SISCR Module 4

Part I:
Introduction
Basic Concepts for Binary Biomarkers (Classifiers) and Continuous Biomarkers

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Module Overview

- Part I: Introductory concepts
- Part II: Evaluating Risk Models
- Part III: Evaluating the Incremental Value of New Biomarkers
- Part IV: Some Guidance on Developing Risk Models
- Part V: Prognostic vs. Predictive Biomarkers

- also: R tutorial/demo

Module Overview

- The focus of this module is concepts rather than statistical details
  - we won't be deriving hypothesis tests or distributional results
  - However, we will look at some mathematical expressions as we explore certain concepts

Part I Topics

- Motivating and illustrative examples
- True and false positive rates (TPR, FPR)
- Predictive values (PPV, NPV)
- ROC curves and area under the curve (AUC)
- Risk models
- What is "personal risk"?

Part 1 Overview

- Some examples
- To start: 1 marker X is binary (a “test”)
- We then move on: 1 marker X is continuous
- Multiple markers X, Y, …, and risk model P(bad outcome | X, Y, …)

What is a Marker?

- DEF: a quantitative or qualitative measure that is potentially useful to classify individuals for current or future status
  - current → diagnostic marker
  - future → prognostic marker
- Includes biomarkers measured in biological specimens
- Includes imaging tests, sensory tests, clinical signs and symptoms, risk factors

What is the purpose of a classifier or risk prediction tool?

- To inform subjects about risk
- To help make medical decisions
  - Most often: identify individuals with high risk – high risk individuals have the greatest potential to benefit from an intervention
  - Sometimes: identify individuals with low risk not likely to benefit from an intervention
- To enrich a clinical trial with "high risk" patients

Terminology and Notation

- "case" or "event" is an individual with the (bad) outcome
- "control" or "nonevent" is an individual without the outcome

case	control
D=1	D=0
D	$\overline{D}$
D	N

Terminology and Notation

- X, Y = potential predictors of D (biomarkers, demographic factors, clinical characteristics)
- Often: X is "standard" predictor(s) and Y is a new biomarker under consideration
- risk(X) = r(X) = P(D=1 | X)
  - risk(X,Y) = r(X,Y) = P(D=1 | X, Y)
- prevalence = P(D=1) = ρ ("rho")

What is risk(X)?

- risk(x) ≡ P(D=1 | X=x) is the frequency of events/disease among the group with X = x

- "Personal risk" is not completely personal!
  - Will return to this at the end of Part I

Example: Coronary Artery Surgery Study (CASS)

- 1465 men undergoing coronary arteriography for suspected coronary heart disease
- Arteriography is the “gold standard” measure of coronary heart disease
  - Evaluates the number and severity of blockages in arteries that supply blood to the heart
- Simple cohort study
- Possible predictor: Exercise stress test (EST)
- Possible predictor: chest pain history (CPH)

Example: EDRN Breast Cancer Biomarkers

- Women with positive mammograms undergo biopsy, the majority turn out to be benign lesions
- Provides motivation to develop serum biomarker to reduce unnecessary biopsies

Example: Pancreatic Cancer Biomarkers

- 141 patients with either pancreatitis (n=51) or pancreatic cancer (n=90)
- Serum samples
- Two candidate markers:
  - A cancer antigen CA-125
  - A carbohydrate antigen CA19-9
- Which marker is better at identifying cancer?
- Is either marker good enough to be useful?

Wieand, Gail, James, and James *Biometrika* 1989

Example: Cardiovascular Disease

- Framingham study
- D = CVD event
- Y = high density lipoprotein
- X = demographics, smoking, diabetes, blood pressure, total cholesterol
- n = 3264, n_D=183

Simulated Data

- Artificial data are useful for exploring/illustrating methodology
- Next I introduce artificial datasets that we will use to illustrate some methods
  - Simulated data on DABS website
  - Simulated data from R packages *rmda* (risk model decision analysis) and *BioPET*
  - Normal and MultiNormal biomarker model

Example: Simulated data on DABS website

- n = 10,000, n_D=1017
- Y = continuous, 1-dimensional
- X = continuous, 1-dimensional
- Search "Pepe DABS" or http://research.fhcrc.org/diagnostic-biomarkers-center/
  - "simulated risk reclassification dataset"

Example: Simulated data in R packages

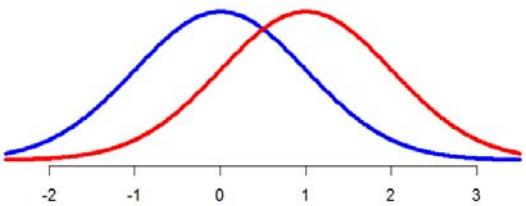
- n = 500, n_D=60
- X = sex, smoking status, Marker1
- Y = Marker2
- These simulated data will not appear in lecture notes, but will appear in software demo

Normal Model with 1 Marker

- Biomarker X Normally distributed in controls and in cases

X ~ N(0,1) in controls

X ~ N(μ,1) in cases



Distribution of X when μ=1

Multivariate Normal Model with 2 Markers (Bivariate Normal)

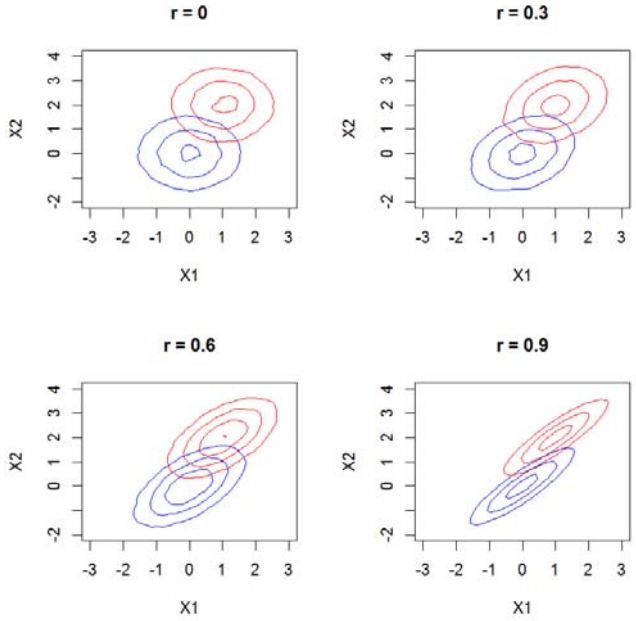
- Biomarkers (X_1, X_2) are bivariate Normally distributed in controls and in cases

$$\vec{X} \sim MVN(\vec{0}, \Sigma) \text{ in controls}$$

$$\vec{X} \sim MVN(\vec{\mu}, \Sigma) \text{ in cases}$$

$$\Sigma = \begin{bmatrix} 1 & r \\ r & 1 \end{bmatrix}$$

In these examples X_1 and X_2 each have mean (0,0) in controls and mean (1,2) in cases. We can picture marker data in 2-dimensional space.



- Biomarkers (X_1, X_2) are bivariate Normally distributed in controls and in cases

$$\vec{X} \sim MVN(\vec{0}, \Sigma) \text{ in controls}$$

$$\vec{X} \sim MVN(\vec{\mu}, \Sigma) \text{ in cases}$$

- This data model is useful in research because the logistic regression model holds for each marker **and** for both markers together.

  logit P(D=1| X_1) is linear in X_1

  logit P(D=1| X_2) is linear in X_2

  logit P(D=1|X_1, X_2) is linear in X_1 and X_2

Generalization: Multivariate Normal Model

- Biomarkers (X_1, X_2, …, X_k) are multivariate Normally distributed in controls and in cases

$$\vec{X} \sim MVN(\vec{0}, \Sigma) \text{ in controls}$$

$$\vec{X} \sim MVN(\vec{\mu}, \Sigma) \text{ in cases}$$

- The linear logistic model holds for every subset of markers

QUANTIFYING CLASSIFICATION ACCURACY (BINARY MARKER OR "TEST")

Terminology

- D = outcome (disease, event)
- Y = marker (test result)

	D=0	D=1
Y=0	true negative	false negative
Y=1	false positive	true positive

Terminology

TPR = true positive rate = P[Y=1|D=1] = sensitivity

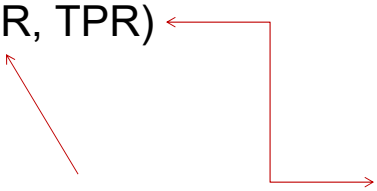
FPR = false positive rate = P[Y=1|D=0] = 1-specificity

FNR = false negative rate = P[Y=0|D=1] = 1-TPR

TNR = true negative rate = P[Y=0|D=0] = 1-FPR

Ideal test: FPR=0 and TPR=1

- (FPR, TPR)



benefit

Later, we will consider the benefits of identifying a true positive

cost

Later, we will consider the costs associated with false positives

Coronary Artery Surgery Study (CASS)

Coronary Artery Disease

Exercise Stress Test	D=0	D=1
Y=0	327	208
Y=1	115	815
	442	1023

FPR=115/442=26%

TPR=815/1023=80%

What about Odds Ratios?

- Odds ratios are very popular:
  - Because logistic regression is popular
  - Odds Ratio estimable from case-control study
  - OR≈relative risk for rare outcome
- $OR = \frac{TPR\,(1-FPR)}{FPR\,(1-TPR)}$
- Good classification (high TPR and low FPR) → large odds ratio
- However, large odds ratio does NOT imply good classification!

Good classification → large odds ratio

E.g., TPR=0.8, FPR=0.10

$$OR = \frac{0.8 \times 0.9}{0.1 \times 0.2} = 36$$

Coronary Artery Surgery Study (CASS)

Coronary Artery Disease

Exercise Test	D=0	D=1
Y=0	327	208
Y=1	115	815
	442	1023

FPR=115/442=26%

TPR=815/1023=80%

OR ≈ 11.1

OR is large but classification performance is not exceptional.

large odds ratio does NOT imply good classification!

Pepe et al, American Journal of Epidemiology 2004; 159:882-890.

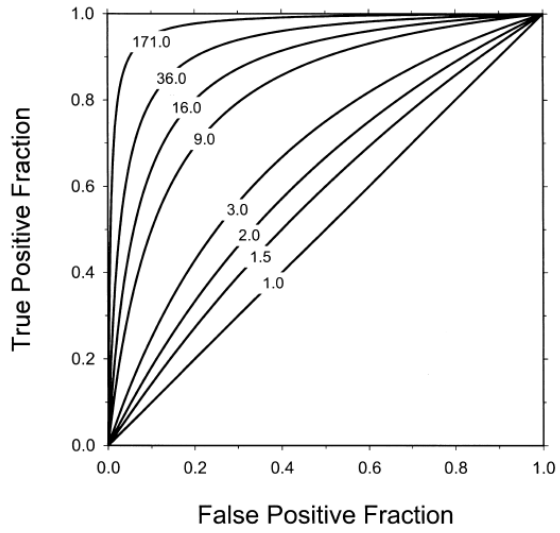


FIGURE 1. Correspondence between the true-positive fraction (TPF) and the false-positive fraction (FPF) of a binary marker and the odds ratio. Values of (TPF, FPF) that yield the same odds ratio are connected.

- Need to report *both* FPR and TPR
- Collapsing into one number (e.g., OR) is not sufficient
  - important information is lost

Misclassification Rate

MR = error rate = $P(Y \neq D)$

$= P(Y=0, D=1) + P(Y=1, D=0)$

$= \rho(1\text{-}TPR)+(1- \rho)FPR$

- ρ is the prevalence $P(D=1)$
- only appropriate if the cost of false positives equals the cost of false negatives
- seldom useful or appropriate in biomedical applications

Misclassification Rate

- There are two kinds of wrong decisions and the MR equates these. In order to be clinically relevant we must consider the cost of each kind of error
  - … later today

- FPR, TPR condition on true status (D)
- they address the question: "to what extent does the biomarker reflect true status?"

Predictive Values

Positive predictive value PPV=P(D=1|Y=1)

Negative predictive value NPV=P(D=0|Y=0)

- condition on biomarker results (Y)
- address the question: "Given my biomarker value is Y, what is the chance that I have the disease?" This is the question of interest for patients and clinicians when interpreting the result of a biomarker or test

Predictive Values

PPV and NPV are functions of TPR and FPR *and* the prevalence ρ

$$PPV = \frac{\rho\, TPR}{\rho\, TPR + (1-\rho)FPR}$$

$$NPV = \frac{(1-\rho)(1-FPR)}{(1-\rho)(1-FPR) + \rho(1-TPR)}$$

- TPR, FPR are properties of a test, but PPV, NPV are properties of *a* test *in a population*
- For low prevalence conditions, PPV tends to be low, even with very sensitive tests

Predictive Values - Example

A serious disease affects 1 in 10,000 in a patient population.

A company markets a screening test as “98% accurate” because both sensitivity and specificity have been estimated to be 98%.

Those who test positive are recommended to undergo an invasive procedure for definitive diagnosis.

Should there be general screening for the patient population?

NPV = ?

PPV = ?

False Discovery Rate

False Discovery Rate FDR=P(D=0|Y=1)

=1 – PPV

"False Discovery Rate" and "False Positive Rate" sound similar, but they are not the same!

- FPR: among all those who are not diseased, how many were called positive
- FDR: among all those you called positive, how many were not actually diseased.
- We will not use or further discuss FDR further today.

CONTINUOUS MARKERS: ROC CURVES

Motivation

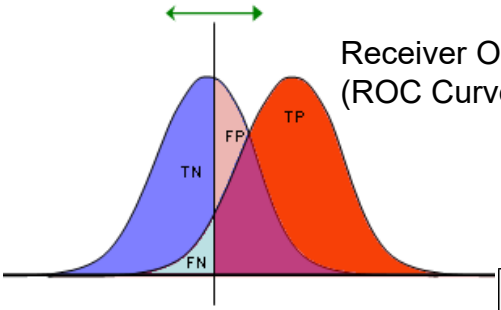
- Most biomarkers are continuous

Convention

- Assume larger Y more indicative of disease
  - otherwise replace Y with -Y
- Formally: P(D=1 | Y) increasing in Y

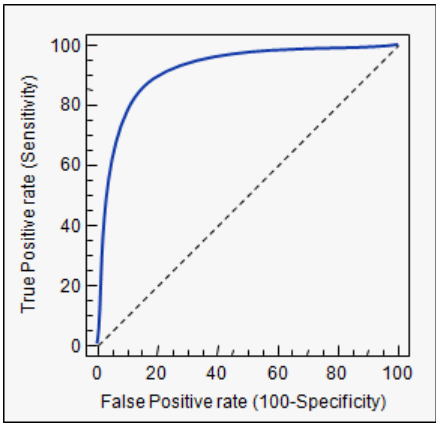
Receiver Operating Characteristic (ROC) Curve

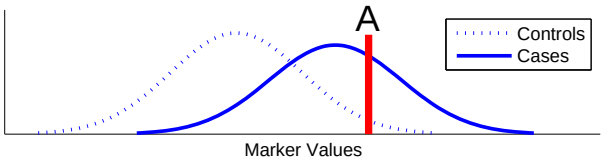
- generalizes (FPR, TPR) to continuous markers
- considers rules based on thresholds "Y≥c"
  - makes sense if P(D=1|Y) increasing in Y
- TPR(c)=P(Y ≥ c | D=1)
- FPR(c)=P(Y ≥ c | D=0)
- ROC(·)={FPR(c), TPR(c) ; c in (-∞,∞)}

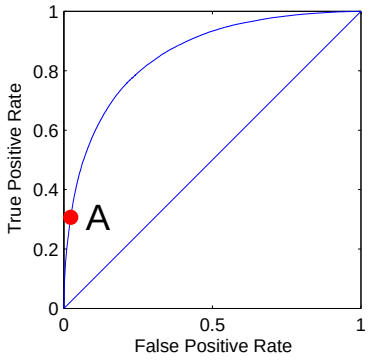


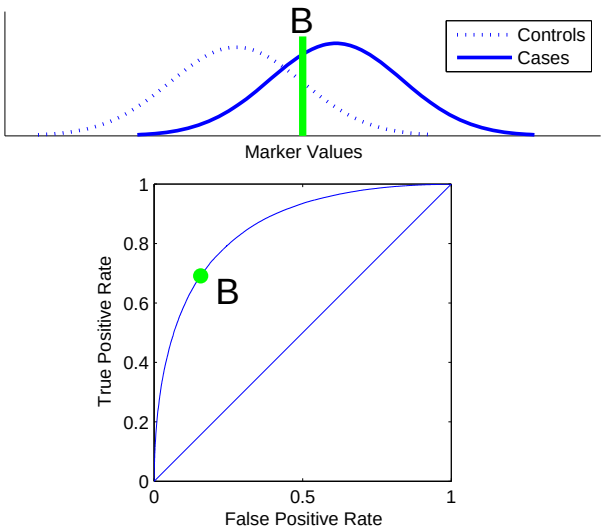
Receiver Operating Characteristic Curve (ROC Curve)

Each point on the ROC curve corresponds to a threshold for declaring "marker-positive."

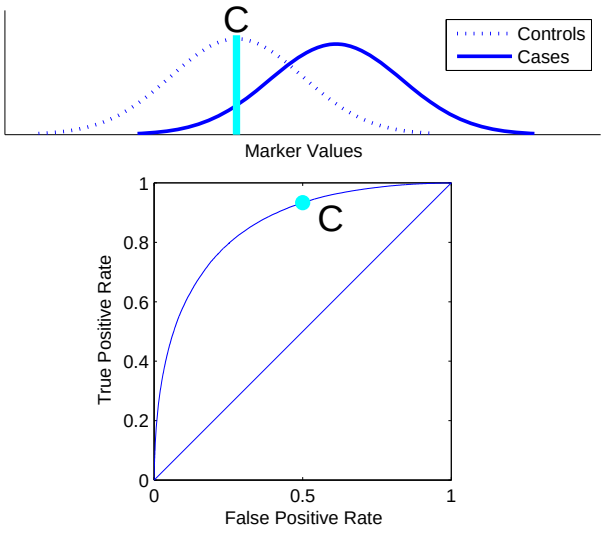




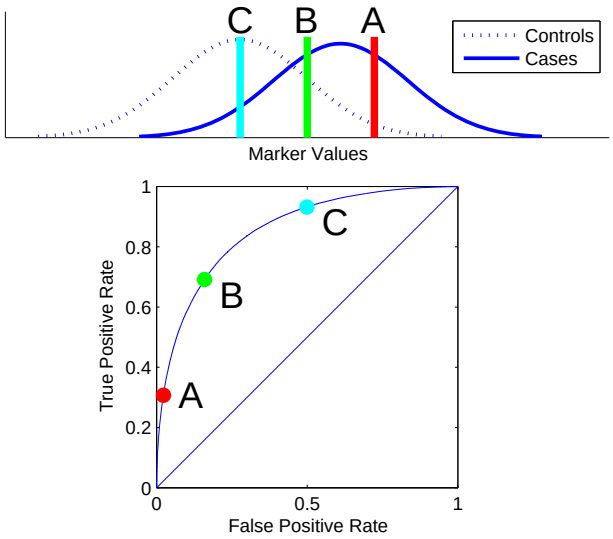



B
Controls
Cases
Marker Values
1
0.8
0.6
0.4
0.2
0
True Positive Rate
B
0
0.5
1
False Positive Rate

45


C
Controls
Cases
Marker Values
1
0.8
0.6
0.4
0.2
0
True Positive Rate
C
0
0.5
1
False Positive Rate

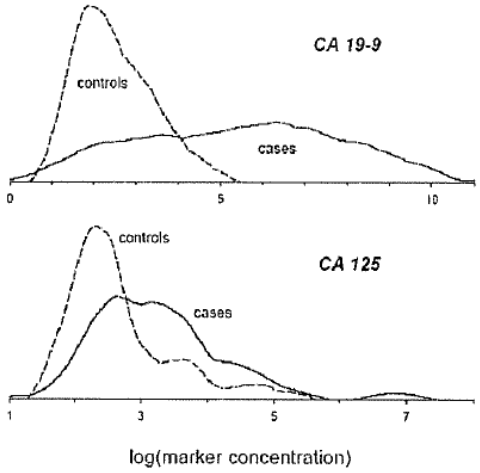
46

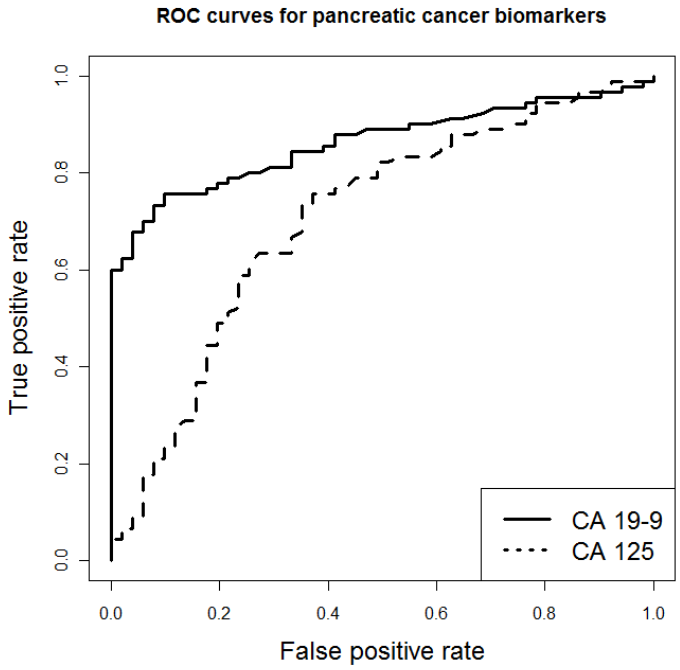


Properties of ROC curves

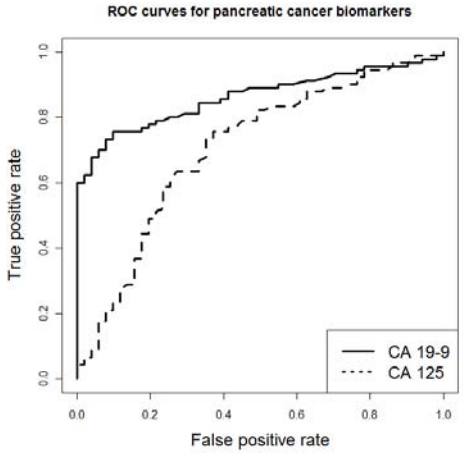
- non-decreasing from (0,0) to (1,1) as threshold decreases from c=∞ to c= −∞
- *ideal* marker has control distribution completely disjoint from case distribution; ROC through (0,1)
- *useless* marker has ROC equal to 45 degree line
- doesn't depend on scale of Y: invariant to monotone increasing transformations of Y
- puts different markers on a common relevant scale
- shows entire range of possible performance

Pancreatic cancer biomarkers (Wieand et al 1989)





CA-19-9 appears to be the more accurate diagnostic biomarker for pancreatic cancer



- for most fixed FPR, CA-19-9 has the better corresponding TPR
- for most fixed TPR, CA-19-9 has the better corresponding FPR

Summarizing ROC Curves: AUC

- AUC is Area under ROC curve
- AUC = $\int_0^1 ROC(t)\,dt$ = average(TPR)
  - average is uniform over (0,1)
- commonly used summary of an ROC curve
  - also called the c-index or c-statistic
- ideal test: AUC=1.0
- useless test: AUC=0.5
- A single number summary of a curve is necessarily a crude summary

AUC: probabilistic interpretation

- $P(Y_D > Y_N)$ for a randomly selected case D and a randomly selected control N
  - Provides an interpretation for AUC beyond "area under ROC curve"
- The AUC is a summary of an ROC curve that is commonly used to compare ROC curves – it is interpretable, but the interpretation also shows that AUC is not clinically meaningful

RISK PREDICTION

Risk Model: Huntington's Disease

- Huntington's Disease is caused by the gene *HTT* on human chromosome 4. There is a CAG segment that is repeated 10-35 times in non-diseased individuals. If the segment is repeated 36-120+ times, a person always* develops Huntington's Disease in middle-age. The genetic abnormality is dominant, meaning one abnormal gene causes disease.
  - *40+ times: always develop HD
  - *36-39 times: might not develop HD (ignoring this small possibility for this example)

Risk Model: Huntington's Disease

- Relevant Population: Individuals with a biological parent who have Huntington's Disease
- Within this population, an individual has a 50% chance of developing HD depending on whether he or she inherited the abnormal or normal version of the gene from the affected parent.
- P(D) = ½ = ρ in this population.

Risk Model: Huntington's Disease

- An individual can choose to have his *HTT* gene genotyped. Say HTT=0 means 0 copies of abnormal gene; HTT=1 means 1 copy of abnormal gene.
- P(D|HTT=0)=0% ; P(D|HTT=1)=100%.
- The marker HTT *stratifies* the patient population (risk=50%) into the subgroup with 0% risk and the subgroup with 100% risk.

Risk model

- risk prediction model – gives a risk for a marker value or a combination of markers
- Predicted risks are in the interval [0,1] and interpreted as probabilities
- It is rare that a risk model is definitive like the HD example
  - In fact, because the genetic test for Huntington's Disease is definitive, most people do not even think of it as a risk model

Risk model examples

- Most risk models combine information from multiple risk factors
- E.g., Gail model for breast cancer risk
  - for use in women with no history of breast cancer
  - Estimates 5-year risk of breast cancer based on current age, age at menarche, age at first birth, family history, race.
- E.g., Framingham CHD risk score
  - Estimates risk of CHD based on age, sex, smoking status, total and HDL cholesterol, blood pressure

Risk model examples

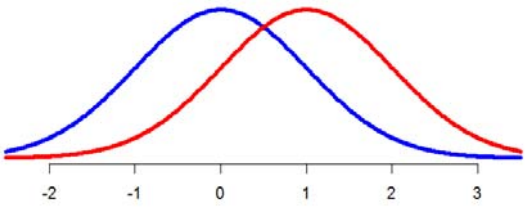
- E.g. STS risk score for dialysis following cardiac surgery is formed via:
  - STS risk score = $f(\alpha + \beta_1$ Age + β_2 Surgery Type + β_3 Diabetes + β_4 MI Recent + β_5 Race + β_6Chronic Lung Disease + β_7 Reoperation + β_8NYHA Class + β_9 Cardiogenic Shock+ β_{10}Last Serum Creatinine)

What is “personal risk”?

- Recall: risk(x) ≡ P(D=1 | X=x) is the frequency of events among the group with marker values x
- “Personal risk” is not completely personal!
  – (next example)

What is “personal risk”?

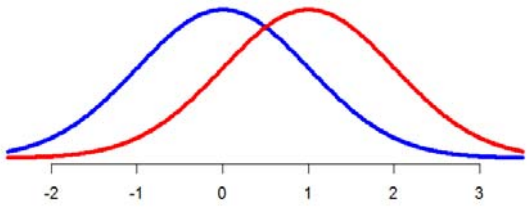
- Suppose the prevalence of D in “Population A” is 1%
  – Without any additional information, the only valid risk prediction instrument is to assign everyone in the population risk=1%
- Suppose we have a marker X that tends to be higher in cases than controls



Distribution of marker X in controls (blue) and cases (red)

What is “personal risk”?

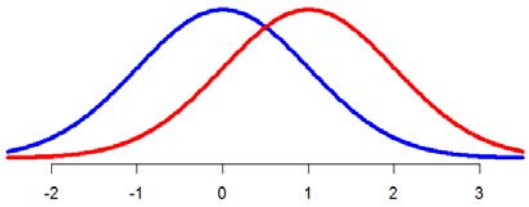
- Suppose an individual in Population A has X measured as 1.
- We can calculate his risk(X=1)≈1.6%
  - calculation uses Bayes’ rule



Distribution of marker X in controls (blue) and cases (red)

What is “personal risk”?

- Suppose the marker acts exactly the same in Population B. The only difference between Populations A and B is that B has prevalence=10%.
- An individual in Population B has X=1. For that individual, his risk is ≈15.5%



Distribution of marker X in controls (blue) and cases (red)

What is “personal risk”?

- “Personal risk” is a term that is prone to be misconstrued
- Risk is personal when calculated based on personal characteristics
- However, personal risk is not completely divorced from population characteristics. The previous example shows that the population (specifically, the population prevalence) affects “personal” risk.

What is “personal risk”?

- Occasionally one hears mention of estimating a person’s “individual risk” or “true personal risk.”
- Frequentist statisticians cannot really claim to do so.
- One might claim John’s “true risk” of a heart attack in the next 5 years is 7%. But we can only observe John having or not having a heart attack in the next 5 years. I cannot observe John having a heart attack in 7% of 5-year periods.
- The best I can claim is that “among people with John’s characteristics, 7% will have a heart attack in the next 5 years.”
  - More than one way to define “people like John.”

Summary

- Some example datasets
- FPR, TPR
- PPV, NPV
  - function of FPR, TPR and disease prevalence
- ROC curves
- AUC
  - geometric interpretation as area under curve
  - probability interpretation
- risk model: risk(X)=P(D=1|X)