Study design and endpoints in ‘omics-based biomarker studies

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Biomarker study design considerations

- Proposed context of use (COU)
- Weight of evidence required for COU
- Nature of evidence for COU – truth standards
- Design: efficient & biased vs. inefficient & pure
- Biomarker selection: candidate vs. hypothesis-free*
- Dimensionality reduction strategies*
- Biological plausibility: important or useless?*
- Performance: how good is good enough?

Context of use: FDA's Drug development tools qualification program

- "Context of use," or COU, is a comprehensive and clear statement that describes the manner of use, interpretation, and purpose of use of a biomarker in drug development.

- How this helps us:
  - Avoids the concept of "universal validity" where biomarkers are applied in new contexts for which they are not qualified
  - Defines the nature of evidence required to qualify the biomarker in a defined COU
  - Defines the consequences of errors for that COU
  - Defines the intended benefit of success for that COU

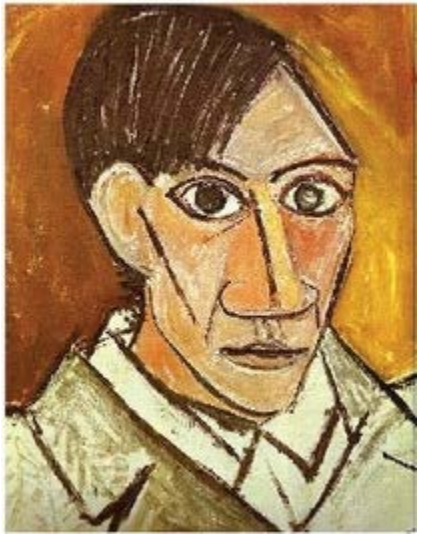
A hypothetical example for NASH

- COU#1
  - A noninvasive substitute for liver biopsy, which mimics histopathological scores for liver fat, fibrosis, inflammation and ballooning, with accuracy similar to inter-pathologist variation, for use in phase II studies of NASH, enabling an end-of-phase go/no-go decision acceptable to the sponsor and the regulatory authorities, independent of drug mechanism.
    - Application in phase III or for registration would be a different COU (greater weight of evidence, same nature of evidence)
    - Biopsy substitution at only intermediate time points, retaining biopsy at beginning and end, would require lesser weight of evidence, same nature of evidence
    - Trial enrichment for rapid progressors would be a different nature of evidence (prognosis) but likely similar weight of evidence

Truth standards

- All truth standards are wrong, some are useful

A

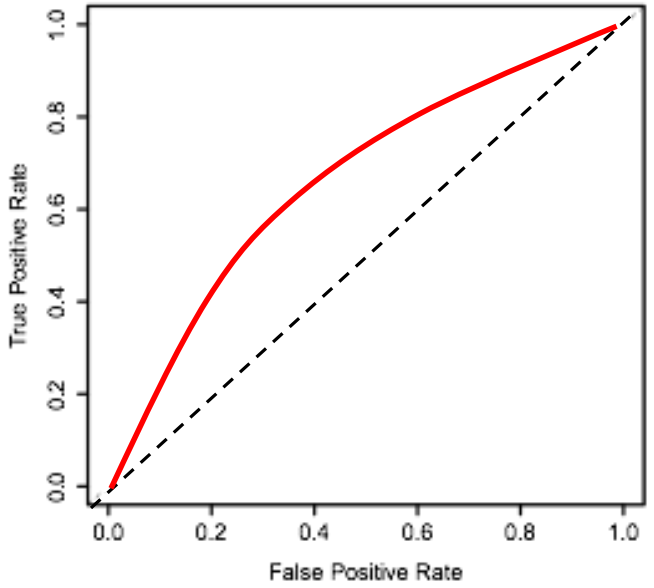


Histopathology?

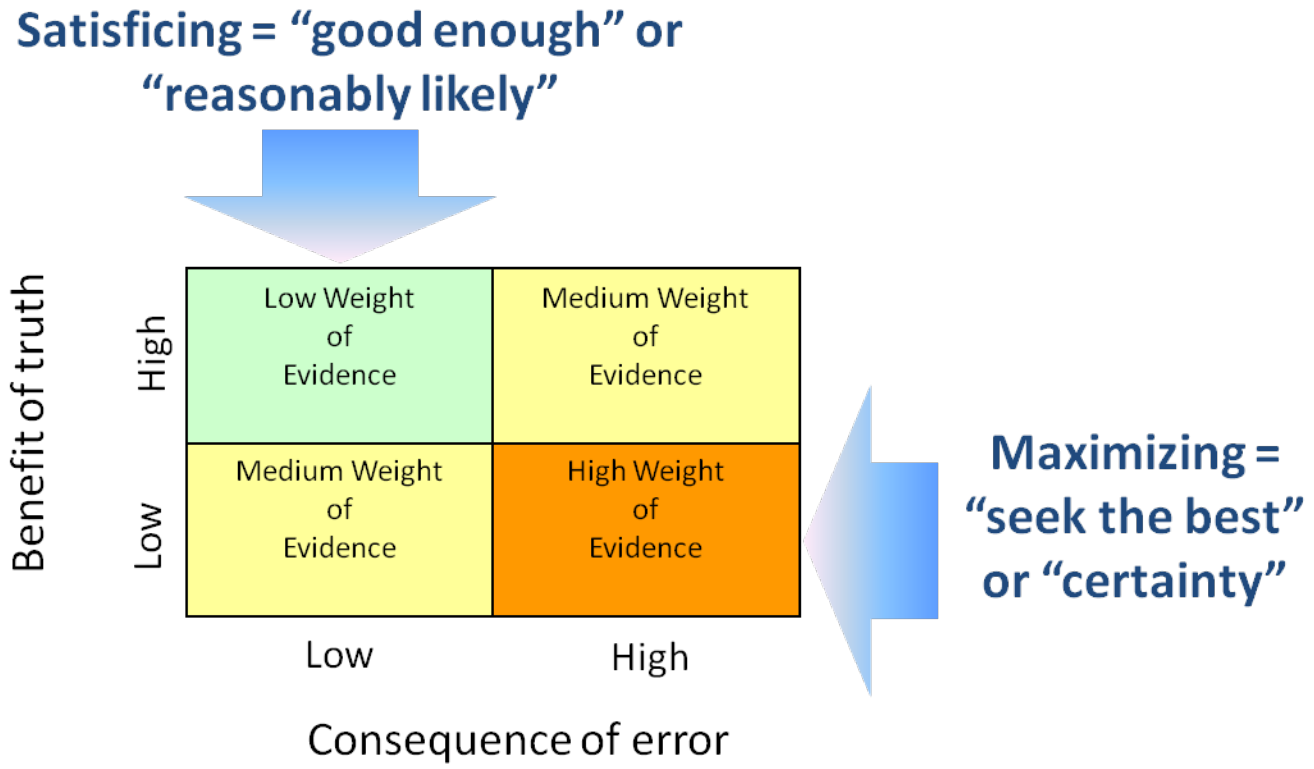
B

Time to cirrhosis?
+
Cardiovascular deaths?
+
Transplant rate?

AUC of recognizing Picasso B in this room if A is the truth standard

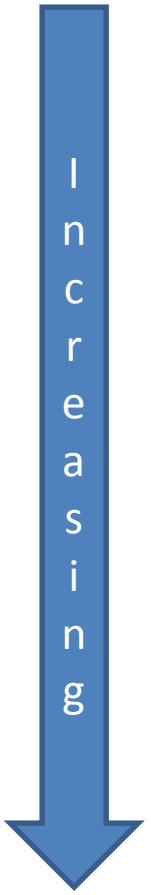


Weight of evidence for biomarker qualification is modulated by risk:benefit



Weight of evidence: What it means

- Single study in a few hundred subjects in a similar population to clinical trials with cross-validation/bootstrap of models
- Above plus independent retrospective validation set in a few hundred subjects
- Above plus exact intended use population in a retrospective study
- Above plus geographic and population variability/robustness in a few thousand subjects
- Above plus prospective application in exact intended use population
- Above plus multiple prospective applications in exact intended use populations



Populations and study efficiency

- What is the “intended use population”? Does your discovery/validation study match it exactly?
  - Easiest if prevalence of cases and controls is near equal, in which case, run a cohort study
- Deliberate mismatches for efficiency:
  - If prevalence of cases and controls is very unequal:
    - Compare the extremes (very efficient for discovery of physiology but does not match intended use)
    - Case:control (efficient but controls who don’t look like cases are missing from the evaluation so performance isn’t representative)
    - Case:cohort (efficient and represents everyone in the intended use population, performance is representative, but physiology is diluted and/or biased e.g. by age, gender)

Biomarker selection strategies

Favored list

PROS

- Fewer measurements
- Easier control of false discovery rate
- Familiar: psychological acceptance easier
- Uses a-priori evidence – efficient

CONS

- Don't find "black swans" – un-anticipated biology
- Unidimensional selection process misses complex signals
- A-priori evidence might be wrong: failure to replicate is common

Hypothesis free

PROS

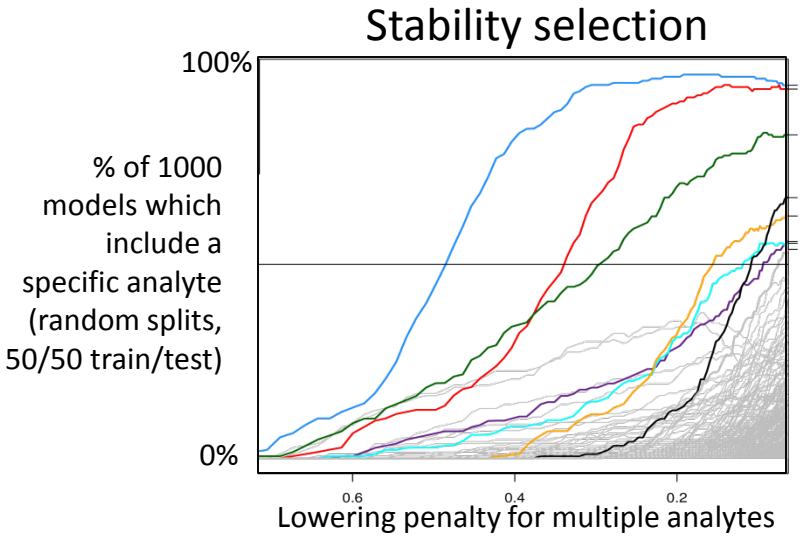
- Does not depend on favorites
- Optimal combinations possible – likely better performance
- Black swans (un-anticipated biology) can be found

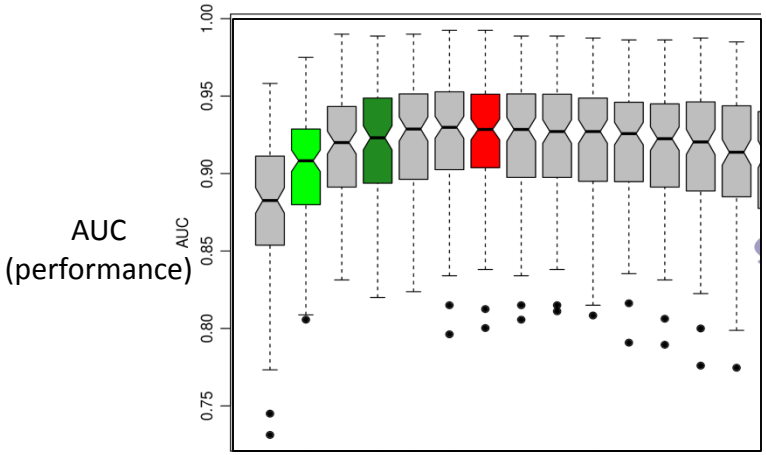
CONS

- Demands large numbers of precise measurements
- Psychological barrier to "Fishing Expeditions"
- Control of false discovery rate requires more samples/skills

Dimensionality reduction strategies

- Purpose: When many measurements are made, to eliminate false positives and to include only the best combination of markers in a model
- Crude strategy: generate unidimensional lists by p-value and chop off the bottom
- Semi-crude strategy: iterate. Use first study to create an enriched list. Use second study to refine enriched list. Repeat….
- Sophisticated mathematical strategies:
  - Stability selection process (penalized popularity contest for marker inclusion in models)
  - Multi-dimensional feature selection of stable analytes





Biological plausibility: Necessary?

Pros

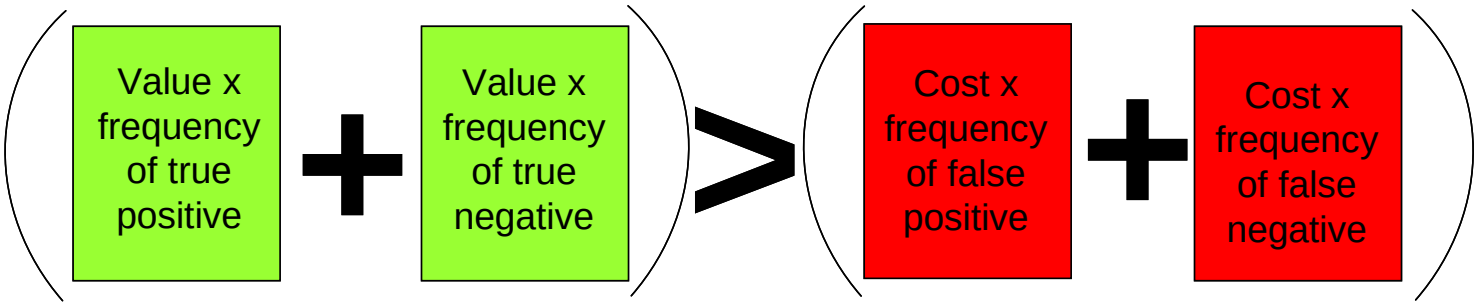
- Additional evidence of biomarker relevance (beyond statistical)
- Uncovers new drug targets
- Listed in ICH requirements for surrogate endpoints
- FDA support as criterion for surrogate endpoints
- Causality implications are useful

Cons

- Easy to make up a story
- Historically does not discriminate between successes and failures in surrogate endpoints
- Humans like unidimensional or linear stories; biology is more complex than that
- Excludes biomarkers where plausibility is weak/unknown

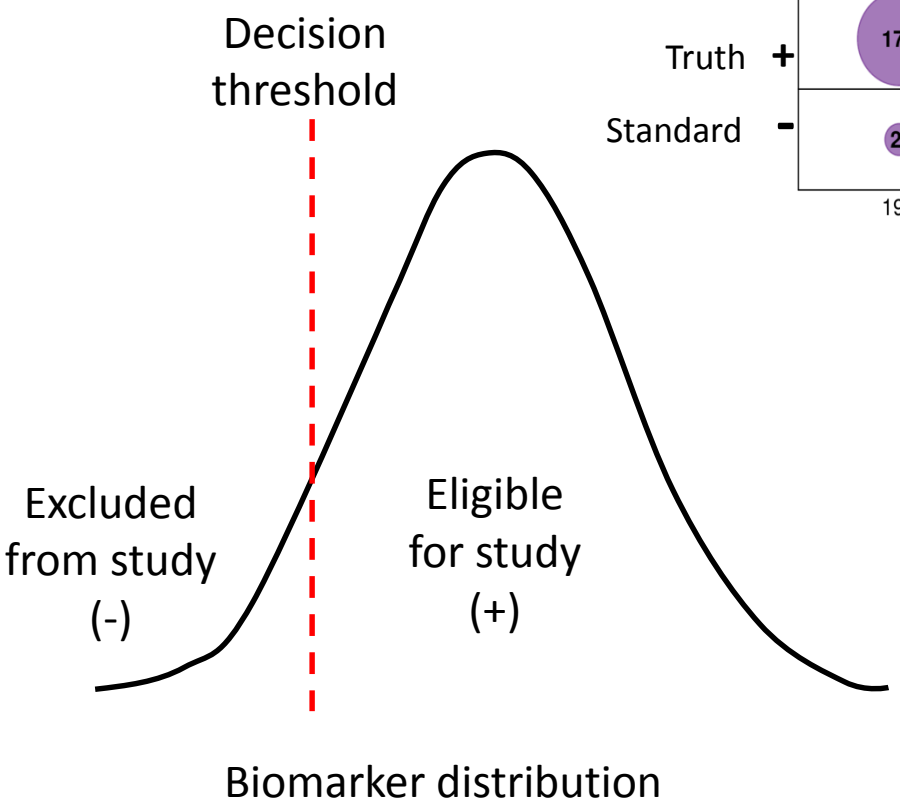
Biomarker performance: How good is good enough?

- Utilitarian/economic concept:
  - An endpoint is qualified when the value of the true signals is greater than the cost of the false signals
  - May also require superiority to the best available alternative



Performance metrics (a)

- Binary models: Why ROC curves are not the most important measure

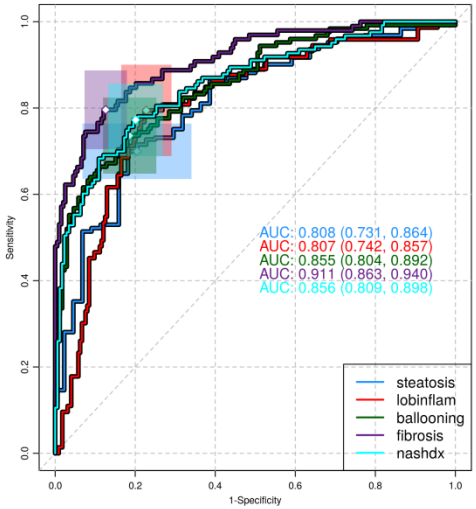


Biomarker prediction

		+	-	
Truth	+	173	25	198
Standard	-	20	78	98
		193	103	296

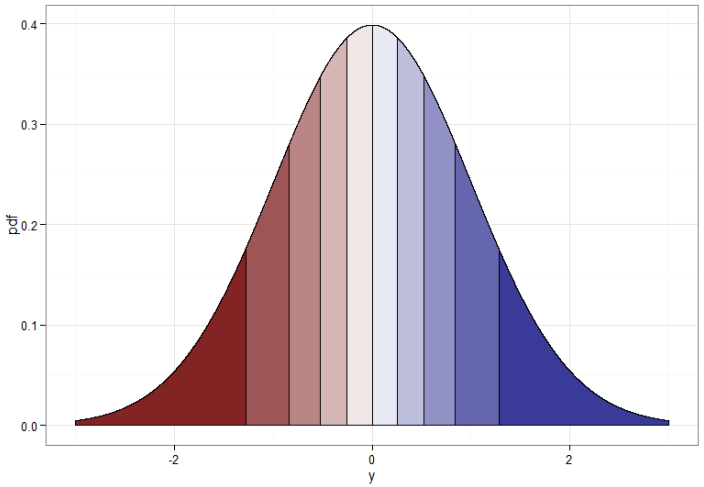
Comparison vs. another measure:
NRI
IDI

ROC curves

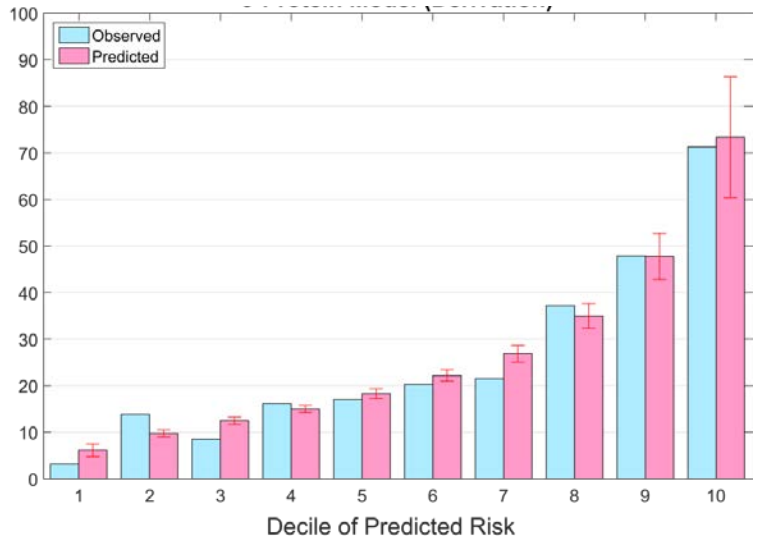


Performance metrics (b)

- Categorical models: Calibration



Biomarker distribution by population deciles or category



Calibration plot: predicted (pink) vs. observed truth (blue)

Summary

- Create a comprehensive evaluation of the context of use (COU) before even thinking of starting a study…
  - This determines the nature of evidence needed, including the truth standard
- For that COU, evaluate the weight of evidence needed (high value low consequence = low weight)
- Determine the appropriate study population and design considerations for efficiency
- Choose a biomarker selection strategy and a dimensionality reduction strategy
- Determine the appropriate performance metrics and how good is good enough in this COU
- Execute the program! Adapt to unexpected complexities…..