

Making clinical trials more efficient and inclusive with real-world data and AI



James Zou
Stanford University

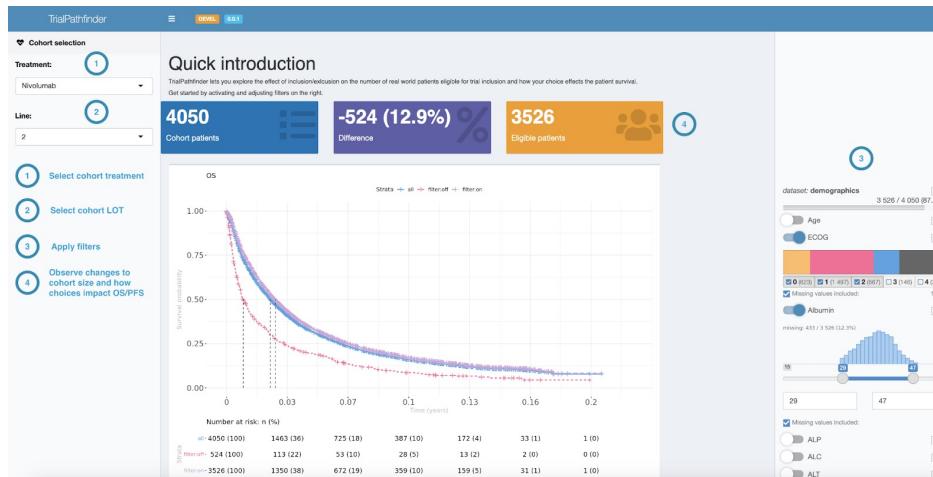
AI to make clinical trials more inclusive

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



Ruishan Liu



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

- Often copied from previous trials
- Modified by clinicians by experience

Protocol draft: Ipatasertib

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 – $1500/\mu\text{L}$
 - Hemoglobin ≥ 89 g/dL
 - Platelet count $\geq 100 \times 10^9/\text{L}$
 - Serum albumin ≥ 3 g/dL
- ~~Adequate renal function including creatinine $< 2 \times \text{ULN}$ unless related to the disease~~

e? [REDACTED] 4:49 AM May 28 Resolve

Safety: Can we change to 1000/microL

From imported document

e? [REDACTED] {MDSB~South ... 8:59 AM Jun 18

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

From imported document

e? [REDACTED] 6:56 AM Jun 24

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

Eligibility criteria often anecdotal

- Often copied from previous trials
- Modified by clinicians by experience

Protocol draft: Ipatasertib

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~~/ μ L
 - Hemoglobin ≥ 89 g/dL
 - Platelet count $\geq 100 \times 10^9$ /L
 - Serum albumin ≥ 3 g/dL
- Adequate renal function including creatinine $< 2x$ ULN unless related to the disease

e? [REDACTED]... 4:52 AM May 28 Resolve :

Safety: Can we change to 8g/dL

From imported document

e? [REDACTED] {MDSB~South ... 9:02 AM Jun 18

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

From imported document

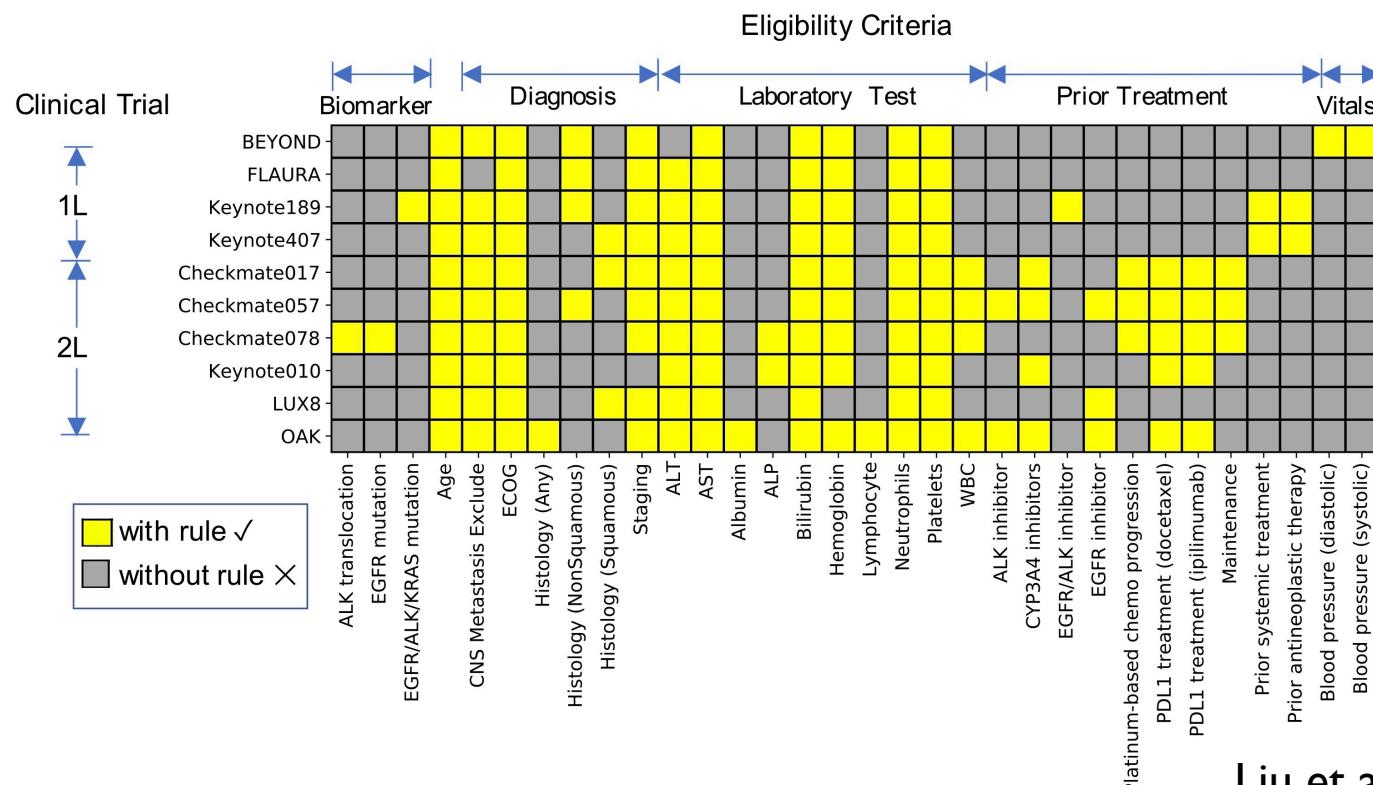
e? [REDACTED] {MNAJ~Sout... 6:03 AM Jun 25

Christine to follow-up

From imported document

Eligibility criteria often anecdotal

- Often copied from previous trials
- Modified by clinicians by experience



The 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.

National cancer institute: Report of the national cancer institute clinical trials program review group. http://deainfo.nci.nih.gov/advisory/bsa/bsa_program/bsactprgmin.pdf

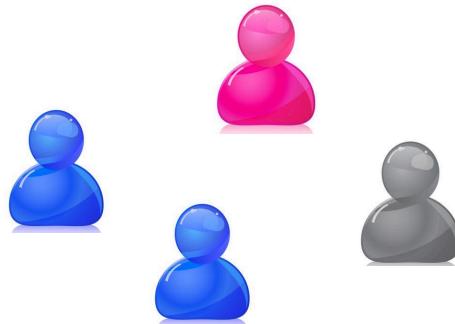
Using EHR to emulate a trial

Trial = (treatment, control,
Bilirubin < 1)

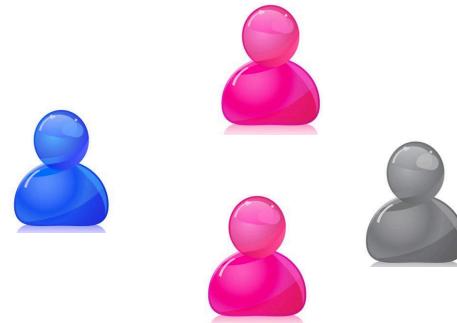


Flatiron >200k
cancer patients EHR

Patients who took **treatment**



Patients who took **control**



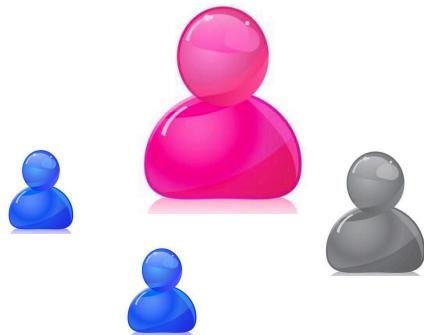
Using EHR to emulate a trial

Trial = (treatment, control,
Bilirubin < 1)

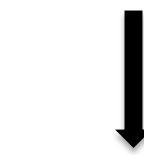


Flatiron >200k
cancer patients EHR

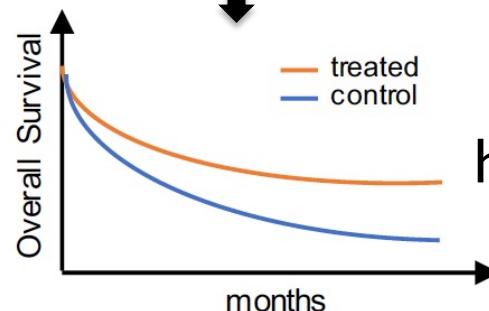
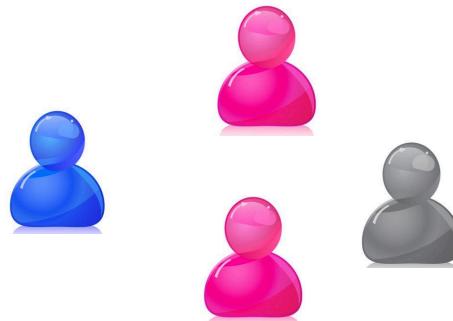
Patients who took **treatment**



match
distributions



Patients who took **control**



hazard ratio

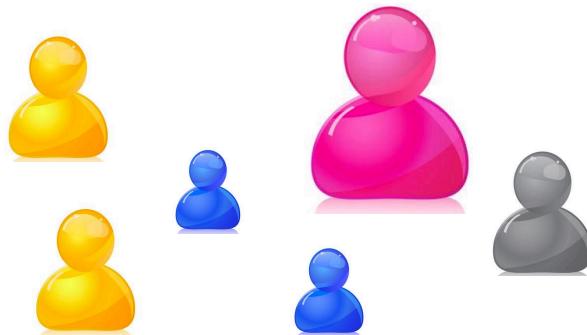
Using EHR to evaluate trial eligibility

Trial = (treatment, control,
~~Bilirubin < 1, Bilirubin < 2~~)



Flatiron >200k
cancer patients EHR

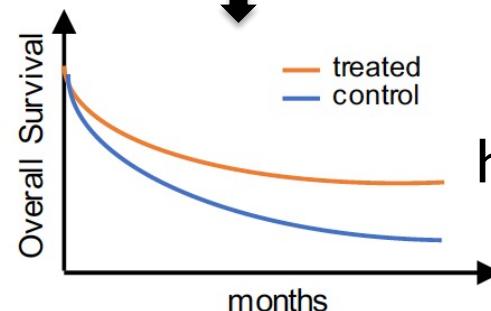
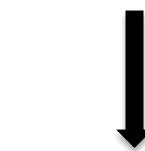
Patients who took **treatment**



Patients who took **control**



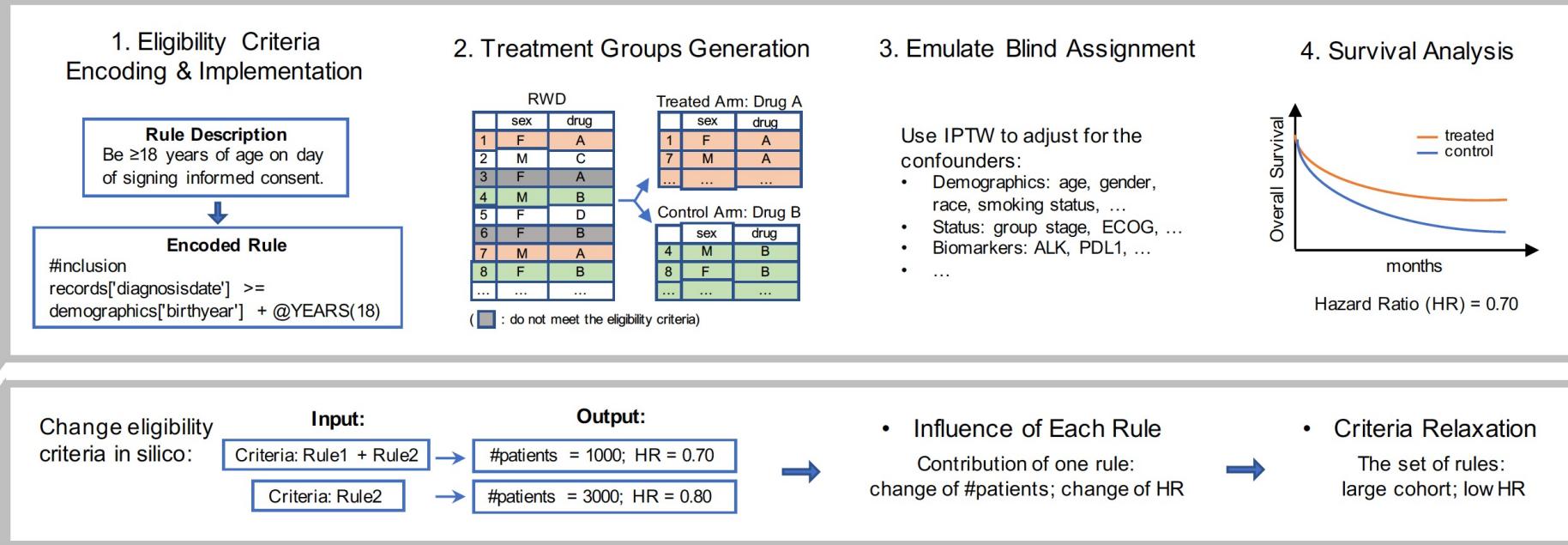
match
distributions



hazard ratio

Trial Pathfinder uses EHR + AI to design eligibility criteria

Trial Emulation
Analysis



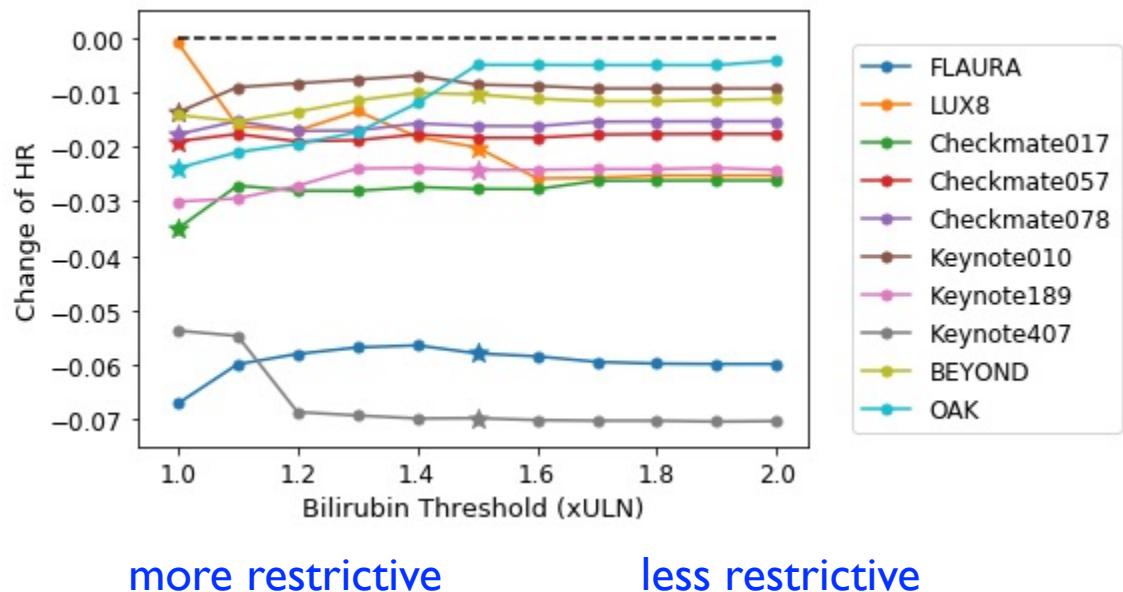
Emulates millions of trials with different eligibility rules.
Uses Flatiron database of >200k cancer patients.
Uses Shapley value to quantify the impact of each eligibility rule.

Case study: relaxing bilirubin threshold

Original eligibility criteria

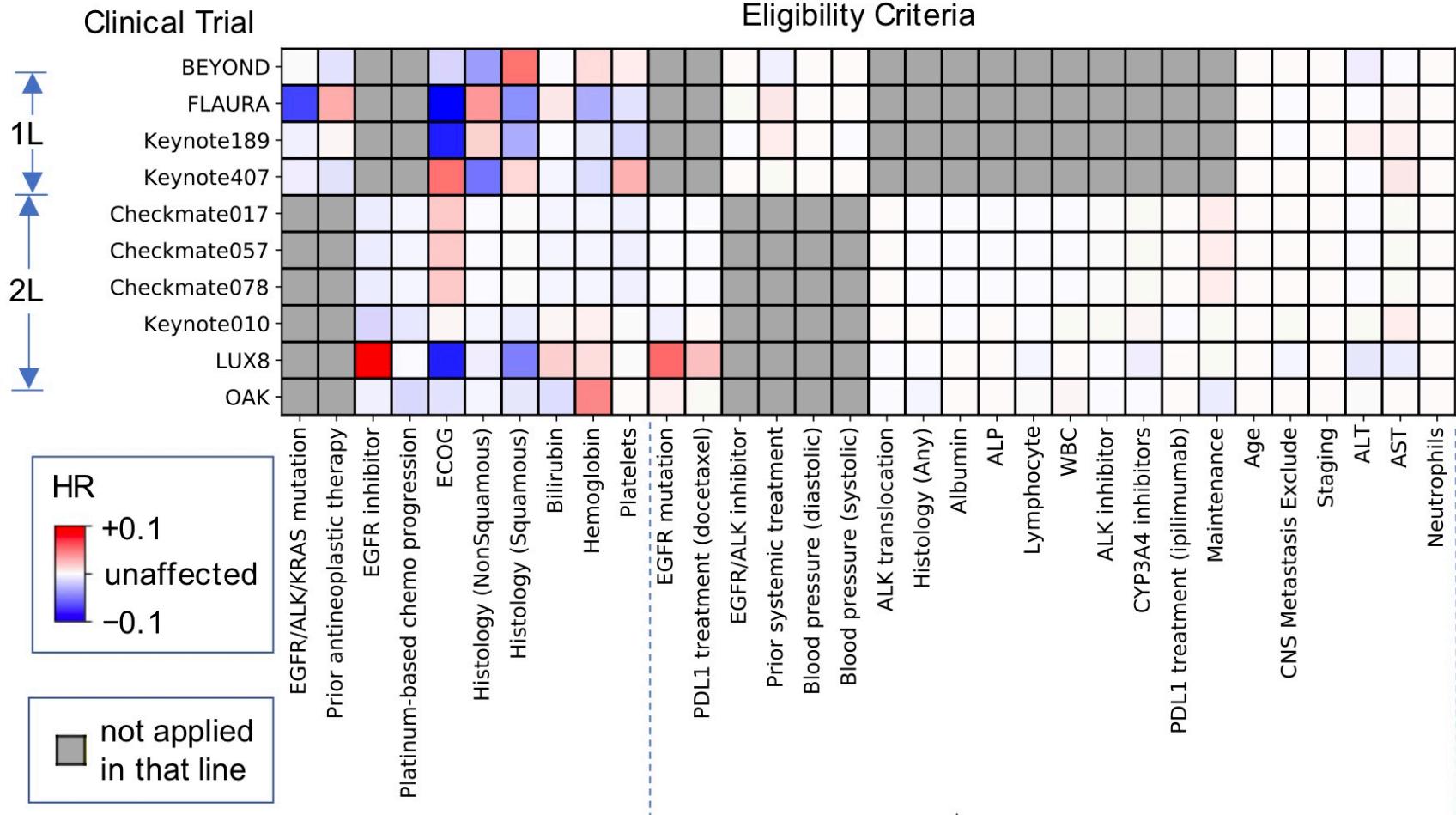
Trial Name	Bilirubin threshold
FLAURA	$\leq 1.5 \times \text{ULN}$
LUX8	$\leq 1.5 \times \text{ULN}$
Checkmate017	$\leq 1.0 \times \text{ULN}$
Checkmate057	$\leq 1.0 \times \text{ULN}$
Checkmate078	$\leq 1.0 \times \text{ULN}$
Keynote010	$\leq 1.0 \times \text{ULN}$
Keynote189	$\leq 1.5 \times \text{ULN}$
Keynote407	$\leq 1.5 \times \text{ULN}$
Beyond	$\leq 1.5 \times \text{ULN}$
OAK	$\leq 1.0 \times \text{ULN}$

Emulated trials



Similar for exclusion based on platelets, hemoglobin and alkaline.

Data-driven evaluation of eligibility rules



Data-driven criteria doubles # eligible patients and reduces hazard

Trial Name	Original Trial Criteria			Fully Relaxed Criteria		Data-driven Criteria		
	#Criteria	#Patients	HR	#Patients	HR	#Criteria	#Patients	HR
FLAURA	10	2277	0.81	3819	0.82	4	2546	0.75
LUX8	11	129	0.65	1350	0.81	5	141	0.58
Checkmate017	17	523	0.67	4900	0.71	7	4085	0.71
Checkmate057	19	792	0.75	4900	0.71	9	2594	0.66
Checkmate078	18	1509	0.74	4900	0.71	9	3348	0.68
Keynote010	13	806	0.56	1950	0.51	1	1948	0.51
Keynote189	15	4066	0.88	8818	0.94	7	4595	0.85
Keynote407	13	2031	1.13	10437	1.07	4	9173	1.04
BEYOND	12	2902	1.09	9310	1.14	4	3043	1.08
OAK	19	493	0.88	1288	0.87	6	620	0.80
Average	15	1553	0.82	5167	0.83	6	3209	0.77

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

Discussion

- Real-world data + AI make trials more inclusive.
- Validated using clinical trial data and other cohorts.
- Insights can be adopted to new drugs and other diseases.



Thanks!

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](#)

Ruishan Liu



Shemra Rizzo



Ryan Copping



Marius Garmhausen, Sam Whipple, Navi Pal, Arturo Pineda, Michael Lu, Brandon Arnieri, Bill Capra