SISCER Module 5

Part IV: Combining Biomarkers and Developing Risk Models

July 12-13, 2021

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

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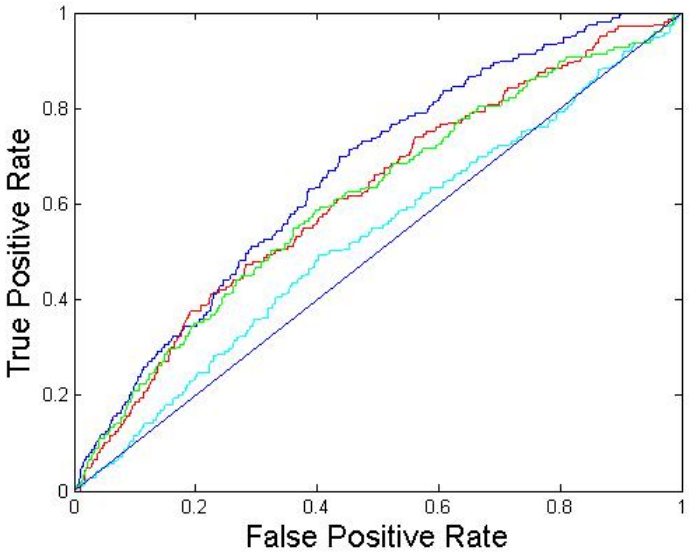
Caveat

- This set of material should provide you with some guidance, but will not provide you with a recipe.

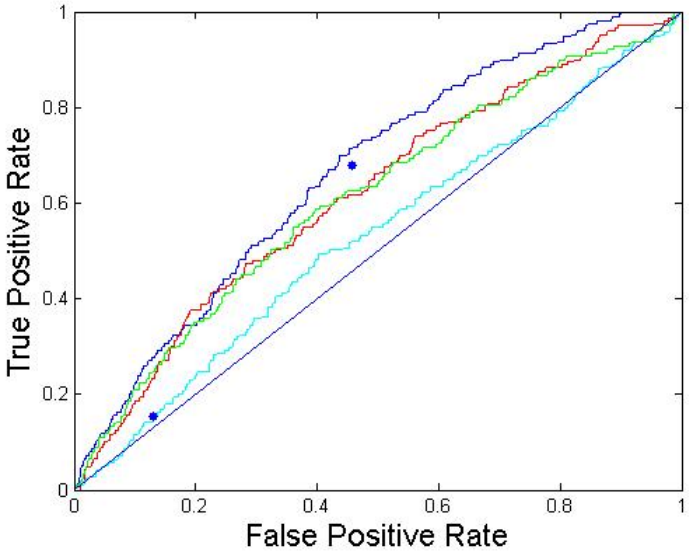
A shared experience

- Investigators interested in predicting an outcome D have a collection of modestly predictive biomarkers
- They combine the markers together with logistic regression. This results in…
- … a modestly predictive combination

Framingham risk factors individually…

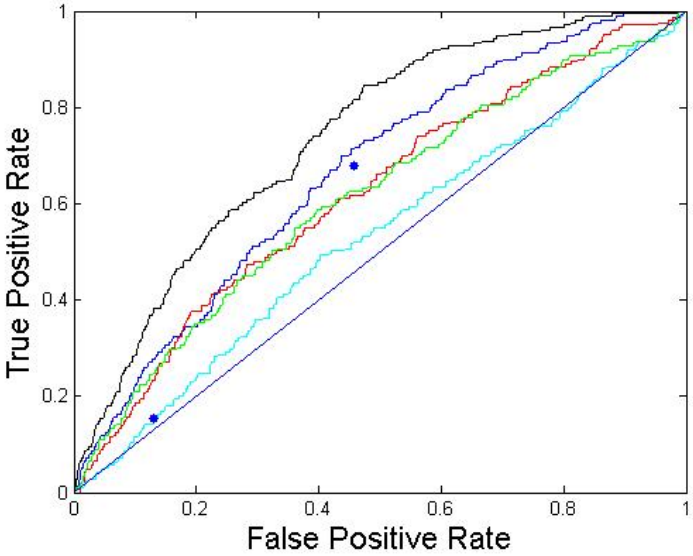


Framingham risk factors individually…



405

Framingham risk factors in combination



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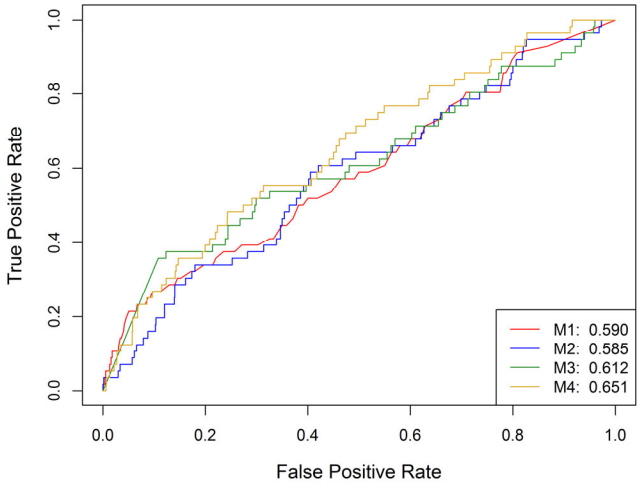
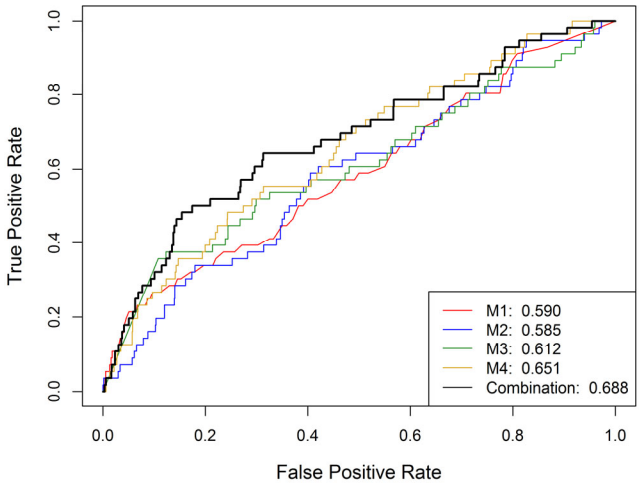
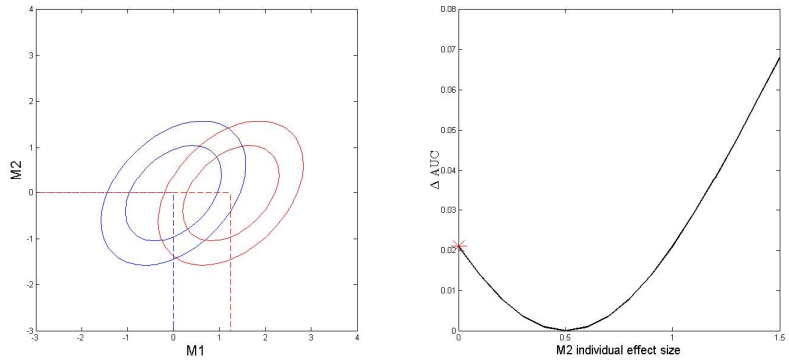
AKI biomarkers individually…

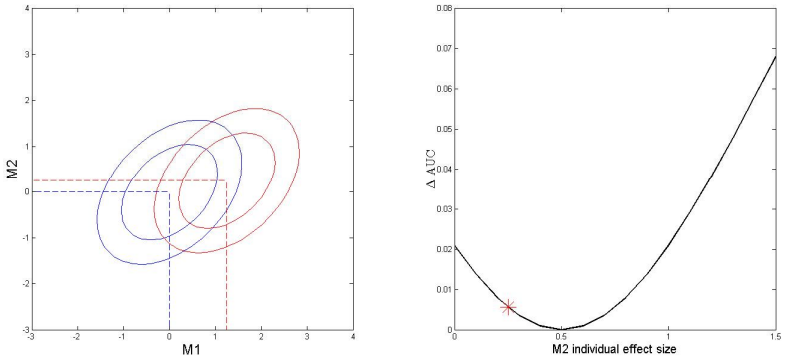


AKI biomarkers in combination

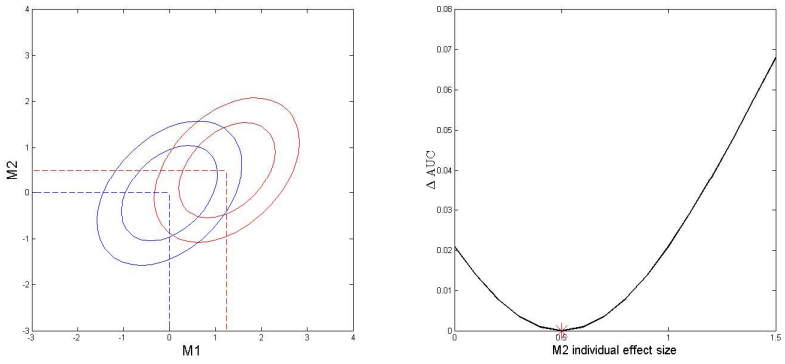


- The previous examples used linear combinations to combine predictors
- Is the problem that we don't know the right way to combine markers? Should we use something more sophisticated than logistic regression?
- Let's return to the BiNormal Model

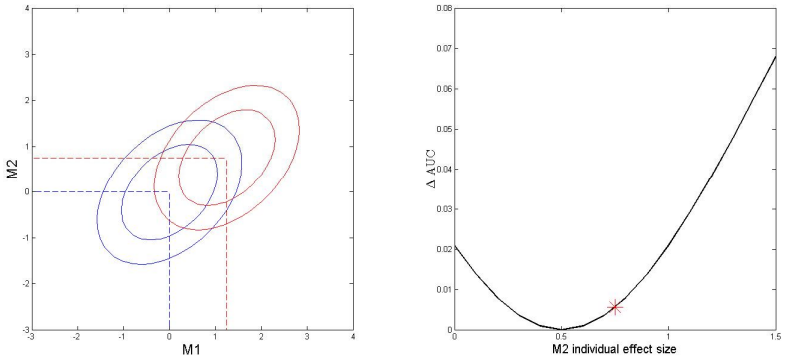



M2
M1
Δ AUC
M2 individual effect size

411


M2
M1
Δ AUC
M2 individual effect size

412


M2
M1
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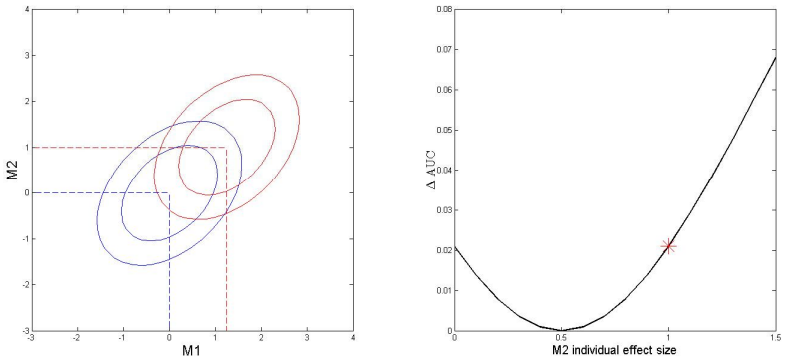
413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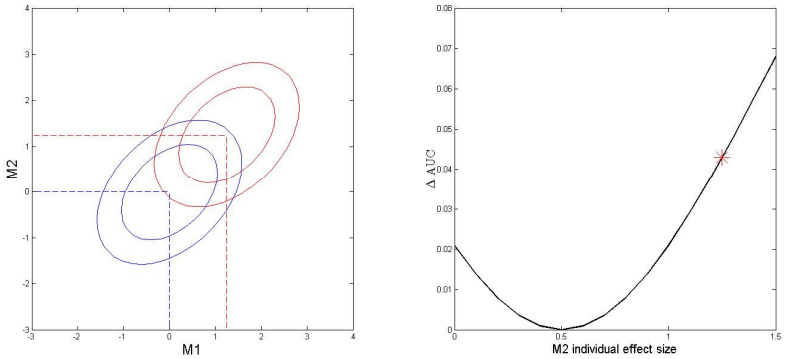
M2
M1
Δ AUC
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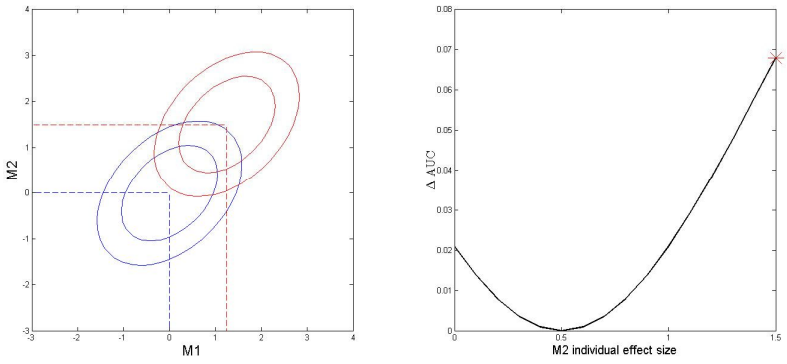
415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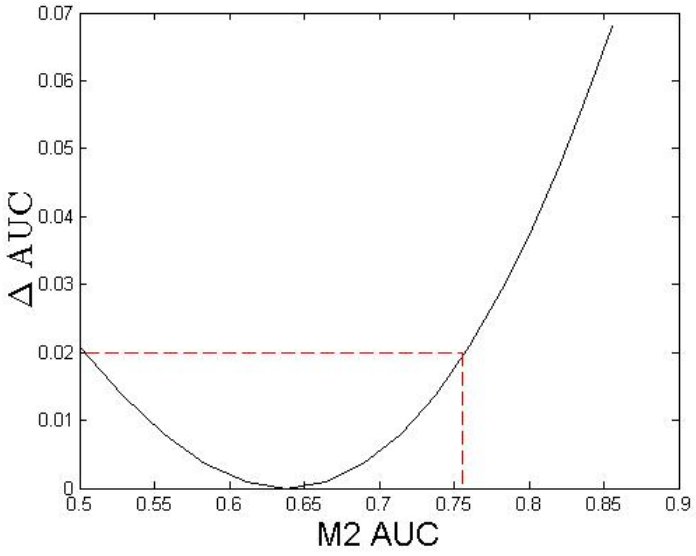
416



Lessons from the example:

- A marker with no predictive capacity by itself can have positive incremental value.
- A marker with prognostic capacity by itself can have 0 incremental value.
- Incremental value is **not** a simple, monotone function of a biomarker's individual predictive capacity.
- To get large incremental value, we may need new biomarkers that are *as good as or better than* existing markers.

Observations about the example:

- In the example, the true risk scores are known theoretically and exactly
  - risk(D | M1)
  - risk(D | M2)
  - risk(D | M1, M2)
- In particular, we are not *estimating* risk P(D | M1, M2).
- Conclusion: "better methods for combining biomarkers" is not what is lacking in this example

New example

- X1 has mean 0 in controls and mean 1 in cases. SD_{X1}=1 in both.
- X2 has mean 0 in controls and mean 2 in cases, SD_{X2}=1 in both.
- We consider the optimal combination of X1 and X2 for discriminating cases and controls When will we have highest AUC for the combination?

$corr_{cntl}(X1, X2)=corr_{case}(X1, X2)= 0, 0.3, 0.6, 0.9$

X1 and X2 each have mean (0,0) in controls and mean (1,2) in cases. Conditional correlation between X1 and X2 is 0, 0.3, 0.6, or 0.9.

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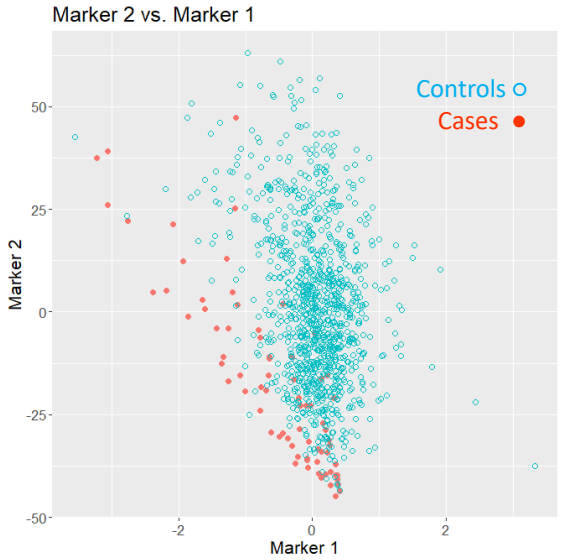
Recent real data example



AUC_{M2} 0.75

$AUC_{M1,M2}$: 0.94 after optimism-correction

Figure credit: David Hu

AUC_{M1}: 0.71

Lessons from Machine Learning

- Lim et al (2000) compared 33 classification algorithms on 32 datasets
  - 22 algorithms to build decision trees
  - 9 statistical algorithms
  - 2 neural network algorithms
- The best performing algorithm "was not statistically different" from 20 other algorithms.
- Logistic regression came in second

Lessons from Machine Learning

- Christodoulou et al (2019) reviewed published papers that reported both logistic regression and a machine learning technique to develop a predictive model
- For studies using best practices to avoid biased results, no evidence of a systematic benefit for machine learning or logistic regression
  - LR included penalized, “boosted”, and “bagged” versions
  - Evaluative metric: AUC

Lessons from Machine Learning

- There is no universally “optimal” way of combining biomarkers
  - For every method, there is probably some data structure for which it is optimal.

Lessons from Statistics and Machine Learning

- Different methods are optimal for different data structures, so should we try out lots of methods?
  - We should worry about "model selection bias"
  - If we try out lots of methods on our data and choose the best, we will have biased estimates of model performance without special methods
  - For modestly sized datasets in biomedicine, choose something sensible and move on.

Recent efforts to provide reporting standards and guidelines for publications reporting new risk models: TRIPOD and RiGoR

Annals of Internal Medicine RESEARCH AND REPORTING METHODS

Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): Explanation and Elaboration

Karel G.M. Moons, PhD; Douglas G. Altman, DSc; Johannes B. Reitsma, MD, PhD; John P.A. Ioannidis, MD, DSc; Petra Macaskill, PhD; Ewout W. Steyerberg, PhD; Andrew J. Vickers, PhD; David F. Ransohoff, MD; and Gary S. Collins, PhD

(TRIPOD co-published in 11 journals)

Kerr *et al. Biomarker Research* (2015) 3:2
DOI 10.1186/s40364-014-0027-7

BIOMARKER RESEARCH

REVIEW Open Access

RiGoR: reporting guidelines to address common sources of bias in risk model development

Kathleen F Kerr[1*], Allison Meisner[1], Heather Thiessen-Philbrook[2], Steven G Coca[3] and Chirag R Parikh[4]

TRIPOD

- Response to common problems with risk models presented in the literature
- In some areas, many risk models are being developed (diabetes, prostate cancer) – which should clinicians use?
- This problem is exacerbated by poor reporting.
  - The existence of existing models not acknowledged, new model not compared to existing models
  - Failure to provide information on the actual model (!)
- https://www.tripod-statement.org/

RiGoR

- Similar effort to TRIPOD (less prominent than TRIPOD)
- More emphasis on addressing possible sources of bias that can arise in risk model development
- Various terms are used to describe these biases
  - optimistic bias
  - overoptimistic bias
  - overfitting bias
  - selection bias
  - parameter uncertainty bias (Steyerberg)
  - model uncertainty bias (Steyerberg)
- Better to have terms that are descriptive and specific

- The RiGoR paper proposes the terms "resubstitution bias" and "model-selection bias" for two sources of bias that commonly arise in risk model development

Resubstitution bias

- If the same data are used to fit a risk model and evaluate its performance, the evaluation will be biased in the "optimistic" direction
  - The process of applying a model to the dataset used to fit the model has been called "resubstitution"
  - Fairly extensive set of methods exist to correct for this bias when evaluating a risk model
    - bootstrapping
    - cross-validation
    - Harrell, *Regression Modeling Strategies* text and `rms` R package: "optimism-corrected AUC" etc
      - R demo

Model-selection bias

- If we pre-specify the exact form for our prediction model, and use the data only to estimate model parameters, then only resubstitution bias is a concern
- Sometimes we also use the data to help us choose our model
  - which variables to include in the model
  - transformations of those variables
  - form of the model (square terms, interaction terms)
- Even if we correct for resubstitution bias in our evaluation of the final model, we can still have model-selection bias

Model-selection bias

- Methods here are less-developed
- If using bootstrapping or cross-validation, a common practice is to incorporate model-selection into the procedure
  - not entirely clear how well this works
  - requires a completely algorithmic method of model-selection
  - note that cross-validation does not actually assess the final, fitted model

Sample-splitting

- Randomly split the data into a training set and a test set (often 50-50, or 2/3-1/3)
  - all model development on the training set
  - when the final model is “locked down”, evaluate its performance on the test set
  - addresses both resubstitution bias and model-selection bias
- Criticized for its statistical inefficiency
  - only using a fraction of the data to build/train your model
  - still, if you have lots of data this might be a good option

Sample-splitting

- In order for sample-splitting to provide an unbiased assessment of model performance, you get “one look” at the test data
- Must “lock down” one or a few models to evaluate on the test data
- If you evaluate a model on the test data, then re-visit the training data to try to come up with a better model, you are no longer getting an unbiased assessment
  - the test data are informing model development, are no longer independent

Internal vs. External Validation

- All of the methods just discussed are methods of “internal” model validation
- “external” validation is a more challenging and more important hurdle: how does the model perform on a new sample of data from the appropriate clinical population?

Bootstrap Approach to Correcting for Resubstitution Bias

- “optimism-corrected estimate of model performance”
- Harrell text: “bias-corrected or overfitting-corrected estimate of predictive accuracy”
- (Illustrated in R Demo)

Bootstrap Approach to Correcting for Resubstitution Bias

1. Fit the (pre-specified) model (call it M) and calculate its performance on the same dataset.
   – "apparent performance" of M
2. Draw a bootstrap sample of size n. Re-fit the model to the bootstrap sample, get M*.
3. Evaluate M* on both the original dataset and the bootstrap dataset used to get M*. The difference between these is the estimate of optimism.
4. Repeat steps 2-3 many times. The average of the estimated optimisms across many bootstrap samples is the estimate of optimism. Subtract the estimated optimism from the apparent estimate of performance.

Summary

- There is no generally optimal way to build a prediction model or risk model
- Logistic regression has been observed to work well in lots of settings
  – need special methods for high-dimensional settings, not addressed here
- The variable that is most predictive on its own will not necessarily offer the most improvement to an existing risk model
- To improve upon an existing risk model we should not necessarily seek markers that are independent of existing markers

Summary

- Risk models are often poorly reported in the literature. Consult reporting standards to do better (TRIPOD, RiGoR)
- Beware of optimistic biases in risk model development: resubstitution bias and model-selection bias
  - There are additional opportunities for biases to enter a study, e.g. selection of cases and controls

References

- Bansal and Pepe, When does combining markers improve classification performance and what are implications for practice? *Statistics in Medicine*, 2013.
- McIntosh and Pepe, Combining several screening tests: optimality of the risk score. *Biometrics*, 2002.
- Lim, Loh, and Shih, A Comparison of Prediction Accuracy, Complexity and Training Time of Thirty-Three Old and New Classification Algorithms. *Machine Learning*, 2000.
- Chrisodoulou, Ma, Collins, Steyerberg, Verbakel, van Calster, A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction model. *J of Clinical Epidemiology* 2019
- Gary Collins et al, TRIPOD papers and website 2015
- Kerr et al, RiGoR, *Biomarker Research* 2015
- Harrell, Regression Modeling Strategies, Springer

Misconceptions about Biomarkers and Risk Models

- A large odds ratio implies that a biomarker is useful for prediction. ✖
- A data analyst can identify the optimal threshold from an ROC curve. ✖
- A data analyst can identify the optimal risk threshold from a Decision Curve. ✖
- 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 ✖
- To assess whether to add new biomarker to a risk model, multiple stages of hypothesis testing are needed. ✖
- We can often use biomarkers to identify which patients will benefit from treatment.