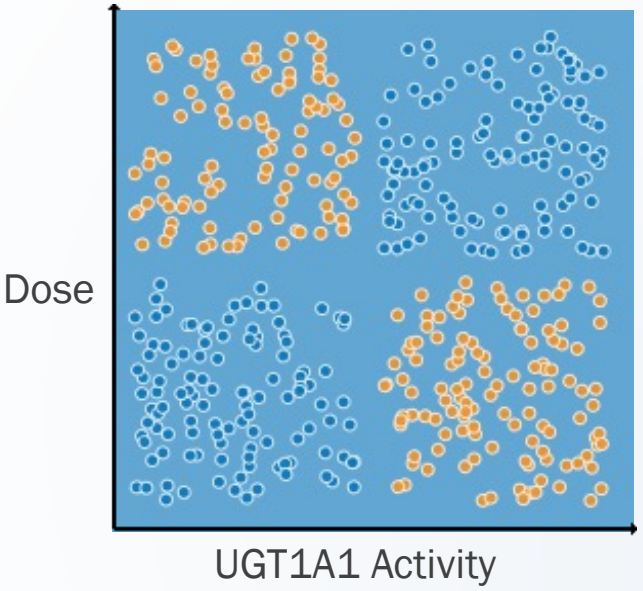
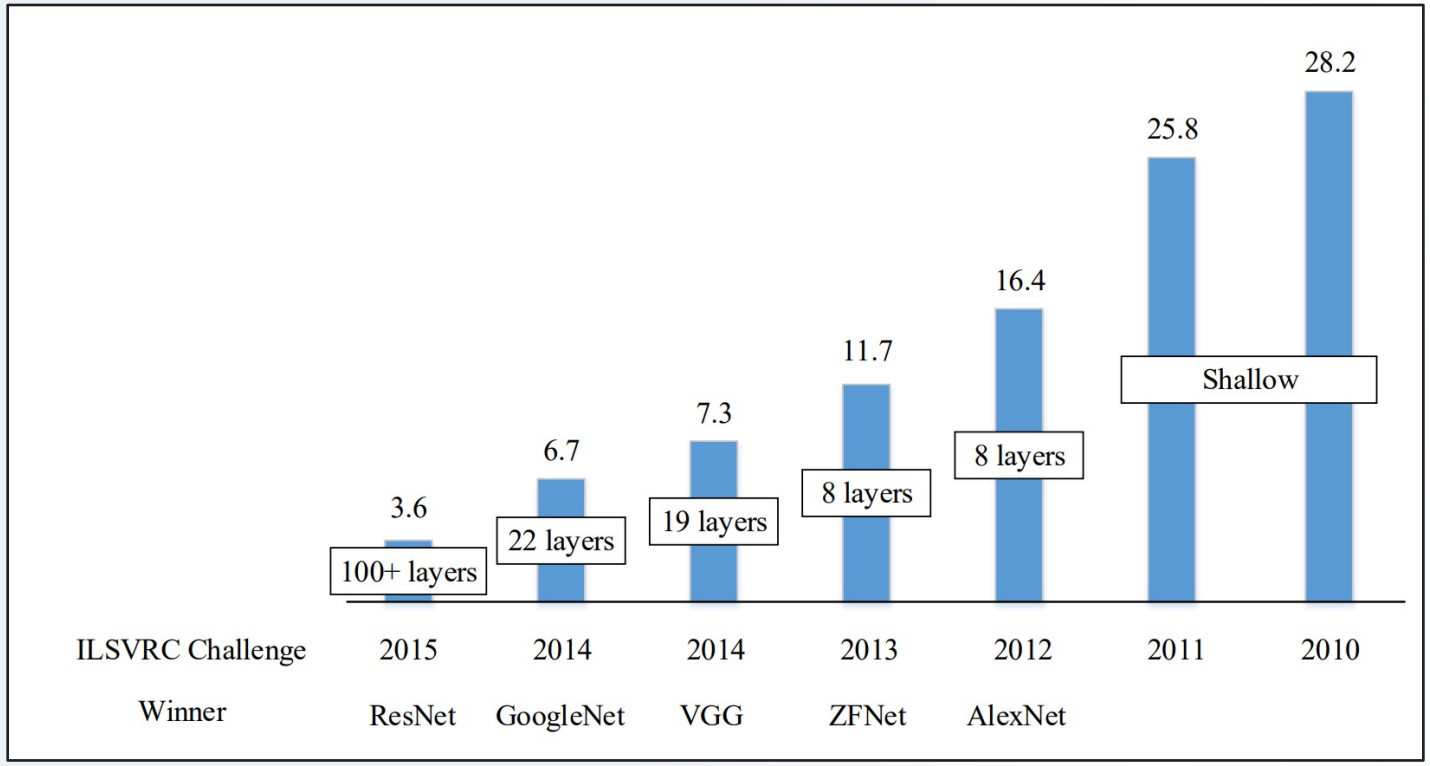


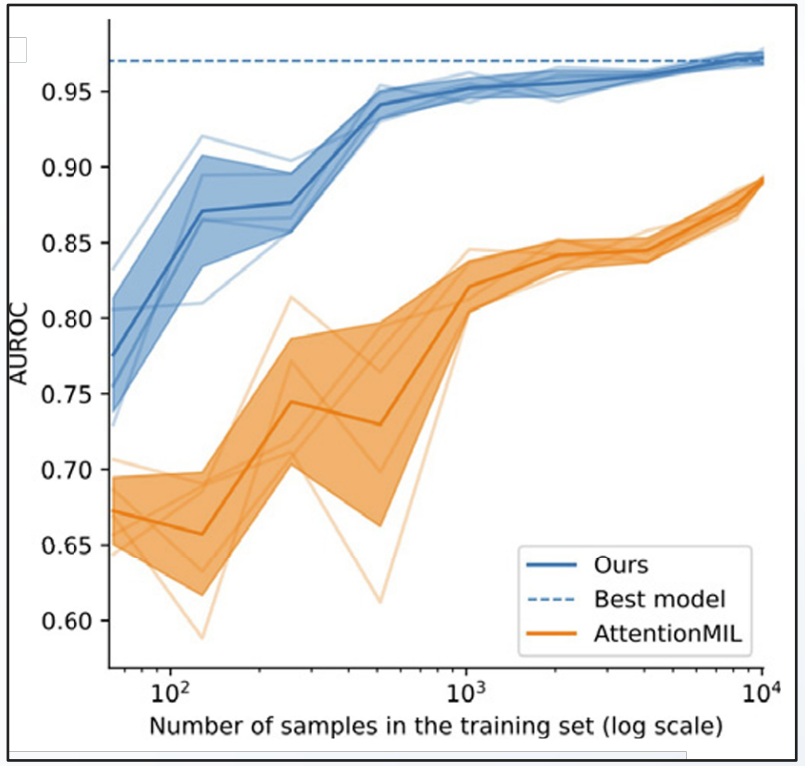


Deeper Models and More Data Can Improve AI Performance

Top 5 Error Rate in Image Classification Falls Dramatically with Deep Networks

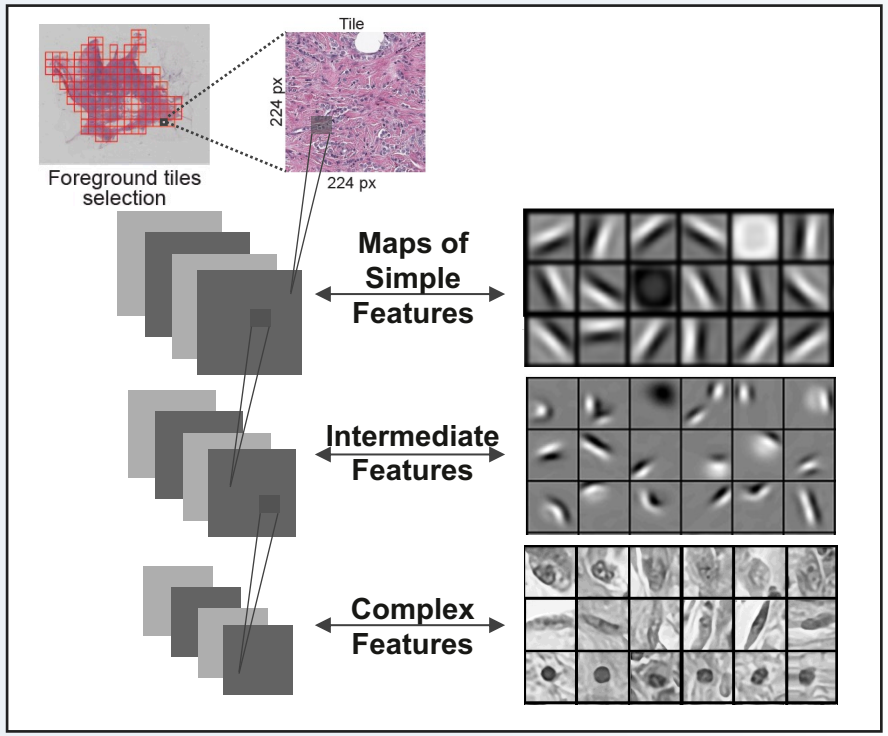


Accuracy for MSI Status Prediction Improves with Additional Training Data

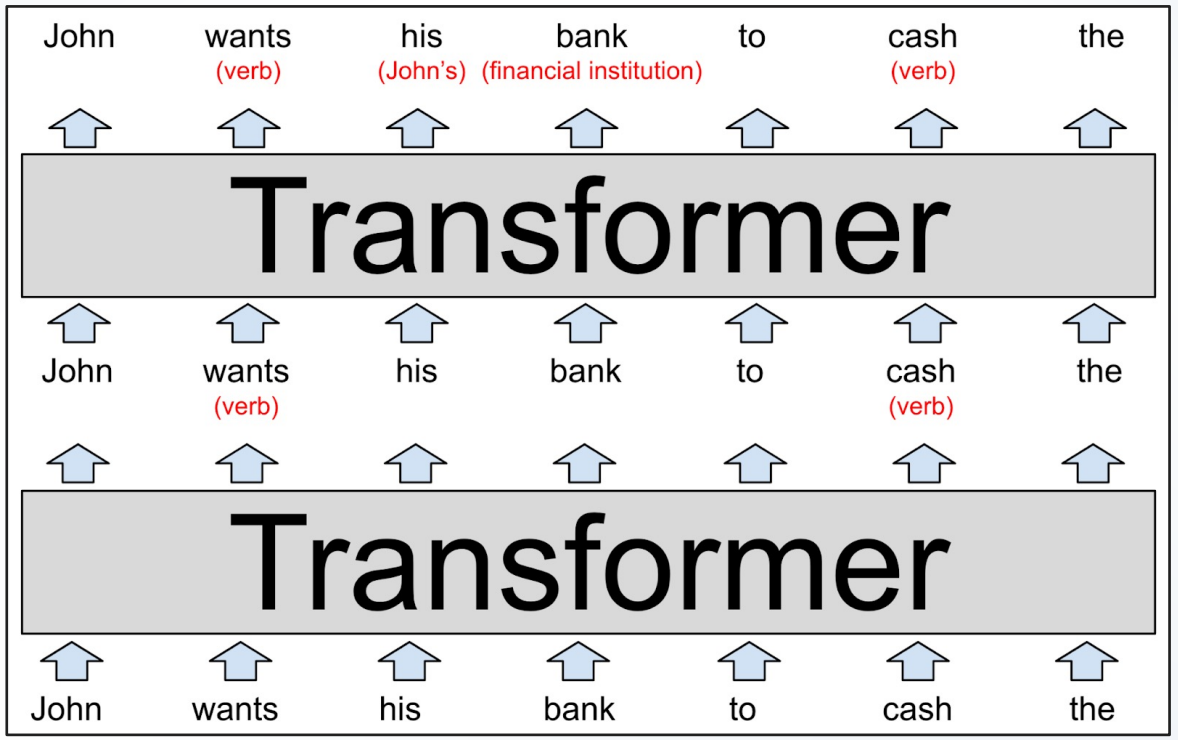


Das et al, Medium 2017; Wagner et al, Cancer Cell 2023

Recent Innovations in AI – Computer Vision and Language



Combinations of Simple Patterns Used To Identify Complex Features

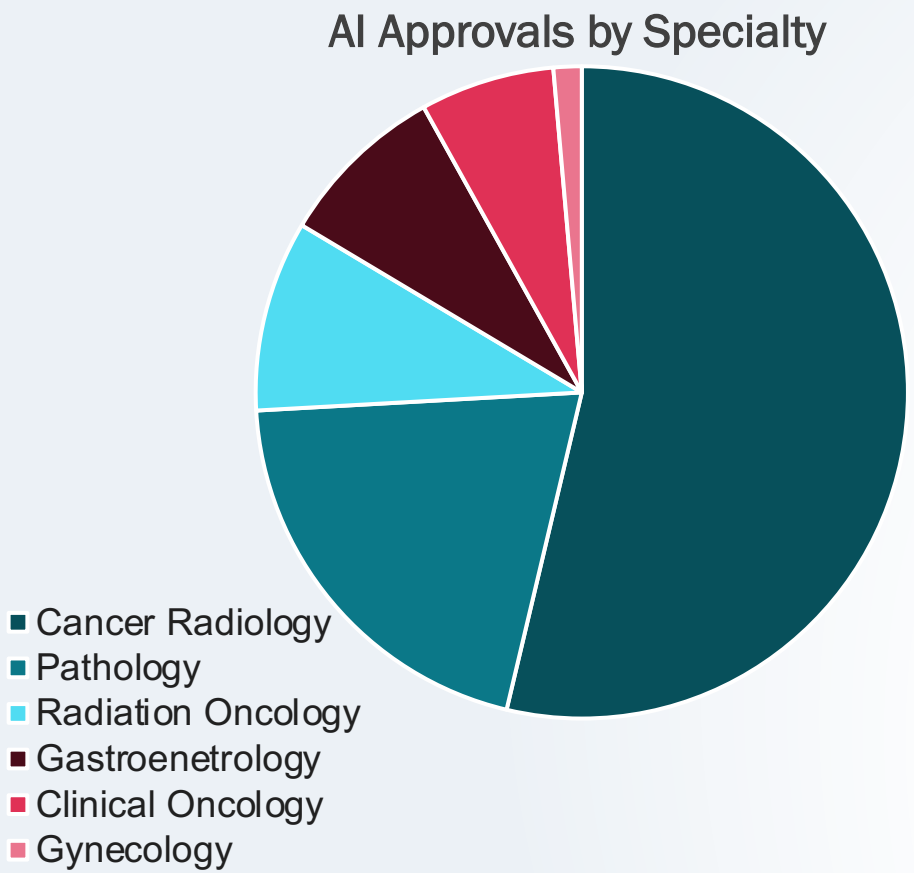


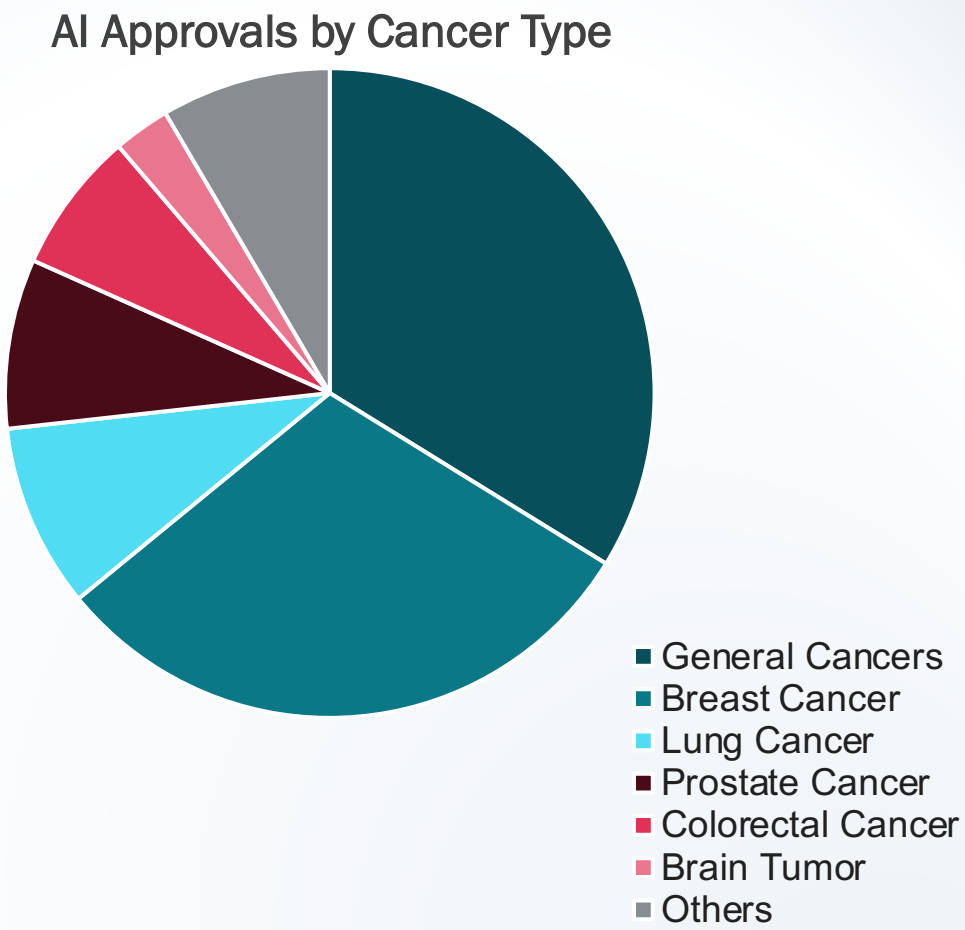
'Attention' layers identify the relationship between words
'Feed forward' layers to predict the next word in a sequence

Lee et al, ICML 2009; Lee and Trott, understandingai.org 2023

Applications of Artificial Intelligence

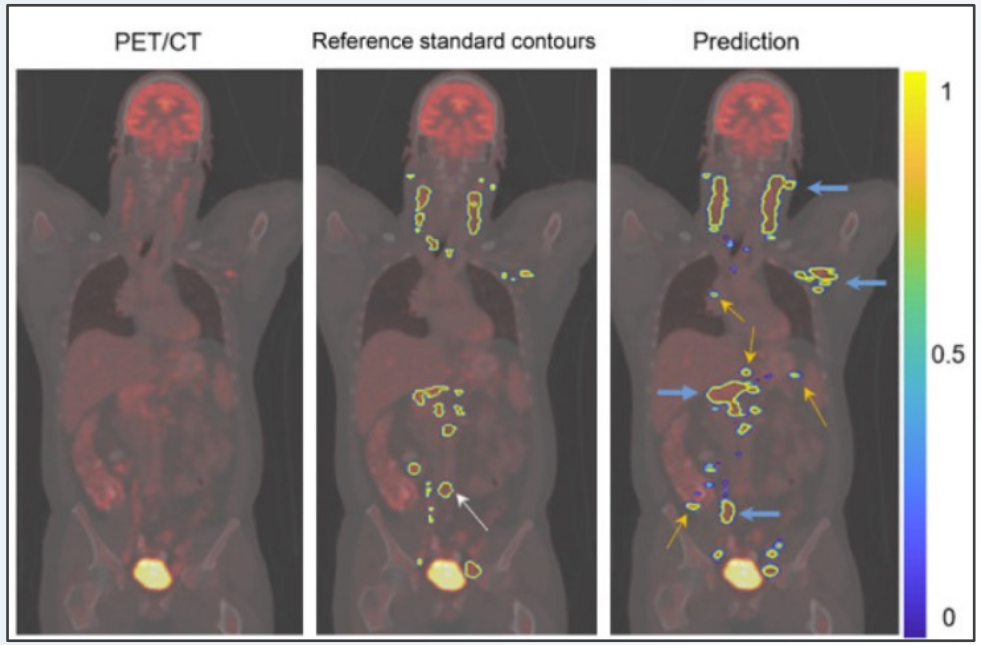
Current Status of Artificial Intelligence in Oncology



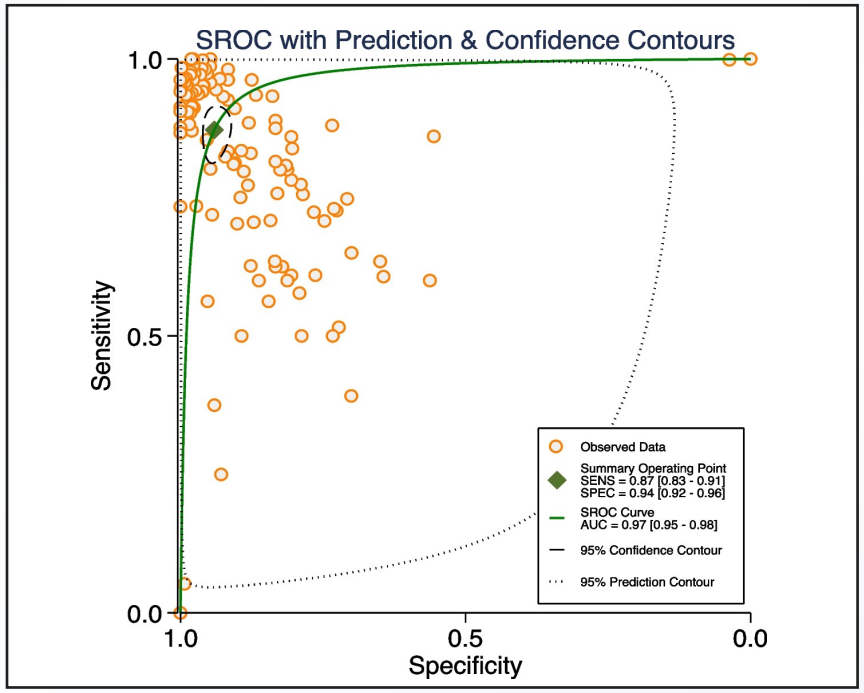


Luchini, British Journal of Cancer 2022

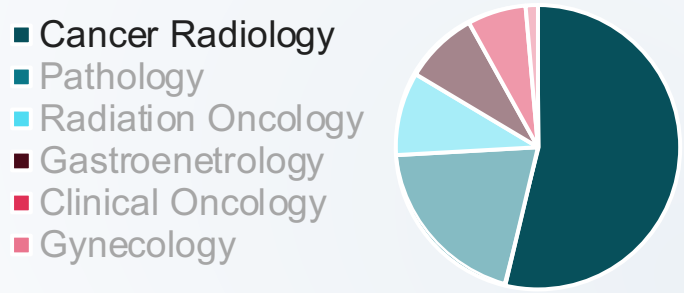
Artificial Intelligence Applications in Lymphoma



Identification of FDG Avid Disease in Mantle Cell Lymphoma

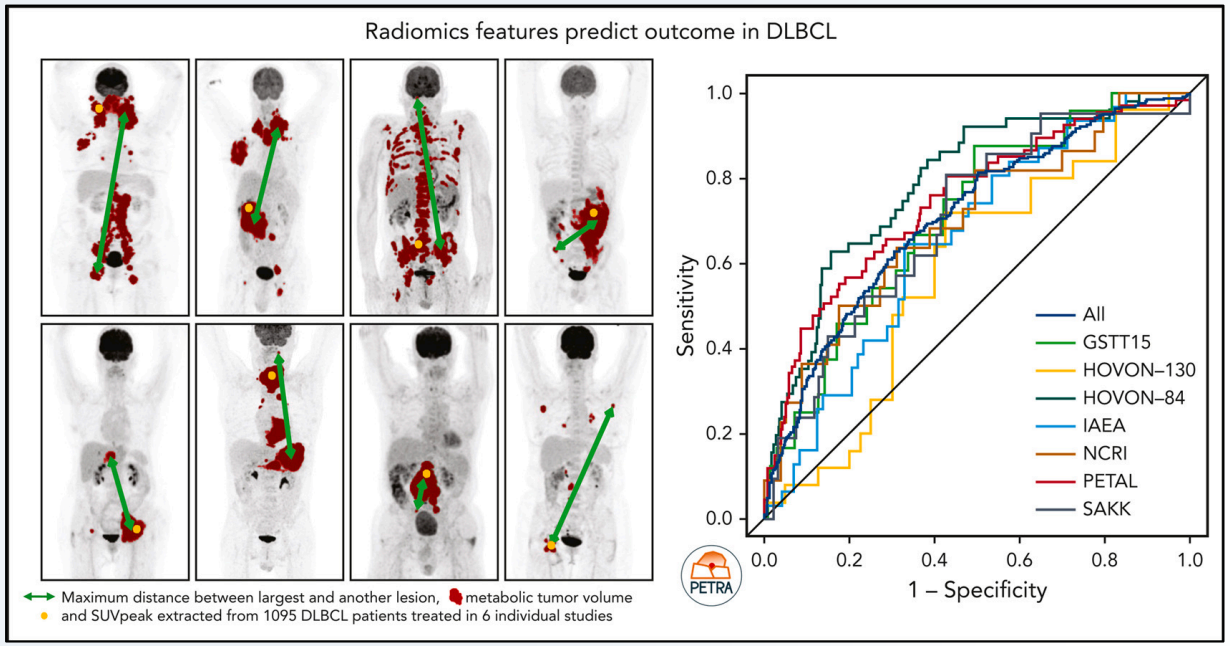


Accuracy of PET for Lymphoma Approaching Clinical Grade Accuracy

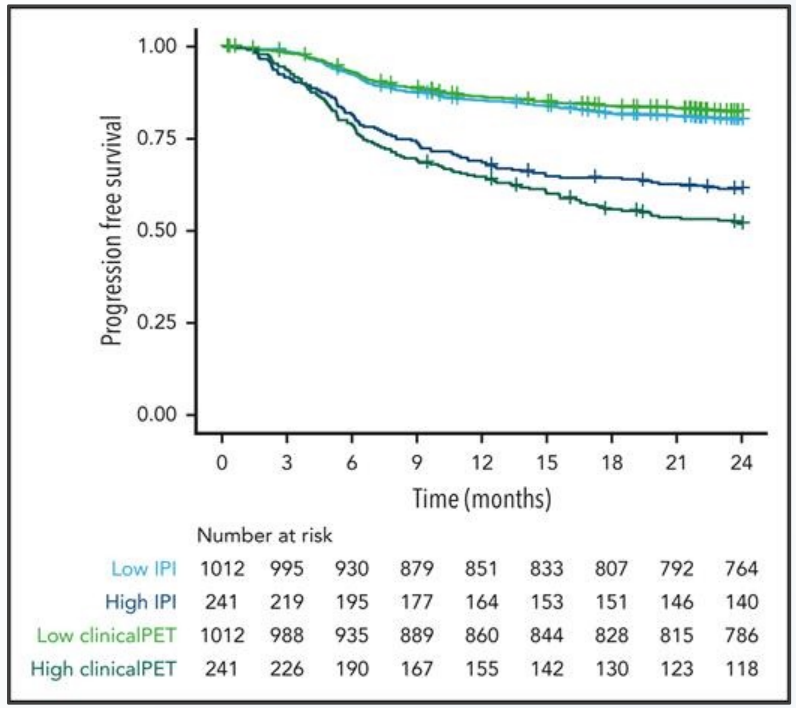


Zhou et al, Am J Nucl Med Mol Imaging 2021; Eertinik, Blood 2023

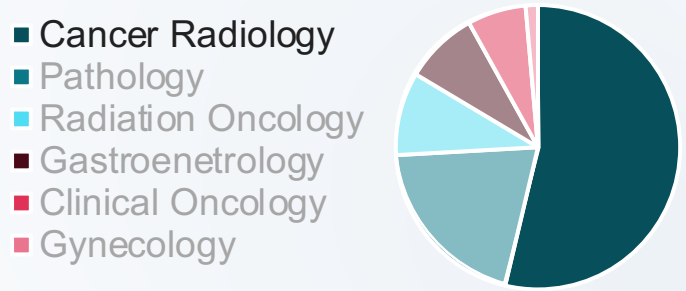
Artificial Intelligence Applications in Lymphoma



Prediction of 2 Year PFS with Clinical / Radiomic Model
Metabolic tumor Volume, Lesion Distance, SUV_{peak}, WHO PS, Age

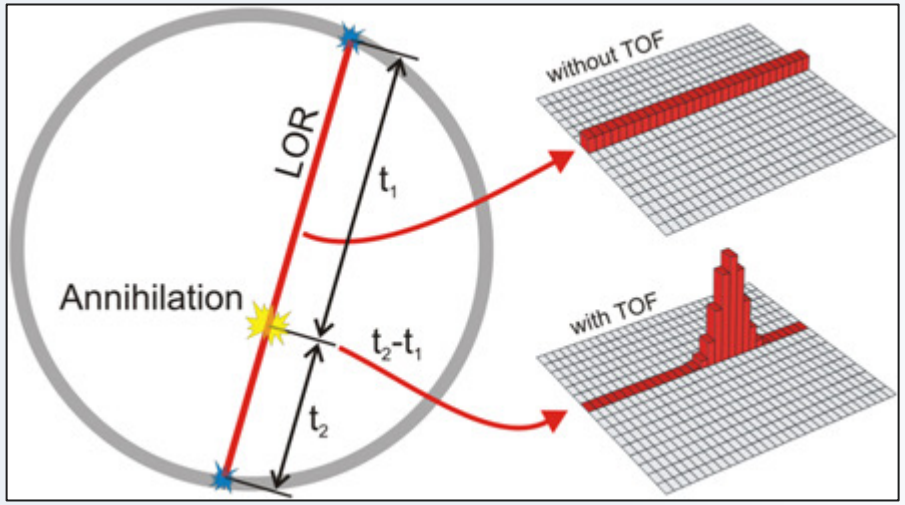


Better Prognostication than the IPI?

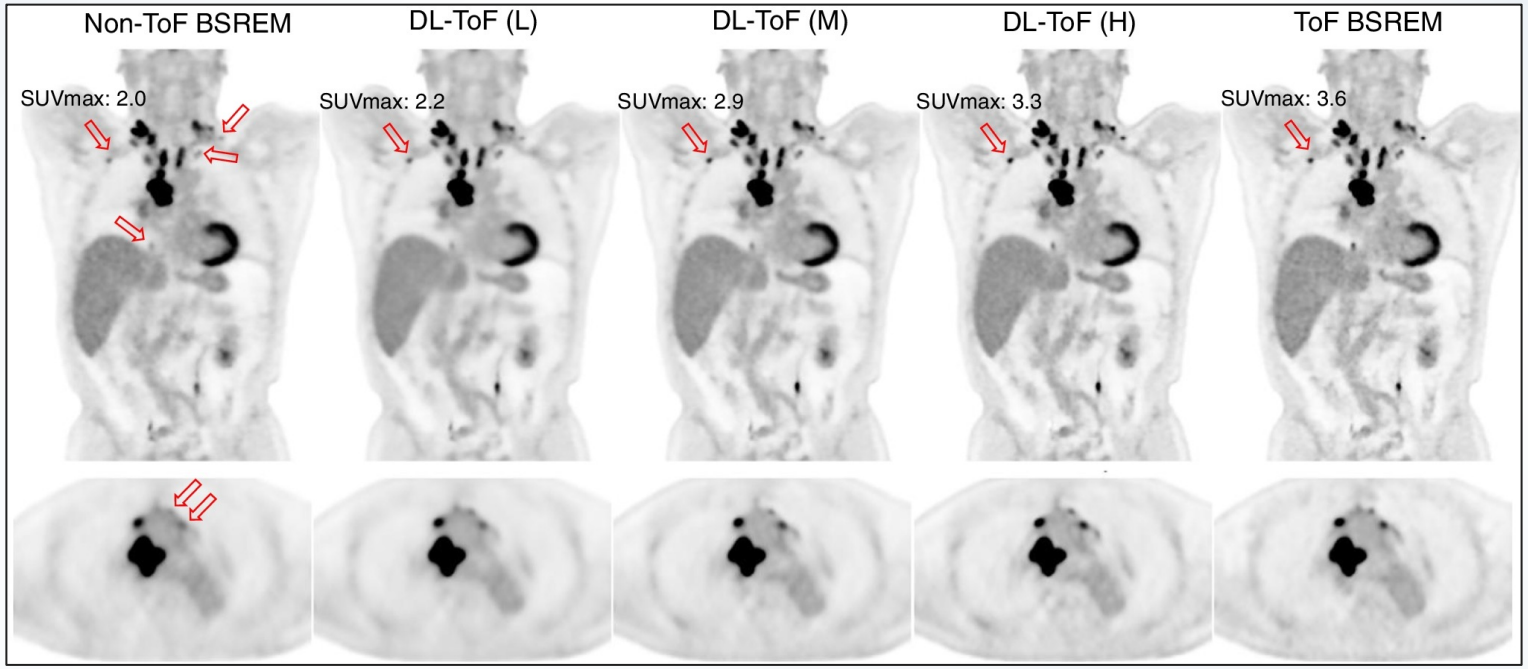


Luchini, British Journal of Cancer 2022; Eertinik, Blood 2023

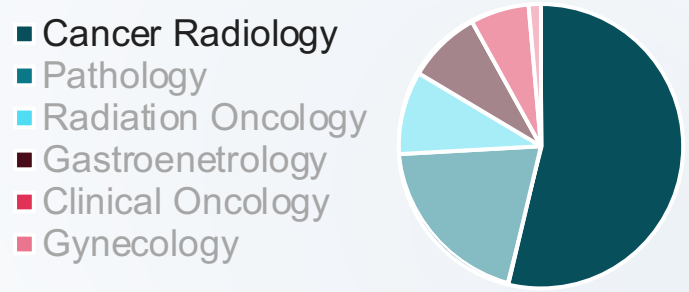
Artificial Intelligence Applications in Lymphoma



Time of Flight Accurately Localizes Smaller Lesions

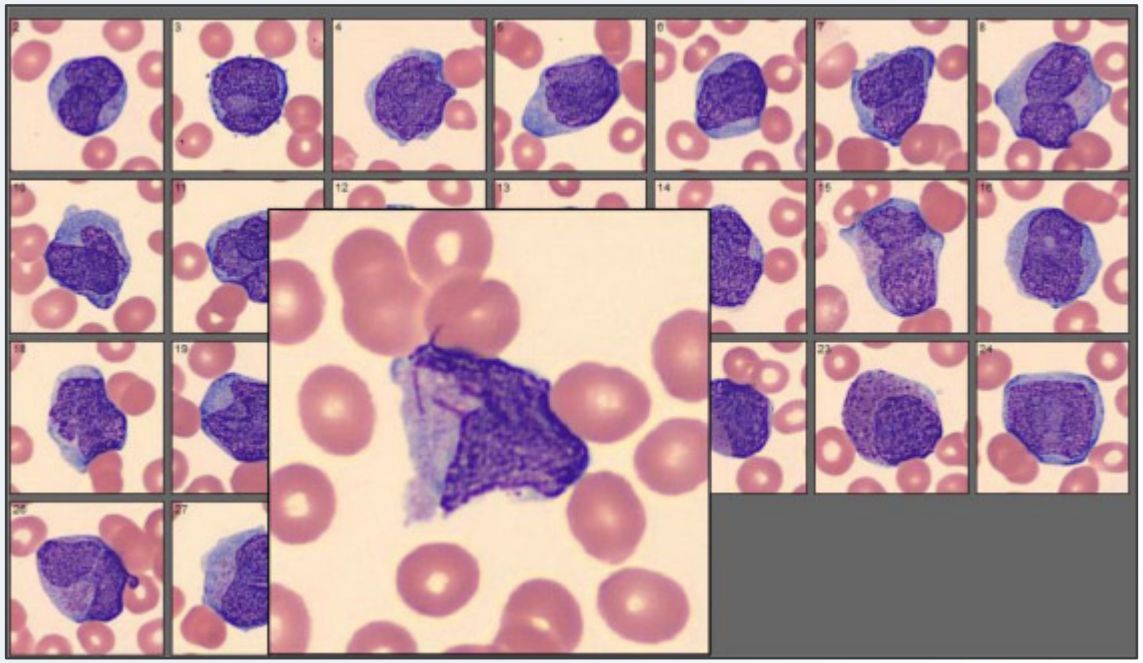


Deep Learning Algorithms to Replicate Time of Flight in PET Images

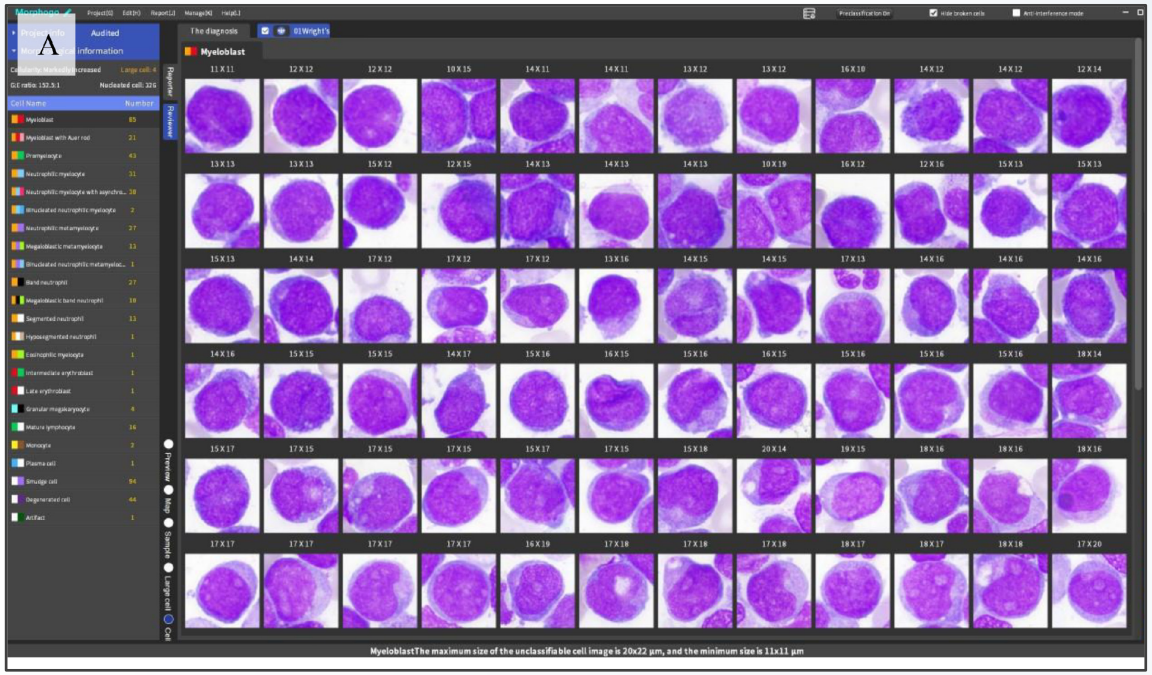


Mehranian et al, European Journal of Nuclear Medicine and Molecular Imaging 2022

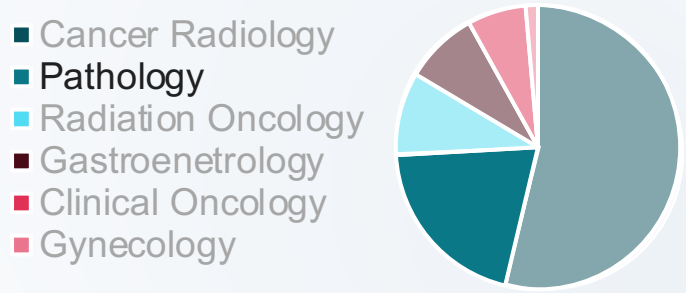
Artificial Intelligence Applications in Lymphoma



FDA Approved Automated Image Analyzer Identifies Immature Mononuclear Cells Leading to Diagnosis of APL

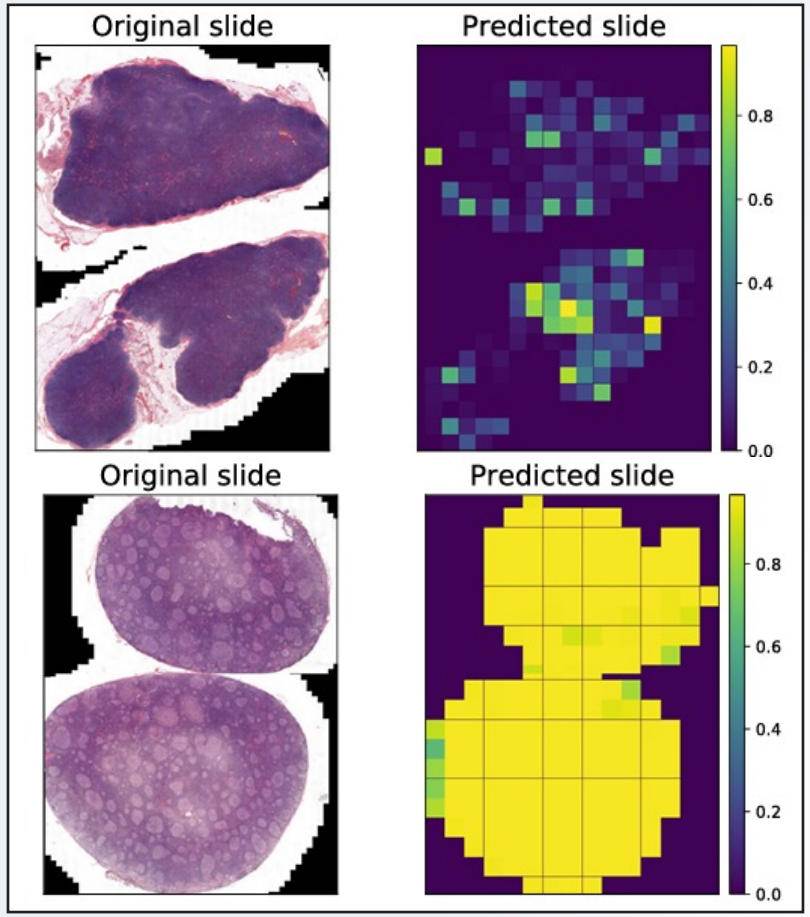


Automated Review of Myeloblasts from Marrow Aspirate

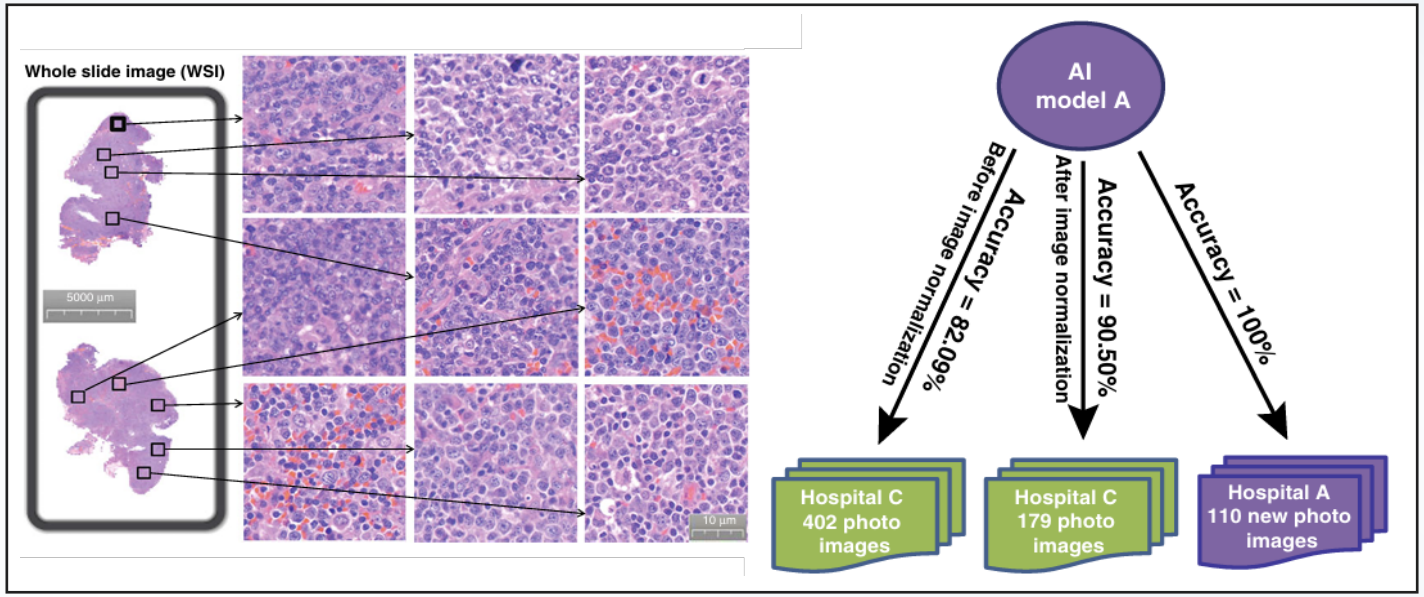


Lin et al, Seminars in Diagnostic Pathology 2023

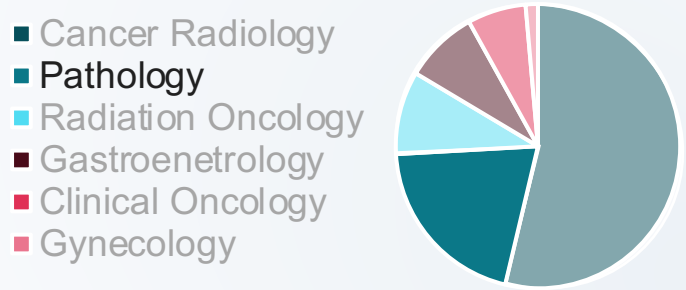
Artificial Intelligence Applications in Lymphoma



Distinguishing Follicular Lymphoma from Hyperplasia

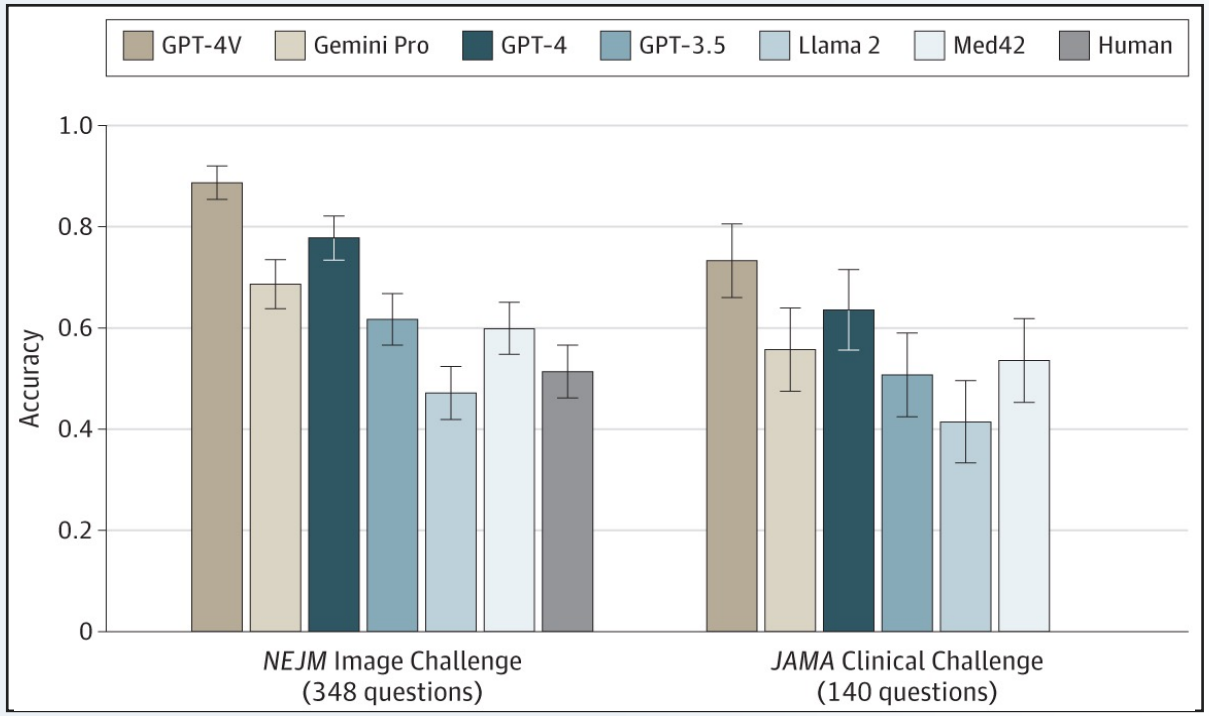


Diagnostic Accuracy for DLBCL versus Benign Lymphoid Tissue

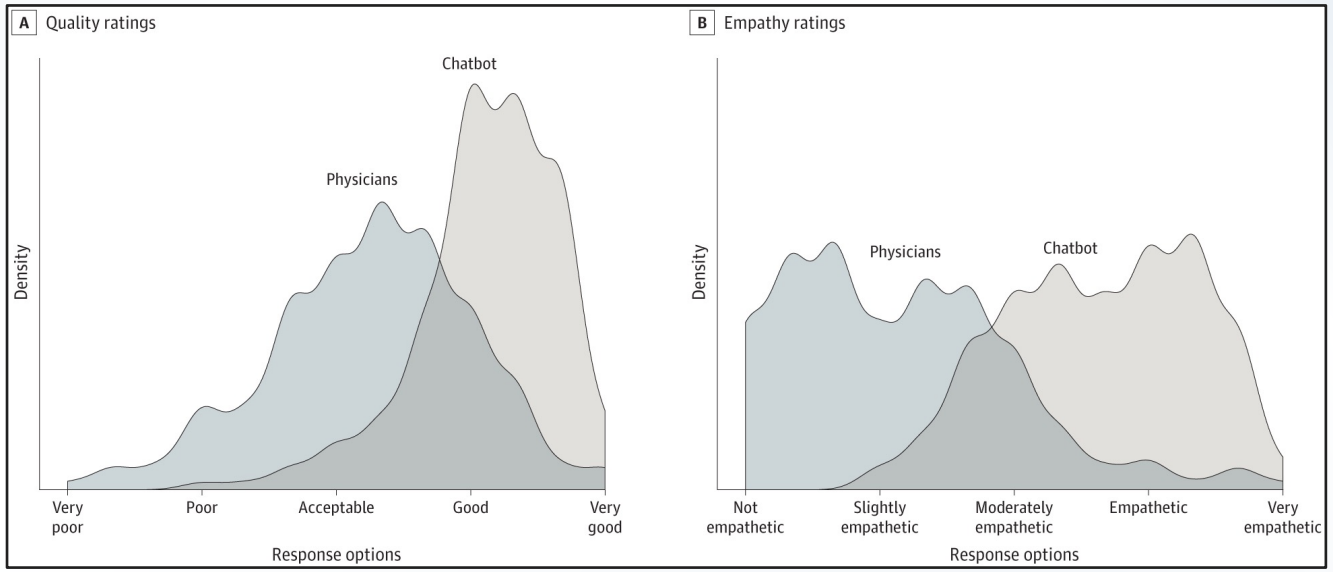


Syrykh et al, NPJ Digital Medicine 2020; Li et al, Nature Communications 2020

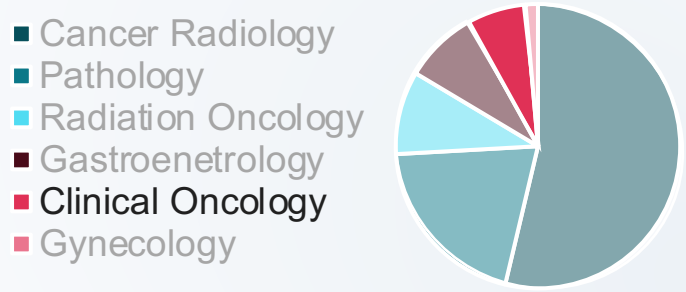
Emerging Directions for Artificial Intelligence



OpenAI's GPT Models Outperform Humans in Complex Clinical / Image Diagnosis Cases



ChatGPT Provides Higher Quality / Empathetic Responses to Online Forum Questions



Han et al, JAMA 2024; Ayers et al, JAMA Internal Medicine 2023

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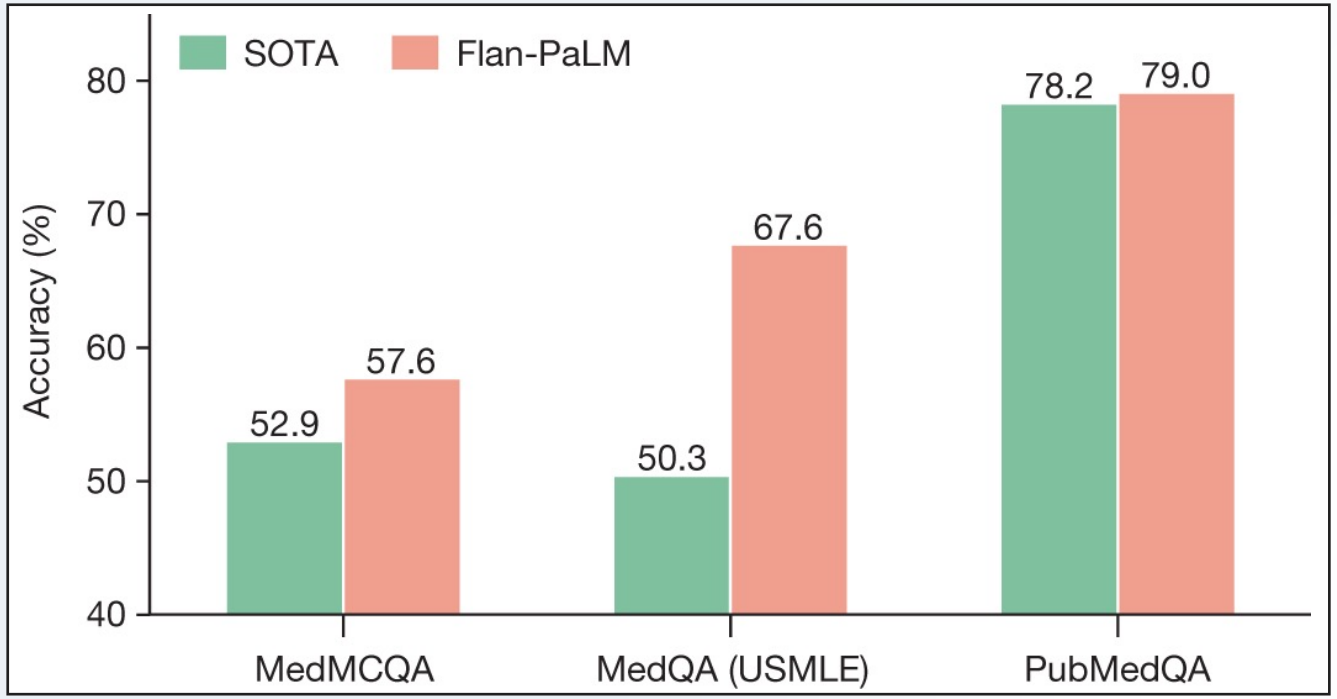
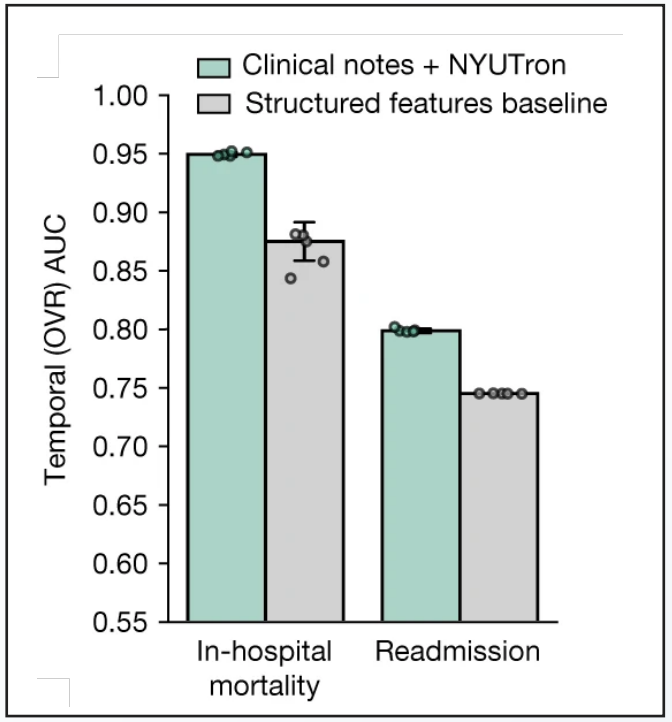
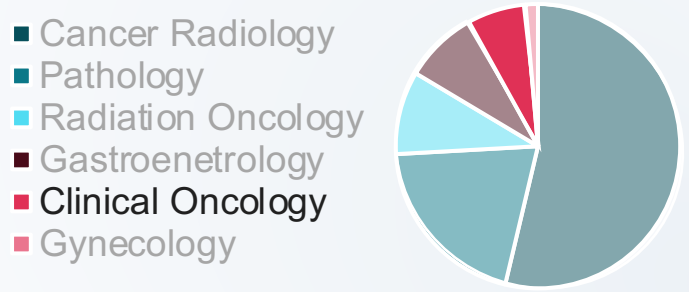


Google Research's Large Language Models can Achieve Passing Scores on Board Exams



Accurate Prediction of Clinical Outcomes using EHR Data

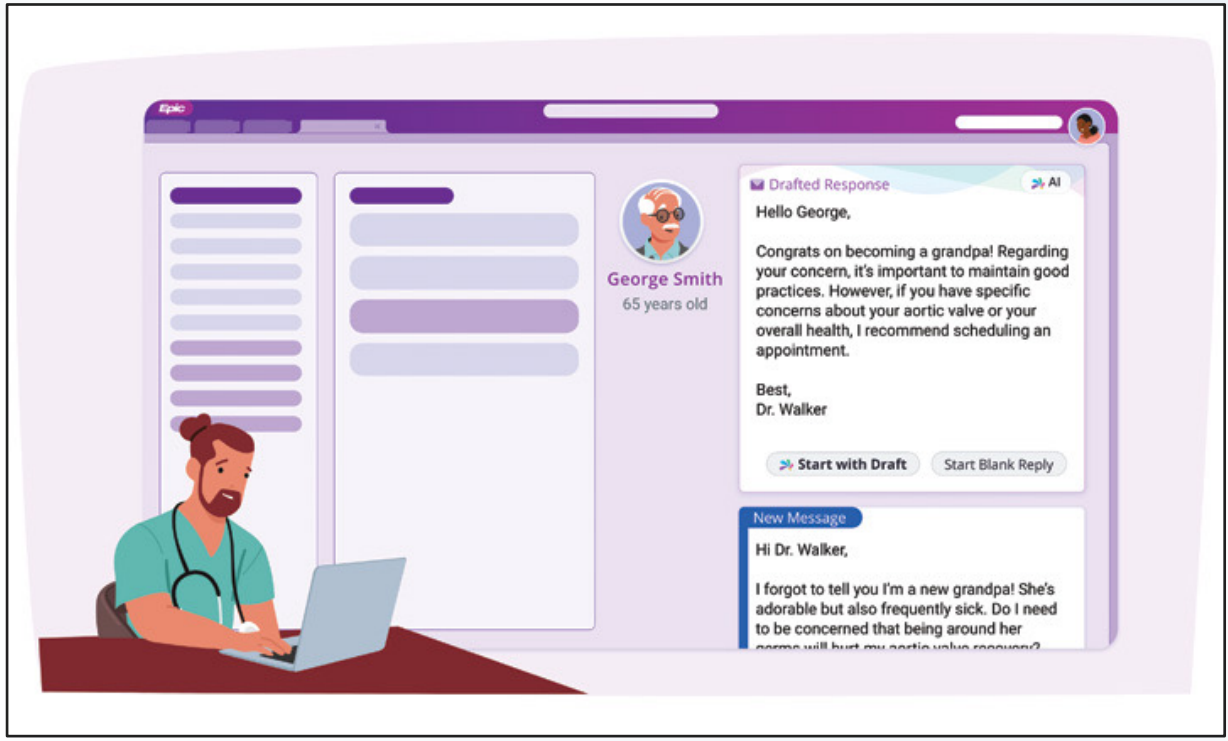


Singhal et al, Nature 2023; Jiang et al, Nature 2023

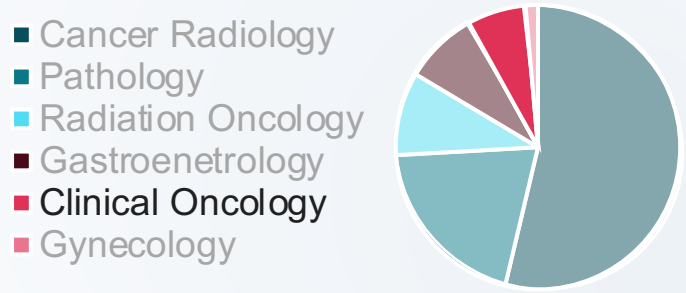
Emerging Directions for Artificial Intelligence

	Adjusted model (Subset of clinicians with note composition data)
Workload variables	
Number of daily appointments	1.01
Minutes spent reviewing charts per week, in 5-min increments	1.01
Patient call messages received per week	
Quartile 1	Ref
Quartile 2	1.65
Quartile 3	1.70
Quartile 4	6.59[c]
Results messages received per week	
Quartile 1	Ref
Quartile 2	1.44
Quartile 3	0.99
Quartile 4	1.55

High Volume of Patient Messages is Associated with Burnout



Epic Implemented ChatGPT to Respond to Patient Queries

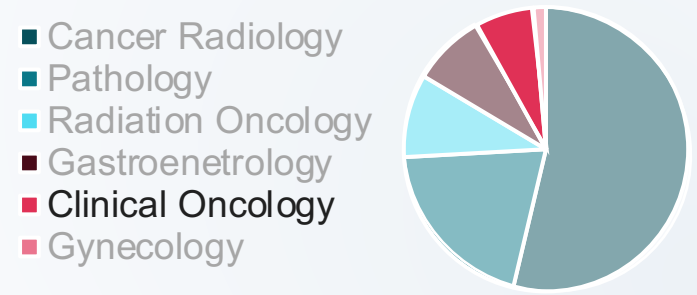


Hilliard et al, JAMIA 2020

Emerging Directions for Artificial Intelligence

TARGET ID AND VALIDATION	HIT ID AND OPTIMIZATION	LEAD OPTIMIZATION	CANDIDATE SELECTION	CANDIDATE PROFILING	CLINICAL TRIALS
• Genetics • Molecular biology • Cell-based studies • Animal studies	• Screening • Hit pharmacology profiling • Medicinal chemistry • *In vitro* ADME • Physiochemical properties	• Medicinal chemistry • Pharmacology • *In vitro and in vivo* ADME • Physiochemical properties • Initial animal efficacy studies	• Higher species PK • Animal efficacy • Preliminary rodent toxicology • Preliminary genotoxicology • Version and form screening • Formulation development	• Version and form selection • Formulation development • Rodent and higher species toxicology • Definitive genotoxicology • IND preparation • GMP synthesis of API	• Phase I trials • Phase II trials • Phase III trials • NDA preparation

Illustration by Health Sciences Center, Fort Worth



Emerging Directions for Artificial Intelligence

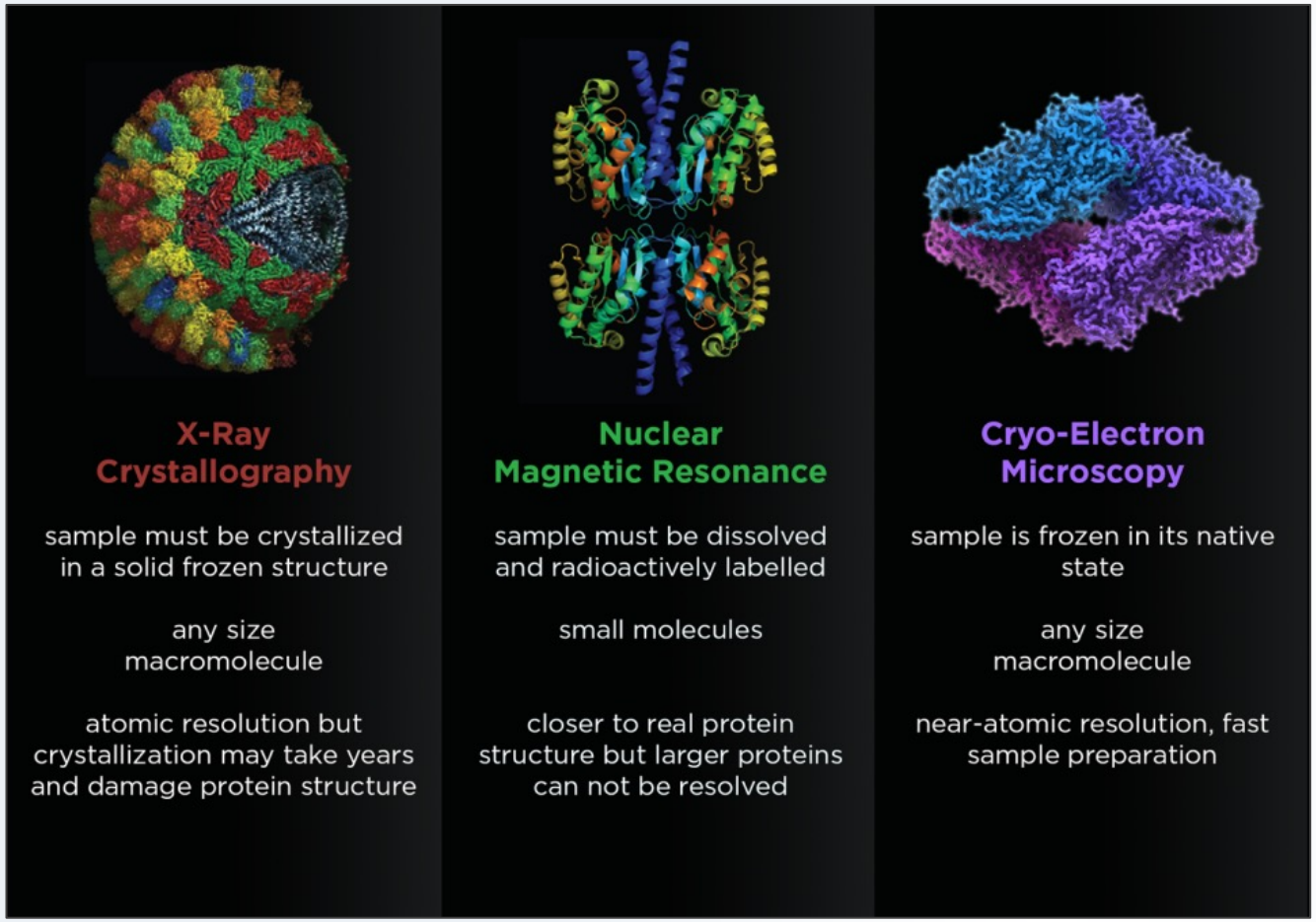
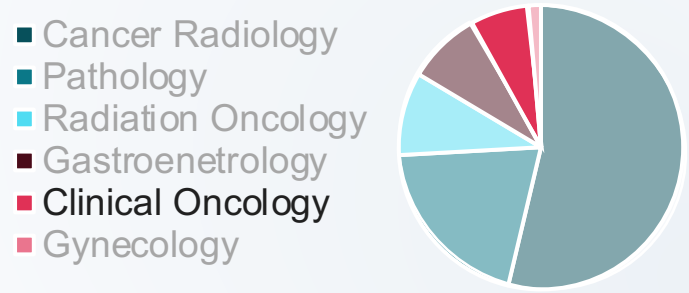
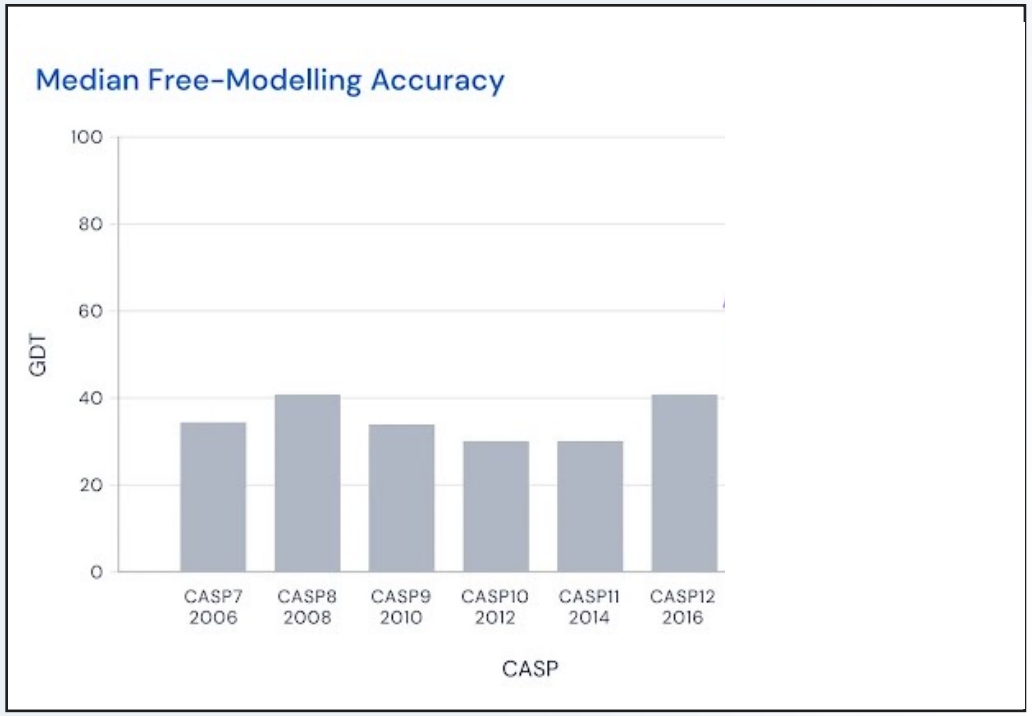


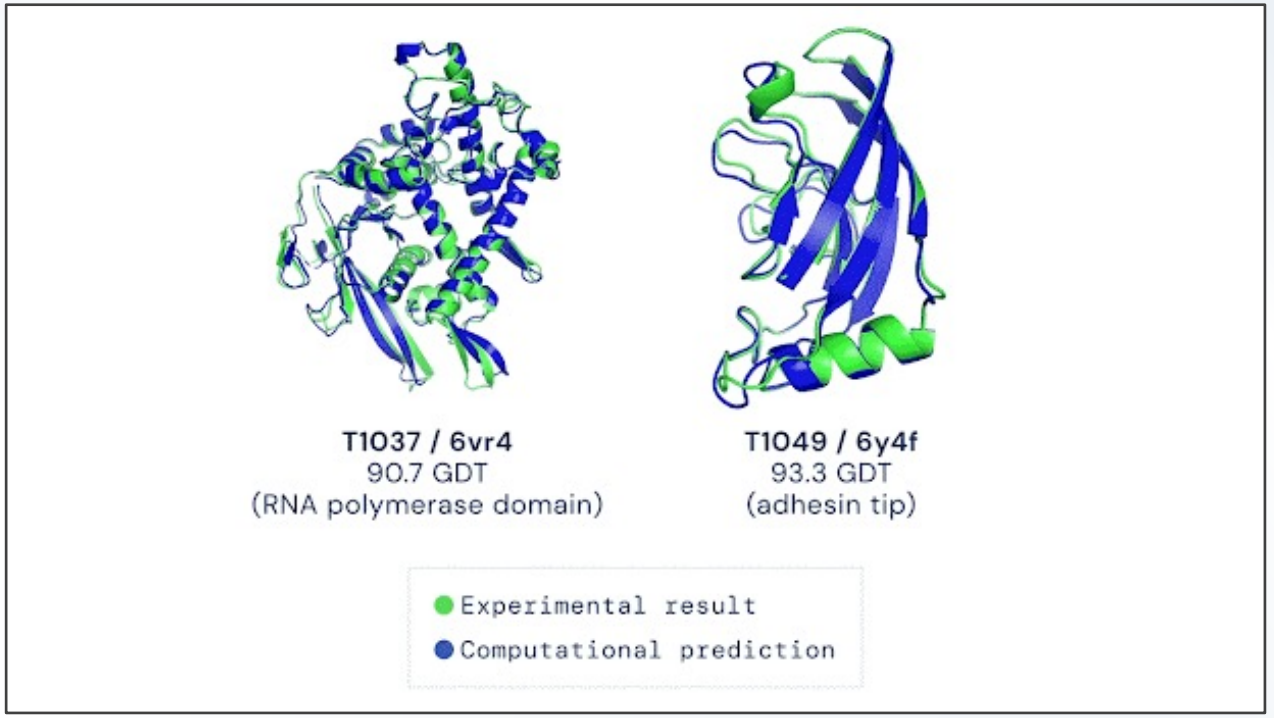
Illustration by Jason Drees

- Rational identification of drug candidates requires knowledge of target structure
- Traditional methods of protein structure identification are costly, time consuming, and can be limited by the size and structure of the protein



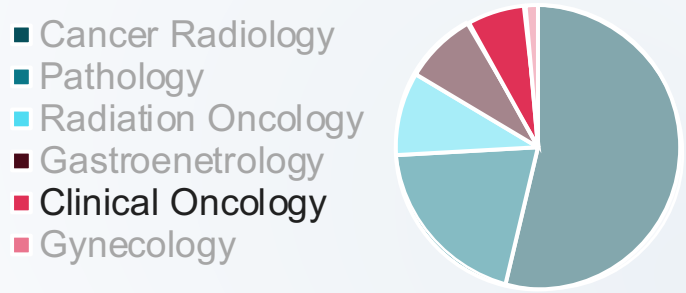
Emerging Directions for Artificial Intelligence





AlphaFold and other AI models Accurately Predict Protein Structure for Drug Target Discovery

Jumper et al, Nature 2021; AlphaFold team, deepmind.google



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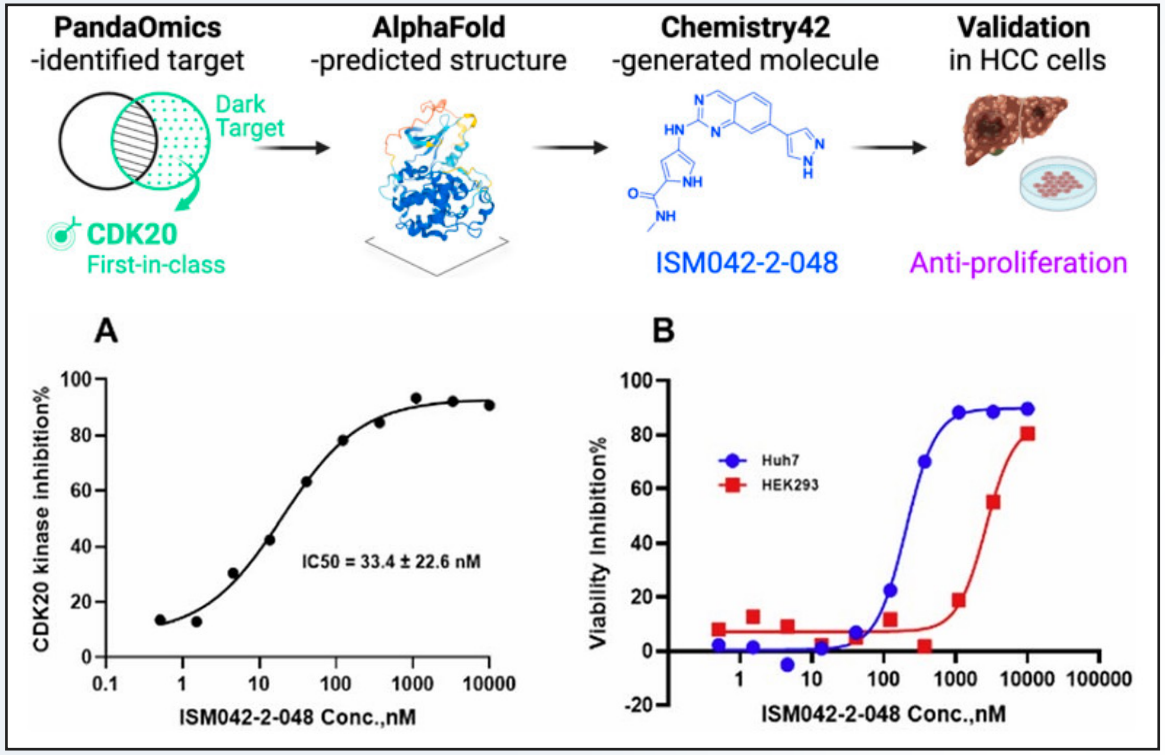
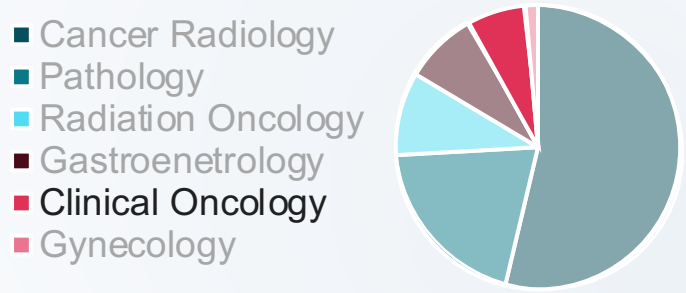


Discovery of a Novel CDK20 Inhibitor with AlphaFold Effective in Cell Lines

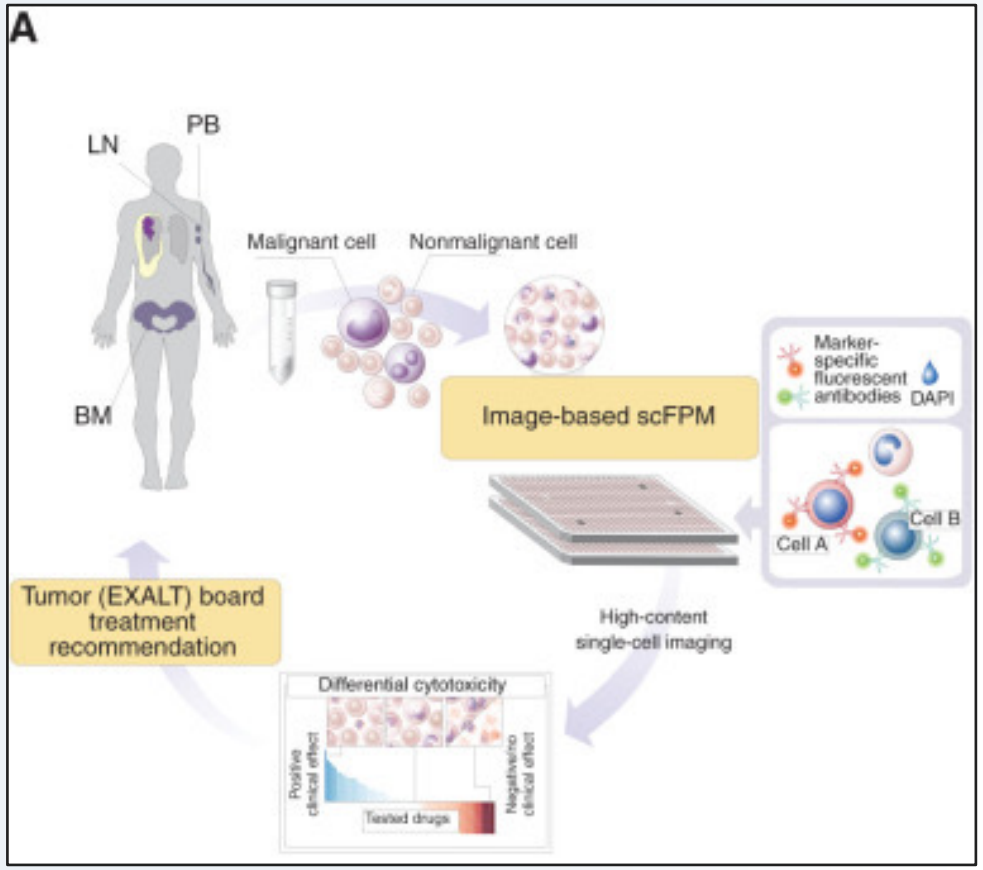
Treatment	Organization	Description	Phase	Lead indication
REC-2282	Recursion	Small molecule pan-HDAC inhibitor	2/3	Neurofibromatosis type 2
REC-994	Recursion	Small molecule superoxide scavenger	2	Cerebral cavernous malformation
REC-4881	Recursion	Small molecule inhibitor of MEK1 and MEK2	2	Familial adenomatous polyposis
INS018_055	InSilico Medicine	Small molecule inhibitor	2	Idiopathic pulmonary fibrosis
BEN-2293	BenevolentAI	Topical pan-tyrosine kinase inhibitor	2a	Atopic dermatitis
EXS-21546	Exscientia and Evotec	A_{2A} receptor antagonist	1b/2	Solid tumors carrying high adenosine signatures.
RLY-4008	Relay Therapeutics	Inhibitor of FGFR2	1/2	FGFR2-altered cholangiocarcinoma
EXS-4318	Exscientia	PKC-θ inhibitor	1/2	Inflammatory and autoimmune conditions
BEN-8744	BenevolentAI	Small molecule PDE10 inhibitor	1	Ulcerative colitis
Undisclosed	Recursion	Small molecular inhibitor of RBM39, a CDK12-associated protein	Pre-clinical	HRD-negative ovarian cancer

Select Drugs Developed with AI in Trials



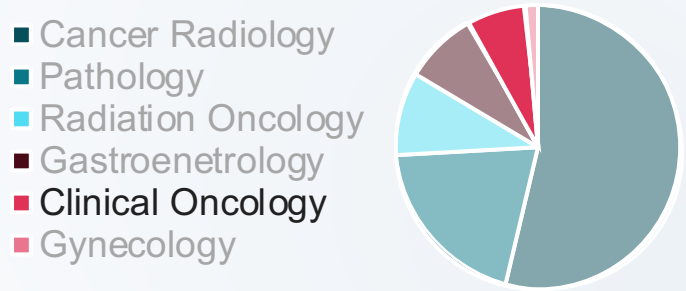
Ren et al, Chemical Science 2023; Arnold, Nature Medicine 2023

Emerging Directions for Artificial Intelligence



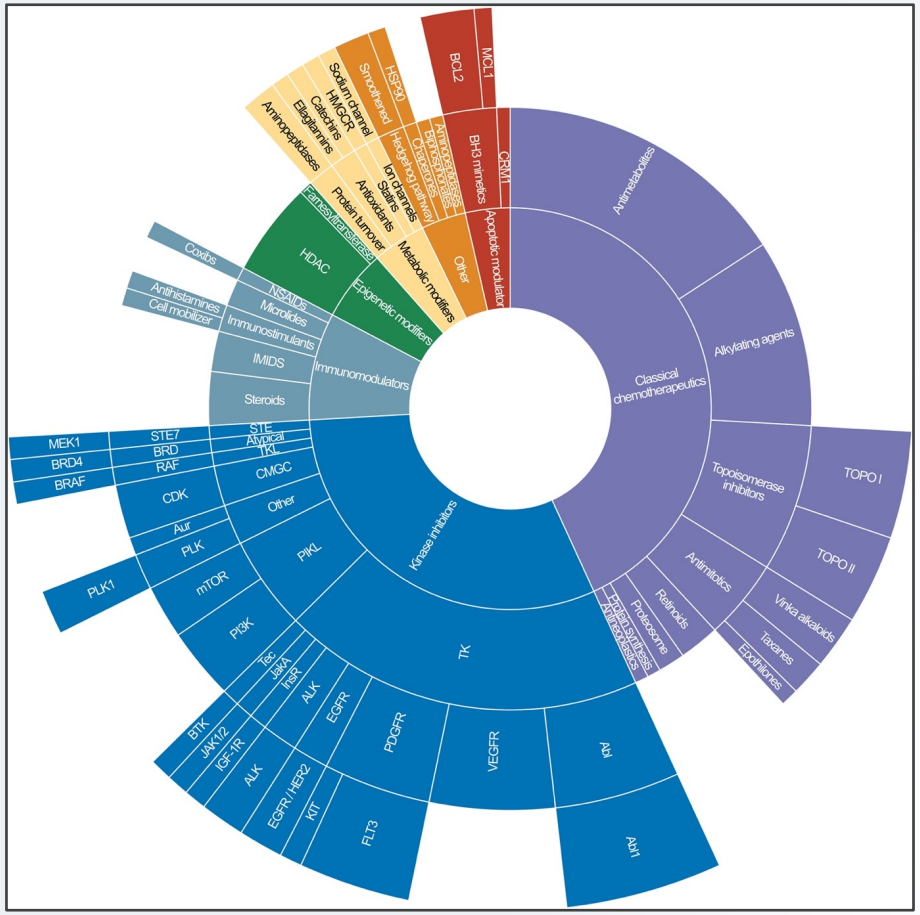
Approach to Treatment in EXALT Trial

- EXALT trial evaluated 'functional precision medicine' approach to refractory lymphoma / leukemia in 56 patients
- Single-cell suspensions of biopsy material were created, and plated on plates containing 136 – 139 drugs at two concentrations.
- Cells incubated with disease specific fluorescent antibodies, with image analysis used to identify fraction of cancer cells relative to incubation with DSMO control

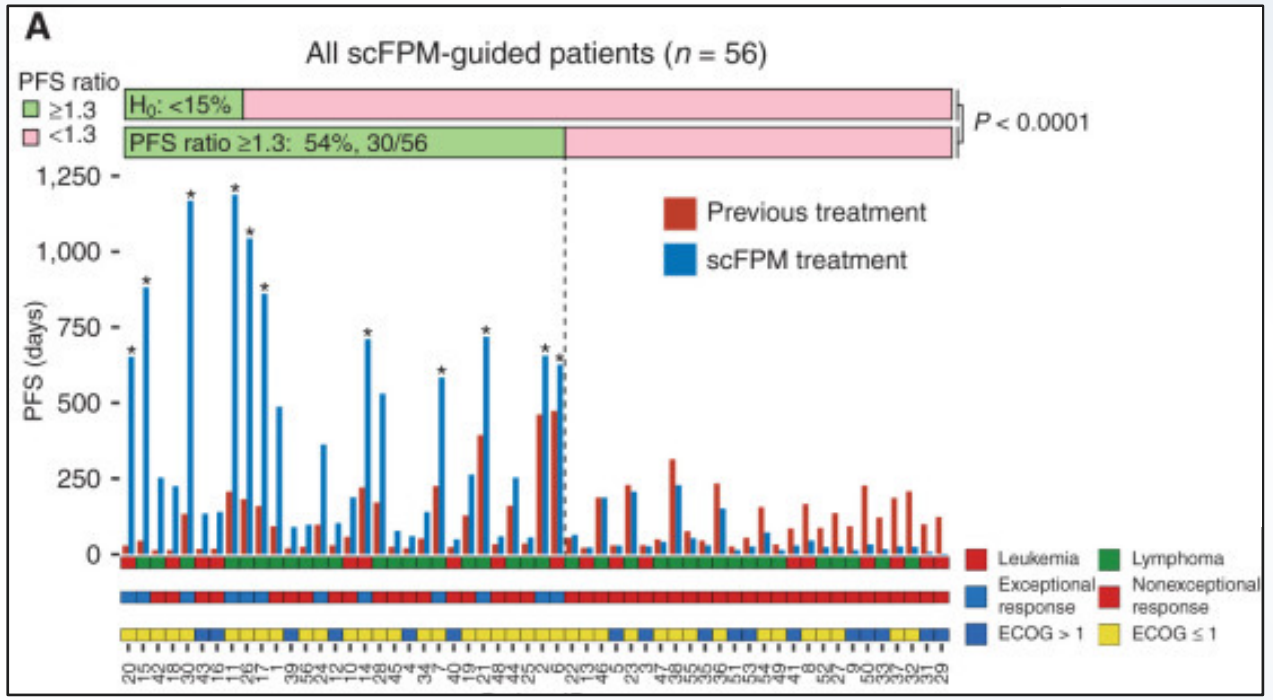


Kornauth et al, Cancer Discovery 2022

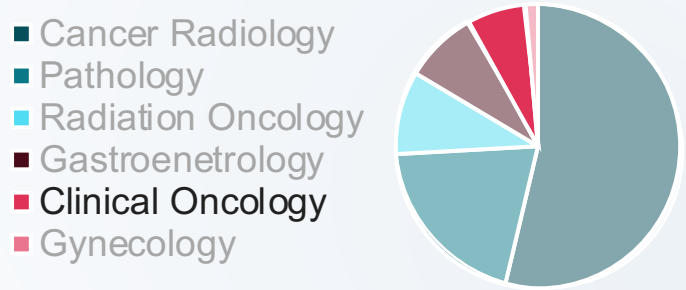
Emerging Directions for Artificial Intelligence



Drugs Tested in EXALT Trial



Half of Patients Had Significant Improvement in PFS Compared to their Prior Treatment



Kornauth et al, Cancer Discovery 2022

Challenges Limiting the Uptake of AI

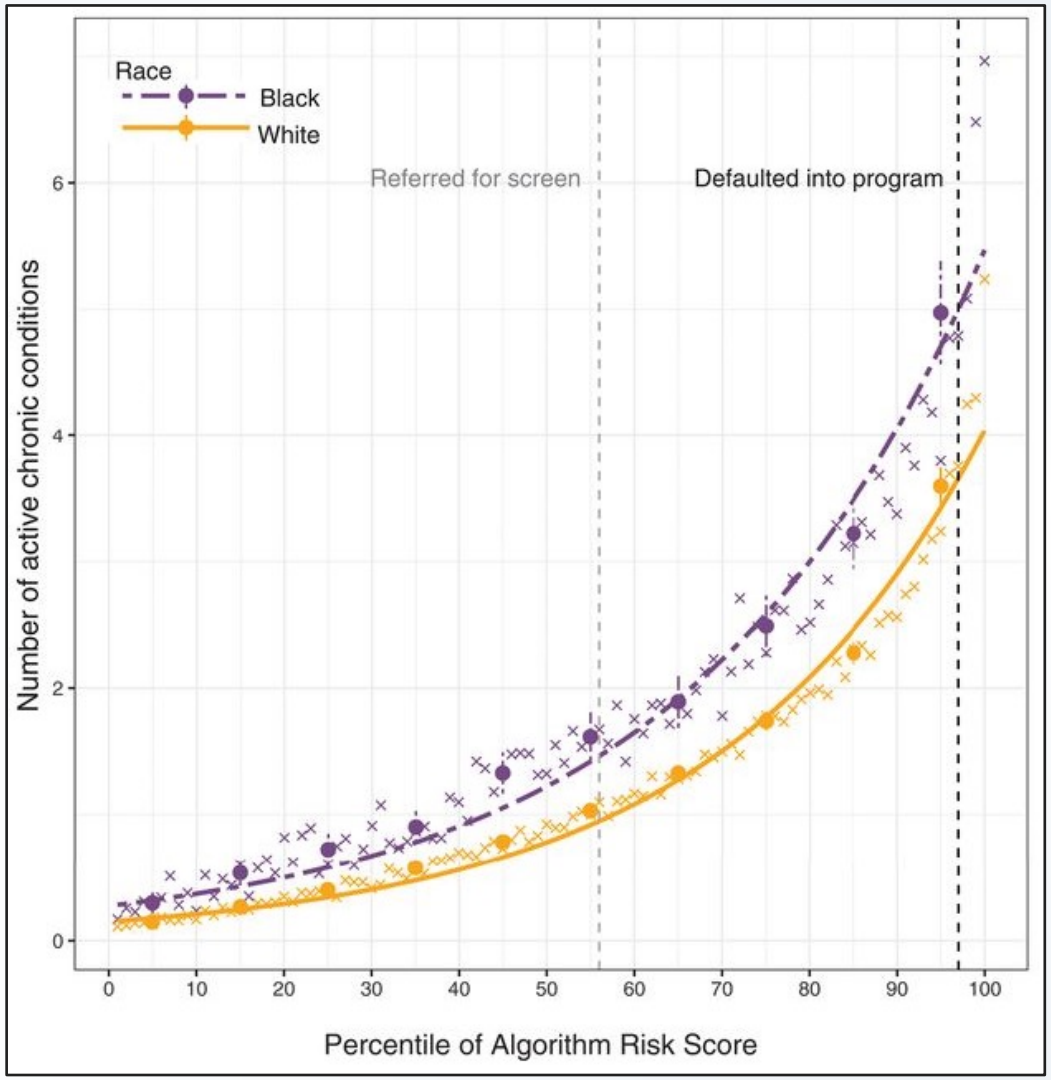
Summary of Challenges in AI Model Implementation

- **Bias and Fairness**
  - Training and assessment needs to be performed in diverse groups of patients representative of real world practice
- **Reliability of predictions**
  - Need for explainable artificial intelligence models (although, at a certain accuracy, does it matter?)
  - 'Uncertainty' quantification –identify when inputs are out of distribution
  - Do pre-analytic variables affect model accuracy? (slide staining, format of EHR data across hospitals, etc)
- **Medical-legal concerns** – who is responsible for AI decisions?

Image source: eyesofthebehaviouralscientist.com

Bias in Artificial Intelligence Models

- **UnitedHealth Group's Optum** used an algorithm to identify 'high-risk' patients in need of additional resources (nursing visits, additional PCP follow-up, etc)
- Algorithm accurately identifies expected cost of care per patient, but high-risk Black patients are likely to have more comorbidities – reflective of racial differences in care utilization



Obermeyer, Science 2019

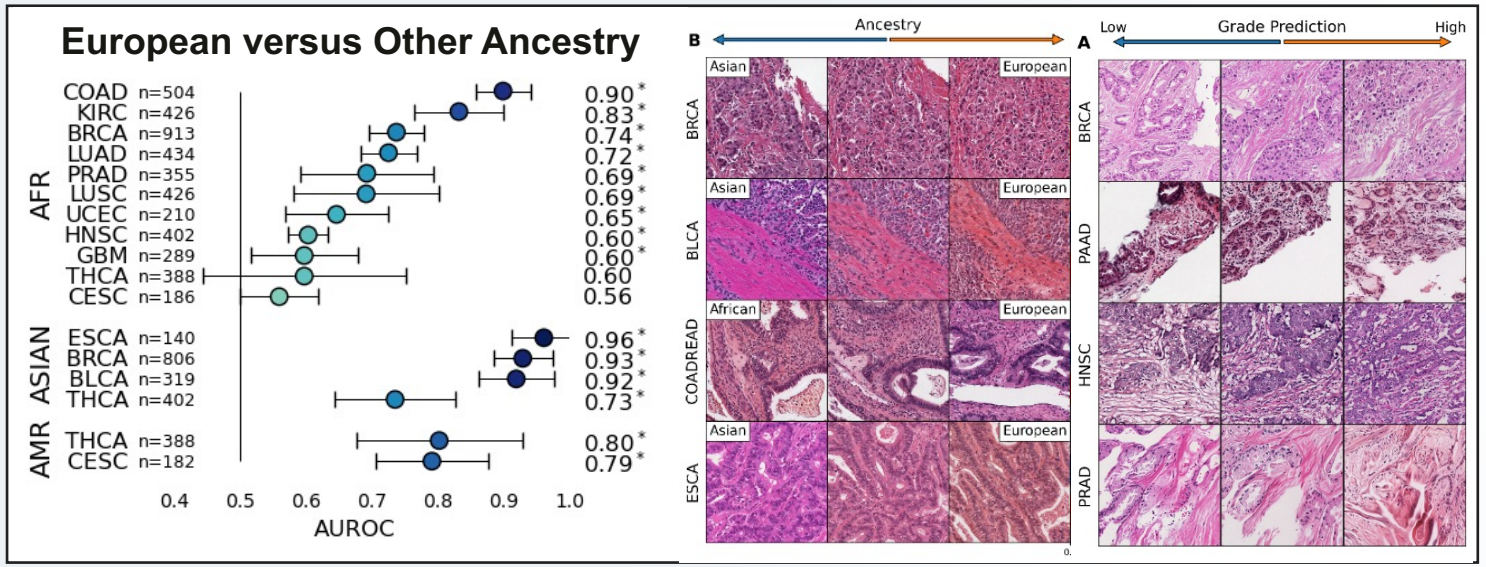
Why did AI Misclassify this Husky as a Wolf?

Husky Classified as Wolf in Vision Model

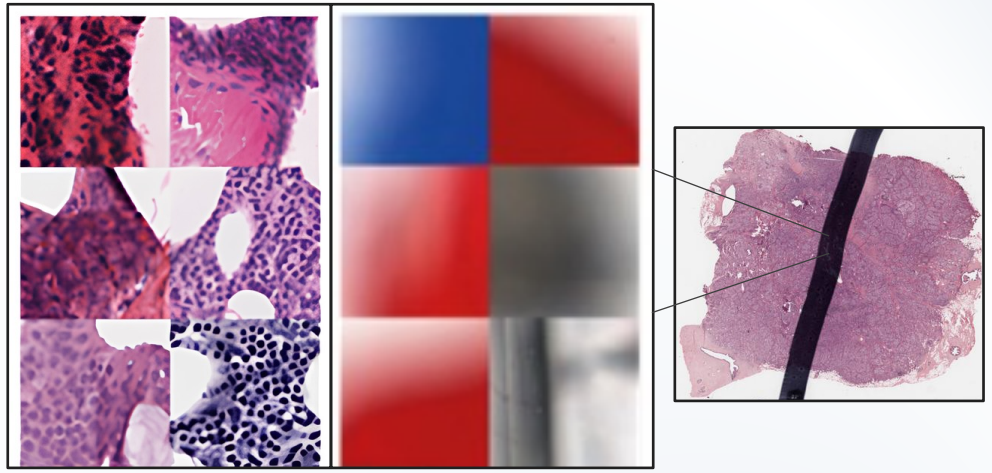
Only Background Information Used in Prediction

Ribeiro et al, arXiv 2016

AI Models Prone to Use Non-Biologic Features in Predictions



Ancestry Prediction (but not grade) in TCGA is Driven by Slide Staining Differences



Features Predictive of Homologous Recombination Deficiency – Lymphocytes....and Pen Marks?

Howard et al, Nature Comm 2021; bioRxiv 2024; Lazard et al Cell Med Reports 2022

Take Home Points

- Artificial intelligence refers to a heterogeneous set of tools that process large amounts of data – particularly effective for vision and language tasks
- These models will (if not already) be part of routine clinical practice in oncology
- Growing focus on development of models incorporating multiple forms of data to lead to accurate predictions
- It will be increasingly important to understand the strengths and weaknesses of AI models, as for the foreseeable future we will be responsible for their use in clinical practice

Image source: eyesofthebehaviouralscientist.com