Development and evaluation of multi-marker risk scores for clinical prognosis: Supplementary material

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In this supplement, we provide R code to estimate the net reclassification improvement (NRI) in the context of censored survival outcomes using simulated data. Recall that the NRI quantifies the predictive accuracy of a marker or set of markers by examining the difference in the proportions 'moving up' into a higher risk category and 'moving down' into a lower risk category among cases and controls between models with and without the marker(s) of interest.[1] For survival outcomes, risk at time t can be quantified by estimated survival probabilities obtained from a Cox regression model. Because subjects may be censored before time t, their true 'case' or 'control' status is unknown at t. Within cross-classified risk strata, the Kaplan-Meier risk estimate can be used to estimate the number of cases and controls at time t.[2,3] Thus for censored survival outcomes, the NRI at time t can be calculated for the estimated number of cases and controls 'moving up' or 'moving down' risk categories. Alternatively, a general 'prospective form' of the NRI may be obtained by exploiting Bayes' rule.[3]

R Code

```
## Load requisite extension packages

library(survival)
library(mvtnorm)
library(pec)

## Assign values for parameters

n <- 300
beta1 <- 0.75
beta2 <- 0.5
gamma <- 1.5
sigma <- matrix(c(1, 0.3, 0.3, 1), nrow=2, ncol=2)
```

```
## Generate biomarker X, covariate Z, and marker combination M

X.and.Z <- rmvnorm(n=n, sigma=sigma)
X <- X.and.Z[,1]
Z <- X.and.Z[,2]
M <- beta1*X + beta2*X*X + gamma*Z

## Generate survival times

time <- rep(NA, n)
for(i in 1:n){time[i] <- rexp(1, rate=exp(M[i]))}
ctime <- rexp(n, rate=0.2)
status <- ifelse(time<ctime, 1, 0)
stime <- ifelse(time<ctime, time, ctime)

data <- data.frame(X, X*X, Z)
colnames(data) <- c("X", "I(X * X)", "Z")

## Fit Cox regression models for Z alone and for the optimal combination of X and Z

m1 <- coxph(Surv(stime, status) ~ Z)
m2 <- coxph(Surv(stime, status) ~ X + I(X*X) + Z)

## Obtain predicted survival probabilities at time 0.25

p1 <- predictSurvProb(object=m1, newdata=data.frame(data[,c(3)]), times=c(0.25))
p2 <- predictSurvProb(object=m2, newdata=data.frame(data[,c(1,2,3)]), times=c(0.25))

## Categorize event probabilities according to risk thresholds (25%, 50%, 75%)

gp1 <- cut(1-p1, c(0, 0.25, 0.5, 0.75, 1), include.lowest=TRUE, right=FALSE)
gp2 <- cut(1-p2, c(0, 0.25, 0.5, 0.75, 1), include.lowest=TRUE, right=FALSE)
group <- interaction(gp2, gp1)

## Obtain Kaplan-Meier survival estimates at time 0.25 for each category and overall

km1 <- survfit(Surv(stime, status) ~ factor(group))
survest <- summary(km1, time=0.25, extend=TRUE)$surv

km1.t <- survfit(Surv(stime, status) ~ 1)
survest.t <- summary(km1.t, time=0.25, extend=TRUE)$surv

## NB: Some categories may not have any subjects

test <- is.element(1:dim(table(gp1, gp2))[1]^2, sort(unique(as.numeric(group))))
```

```
survest.final <- NULL
j <- 1
for (i in 1:length(test)){
  if (test[i]){
    survest.final <- c(survest.final, survest[j])
    j <- j+1}
  else {
    survest.final <- c(survest.final, NA)}}

survmat <- t(matrix(survest.final, nrow=4, ncol=4))

## Use Kaplan-Meier survival estimates to estimate cases and controls

cases <- table(gp1, gp2)*(1-survmat)
controls <- table(gp1, gp2)*survmat

## Obtain NRI

nricase <- (sum(cases[upper.tri(cases)], na.rm=TRUE)
  - sum(cases[lower.tri(cases)], na.rm=TRUE))/((1-survest.t)*n)
nricontrol <- (sum(controls[lower.tri(controls)], na.rm=TRUE)
  - sum(controls[upper.tri(controls)],na.rm=TRUE))/(survest.t*n)
nri <- nricase + nricontrol
```

References

1. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond. *Statistics in Medicine* 2008 **27**: 157–72.

2. Viallon V, Ragusa S, Clavel-Chapelon F, Bénichou J. How to evaluate the calibration of a disease risk prediction tool. *Statistics in Medicine* 2009; **28**: 901–16.

3. Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Statistics in Medicine* 2011; **30**: 11-21.