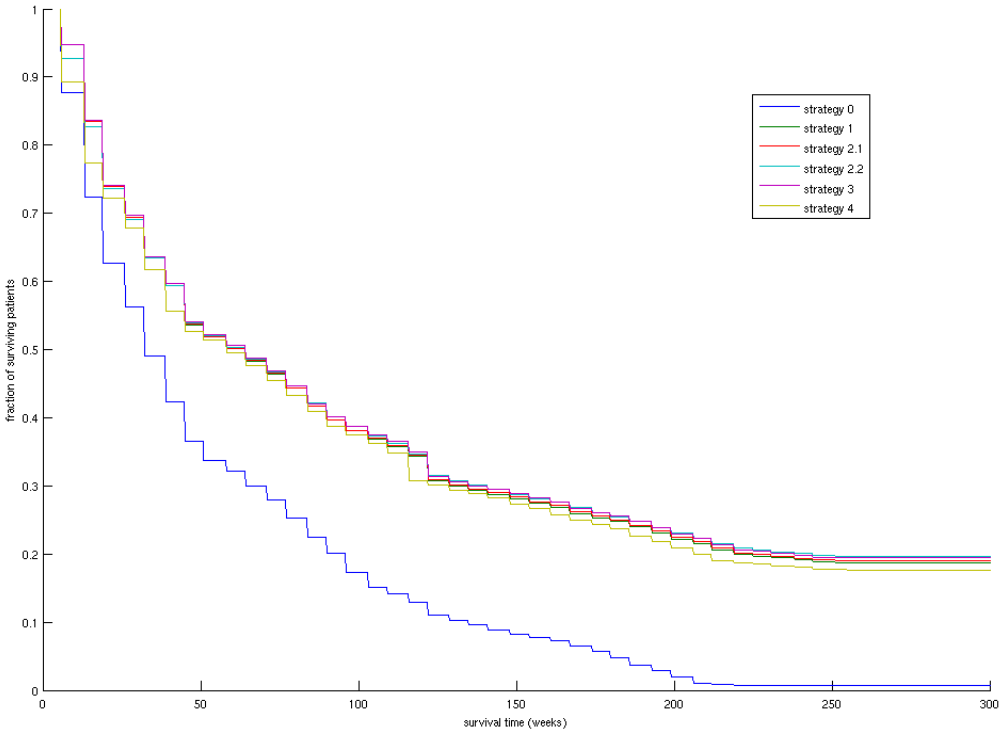
# Summary

- Tumors are genetically unstable, increasing the clinical importance of evolutionary dynamics. Analysis by:
  - Efficiency of carcinogenesis
  - Focused quantitative modeling
  - Predicted features of current experimental data before TCGA
- We have developed nonstandard personalized medicine strategies that significantly improve predicted survival times and cure rates
- Current personalized medicine strategies focus on:
  - average molecular properties of a tumor sample
  - at a particular point in time (usually at diagnosis)
  - with the goal of optimizing the next 1-2 therapeutic maneuvers
- Nonstandard personalized medicine strategies explicitly consider:
  - sub-clonal structure
  - evolutionary dynamics
  - risks of predicted future states
  - with the goal of optimizing the entire multi-step therapeutic plan

# Benefit of nonstandard personalized medicine is very general



# Nonstandard 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 about this model or these strategies
- Benefits are potentially highly significant and very general across a large variety of tumor and therapy characteristics

# Nonstandard Personalized Medicine Strategies for Cancer May Improve Patient Outcomes

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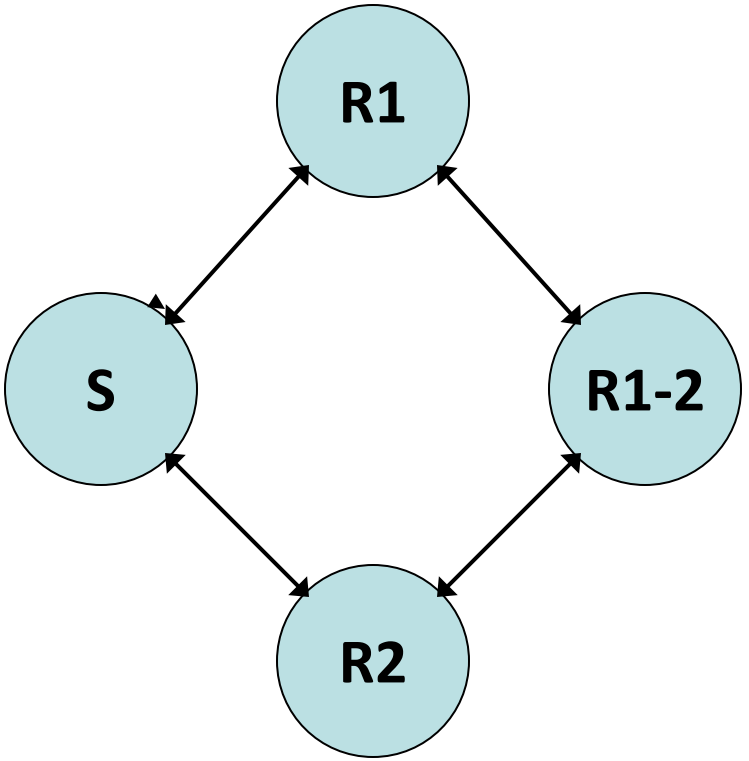
# Publications


1. Beckman, Robert A., Schemmann, Gunter S., and Yeang, Chen-Hsiang. 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, 109: 14586-14591 (2012).
2. Beckman, Robert A. Efficiency of Carcinogenesis: Is the Mutator Phenotype Inevitable? *Seminars in Cancer Biology*, 20: 340-352 (2010).
3. Beckman, Robert A. Mutator Mutations Enhance Tumorigenic Efficiency across Fitness Landscapes, *PLoS One*, 4: e5860 (2009).
4. Loeb, Lawrence A., Bielas, Jason H., and Beckman, Robert A. Cancers Exhibit a Mutator Phenotype: Clinical Implications, *Cancer Research*, 68: 3551 (2008).
5. Beckman, Robert A., and Loeb, Lawrence A. Efficiency of Carcinogenesis With and Without a Mutator Mutation, *Proceedings of the National Academy of Sciences,* 103, 14140 (2006).
6. Beckman, Robert A., and Loeb, Lawrence A. Negative Clonal Selection in Tumor Evolution. *Genetics*, 171, 2123 (2005).
7. Beckman, Robert A., and Loeb, Lawrence A. Genetic Instability in Cancer: Theory and Experiment. *Seminars in Cancer Biology*, 15, 423 (2005).

# A Simple Model

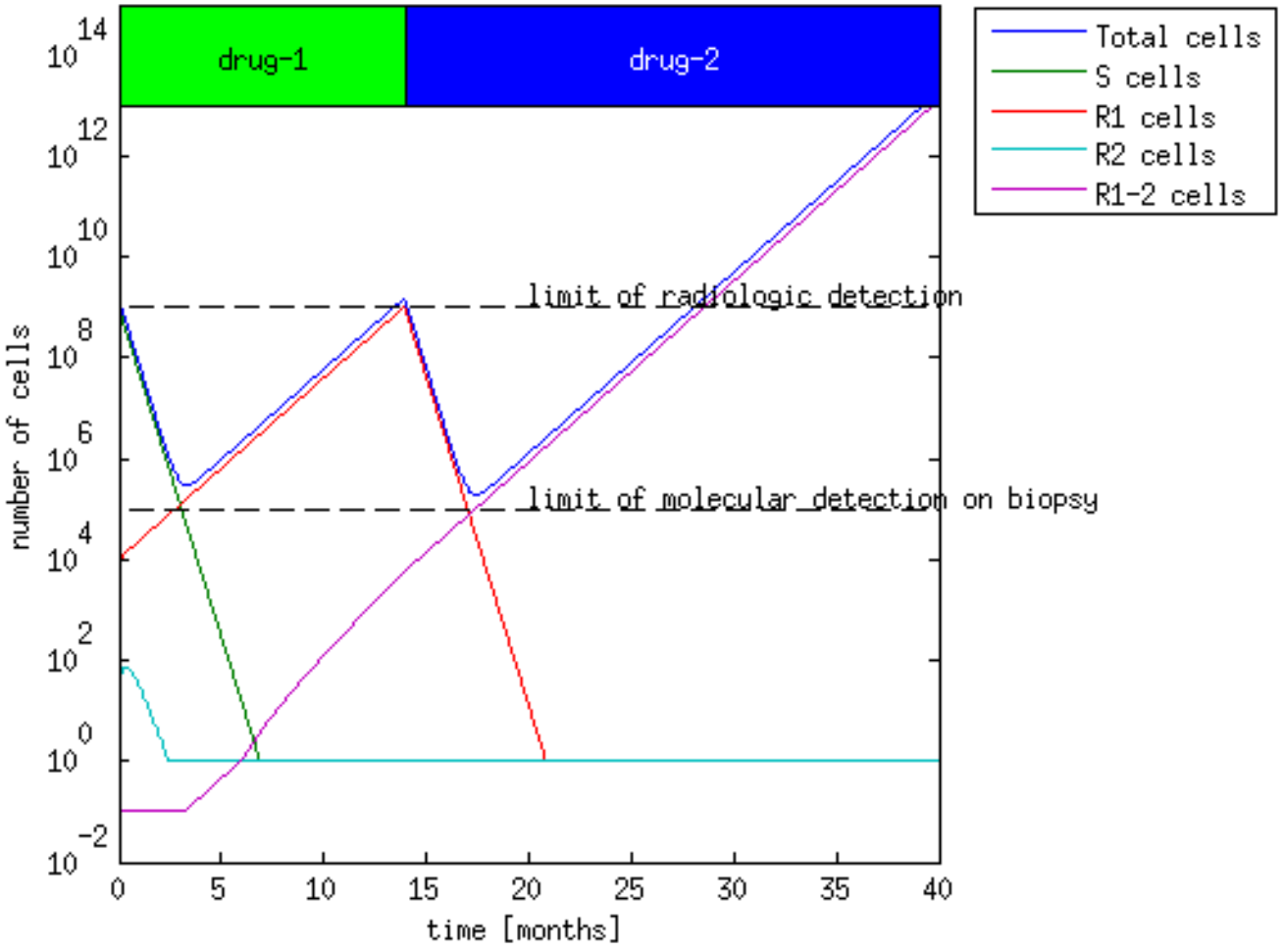
- Two non cross resistant drugs or drug combos: Drug-1 and Drug-2 (i.e. RAF-MEK, PI3K)
- Four cell types:
  - Sensitive cell S, killed by both Drug-1 and Drug-2
  - Resistant cell R1, killed only by Drug-2
  - Resistant cell R2, killed only by Drug-1
  - Incurable doubly resistant cell R1-2
- Genetic 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



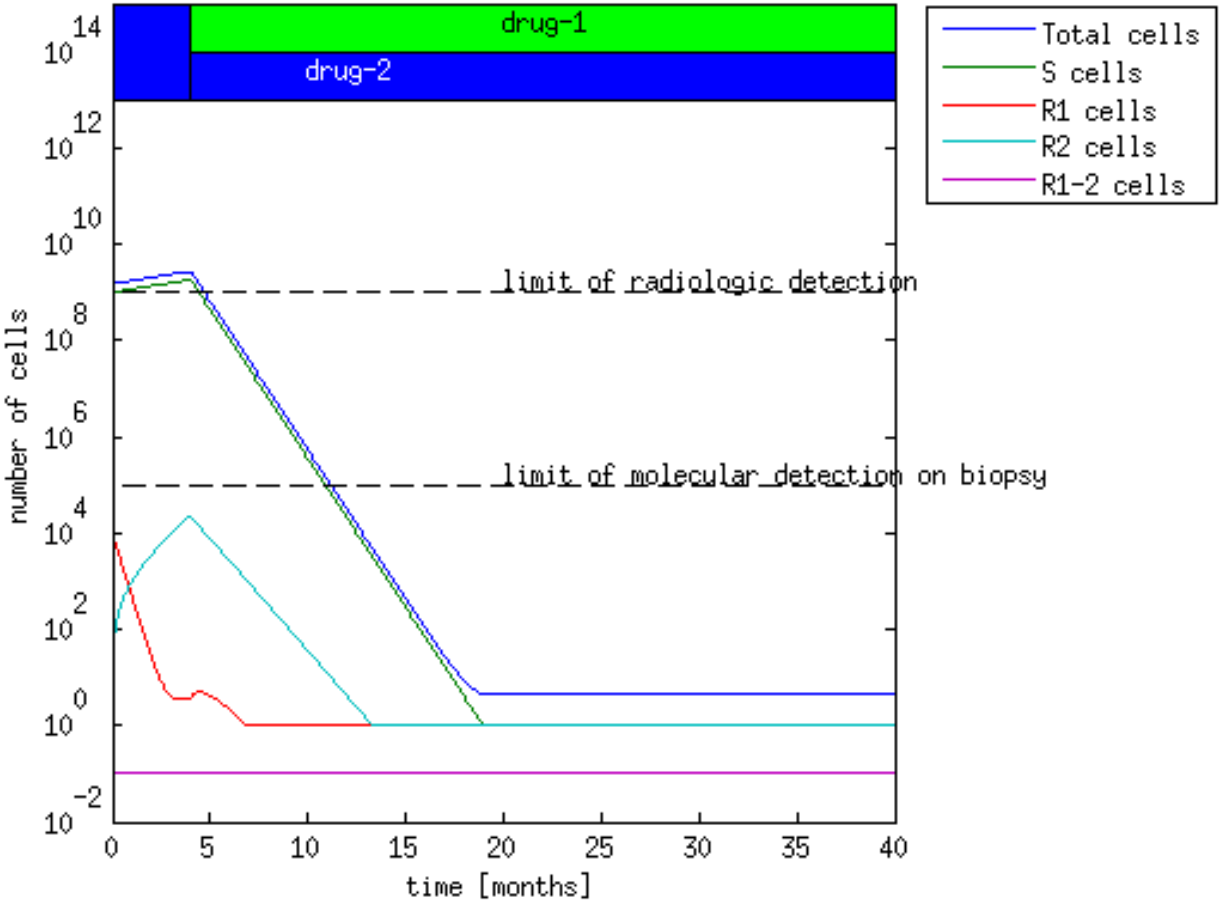
# This Model Addresses Real Systems

- Anti-EGFR therapy in non-small cell lung cancer:
  - patients with sensitizing mutations develop resistance by EGFR T790M mutations
  - hsp90 inhibitors and other agents may address these populations
  - Sensitive subclone persists
- Vemurafenib therapy in b-raf mutated melanoma: other targeted agents may address some mechanisms of resistance outside the ras-raf-mek pathway
- FLT-3 ITD AML: different specific inhibitors available for different resistance mutations

# Current Personalized Medicine: 28 months to incurable relapse



# Nonstandard Personalized Medicine



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

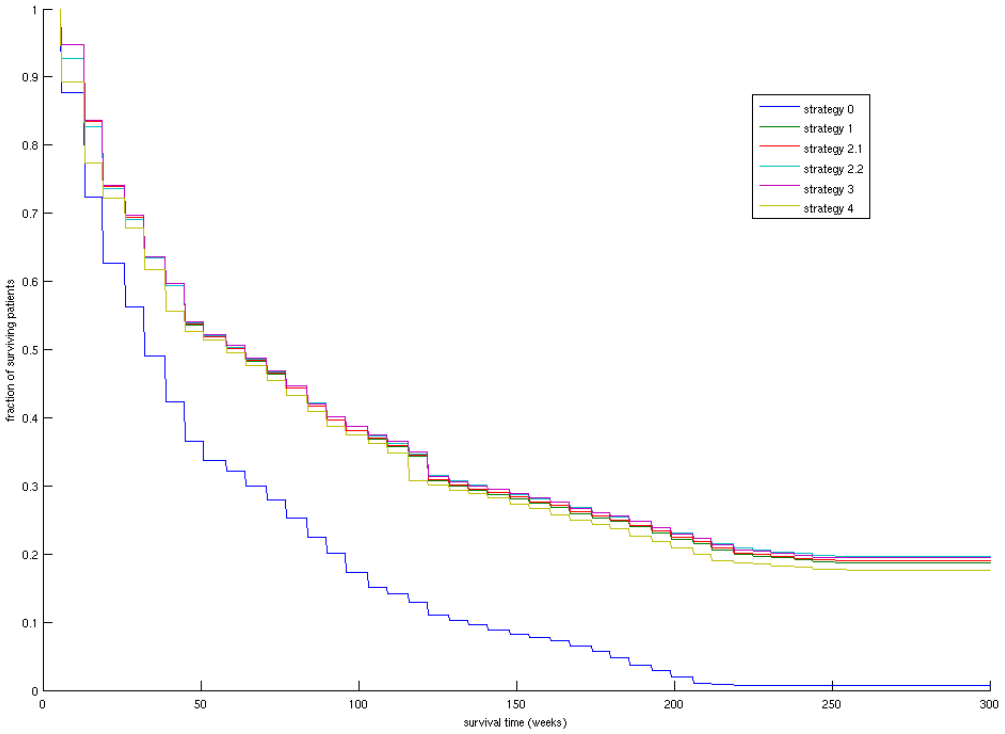
Examined 30 million parameter configurations encompassing:

- Different initial populations
- Different growth rates
- Different transition rates
- Different levels of sensitivity and resistance to drugs
- Parameters were chosen to encompass all reasonable possibilities based on preclinical and clinical literature and experience, providing:
  - A pan oncology sensitivity analysis

# 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.
    - **note: each "drug" may itself be a combination designed to kill a single subclone**
  - 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 nonstandard personalized medicine is very general



# Benefit of nonstandard personalized medicine is significant

| | Strategy 0 | Strategy 1 | Strategy 2.1 | Strategy 2.2 | Strategy 3 | Strategy 4 |
|---|---|---|---|---|---|---|
| Median survival,weeks | 26 | 58 | 58 | 58 | 58 | 51 |
| Mean survival, weeks | 48.4 | 95.3 | 95.7 | 96.5 | 96.8 | 91.7 |
| 5 year survival, percent | 0.7 | 18.7 | 19.0 | 19.7 | 19.4 | 17.6 |

# Differences between Current Personalized Medicine and Nonstandard Personalized Medicine

| **Current Personalized Medicine:** | **Nonstandard Personalized Medicine:** |
| --- | --- |
| Focus on average molecular characteristics | Minority subpopulations may be important |
| Focuses on current molecular characteristics and/or those at dx | Considers endgame, especially “penultimate states” |
| Thinks primarily of current step | Attempts to think several steps ahead |
| Mathematical optimization for signature development at current step | Piecewise, or even global, optimization across the treatment course |

# Nonstandard 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
  - The statement above is not obvious to the oncology mainstream
  - It's not about this model or these strategies
- Benefits are potentially highly significant and very general across a large variety of tumor and therapy characteristics

# Testing the Hypothesis

# What Hypothesis Are We Testing

- The evolutionary simulation identifies over one million cases out of three million simulated where evolutionarily-driven therapy is significantly superior to current personalized medicine paradigms
  - An important theoretical goal is to cluster these many cases to identify a manageable number of hypotheses about cancer therapy. The simulation might contain up to one million testable hypotheses. At least, it is unlikely that each of these cases teaches the same lesson
- One testable hypothesis has clearly been identified in the example case given in the Beckman, Schemmann, Yeang PNAS 2012 paper on non-standard personalized medicine:
  - The hypothesis in this case is that a rare subclone should be the priority for treatment if it is at high risk for acquiring resistance to all available agents (“incurability”). Treatment according to the model will give the counterintuitive recommendation to first eradicate this high risk sub-clone unless the tumor burden is acutely life-threatening

# Experimental Validation: Specific Aims

- Identify two or more non-cross resistant targeted agents of clinical relevance
  - Develop cells that are sensitive and singly resistant to each of these agents (in vitro) (may use Schlegel methods)
  - Tag cells with lentiviral integration (DNA barcoding), fluorescent tag or other methods
  - Measure growth, death, drug sensitivity parameters for these cell types (in vitro)
  - Measure heritable transition rates between phenotypic states (may need to increase mutation rate; methods are available)
  - Molecular characterization of resistance mechanisms
- In vitro or in vivo (mice or zebrafish):
  - Establish transplant models doped with predefined ratios of sub-populations
  - Test and iteratively refine strategies using tagged cells

# Prerequisites for Clinical Study

- Identify disease state that does not require instant therapeutic decisions (ie not AML or high grade lymphoma)
- Identify two or more non-cross-resistant targeted agents important in treatment of disease
- Develop methods for quantifying resistant and sensitive populations to both drugs from blood or marrow samples
  - Either: clonal growth of limiting dilutions on agar
  - Or: identify by genetic state tied to resistance---ie PCR
- Optional for heme malignancies:
  - Measure growth and death rates of these types of cells with and without drug and transition rates between phenotypic states in the lab
  - See preclinical deck for details

# CTCs for Observing Dynamics

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Detection of Mutations in *EGFR* in Circulating Lung-Cancer Cells

Shyamala Maheswaran, Ph.D., Lecia V. Sequist, M.D., M.P.H., Sunitha Nagrath, Ph.D., Lindsey Ulkus, B.S., Brian Brannigan, B.A., Chey V. Collura, M.S., Elizabeth Inserra, B.S., Sven Diederichs, Ph.D., A. John Iafrate, M.D., Ph.D., Daphne W. Bell, Ph.D., Subba Digumarthy, M.D., Alona Muzikansky, M.S., Daniel Irimia, Ph.D., Jeffrey Settleman, Ph.D., Ronald G. Tompkins, M.D., Thomas J. Lynch, M.D., Mehmet Toner, Ph.D., and Daniel A. Haber, M.D., Ph.D.

# Clinical trial part 1: information gathering

- Treat a cohort of patients with single agent or combinations of the two non-cross resistant targeted therapies
- Measure burden of sensitive, singly resistant and doubly resistant cells frequently
- Onco-Mind will use this data to estimate growth and death rates with and without therapy and transition between states in the patients
- Based on these estimates, Onco-Mind will develop an evolutionary model that can rapidly produce dynamic recommendations for therapy in a future cohort of patients

# Clinical trial part 2: randomized test of evolutionary dynamics directed therapy

- Arm A: use of two targeted agents according to standard methods
- Arm B: use of the two targeted agents guided by evolutionary dynamics
  - At time 0 and at regular intervals, evolutionary dynamics recommendations will be updated based on blood sampling.
  - Rate limiting step for turnaround time is likely to be measuring the cell numbers. TAT once data reaches Onco-Mind can be in one day