Integrating Predictive Biomarkers and Classifiers into Oncology Clinical Development Programs

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Predictive Biomarkers are Sometimes Essential for Any Approval At All

- Detailed simulation: Herceptin® would not have succeeded if studied in general population
- Iressa® failed in early lung cancer because predictive biomarker of epidermal growth factor receptor (EGFR) mutations was not appreciated
- Vectibix®: K-ras mutation status required for approval in colorectal cancer

Sometimes the Need for a Predictive Biomarker Sneaks Up on You

- Erbitux®: K-ras mutation status will likely soon be required for colorectal cancer, altering Imclone's market

Sometimes a Biomarker Doesn't Work, or Isn't Needed

- EGFR expression does not predict response to Erbitux® in colorectal cancer
- Biomarker subsets were not required for sorafenib approval in renal cell cancer
  - But cost per QALY may suggest some biomarker work will be needed for these scenarios in the future

When Biomarkers Work, They Will…

- Generate products with real value, obvious to payors
- Result in smaller, cheaper Phase 3 studies:
  - Effective biomarker targeting means greater benefit
  - Needed Phase 3 study size gets 4 times smaller if the benefit doubles
- Reduce chance of failed Phase 3 studies, the largest contributor to poor ROI.
  - Herceptin® would have failed Phase 3 without predictive biomarker

When Biomarkers Don’t Work, They Will…

- Add cost
- Add complexity
- Add time

A Cross Functional Consensus

- Several years of cross functional discussion
- New clinical trial designs developed based on discussions
- Summarized in:
  - Beckman, R.A., Clark, J. & Chen, C. Integrating predictive biomarkers and classifiers into oncology clinical development programmes. *Nature Reviews Drug Discovery* **10,** 735-748 (2011)

Objectives

- **Increase utilization of biomarkers** in oncology clinical development plans
- **Provide broad *guidelines*** for incorporation of biomarkers into clinical development plans
- **Maximize efficiency of development** of personalized medicines (greatest throughput per resource unit expended)
- Manage risk across oncology portfolio by series of **adaptive, data-driven decisions**
- Create biomarker driven strategies which **address regulatory, commercial, and clinical execution issues**
- Achieve **cross-functional consensus** on clinical strategies in biomarker driven environment

Proposed Strategic Principles

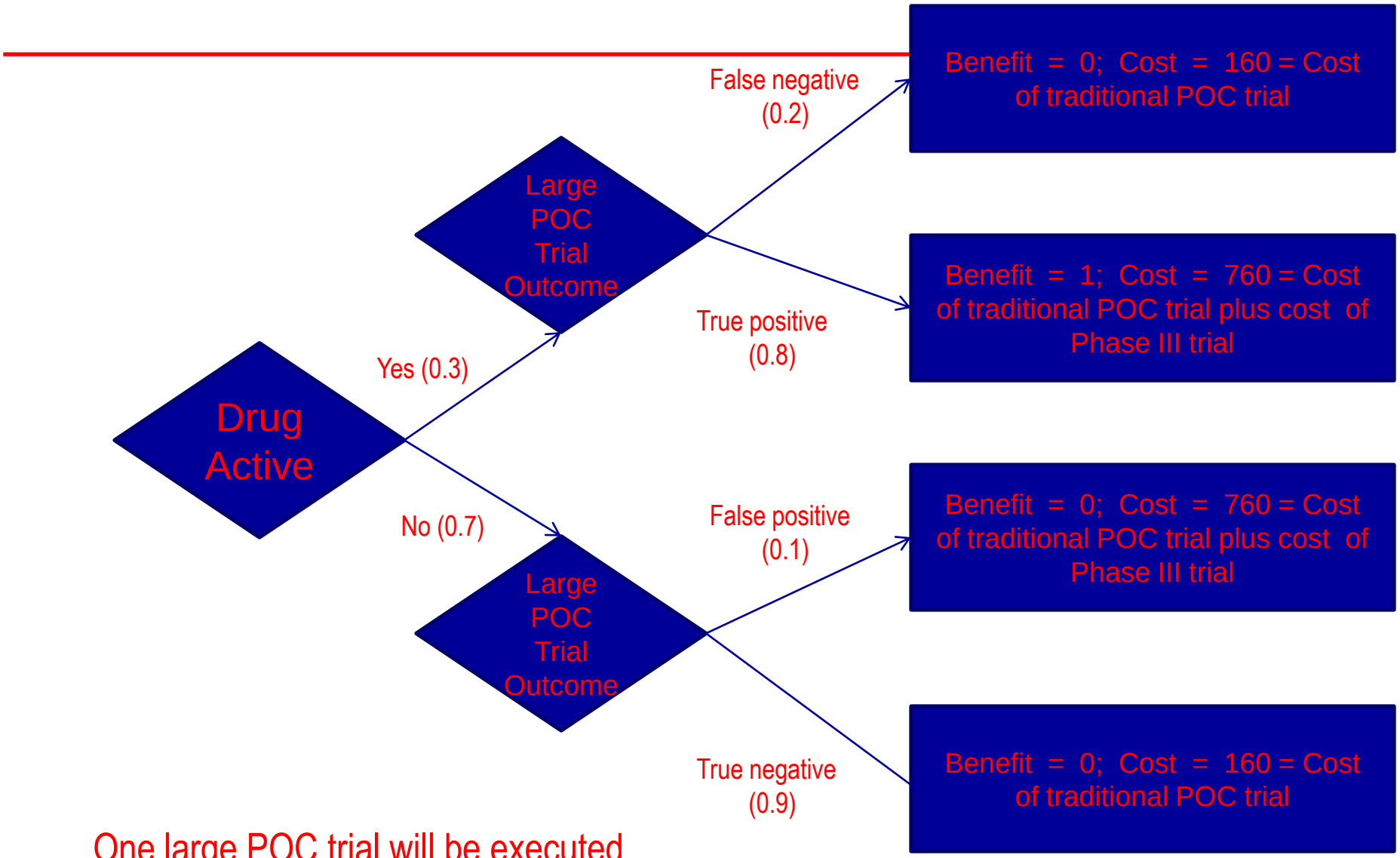
- Adaptive decision making
- Continuous integration of biomarker and clinical information
- Validation of clinical benefit ID hypothesis against qualified clinical endpoints
- Strategies designed to maximize objective functions such as utility per resource unit expended

Optimizing efficiency of clinical trials: example

- Efficiency optimized Phase 2 (P2) study*:
  - power and alpha chosen to maximize objective function of correctly identified effective drug per resource unit expended in P2/P3 development.
  - Results in smaller, more efficient *RANDOMIZED* studies, making biomarker work feasible.

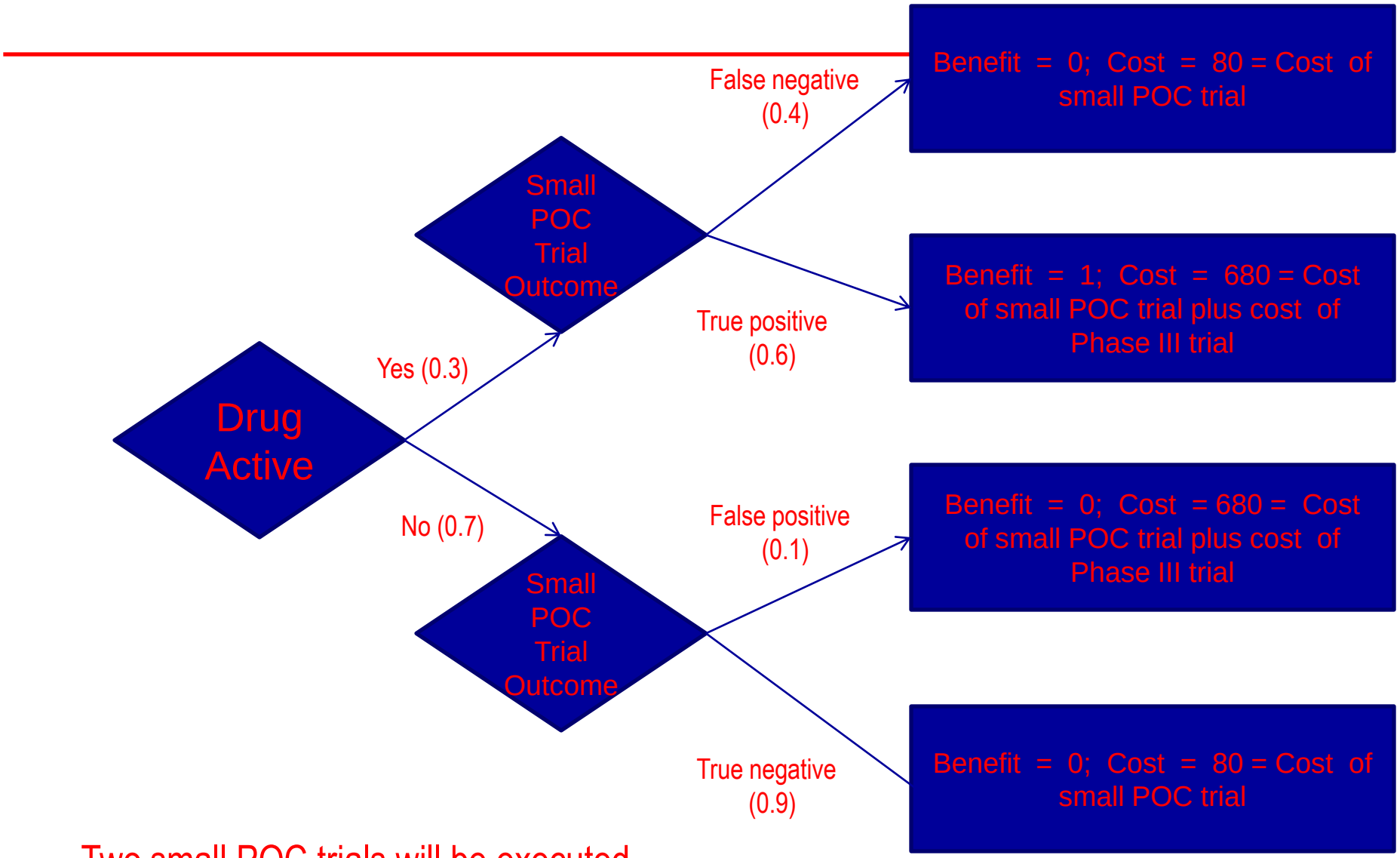
*Chen, Cong and Beckman, Robert A. Optimal Cost-Effective Designs of Phase II Proof of Concept Trials and Associated Go-No Go Decisions, *Journal of Biopharmaceutical Statistics*, 19: 424-436 (2009).

*Chen, Cong and Beckman, Robert A. Maximizing Return on Socioeconomic Investment in Phase II Proof-of-Concept Trials, *Clinical Cancer Research*, Published online before print, February 13, 2014.



One large POC trial will be executed

Risk adjusted benefit = 0.24; Risk adjusted cost 346 patients; Efficiency = 6.9×10^{-4}



Two small POC trials will be executed

Risk adjusted benefit = 0.18 X 2; Risk adjusted cost = 460 patients; Efficiency $7.8X10^{-4}$

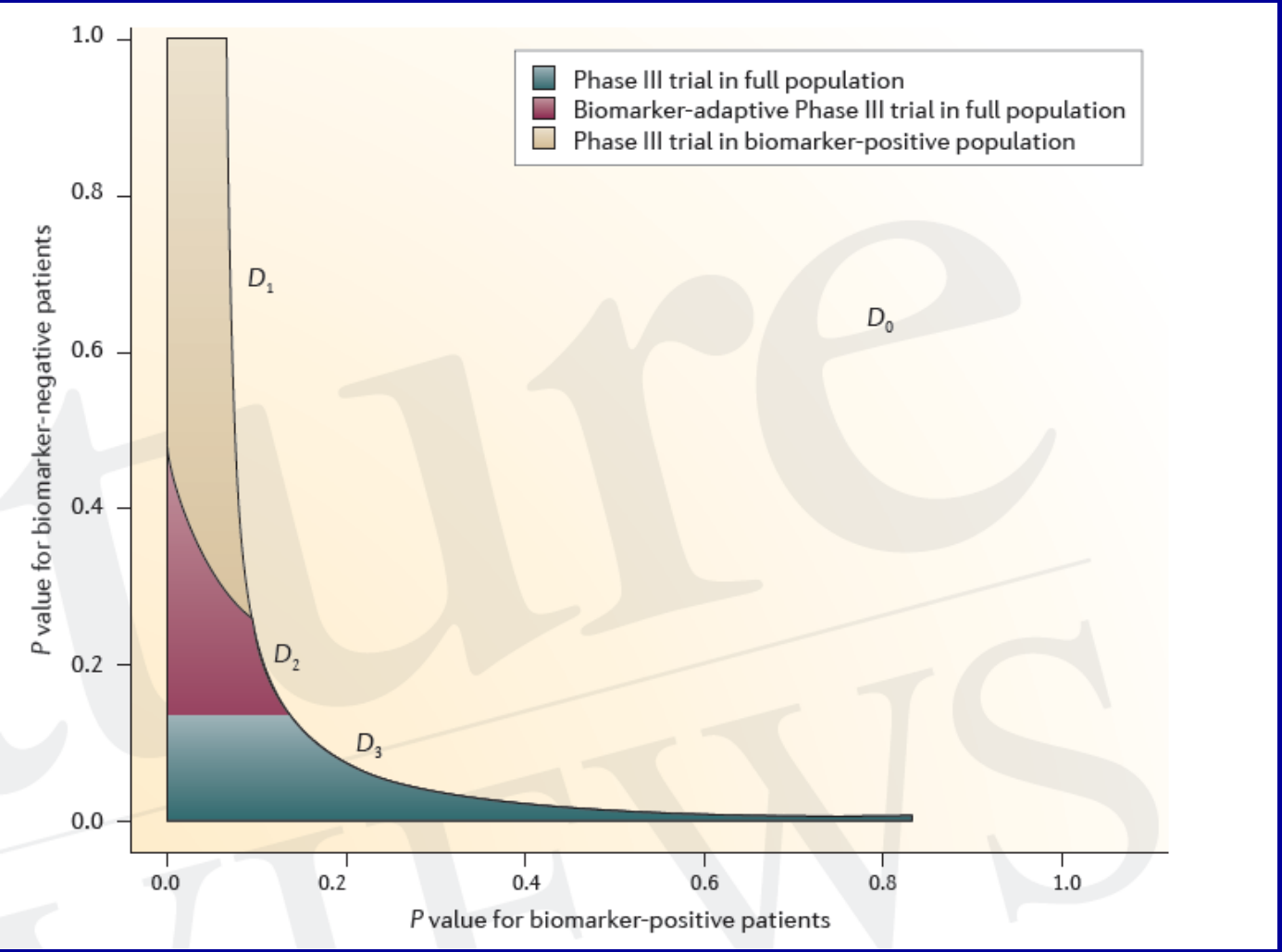
Departing from Tradition and the Type III Error

- Traditional Type I and II error describe the false positive and negative rates
- Type III error describes the opportunity cost of not investigating valid hypotheses due to budgetary limitations
- Under a fixed budget, smaller than traditional randomized Phase 2 studies are optimal

Example of adaptive study design (I)
The Biomarker enriched P2 study

- Biomarker (BM) enriched P2 study:
  - Designed to optimally test BM hypothesis by enrolling 50% BM+.
  - Trial powered for independent analysis of BM+ and BM- subsets.
  - Study has 4 groups: BM+ experimental, BM+ control, BM- experimental, BM- control
  - Size using Chen-Beckman method applied to BM+ and BM- subsets
- 2D decision rule (Clark): see next slide

2D Decision rule for MK-0646 triple negative breast cancer (Clark)

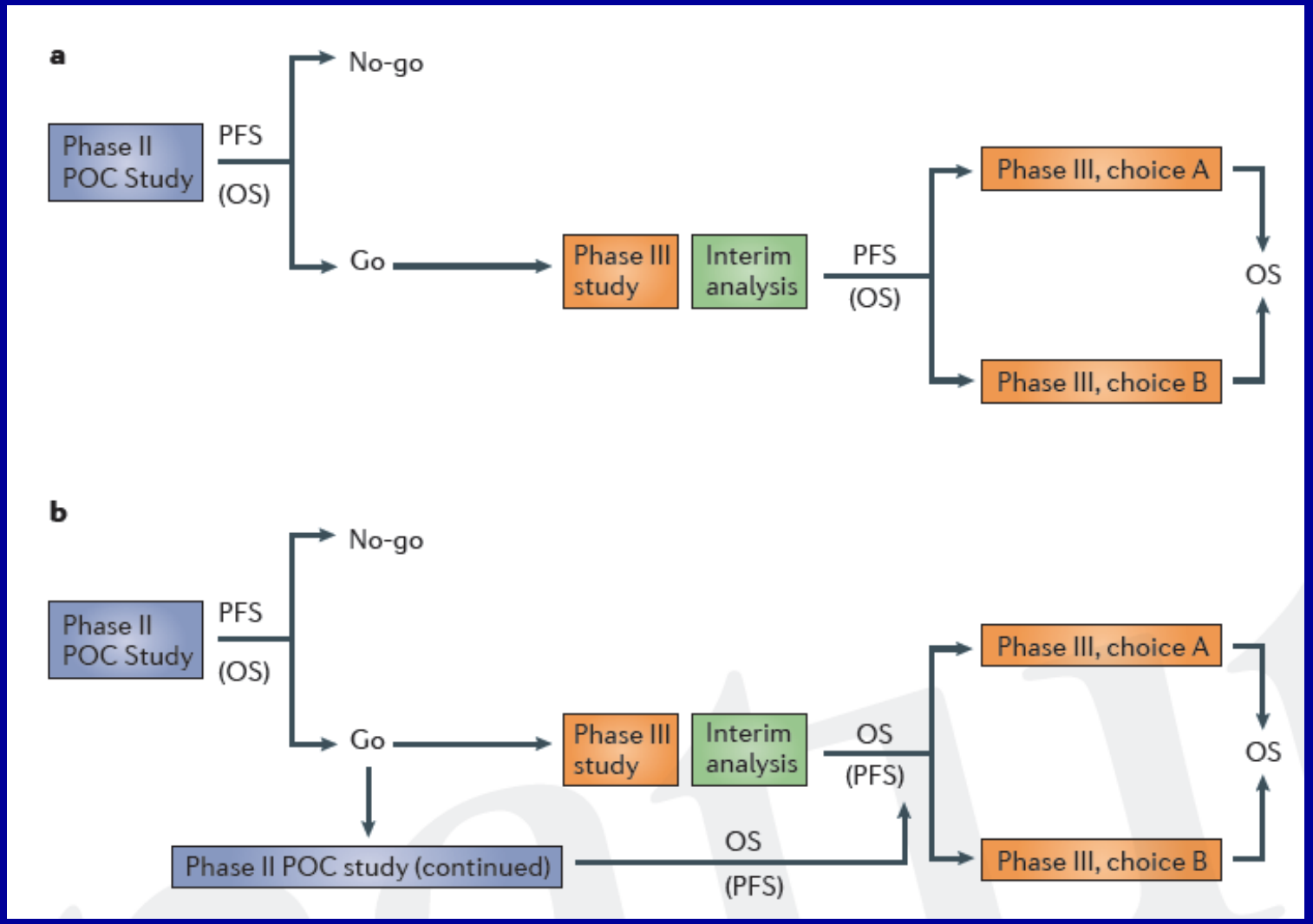


Example of adaptive study design (II)
The Biomarker adapted P3 study

- BM Adaptive P3*
  - Study proceeds in full population.
  - Use data from P3 up to interim analysis **and maturing data from P2** to:
    - Optimally focus analysis ("allocate alpha") between full and sub-population
    - Maximize utility per cost function, such as power per study size, or expected ROI
  - Greater ROI than either traditional or biomarker driven P3

*Chen, Cong, and Beckman, Robert A. Hypothesis Testing in a Confirmatory Phase III Trial with a Possible Subset Effect, *Statistics in Biopharmaceutical Research*, 1: 431-440. (2009).

Phase 2 Influencing Phase 3 Adaptation: The Phase 2+ Method



Summary

- Predictive biomarkers will be increasingly essential to deliver competitive patient value
- Proposed guidelines for incorporation of biomarker hypotheses into clinical plans
- Key features:
  - Prioritization of clinical benefit id biomarker hypotheses
  - Validation of primary biomarker hypothesis against qualified clinical benefit endpoints
  - Adaptive decision-making within programs to progress to decision of whole population or biomarker selected subset
  - Use of IVD candidate in late phase studies $\rightarrow$ available for simultaneous registration with product
  - Health authority buy-in

Next Generation Personalized Medicine*

*Beckman RA, Schemmann GS, and Yeang CH. Impact of genetic dynamics and single-cell heterogeneity on development of nonstandard personalized medicine strategies for cancer. Proceedings of the National Academy of Sciences USA. Published online before print August 13, 2012, doi: 10.1073/pnas.1203559109

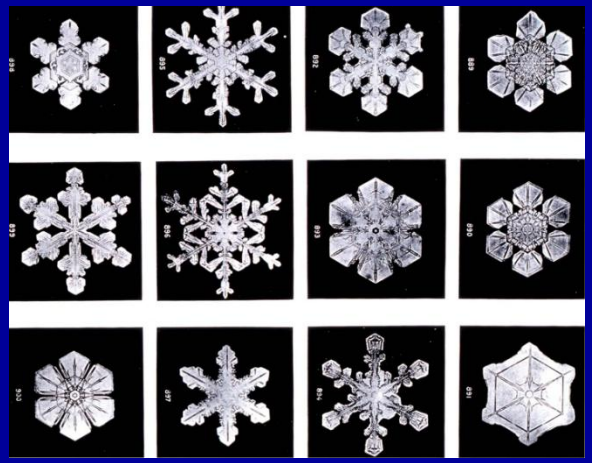
Heterogeneity *Within* Tumors

- Tumors are genetically unstable; this is the most efficient way for cancer to evolve*
- Genetic instability leads to multiple sub-populations of tumor cells
- Resistant sub-populations are selected in response to therapy
- This is likely the reason why targeted therapies generally work best as a complement to non-specific therapies like chemotherapy

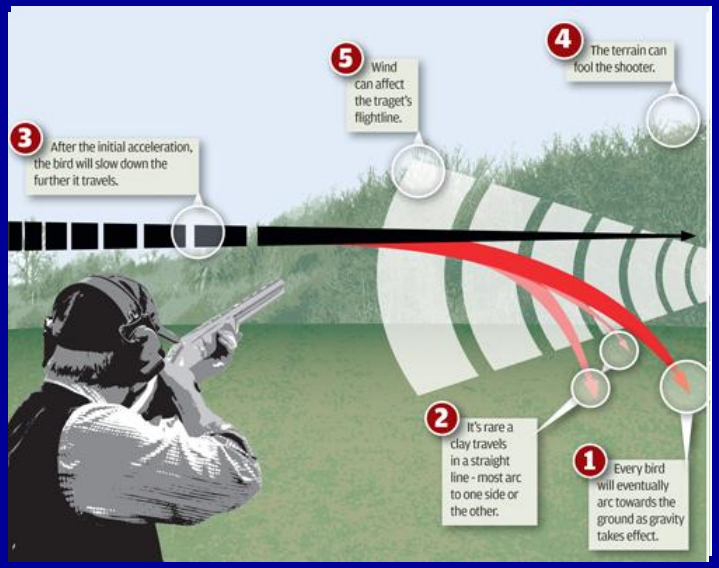
*Loeb, LA, Springgate CF, & Battula, N, "Errors in DNA Replication as a Basis of Malignant Changes," Cancer Research, 34: 2311-2321 (1974); Beckman, RA & Loeb, LA, "Efficiency of Carcinogenesis With and Without a Mutator Mutation," Proc. Nat. Acad. Sci. USA 103:14140-14145 (2006); Bielas, JH, Loeb, KR, Rubin, BP, True LD, and Loeb LA, "Human Cancers Express a Mutator Phenotype," Proc. Nat. Acad. Sci. USA 103: 18238-18242 (2006); Beckman, RA, "Mutator Mutations Increase Tumorigenic Efficiency Across Fitness Landscapes," PLoS One, 4: e5860 (2009); Beckman, RA. "Efficiency of carcinogenesis: is the mutator phenotype inevitable," Seminars in Cancer Biology, 20: 340-352 (2010)

Clinical Significance of the Mutator Hypothesis

- Heterogeneity

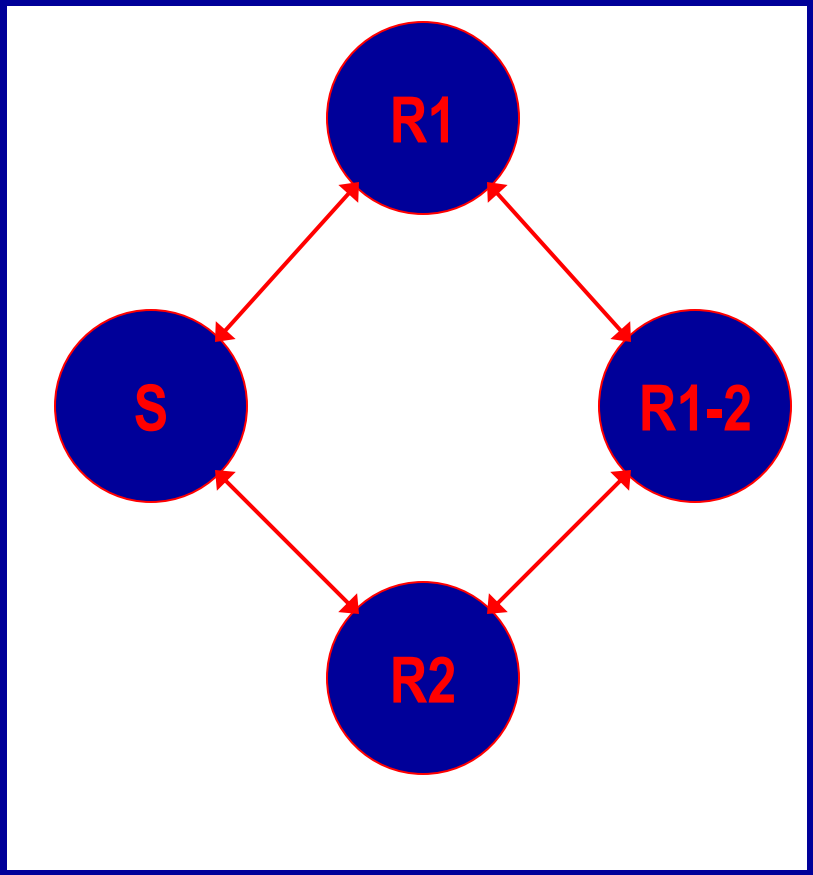


- Moving Target

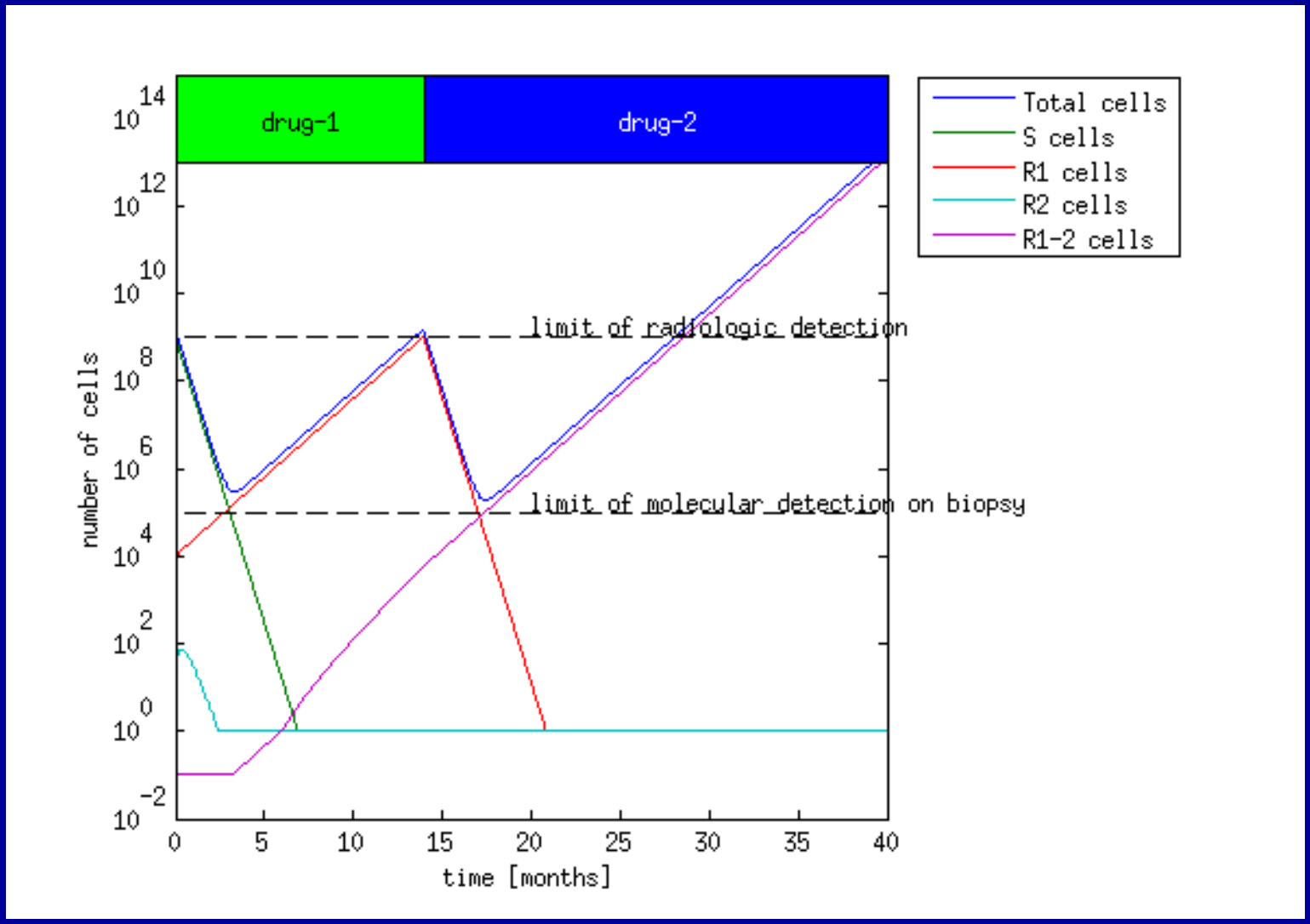


A Simple Model

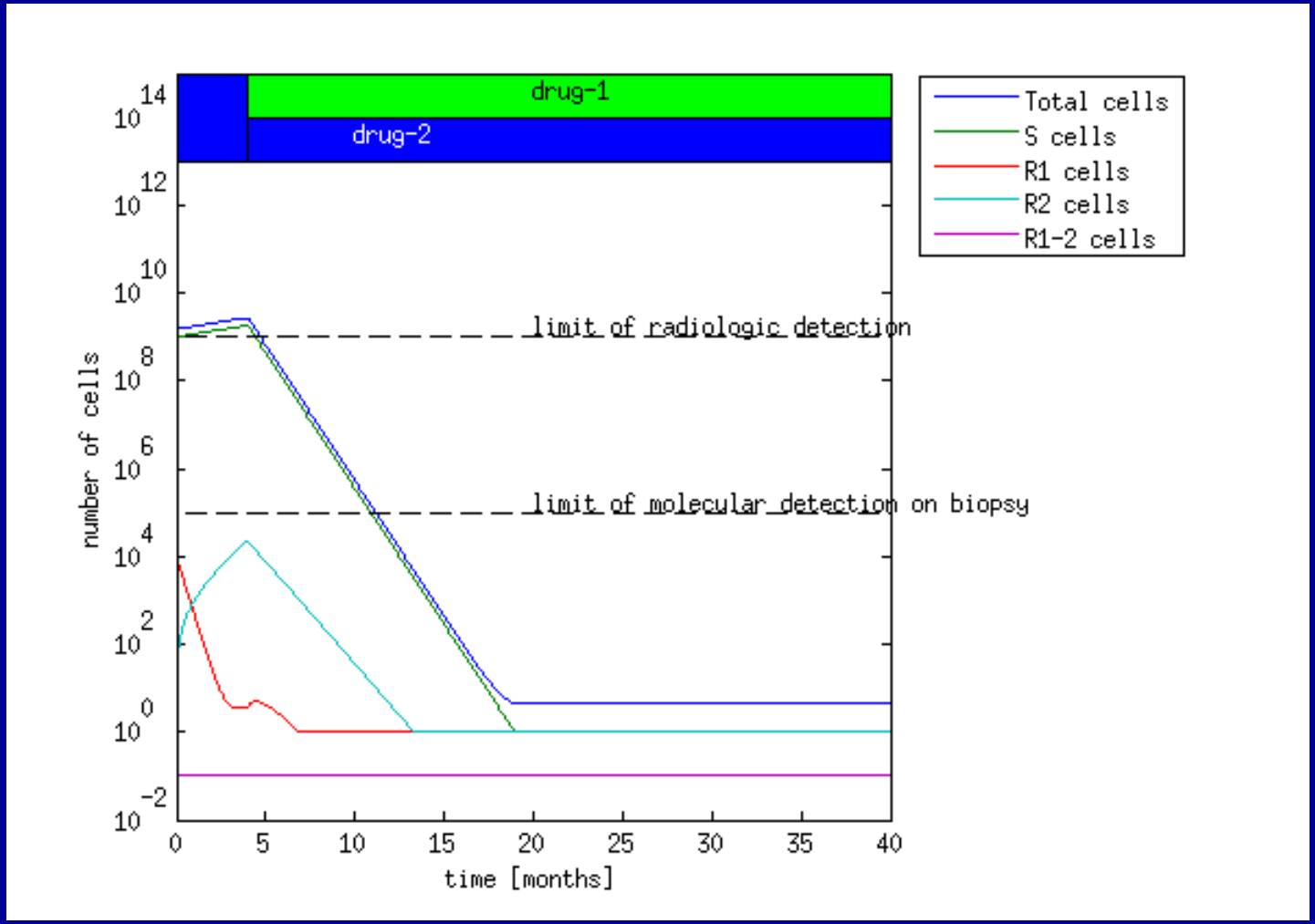
- Two drugs: Drug-1 and Drug-2
- Four cell types:
  - Sensitive cell S, killed by both Drug-1 and Drug-2
  - Resistant cell R1, killed only by Drug-2
  - Resistant cell R2, killed only by Drug-1
  - Incurable doubly resistant cell R1-2
- Genetic and epigenetic transitions between cell types
- Cell growth and death affected by drugs in dose dependent manner
- Partial resistance
- Patient can have a **mixture** of cells, which **evolves** over time



Current Personalized Medicine: 28 months to incurable relapse



Next Generation Personalized Medicine: Cure



Key questions

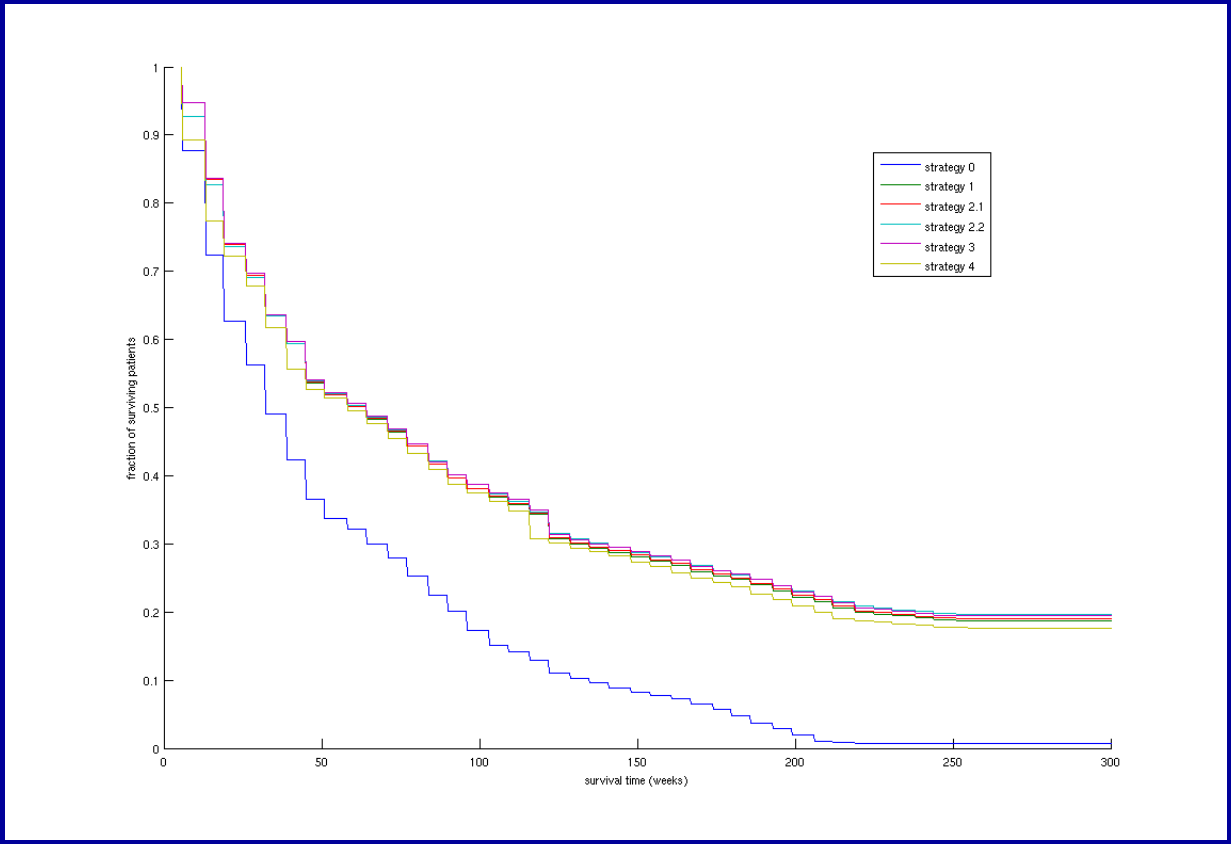
- How general are the benefits of this illustrative example?
- How great are the potential benefits of next generation personalized medicine?
- When is it important to focus on prevention of resistance as an even higher priority than treatment of the current tumor?

In Silico “Clinical Trial”: 3 million “patients”

Strategies

- A **strategy** is a data-driven method for planning a sequence of therapies
  - When to treat with a combination and when to treat with sequential monotherapy
  - When to change therapies
- Like therapies, ***strategies*** may be individualized
- The simulation compared 6 strategies
  - Strategy 0 is the personalized medicine strategy: the patient is treated with the best drug for the observed predominant cell type and switched to the alternative drug upon tumor progression or relapse.
  - Strategies 1, 2.1, 2.2, 3, and 4 (see backup for detail):
    - Used the evolutionary model to predict the total cell number and the likelihood of forming an incurable cell at the next 45 day timepoint
    - Gave therapy that minimized either total cell number or incurable cell likelihood
    - Differed in method of prioritizing total cell number vs incurable cells

Benefit of next generation personalized medicine is very general



Differences between Current Personalized Medicine and Next-Generation Personalized Medicine

Current Personalized Medicine:

Focus on average molecular characteristics

Focuses on current molecular characteristics and/or those at dx

Thinks primarily of current step

Mathematical optimization to inform current step (signatures)

Next Generation Personalized Medicine:

Minority subpopulations may be important

Considers endgame, especially "penultimate states"

Attempts to think several steps ahead

Piecewise, or even global, optimization of entire treatment course

Next Generation Personalized Medicine: High Level Conclusions

- The current strategy used for personalized therapy of cancer is not the only possible one
- Genetic heterogeneity and evolutionary dynamics can greatly influence the optimal strategy for personalized medicine
- The systematic study of **non-standard personalized medicine strategies** as a function of population substructure and evolutionary dynamics is an important area for investigation
  - It's not just about these particular models or strategies
- Benefits are potentially highly significant and very general across a large variety of tumor and therapy characteristics

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