Evaluating a New Marker for Risk Prediction: Decision Analysis to the Rescue

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Supplementary File – Appendices A-D

Appendix A

This Appendix derives the formulas relating false and true positive rate and observed risk. Let \( J \) denote the risk interval and \( D=1 \) denote develop disease and \( D=0 \) denote not develop disease.

With the understanding that population quantities are being discussed, \( R_j = \text{pr}(D=1 \mid J=j) \), \( W_j = \text{pr}(J=j) \), \( P = \text{pr}(D=1) = \sum_j \text{pr}(D=1 \mid J=j) \text{pr}(J=j) = \sum_j R_j W_j \), and

\[
    TPR_j = \text{pr}(J \geq j \mid D=1) = \text{pr}(J \geq j+1 \mid D=1) + \text{pr}(J=j \mid D=1)
    = \text{pr}(J \geq j+1 \mid D=1) + \text{pr}(D=1 \mid J=j) \text{pr}(J=j) / \text{pr}(D=1)
    = TPR_{j+1} + R_j W_j / P,
\]

\[
    FPR_j = \text{pr}(J \geq J \mid D=0) = \text{pr}(J \geq j+1 \mid D=0) + \text{pr}(J=j \mid D=0)
    = \text{pr}(J \geq j+1 \mid D=0) + \text{pr}(D=0 \mid J=j) \text{pr}(J=j) / \text{pr}(D=0)
    = FPR_{j+1} + (1-R_j) W_j / (1-P).
\]

The estimates corresponding to the above quantities are computed starting with \( R_j = X_j / N_j \) and \( W_j = N_j / \sum_j N_j \). Also for four risk intervals, the above calculations of \( FPR_j \) and \( TPR_j \) begin with \( FPR_5 = TPR_5 = 0 \). The slope of the ROC curve corresponding to interval \( j \) is \( \text{ROCSlope}_j = (TPR_j - TPR_{j+1}) / (FPR_j - FPR_{j+1}) \) which implies that \( \text{ROCSlope}_j = \{1-P\} / P \{R_j / (1-R_j)\} \).
Appendix B

Linear interpolation is used to compute relative utility at other risk thresholds. For example, if $T$ is between $R_j$ and $R_{j+1}$, the relative utility at risk threshold $T$ is computed as $RU(T) = RU_j + (T - R_j) \frac{(RU_{j+1} - RU_j)}{(R_{j+1} - R_j)}$.

Appendix C

This Appendix derives the formula for $NNT_{est}(T)$. Let $C_{Test}$ denote the cost of testing for all markers, which is in the same units as $B$. The net benefit of risk prediction at risk threshold $T$ that includes the cost of marker testing is

$$NB_{WithTest}(T) = P RU(T) - C_{Test}. \tag{B.1}$$

Let $NB_{WithTest1}(T)$ and $NB_{WithTest2}(T)$ denote $NB_{WithTest}(T)$ for Models 1 and 2, respectively. Adding a new marker increases net benefit including testing cost if

$$NB_{WithTest2}(T) - NB_{WithTest1}(T) > 0. \tag{B.2}$$

Because $NB(T) = P RU(T)$, equation (B.2) can be written as

$$\{P B RU(T)_{2} - C_{Test2}\} - \{P B RU(T)_{1} - C_{Test1}\} > 0, \tag{B.3}$$

which implies

$$B / \Delta C_{Test} > 1 / \{P \Delta RU(T)\} = NNT_{est}(T), \tag{B.4}$$

where $\Delta C^{*} = C_{Test2} - C_{Test1}$ is the cost of testing for the new marker. The quantity $B / \Delta C_{Test}$ is the number of tests for a new marker per true positive. (To understand how a ratio of benefit to cost leads to a tradeoff in numbers, suppose a true positive has benefit of 10 units and is obtained with one marker test costing 1 unit, then 10 marker tests would be traded for 1 unit of benefit.)

From equation (B.4), $NNT_{est}(T)$ is the minimum number of tests for a new marker per true positive so that the net benefit of risk prediction including testing costs is greater than zero.
Appendix D

This Appendix describes computation of 95% confidence intervals for \textit{minNNTest}(T) using standard errors to speed computation. Let $\Delta NB(T) = P \Delta RU(T)$ with bootstrap standard error denoted $\text{se}\Delta NB(T)$. The 95% confidence interval for $\Delta NB(T)$ has lower bound $\Delta NB(T)_{LB} = \Delta NB(T) - 1.96 \text{se}\Delta NB(T)$ and upper bound $\Delta NB(T)_{UB} = \Delta NB(T) + 1.96 \text{se}\Delta NB(T)$, which is reasonable as this distribution is likely symmetric. The 95% confidence interval for $NNTest(T)$ has lower bound $1 / \Delta NB(T)_{UB}$ and upper bound $1 / \Delta NB(T)_{LB}$. 