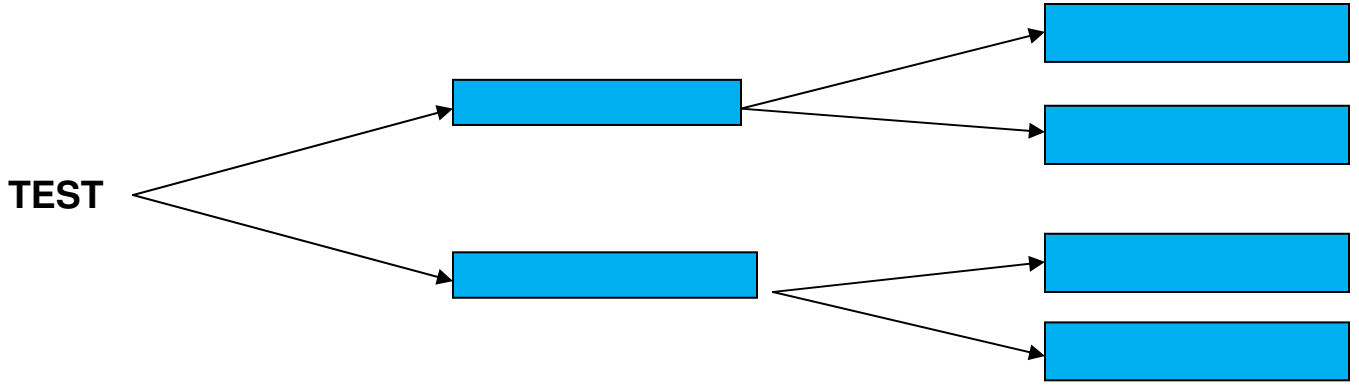

Randomized Clinical Trials versus Practical Clinical Trials in Pharmacogenomics

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Department of Psychiatry and Abramson Cancer Center
University of Pennsylvania
PNAT

A Shift Toward Evidence-Based Medicine: Comparative Effectiveness Research

"More than half of the treatments delivered today {are} lacking clear evidence of effectiveness."

"The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care."

Institute of Medicine (IOM), June 2009

Aligning Pharmacogenomics with CER

Reframe the question:

- CER: Does the intervention work across populations?
- PGx: Does the intervention benefit or harm particular patients?
- Is genomic-targeted therapy worth doing?

Adapt the methods:

- Enhance *internal validity* (proof of efficacy and effectiveness)
- Enhance *external validity* (generalizability and clinical utility)

Pharmacogenetic Research Strategies

Cohort Designs: Observational evaluation of association of marker with outcome

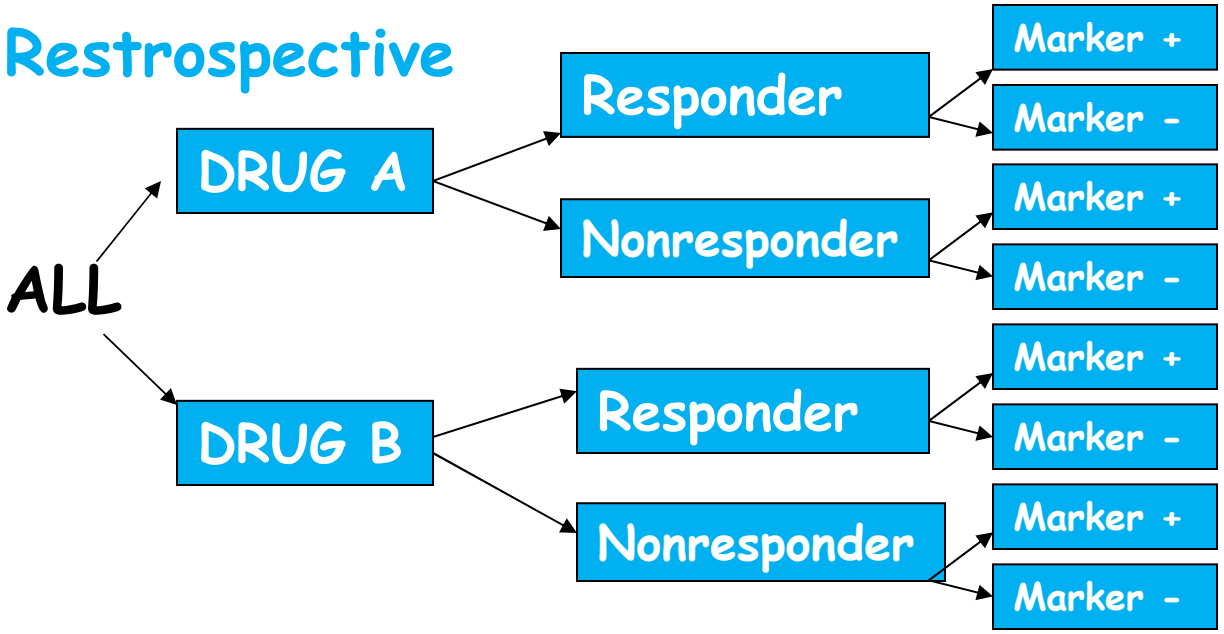
Randomized Clinical Trials: Experimental evaluation of efficacy of PGx

-Controlled exposure to treatment
-Avoids confounding of patient characteristics and treatment selection

based on accumulated data

Pharmacogenomic Trial Designs

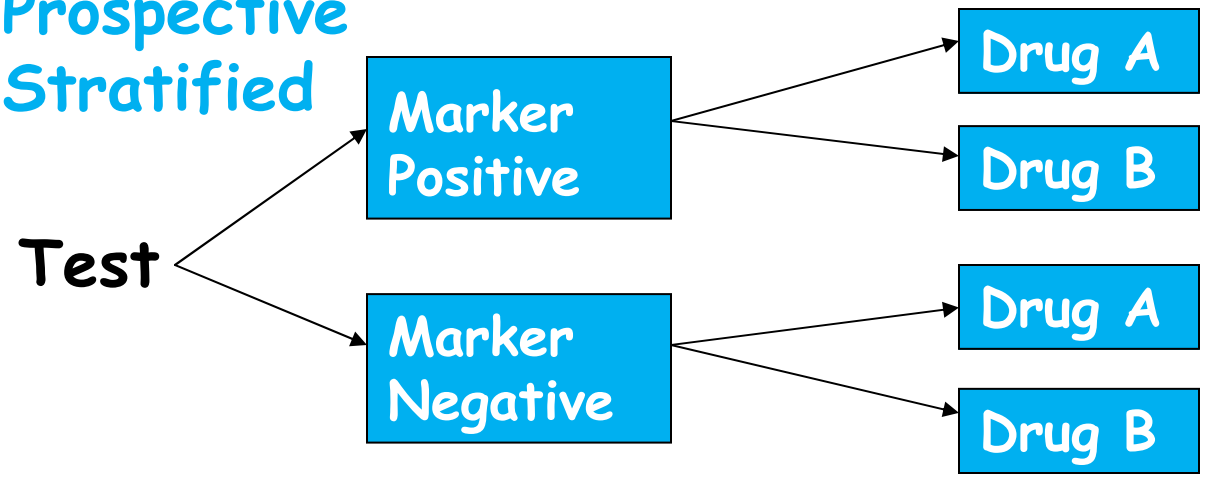
Restrospective



Best Uses:
- Marker unknown at trial initiation
- Hypothesis generation
- Independent validation

Limitations:
- Unbalanced groups
- Reduced power
- Missing data

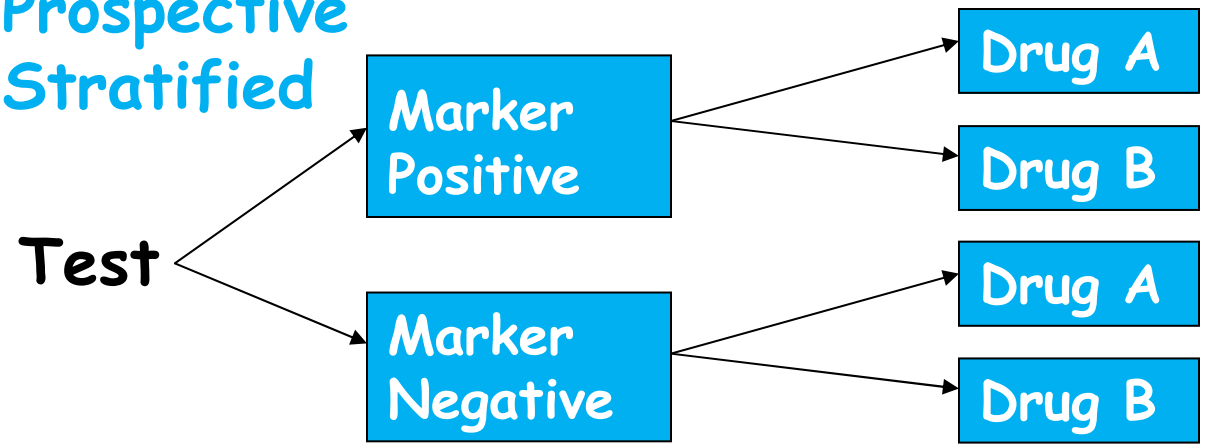
Prospective Stratified



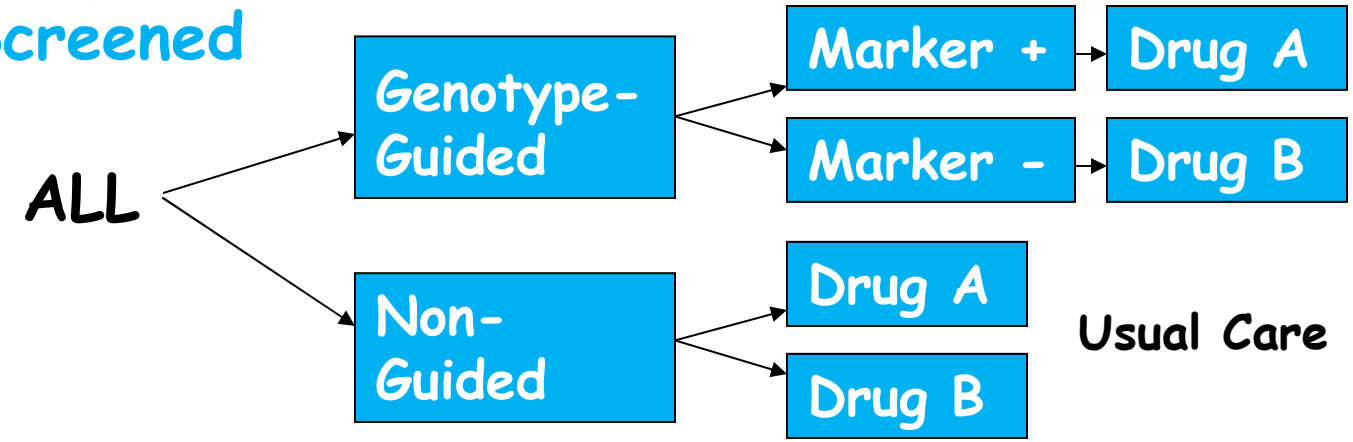
Advantages:
- Trial based on a piori hypothesis
- Allows for "enrichment"
- Balances Tx assignment

Pharmacogenomic Trial Designs

Prospective Stratified



Prospective Screened



Usual Care

High ecological ('real world') validity

True Test of Whether Personalized Medicine is Effective?

Lost in Translation?

- Increase generalizability to clinical practice settings
- Demonstrate improvement of health outcomes and cost-effectiveness
- Establish evidence-based guidelines
- Enhance adoption in clinical practice

Khoury, Genomic Medicine, 2009

- Strict eligibility criteria
- Highly controlled setting
- Protocol-driven treatment
- Compliance closely monitored

- Diverse population
- Heterogeneous settings
- Flexible treatment based on clinical judgment
- Compliance variable

Brass, Clin Pharm Ther, 2010

RCTs versus PCTs

	Classic RCT/Efficacy	PCT/Effectiveness
Research Question	Does it work in ideal circumstances	Does it work under best practice conditions
Population	Selective, homogeneous	Diverse, heterogeneous
Setting	Specialized, controlled	Clinical practice
Intervention	Fixed, protocol-driven	Flexible, clinician judgment
Comparator	Placebo or active	Usual care, least $
Compliance	Closely monitored, high	Highly variable
Assessments	Elaborate, complex	Simple outcomes
Goal	FDA approval	Adoption in practice

Balance experimental rigor with generalizability

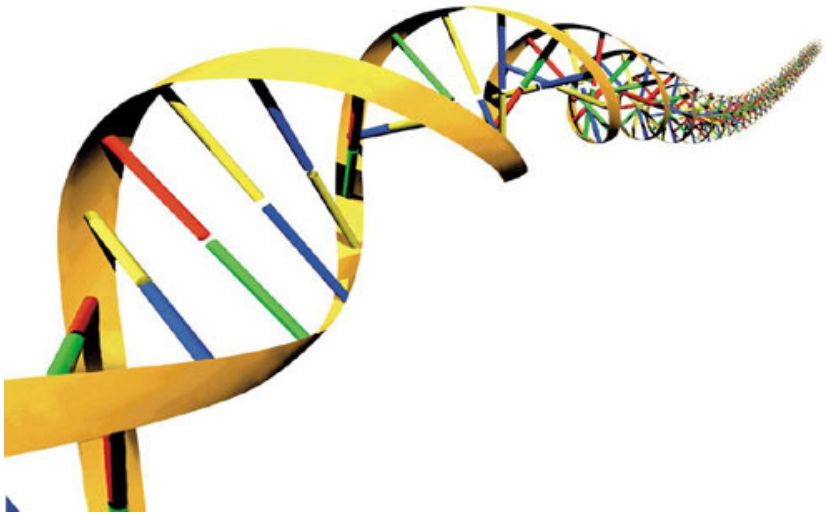
Pros and Cons of PCTs

Advantages

- More reflective of patients and practice
- More efficient, less burdensome
- Results more likely to generalize to practice

Disadvantages

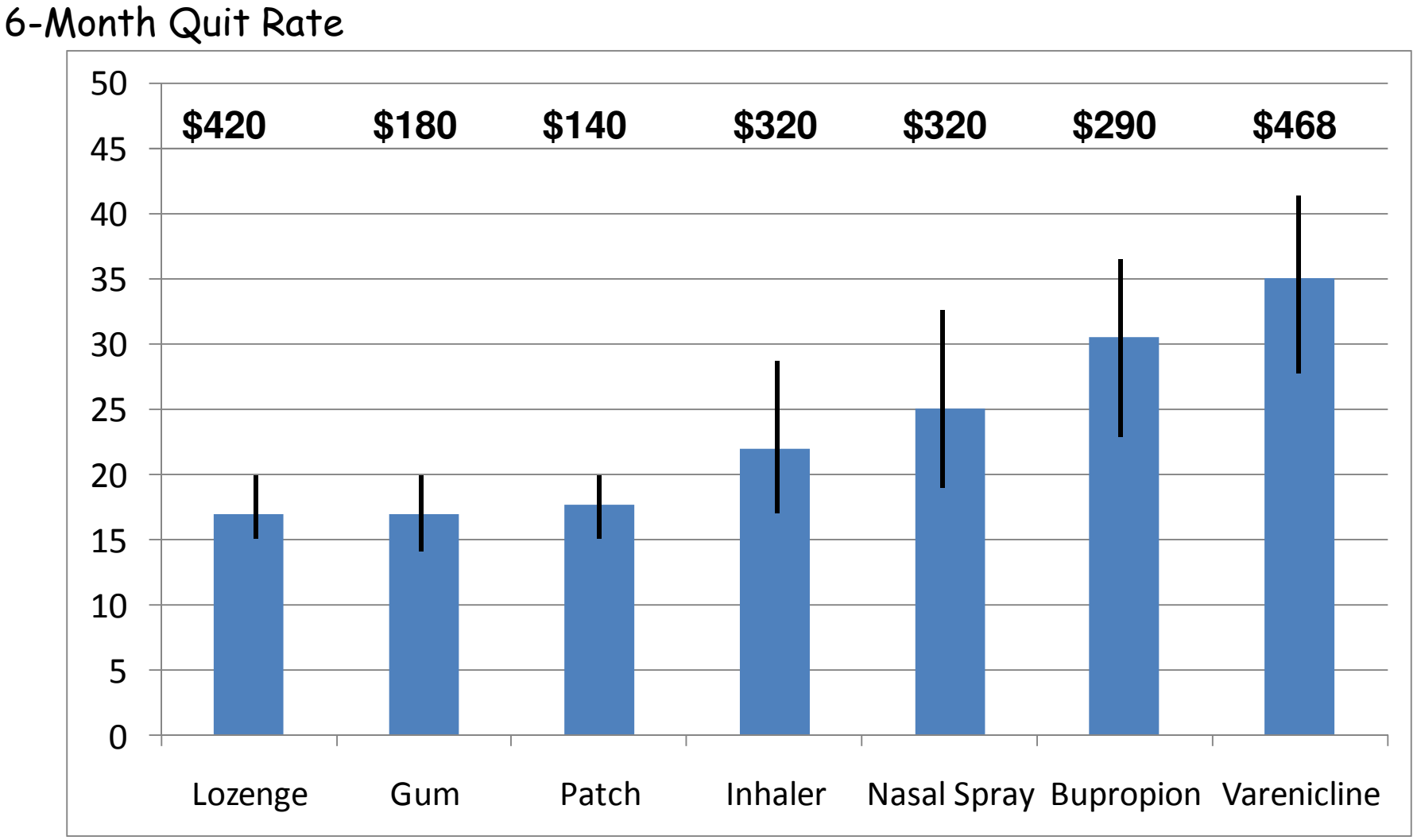
- Less experimentally rigorous
- Usual care may not be a stable comparator
- Increased heterogeneity reduces signal



Case Example: Pharmacogenetics of Nicotine Addiction Treatment (PNAT)

PIs: Caryn Lerman and Rachel Tyndale
Funding: Pharmacogenetics Research Network
NIDA, NCI, NHGRI, NIGMS

Pharmacogenetic Rationale

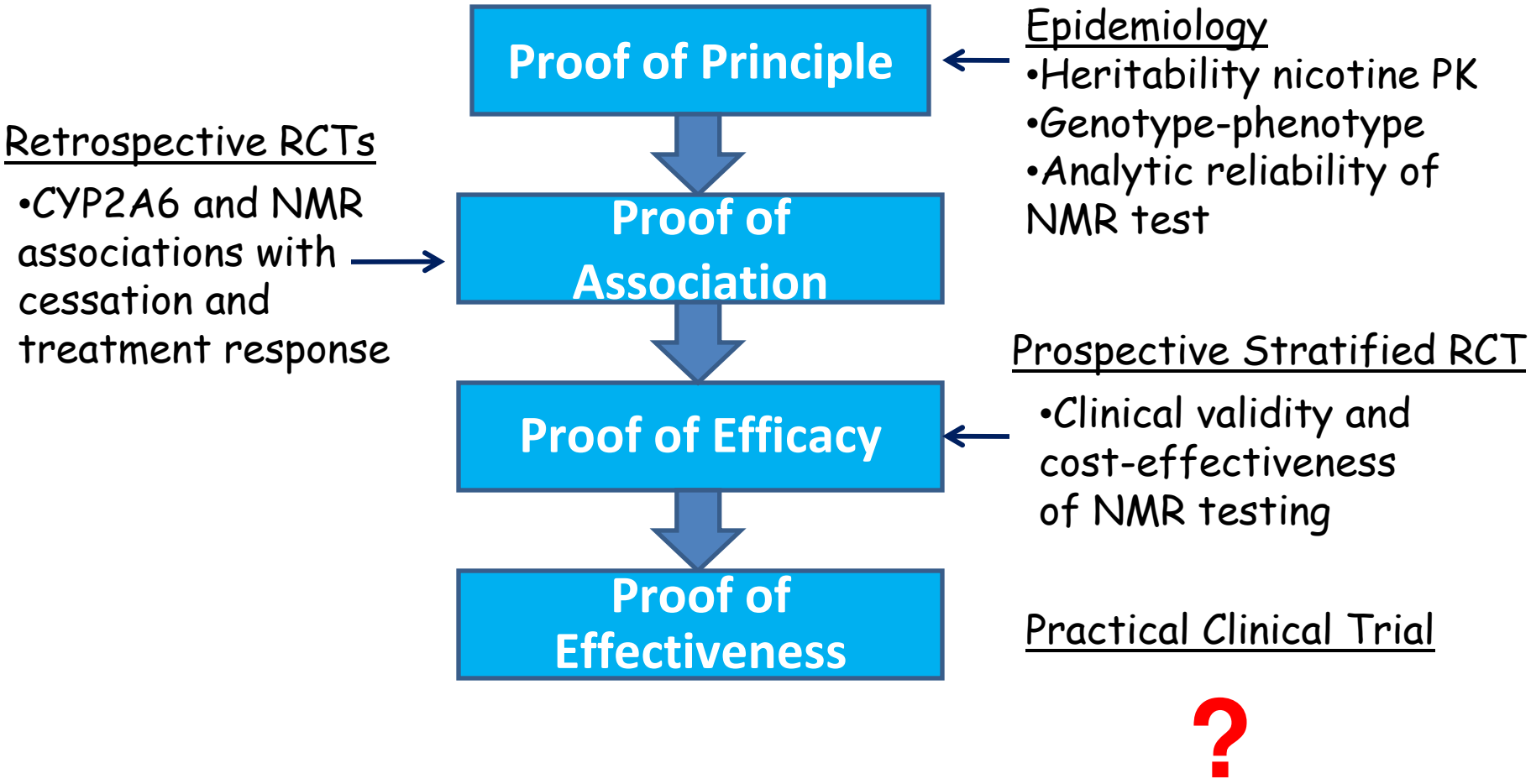


Validation of a Novel (Simple) Biomarker

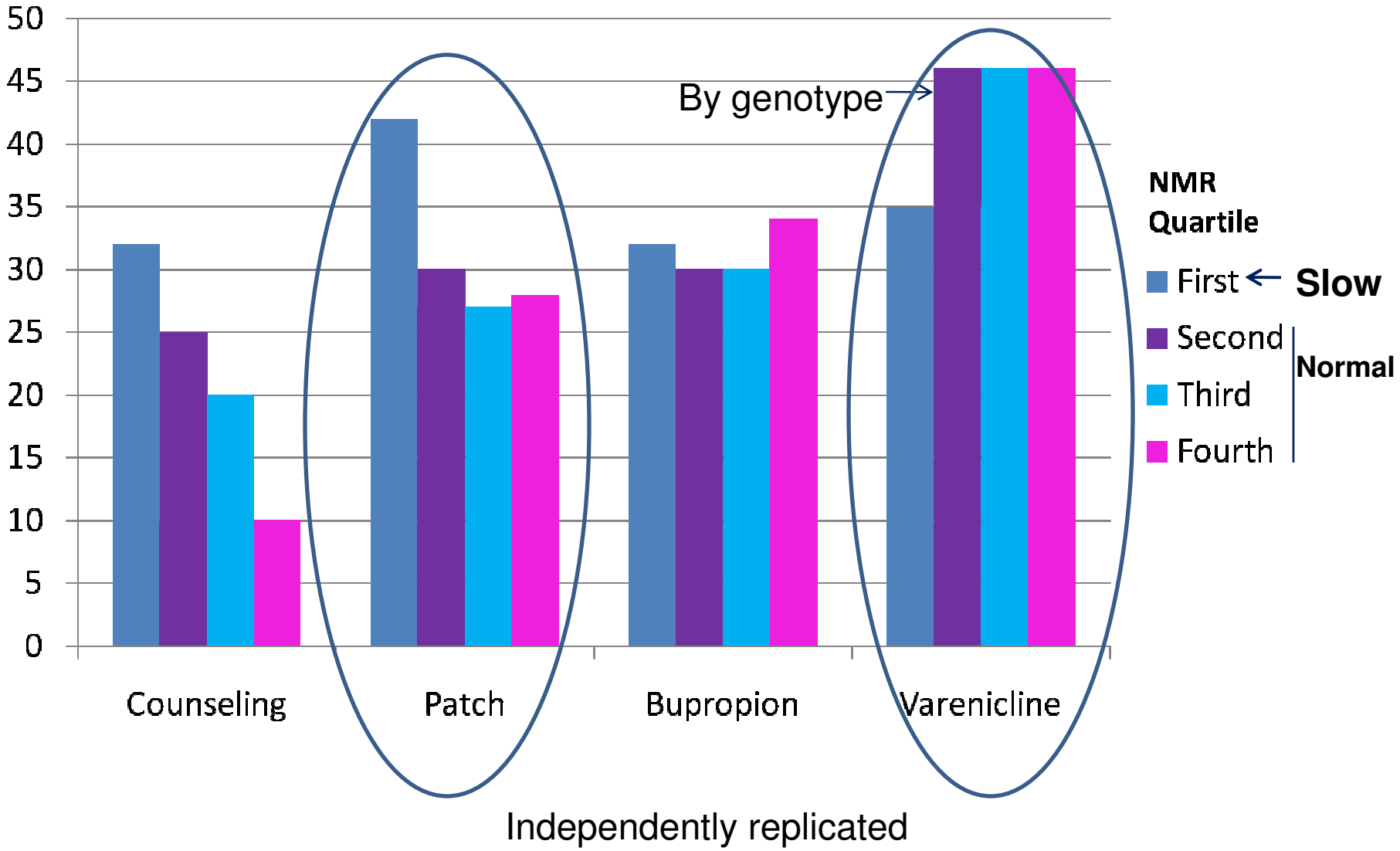
- The ratio of nicotine metabolites: 3'hydroxycotinine/cotinine
- A heritable and stable measure of nicotine metabolism rate derived from smoking
- Independent of time since last cigarette
- Can be measured in saliva, plasma, & urine
- Reflects genetic (CYP2A6) and environmental influences on nicotine clearance

Easy to perform in clinical practice

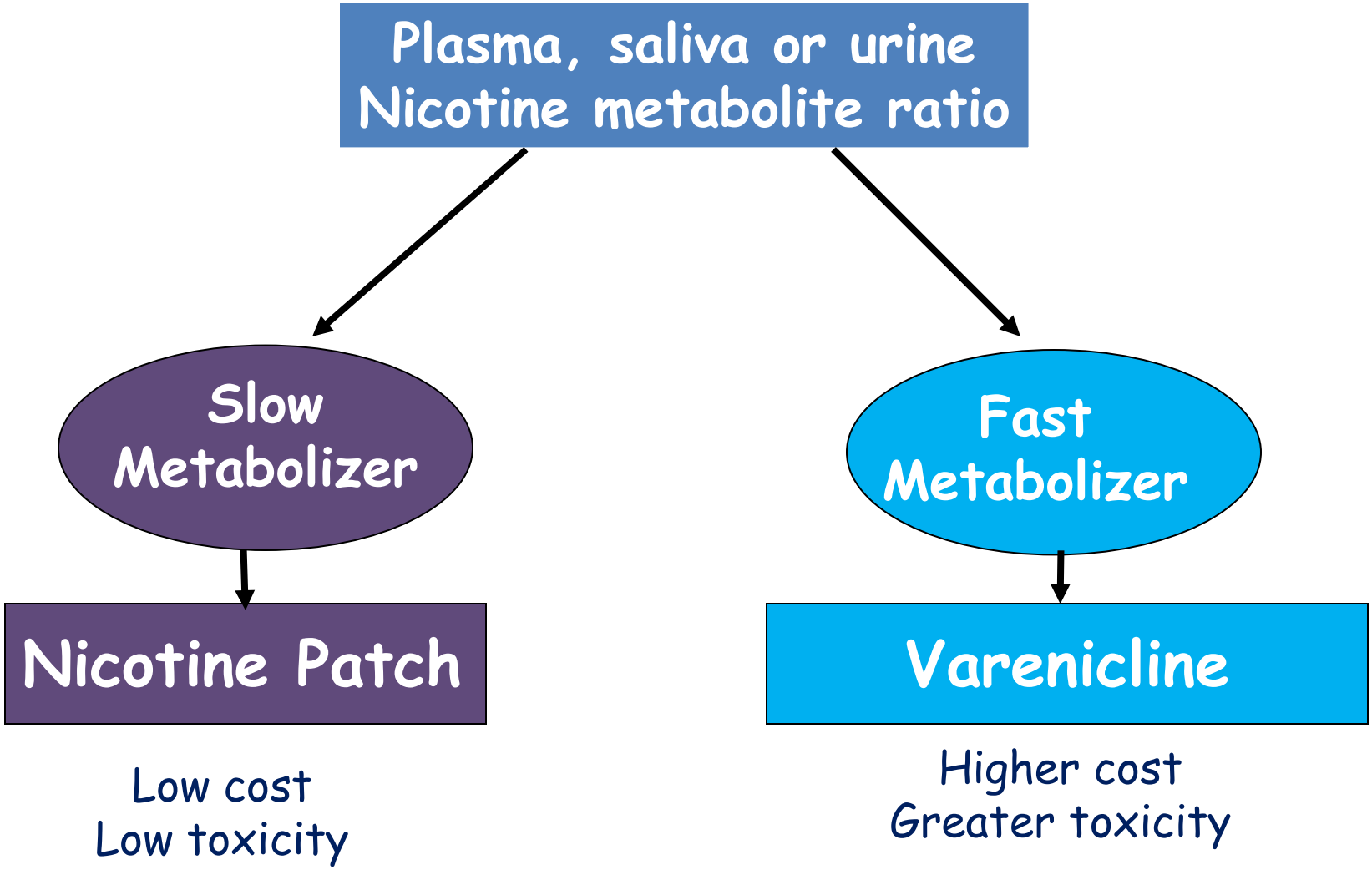
Validation Pathway for Genomically-Informed Biomarker



Retrospective Evidence for Association from Four Trials

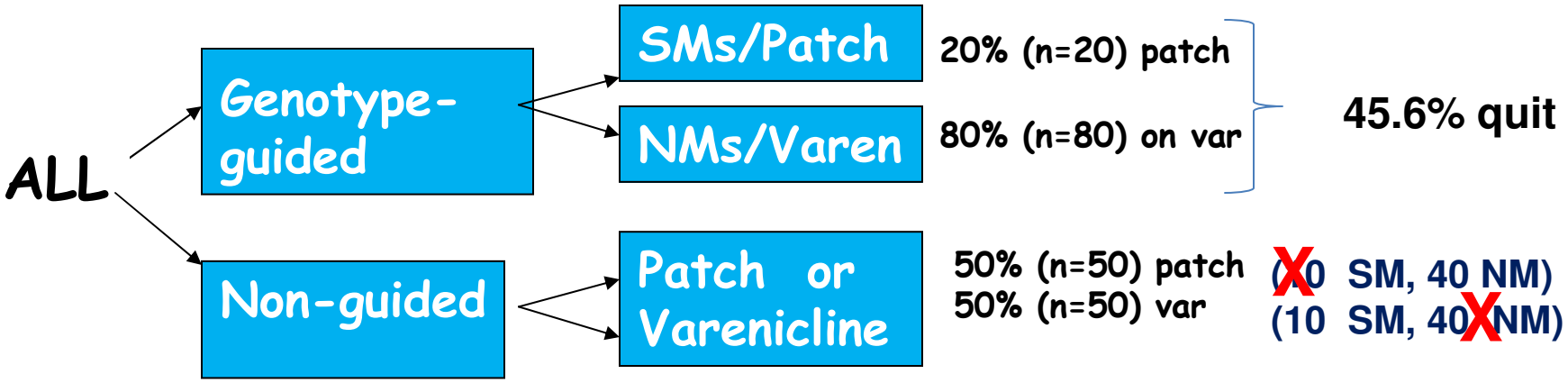


Algorithm for Use of Nicotine Metabolite Ratio to Personalize Choice of Therapy



Genotype-guided vs. Usual Care

For illustration: n=100/group, SM (20%) NM (80%)



10% (n=10) SMs **in both arms** get patch
40% (n=40) NMs **in both arms** get varenicline
50% (n=50) of participants in each arm get the same treatment!

As a Practical Clinical Trial, the level of noise would be increased significantly!

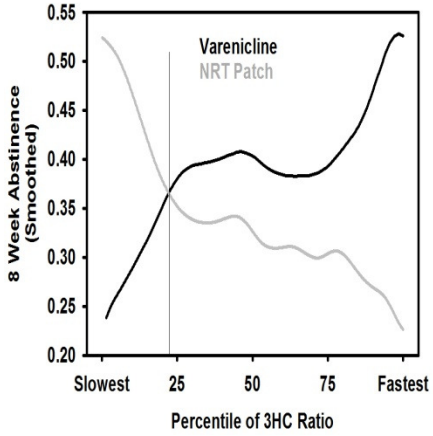
Prospective Stratified RCT

Quit Rate Estimates

Slow Metabolizers (SMs)

oversampled

N=675



N=675

Normal Metabolizers (NMs)

Test

A Placebo 30%

B Patch 44%

C Varenicline 35%

D Placebo 19%

E Patch 28%

F Varenicline 46%

Efficacy hypothesis

Costs and side effects tested similarly

Principles

1. One design does not fit all

   -retrospective and prospective RCTs are valid

   -prospective trials can overcome limitations, and use enrichment designs

   -in context of health care reform, an additional level of evidence may be required

Principles

2. PCTs address the translational gap

-not likely to supplant RCTs

-genotype guided vs. usual care designs inefficient under some scenarios

-by identifying limitations in generalizability through PCTs, one can identify issues to address (e.g., patient or provider nonadherence)

-consider PCTs as part of the validation pathway

Barriers

1. Consequences of enhancing generalizability at the expense of internal validity
2. Electronic health records
3. Research infrastructure
4. Peer review
5. Funding

Key Sources

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