UNIVERSITY OF GOTHENBURG

Predicting bone metastasis in men with prostate cancer – from register data to nomogram

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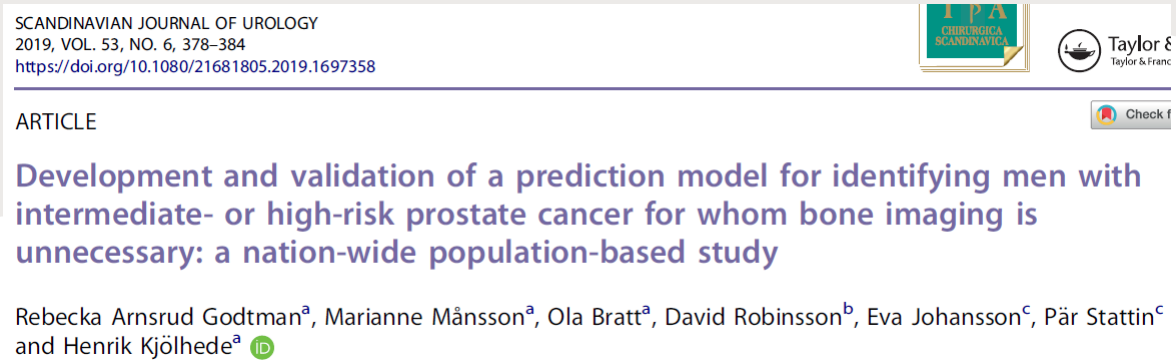
Outline

Presentation based on:



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ARTICLE

Development and validation of a prediction model for identifying men with intermediate- or high-risk prostate cancer for whom bone imaging is unnecessary: a nation-wide population-based study

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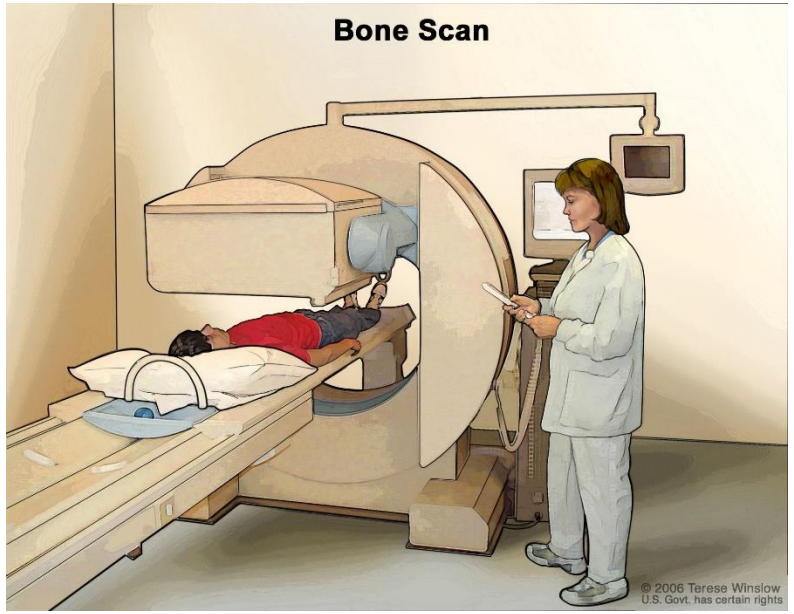
- Background and objective
- Data
- Model development
- Model performance – Comparison of potential models
- Comparison of ”best” model to guidelines
- Model validation, external
- User-friendly versions of the model
- Conclusions

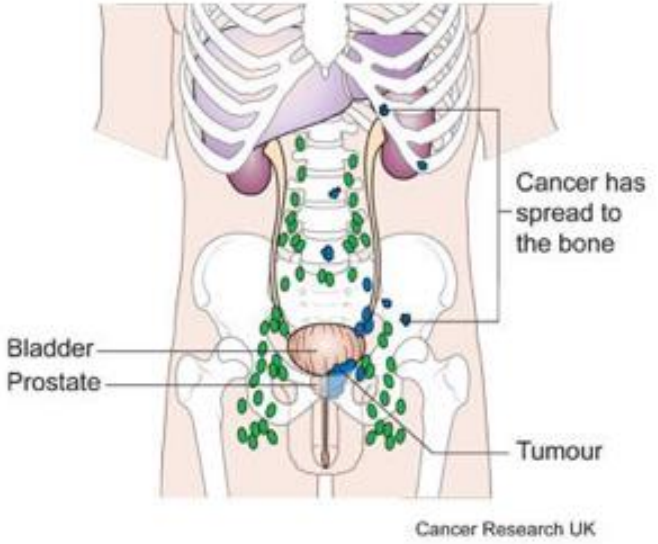
Introduction to Decision Curve Analysis (DCA)

Background and objective

- ~10 000 men diagnosed with prostate cancer (PC) in Sweden each year
- Bone imaging used to assess presence of bone metastasis
- Bone imaging resource demanding and costly; stressful for the men
- Which men need bone imaging?
  - Different guidelines – different recommendations

- Objectives:
  - Develop a prediction model that identifies men for whom bone imaging is unnecessary
  - Compare to present guidelines



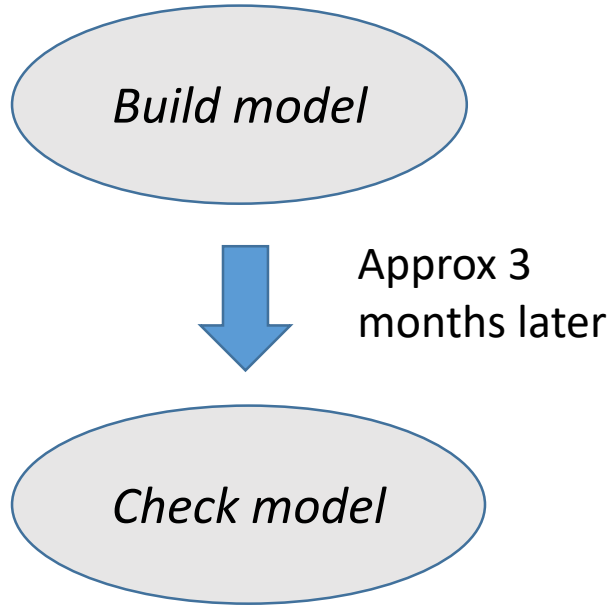


Data

- Register: National Prostate Cancer Register (NPCR) of Sweden

- Development dataset
  - N = 5084 men
  - Diagnosed in 2015–2016
  - 10% had bone metastasis on pre-treatment bone imaging

- Validation dataset (not available during development):
  - N = 2554 men
  - Diagnosed in 2017
  - 11% had bone metastasis on pre-treatment bone imaging



Available variables

- Outcome variable: Bone metastasis (yes / no)

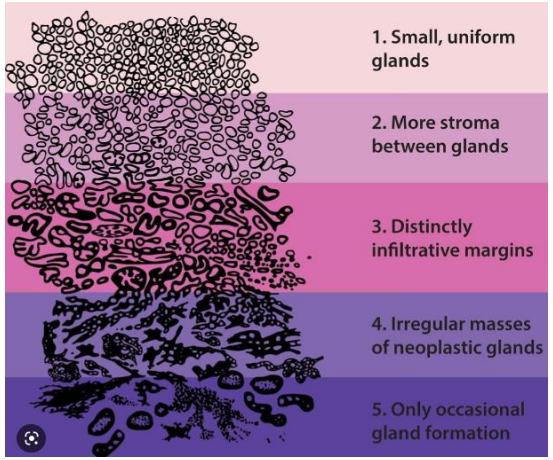
- Potential predictor variables:
  - Age
  - Prostate volume
  - PSA (prostate-specific antigen, blood test)
  - ISUP grade (histology, 4 categories)
  - T-stage (clinical tumour stage, 3 categories)
  - PC in biopsy cores (percentage biopsy cores with cancer)

Known risk factors: Must be included in prediction model

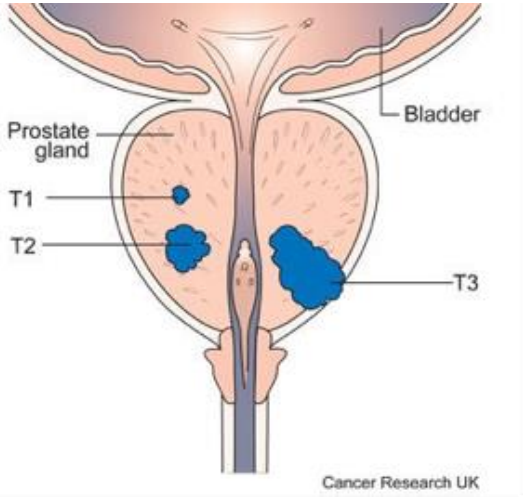
Not always available

PSA

ISUP grade



T-stage

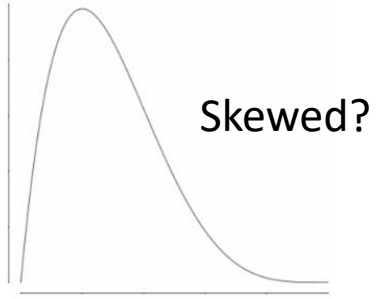


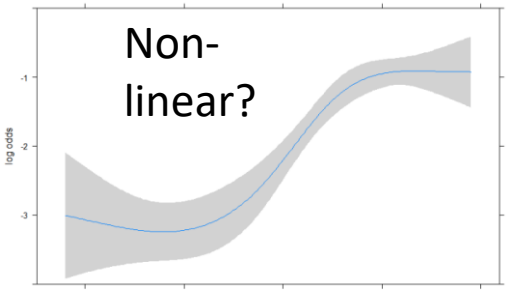
Model development

Potential multivariable logistic regression model:

Metastasis (yes/no) ~ PSA + ISUP + T-stage + PC in biopsy + prostate volume + age

- Log transformation of continuous variables?
  - Yes: PSA, prostate volume
- Non-linear terms (restricted cubic splines)?
  - No
- Interactions?
  - No
- Are all variables necessary?
  - First check: Age can be excluded directly





Model development, contd

Five potential predition models fitted by means of penalized maximum likelihood to avoid overfit:

- Meta ~ **PSA + ISUP** + T-stage + PC in biopsy + prostate volume
- Meta ~ **PSA + ISUP** + T-stage + PC in biopsy
- Meta ~ **PSA + ISUP** + T-stage
- Meta ~ **PSA + ISUP** + PC in biopsy
- Meta ~ **PSA + ISUP**

Compare model performance:

Discrimination: Boxplots and AUC

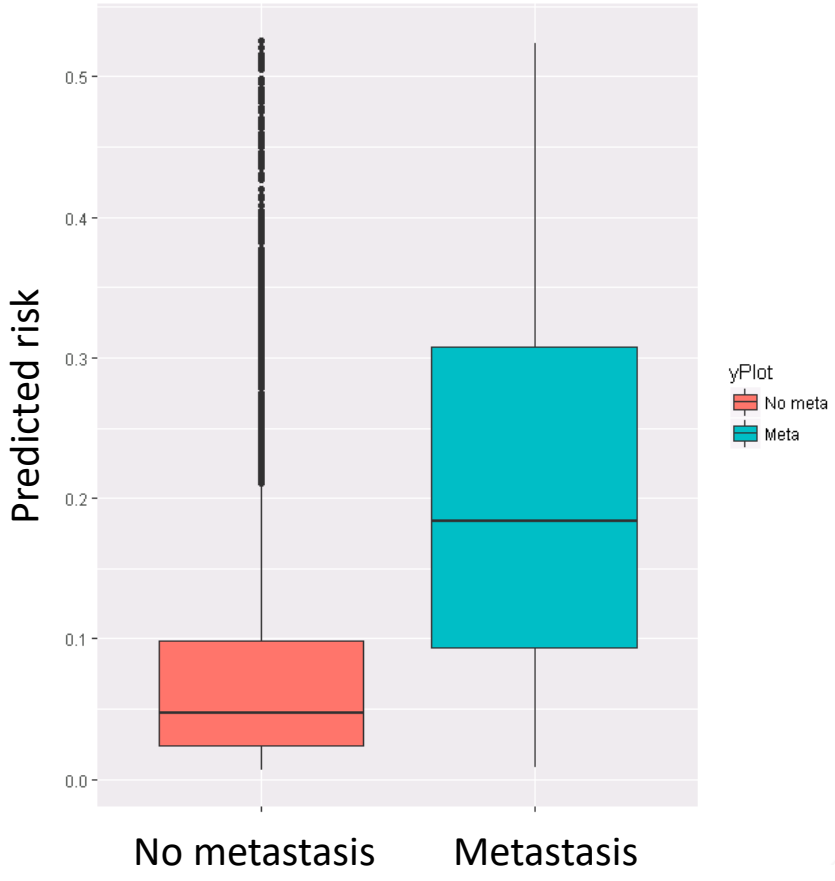
Calibration: Calibration plots

Clinical usefulness: Decision curve analysis

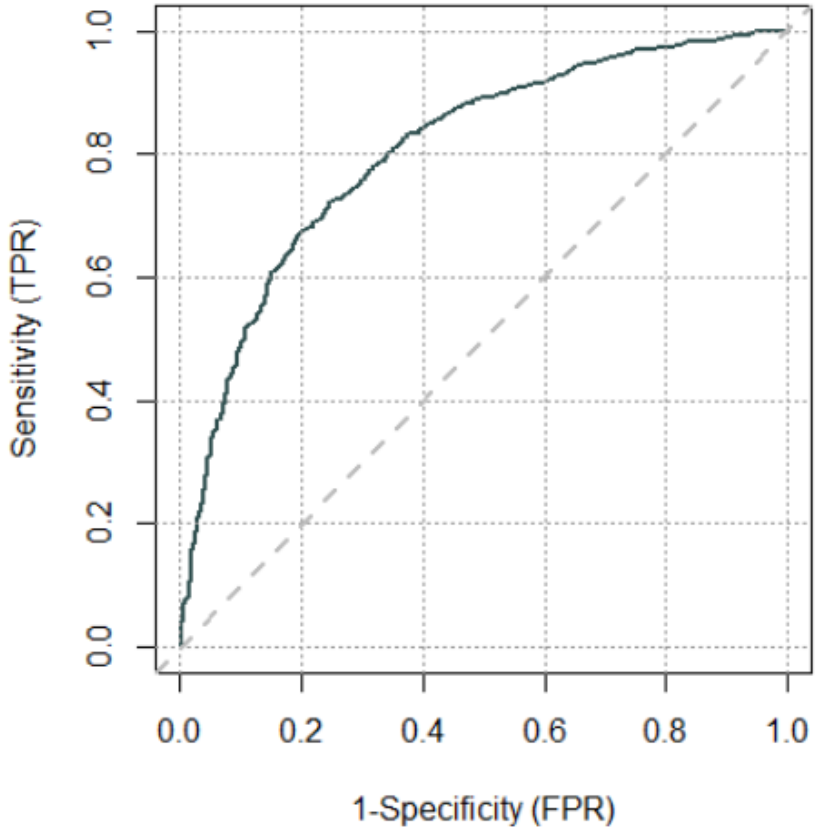
Model performance: Discrimination

Are risk predictions in men with/without metastatis well separated?

Box plot



ROC curve (Receiver Operating Characteristic)



AUC (Area Under Curve):
0.80 (95% CI 0.78–0.82)
Optimism adjusted AUC: 0.79

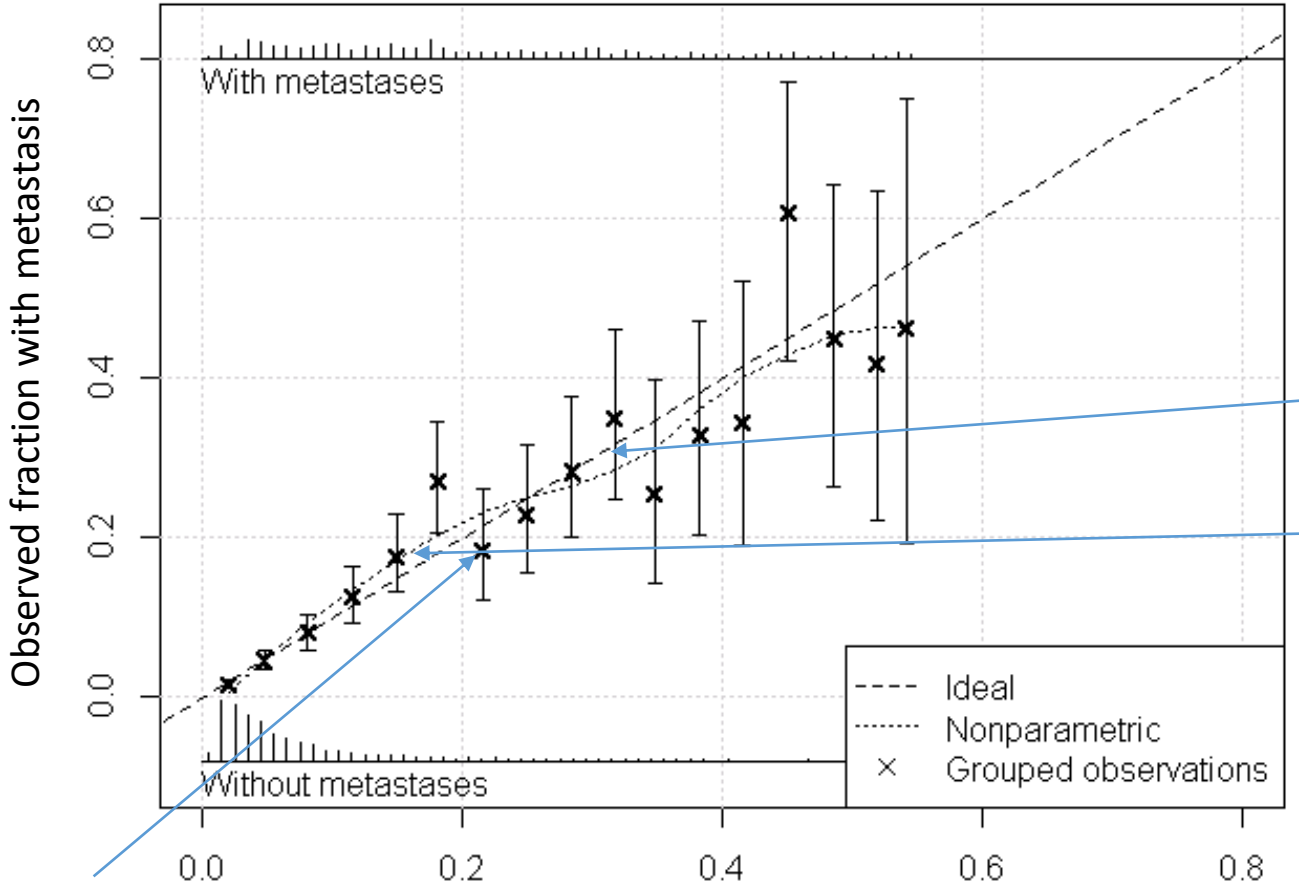
Adjusted for overfit using bootstrap

Probabilistic interpretation of AUC

*The probability that a randomly selected man **with metastasis** has **higher predicted risk** than a randomly selected man without metastasis is 80%*

Model performance: Calibration

Do predicted risks agree with true risks? Over- underestimation?

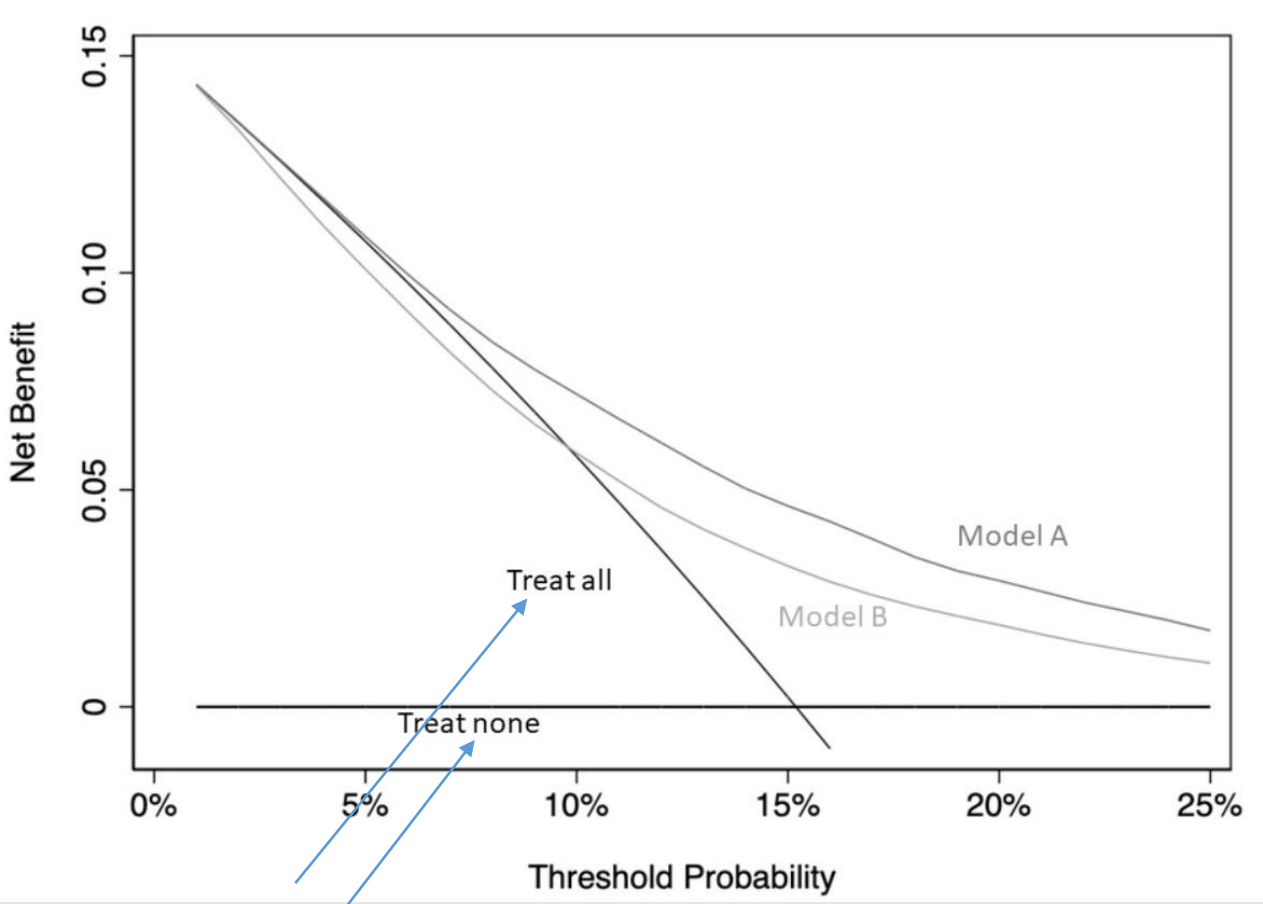


Small overestimation for risks > 25%

Small underestimation for metastasis risks 10% -25%

Ex: all men with pred risk 0.20-0.22:
x = mean of their pred risk
y = fraction with metastasis

Introduction to Decision Curve Analysis (DCA)



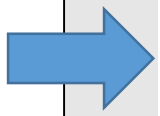
References
in all DCA

Graph from Wikipedia

DCA is used to evaluate the clinical value of a predictor, taking benefit and harm into account

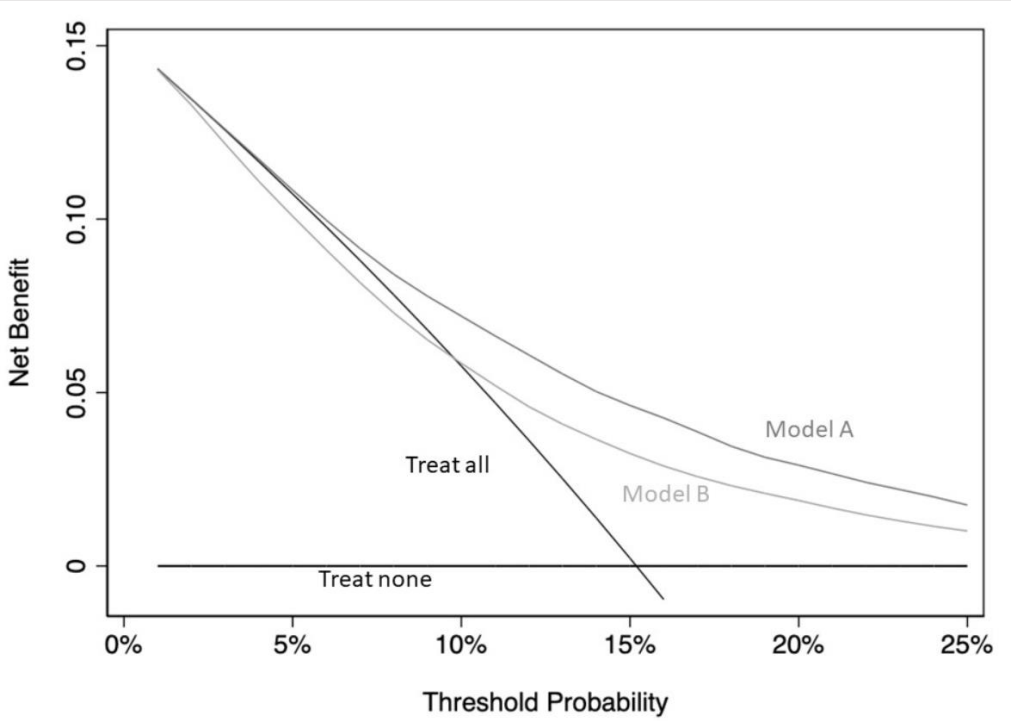
Short history of DCA

- **1884:** Peirce. The numerical measure of the success of predictions
- **2006:** Vickers & Elkin. Decision curve analysis: a novel method for evaluating prediction models
- **2006-2019:** DCA more and more common. Recommended by JAMA, BMJ, Ann Intern Med, …
- **2019:** Vickers, van Calster, Steyerberg. A simple, step-by-step guide to interpreting decision curve analysis
- **Today:** Often demanded by journals for publishing of prediction models (at least within prostate cancer field)



That said, there does appear to be widespread misunderstanding of and confusion about decision curve analysis. For instance, a well-respected epidemiologist claimed that he had yet to find more than a couple of people in the world who could explain what decision curves meant and that he himself was not clear on their interpretation. We

DCA: Threshold probability (Pt)



Ex. Pt = 10% , 1-Pt = 90% <-> odds 1:9 of disease →
Not treating person with disease ~ 9 times worse than treating healthy person

Doctor/patient/decision-maker decide Pt based on:

Benefit/harm of

- Treatment if patient has disease/no disease
- No treatment if patient has disease/no disease

Threshold probability Pt:

If risk of disease for patient above Pt →
Action (treatment, biopsy, further investigations, …)
Otherwise no action

”Harm to benefit ratio” =

odds of disease at threshold =

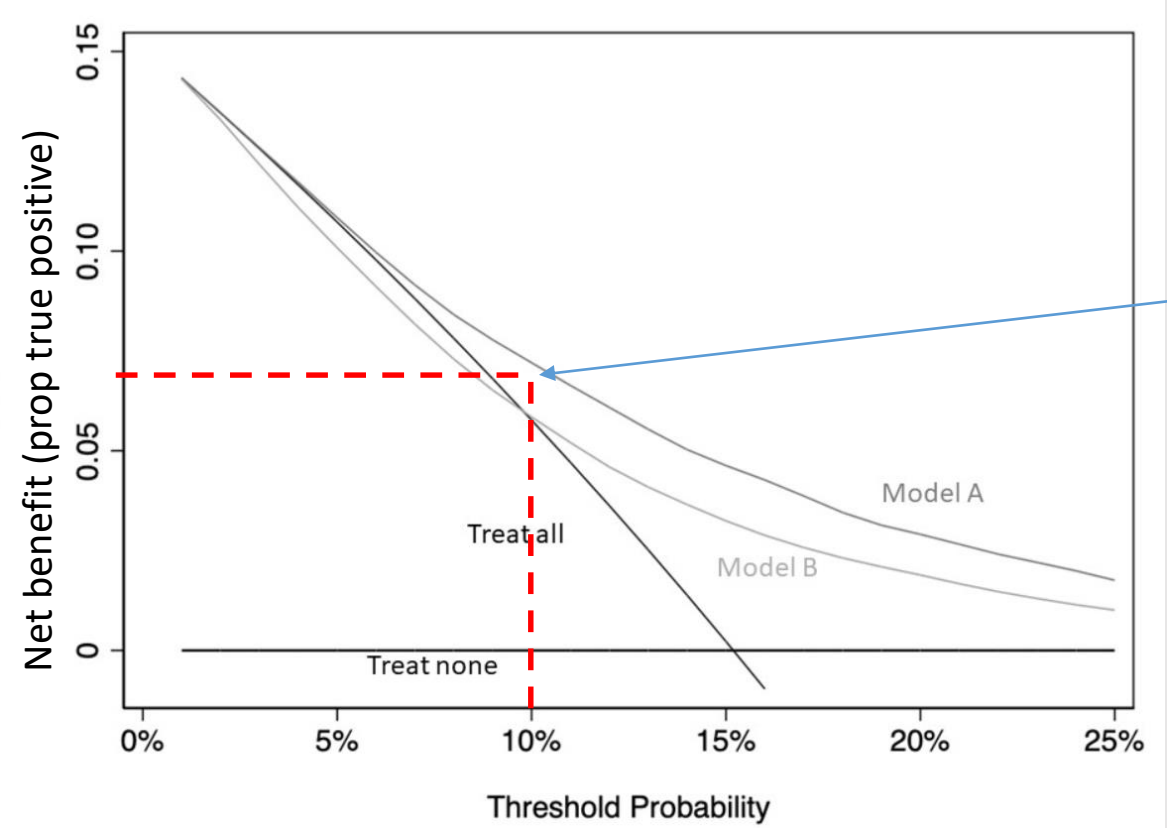
Pt / (1-Pt)

DCA: Net benefit (NB) (for model, not for a single patient)

$$\text{For each Pt: NB} = \frac{(\#\text{ true positive} - \#\text{ false positive} * \text{weight})}{\text{number in study}}$$

weight = Pt/ (1-Pt) =

"Harm to benefit ratio"



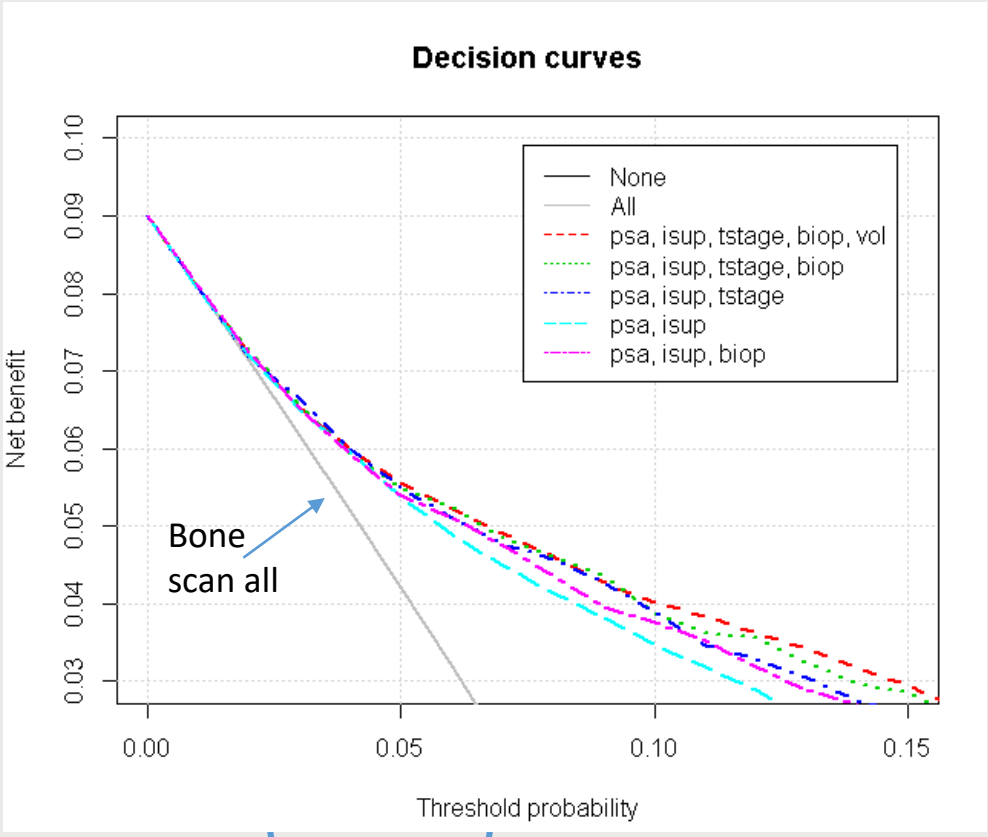
Ex: Pt = 10% → NB = 0.07 for model A

NB = 0.07 can correspond to eg:

- 7% true pos and 0% false pos
- 12% true pos and 45% false pos (w = 1/9)

Model performance: DCA

Are models clinically useful in important risk range?



Important range for risk of metastasis

- All models higher net benefit compared to scanning all men in important risk range
- Models similar NB in important risk range
- At Pt = 5%, Model: NB = 0.06

Corresponds to ”net” 6% true positive (of 100 men, 6 test positive → bone scan → metastasis detected)

Pt = 5% <-> odds 1:19 for metastasis →
Missing metastasis ~ 19 times worse than scanning man without metastasis

Final prediction model

- Based on model performance (discrimination, calibration, clinical usefulness):

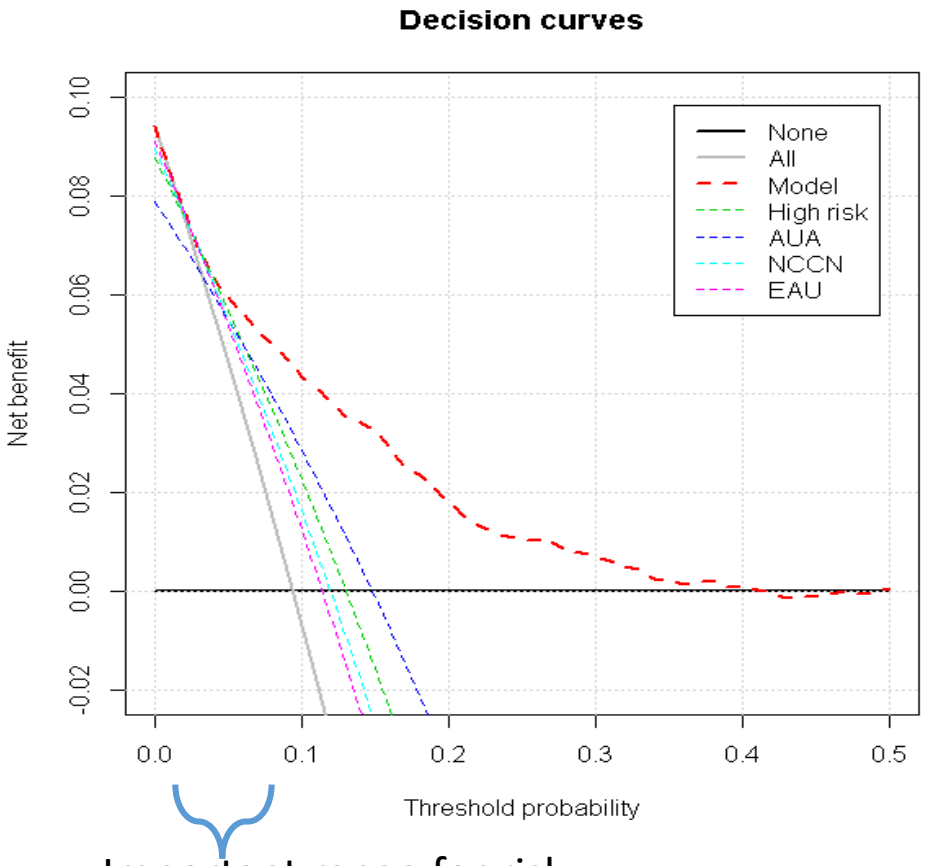
→ Final logistic regression model:

Metastasis (yes/no) ~ PSA + ISUP + T-stage

- Is this model better than guidelines?
  - **Clinical usefulness**: Decision curve analysis
  - **Clinical consequences:** number of bone imaging performed, missed metastases…

Description	Coefficient (95 % CI)	Odds Ratio (95 % CI)
Intercept	-5.75 (-6.22– -5.28)	
$\log_2$ PSA	0.46 (0.38–0.54)	1.59 (1.47–1.72)
Gleason grade group		
1-2	0	1 (ref)
3	0.64 (0.28–1.00)	1.9 (1.33–2.76)
4	1.14 (0.79–1.59)	3.13 (2.21–4.43)
5	1.55 (1.23–1.87)	4.70 (3.42–6.46)
Clinical tumour stage		
cT1	0	1 (ref)
cT2	0.36 (0.06–0.66)	1.43 (1.06–1.93)
cT3-4	1.06 (0.77–1.36)	2.90 (2.15–3.90)

Final model compared to guidelines: DCA
Model better in important risk range?



Important range for risk of metastasis

- Higher net benefit (NB) than guidelines from threshold ~3%
- Compare with guidelines at Pt=5%:

  NB: Model – EAU guidelines = 0.01 →

  Out of 100 men, 1 additional man with metastasis will be detected (net)

Final model compared to guidelines:

Tabulation of bone imaging avoides, missed metastases, etc for different model risk thresholds

- Number of
  - Men above threshold (imaging) / below threshold (no imaging)
  - Found / missed metastases
  - Avoided imaging compared to guidelines
  - Missed metastasis compared to guidelines
  - Etc

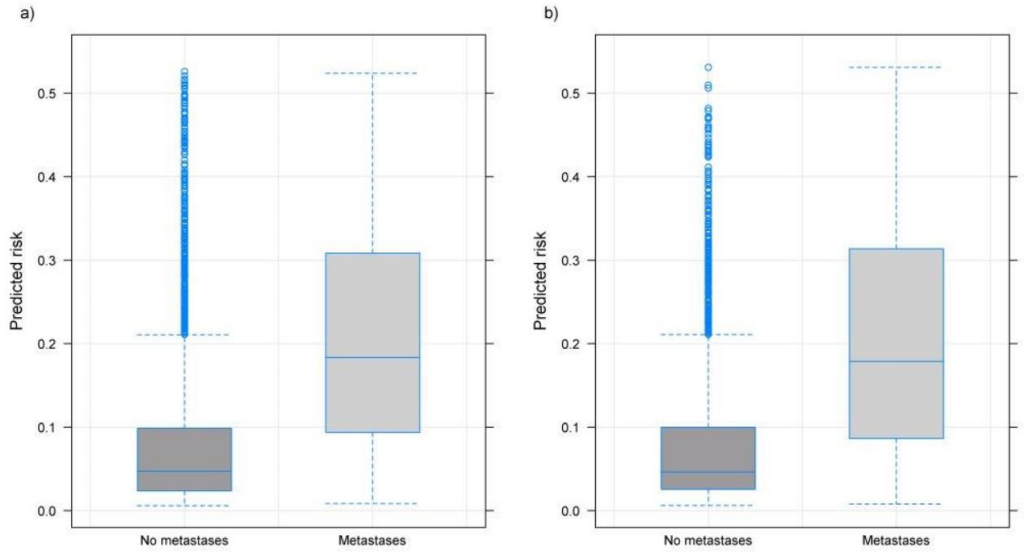
- If predicted risk ≥ 4% → bone imaging, then
  - 25% fewer scans compared to EAU guidelines
  - 3% of these have had metastasis

External Validation
Performance of final model on new data set

- Validation dataset, n = 2554 (not available during development)
- Estimate risk of bone mestastasis for these men based on final model (built on development data set)
- Check performance
  - Discrimination, Calibration, Decision curves, Saved bone scans, missed metastases…

Discrimination

Development | Validation

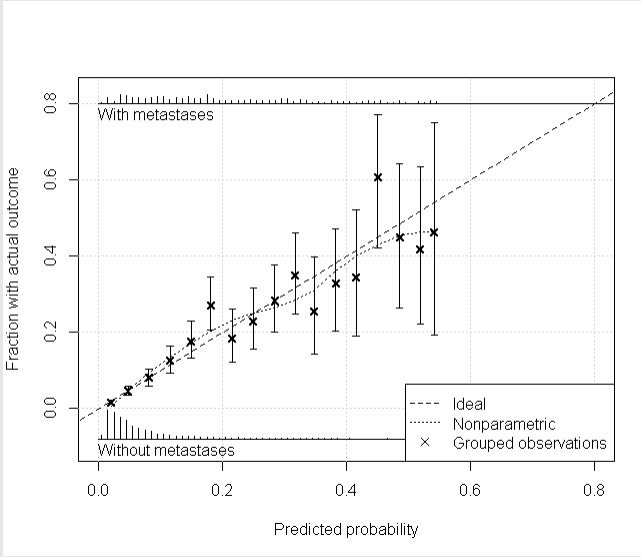


AUC 0.80, 95% CI 0.78–0.82

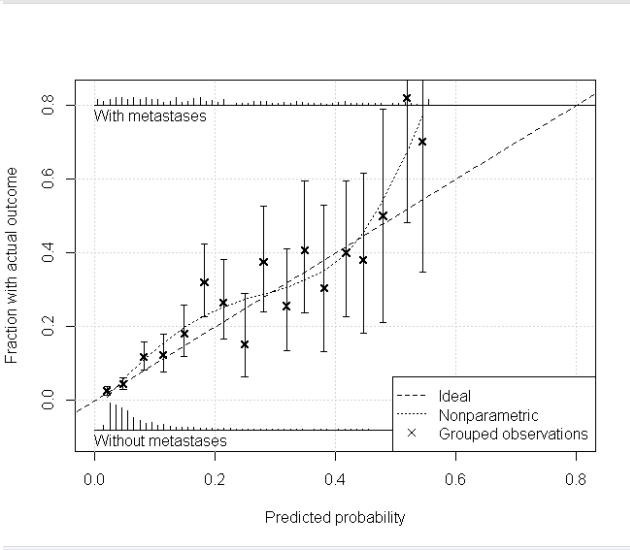
AUC 0.80, 95% CI 0.77–0.82

Calibration

Development

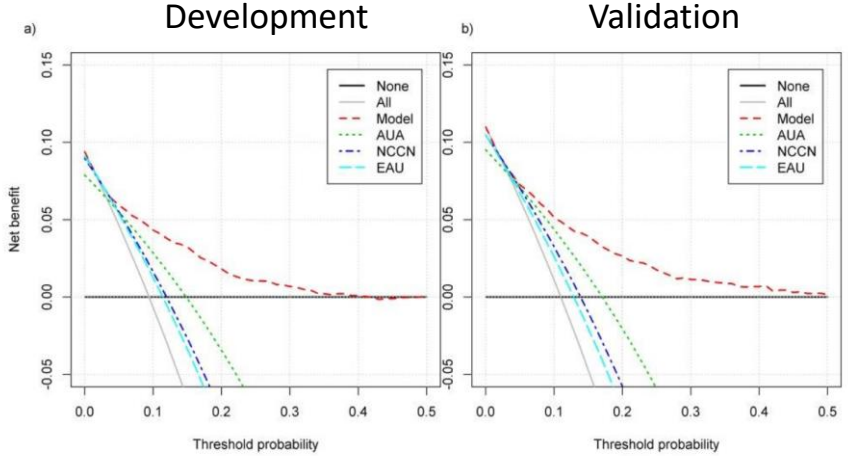


Validation



Decision curves

Development | Validation



Clinical consequences (4% risk cut-off)

Development

Model vs EAU guidelines:
- 25% fewer scans
- 3% of these had metastasis

Validation

Model vs EAU guidelines:
- 25% fewer scans
- 2% of these had metastasis

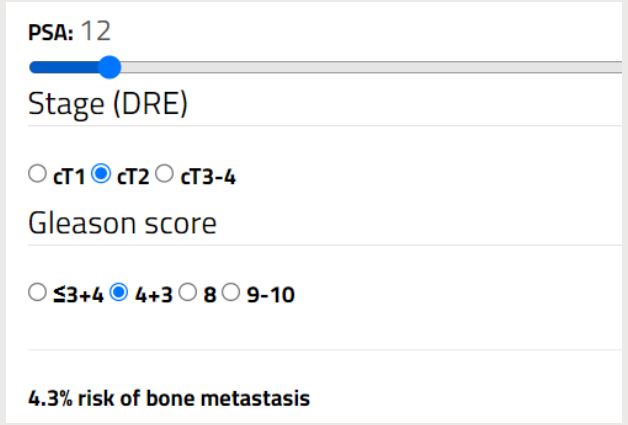
Final model → User friendly format

- Final model

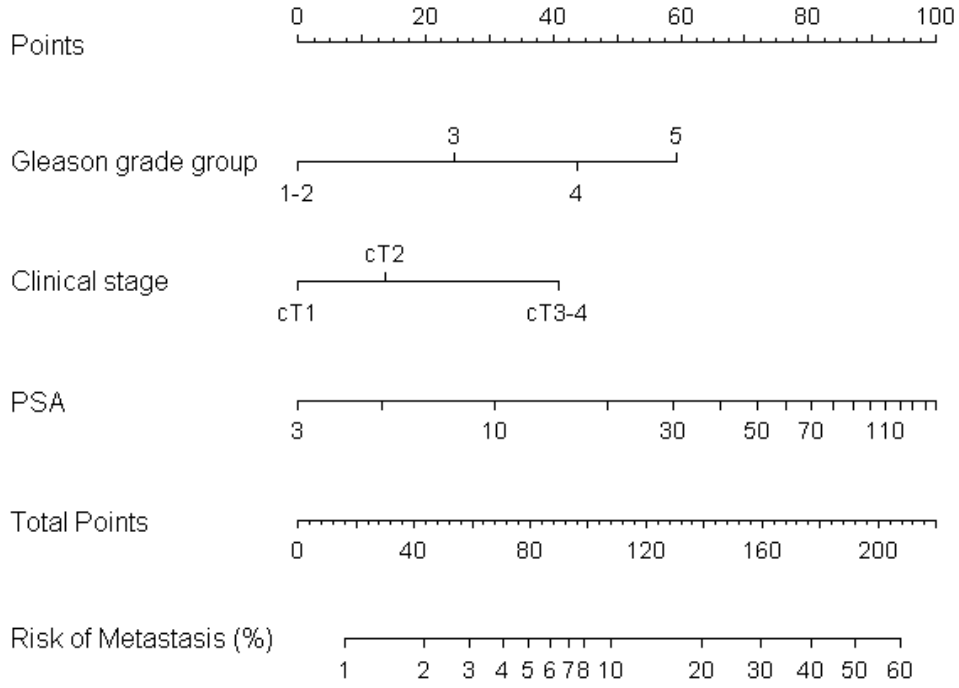
  logit(probability of metastasis) =
  0.46 log2(PSA) +
  0.64 * 1_{ISUP = 3} + … +
  1.06 * 1_{T-stage = cT3-4}

- App

Available on https://npcr.se/lankar/nomogram/



- Nomogram
  - Calculate risk prediction without regression equation
  - A way to illustrate the impact of the variables in the model



Conclusions

Guidelines: TRIPOD
Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis

- **Modelling**
  - Model performance evaluated and reported according to TRIPOD
  - External validation: Performance as good as for development data
  - Model available as nomogram and app

- **Clinical**
  - Scan men with model estimated risk ≥ 4% risk →
    ~25% of bone scans avoided
    ~2% metastasis missed
    compared with EAU guidelines
  - In Sweden, approximately 1000 scans per year could be avoided (€250 000 – €1 500 000)

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Thank you for your attention!

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