SISCER 2023 Module 5: Evaluation of Biomarkers and Risk Models

Part III: Comparing Two Risk Models

July 13-14, 2023

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

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Outline of Part III

1. How to compare two risk models
2. How to assess the incremental value of a new biomarker
3. How *not* to assess the incremental value of a new biomarker

1. How to compare two risk models

In a nutshell:

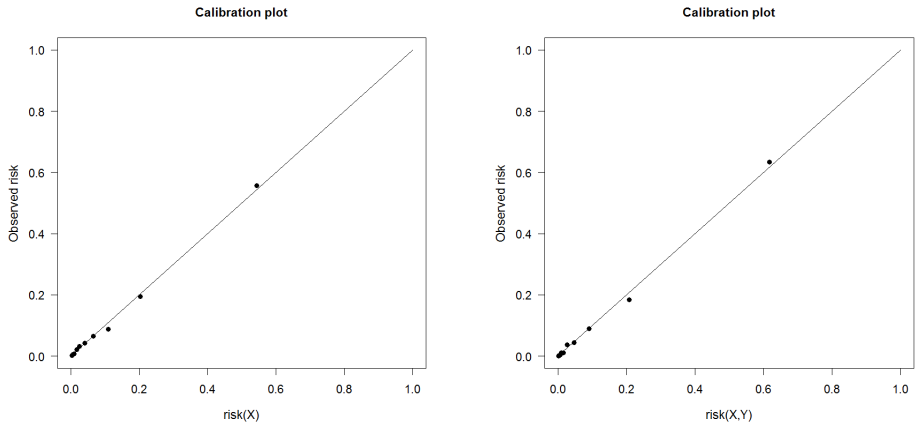
- What is your preferred measure for evaluating a risk model?
  - Guiding principle: ideally a risk model will be evaluated in a way that reflects how it will be used.
- Calculate that measure for the two risk models you want to compare.

Example

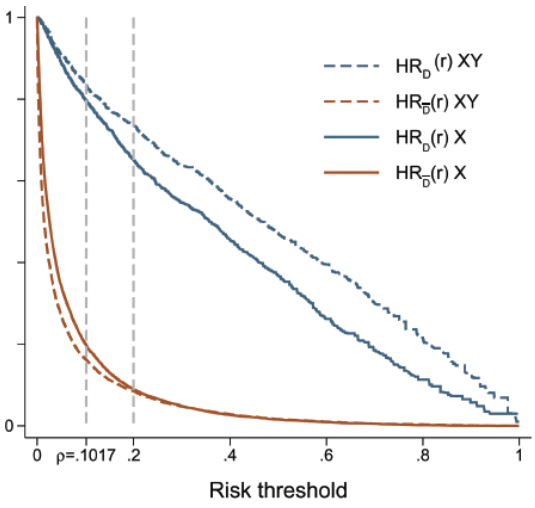
- risk(X) and risk(X,Y) for simulated dataset on DABS
- Both models appear well-calibrated (in the moderate sense):

$$P(D=1 \mid \text{predicted risk } r) \approx r$$

(moderate calibration criterion)



High risk classification for cases and controls



$\rho = 0.1017$

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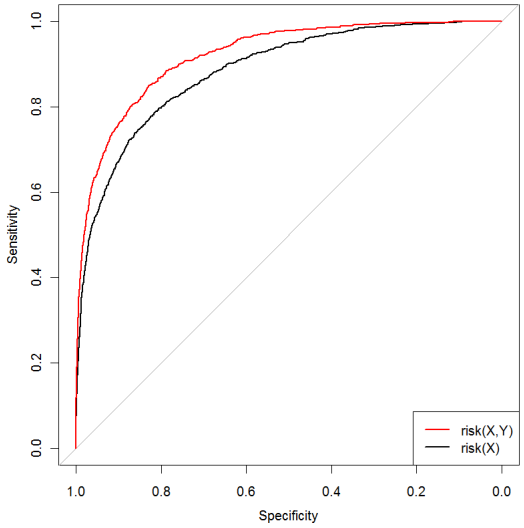
Compare ROC Curves



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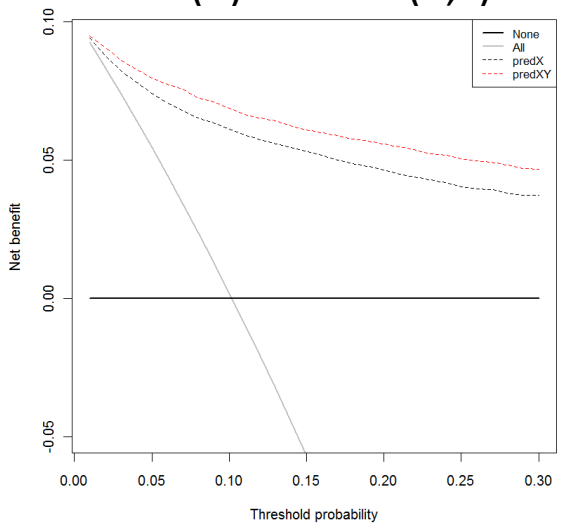
Decision Curves – compare the NB of risk(X) and risk(X,Y)



(Also Recall: Prostate Cancer Example in Part II)

Most appealing summary measures

assuming r_H=20% is an appropriate high risk threshold; and ρ=0.1017

		risk(X)	risk(X,Y)	Δ
Proportion of Cases High Risk	$HR_D(r_H)$	65.2%	73.5%	8.4%
Proportion of Controls High Risk	$HR_{\bar{D}}(r_H)$	8.9%	8.4%	-0.5%
% of maximum possible benefit	sNB	45.5%	55.0%	9.5%

Less appealing summary measures

	risk(X)	risk(X,Y)	Δ	comments
AUC	0.884	0.920	0.036	ΔAUC is popular metric
MRD	0.322	0.416	0.094	ΔMRD is also known as IDI
AARD	0.599	0.673	0.074	
ROC(0.20) i.e., TPR when FPR is 20%	0.672	0.758	0.087	Sensitivity at fixed specificity

2. Incremental Value of New Biomarkers

- *Incremental Value* or *Prediction Increment*: the improvement in prediction from using a new marker in addition to existing markers.
- Kattan (2003): "Markers should be judged on their ability to improve an already optimized prediction model."

A common approach:
2-stage approach for evaluating incremental value

- Use a regression model to estimate $P(D|\ X, Y)$ where X is the established predictor(s) and Y is the new marker

  e.g., $\text{logit}\ P(D=1|X, Y)=\beta_0+\beta_X X+\beta_Y Y$

  Test H_0: $\beta_Y=0$
- If test is significant, then examine $AUC_{X,Y}$ and test

$$H_0: AUC_{X,Y} = AUC_X$$

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Empirical argument against the two-stage approach:

Vickers *et al. BMC Medical Research Methodology* 2011, **11**:13
http://www.biomedcentral.com/1471-2288/11/13

BMC Medical Research Methodology

DEBATE Open Access

One statistical test is sufficient for assessing new predictive markers

Andrew J Vickers[1*], Angel M Cronin[2], Colin B Begg[1]

Theoretical argument – see next slide:

Research Article

Statistics in Medicine

Received 19 December 2011, Accepted 11 December 2012 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.5727

Testing for improvement in prediction model performance

Margaret Sullivan Pepe,[a*†] Kathleen F. Kerr,[b] Gary Longton[a] and Zheyu Wang[b]

Equivalent Null Hypotheses

- Pepe *et al* (2013) prove the following null hypotheses are equivalent:
  - risk(X,Y)=risk(X)
  - $AUC_{X,Y}=AUC_X$
  - $ROC_{X,Y}(\cdot)=ROC_X(\cdot)$
  - $ROC_{Y|X}$ is the 45° line
  - IDI = 0
  - $NRI^{>0}=0$
  - (and a few others)

This is the null hypothesis when testing $\beta_Y=0$

In the two-stage approach, this test is done after the first test

- To say that these null hypotheses are the same is NOT to say that the associated statistical tests are the same.
- However, it doesn't make sense to test the same null hypothesis twice.
  - first, with a well-developed, powerful test
  - second, with an under-developed test with poor power (p-value from software might not be valid, might be excessively conservative)
  - Illogical scientific approach

More details about why the AUC-based test is wrong:

Research Article

Statistics in Medicine

Received 22 December 2010, Accepted 6 January 2012 Published online 13 March 2012 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.5328

Misuse of DeLong test to compare AUCs for nested models

Olga V. Demler,[a*†] Michael J. Pencina[a] and Ralph B. D'Agostino, Sr.[b]

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- Hypothesis testing has limited value. Quantifying incremental value is much more important.
  - A statistical test examines the evidence that a marker has *any* incremental value.
  - It is much more important to *quantify the improvement* offered by the new predictor.
  - The strength of evidence to establish whether a new predictor is *useful* far exceeds what is needed to obtain statistical significance.
  - Compared to hypothesis testing, it is *more challenging* to quantify incremental value; we must decide how we value a risk model.

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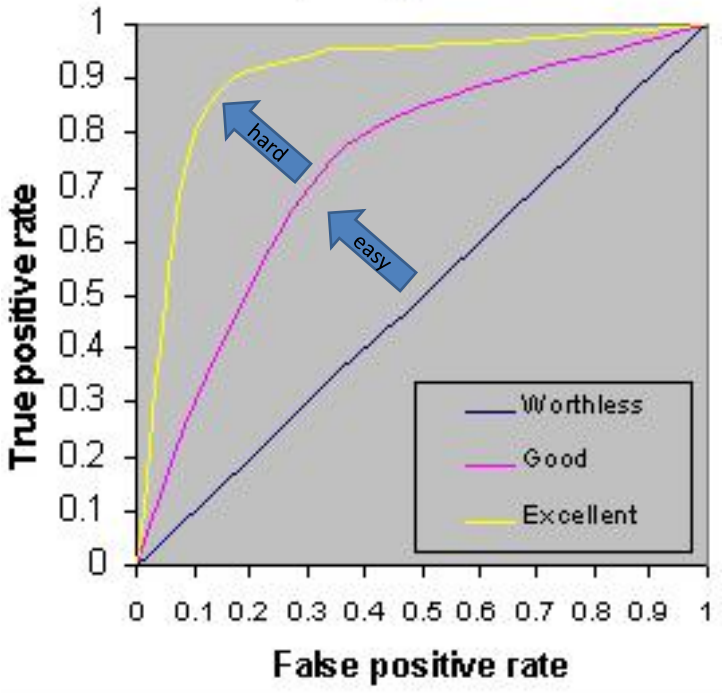
3. How not to assess incremental value

- Most common approach is to examine increase in AUC
- Since AUC is not a clinically meaningful measure, how do we know whether the increase in AUC is "enough"?

- ΔAUC ($AUC_{X,Y}$ compared to AUC_X). Some investigators consider this metric to be "insensitive" (e.g., Cook 2007)
  - This might mean that a favorite biomarker produced a disappointing ΔAUC.
  - "Sensitivity" of ΔAUC is probably not the problem. Why is there a perception that AUC is "insensitive"?
    - The scale of AUC is such that an increase of 0.02 is "large"
    - p-values computed for ΔAUC are wrong; incorrect methodology tends to produce conservative (too-large) p-values
    - It's fundamentally hard to improve upon a risk model that has moderately good predictive ability



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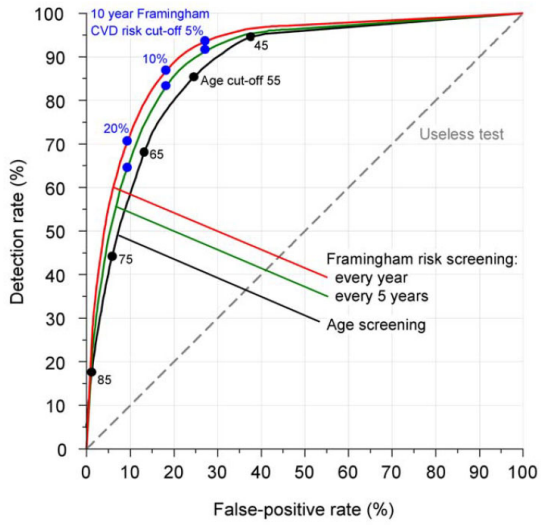
OPEN ACCESS Freely available online
PLoS one

Screening for Future Cardiovascular Disease Using Age Alone Compared with Multiple Risk Factors and Age

Nicholas J. Wald*, Mark Simmonds, Joan K. Morris

Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom



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Wald, Simmonds, Morris 2011: Are cardiovascular risk factors “worth it”?

- Analysis based on simulated/synthetic data
- Conclusion: Age screening for future CVD events is simpler than Framingham screening with a similar screening performance and cost-effectiveness. It avoids blood tests and medical examinations. These practical advantages and minimal difference in prognostic capacity warrant considering screening based on age-alone instead of multiple risk factor screening.

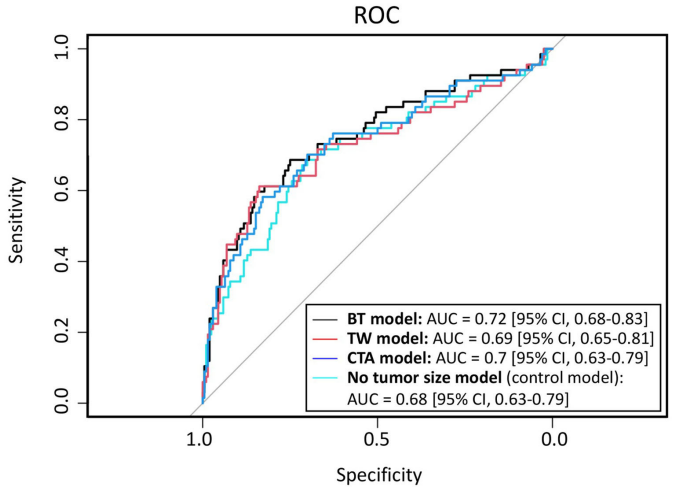
Predict metastasis in patient with primary melanoma

- Baseline model includes clinical and pathologic variables, including patient age at diagnosis, sex, mitotic rate, tumor ulceration, and lymphovascular invasion. No measure of tumor size in the model.

- Is prediction better incorporating any of Breslow Thickness (BT), Tumor Width (TW), or Calculated Tumor Area (CTA)?

Jeves, Todd, Johnson, *Journal of the American Academy of Dermatology*, July 2023

Only Breslow Thickness (BT) resulted in a statistically significant improvement in AUC – and a modest increase



Phung *et al. BMC Cancer* (2019) 19:230
https://doi.org/10.1186/s12885-019-5442-6

BMC Cancer

RESEARCH ARTICLE Open Access

Prognostic models for breast cancer: a systematic review

Minh Tung Phung*, Sandar Tin Tin and J. Mark Elwood

- Identified 58 models that predict mortality (n=28), recurrence (n=23), or both (n=7).

- When tested on independent populations, most breast cancer prognostic models under-perform.
- The Nottingham Prediction Index (NPI) is one of the simplest and oldest models. Unlike other models, the NPI has performed well in many different populations.
- NPI uses only nodal status, tumor size, tumor grade. There have been multiple attempts to improve NPI by adding predictors such as age at diagnosis, hormonal receptor status, and HER2 status. Such extensions have not proven to be better when evaluated in independent populations.

A new approach: Reclassification
(Cook, *Circulation* 2007)

- Proposed that a new marker is useful if it re-classifies lots of people
  - reclassification table, next slide

TABLE 3. Comparison of Observed and Predicted Risks Among Women in the Women's Health Study*

	Model With HDL 10-Year Risk (%)				
Model Without HDL 10-Year Risk (%)	0 to <5%	5 to <10%	10 to <20%	20%+	% Reclassified
0% to <5%					
Total, n	22655	696	6	0	...
%†	97.0	3.0	0.0	0.0	3.0
Observed 10-year risk (%)‡	1.5	5.9	0.0	...	...
5% to <10%					
Total, n	593	1712	291	0	...
%	22.8	66.0	11.2	0.0	34.0
Observed 10-year risk (%)	3.7	7.6	14.7	...	...
10% to <20%					
Total, n	3	214	512	76	...
%	0.4	26.6	63.6	9.4	36.4
Observed 10-year risk (%)	0.0	7.5	10.7	23.3	...
20%+					
Total, n	0	0	41	102	
%	0.0	0.0	28.7	71.3	28.7
Observed 10-year risk (%)	...	...	15.8	32.5	...

*This comparison uses models that include Framingham risk factors with and without HDL. All estimated and observed risks represent 10-year risk of cardiovascular disease.
†Percent classified in each risk stratum by the model with HDL.
‡Observed proportion of participants developing cardiovascular disease in each category.

Reclassification Tables: Considerations

- Original proposal did not account for whether reclassification was in the "correct" direction
- 'Percent reclassified' does not teach us about the performance of either risk(X) or risk(X, Y)
- If presented separately for cases and controls, a reclassification table can be interesting
  - Still, table doesn't directly help us assess whether a new biomarker offers clinically meaningful improvements in risk prediction

Reclassification Tables: Considerations

- Lots of reclassification does not imply improved performance.

		$r(X, Y)$ Low	Med	High	Total
$r(X)$	Low	10	10	0	20
	Med	5	20	10	35
	High	5	5	35	45
	Total	20	35	45	100

% reclassification= 35%

Net Reclassification Index (NRI)

- Proposed in 2008
  - Pencina, D'Agostino, D'Agostino, Vasan, *Statistics in Medicine*, 2008
- Followed on the heels of 2007 paper proposing reclassification as a key concept
- NRI is really a family of statistics

NRI terminology

event	person with the condition or destined to have the condition ("case")
nonevent	not an event ("control")
old	risk model with established predictors ("baseline")
new	risk model with established predictors and new predictor ("expanded")

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Net Reclassification Improvement (NRI)

NRI = P(up | event) - P(down | event) + P(down | nonevent) - P(up | nonevent)

"up" means an individual moves to a higher risk category using new model compared to old

"down" means an individual moves to a lower risk category in new model compared to old

The categorical NRI (original proposal) uses fixed risk categories

- 2 categories (low risk, high risk)
- 3 categories (low risk, medium risk, high risk)
- 4 categories (e.g., Cook's paper)
- Etc.

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Net Reclassification Improvement (NRI)

$$NRI = \underbrace{P(\text{up} \mid \text{event}) - P(\text{down} \mid \text{event})}_{NRI_e} + \underbrace{P(\text{down} \mid \text{nonevent}) - P(\text{up} \mid \text{nonevent})}_{NRI_{ne}}$$

NRI is the sum of the "event *NRI*" and the "nonevent *NRI*":

Net Reclassification Improvement (NRI)

$$NRI = \underbrace{P(\text{up} \mid \text{event}) - P(\text{down} \mid \text{event})}_{NRI_e^{>0}} + \underbrace{P(\text{down} \mid \text{nonevent}) - P(\text{up} \mid \text{nonevent})}_{NRI_{ne}^{>0}}$$

The ``category-free NRI'' interprets this formula for any upward or downward movement in predicted risk. Denote $NRI^{>0}$

Net Reclassification Indices for Evaluating Risk Prediction Instruments

A Critical Review

Kathleen F. Kerr,[a] Zheyu Wang,[a] Holly Janes,[b] Robyn L. McClelland,[a] Bruce M. Psaty,[c] and Margaret S. Pepe[b]

Epidemiology • Volume 25, Number 1, January 2014

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Numerous problems with NRI statistics

- Difficult to Interpret (often mis-interpreted)
  - **Not** a proportion, but often interpreted as such
- Why a simple sum of metric for non-events and events?
  - In most applications, most of the population are non-events
- Does not contrast a measure of model performance
- 3+ categorical NRI and category-free NRI weights reclassifications indiscriminately
- Not a "proper scoring rule" – can make overfit or poorly calibrated models look good

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Research Article

Statistics in Medicine

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(wileyonlinelibrary.com) DOI: 10.1002/sim.5804

A note on the evaluation of novel biomarkers: do not rely on integrated discrimination improvement and net reclassification index

Jørgen Hilden and Thomas A. Gerds*†

JNCI JOURNAL OF THE NATIONAL CANCER INSTITUTE

Net Risk Reclassification *P* Values: Valid or Misleading?

Margaret S. Pepe, Holly Janes and Christopher I. Li

+ Author Affiliations

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Revision received December 24, 2013.
Accepted January 23, 2014.

NRI is not a proper scoring rule: Simulations

- X is predictive (to varying degrees)
- new marker Y is noise

Bivariate Normal Simulation Model

$$\text{Among controls: } \begin{pmatrix} X \\ Y \end{pmatrix} \sim N(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & r \\ r & 1 \end{pmatrix})$$

$$\text{Among cases: } \begin{pmatrix} X \\ Y \end{pmatrix} \sim N(\begin{pmatrix} \mu_X \\ \mu_Y \end{pmatrix}, \begin{pmatrix} 1 & r \\ r & 1 \end{pmatrix})$$

$$\text{logit}P(D=1|X=x) = \text{logit}(\rho) - \frac{1}{2}\mu_X^2 + \mu_X x$$

$$\text{logit}P(D=1|X=x, Y=y) = \text{logit}(\rho) - \frac{\mu_X^2 + \mu_Y^2 - 2r\mu_X\mu_Y}{2(1-r^2)} + \frac{\mu_X - r\mu_Y}{1-r^2}x + \frac{\mu_Y - r\mu_X}{1-r^2}y$$

In our simulations, *Y* is useless. Set $\mu_Y = 0$ and $r = 0$

- Performance of model with useless marker added: ΔAUC is negative, on average

prev	AUC_X	N-train	N-test	Δ AUC	NRI
0.1	0.6	250	25,000	-1.23 (2.6)	
0.1	0.7	250	25,000	-0.88 (1.29)	
0.1	0.8	250	25,000	-0.46 (0.64)	
0.1	0.9	250	25,000	-0.23 (0.33)	
0.5	0.6	50	5,000	-1.36 (3.45)	
0.5	0.7	50	5,000	-1.65 (2.49)	
0.5	0.8	50	5,000	-1.01 (1.61)	
0.5	0.9	50	5,000	-0.62 (0.93)	

- Performance of model with useless marker added: $NRI^{>0}$ is positive, on average

prev	AUC_X	N-train	N-test	Δ AUC	NRI
0.1	0.6	250	25,000	-1.23 (2.6)	0.15 (2.83)
0.1	0.7	250	25,000	-0.88 (1.29)	0.93 (5.21)
0.1	0.8	250	25,000	-0.46 (0.64)	3.13 (9.36)
0.1	0.9	250	25,000	-0.23 (0.33)	7.56 (16.08)
0.5	0.6	50	5,000	-1.36 (3.45)	0.59 (5.11)
0.5	0.7	50	5,000	-1.65 (2.49)	2.5 (9)
0.5	0.8	50	5,000	-1.01 (1.61)	7.24 (14.77)
0.5	0.9	50	5,000	-0.62 (0.93)	17.6 (28.28)

MESA example: Polonsky et al, JAMA 2010 Adding CACS to Framingham risk factors to predict CHD events

- Risk categories 0-3%, 3-10%, >10%
- model with CACS reclassifies 26% of the sample
- 3-category NRI_{event} = 0.23
- 3-category $NRI_{nonevent}$= 0.02

These are summaries of the reclassification tables (next slide)

How do we interpret these NRI statistics? Do they help us understand the clinical or public health benefit of incorporating CACS into the model?

Nonevents

Old Model	Model with CACS 0-3%	3-10%	>10%	Total
0–3%	58%	7%	1%	
	3276	408	5	65%
3–10%	12%	14%	4%	
	697	791	244	31%
>10%	1%	1%	3%	
	30	63	155	4%
Total	71%	22%	7%	5669

Events

Old Model	Model with CACS 0-3%	3-10%	>10%	Total
0–3%	16%	11%	0%	
	34	22	1	27%
3–10%	7%	25%	23%	
	15	52	48	55%
>10%	1%	3%	13%	
	2	7	28	18%
Total	24%	39%	37%	209

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Risk	Old risk model		New risk model (model with CACS)	
Category	nonevent	event	nonevent	event
0-3%	67.1%	27.3%	70.6%	24.4%
3–10%	30.6%	55.0%	22.3%	38.8%
>10%	4.4%	17.7%	7.1%	36.8%
Total	5669	209	5669	209
	100%	100%	100%	100%

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Summary

- The best way to compare two risk models is to compare them on a risk model performance measure that you care about
  - e.g., Net Benefit of using the risk model to recommend treatment
- The same principle applies to assessing the incremental contribution of a new marker Y to risk prediction: is the performance of risk(X,Y) better than the performance of risk(X)?
- We don't need special metrics to compare two risk models

Summary

- Often $AUC_{X,Y}$ will not be much larger than AUC_X. This is not a reason to discard AUC.
  - BUT there **are** good reasons to seek alternatives: AUC is not a clinically meaningful measure of risk model performance

Summary

- NRI statistics do not help us assess the incremental value of new markers
  - despite ~5000 citations of original 2008 paper
- NRI statistics have many of the same problems as ΔAUC, and some new problems
  - Not interpretable
  - Not a proper scoring rule; potential to mislead and make useless new markers look promising

Misconceptions about Biomarkers and Risk Models

- A large odds ratio means a biomarker is useful for prediction. ✖
- ROC curves are useful to identify the best biomarker cut-point. ✖
- Decision curves are useful to identify the best risk threshold. ✖
- To assess whether to add new biomarker to a risk model, multiple stages of hypothesis testing are needed. ✖
- 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.
- We can often use biomarkers to identify which patients will benefit from treatment.