Developing & Validating Genomic Classifiers

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“Biomarkers”

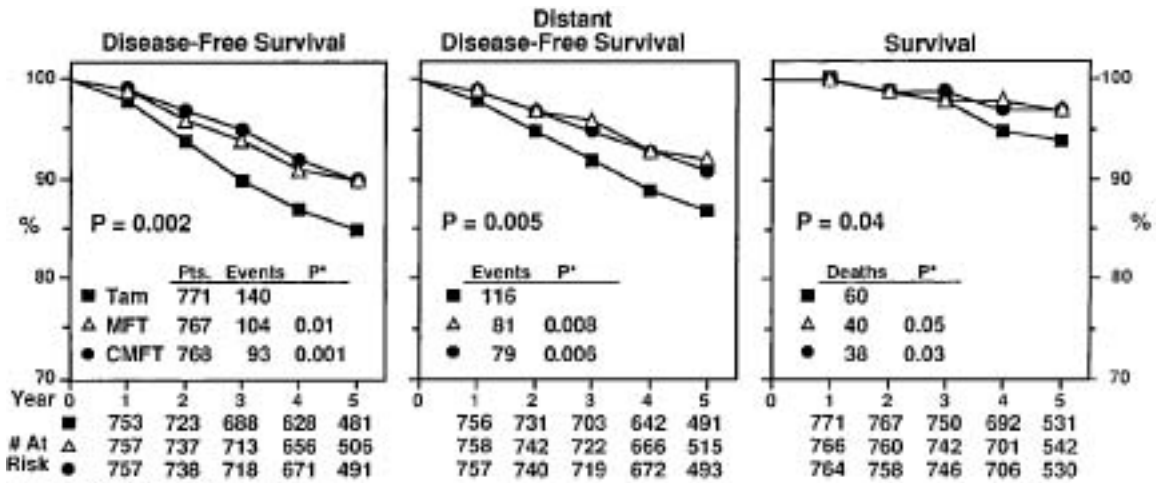
- Surrogate endpoints
  - A measurement made on a patient before, during and after treatment to determine whether the treatment is working
- Predictive classifier
  - A measurement made before treatment to predict whether a particular treatment is likely to be beneficial

Surrogate Endpoints

- It is extremely difficult to properly validate a biomarker as a surrogate for clinical outcome. It requires a series of randomized trials with both the candidate biomarker and clinical outcome measured
- Biomarkers for use in phase I/II studies need not be validated as surrogates for clinical outcome

Predictive Biomarkers

- Most cancer treatments benefit only a minority of patients to whom they are administered
  - Particularly true for molecularly targeted drugs
- Being able to predict which patients are likely to benefit would
  - save patients from unnecessary toxicity, and enhance their chance of receiving a drug that helps them
  - Help control medical costs



* Comparison to Tamoxifen

	RELATIVE RISK (95% CONFIDENCE INTERVAL)		
MFT/Tam	0.72 (0.56-0.93)	0.68 (0.51-0.90)	0.67 (0.45-0.99)
CMFT/Tam	0.65 (0.50-0.84)	0.67 (0.50-0.89)	0.64 (0.42-0.95)

Oncology Needs Predictive Markers not Prognostic Factors

- Most prognostic factors are not used because they are not therapeutically relevant
- Most prognostic factor studies use a convenience sample of patients for whom tissue is available. Generally the patients are too heterogeneous to support therapeutically relevant conclusions

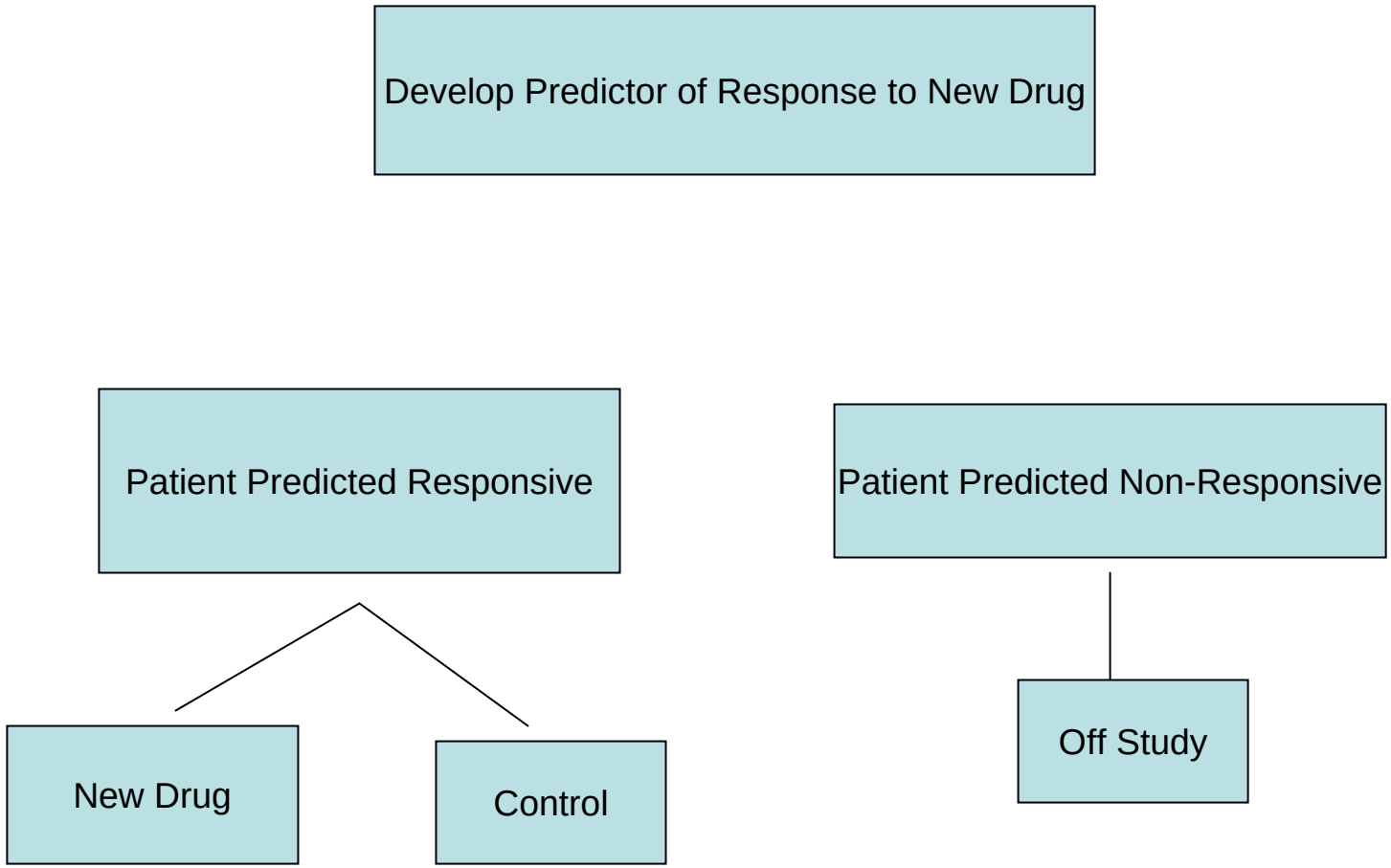
- Criteria for validation of surrogate endpoints should not be applied to biomarkers used in treatment selection

- Targeted clinical trials can be much more efficient than untargeted clinical trials, if we know who to target

- In new drug development, the role of a classifier is to select a target population for treatment
  - The focus should be on evaluating the new drug in a population defined by a predictive classifier, not on “validating” the classifier

Developmental Strategy (I)

- **Develop** a diagnostic classifier that identifies the patients likely to benefit from the new drug
- Develop a reproducible assay for the classifier
- **Use** the diagnostic to restrict eligibility to a prospectively planned evaluation of the new drug
- Demonstrate that the new drug is effective in the prospectively defined set of patients determined by the diagnostic


Develop Predictor of Response to New Drug
Patient Predicted Responsive
Patient Predicted Non-Responsive
New Drug
Control
Off Study

Evaluating the Efficiency of Strategy (I)

- Simon R and Maitnourim A. Evaluating the efficiency of targeted designs for randomized clinical trials. Clinical Cancer Research 10:6759-63, 2004.
- Maitnourim A and Simon R. On the efficiency of targeted clinical trials. Statistics in Medicine 24:329-339, 2005.
- reprints and interactive sample size calculations at http://linus.nci.nih.gov/brb

Randomized Ratio $n_{untargeted}/n_{targeted}$

Proportion Assay Positive	No Treatment Benefit for Assay Negative Patients	Treatment Benefit for Assay Negative Patients is Half That for Assay Positive Patients
0.75	1.78	1.31
0.5	4	1.78
0.25	16	2.56

Comparison of Targeted to Untargeted Design

Simon R, Development and Validation of Biomarker Classifiers for Treatment Selection, JSPI

Treatment Hazard Ratio for Marker Positive Patients	Number of Events for Targeted Design	Number of Events for Traditional Design		
		Percent of Patients Marker Positive		
		20%	33%	50%
0.5	74	2040	720	316
0.67	200	5200	1878	820

- For Trastuzumab, even a relatively poor assay enabled conduct of a targeted phase III trial which was crucial for establishing effectiveness
- Recent results with Trastuzumab in early stage breast cancer show dramatic benefits for patients selected to express Her-2

You Can Evaluate How This Design Might Work For You

- http://linus.nci.nih.gov/brb/

biomathematics, and computational biology, on topics ranging from methodology to facilitate understanding at the molecular level of the pathogenesis of cancer to methodology to enhance the conduct of clinical trials of new therapeutic and diagnostic approaches.

Research Areas

Clinical trials, Drug Discovery, Molecular Cancer Diagnosis, Biomedical Imaging, Computational and Systems Biology, and Biostatistical Research

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Sample Size Calculation

BRB Annual Report 2005

Mathematics And Oncology

- The Norton-Simon Hypothesis
- The Norton-Simon Hypothesis and Breast Cancer Mortality in National Randomized Trial

Position Available

Post-doctoral fellow positions available

Software Download

- Accelerated Titration Design Software
- Optimal Two-Stage Phase II Design Software

Sample Size Calculation for Randomized Clinical Trials

- **Optimal Two-Stage Phase II Design**

- **Biomarker Targeted Randomized Design***

1. **Binary Outcome Endpoint**
2. **Survival and Time-to-Event Endpoint**

* Targeted design randomizes only marker positive patients to treatment or control arm. Untargeted design does not measure marker and randomizes all who otherwise are eligible.

Sample Size Calculation: Binary Outcome Endpoint

Evaluating the efficiency of targeted designs for randomized clinical trials and Supplement by Richard Simon and Aboubakar Maitournam. (Clinical Cancer Research 10:6759-6763, 2005)

pc	
gamma	
delta1	
delta0	
alpha	0.05
power	0.90

Submit

pc = probability of "response" for control arm

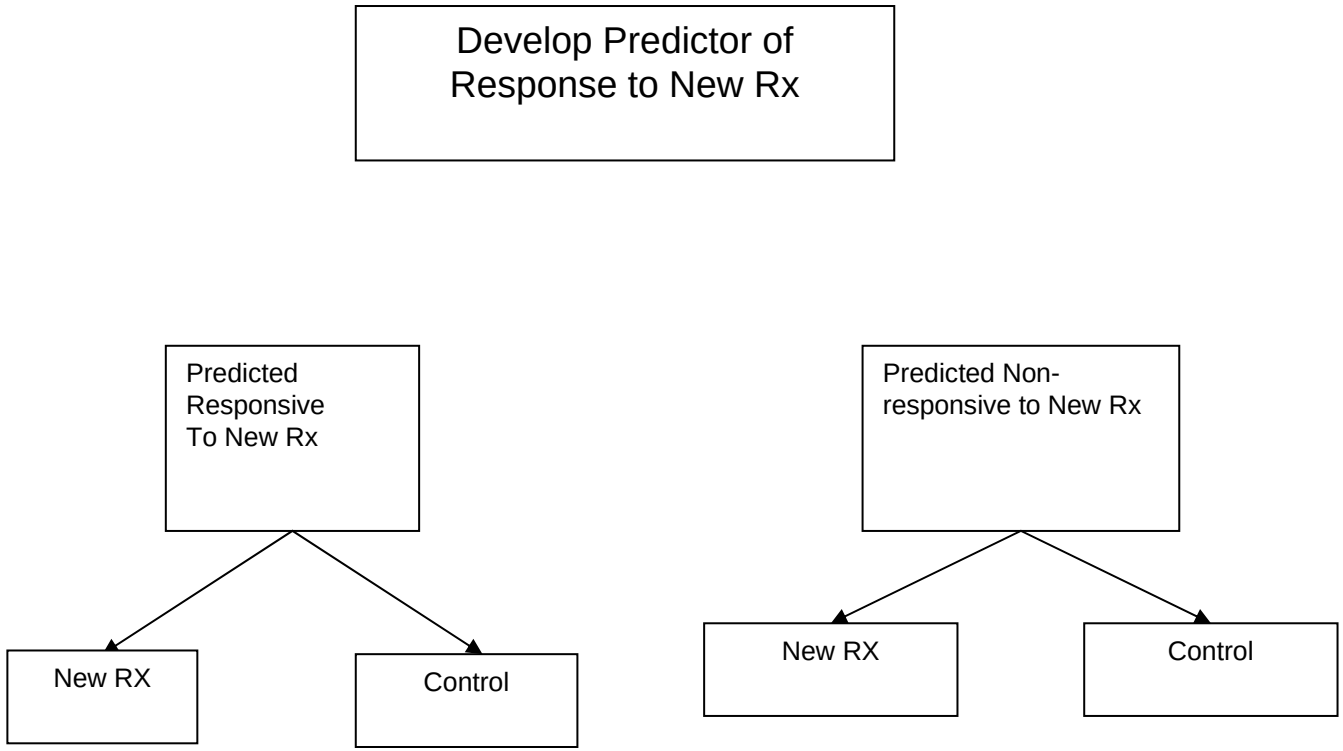
gamma = proportion of patients who are classifier negative (i.e. less responsive to new treatment

delta1 = improvement in response probability for new treatment in classifier positive patients

delta0 = improvement in response probability for new treatment in classifier negative patients

alpha = two-sided significance level

Developmental Strategy (II)



Developmental Strategy (II)

- Do not use the diagnostic to restrict eligibility, but to structure a prospective analysis plan.
- Compare the new drug to the control overall for all patients ignoring the classifier.
  - If $p_{overall} \leq 0.04$ claim effectiveness for the eligible population as a whole
- Otherwise perform a single subset analysis evaluating the new drug in the classifier + patients
  - If $p_{subset} \leq 0.01$ claim effectiveness for the classifier + patients.

Key Features of Design (II)

- The purpose of the RCT is to evaluate treatment T vs C overall and for the pre-defined subset; not to re-evaluate the components of the classifier, or to modify or refine the classifier

The Roadmap

1. Develop a completely specified genomic classifier of the patients likely to benefit from a new drug
2. Establish reproducibility of measurement of the classifier
3. Use the completely specified classifier to design and analyze a new clinical trial to evaluate effectiveness of the new treatment with a pre-defined analysis plan.

Guiding Principle

- The data used to develop the classifier must be distinct from the data used to test hypotheses about treatment effect in subsets determined by the classifier
  - Developmental studies are exploratory
  - Studies on which treatment effectiveness claims are to be based should be definitive studies that test a treatment hypothesis in a patient population completely pre-specified by the classifier

Use of Archived Samples

- From a non-targeted “negative” clinical trial to develop a binary classifier of a subset thought to benefit from treatment
- Test that subset hypothesis in a separate clinical trial
  - Prospective targeted type (I) trial
  - Prospective type (II) trial
  - Using archived specimens from a second previously conducted clinical trial

Development of Genomic Classifiers

- Single gene or protein based on knowledge of therapeutic target
- Single gene or protein culled from set of candidate genes identified based on imperfect knowledge of therapeutic target
- Empirically determined based on correlating gene expression to patient outcome after treatment

Development of Genomic Classifiers

- During phase II development or
- After failed phase III trial using archived specimens.
- Adaptively during early portion of phase III trial.

Adaptive Signature Design

An adaptive design for generating and prospectively testing a gene expression signature for sensitive patients

Boris Freidlin and Richard Simon

Clinical Cancer Research 11:7872-8, 2005

Adaptive Signature Design
End of Trial Analysis

- Compare E to C for **all patients** at significance level 0.04
  - If overall H_0 is rejected, then claim effectiveness of E for eligible patients
  - Otherwise

- Otherwise:
  - Using only the first half of patients accrued during the trial, develop a binary classifier that predicts the subset of patients most likely to benefit from the new treatment E compared to control C
  - Compare E to C for patients accrued in second stage who are predicted responsive to E based on classifier
    - Perform test at significance level 0.01
    - If H_0 is rejected, claim effectiveness of E for subset defined by classifier

Treatment effect restricted to subset.
10% of patients sensitive, 10 sensitivity genes, 10,000 genes, 400 patients.

Test	Power
Overall .05 level test	46.7
Overall .04 level test	43.1
Sensitive subset .01 level test (performed only when overall .04 level test is negative)	42.2
Overall adaptive signature design	85.3

Overall treatment effect, no subset effect.
10,000 genes, 400 patients.

Test	Power
Overall .05 level test	74.2
Overall .04 level test	70.9
Sensitive subset .01 level test	1.0
Overall adaptive signature design	70.9

Use of DNA Microarray Expression Profiling

- For settings where you don’t know how to identify the patients likely to be responsive to the new treatment based on its mechanism of action
- Only pre-treatment specimens are needed
- Expression profiling should be used to identify informative genes and form a binary classifier that can be used to select patients for study of for a pre-defined subset analysis
  - A set of genes is not a classifier

Collaborators

- Boris Freidlin
- Aboubakar Maitournam
- Yingdong Zhao

Simon R. Using DNA microarrays for diagnostic and prognostic prediction. Expert Review of Molecular Diagnostics, 3(5) 587-595, 2003.

Simon R. Diagnostic and prognostic prediction using gene expression profiles in high dimensional microarray data. British Journal of Cancer 89:1599-1604, 2003.

Simon R and Maitnourim A. Evaluating the efficiency of targeted designs for randomized clinical trials. Clinical Cancer Research 10:6759-63, 2004.

Maitnourim A and Simon R. On the efficiency of targeted clinical trials. Statistics in Medicine 24:329-339, 2005.

Simon R. When is a genomic classifier ready for prime time? Nature Clinical Practice – Oncology 1:4-5, 2004.

Simon R. An agenda for Clinical Trials: clinical trials in the genomic era. Clinical Trials 1:468-470, 2004.

Simon R. Development and Validation of Therapeutically Relevant Multi-gene Biomarker Classifiers. Journal of the National Cancer Institute 97:866-867, 2005.

Simon R. A roadmap for developing and validating therapeutically relevant genomic classifiers. Journal of Clinical Oncology 23(29), 2005.

Freidlin B and Simon R. Adaptive signature design. Clinical Cancer Research 11:7872-8, 2005.

Simon R. Guidelines for the design of clinical studies for development and validation of therapeutically relevant biomarkers and biomarker classification systems. In Biomarkers in Breast Cancer, Hayes DF and Gasparini G, Humana Press, pp 3-15, 2005.

Simon R and Wang SJ. Use of genomic signatures in therapeutics development in oncology and other diseases. The Pharmacogenomics Journal, 2006.