*SISCER Module 3*
Part V:
Notes on prognostic and predictive biomarkers
(and "personalized medicine")

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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 treatment benefit.

A. Prognostic Biomarker

B. Predictive Biomarker

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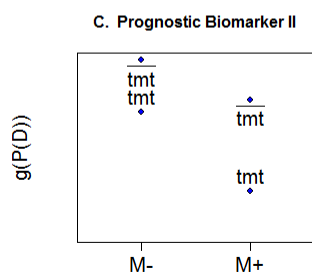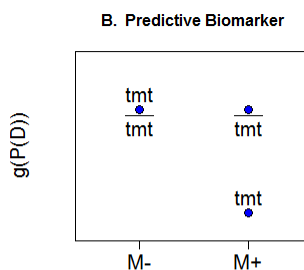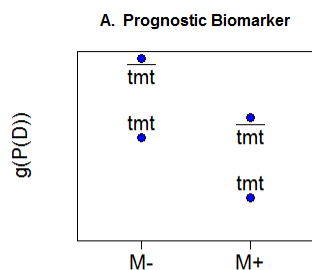
A. Prognostic Biomarker not useful for selecting treatment.
B. Biomarker that is not prognostic but is predictive –useful for selecting treatment
C. Prognostic biomarker that also predicts the magnitude of the treatment effect but is not a treatment-selection biomarker.

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# 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### DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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)
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Clinical Medical

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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.

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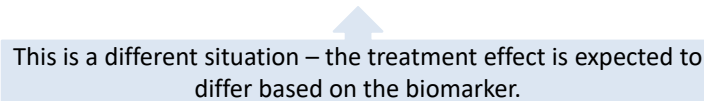
Discussed in Part II today – evaluating a biomarker for prognostic enrichment. The biomarker was not expected to predict the treatment effect.

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.

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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. 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 and bad)

- 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

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# 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 no treatment and bad outcome with treatment

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# Sensitivity and Specificity for a Predictive Biomarker

Sensitivity:  P(biomarker + | benefit from tmt)

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

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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 |

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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 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%

| | | 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 |
| Marker 1 | Positive | 200 | 350 | 200 | 150 |
| Marker 2 | Negative | 100 | 350 | 500 | 150 |
| Marker 2 | 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 |
| Marker 1 | Positive | 100 | 100+175 | 100+100 | 175 |
| Marker 2 | Negative | | | | |
| Marker 2 | 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 |
| Marker 1 | Positive | 200 | 350 | 200 | 150 |
| Marker 2 | Negative | 100 | 350 | 500 | 150 |
| Marker 2 | 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 |
| Marker 1 | Positive | 100+75 | 100+175 | 100+100 | 175+75 |
| Marker 2 | Negative | | | | |
| Marker 2 | 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 look the same 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:
225/500 = 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 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

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"

# Closing Thoughts

- Be skeptical of claims that a biomarker can predict individual treatment benefit.
- Most of the time, 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

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