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AI for evidence-based covariate adjustment in clinical trials

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1- Covariate adjustment

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Covariate adjustment can increase the statistical power of randomized clinical trials

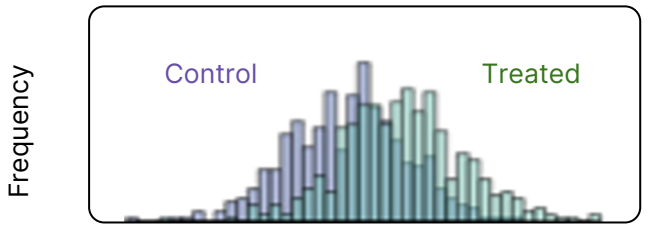
Randomized control trials (RCT)

- → The goal of RCT is to test the presence of a treatment effect (i.e., null hypothesis is **b1**=0)
- → Y = outcome
- → T = Treatment allocation
- → Prognostic covariate X that is associated with Y

↳ Adjusting the efficacy analysis on **covariate X** allows researchers to make a more precise estimation of the treatment effect **b1** and increase the statistical power of the trial.

Original

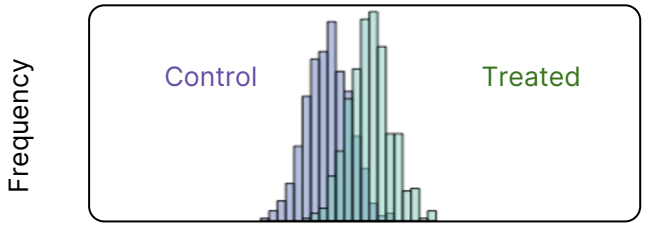
Y = b0 + **b1**T + eps*



Unadjusted outcomes (overlapping)

Adjusted

Y = b0 + **b1**T + b2X+ eps'



Adjusted outcomes (more separated)

*eps: residual noise

A metaphor for covariate adjustment: noise on the subway

↳ Corrects clinical outcomes for biological “noise” to clarify drug response “signal”

Listening to music on the subway		Enhancing the measurement of treatment effect
Music	⟷	Treatment effect
Subway background noise	⟷	Biological variability*
Increasing the music volume	⟷	Increasing the sample size
Noise cancelling headset	⟷	Adjusting on prognostic covariates

* Examples: comorbidities, ECOG, biological measures pre-treatment measures

Evidence-based covariate adjustment to improve trials

↳ Data external to the trial helps identify prognostic signal

Training data

CT-Scan[1] H&E Stains[2]

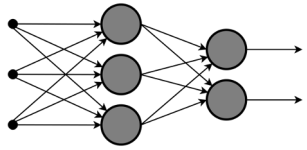
EHR/eCRF[3]

Train

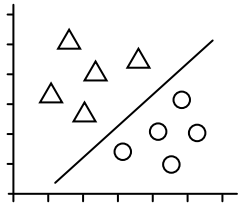
Train

Model

Learns pre-treatment covariates that predict patient outcomes



Combine image features to predict outcomes



Find most prognostic eCRF covariates

Apply

Apply

Trial data

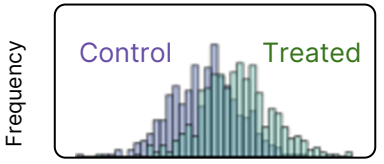
CT-Scan[1] H&E Stains

eCRF

Adjustment

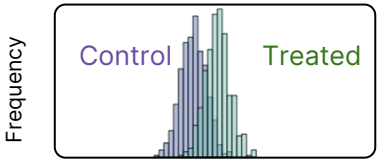
Use covariate model to remove pre-treatment effects from patient outcomes

Original



Unadjusted outcomes (overlapping)

Adjusted



Adjusted outcomes (more separated)

[1] CT-Scan: Computed tomography (CT) scan [2] H&E:hematoxylin and eosin stain [3] EHR/eCRF: Electronic Health Record/electronic Case Report Form

Case study: Owkin reduced p-value from 0.08 to 0.01 for a large phase III oncology trial by using covariate adjustment methods

At a glance

Covariate adjustment

Clinical data

Pharma partner

Context

A top-5 Pharma needed to reconsider a phase-3 trial that had failed to demonstrate superiority of its immunotherapy against the standard of care in an advanced cancer setting

Solution

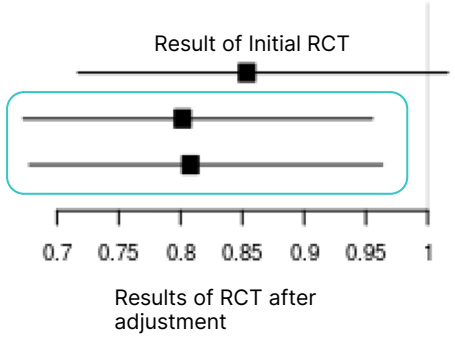
Method - We applied Owkin's machine-learning expertise to identify novel prognostic covariates from an *external dataset* in the same indication.

Efficacy analysis of the client's trial was adjusted based on these prognostic risk scores and/or on selected variables.

Results

Our tool enabled our Pharma partner to achieve a dramatic improvement in the statistical significance of the efficacy of their immunotherapy drug.

Adjustment	HR	95% CI	p-value
Original stratified analysis	0.86	[.72,1.03]	.08
Lasso + strat	0.80	[.67,.96]	.01
Selected variables + strat	0.81	[.68,.96]	.02



Covariate adjustment can derisk and accelerate trials

2- Determinants of power gains

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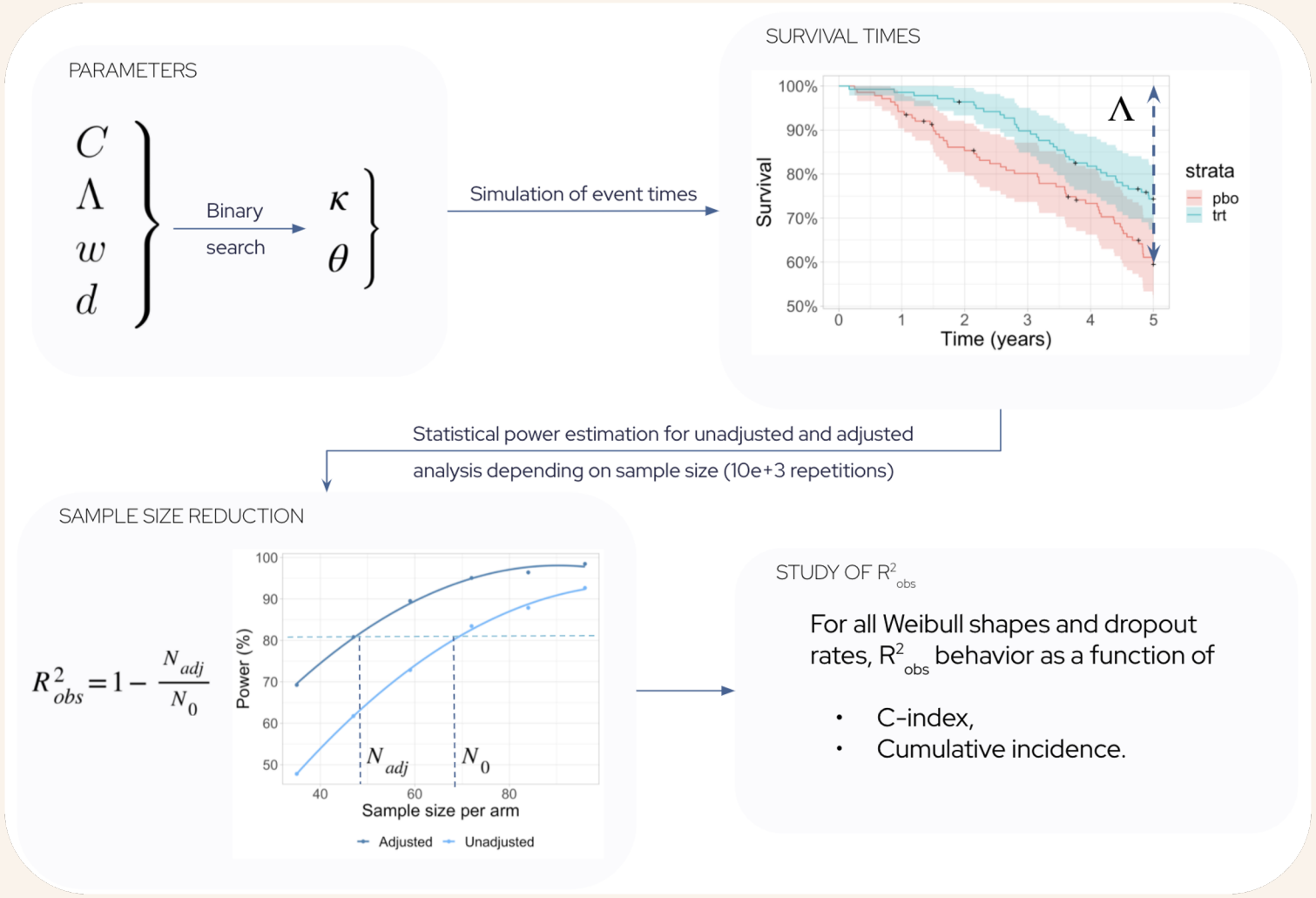
Simulation framework for evaluating impact of covariate adjustment

↳ Impact = sample size reduction for 80% statistical power

The Cox proportional model is assumed to hold

The main parameters are :

- C the c-index of the prognostic covariates
- Λ the cumulative incidence of the event in the placebo arm at the end of the trial
- Weibull shape *w*
- drop-out rate *d*



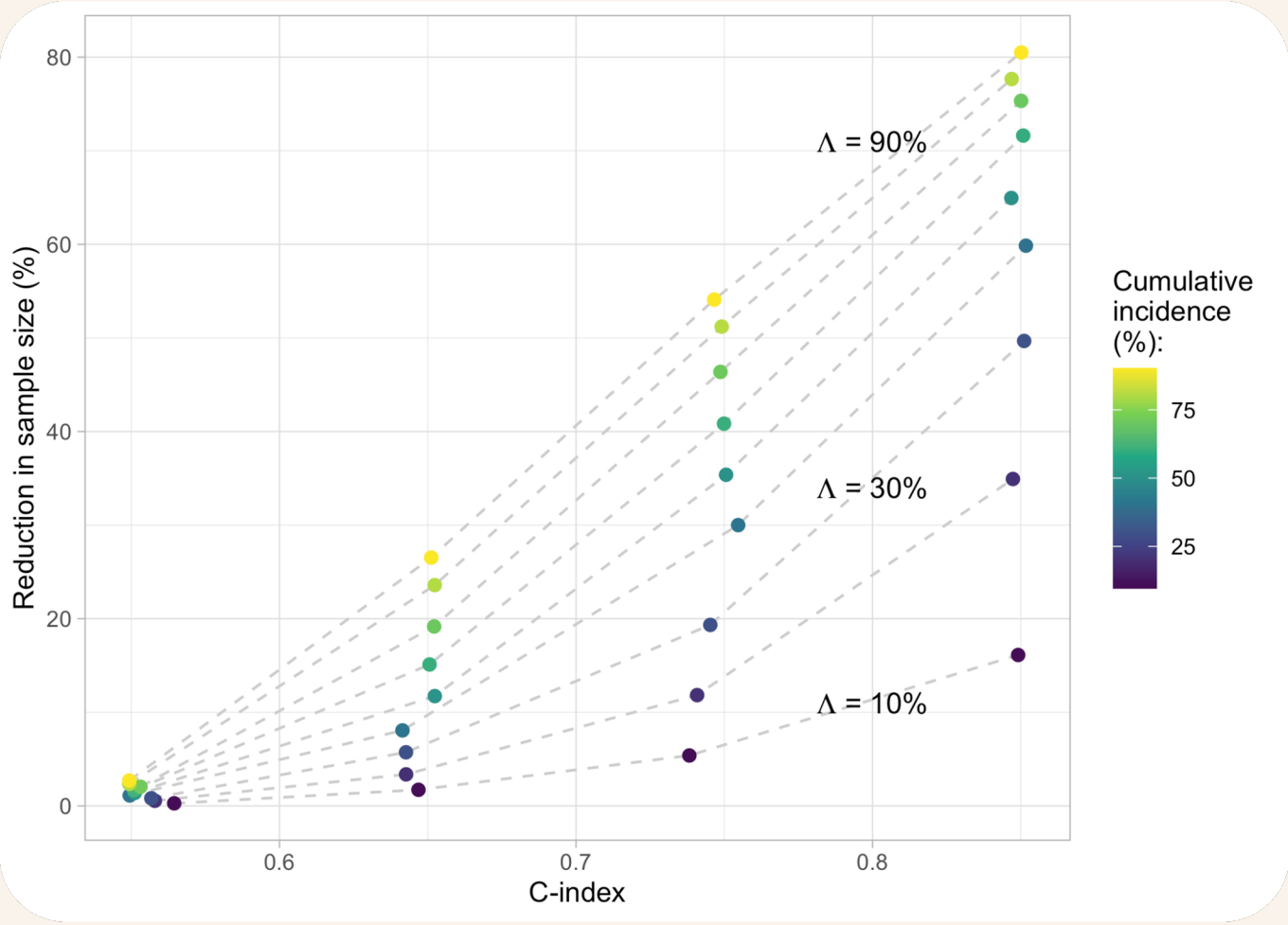
Results of the simulation study

↳ Impact = sample size reduction for 80% statistical power

In all settings (all tested treatment effects, Weibull shapes and dropout rates):

- ❏ Increase with C-index
- ❏ Increase with cumulative incidence **Λ**

→ Statistical power is a function of **Λ**, C and n



The impact of covariate adjustment is larger:

- when we identify all possible sources of prognostic signal
- for diseases with large proportion of events in trials e.g. metastatic cancer more than secondary cardiovascular disease

3- Broadening eligibility criteria

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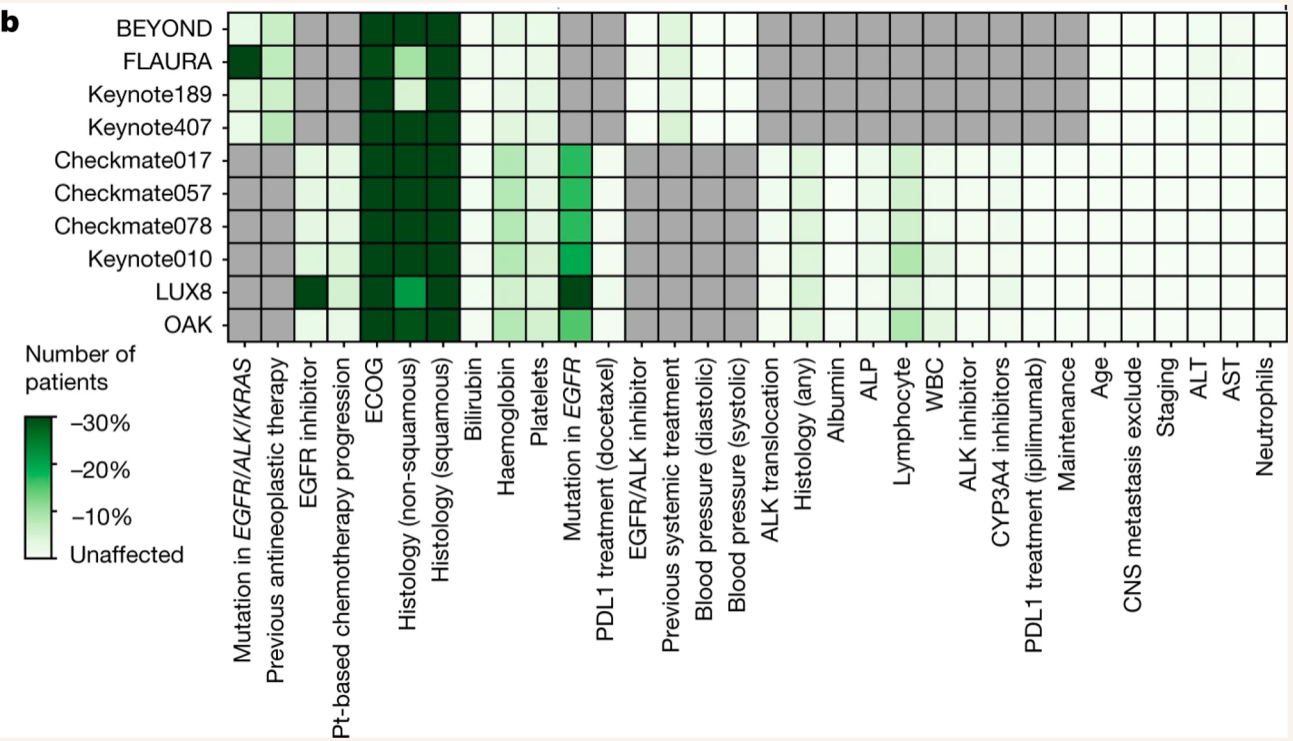
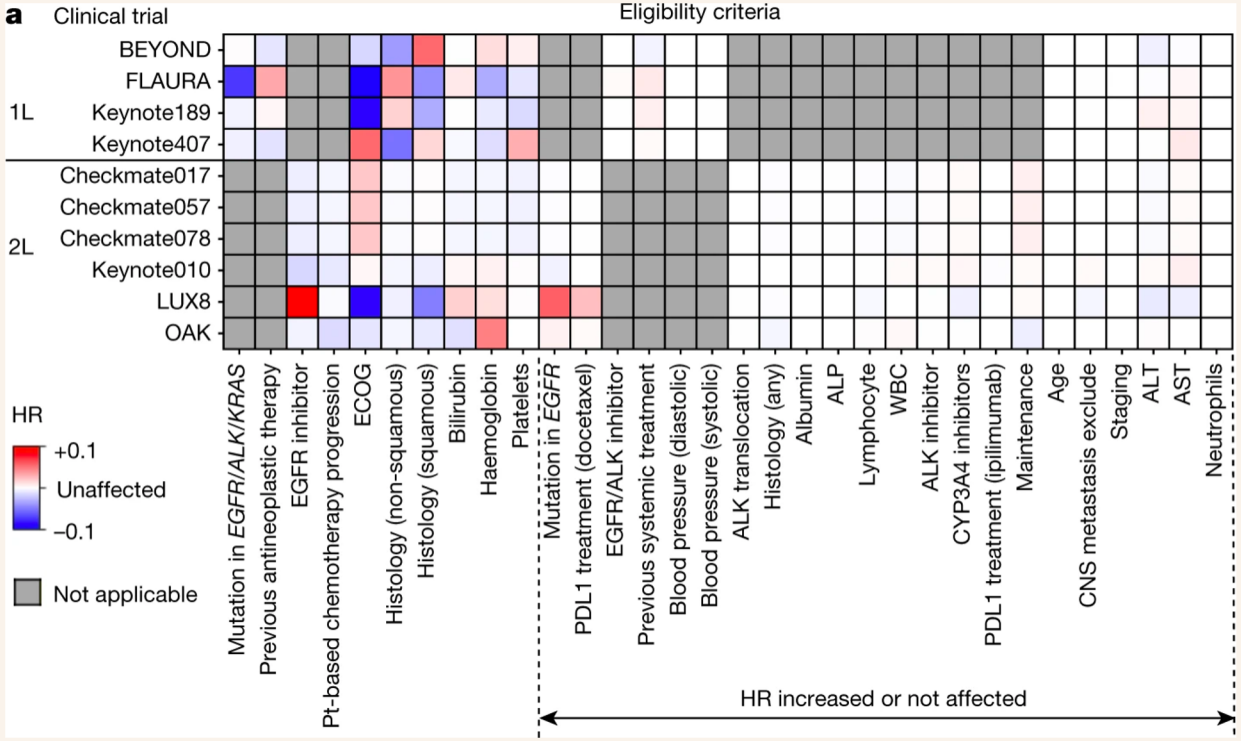
Eligibility criteria in clinical trials are too restrictive

Genentech researchers have shown using Flatiron health data that NSCLC trials could be much more inclusive while achieving their primary endpoint (Liu et al. *Nature* 2021).



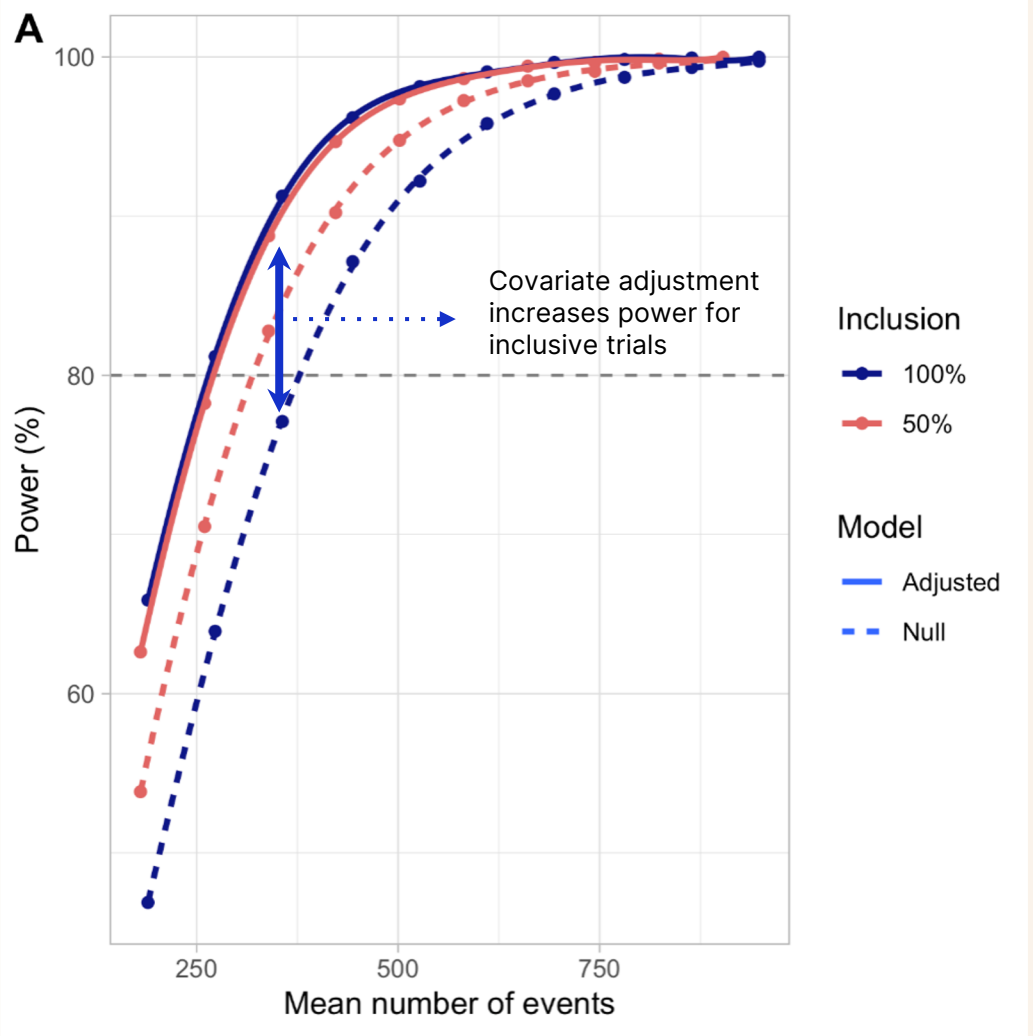


Covariate adjustment removes the incentive for strict eligibility criteria

Using restrictive eligibility criteria homogenizes the trial population and leads to an increase in power.

However, once we adjust on the variable used for inclusion, the inclusive or restrictive population have the same statistical power

↳ Evidence-based covariate adjustment can allow for broader eligibility criteria. This means **faster enrollment** and **better generalizability**



Better covariate adjustment allows for more inclusive trials

4-New covariates using deep learning on histological slides

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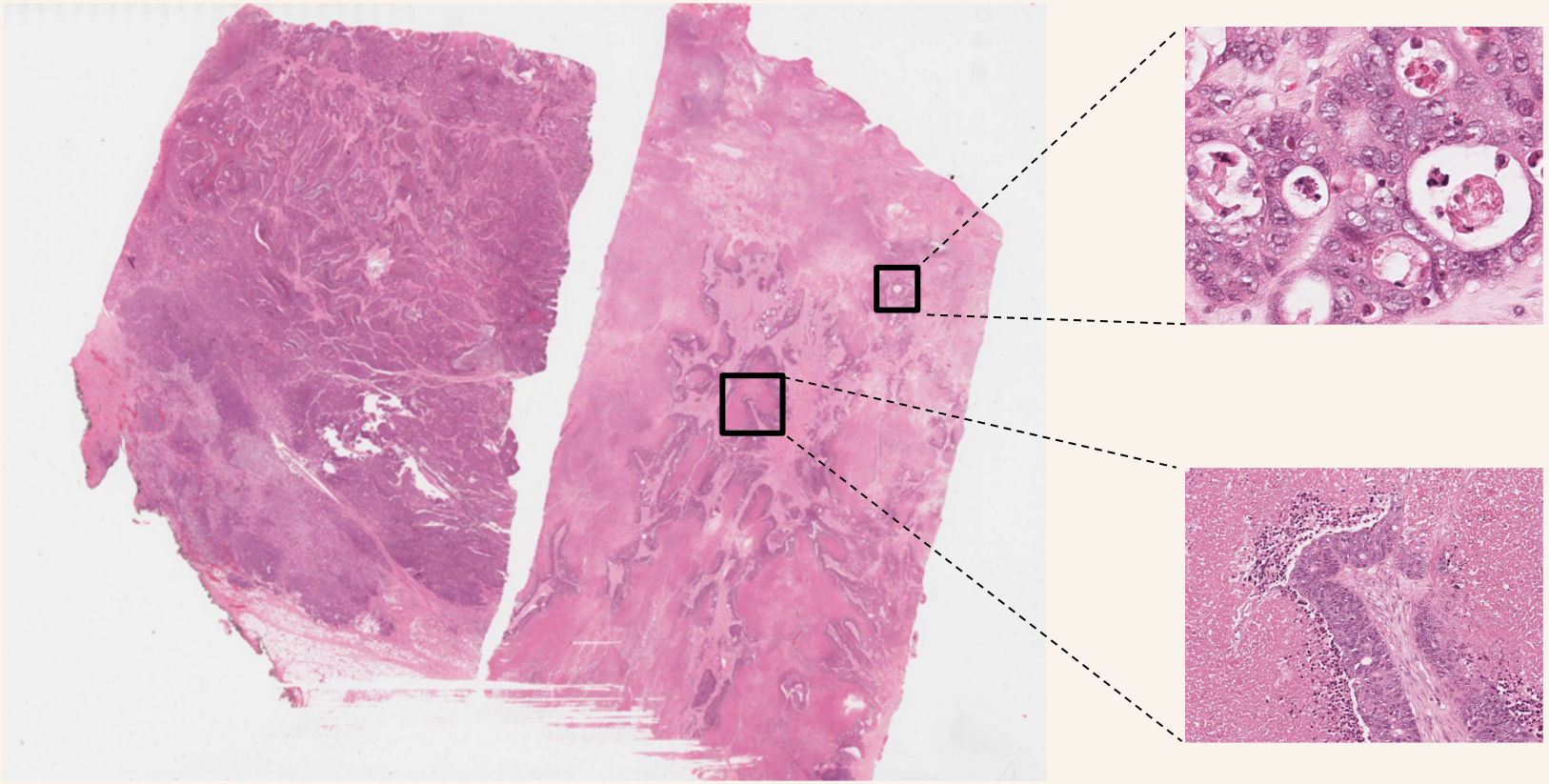
Digital pathology: the ideal playground for deep learning

Ultra-high dimensional data are contained in H&E slides

AI can help to process and better understand this vast amount of information



H&E slides

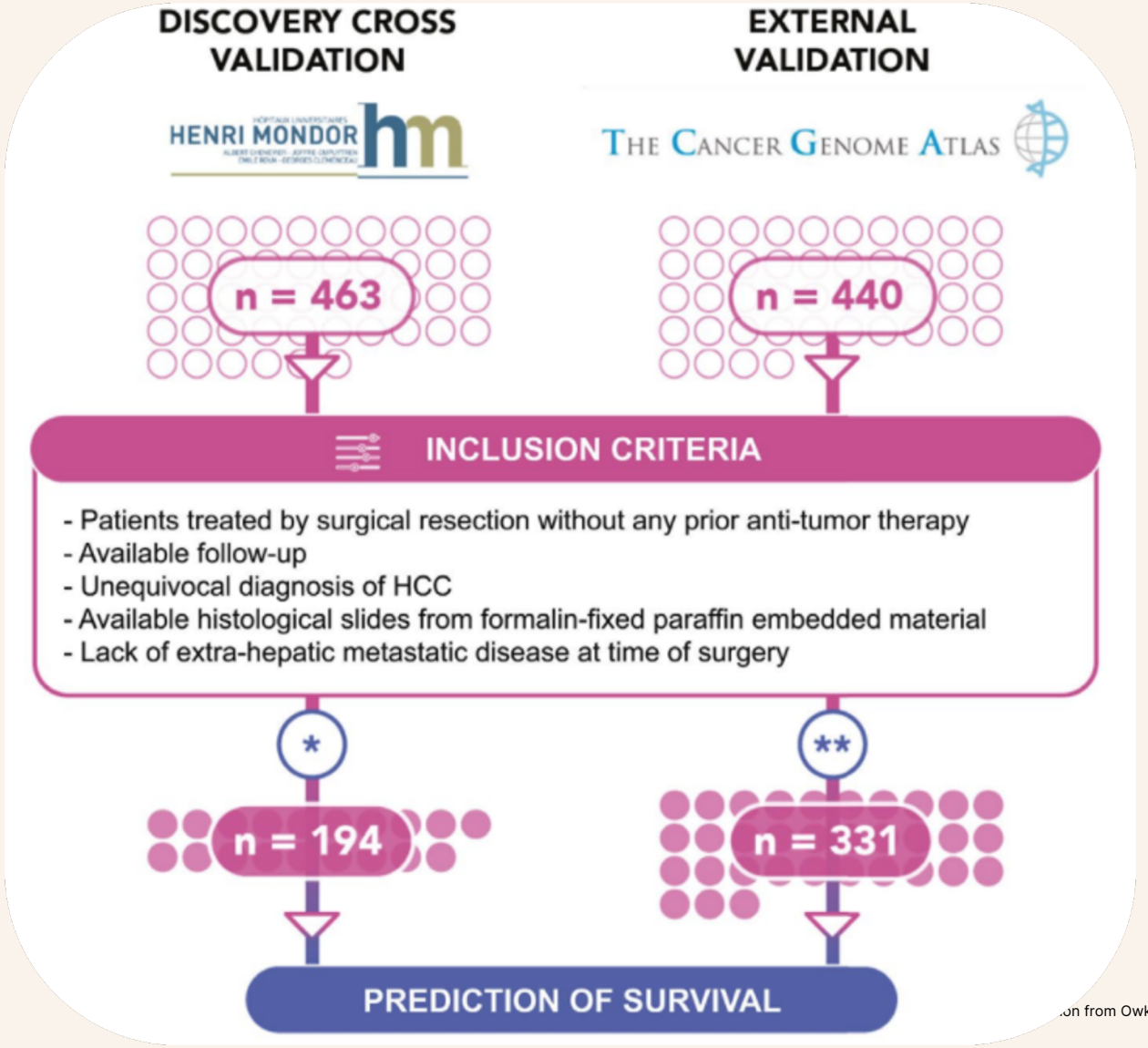
- Extracted from biopsy or resection pieces
- Commonly utilized throughout the patient journey
- Digitized and high dimensional data

each slide = 2GB file
contains approx
100k x 100k pixels

HCCnet: Deep learning prognostic model for resected hepatocellular carcinoma

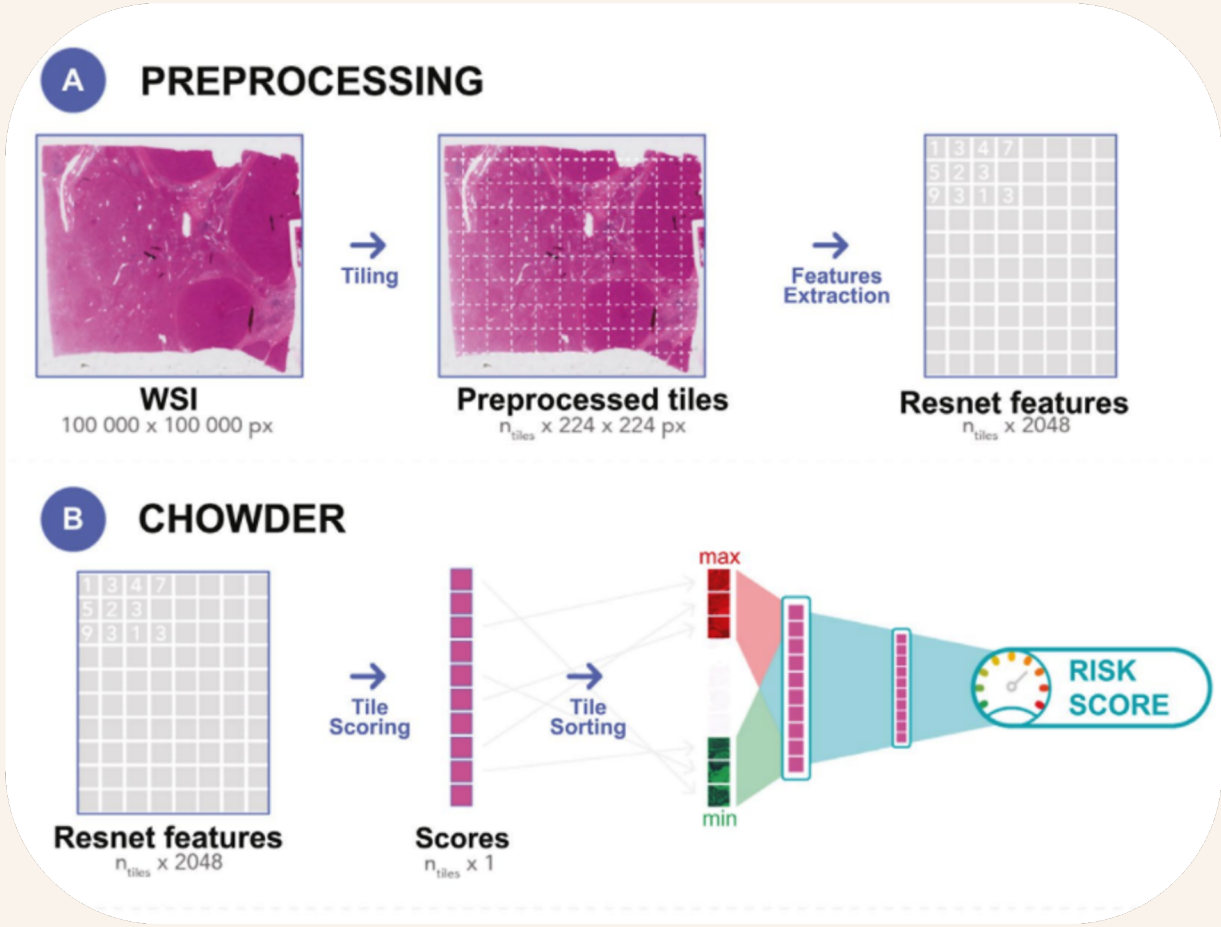
No adjuvant treatment exists for resected hepatocellular carcinoma despite unmet medical need

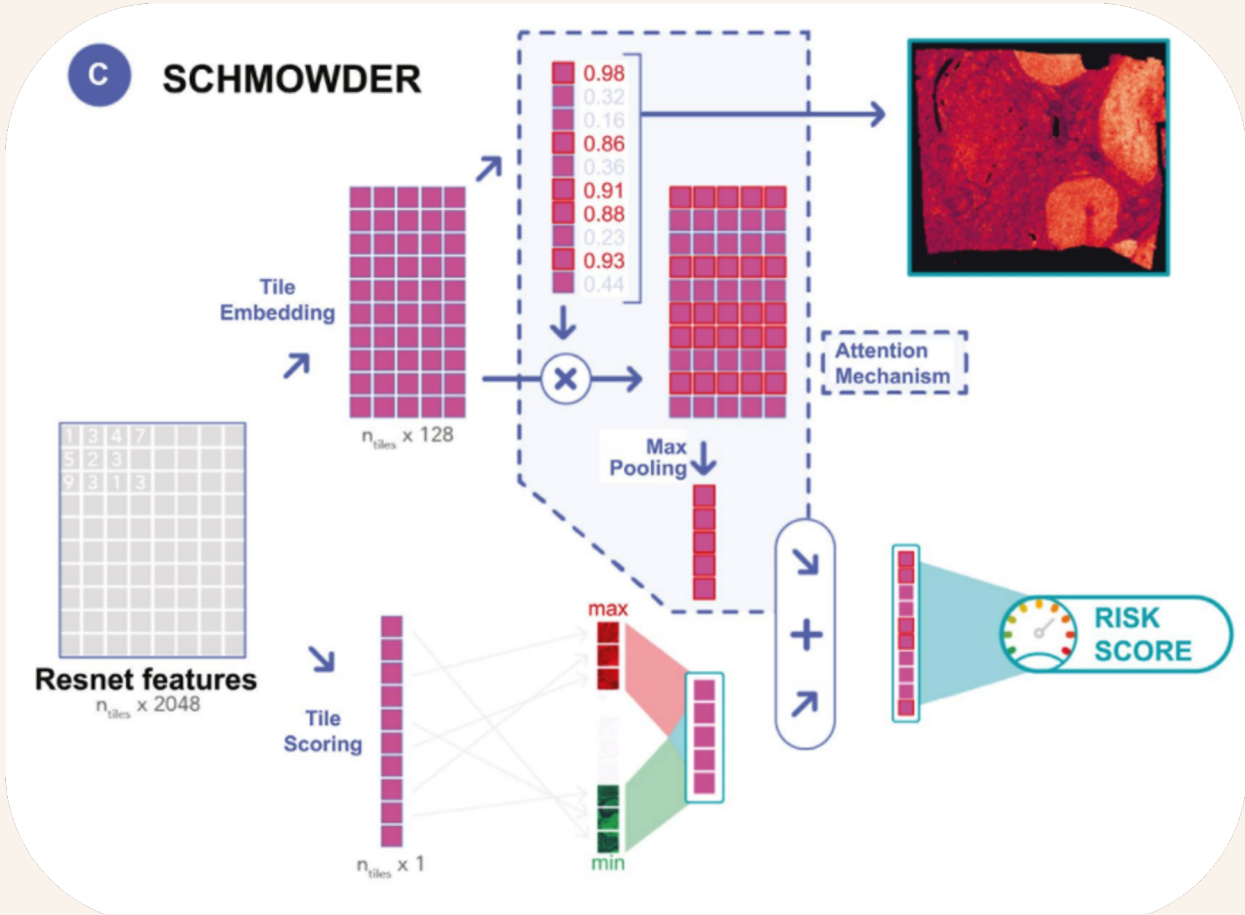
Death rate at 5 years is 32% in TCGA



Deep learning methodology tailored to histopathology

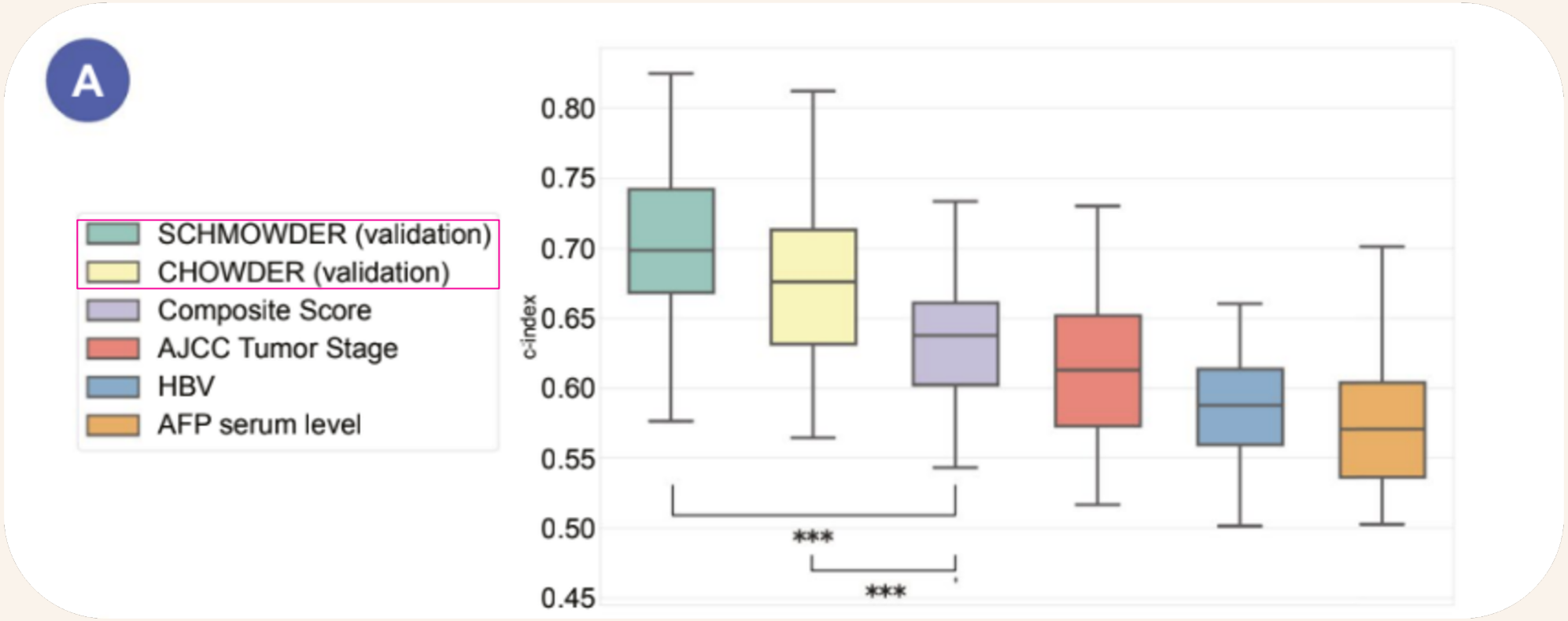
↳ Large images with information localized to the tumor





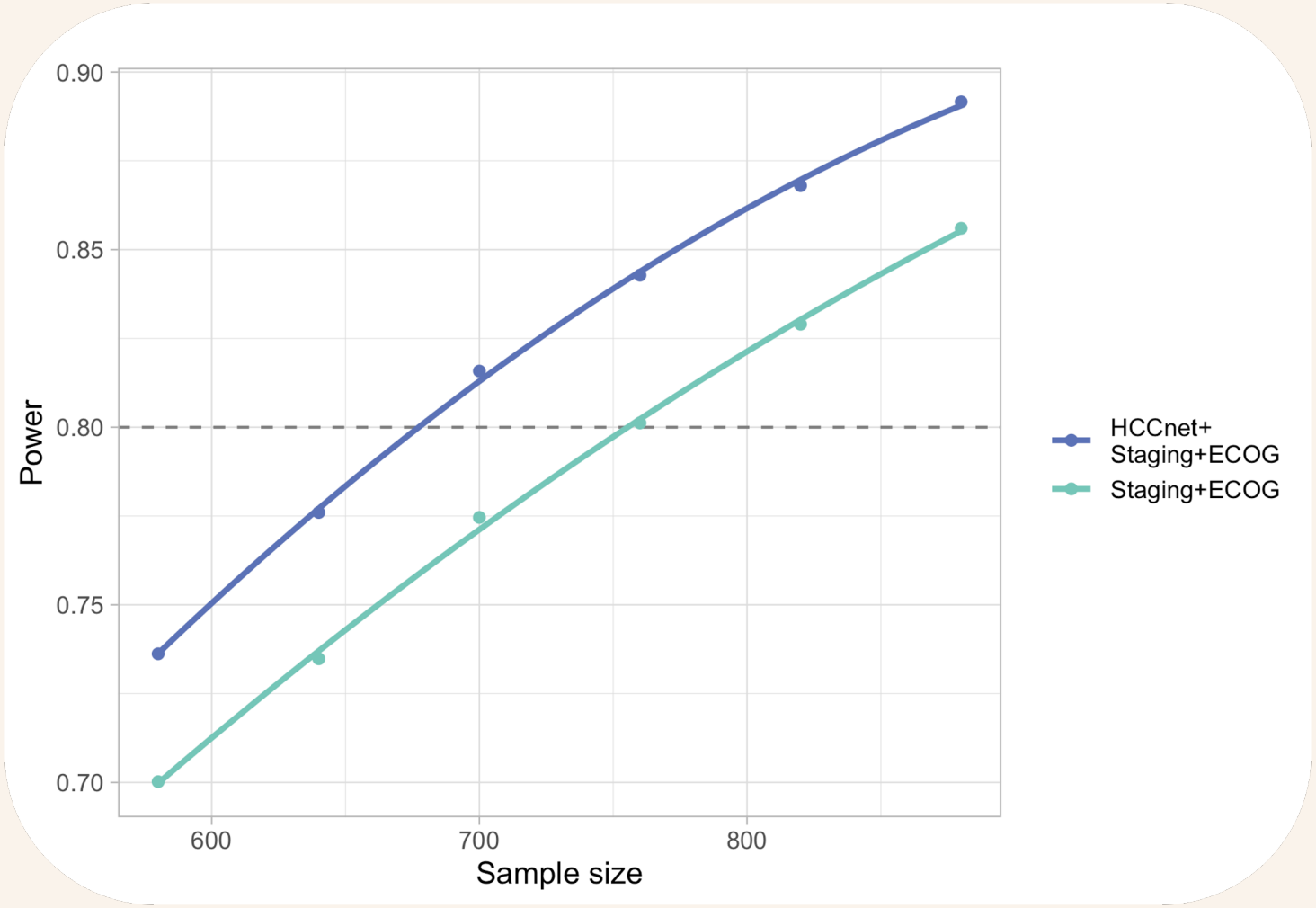
Results in the validation set

↳ HCCnet obtained a c-index of 0.70 vs 0.64 for traditional clinical variables



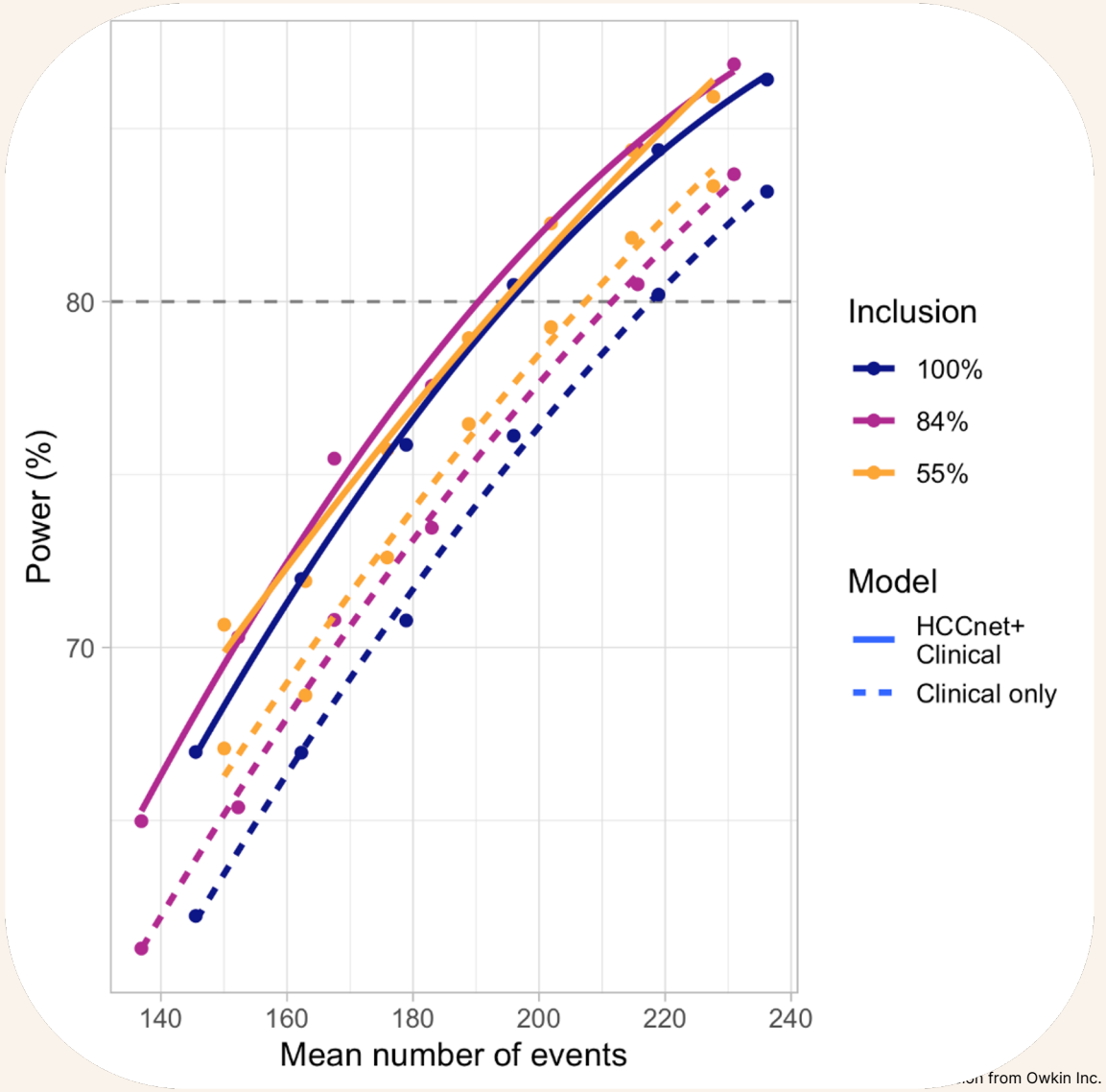
Adjustment for HCCnet would lead to 10% reduction in sample size

↳ Using semi-synthetic simulations based on the TCGA validation set



Broader eligibility criteria enabled by covariate adjustment

Eligibility level	Nested inclusion criteria	N (%)
Less restrictive	All patients included in the validation of HCCnet on TCGA	328 (100%)
Mildly restrictive	Child Pugh classification is A ECOG 0 or 1	275 (84%)
Most restrictive	ECOG score of 0 No macrovascular invasion No cumulated hepatitis B and C infection	180 (55%)



Covariate adjustment is viewed positively by regulators

We have received positive feedback and scientific advice from the EMA about the relevance of adjusting on deep learning histological covariates

FDA

The **FDA** published a draft guidance in 2021:

"Although an unadjusted analysis is acceptable for the primary analysis, adjustment [...] generally reduce the variability of estimation of treatment effects and thus lead to [...] more powerful hypothesis testing.

Covariate adjustment leads to efficiency gains when the covariates are prognostic for the outcome of interest in the trial."

EMA

The **EMA** has produced a guideline in 2015:

"The main reason to include a covariate in the analysis of a trial is evidence of strong or moderate association between the covariate and the primary outcome measure. Adjustment for such covariates generally improves the efficiency of the analysis and hence produces stronger and more precise evidence (smaller p-values and narrower confidence intervals) of an effect."

Prognostic signal in new modalities unlocked by AI can impact clinical trials

Thank you

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