Unlocking Potential – Using AI in Clinical Research

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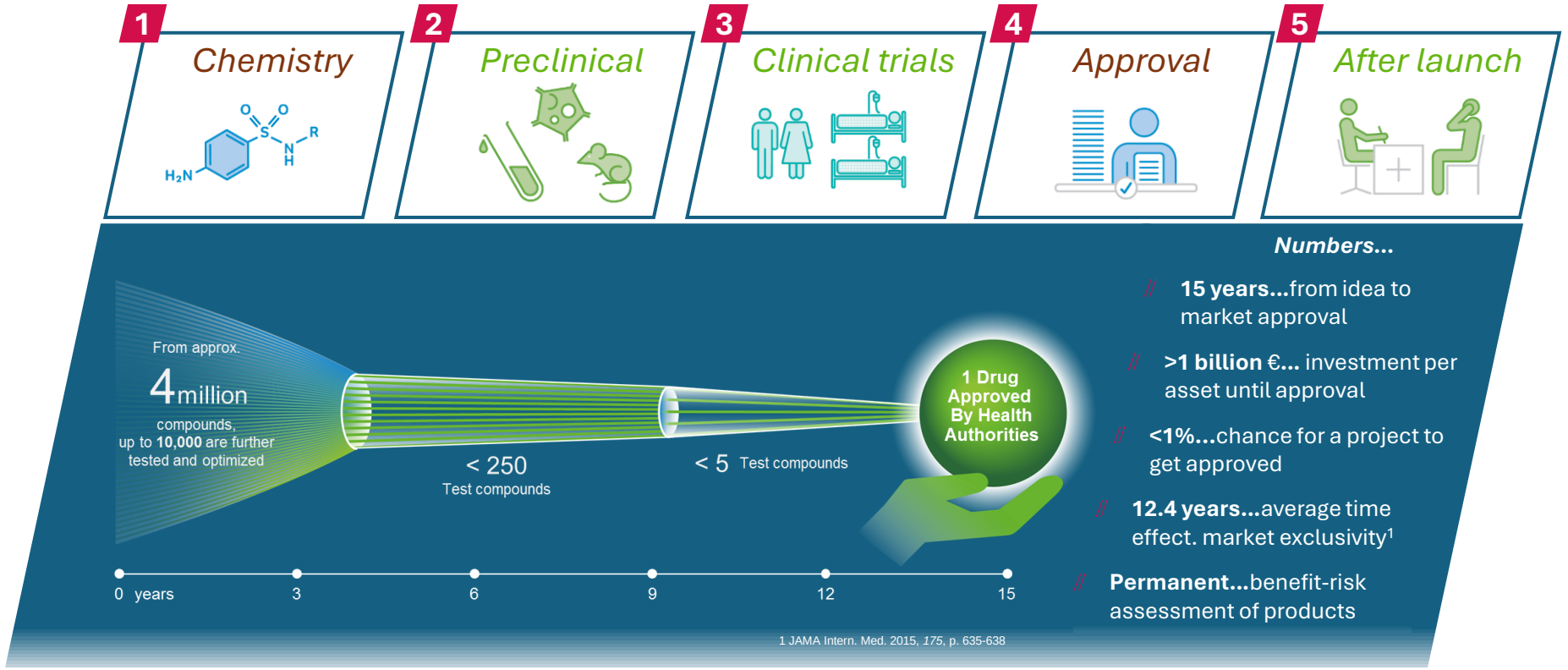
Drug development is a highly-regulated, long and costly endeavor with a low probability of success



INCREASED TRIAL COMPLEXITY

The cost of drug development continues to rise, and the size and complexity of clinical trials is a major factor. In the past two decades, the number of countries in which a clinical trial is conducted has more than doubled, and the average number of data points collected has grown dramatically. There are more endpoints — outcomes of a clinical trial that help to determine the efficacy and safety of an experimental therapy — and procedures to measure these outcomes, such as blood tests and heart-activity assessments. By comparison, eligibility criteria for participants, which include demographics such as age and sex and whether a participant is a healthy or a patient volunteer, have remained relatively consistent.

Category	2001–05	2011–15	2016–20	20-year overall rise
Endpoints*	7	13	22	214%
Procedures*	110	187	263	139%
Eligibility criteria*	31	30	30	–3%
Countries*	6	9	15	150%
Data points collected*	494,236	929,203	3,453,133	599%

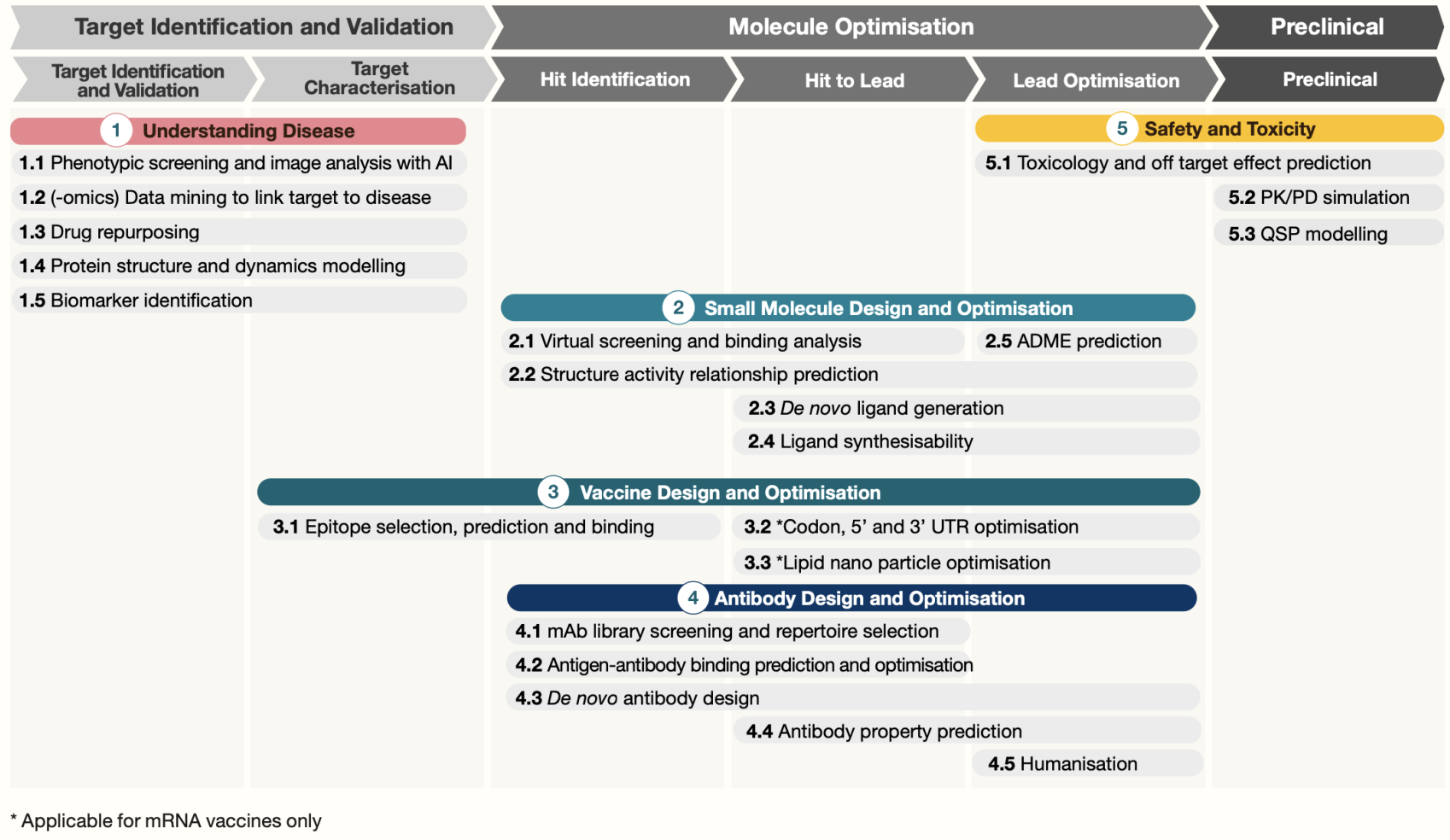
*Mean of total numbers

Looking to AI to increase efficiency….

- Drug discovery
- Trial design and conduct
- Searching for patients
- Keeping patients
- Endpoint assessment
- Identifying responders

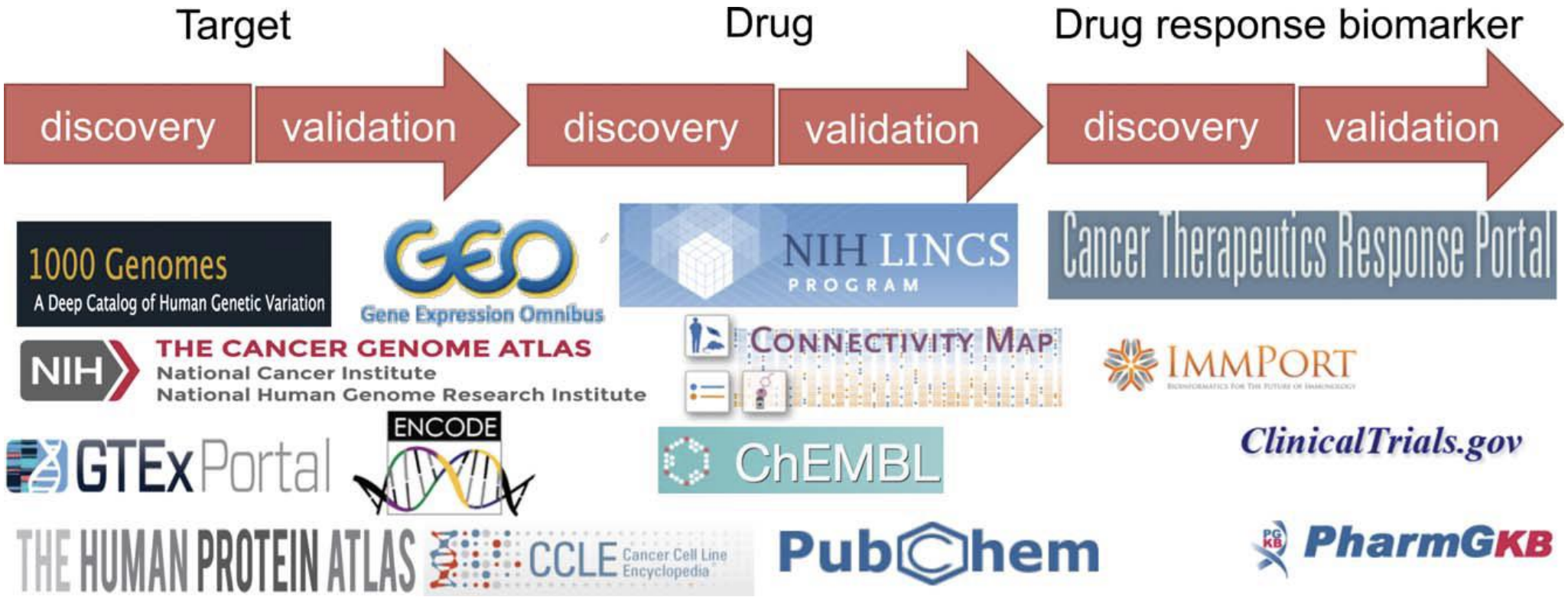
- …… Submission of documents/writing the paper

Drug discovery… the target and the molecule



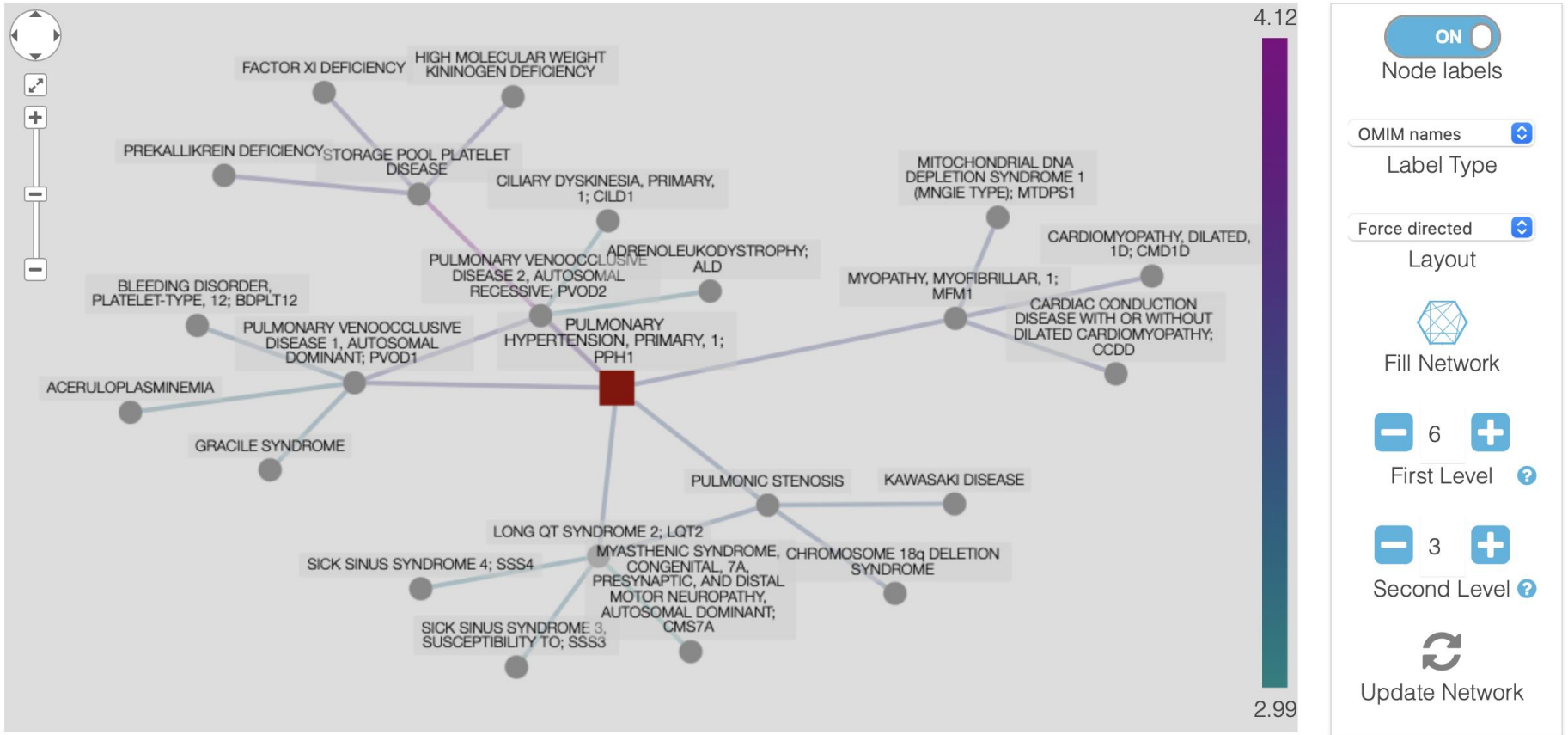
https://wellcome.org/reports/unlocking-potential-ai-drug-discovery

Publically available datasets

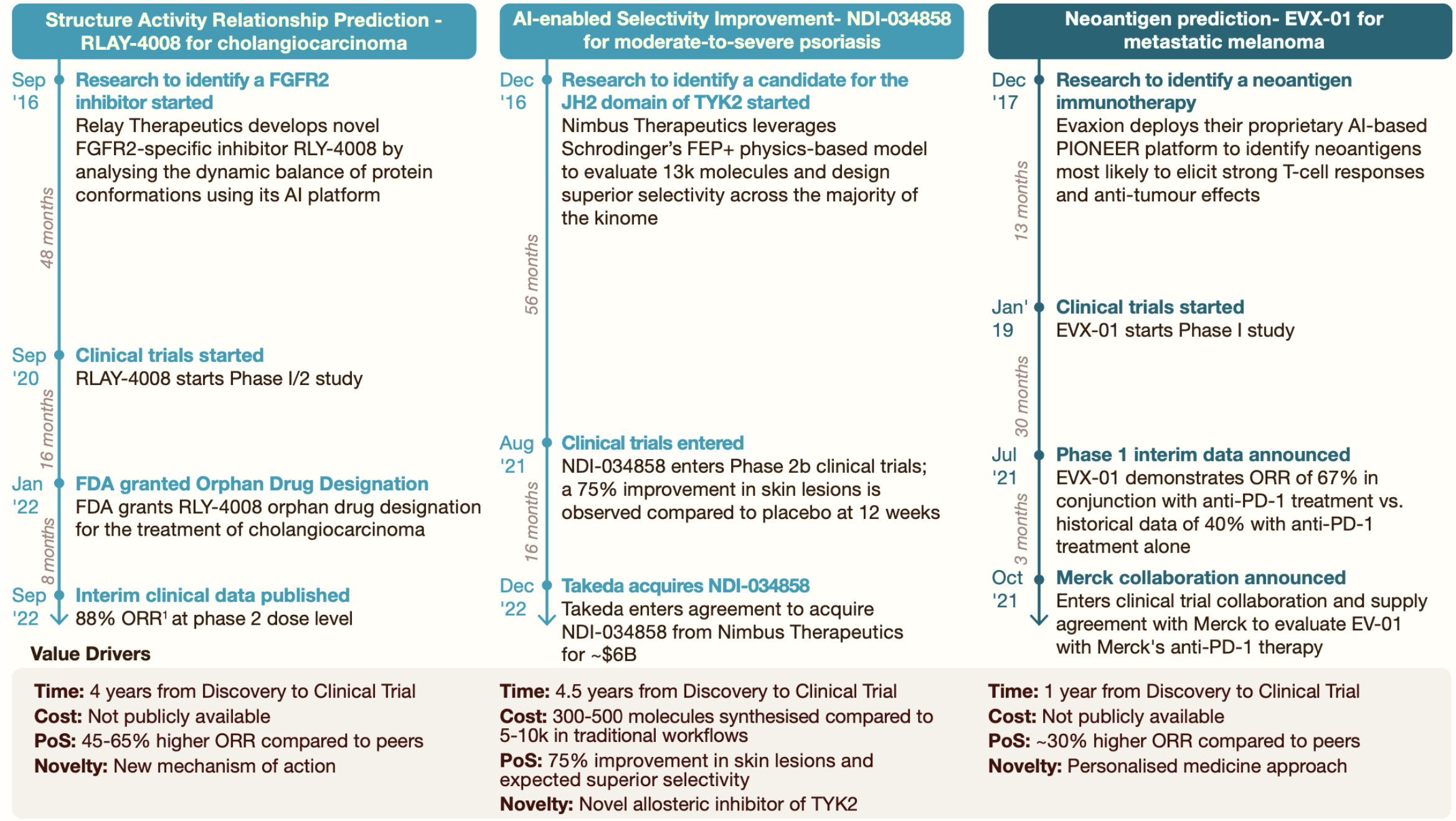


Chen & Butte Clin Pharm Therap 2016

Phenotype comparisons



https://paccanarolab.org/landis/explore/178600/



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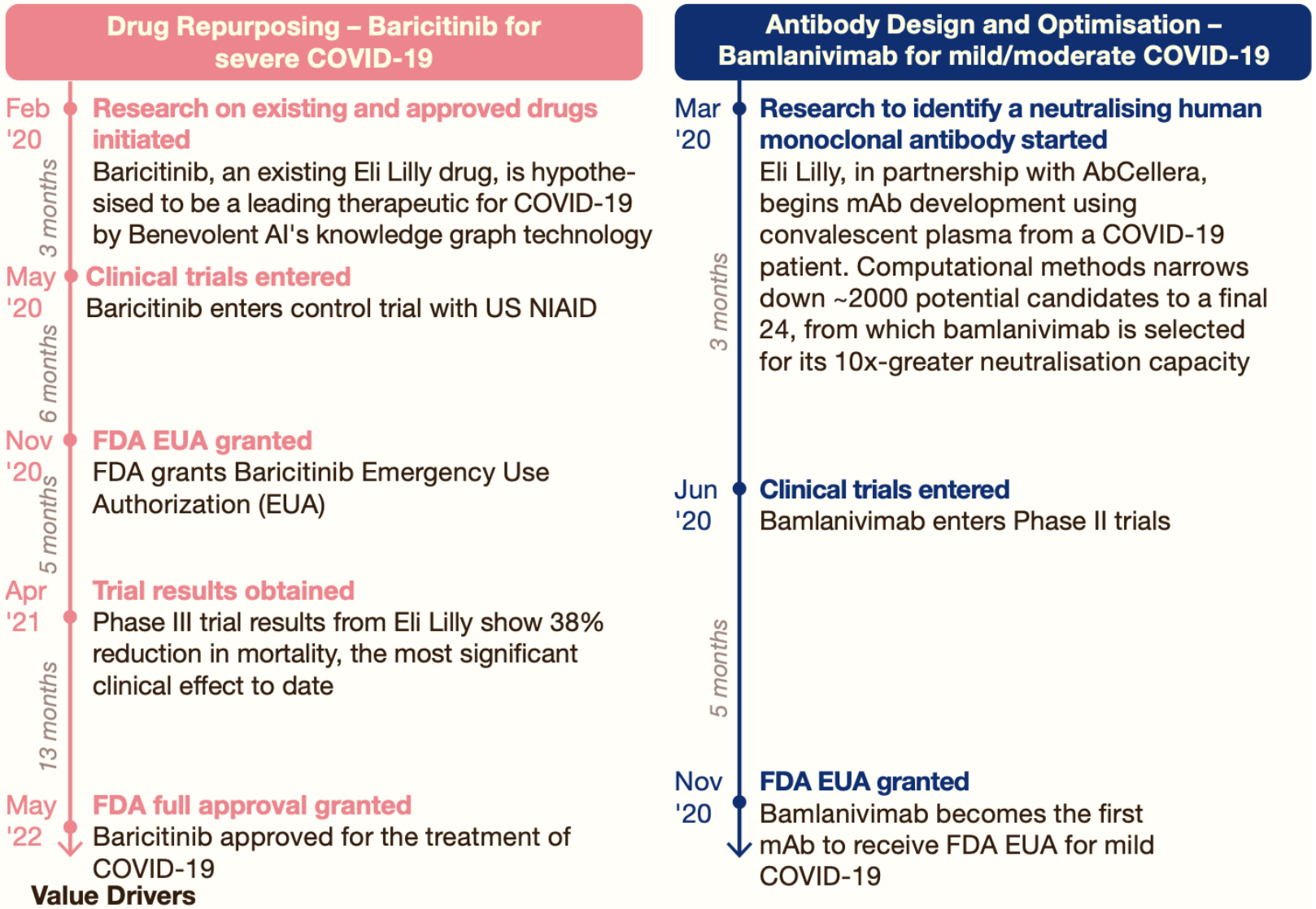

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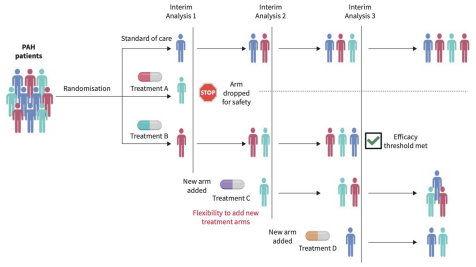
Testing in humans….. across the spectrum

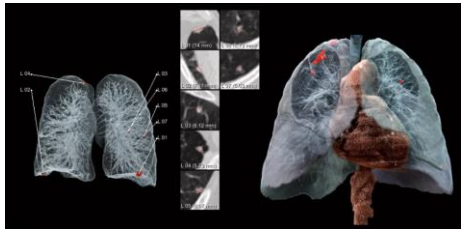
Trial design



Patient identification

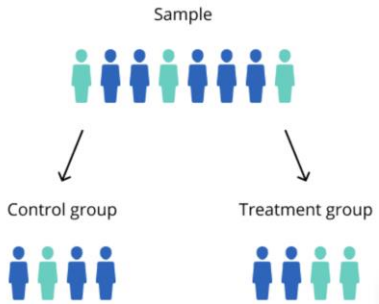
Treatment and follow up

Endpoint evaluation



Inclusion/exclusion

Randomisation

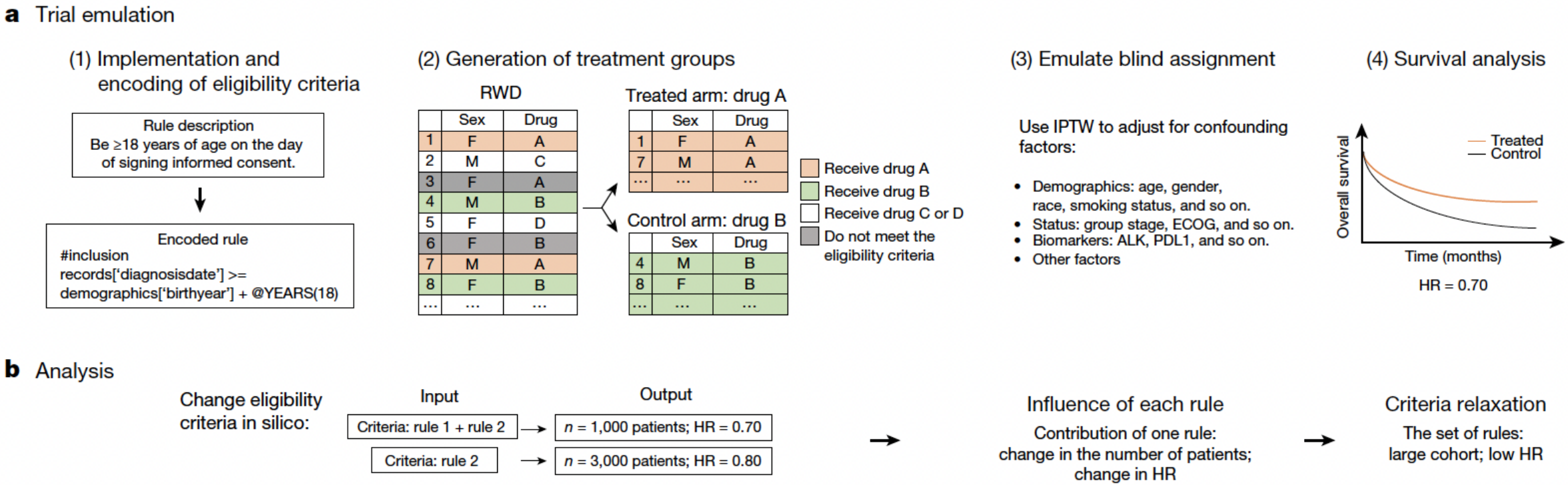


Responders Vs Non-responders

Designing the experiment….

- The aim is to demonstrate efficacy (and safety)
- Trial simulation with different inclusion/exclusion criteria and exploring potential outcomes allows researchers to choose the most effective and efficient protocols.

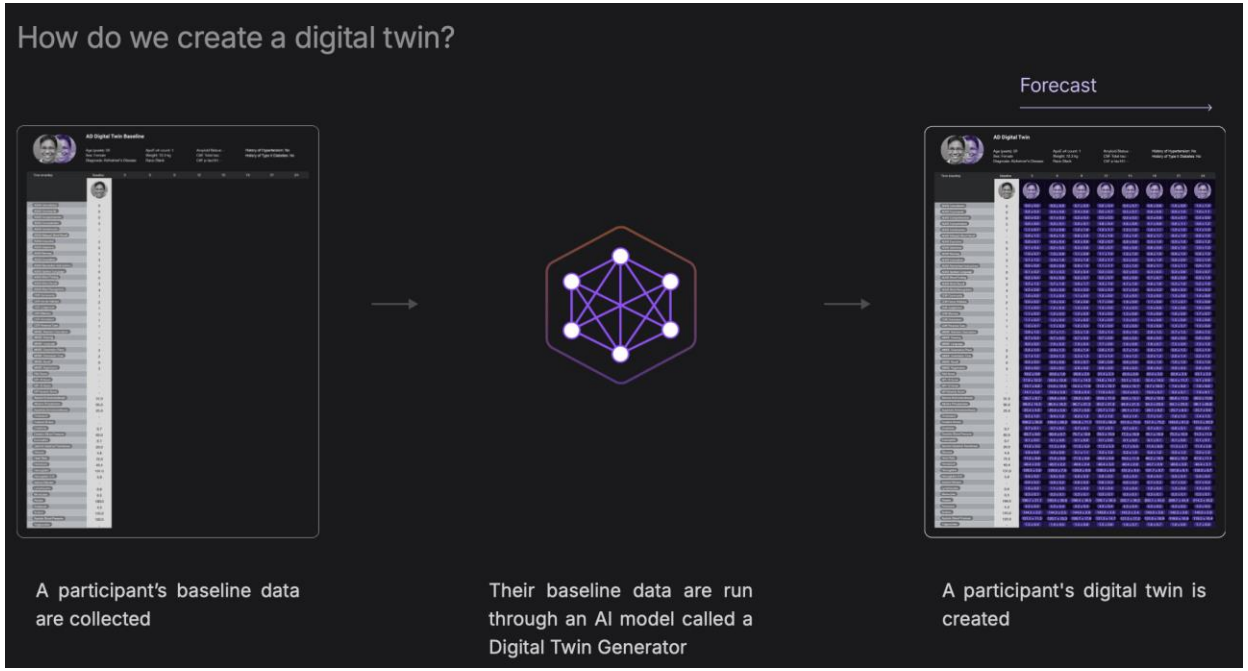
Trial Pathwayfinder…

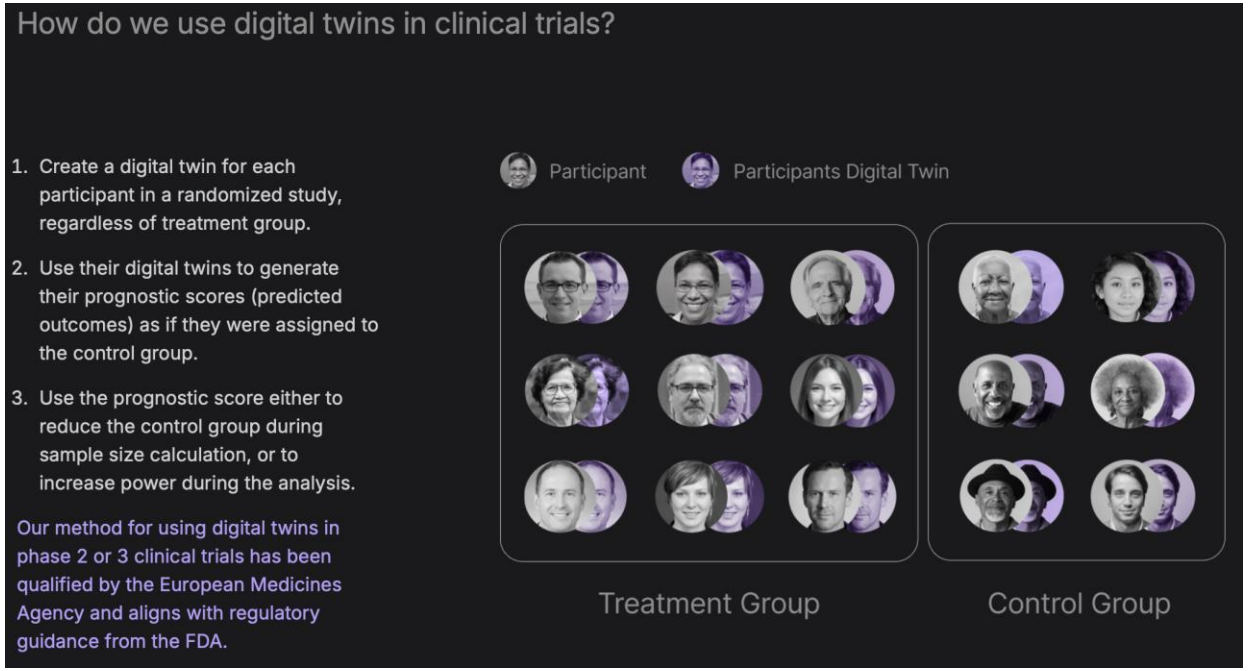


Select individuals in the real-world dataset who met the available eligibility criteria.
Systematically vary the eligibility criteria in silico and quantify how the hazard ratio of overall survival changes with different combinations of criteria

Liu et al Evaluating eligibility criteria… Nature 2021

Use of digital twins….





Uses data collected from each participant at their first visit to create a digital twin—one for each participant in the study – and then uses the participants' digital twins to forecast their control outcomes.

Effectively reduces the number of patients required to detect an effect

https://www.unlearn.ai

Identifying suitable patients….

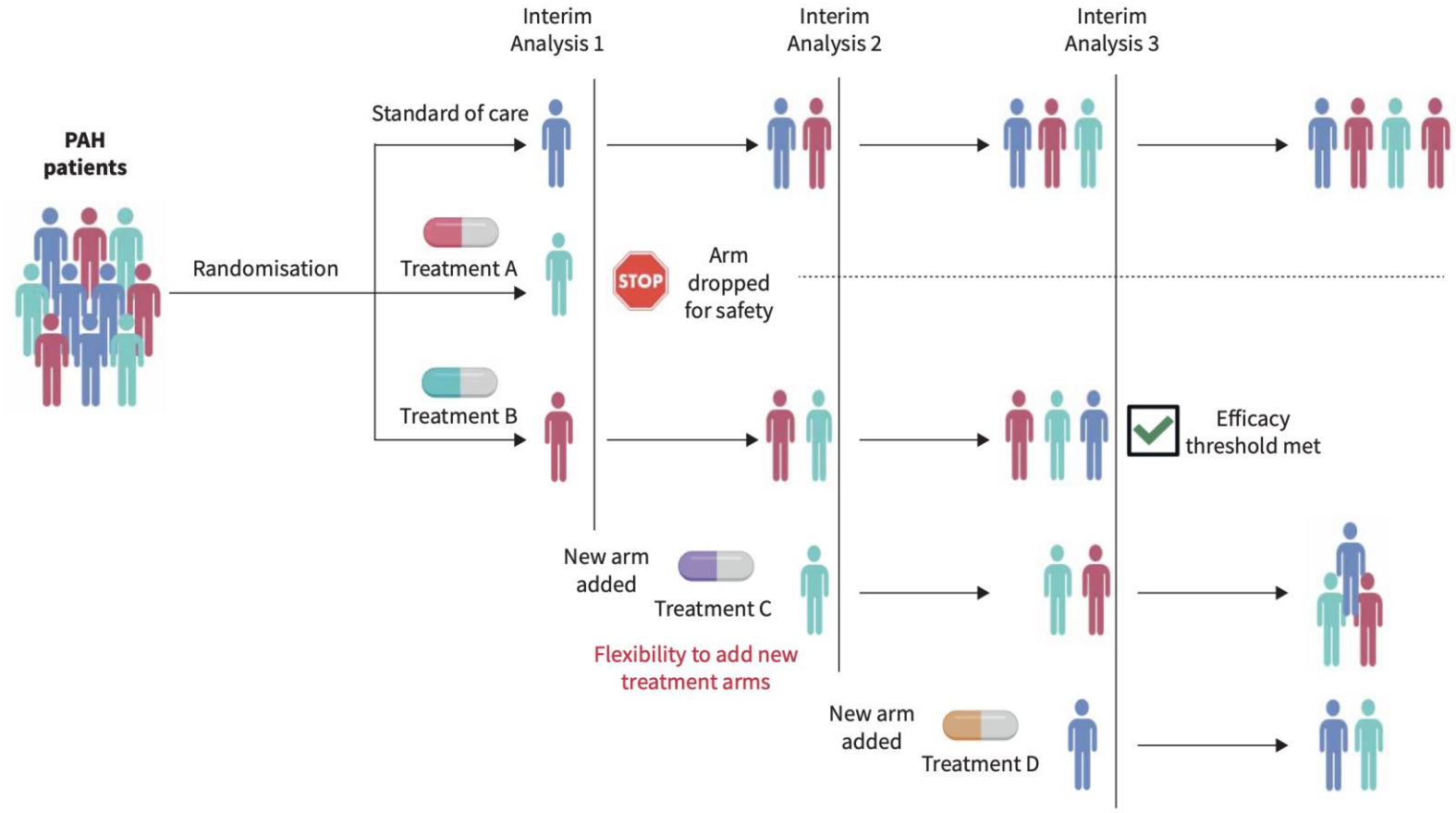
- Estimated to take up to one third the length of study
- One fifth don’t recruit enough
- Almost all exceed timelines for recruitment
- Entry criteria restrictive and don’t reflect real world
- Artificial intelligence can screen databases (eg EHR, registries) to define and model eligibility criteria, and identify and predict which patients are more likely to enrol in trials

Mining large datasets….

- **Criteria2Query:** Users type inclusion and exclusion criteria in natural language into a web-based interface , or enter a trial's identification number, and the program turns the eligibility criteria into a formal database query to find matching candidates in patient databases.
- **AutoTrial:** Considers similar precedent trials and their eligibility criteria to ensure sufficient patient coverage.
- **AutoCriteria:** Uses a large language model to extract eligibility requirements from clinical trial descriptions and format them into a table
- **DQuesST:** Utilises the ClinicalTrials.gov repository
- **TrialGPT:** A large language model framework to assist patient-to-trial matching

Application during the conduct of a trial…..

- AI can be used to modify protocols in real-time based on interim results



Patient retention….

- Drop-out rates are high
- In one analysis of 95 clinical trials, nearly 40% of patients stopped taking the prescribed medication in the first year

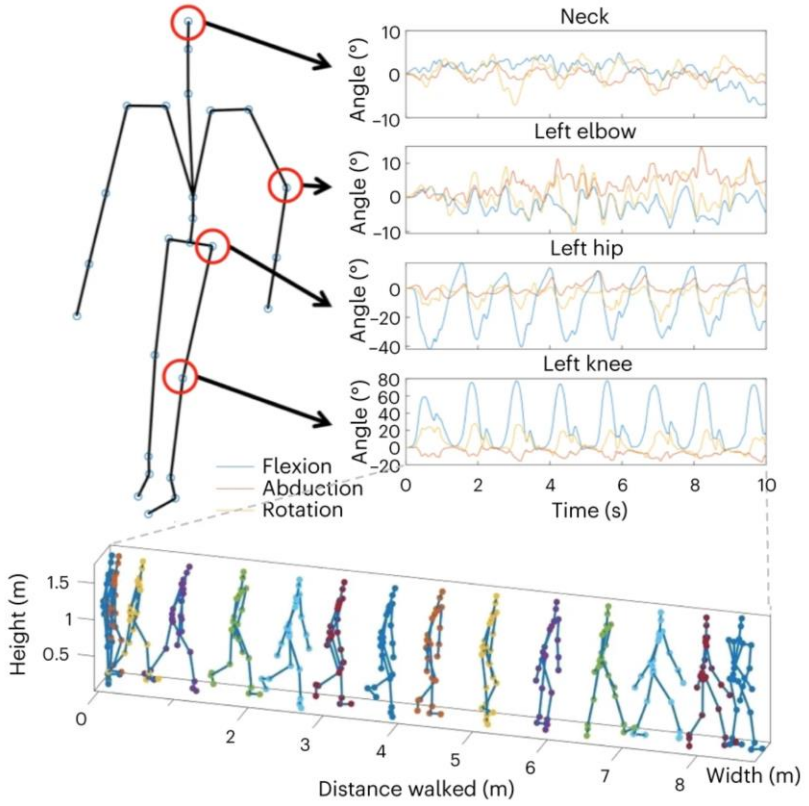
How can AI help….

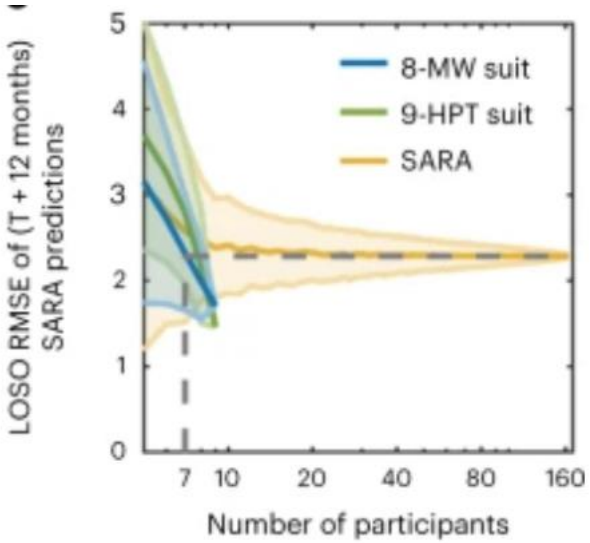
- Personalized Engagement: Analysing patient data and use of ChatBots to personalise participant engagement throughout the trial.
- Behavioral Monitoring: Remote monitoring reduces frequency of attendance and can track patient behaviour and adherence to treatment protocols, providing researchers with real-time feedback and allowing for timely interventions if issues arise.
- Predictive Modeling: To predict which patients are at risk of dropping out and enable researchers to take proactive measures.

Improving endpoint analysis…

- Reduce variation in endpoint: Reduces patient numbers needed to show an effect;
- Reduce time to final analysis: Increases efficiency

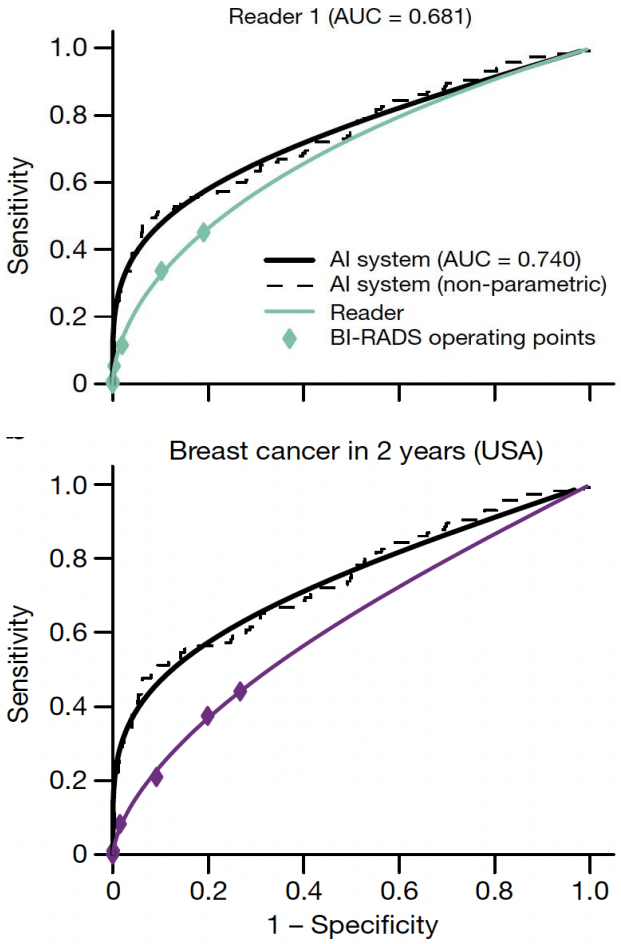
Improving endpoint measurment….

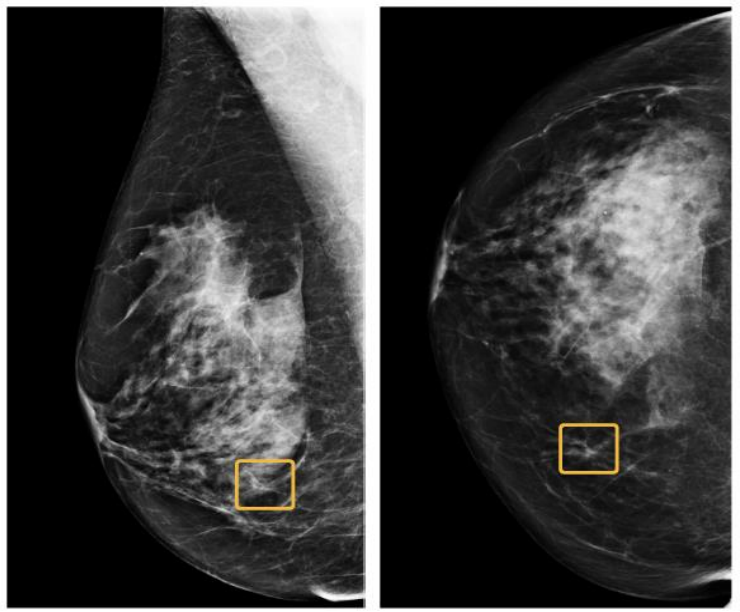




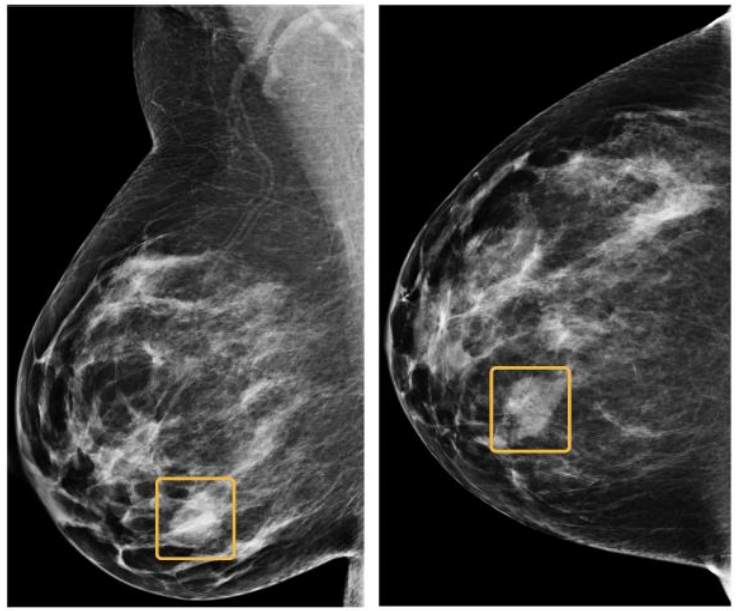
Kadirvelu et al Nat Med 2023

Improving endpoint measurement ….





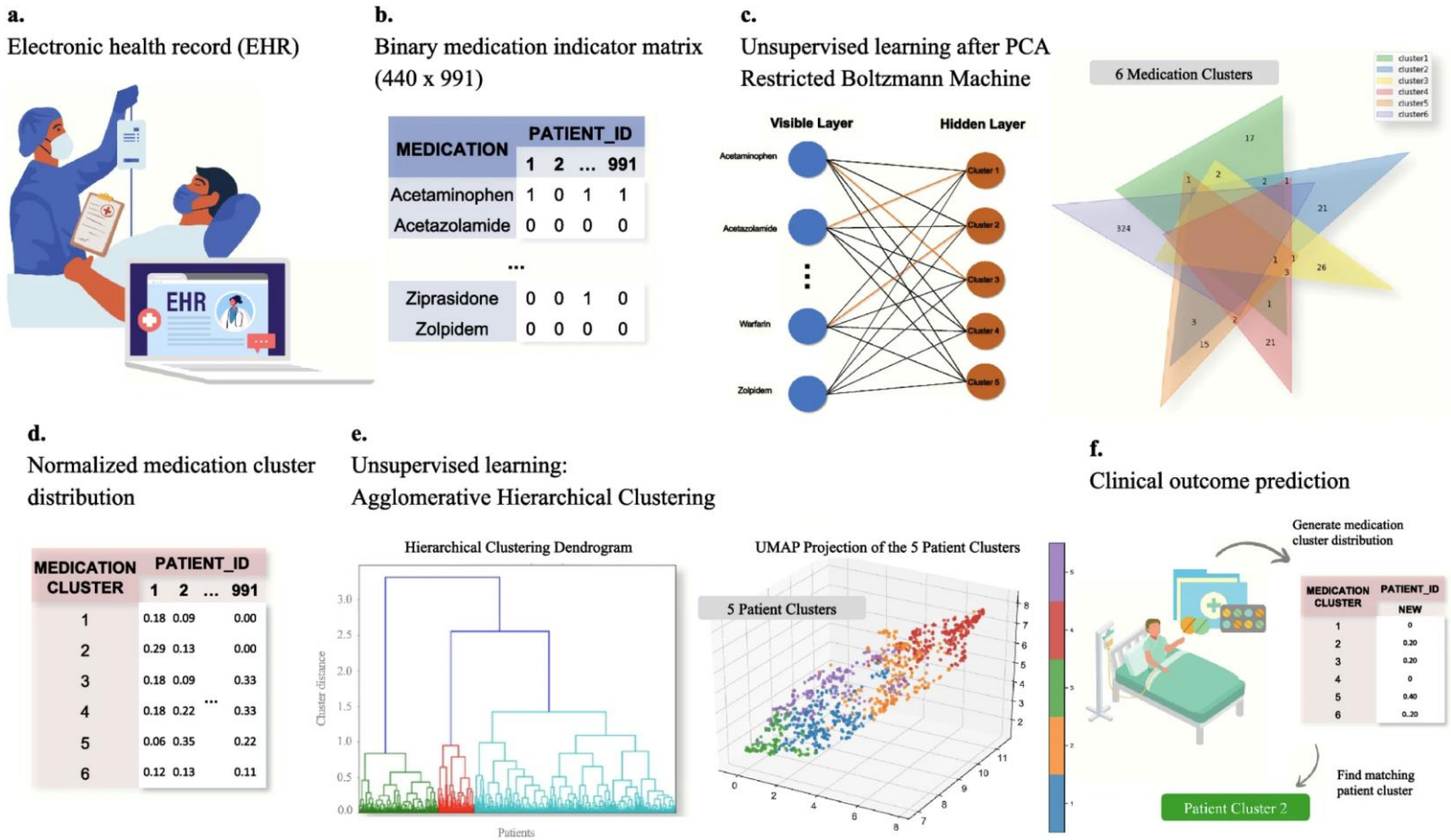
Breast cancer missed by 6 experts…
detected by AI



Breast cancer missed by AI….
But detected by 6 experts

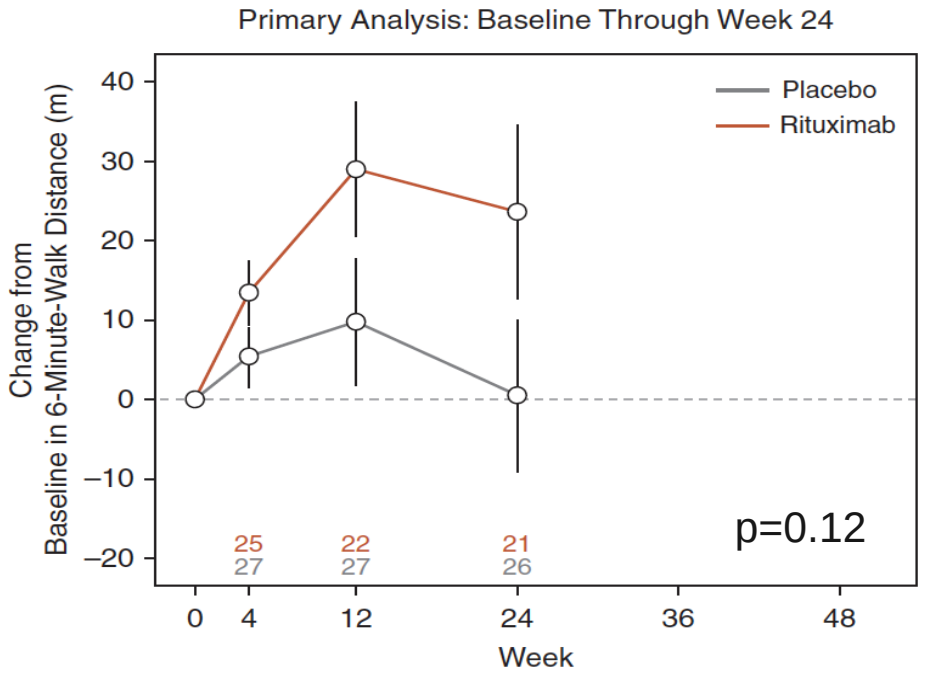
Identifying (potential) responders…

- e.g. cluster analysis to find and define characteristics of responders



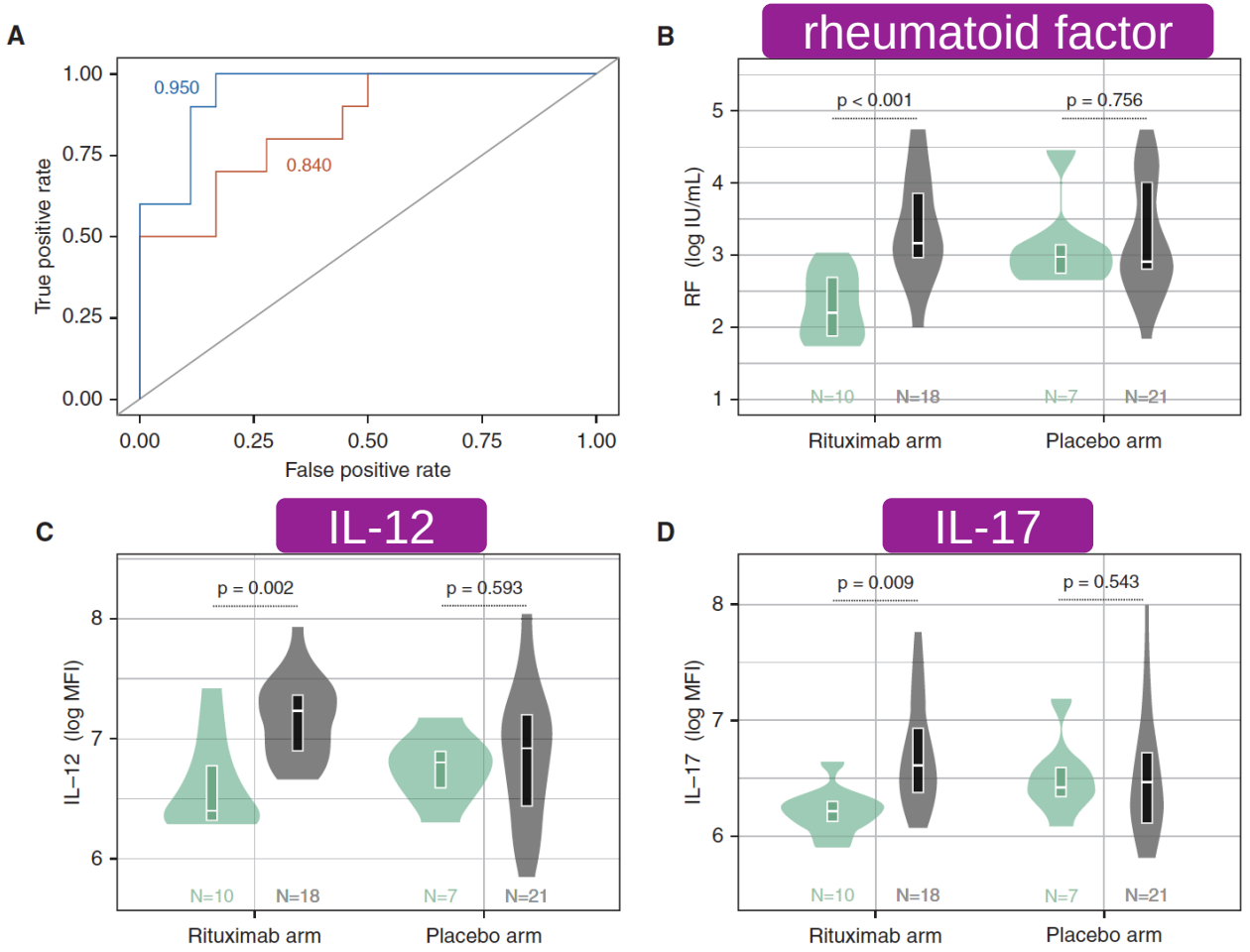
Sikora et al Sci Reports 2023

Identifying (potential) responders…



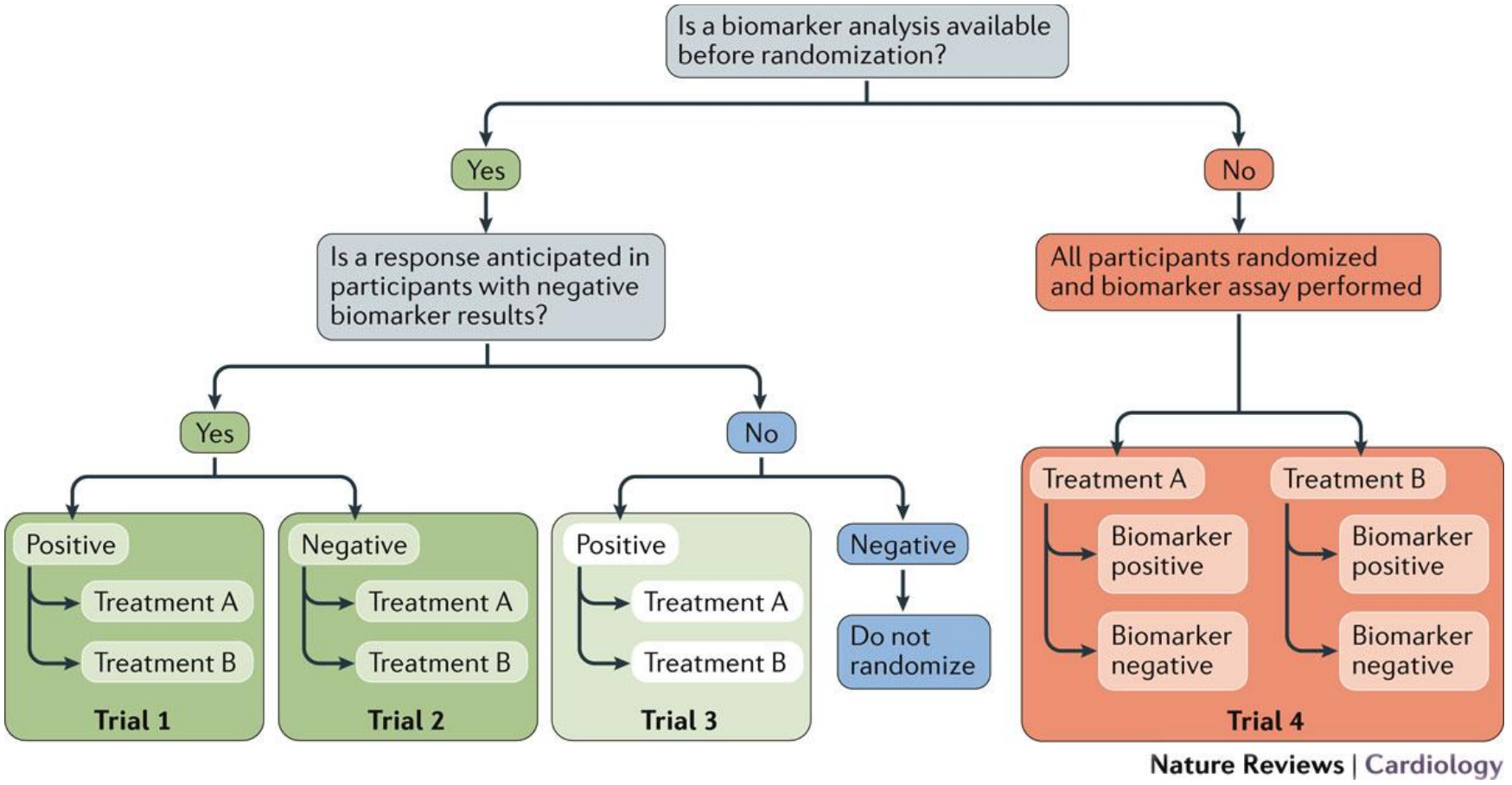
Negative Phase 2 RCT
Primary endpoint: change in 6MWD (W24)

Supervised ML models to classify Rituximab clinical responders (6MWD improvement >33 m)



Zamanian RT, et al. Am J Respir Crit Care Med. 2021

Prospective biomarker by treatment interaction design



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Writing up the story….

- Regulatory Submissions: AI can streamline the preparation and submission of regulatory documents … and write the paper.
- Marketing Surveillance: AI can analyse data from various sources, including EHRs and social media, to monitor the long-term safety and effectiveness of new treatments.
- Real-world evidence: AI can integrate clinical trial data with real-world data to inform healthcare policies etc.

Some AI concerns…

“All models are wrong, but some are useful” George Box 1979

- AI models can be biased.
- Their results can be hard to reproduce.
- They require large amounts of training data, which could violate patient privacy or create security risks.
- Researchers might become too dependent on AI.
- Algorithms can be too complex to understand.

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