A New Paradigm for the Utilization of Genomic Classifiers for Patient Selection in the Critical Path of Medical Product Development

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

- http://linus.nci.nih.gov/brb
  - Powerpoint presentation
  - Reprints & Technical Reports
  - BRB-ArrayTools software

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Pharmacogenomic Targeting

- Enables patients to be treated with drugs that actually work for them
- Avoids false negative trials for heterogeneous populations
- Avoids erroneous generalizations of conclusions from positive trials

“If new refrigerators hurt 7% of customers and failed to work for another one-third of them, customers would expect refunds.”

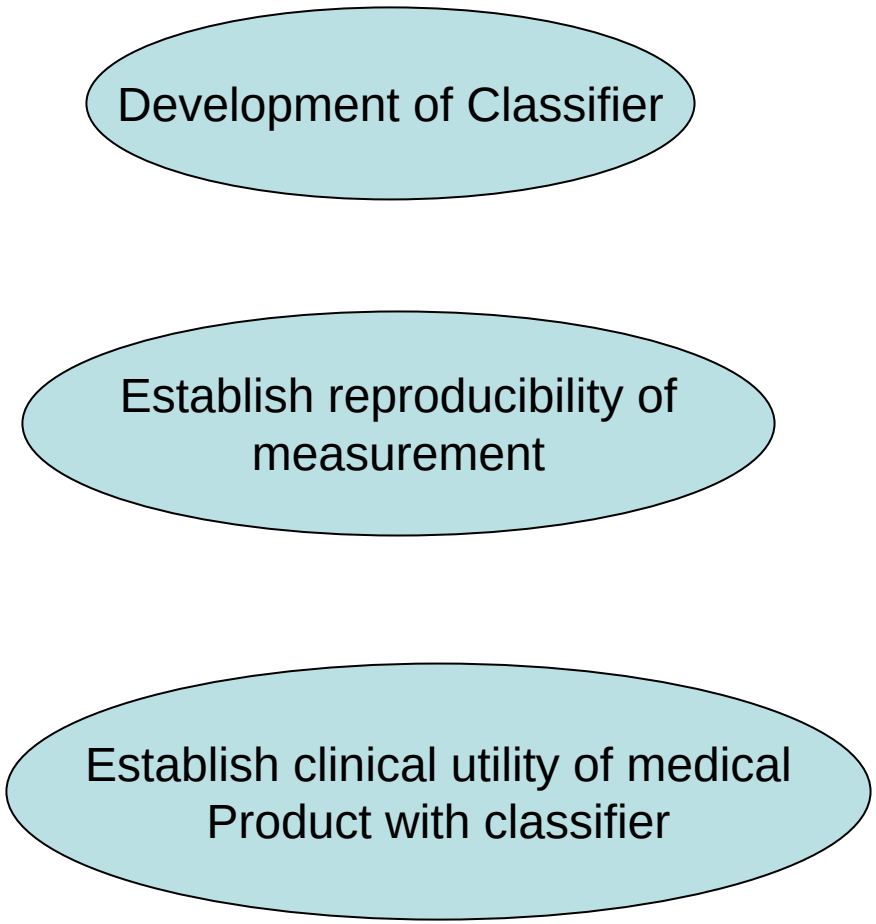
BJ Evans, DA Flockhart, EM Meslin Nature Med 10:1289, 2004

- “Hypertension is not one single entity, neither is schizophrenia. It is likely that we will find 10 if we are lucky, or 50, if we are not very lucky, different disorders masquerading under the umbrella of hypertension. I don’t see how once we have that knowledge, we are not going to use it to genotype individuals and try to tailor therapies, because if they are that different, then they’re likely fundamentally … different problems…”
  - George Poste

- Clinical trial for patients with breast cancer, without nodal or distant metastases, Estrogen receptor positive tumor
  - 5 year survival rate for control group (surgery + radiation + Tamoxifen) expected to be 90%
  - Size trial to detect 92% survival in group treated with control modalities plus chemotherapy

The Paradigm

1. Develop a completely specified pharmacogenomic (PG) classifier of the patients likely to benefit from a new medical product (E)
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 E in the overall population or pre-defined subsets determined by the classifier.


Development of Classifier
Establish reproducibility of measurement
Establish clinical utility of medical Product with classifier

- 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 hypothesis testing studies based on completely pre-specified classifiers

A set of genes is not a classifier

- Gene selection
- Mathematical function for mapping from multivariate gene expression domain to prognostic or diagnostic classes
- Weights and other parameters including cut-off thresholds for risk scores

Linear Classifiers for Two Classes

$$l(\underline{x}) = \sum_{i \varepsilon G} w_i x_i$$

$\underline{x}$ = vector of expression measurements

G = genes included in model

w_i = weight for i'th gene

decision boundary $l(\underline{x})$ > or < d

Strategies for Development of Genomic Classifiers

- Uni-dimensional based on knowledge of molecular target of therapy
- Empirically determined based on correlating gene expression or genotype to patient outcome after treatment
- During phase I/II development
- After failed phase III trial using archived specimens
- There is no need for FDA to regulate methods of classifier “development”

Genomic Classifiers Used for Selecting and Stratifying Patients in Drug Development

- The components of the classifier should not have to be “valid disease biomarkers” in the FDA sense

Biomarker

- “Any biological measurement that provides actionable information regarding disease progression, pharmacology, or safety that can be used as a basis for decision making in drug development.”
  - J. Boguslavsky

- “I don’t know what ‘clinical validation’ [of a biomarker] means. The first thing you have to do is define a purpose for the biomarker. Validation is all about demonstrating fitness for purpose.”
  - Dr. Stephen Williams, Pfizer

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There Should Be No Requirement For

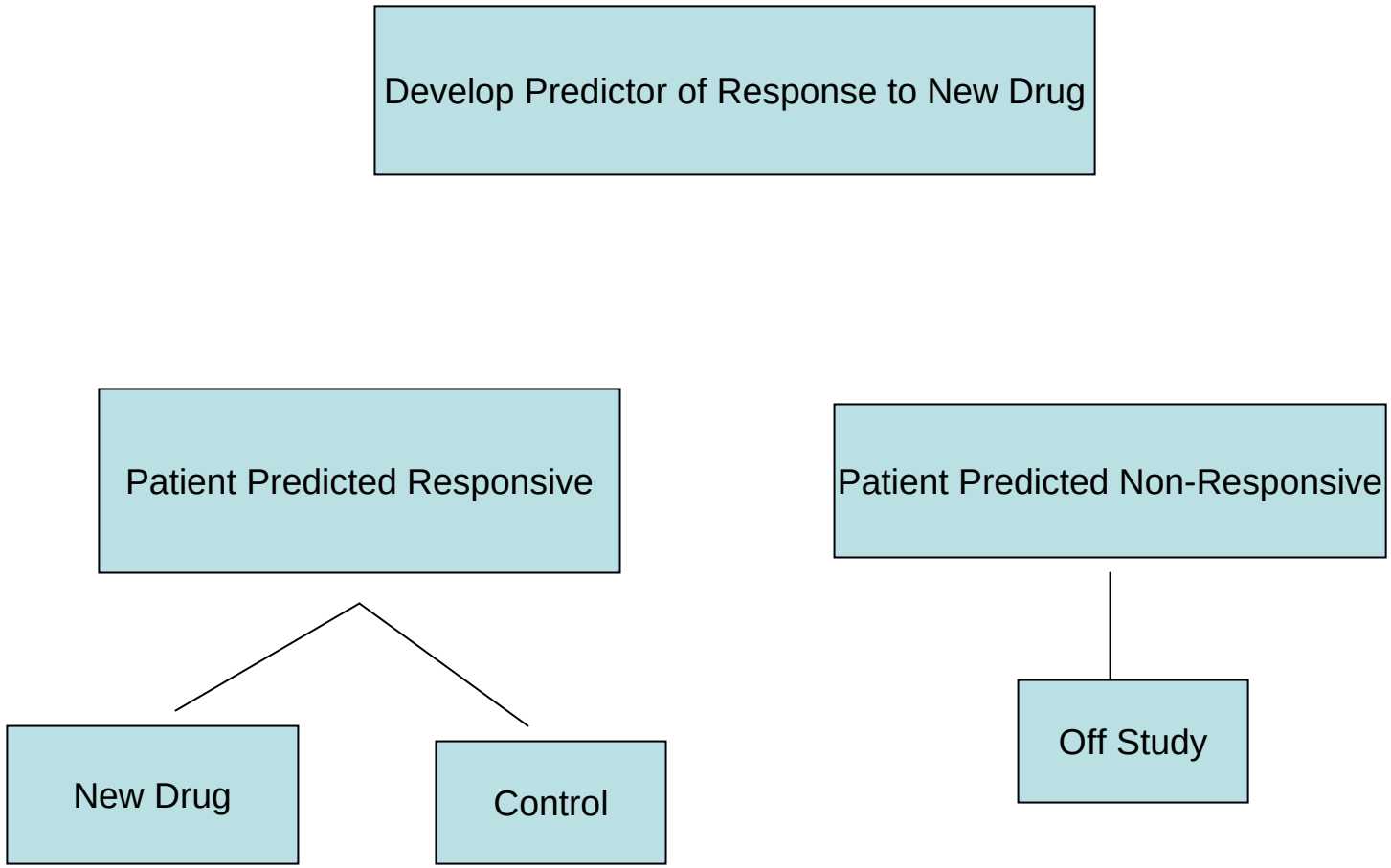
- Demonstrating that the classifier or any of its components are “validated biomarkers of disease status”
- Ensuring that the individual components of the classifier are correlated with patient outcome or effective for selecting patients for treatment
- Demonstrating that repeating the classifier development process on independent data results in the same classifier

One Should Require That

- The classifier be reproducibly measurable
- The classifier in conjunction with the medical product has clinical utility

Using the Classifier in Evaluation of a New Therapeutic (I)

- Develop a diagnostic classifier that identifies the patients likely to benefit from the new drug
- Use the diagnostic as eligibility criteria in a prospectively planned evaluation of the new drug
- Demonstrate that the new drug is effective in a prospectively defined set of patients determined by the diagnostic
- Demonstrate that the diagnostic can be reproducibly measured
- Confirmatory phase III trial


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

Randomized Clinical Trials Targeted to Patients Predicted to be Responsive to the New Treatment Can Be Much More Efficient than Traditional Untargeted Designs

- Simon R and Maitnourim A. Evaluating the efficiency of targeted designs for randomized clinical trials. Clinical Cancer Research 10:6759-63, 2004.
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- reprints at http://linus.nci.nih.gov/brb

Two Clinical Trial Designs

- Un-targeted design
  - Randomized comparison of E to C without screening for probability of benefit from E
- Targeted design
  - Classify patients based on probability of benefit from E
  - Randomize only patients likely to benefit

- Compare the two designs with regard to the number of patients required to achieve a fixed statistical power for detecting treatment effectiveness and the number of patients needed for screening

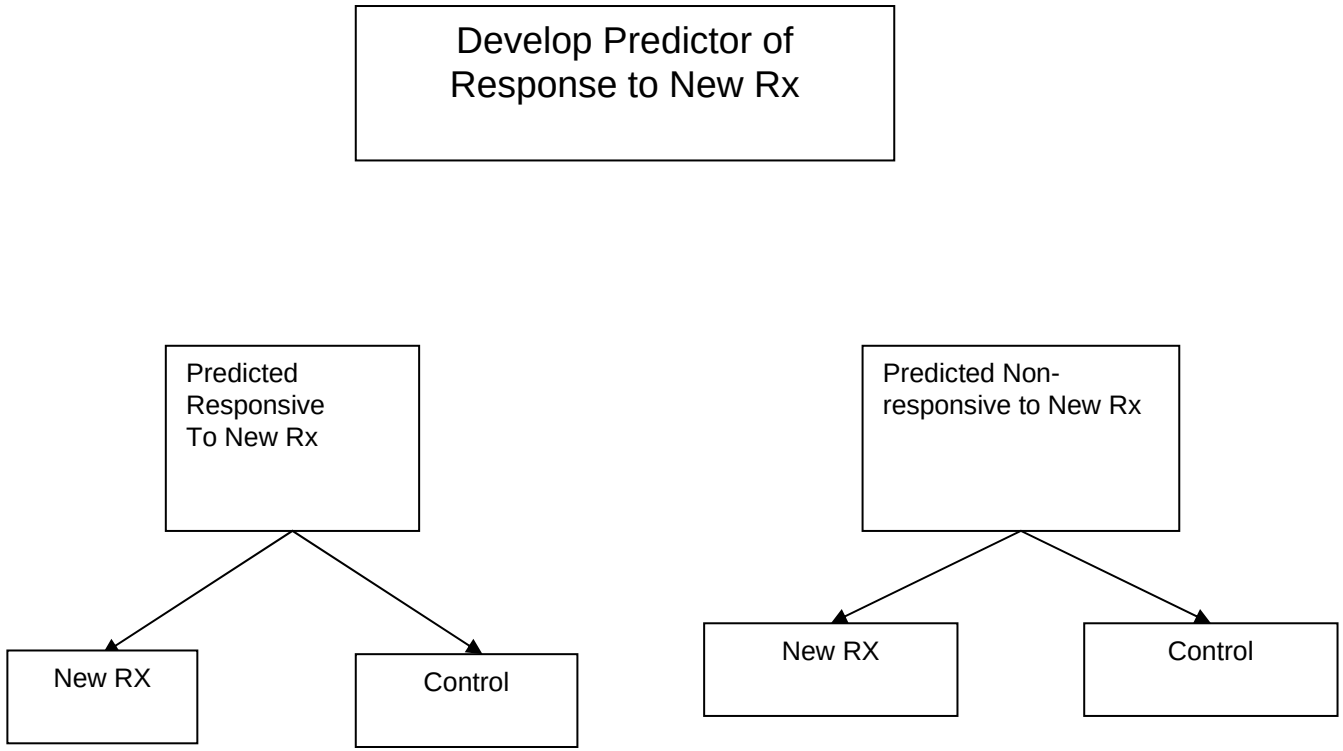
- For Herceptin, even a relatively poor assay enabled conduct of a targeted phase III trial which was crucial for establishing effectiveness

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

Using the Classifier in Evaluation of a New Therapeutic (II)



Using Genomics in Development of a New Therapeutic (II)

- Develop a diagnostic classifier that identifies the patients likely to benefit from the new drug
- Do not use the diagnostic to restrict eligibility, but rather to structure a prospectively planned analysis strategy of a randomized trial of the new drug.
- Compare the new drug to the control overall for all patients ignoring the classifier.
  - If the treatment effect on the primary pre-specified endpoint is significant at the 0.04 level, then claim effectiveness for the eligible population as a whole.
- If the overall test is not significant at the 0.04 level, then perform a single subset analysis evaluating the new drug in the classifier + patients.
  - If the treatment effect is significant at the 0.01 level, then claim effectiveness for the classifier + patients.
- Demonstrate that the diagnostic can be reproducibly measured
- Confirmatory 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 (In Press)

Adaptive Signature Design

- Randomized trial comparing E to C
  - Rapidly observed endpoint
- Stage 1 of accrual (half the patients)
  - Develop a binary classifier based on gene expression profile for the subset of patients that are predicted to preferentially benefit from the new treatment E compared to control C

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, compare E to C for patients accrued in second stage who are predicted responsive to E based on classifier developed during first stage.
    - 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

Conclusions

- New technology and biological knowledge makes is increasingly feasible to identify which patients are most likely to benefit from a new treatment
- Targeting treatment can make it much easier to convincingly demonstrate treatment effectiveness
- Targeting treatment can greatly improve the therapeutic ratio of benefit to adverse effects, the proportion of treated patients who benefit

Conclusions

- Effectively defining and utilizing PG classifiers in drug development offers multiple challenges
- Much of the conventional wisdom about how to develop and utilize biomarkers is flawed and does not lead to definitive evidence of treatment benefit for a well defined population

Conclusions

- With careful prospective planning, genomic classifiers can be used in a manner that provides definitive evidence of treatment effect
  - Trial designs are available that will support broad labeling indications in cases where drug activity is sufficient, and the opportunity to obtain strong evidence of effectiveness in a well defined subset where overall effectiveness is not established

Conclusions

- Prospectively specified analysis plans for phase III data are essential to achieve reliable results
  - Biomarker analysis does not mean exploratory analysis except in developmental studies
  - Biomarker classifiers used in phase III evaluations should be completely specified based on external data
- In some cases, definitive evidence can be achieved from prospective analysis of patients in previously conducted clinical trials with extensive archival of pre-treatment specimens

Acknowledgements

- Boris Freidlin
- Aboubakar Maitournam
- Sue-Jane Wang