NyquistAI

Can ChatGPT Run Clinical Trials

James Zou

Assistant professor at
Stanford University

Michelle Wu

Co-Founder / CEO
NyquistAI

Chris Pepper

Clinical Business Development
Executive

May 2023

Webinar Presented by NyquistAI

James Zou

Assistant professor of biomedical data science and, by courtesy, of CS and EE at Stanford University

Stanford University

Expertise

- Novel machine and deep learning algorithms
  - Strong statistical guarantees
  - Adopted by the industry
- Important questions important for the broader impacts of AI
  - Interpretations
  - Robustness
  - Transparency

Notable Achievements

- Publication in Nature
- Best paper awards:
  - Google Faculty Award
  - Chan-Zuckerberg Investigator
  - Tencent AI award

Generative AI for clinical trials

James Zou
Stanford University
5/31/2023

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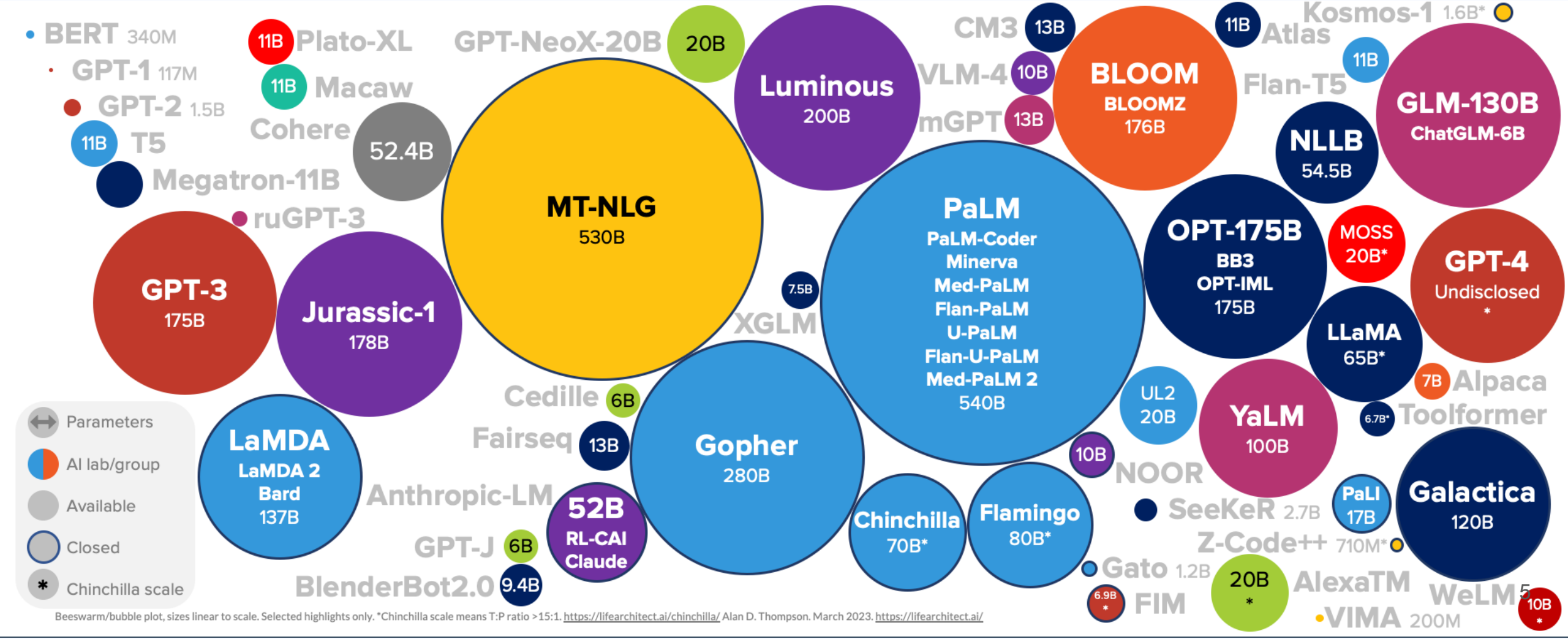
Tremendous advances in generative AI

Generative AI for art

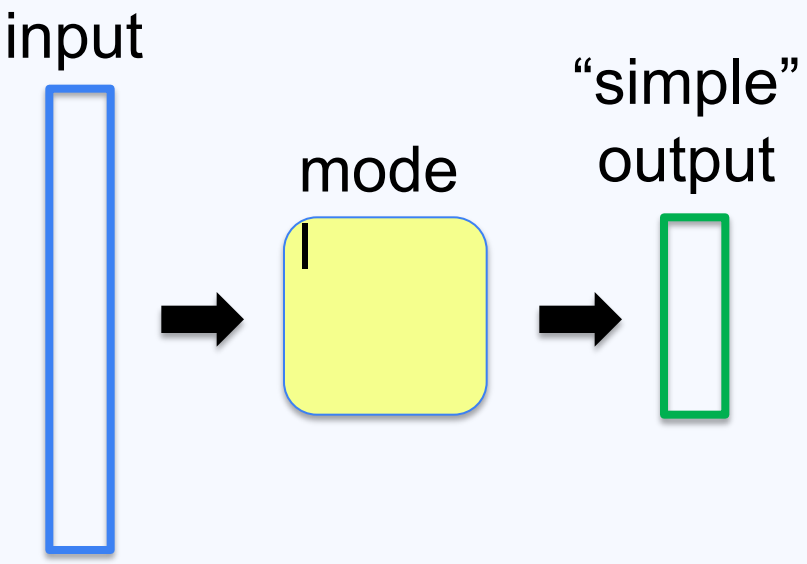
ArtWhisperer.io

Large language models



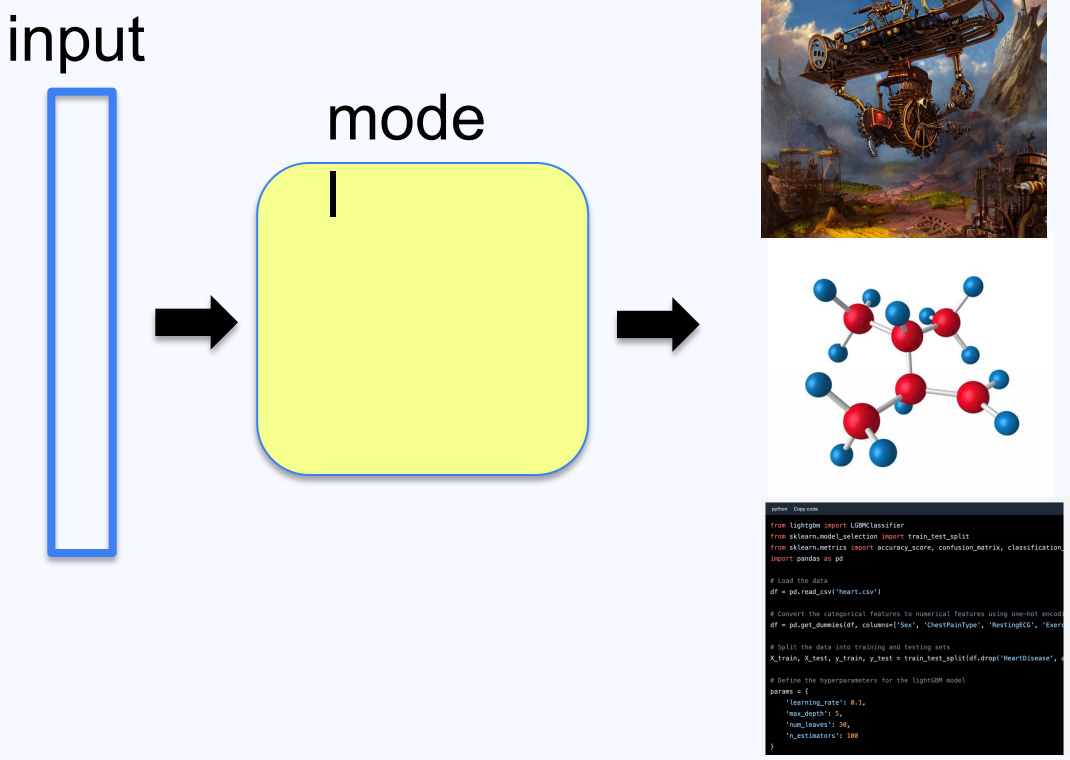
Beeswarm/bubble plot, sizes linear to scale. Selected highlights only. *Chinchilla scale means T:P ratio >15:1. https://lifearchitect.ai/chinchilla/ Alan D. Thompson. March 2023. https://lifearchitect.ai/

Standard regression/classification



Generative models

rich output



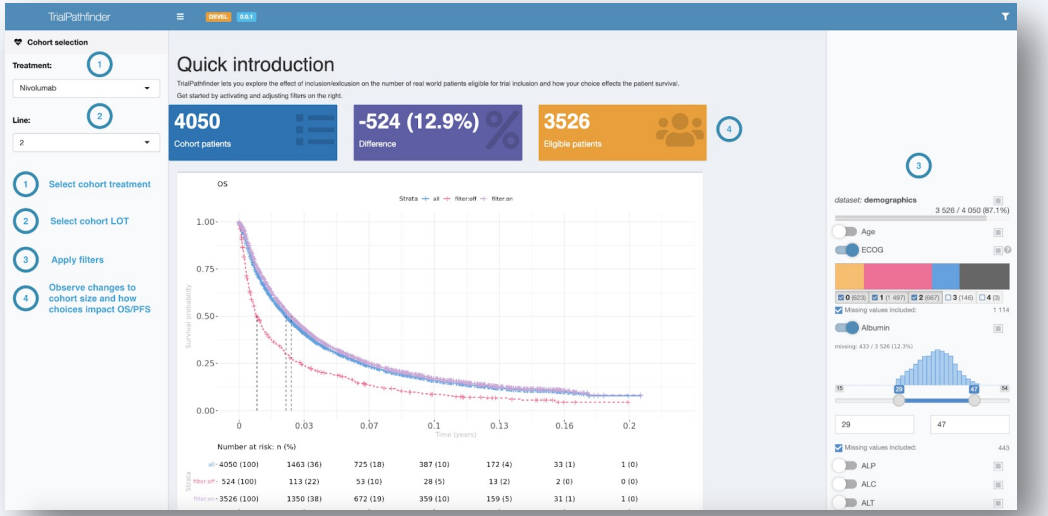
AI designed clinical trials more diverse and efficient

Article | Published: 07 April 2021

Evaluating eligibility criteria of oncology trials using real-world data and AI

Ruishan Liu, Shemra Rizzo, Samuel Whipple, Navdeep Pal, Arturo Lopez Pineda, Michael Lu, Brandon Arnieri, Ying Lu, William Capra, Ryan Copping ✉ & James Zou ✉

Nature **592**, 629–633(2021) | Cite this article



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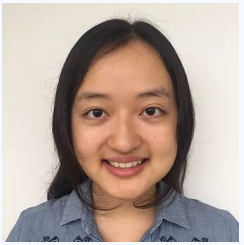
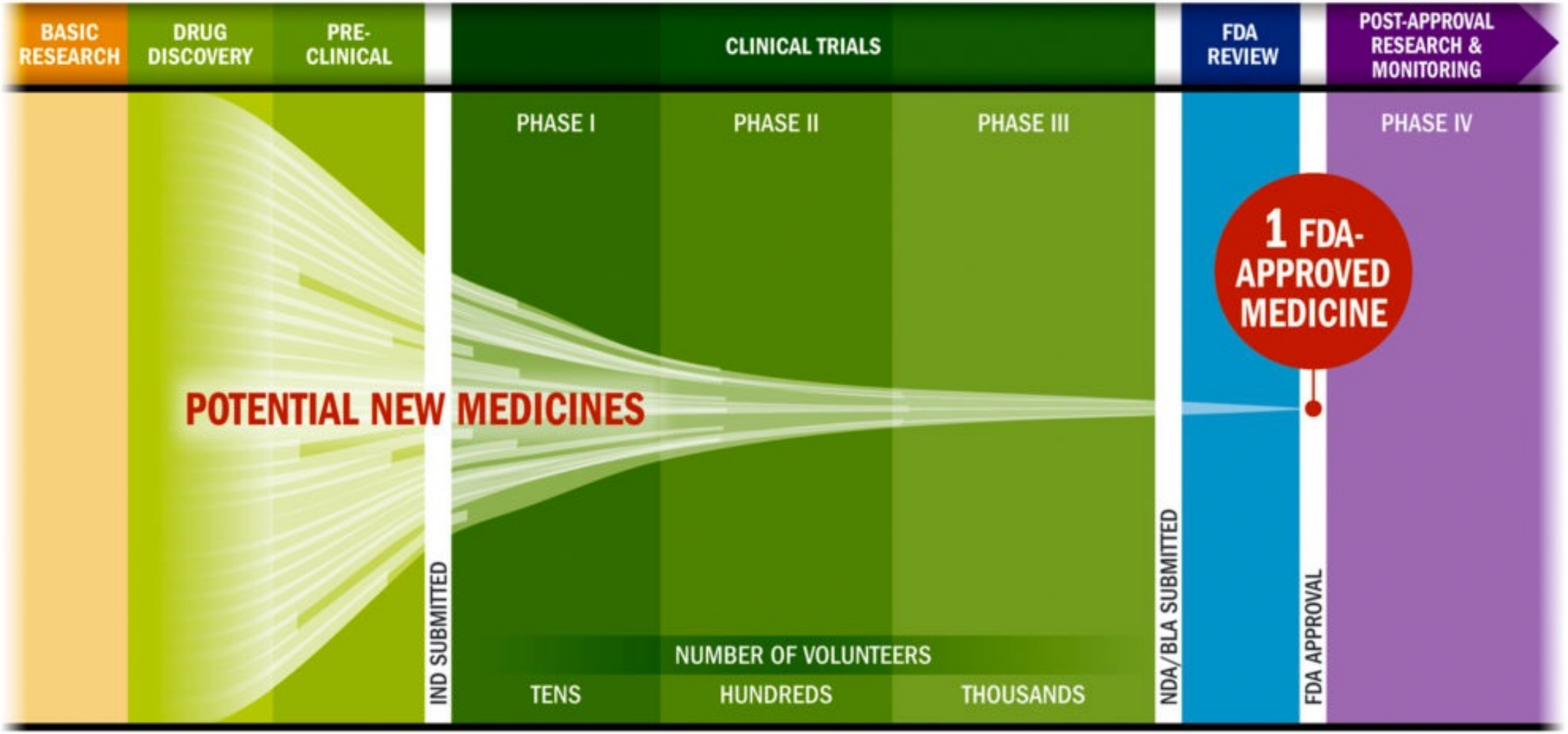
Global Pharma Awards 2021

TOP 10
CLINICAL RESEARCH
ACHIEVEMENT AWARDS
PRESENTED BY CLINICAL RESEARCH FORUM

Ruishan Liu



Liu et al. Nature 2021



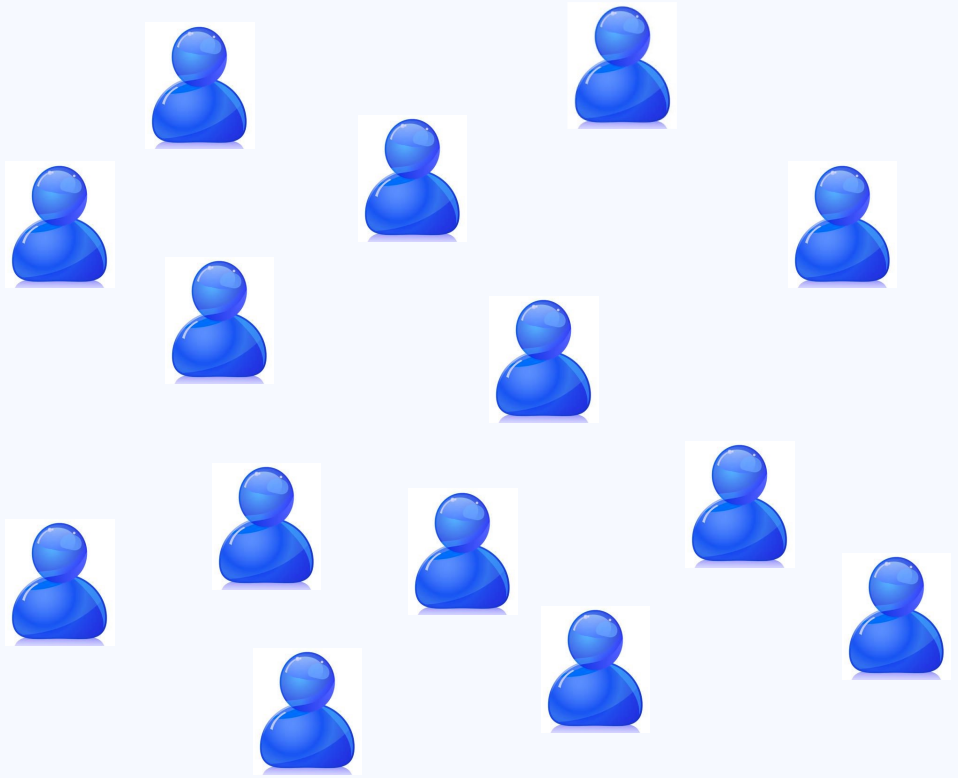
Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

* The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be $2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

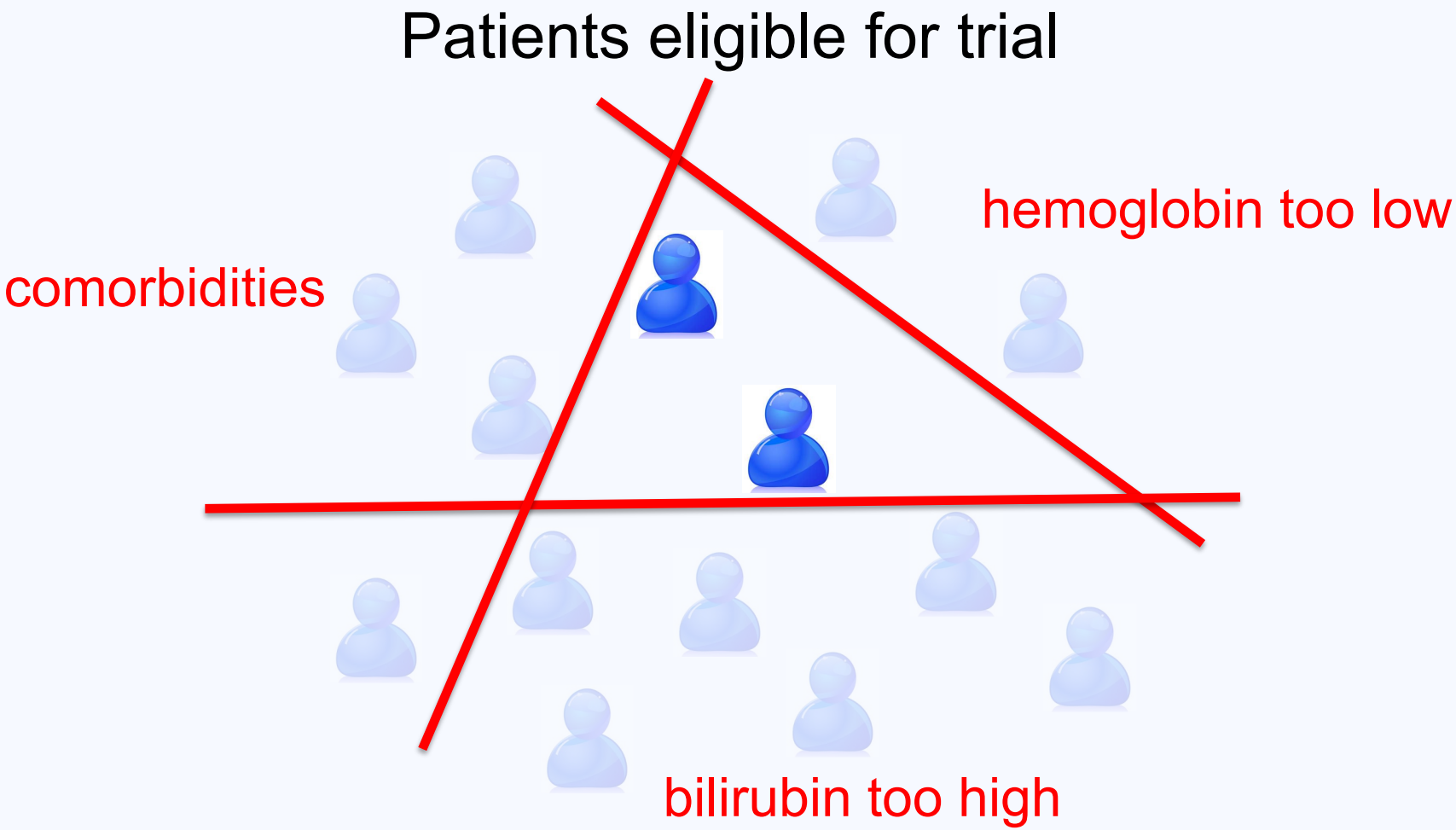
Source: PhRMA adaptation based on Tufts Center for the Study of Drug Development (CSDD) Briefing: "Cost of Developing a New Drug," Nov. 2014. Tufts CSDD & School of Medicine., and US FDA Infographic, "Drug Approval Process," http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/UCM284393.pdf (accessed Jan. 20, 2015).

Clinical trials are highly selective

All patients with the disease



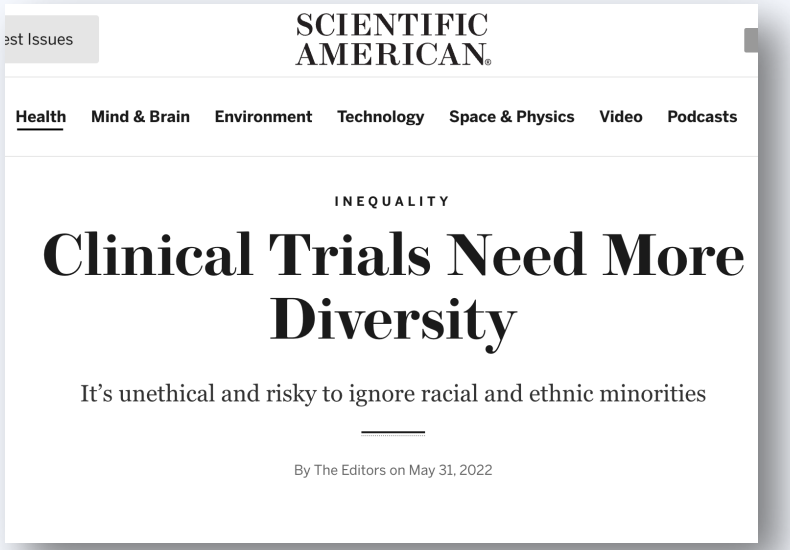
Clinical trials are highly selective



Overly strict eligibility is a major barrier

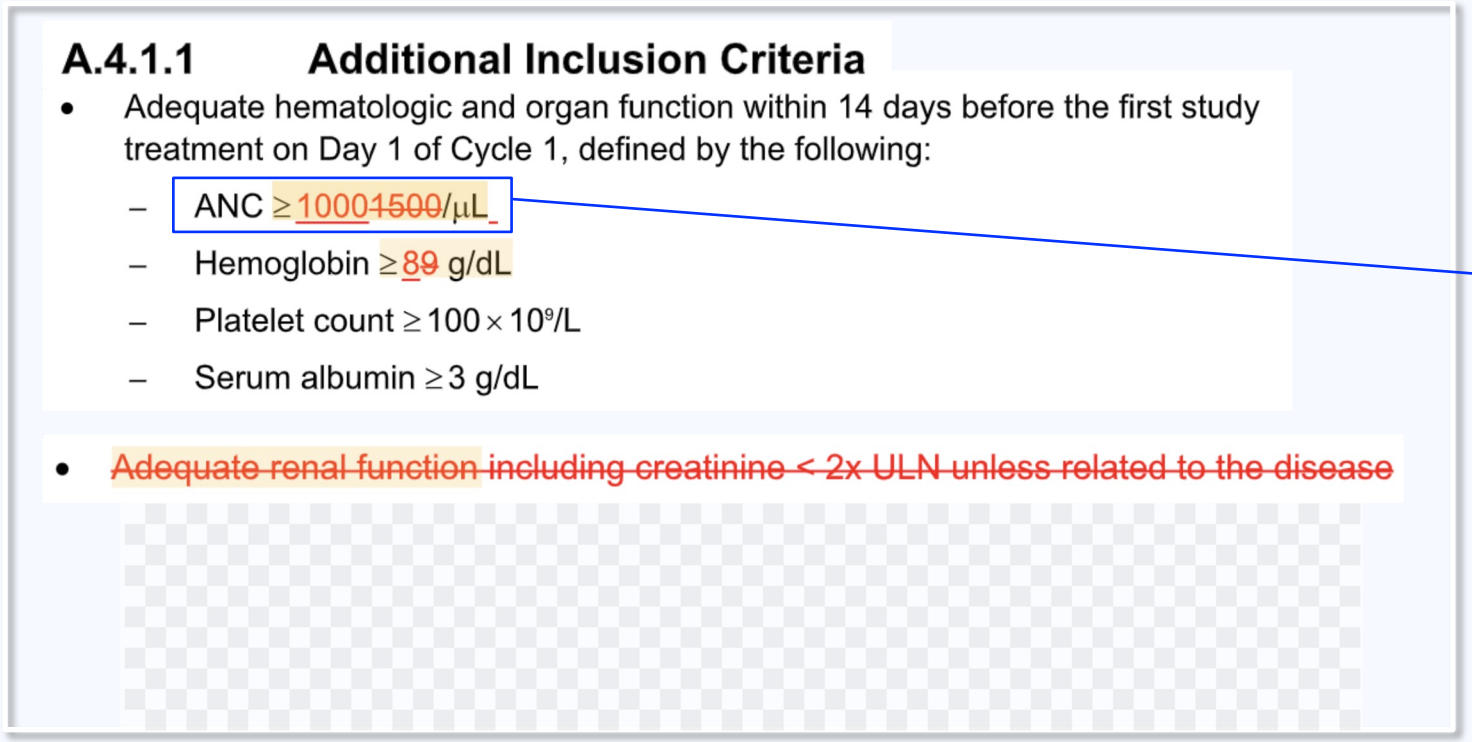
40% of cancer trials fail to reach minimum enrollment

Trial cohorts don’t reflect real-world population



Eligibility Criteria Often Anecdotal

Working protocol draft from Roche



A.4.1.1 Additional Inclusion Criteria

- Adequate hematologic and organ function within 14 days before the first study treatment on Day 1 of Cycle 1, defined by the following:
  - ANC ≥ 1000~~1500~~/µL
  - Hemoglobin ≥ ~~8~~9 g/dL
  - Platelet count ≥ 100 × 10^9/L
  - Serum albumin ≥ 3 g/dL
- ~~Adequate renal function including creatinine < 2x ULN unless related to the disease~~

Clinician 1

Safety: Can we change to 1000/microL

From imported document

Clinician 2

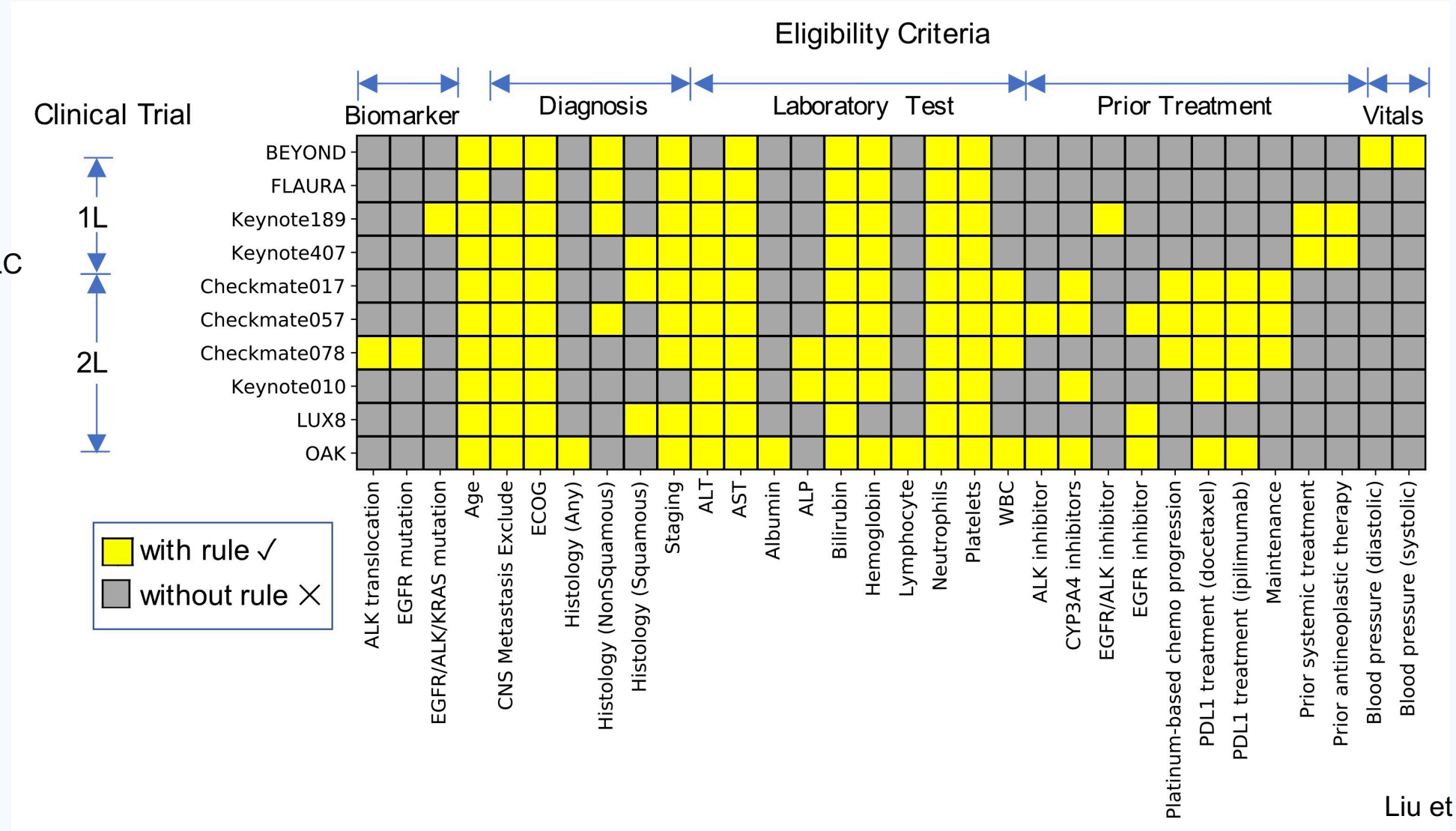
1500 for consistency with other ipat program protocols. This is currently a potential risk, and we are still accruing data.

From imported document

Clinician 3

Elegibility criteria should match all the current trials. I fully agree with and this should not be modified given the associated risk of neutropenia and anemia,

Trials for similar drugs have different exclusions



Liu et al. Nature 2021

The U.S. National Cancer Institute concluded that:

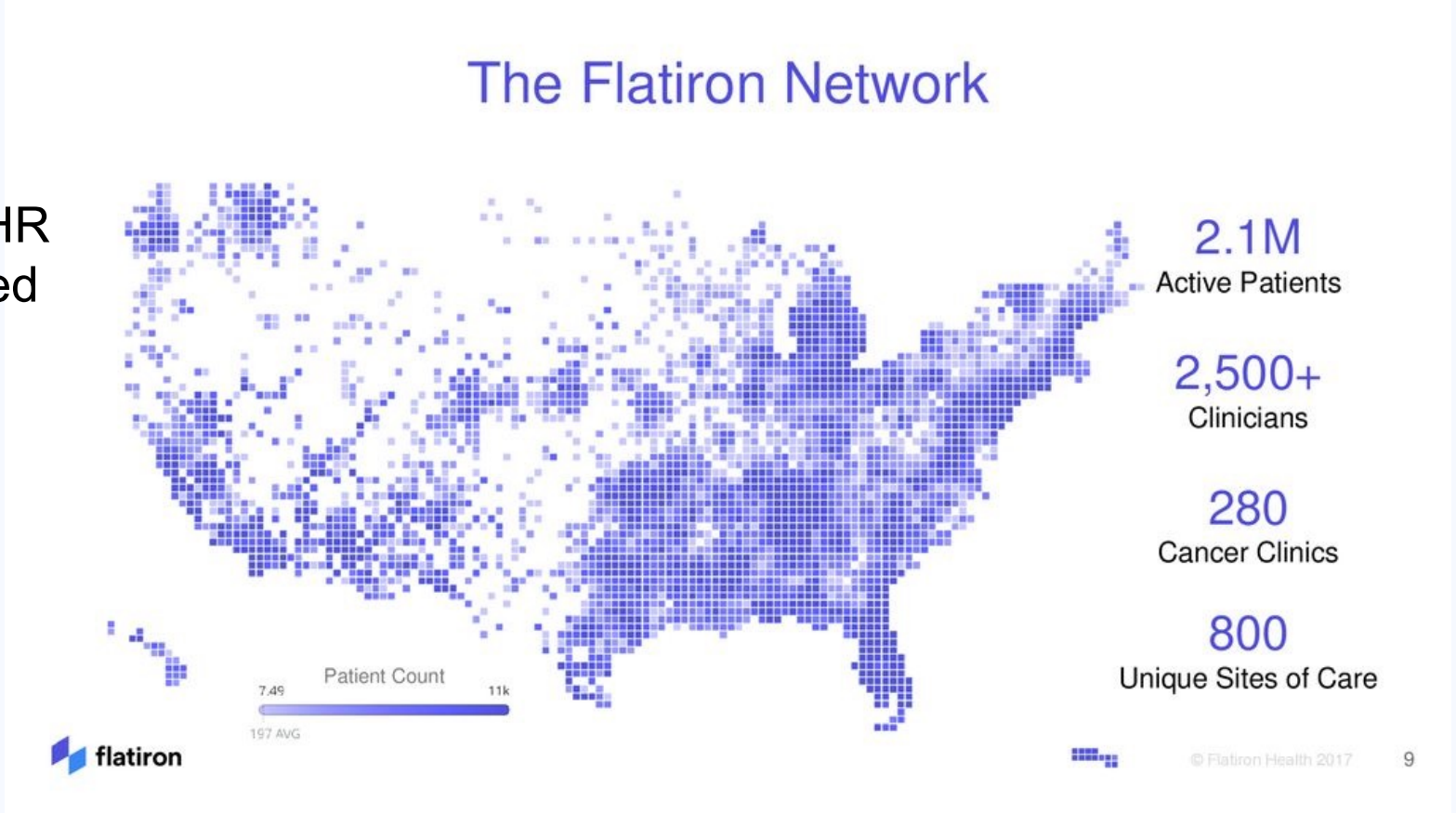
> "The eligibility criteria for all cancer clinical trials should be simplified in order to require minimal input at the time of registration of individuals."

But how to design eligibility is challenging and we want to help.

Report of the National Cancer Institute clinical trials program review group.

Idea: use generative AI on EHR data to emulate clinical trials and guide design of new trials.

We use EHR data curated by Flatiron



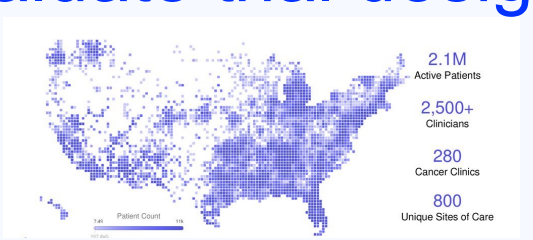
In silico evaluation of trial designs

1.Generate trial eligibility rules

- Bilirubin < 1
- Hemoglobin > 9
- ANC > 1500
- Albumin > 3

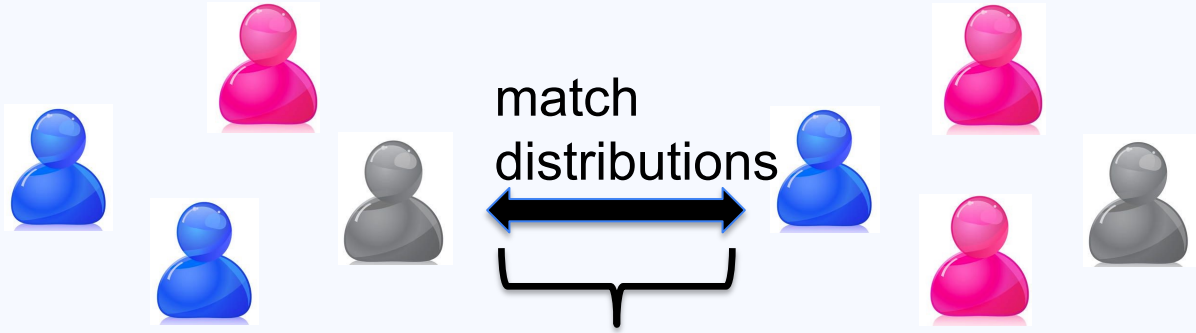
... (20-50 other rules)

2. Evaluate trial design via EHR



Treatment patients

Control patients



- Safety + efficacy
- # of eligible patients
- How easy to implement

Liu et al. Nature 2021

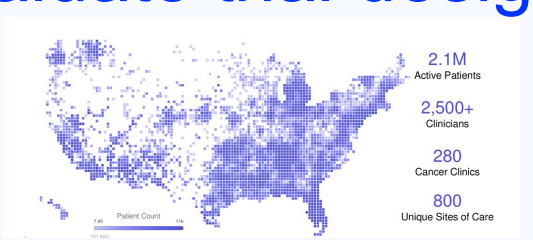
In silico evaluation of trial designs

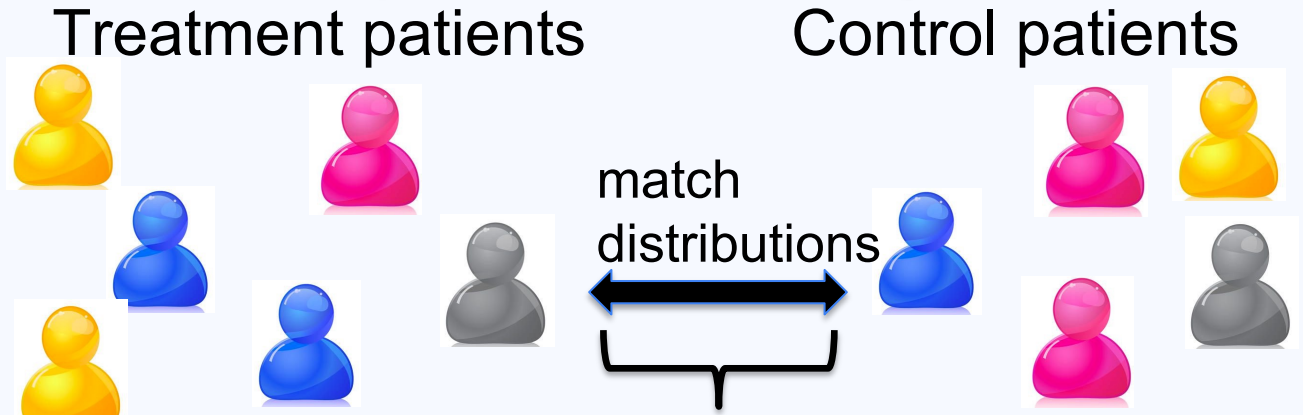
1.Generate trial eligibility rules

- Bilirubin ~~< 1~~ 2
- Hemoglobin > 9
- ANC > ~~1500~~ 1000
- Albumin > 3

... (20-50 other rules)

2. Evaluate trial design via EHR

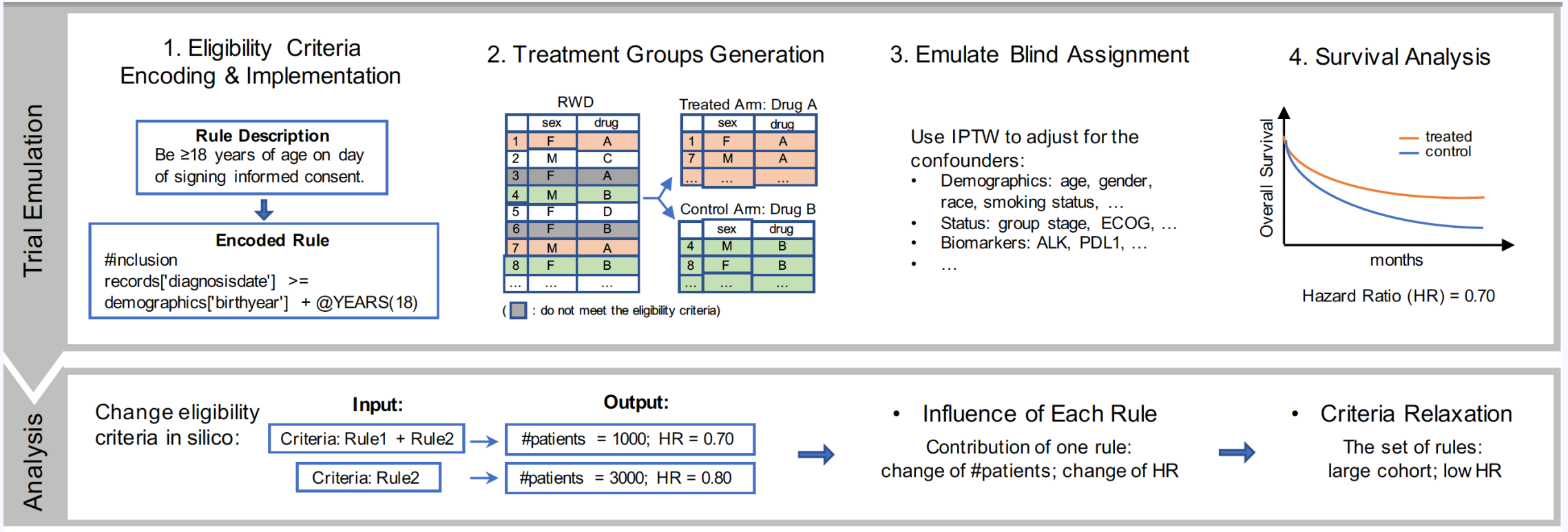




- Safety + efficacy
- # of eligible patients
- How easy to implement

Liu et al. Nature 2021

Trial Pathfinder uses EHR + AI to design eligibility criteria

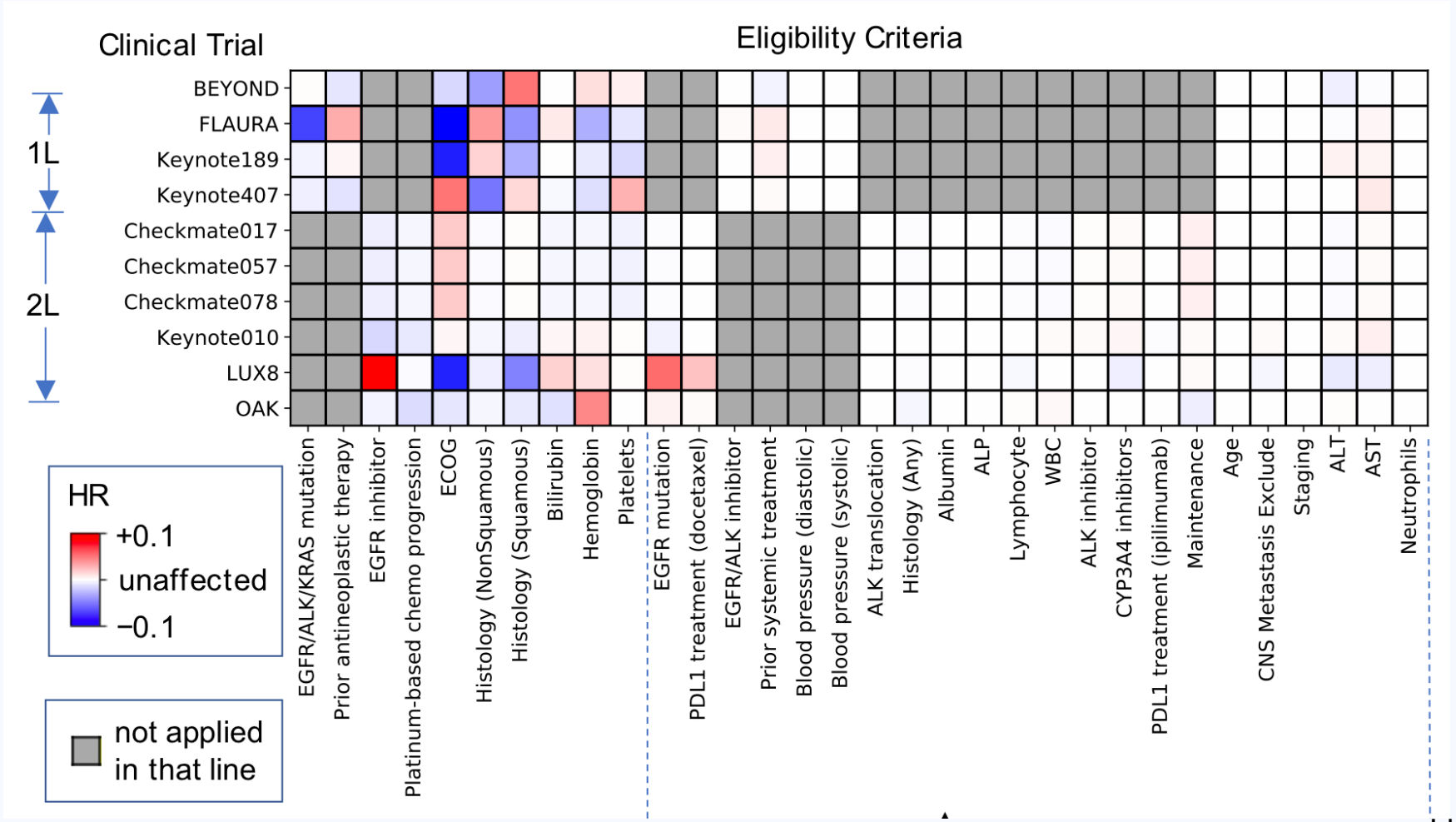


Emulates millions of trials with different eligibility rules.
Uses Flatiron database of >200k real-world cancer patients.
Uses Shapley value to quantify the impact of each eligibility rule.

Liu et al. Nature 2021

Data-driven generation of trial eligibility

Broadening eligibility thresholds for lab values (e.g. bilirubin, platelets, hemoglobin)



Liu et al. Nature 2021

Data-driven criteria doubles # eligible patients and reduces hazard

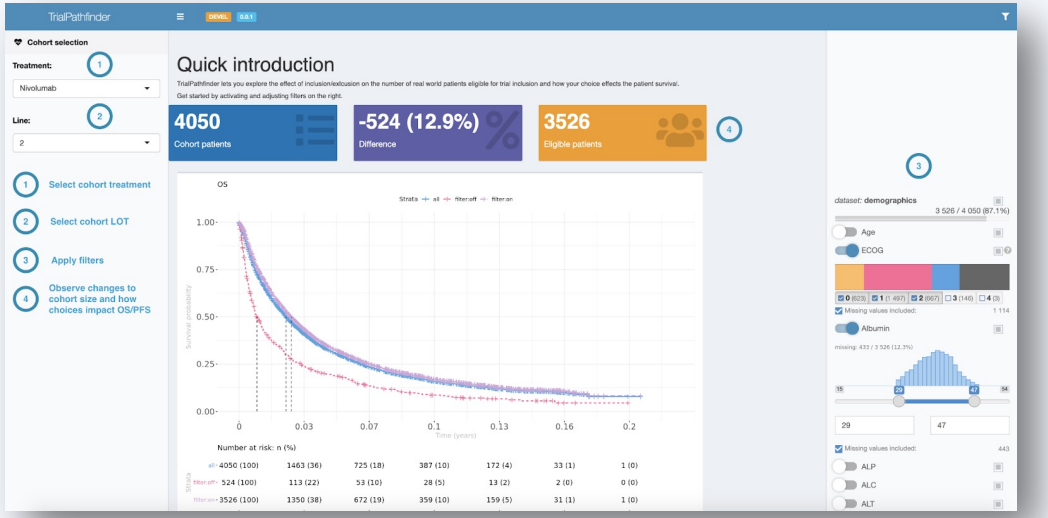
aNSLC trials	Original Trial Criteria		Data-driven Criteria	
	Number of Patients	Hazard Ratio	Number of Patients	Hazard Ratio
FLAURA	2277	0.81	2546	0.75
LUX8	129	0.65	141	0.58
Checkmate017	523	0.67	4085	0.71
Checkmate057	792	0.75	2594	0.66
Checkmate078	1509	0.74	3348	0.68
Keynote010	806	0.56	1948	0.51
Keynote189	4066	0.88	4595	0.85
Keynote407	2031	1.13	9173	1.04
BEYOND	2902	1.09	3043	1.08
OAK	493	0.88	620	0.80
Average	**1553**	**0.82**	**3209**	**0.77**

Enables more women, minorities and older patients to access trials.

Liu et al. Nature 2021

Trial Pathfinder summary

- Data driven design makes trials more inclusive.
- Validated using clinical trial data and independent cohorts.
- Method can be extended to other diseases.



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TOP 10 CLINICAL RESEARCH ACHIEVEMENT AWARDS

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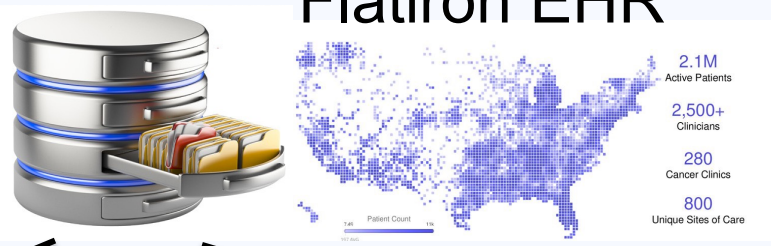
Liu et al. Nature 2021

Use in silico trial to find predictive mutations

Bladder cancer patients
who took immunotherapy

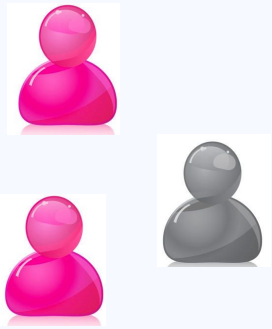
Flatiron EHR

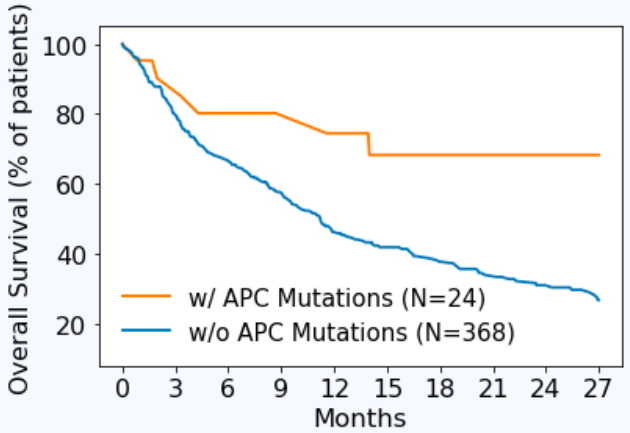


Patients w/ APC gene mutated

Patients w/o APC mutation

match
distribution
s

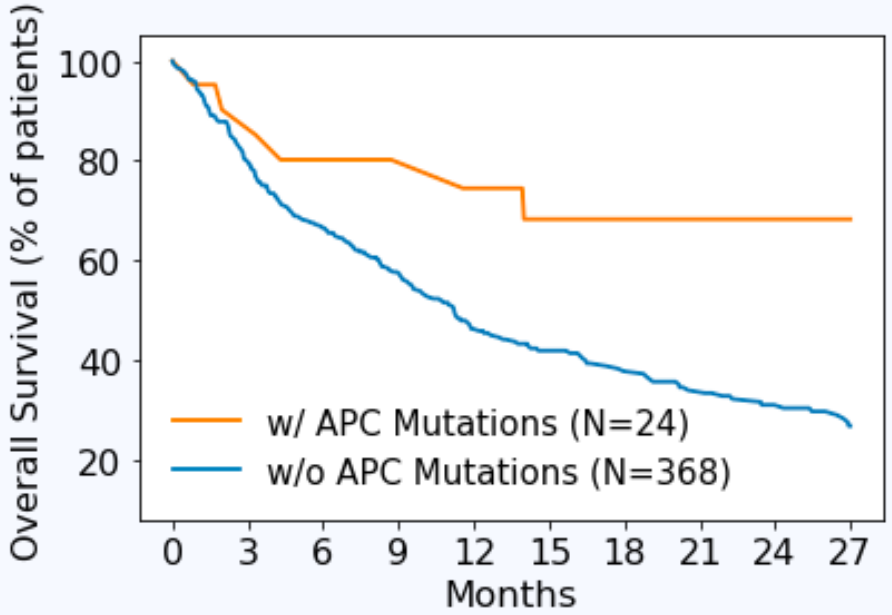




Liu et al. Nature Medicine 2022

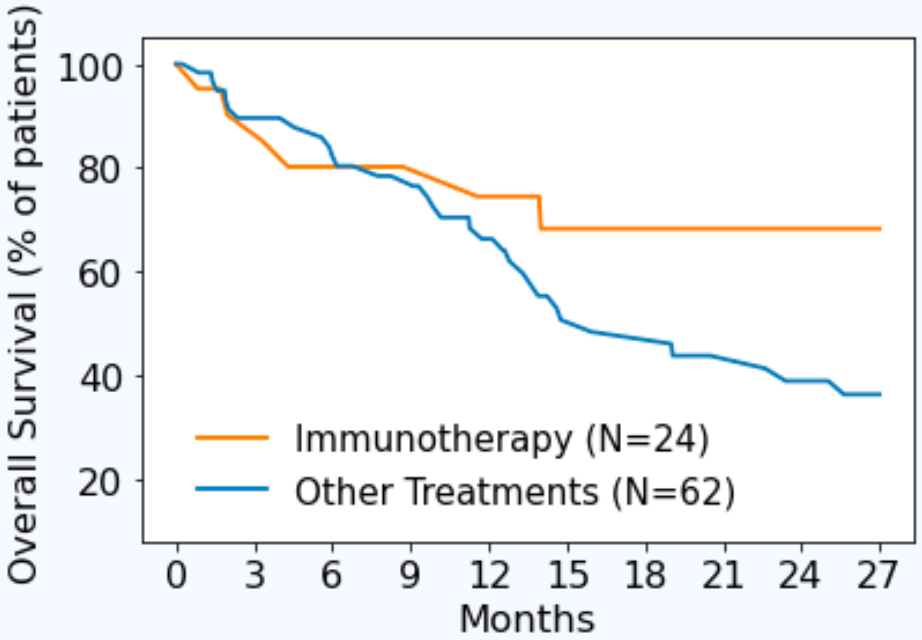
Example: APC mutation → better immunotherapy response in bladder cancer patients

patients on immunotherapy



APC is a tumor suppressor

patients w/ APC mutation



interaction effect

$$\text{Survival} \sim \beta_0 \cdot \text{confounders} + \beta_g \cdot \text{genotype} + \beta_t \cdot \text{treatment} + \beta \cdot \text{genotype} \cdot \text{treatment}$$

Example: APC mutation → better immunotherapy response in bladder cancer patients

Replicated interaction in randomized clinical trials.

920 bladder cancer patients on atezolizumab and chemotherapy.

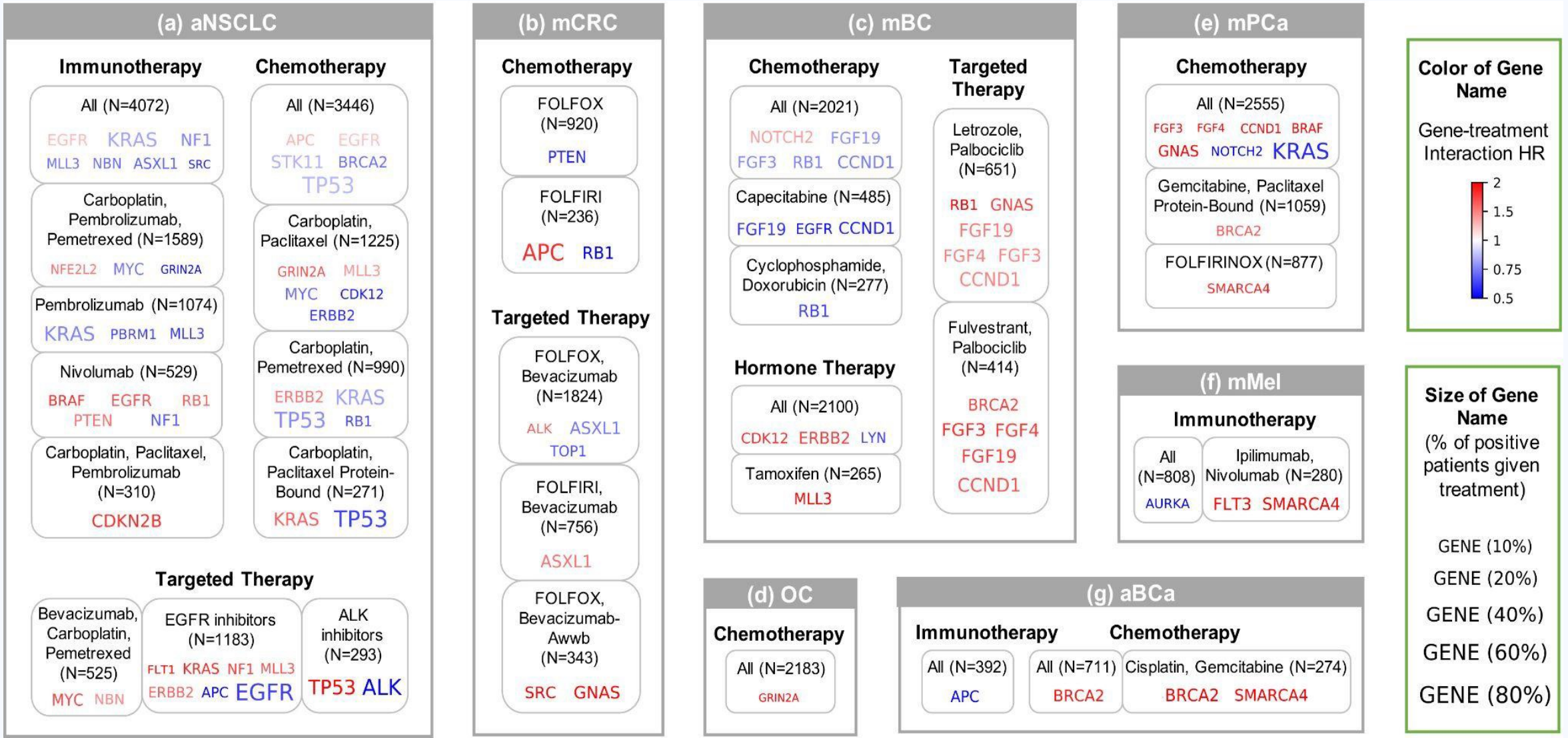
Foundation Medicine mutation profiling for everyone.

APC-immunotherapy interaction HR = 0.16 (0.03, 0.72)

$$\text{Survival} \sim \beta_0 \cdot \text{confounders} + \beta_g \cdot \text{genotype} + \beta_t \cdot \text{treatment} + \beta \cdot \text{genotype} \cdot \text{treatment}$$

458 mutation-treatment interactions

Only <60 interactions were previously known. Our FDR < 5% (Liu et al. Nat. Med. 2022)



Summary

Use GenAI + high quality real-world data to computationally emulate expensive studies.

Validated w/ clinical trials data

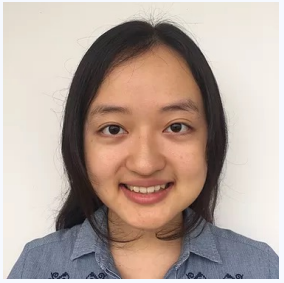
Applications:

- Data-driven (more inclusive) clinical trial design
- New biomarkers predict treatment outcomes
- Many more!

Refs: Liu et al. Nature 2021; Liu et al. Nature Med. 2022
www.precision-cancer.org

Acknowledgment

Ruishan Liu Shemra Rizzo Ryan Copping



Genentech: Marius Garmhausen, Sam Whipple, Navi Pal, Arturo Pineda, Michael Lu, Lisa Wang

Stanford: Sarah Waliany, Joel Neal, Zhi Huang

Support: Emerson, Sloan Fellowship NSF CAREER, Genentech, Google

Biography

Clinical Business Development Executive

Advisor on clinical development strategy with clients developing interventional, implantable devices as well as software based

---

- Former Director, LifeSciences Strategy and Research at Arterys, now Tempus
- Consults on validation of clinical evidence, model deployment, and clinical trial applications
- 10+ Years supporting medical image and wearable device data acquisition and analysis in clinical trials, primarily device focused
- Clinical Associate Member European Society of Radiology (ESR) and the Society of NeuroInterventional Surgery (SNIS)

Framework for Reference

Clinical trial application resides in one of two prominent frameworks.

Generative Pre-trained Transformer (GPT)

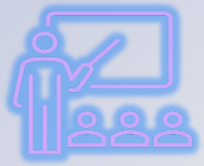
VS

Generative Adversarial Network (GAN)

GPT Applications

Start-up

- Site Identification
- Document Support
- Training
- Programming

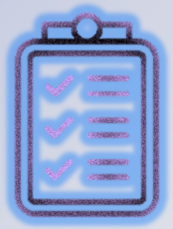


Enrollment / Procedure

- Subject Engagement
- Procedural Guidance
- Randomization

Follow-up

- Subject Engagement
- Supplemental Reporting
  - Clinician
  - Safety
  - Monitoring



Close Out

- TLF Development
- Reporting
- Summary Support

GPT Efficiency Example: Documentation Support

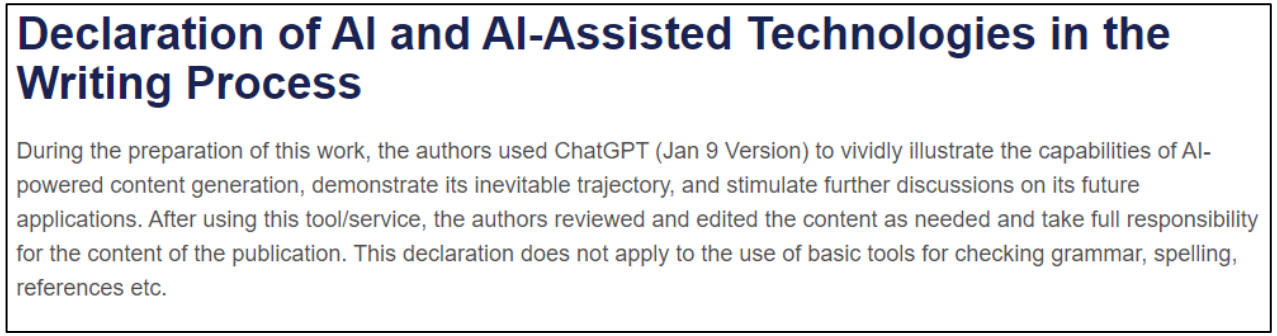
JACR Journal of the American College of Radiology

ARTICLE IN PRESS

OPINION

New Horizons: The Potential Role of OpenAI's ChatGPT in Clinical Radiology

Ahmed Ismail, BA, Nima S. Ghorashi, BS, Ramin Javan, MD



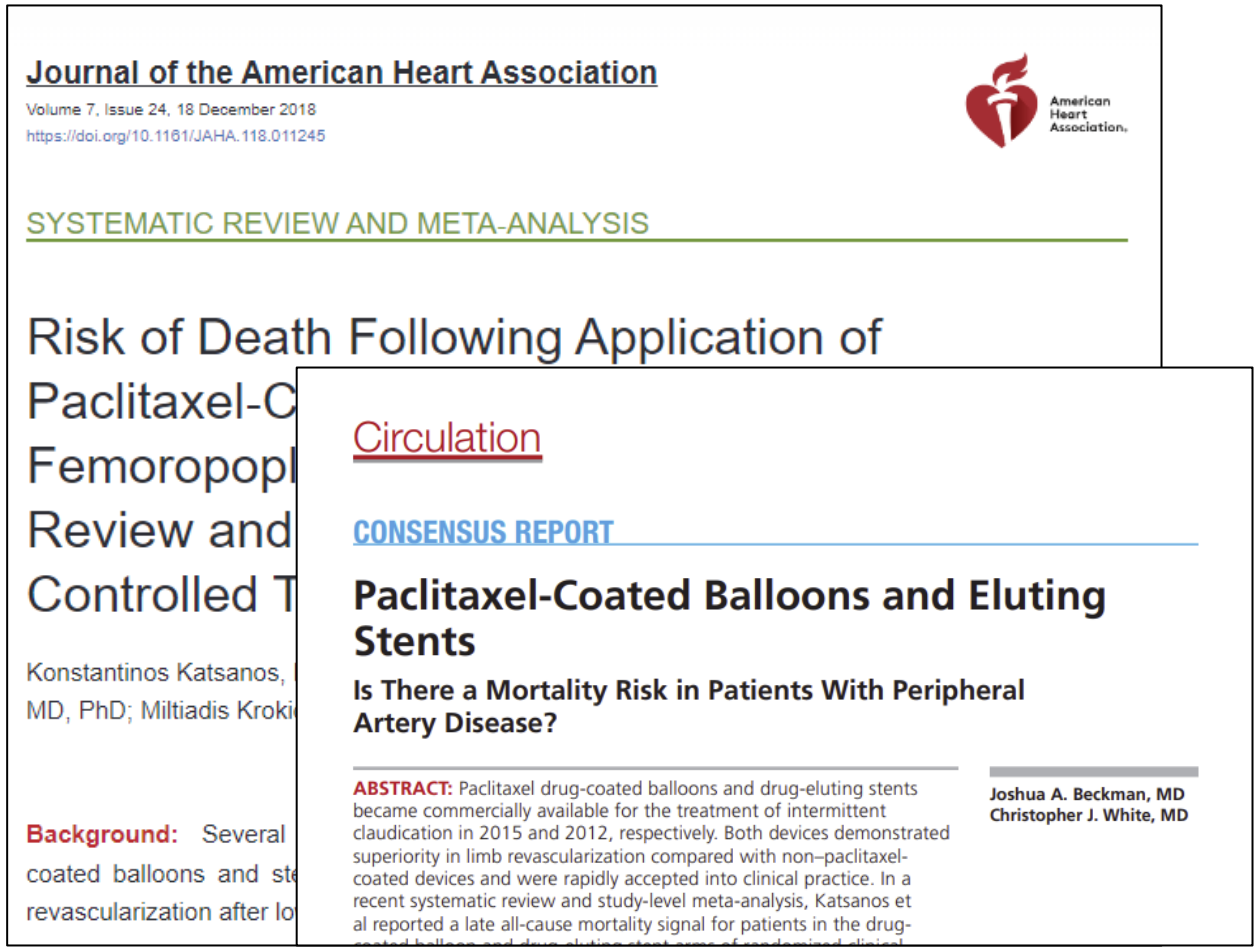
Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT (Jan 9 Version) to vividly illustrate the capabilities of AI-powered content generation, demonstrate its inevitable trajectory, and stimulate further discussions on its future applications. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication. This declaration does not apply to the use of basic tools for checking grammar, spelling, references etc.

Case Study: ChatGPT et al

- JACR Publication on ChatGPT in Radiology
- Article partially written by ChatGPT. Author time efficiency
- Example of Study Documentation Support, that can be applied to regulatory documents or clinical trial reports utilizing ChatGPTs Application Programming Interface for any software

GPT Efficiency Example for Statistics



Journal of the American Heart Association

Volume 7, Issue 24, 18 December 2018

https://doi.org/10.1161/JAHA.118.011245

SYSTEMATIC REVIEW AND META-ANALYSIS

Risk of Death Following Application of Paclitaxel-C
Femoropopl
Review and
Controlled T

Konstantinos Katsanos,
MD, PhD; Miltiadis Kroki

Background: Several
coated balloons and ste
revascularization after lo

Circulation

CONSENSUS REPORT

Paclitaxel-Coated Balloons and Eluting Stents

Is There a Mortality Risk in Patients With Peripheral Artery Disease?

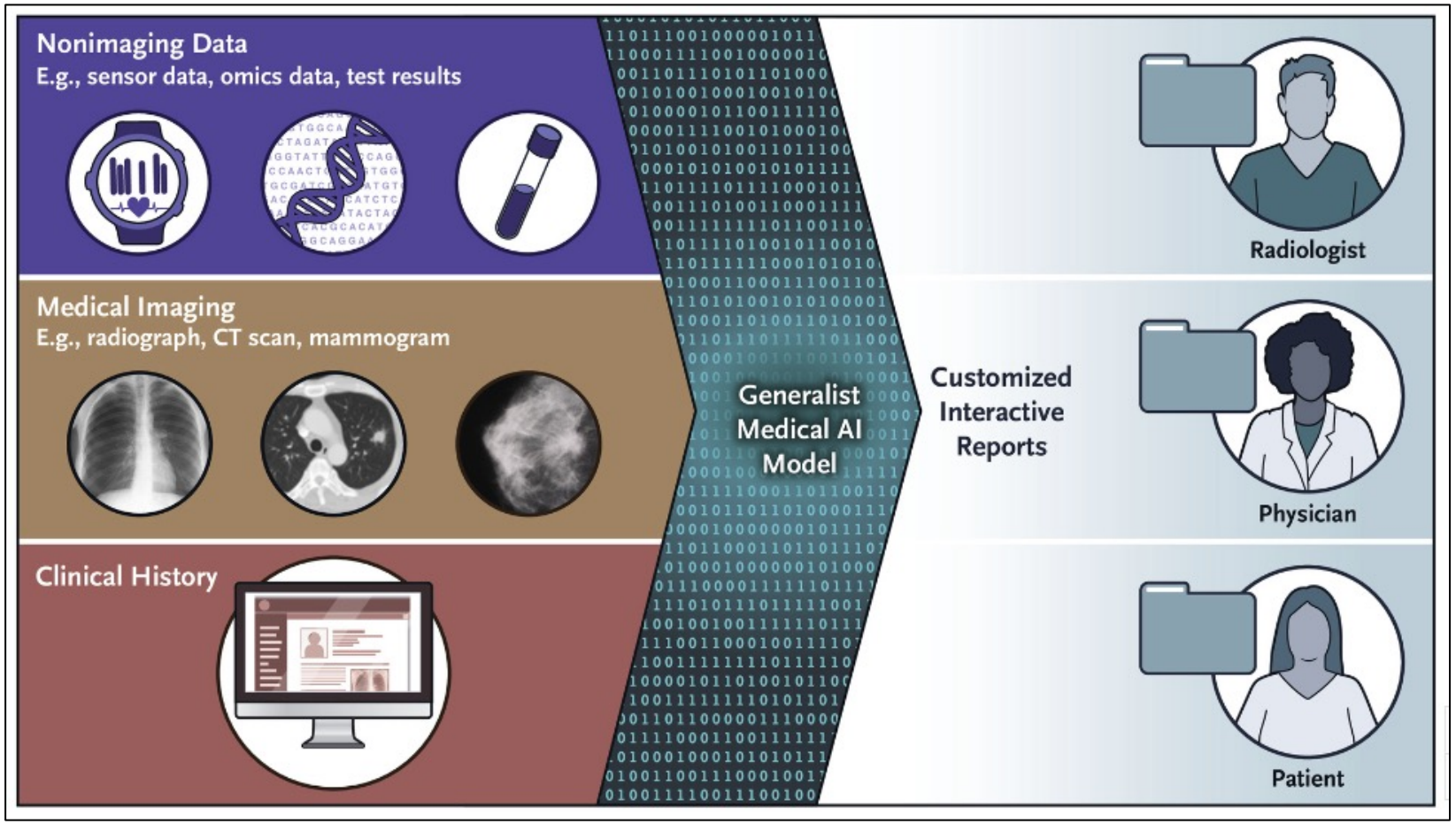
ABSTRACT: Paclitaxel drug-coated balloons and drug-eluting stents became commercially available for the treatment of intermittent claudication in 2015 and 2012, respectively. Both devices demonstrated superiority in limb revascularization compared with non–paclitaxel-coated devices and were rapidly accepted into clinical practice. In a recent systematic review and study-level meta-analysis, Katsanos et al reported a late all-cause mortality signal for patients in the drug-

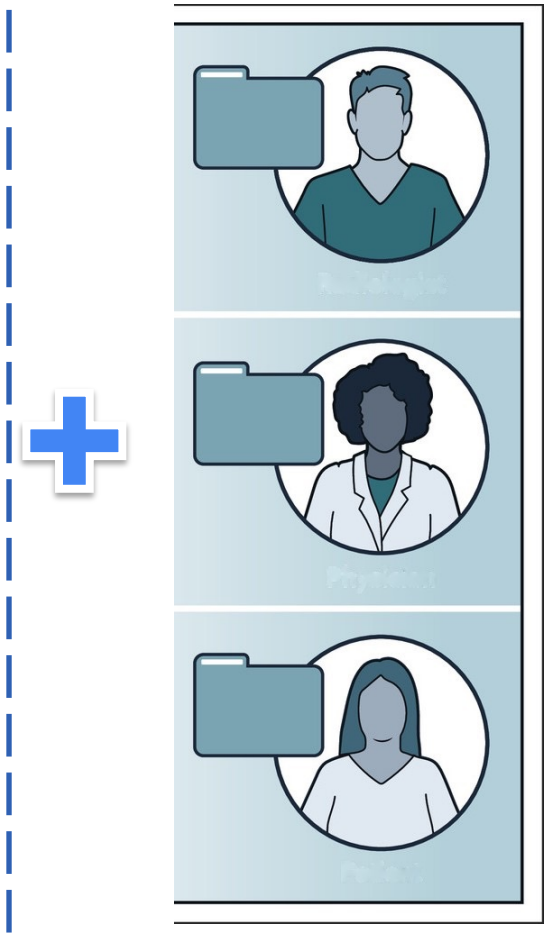
Joshua A. Beckman, MD
Christopher J. White, MD

Case Study: PCT Meta Analysis

- 28 Randomized, Controlled Trials
- Patient-Level Analysis Conducted by NAMSA & VIVA Physicians
- Required roughly ~250 hours of programming and analysis
- GPT model with EMR, publication, and supplemental input would reduced time by 20%
- If the data was harmonized/standardized, the potential would be even greater

Data Standardization = Less Manual Analyzation = > Efficiencies





Study Sponsors

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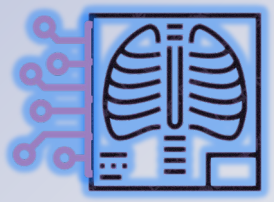
CROs

Rajpurkar et al, Current and Future State of AI Interpretation of Medical Images, NEJM 2023; 388:1981-1990

GAN Applications



Synthetic Data Generation

- Sample Size Scaling
- Data Diversity
- PHI Avoidance

Data Augmentation

- Image Enhancement
  - Reconstruction
  - Subtraction
- Data Imputation

Virtual Analysis

- Clinical Trial Simulation
- Virtual Patients
- Risk Stratification

Synthetic Lung Nodule X-Ray Example

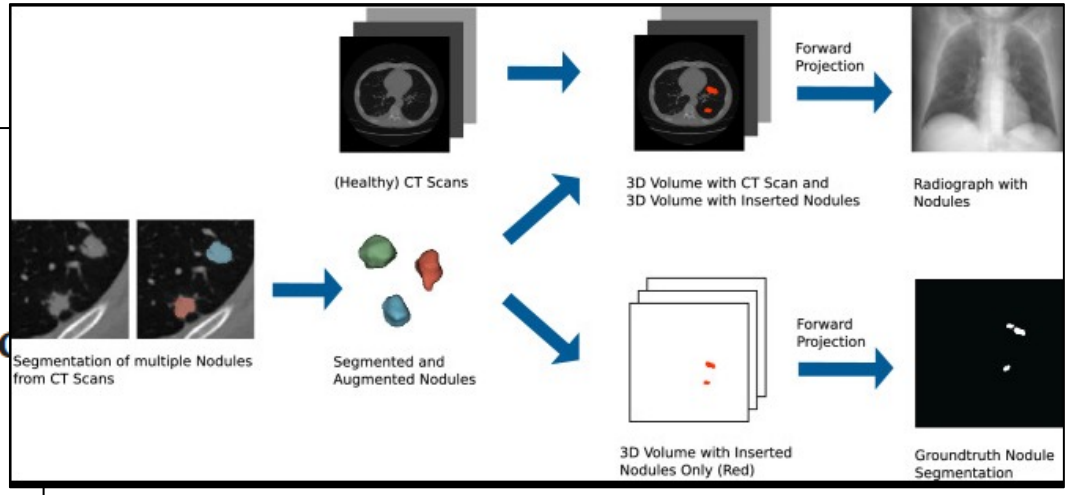
Comparative Study > Sci Rep. 2021 Aug 4;11(1):15857. doi: 10.1038/s41598-021-94750-z.

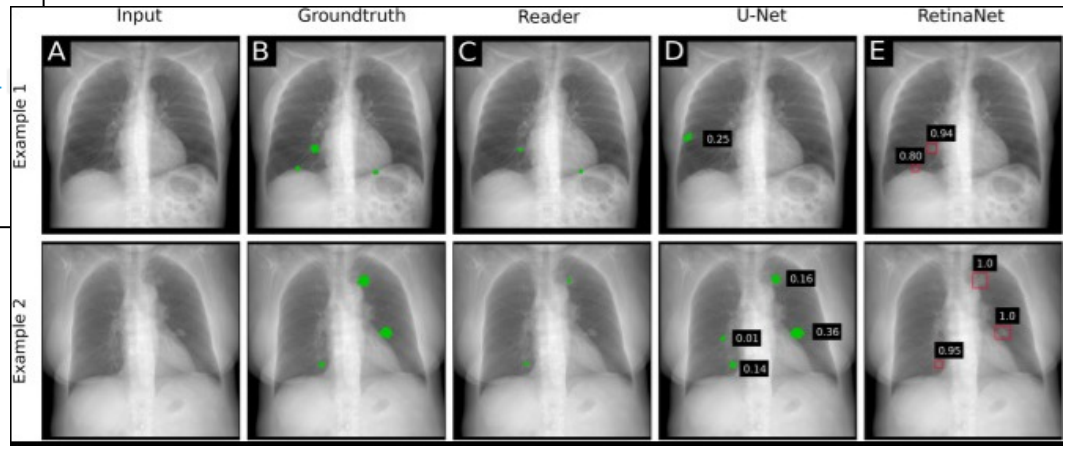
Lung nodule detection in chest X-rays using synthetic ground-truth data comparing CNN-based diagnosis to human performance

Manuel Schultheiss [1 2], Philipp Schmette [3], Jannis Bodden [4], Juliane Aichele [4], Christina Müller-Leisse [4], Felix G Gassert [4], Florian T Gassert [4], Joshua F Gawlitza [4], Felix C Hofmann [4], Daniel Sasse [4], Claudio E von Schacky [4], Sebastian Ziegelmayer [4], Fabio De Marco [3], Bernhard Renger [4], Marcus R Makowski [4], Franz Pfeiffer [3 4], Daniela Pfeiffer

Affiliations + expand

PMID: 34349135 PMCID: PMC8339004 DOI: 10.1038/s41598-021-94750-z





Pros	Cons
< Time	
< Cost	
+ Trial Designs	Generator Bias

Where do we stand?

- GPT Framework will definitely enable trial efficiencies and decrease costs
- GANs are already helping determine appropriate interventions and study designs through simulation, and they have the ability to power studies with less subjects and visits, but consensus on data transparency is undefined
- Generative AI will not replace functional service roles or provider roles in clinical trials, but will supplement resources to more efficiently accomplish tasks
- Subject participation and input is still required

Thank you for joining us!

Questions? Contact us at Info@NyquistAI.com

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