SISCER 2023 Module 5: Evaluation of Biomarkers and Risk Models

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

July 13-14, 2023

8:30am-Noon PT / 11:30am-3pm ET

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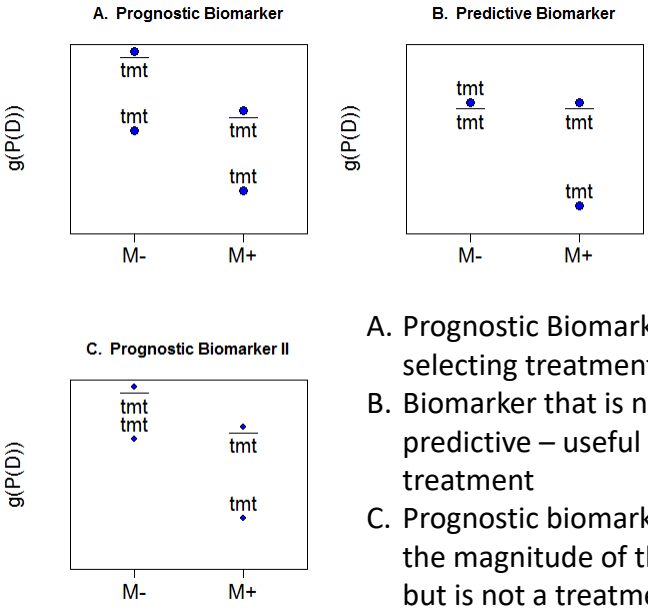
Prognostic vs. Predictive Biomarker

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

- A predictive biomarker gives information about the likelihood of treatment benefit.



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.

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Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products
Guidance for Industry

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)

March 2019
Clinical/Medical

Discussed in Part II – evaluating a biomarker for prognostic enrichment. The biomarker does not predict the treatment effect.

(2) Prognostic enrichment strategies — These include 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) (see section IV., Prognostic Enrichment Strategies — Identifying High-Risk Patients). These strategies would increase the absolute effect difference between groups but would not be expected to alter relative effect.

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(3) Predictive enrichment strategies — These include choosing patients who are 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 can permit use of a smaller study population. Selection of patients could be based on a specific aspect of a patient's physiology, a biomarker, or a disease characteristic that is related in some manner to the study drug's mechanism. Patient selection could also be empiric (e.g., the patient has previously appeared to respond to a drug in the same class) (see section V., Predictive Enrichment — Identifying More-Responsive Patients).

Different situation – the treatment effect differs 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 trials. Who *should* get the treatment? In what patients do we expect the treatment to work?
- Among patients with hypertension, those with high-renin status more likely to respond to drugs in certain classes (e.g. beta-blockers, ACE inhibitors).

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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 sounds good, but is it actually possible?
  - Can we assess the sensitivity and specificity of a biomarker for treatment-selection? What do sensitivity and specificity mean in this context?

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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 (good vs. bad)

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

Predictive Biomarkers

- A patient does NOT benefit from the treatment if
  - bad outcome regardless of treatment
  - good outcome regardless of treatment
  - good outcome with no treatment and bad outcome with 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

		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 1:

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%

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		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

Marker 2:

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.

… but we cannot learn this from the observable data. The observed data are identical for both biomarkers.

45% of patients are biomarker-positive (for either biomarker):

$$\frac{175+275+200+250}{2000} = 45\%$$

		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 negatives:
225/550 = 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 negative

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 positive

		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

OXFORD

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, i.e., 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 a cancer vaccine. Otherwise, it is really "stratified medicine"

Closing Thoughts

- Be skeptical of claims that a biomarker can predict individual treatment benefit.
  - It is usually unknown which individuals benefit from treatment.
- Usually, the best we can claim is that a biomarker identifies *groups of patients* more or less likely to have a good outcome with treatment than without

Misconceptions about Biomarkers and Risk Models

- A large odds ratio means a biomarker is useful for prediction. ✖
- ROC curves are useful to identify the best biomarker cut-point. ✖
- Decision curves are useful to identify the best risk threshold. ✖
- To assess whether to add new biomarker to a risk model, multiple stages of hypothesis testing are needed. ✖
- The best biomarker to improve a risk model is the one with strongest association with the outcome. ✖
- To improve prediction, a new biomarker should be independent of existing predictors. ✖

- We can often use biomarkers to identify which patients will benefit from treatment. ✖

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