# Predicting the risk of pancreatic cancer in individuals with newly-diagnosed type 2 diabetes

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# Rationale for the study

- Improved outcomes could be possible with earlier detection, but there is no screening programme at present
- Identifying 'higher risk' individuals could enrich existing referral pathways, or inform the development of new pathways that seek to find pancreatic cancers earlier
- One approach could be to target adults with newly diagnosed type 2 diabetes (T2DM)
  - Some studies show that 1% of people with newly diagnosed T2DM are diagnosed with pancreatic cancer within the next 2 years
  - Approximately a quarter of people with pancreatic cancer have a history of T2DM
  - T2DM may in some cases be 'Type 3c' diabetes
- NICE guidelines suggest that adults age 60+ years with newly diagnosed T2DM and weight loss be referred for 'fast track' imaging to assess for a possible tumour in the pancreas
- **Could more nuanced ways to assess risk be better at finding people for referral in primary care?**

# Outline of the study approach

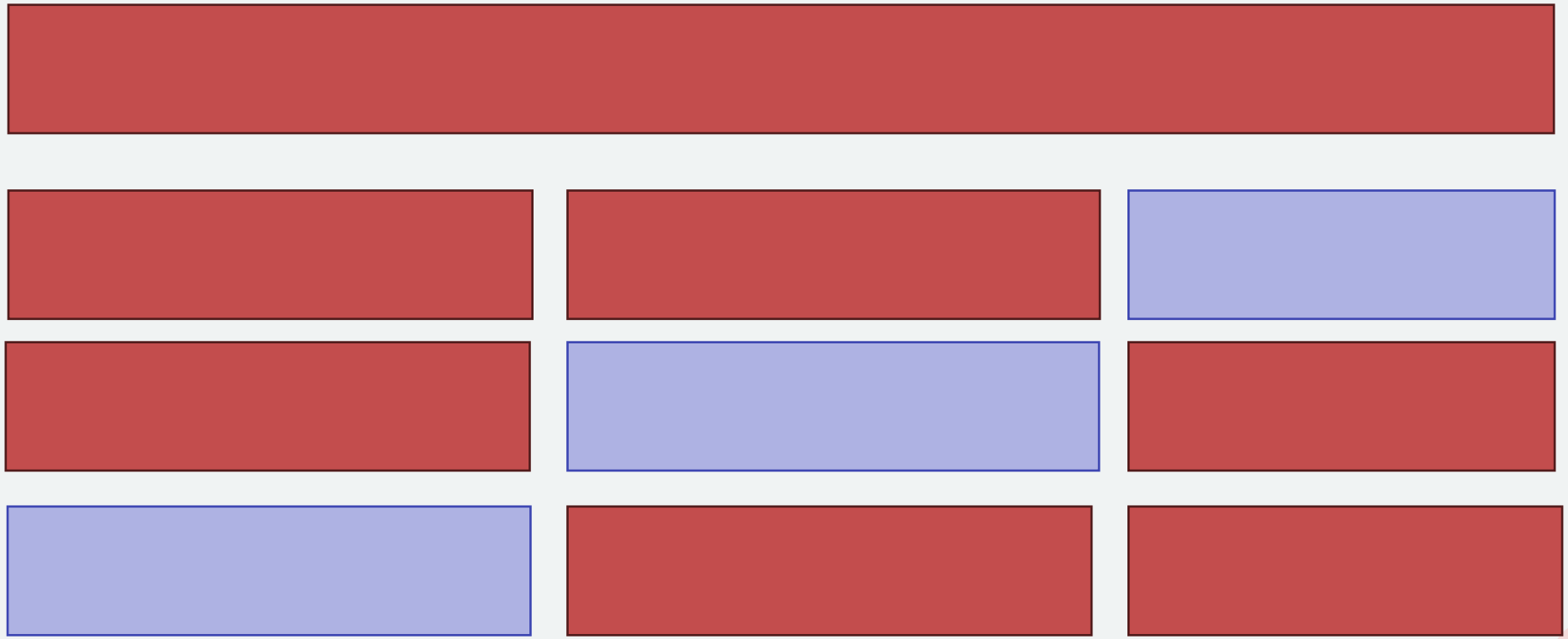
- Exploring different approaches that may be able to accurately estimate the risk of an individual with new-onset type 2 diabetes developing pancreatic cancer (PDAC and PNET)
- Statistical and 'machine learning' approaches – which is the most useful?
  - Cox model, XGBoost, neural networks – tuning with Bayesian optimisation
- **QResearch database** – primary care data with individual level linkage to hospital data, cancer registry and ONS in England
- Identified: adults aged 30-85 years at time of T2DM diagnosis (2010-2021)
  - 253,766 individuals with T2DM in the final study database
  - 767 of these were diagnosed with a pancreatic cancer within the next 2 years
- Exploration of different potential predictors – e.g. age, sex, HbA1c, body mass index, creatinine, platelet count, alcohol intake, previous venous thromboembolism, and symptoms such as abdominal pain, weight loss, indigestion (within the previous 6 months)

# Assessing how well models perform

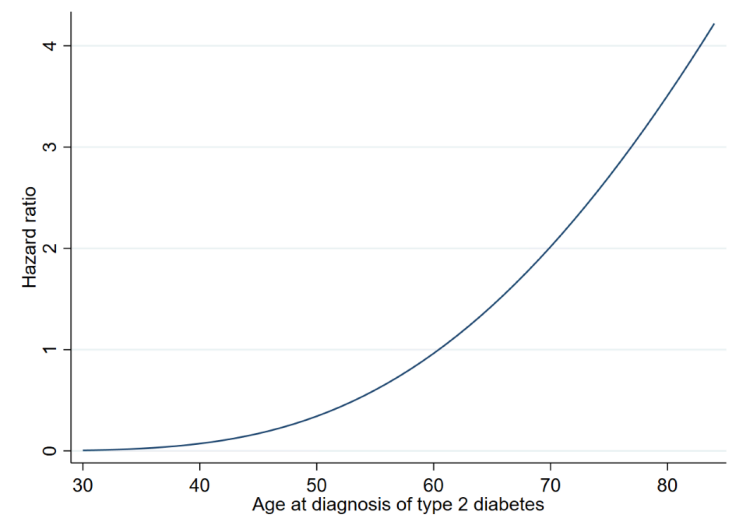
- Discrimination
  - Does the model distinguish between those that did and did not get a pancreatic cancer diagnosis?
  - Harrell's C – goes between 0.5 and 1
  - 0.5 means model is no better than a coin toss, 1 means 'perfect'
- Calibration
  - Do the probabilities produced by the model align with the observed risk?
- Clinical utility (net benefit)
  - Is the model associated with better clinical decision making?
  - Typically, compare against 'test everyone', 'test nobody', or other models
- Using the geographical coverage of QResearch and the linked datasets
  - Estimate key metrics in each held out region, then pool together with meta-analysis
  - Provides an estimate, and an indication of the expected range of performance if applied to a new population

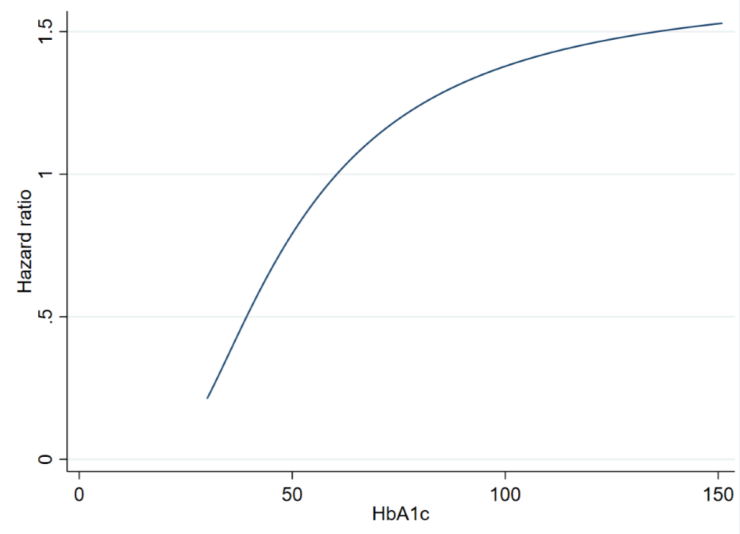
'Train test split'

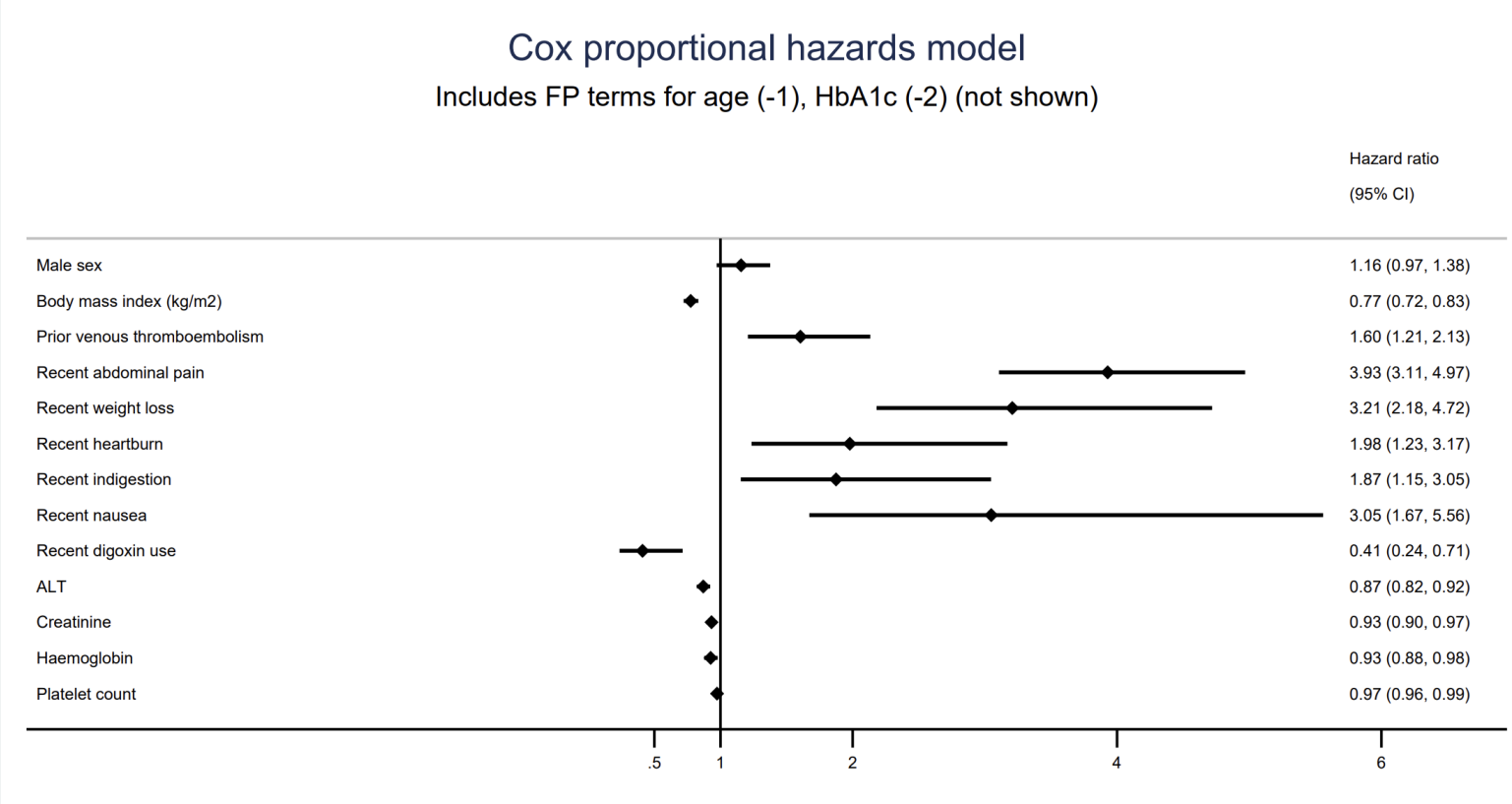
'Cross-validation'



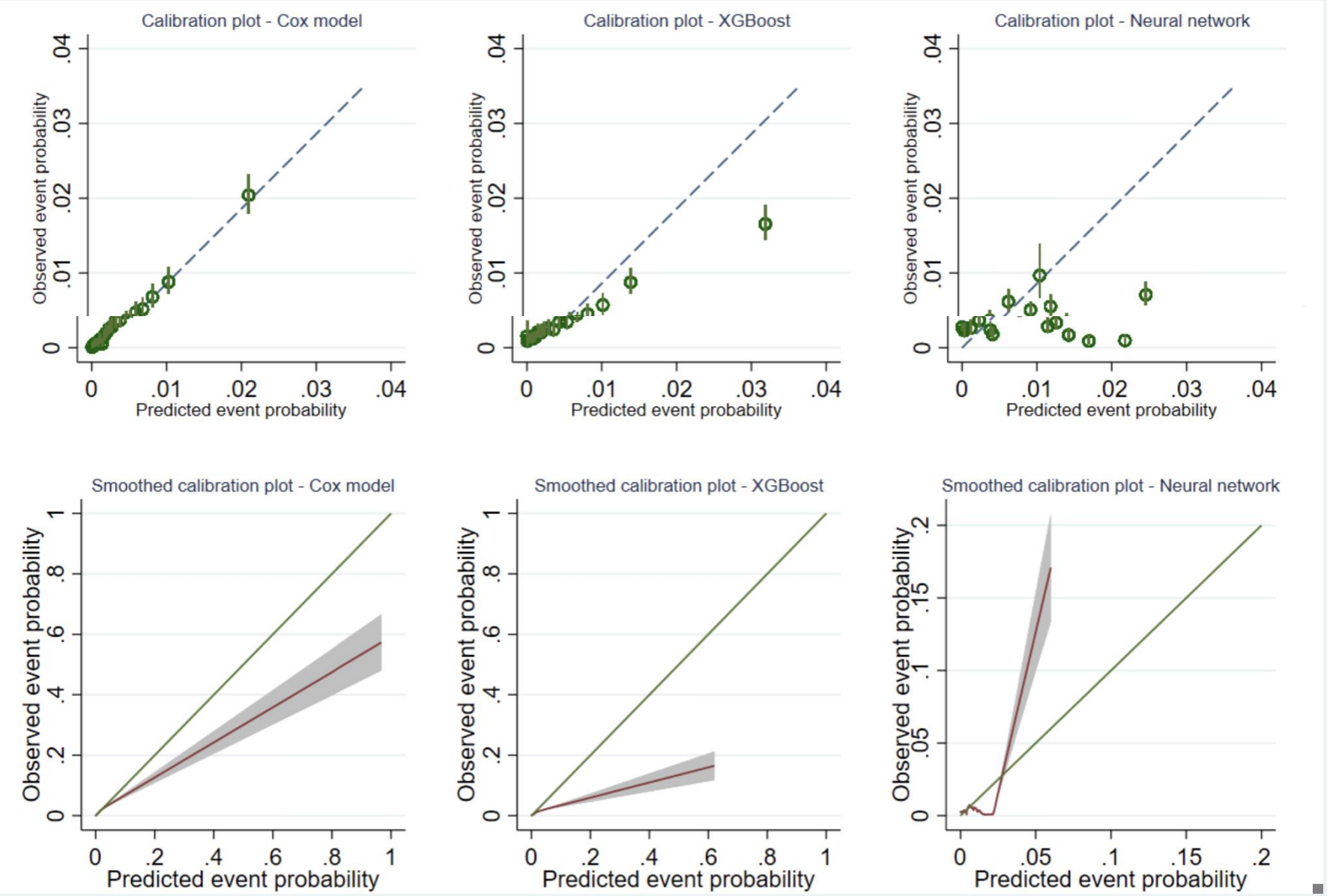
# Key results – Cox model

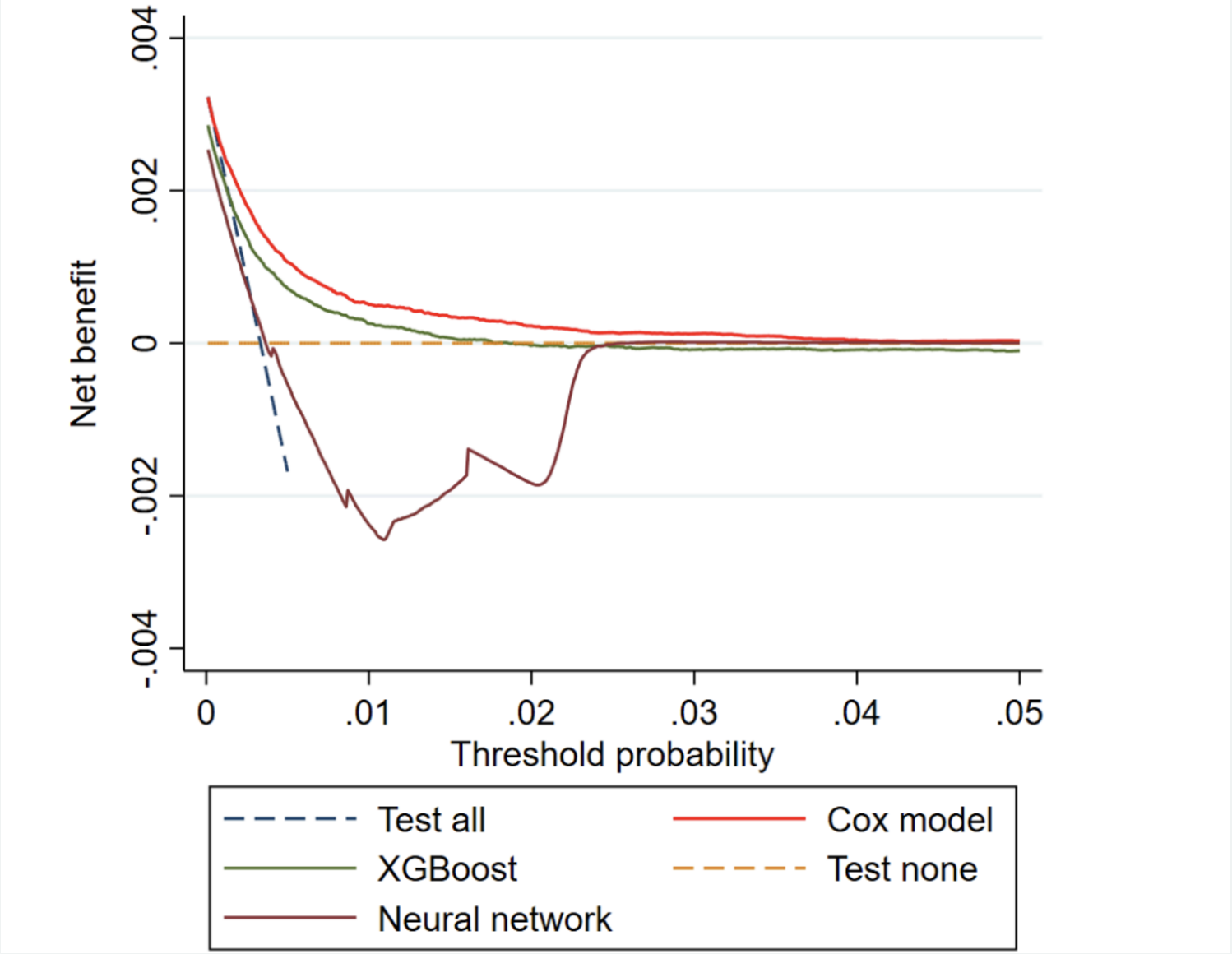


| Metric | Estimate (95% confidence interval) [95% prediction interval] | | |
|---|---|---|---|
| | Cox model | XGBoost | Neural Network |
| Harrell's C-index | 0.802<br>(0.787 to 0.817)<br>[0.766 to 0.839] | 0.723<br>(0.689 to 0.756)<br>[0.628 to 0.817] | 0.650<br>(0.516 to 0.784)<br>[0.202 to 1.000] |
| Calibration slope | 0.980<br>(0.897 to 1.062)<br>[0.778 to 1.182] | 1.180<br>(1.056 to 1.305)<br>[0.781 to 1.580] | 1.855<br>(-0.945 to 4.654)<br>[-7.552 to 11.261] |
| Calibration-in-the-large | -0.020<br>(-0.103 to 0.062)<br>[-0.222 to 0.182] | 0.180<br>(0.056 to 0.305)<br>[-0.219 to 0.580] | 0.855<br>(-1.945 to 3.654)<br>[-8.552 to 10.261] |


Calibration plot - Cox model
Observed event probability
Predicted event probability
Calibration plot - XGBoost
Observed event probability
Predicted event probability
Calibration plot - Neural network
Observed event probability
Predicted event probability
Smoothed calibration plot - Cox model
Observed event probability
Predicted event probability
Smoothed calibration plot - XGBoost
Observed event probability
Predicted event probability
Smoothed calibration plot - Neural network
Observed event probability
Predicted event probability


Net benefit
.004
.002
0
-.002
-.004
0
.01
.02
.03
.04
.05
Threshold probability
Test all
Cox model
XGBoost
Test none
Neural network

# What does it all mean?

- In this study, the sensitivity of the current NICE guidelines was 3.53% overall, and 3.95% in the over 60s
  - The sensitivity for the highest 1% group as assessed by the new model = 12.51%
- The Cox model -> discriminates well, is well calibrated, and associated with better decision making
- We developed a model, understand how well it works, but next we need:
  - External evaluation, including a comparison with other tools
  - Health economic simulations to understand the clinical and cost-effectiveness of new strategies that could be informed by the model's outputs
  - What is the best way to use it?
- No tool is perfect, and no tool in this setting can probably 'find every case', but *progress*

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