SISCR Module 7

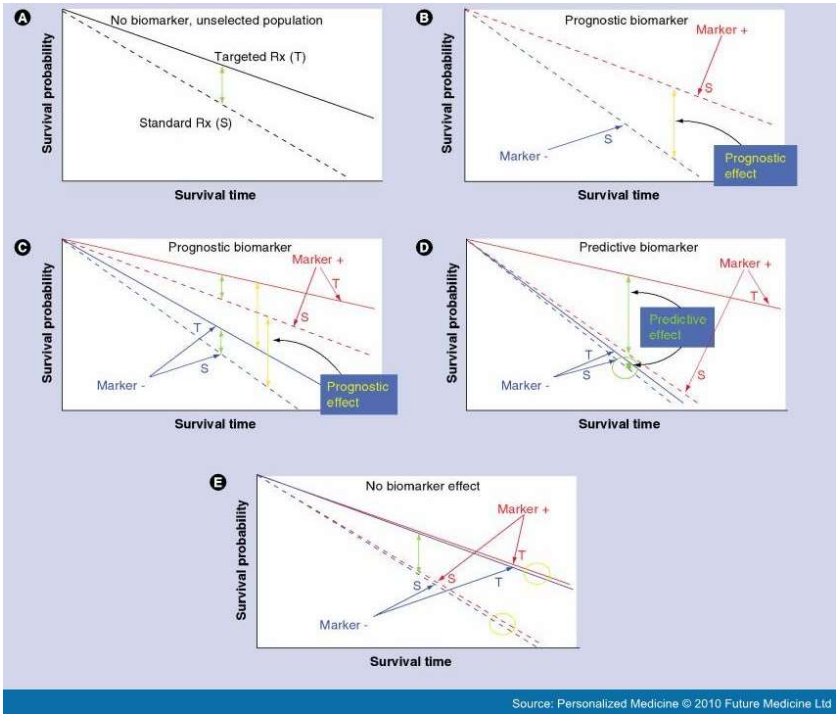
Part V:
Notes on prognostic and predictive biomarkers (and "personalized medicine")

Kathleen Kerr, Ph.D.
Associate Professor
Department of Biostatistics
University of Washington

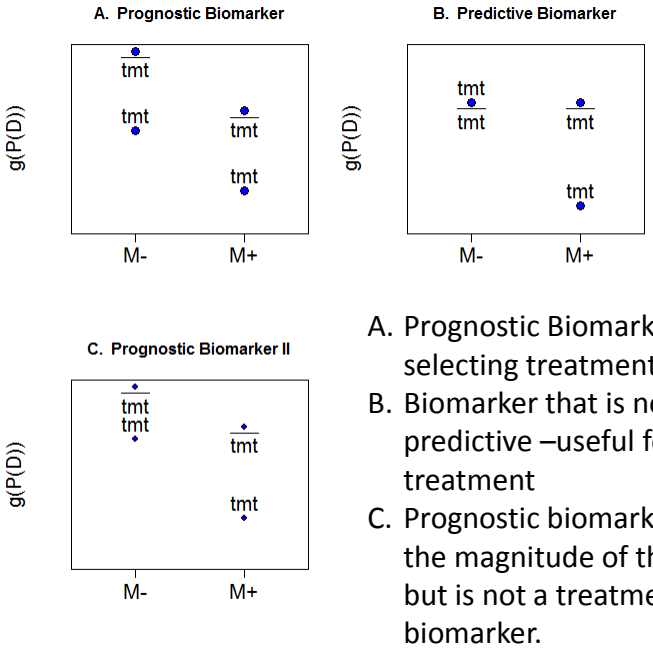
Prognostic vs. Predictive Biomarker

- A prognostic biomarker gives information about which outcomes are likely/unlikely.

- A predictive biomarker gives information about treatment benefit.



3



A. Prognostic Biomarker not useful for selecting treatment.
B. Biomarker that is not prognostic but is predictive –useful for selecting treatment
C. Prognostic biomarker that also predicts the magnitude of the treatment effect but is not a treatment-selection biomarker.

4

Guidance for Industry

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Robert Temple, 301-796-2270, (CBER) Office of Communication, Outreach and Development, 301- 827-1800, or (CDRH) Robert L. Becker, Jr., 301-796-6211.

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
December 2012
Clinical Medical

5

Enrichment strategies fall into three broad categories:

1. *Strategies to decrease heterogeneity* − These include selecting patients with baseline measurements in a narrow range (decreased inter-patient variability) and excluding patients whose disease or symptoms improve spontaneously or whose measurements are highly variable (decreased intra-patient variability). The decreased variability provided by these strategies increases study power (see section III).
2. *Prognostic enrichment strategies* − choosing patients with a greater likelihood of having a disease-related endpoint event (for event-driven studies) or a substantial worsening in condition (for continuous measurement endpoints) (section IV). These strategies will increase the absolute effect difference between groups but will not alter relative effect.
3. *Predictive enrichment strategies* − choosing patients more likely to respond to the drug treatment than other patients with the condition being treated. Such selection can lead to a larger effect size (both absolute and relative) and permit use of a smaller study population. Selection of patients could be based on a specific aspect of a patient's physiology or a disease characteristic that is related in some manner to the study drug's mechanism, or it could be empiric (e.g., the patient has previously appeared to respond to a drug in the same class) (section V).

This guidance describes and illustrates important enrichment strategies within these categories; discusses study design options for different strategies, including advantages and disadvantages of the various designs; and addresses issues of interpretation of the results of enrichment studies.

6

Discussed in Part II today – evaluating a biomarker for prognostic enrichment. The biomarker was not expected to predict the treatment effect.

2. *Prognostic enrichment strategies* – choosing patients with a greater likelihood of having a disease-related endpoint event (for event-driven studies) or a substantial worsening in condition (for continuous measurement endpoints) (section IV). These strategies will increase the absolute effect difference between groups but will not alter relative effect.

3. *Predictive enrichment strategies* – choosing patients more likely to respond to the drug treatment than other patients with the condition being treated. Such selection can lead to a larger effect size (both absolute and relative) and permit use of a smaller study population. Selection of patients could be based on a specific aspect of a patient's physiology or a disease characteristic that is related in some manner to the study drug's mechanism, or it could be empiric (e.g., the patient has previously appeared to respond to a drug in the same class) (section V).

This is a different situation – the treatment effect is expected to differ based on the biomarker.

Examples:

- Proteomic or genetic markers in breast cancer. These markers are understood to be related to a drug's mechanism of action and used to select patients into a trial. Note: Predictive enrichment is not just about running an efficient clinical trial, but also clearly about ethics – who *should* get the treatment.
- Among patients with hypertension, those with high-renin status more likely to respond to drugs in certain classes (e.g. beta-blockers, ACE inhibitors).

Predictive Biomarkers

- Some of the current interest in biomarkers is for selecting treatment
  - (I prefer the term *treatment-selection biomarker* over *predictive biomarker*)
- This is related to the current drive towards "personalized medicine."
- In the context of using biomarkers to select treatment, some have advocated for assessing the accuracy of predictive biomarkers for selecting treatment
  - This is reasonable, but is it actually possible to assess the sensitivity and specificity of a biomarker for selecting treatment?
  - What do sensitivity and specificity mean in this context?

Predictive Biomarkers

- Consider a choice of two treatments
  - standard treatment vs. new intervention
  - standard treatment vs. extended aggressive treatment
  - no treatment vs. treatment

… and a binary outcome (bad vs. good)

- A patient can be said to benefit from the treatment if he will have the good outcome with the new treatment and the bad outcome without the treatment

Predictive Biomarkers

- Consider a choice of two treatments
  - no treatment vs. treatment
- A patient does NOT benefit from the treatment if
  - bad outcome regardless of treatment
  - good outcome regardless of treatment
  - good outcome with standard treatment and bad outcome with new treatment

Sensitivity and Specificity for a Predictive Biomarker

Sensitivity: P(biomarker + | benefit from tmt)

Specificity: P(biomarker − | no benefit from tmt)

Unobservable potential outcomes for 2000 patients in a randomized trial for treatment

		Benefit from Treatment: good outcome with treatment, bad outcome without (n=400)	Bad outcome regardless of treatment (n=600)	Good outcome regardless of treatment (n=600)	Bad outcome with treatment, good outcome without treatment (n=400)
Marker 1	Negative	200	250	400	250
	Positive	200	350	200	150
Marker 2	Negative	100	350	500	150
	Positive	300	250	100	250

13

		Benefit from Treatment: good outcome with treatment, bad outcome without (n=400)	Bad outcome regardless of treatment (n=600)	Good outcome regardless of treatment (n=600)	Bad outcome with treatment, good outcome without treatment (n=400)
Marker 1	Negative	200	250	400	250
	Positive	200	350	200	150

Sensitivity: P(biomarker + | benefit from tmt)

200/400=50.0%

Specificity: P(biomarker − | no benefit from tmt)

(250+400+250)/(600+600+400)=900/1600=56.3%

14

		Benefit from Treatment: good outcome with treatment, bad outcome without (n=400)	Bad outcome regardless of treatment (n=600)	Good outcome regardless of treatment (n=600)	Bad outcome with treatment, good outcome without treatment (n=400)
Marker 2	Negative	100	350	500	150
	Positive	300	250	100	250

Sensitivity: P(biomarker + | benefit from tmt)
300/400=75.0%
Specificity: P(biomarker - | no benefit from tmt)
(350+500+150)/(600+600+400)=1000/1600=62.5%

Marker 2 has higher sensitivity and specificity than Marker 1.

		good outcome with treatment, bad outcome without (n=400)	Bad outcome regardless of treatment (n=600)	Good outcome regardless of treatment (n=600)	Bad outcome with tmt, good outcome without (n=400)
Marker 1	Negative	200	250	400	250
	Positive	200	350	200	150
Marker 2	Negative	100	350	500	150
	Positive	300	250	100	250

Observed Trial Data		No treatment (n=1000)		New treatment (n=1000)	
		Good	Bad	Good	Bad
Marker 1	Negative		100	100	
	Positive		100	100	
Marker 2	Negative				
	Positive				

		good outcome with treatment, bad outcome without (n=400)	Bad outcome regardless of treatment (n=600)	Good outcome regardless of treatment (n=600)	Bad outcome with tmt, good outcome without (n=400)
Marker 1	Negative	200	250	400	250
	Positive	200	350	200	150
Marker 2	Negative	100	350	500	150
	Positive	300	250	100	250

Observed Trial Data		No treatment (n=1000)		New treatment (n=1000)	
		Good	Bad	Good	Bad
Marker 1	Negative		100+125	100	125
	Positive		100+175	100	175
Marker 2	Negative				
	Positive				

		good outcome with treatment, bad outcome without (n=400)	Bad outcome regardless of treatment (n=600)	Good outcome regardless of treatment (n=600)	Bad outcome with tmt, good outcome without (n=400)
Marker 1	Negative	200	250	400	250
	Positive	200	350	200	150
Marker 2	Negative	100	350	500	150
	Positive	300	250	100	250

Observed Trial Data		No treatment (n=1000)		New treatment (n=1000)	
		Good	Bad	Good	Bad
Marker 1	Negative	200	100+125	100+200	125
	Positive	100	100+175	100+100	175
Marker 2	Negative				
	Positive				

		good outcome with treatment, bad outcome without (n=400)	Bad outcome regardless of treatment (n=600)	Good outcome regardless of treatment (n=600)	Bad outcome with tmt, good outcome without (n=400)
Marker 1	Negative	200	250	400	250
	Positive	200	350	200	150
Marker 2	Negative	100	350	500	150
	Positive	300	250	100	250

Observed Trial Data		No treatment (n=1000)		New treatment (n=1000)	
		Good	Bad	Good	Bad
Marker 1	Negative	200+125	100+125	100+200	125+125
	Positive	100+75	100+175	100+100	175+75
Marker 2	Negative				
	Positive				

		good outcome with treatment, bad outcome without (n=400)	Bad outcome regardless of treatment (n=600)	Good outcome regardless of treatment (n=600)	Bad outcome with tmt, good outcome without (n=400)
Marker 1	Negative	200	250	400	250
	Positive	200	350	200	150
Marker 2	Negative	100	350	500	150
	Positive	300	250	100	250

Observed Trial Data		No treatment (n=1000)		New treatment (n=1000)	
		Good	Bad	Good	Bad
Marker 1	Negative	325	225	300	250
	Positive	175	275	200	250
Marker 2	Negative	325	225	300	250
	Positive	175	275	200	250

		good outcome with treatment, bad outcome without (n=400)	Bad outcome regardless of treatment (n=600)	Good outcome regardless of treatment (n=600)	Bad outcome with tmt, good outcome without (n=400)
Marker 1	Negative	200	250	400	250
	Positive	200	350	200	150
Marker 2	Negative	100	350	500	150
	Positive	300	250	100	250

If we could see the complete potential outcomes data, we would know that marker 2 is the better treatment-selection marker. It has higher sensitivity, specificity (and PPV and NPV) compared to marker 1.

21

… but we cannot learn this from the observable data. The observed data look the same for both biomarkers.
Proportion of biomarker-positive patients:
(175+275+200+250)/2000 = 45%

Among biomarker negatives:
225/500 = 40.9% have bad outcome under no tmt
250/550 = 45.5% have bad outcome under tmt
4.6% *more* bad outcomes with tmt when biomarker −

		No treatment (n=1000)		New treatment (n=1000)	
		Good	Bad	Good	Bad
Marker 1	Negative	325	225	300	250
	Positive	175	275	200	250
Marker 2	Negative	325	225	300	250
	Positive	175	275	200	250

Among biomarker positives:
275/450 = 61.1% have bad outcome under no tmt
250/450 = 55.6% have bad outcome under tmt
5.5% *fewer* bad outcomes with tmt when biomarker +

		No treatment (n=1000)		New treatment (n=1000)	
		Good	Bad	Good	Bad
Marker 1	Negative	325	225	300	250
	Positive	175	275	200	250
Marker 2	Negative	325	225	300	250
	Positive	175	275	200	250

JNCI J Natl Cancer Inst (2015) 107(8): djv157

doi:10.1093/jnci/djv157
First published online June 24, 2015
Brief Communication

BRIEF COMMUNICATION

The Fundamental Difficulty With Evaluating the Accuracy of Biomarkers for Guiding Treatment

Holly Janes, Margaret S. Pepe, Lisa M. McShane, Daniel J. Sargent, Patrick J. Heagerty

Recent guidance documents have recommended that the accuracy of predictive biomarkers, ie, sensitivity, specificity, and positive and negative predictive values, should be assessed. …. they cannot be estimated from data without making strong untestable assumptions. Language suggesting that predictive biomarkers can identify patients who benefit from an intervention is also widespread. … [In] general one cannot estimate the chance that a patient will benefit from treatment. We recommend instead that predictive biomarkers be evaluated with respect to their ability to predict clinical outcomes among patients treated and among patients receiving standard of care, and the population impact of treatment rules based on those predictions.

Closing Thoughts

- The terminology of *prognostic* vs. *predictive* biomarkers has become fairly standard
- "Personalized medicine" isn't really new
  - "Stratified medicine," "individualized medicine," "precision medicine" are other terms.
  - *BMJ* 2011;343:d4697: argues that "personalized/individualized medicine" should be reserved for situations where treatment is customized to an individual, e.g. using patient's cells to produce some cancer vaccine. Otherwise, it is really "stratified medicine"
- Be skeptical of claims that a biomarker can predict individual treatment benefit.