Projecting enrollment in a pragmatic trial that utilizes real-world data

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Acknowledgements

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What are pragmatic trials?

Aim to estimate the effects of treatments in routine clinical practice

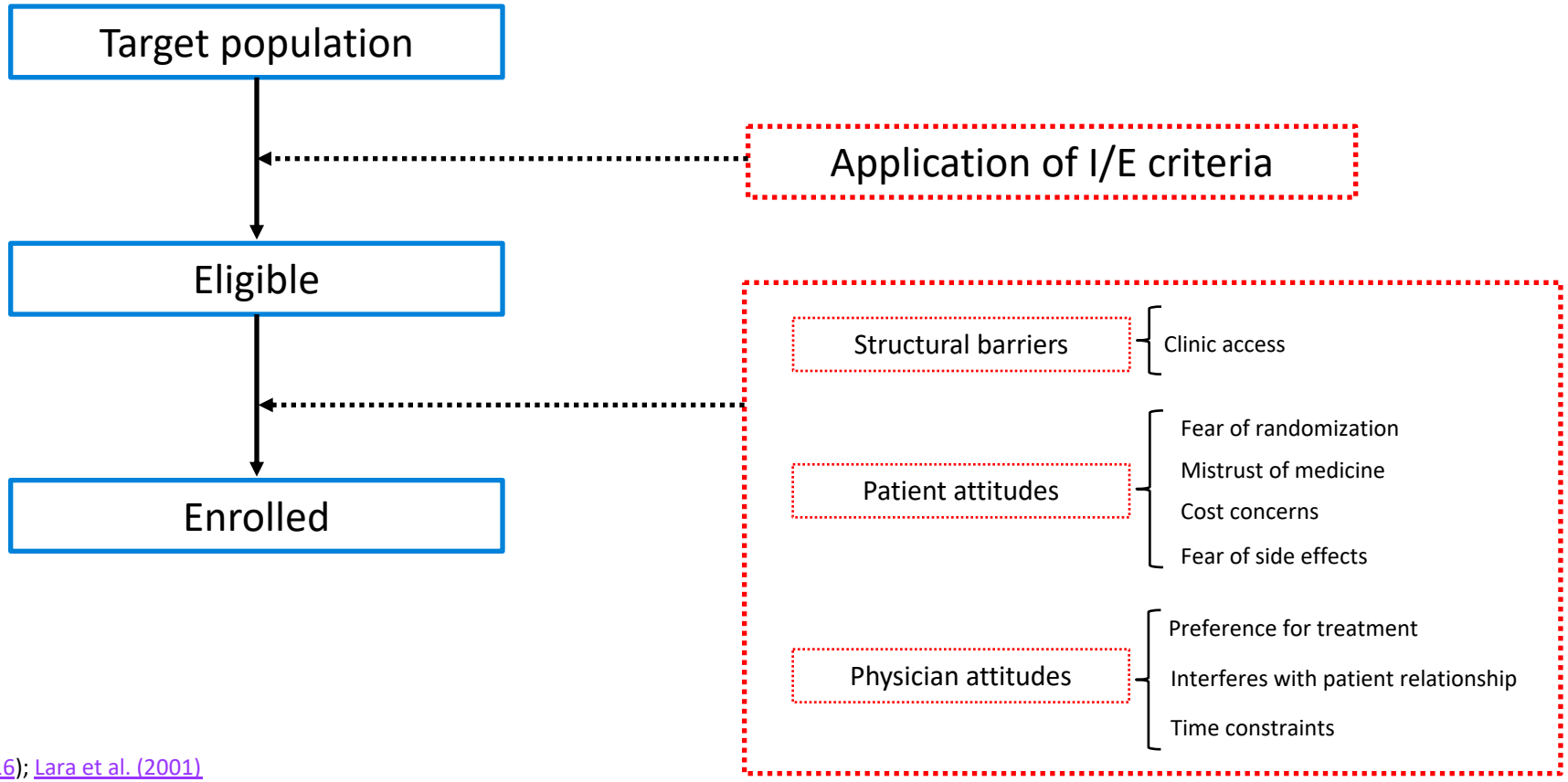
	Clinical trial	Pragmatic trial
Eligibility	Stringent inclusion / exclusion criteria	Simplified inclusion / exclusion criteria
Setting	Academic centers	Community sites
Follow-up	Frequent visits & assessment; shorter-term	Part of routine practice; longer-term; can leverage RWD infrastructure (e.g., EHR)
Adherence	Measures to increase adherence (e.g., additional monitoring)	Patient treated according to current usual care
Intervention	Double blinded placebo controlled	Non-blinded SoC control

Why use pragmatic trials?

- Better external validity
- Larger sample size and longer follow-up
- Increased efficiency and feasibility; reduced R&D costs
- Address the needs of multiple stakeholders (e.g., regulators, clinicians, patients, payers)
- Can incorporate randomization to estimate relative treatment effects

Efficiency and feasibility

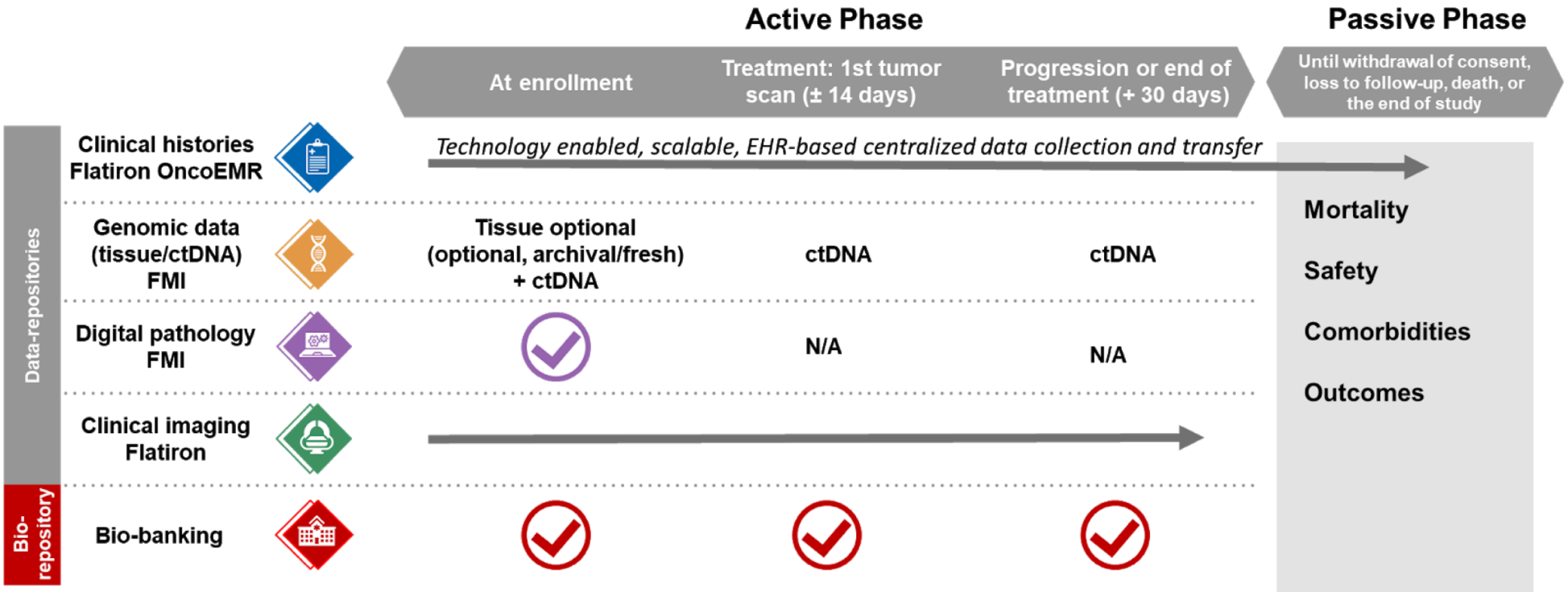
Estimates suggest that <5% of cancer patients participate in clinical trials[1]



[1]Unger et al. (2016); Lara et al. (2001)

The Flatiron/FMI/Genentech prospective clinico-genomic study (PCG)

- *Actively* collect circulating tumor DNA (ctDNA) at 3 defined time points and then *passively* collect data through existing EHR systems
- 1,000 patients with either mNSCLC or ES-SCLC
- *No randomization*



mNSCLC = metastatic non-small cell lung cancer; ES-SCLC = extensive stage small cell lung cancer

PCG has a less stringent inclusion/exclusion criteria than a typical clinical trial

(Example comparison with IMpower150)

PCG

Inclusion criteria

- Diagnosis of mNSCLC
- Planned initiation of SOC systemic anti-cancer treatment
- Age ≥ 18
- Ability to comply with study protocol

Exclusion criteria

- Receiving investigational medicinal product(s) as part of an interventional trial

IMpower150[1]

Inclusion criteria

- Stage IV non-squamous NSCLC
- Age ≥ 18
- Measurable disease as defined by RESIST
- Known PDL-1 status
- ECOG of 0 or 1
- Adequate hematologic and end organ function
- No prior treatment for stage IV non-squamous NSCLC

Exclusion criteria

Comorbidities

- Active or untreated central nervous system metastases
- Malignancies other than NSCLC within 5 years prior to randomization
- Pregnant or lactating women
- History of autoimmune disease
- HIV
- Active hepatitis B or C
- History of a number of lung diseases (e.g., pulmonary fibrosis, pneumonia, pneumonitis)
- Severe infection within 4 weeks prior to randomization
- Significant cardiovascular disease
- Illness that impacts ability to follow/comply study procedures

Prior treatment

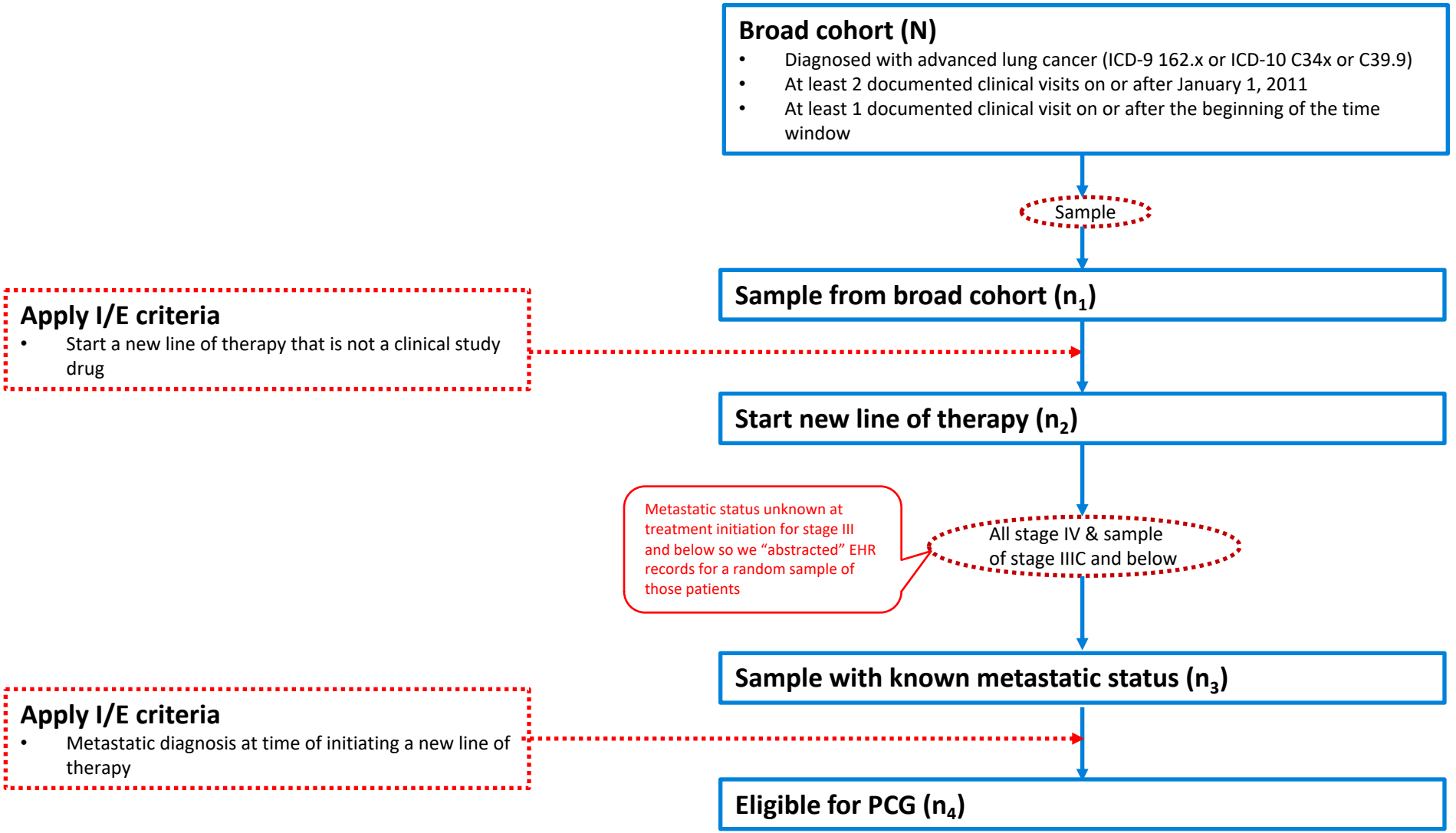
- Cluster of differentiation 137 agonists or immune checkpoint blockade therapies, anti-programmed death-1, and anti-PD-L1 therapeutic antibodies

[1]Randomized open-label study comparing atezolizumab with chemotherapy to chemotherapy alone

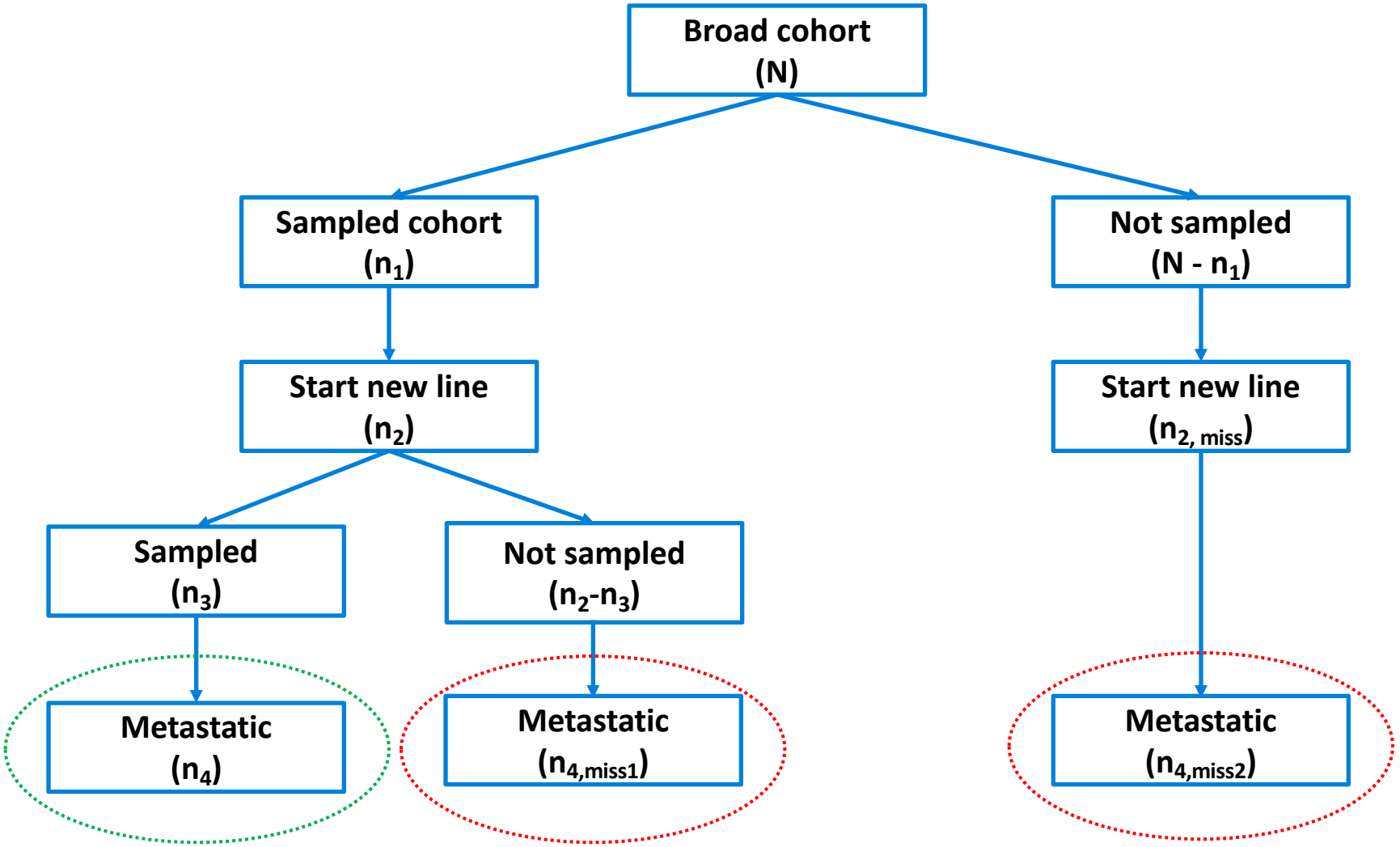
PCG primary analysis

Objectives	Assess feasibility, develop methods to aid planning & protocol extensions, and inform future pragmatic studies
Primary estimand	% of eligible patients that enrolled

Estimation of the number of eligible patients is surprisingly difficult because of a complex cohort selection process *(Illustration for mNSCLC)*



The cohort selection process implies the sampling scheme for a single site



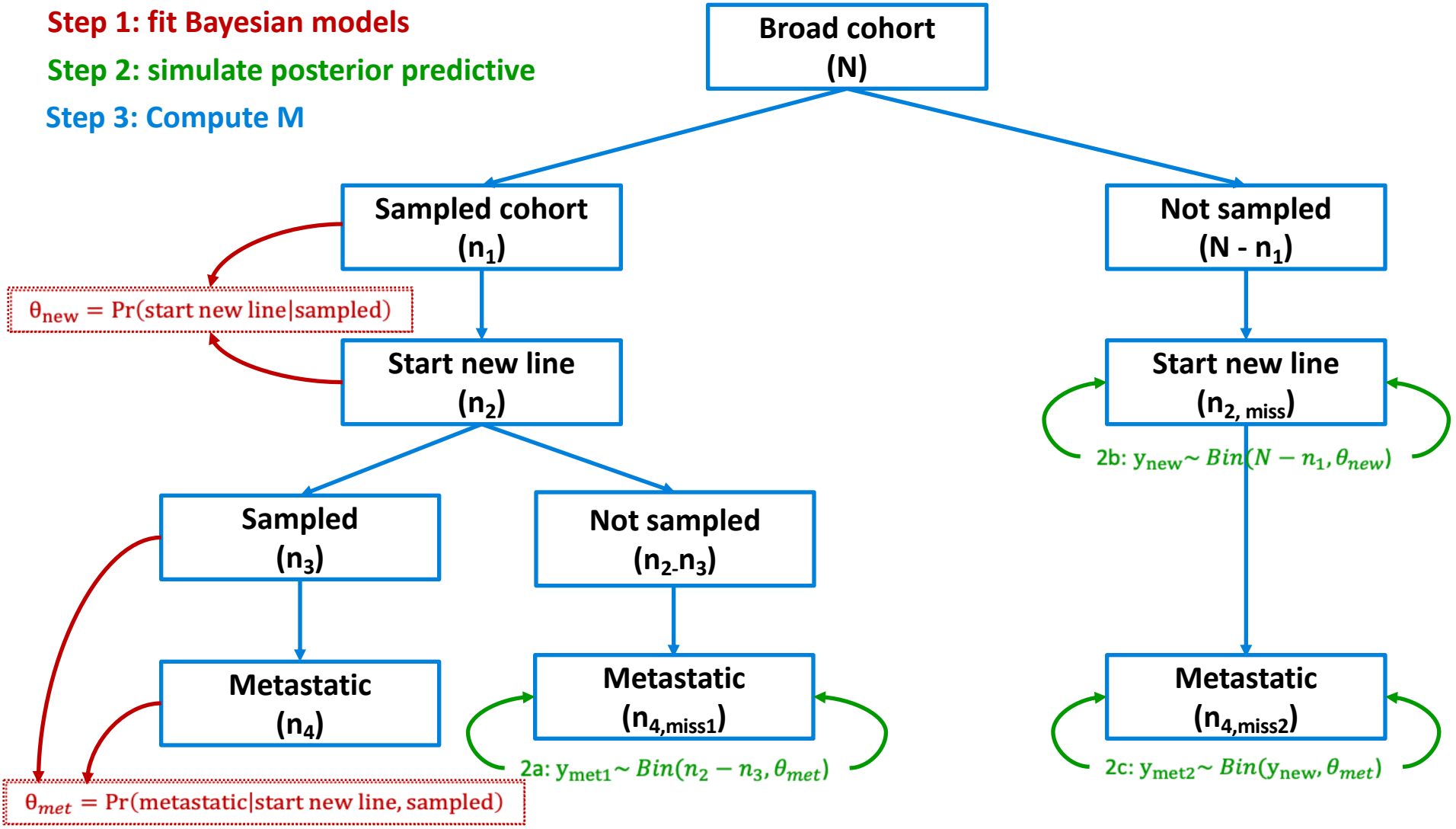
Aim is to estimate $M = n_4 + n_{4,miss1} + n_{4,miss2}$. Can we impute $n_{4,miss1}$ and $n_{4,miss2}$?

Prediction of number eligible for each site

Step 1: fit Bayesian models

Step 2: simulate posterior predictive

Step 3: Compute M



$$M = n_4 + y_{met1} + y_{met2}$$

Estimation of θ_{new} and θ_{met}

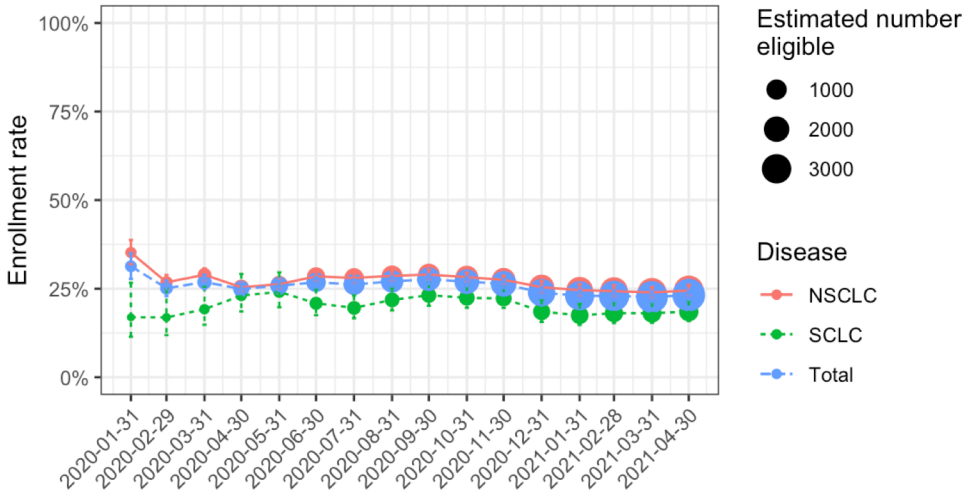
We implemented three models (Bayesian beta-binomial, frequentist, and Bayesian hierarchical), and used the hierarchical model as our primary methodology since it partially pools information across sites

$y_j \sim Bin(n_j, \theta_j)$	y_j= # metastatic n_j = # sampled with known metastatic disease (n_3)
$\theta_j = logit^{-1}(\alpha_j)$	Logistic function to model probability
$\alpha_j \sim N(\mu, \sigma^2)$	Hierarchical prior for log odds shrinks site specific estimates toward overall means
$\mu \sim N(logit(p), 0.5)$	Empirical Bayes prior where p is the proportion of the entire sample that is metastatic
$\sigma \sim N(0,2)$	Weakly informative prior truncated to be nonnegative

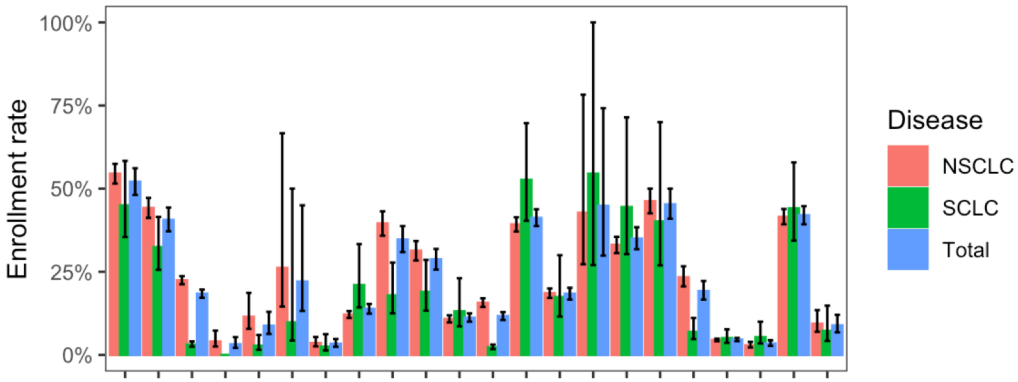
Note: j indexes site

Predicted enrollment rates from the Bayesian hierarchical model

Cumulative enrollment rate over time



Enrollment rate (April 2021) by site



The enrollment rate has been steady over time (~25%) with rates slightly higher for NSCLC than SCLC. There is considerable variation across sites and the hierarchical model improves the stability of the site specific estimates

Summary and conclusions

- PCG is a prospective pragmatic study with active collection of blood samples at three time points combined with passive collection of additional data through existing EHR systems
- We developed a methodology tailored to Flatiron Health's data collection process for estimating enrollment rates in a prospective pragmatic study
- Relatively high enrollment rates suggest that pragmatic studies with community sites are feasible
- The methodology has been used to project enrollment for PCG, including extensions to new target populations; it may also be helpful for future pragmatic studies
- A useful next step is to use the lessons learned from PCG to design and assess a randomized pragmatic trial

Doing now what patients need next