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Developing and validating prediction models using large clustered datasets and meta-analysis

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Prediction

- Risk prediction = foreseeing / foretelling
  … (probability) of something that is yet unknown

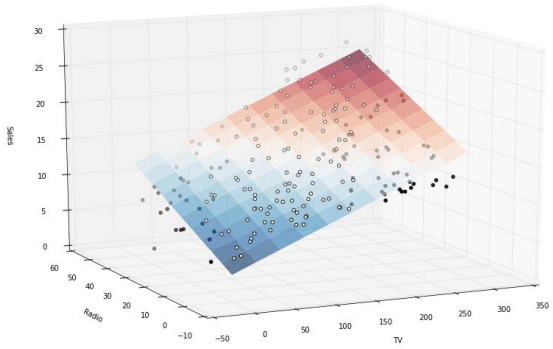
- Turn available information (predictors) into a statement about the probability:
  … of having a particular disease -> **diagnosis**
  … of developing a particular event -> **prognosis**

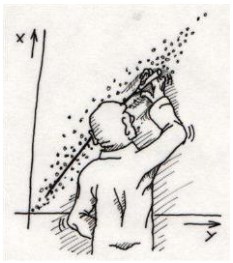
- Use of prognostic information:
  - to inform patients and their families
  - to guide treatment and other clinical decisions
  - to create risk groups
  - …

How do we predict?

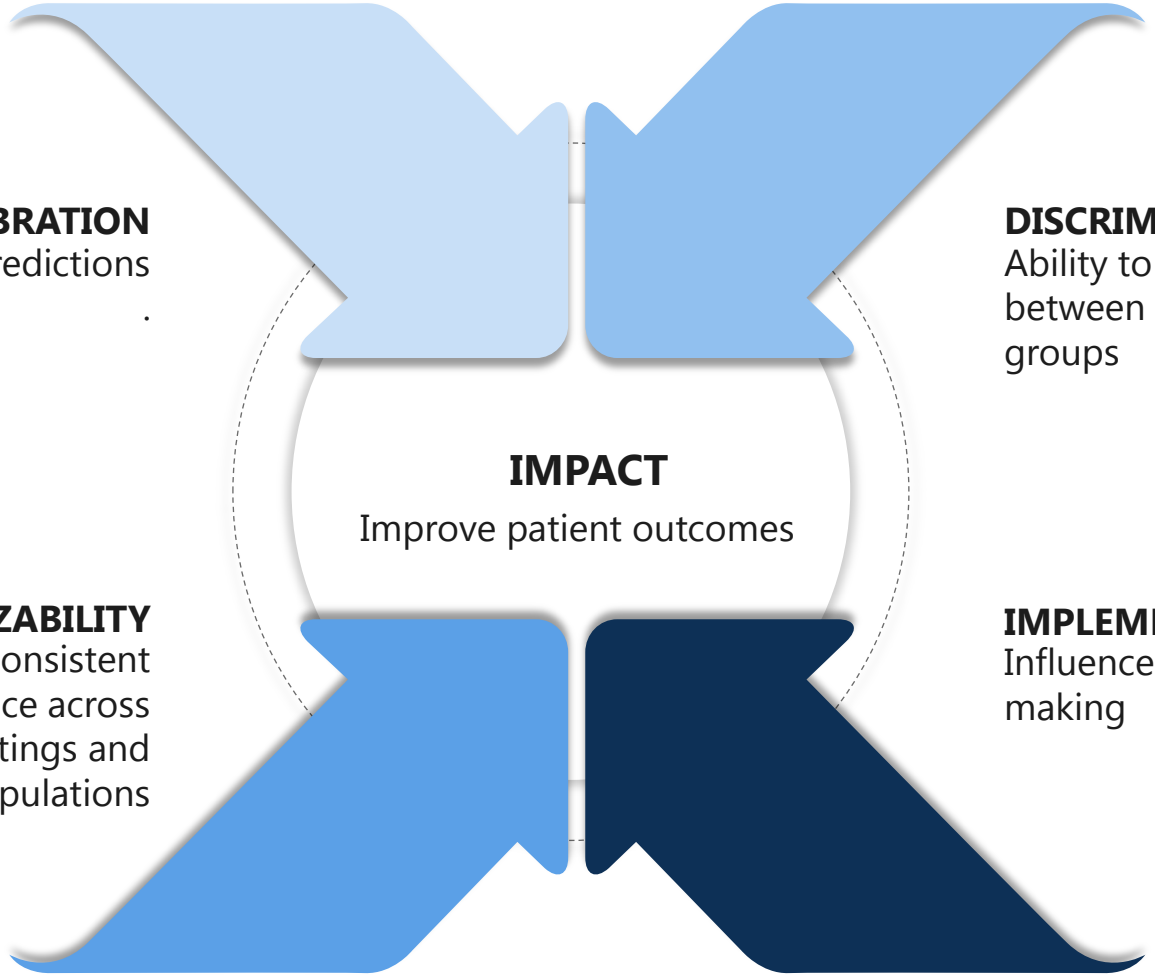
- Combine information from multiple predictors
  - Subject characteristics (e.g. age, gender)
  - History and physical examination results (e.g. blood pressure)
  - Imaging results
  - (Bio)markers (e.g. coronary plaque)

- Develop a multivariable statistical model
  - Need for patient data from large cohort studies
  - Many strategies available (Regression, decision trees, neural networks, …)





What is a good model?



Common pitfalls

Most models are not as good as we think

- Limited sample size
- Flaws in design & analysis
- Incomplete/selective reporting
- Lack of external validation

Most models are not as good as we think

Clinical prediction models are not being validated

Peter Tugwell, J. André Knottnerus (Editors)

JCE JOURNAL OF CLINICAL EPIDEMIOLOGY

External validation of new risk prediction models is infrequent and reveals worse prognostic discrimination

George C.M. Siontis[a,1], Ioanna Tzoulaki[a,b], Peter J. Castaldi[c], John P.A. Ioannidis[d,e,f,*]

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External validation of multivariable prediction models: a systematic review of methodological conduct and reporting

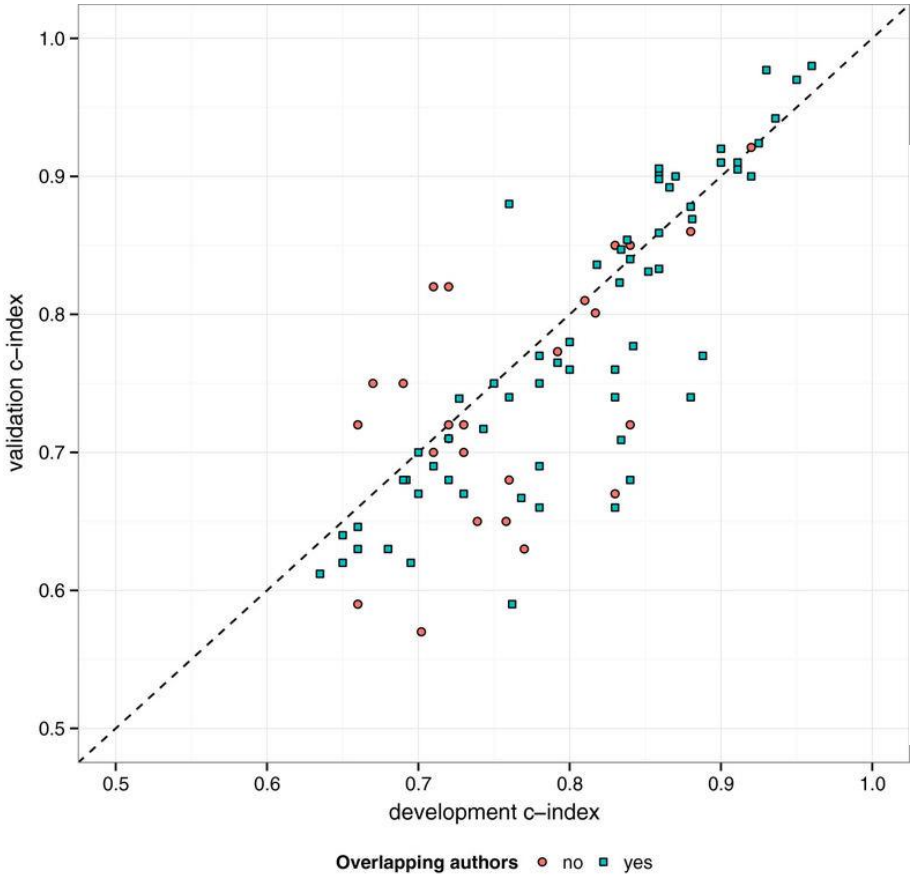
Gary S Collins[1*], Joris A de Groot[2], Susan Dutton[1], Omar Omar[1], Milensu Shanyinde[1], Abdelouahid Tajar[1], Merryn Voysey[1], Rose Wharton[1], Ly-Mee Yu[1], Karel G Moons[2] and Douglas G Altman[1]

Assessment of Claims of Improved Prediction Beyond the Framingham Risk Score

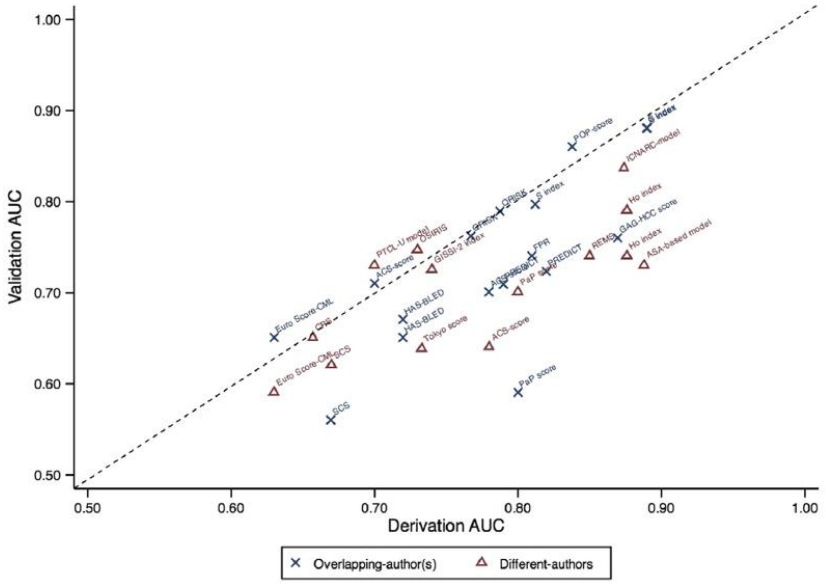
Ioanna Tzoulaki, PhD; George Liberopoulos, MD; John P. A. Ioannidis, MD

JAMA®
The Journal of the American Medical Association

Most models are not as good as we think



Collins et al (BMC Med Res Methodol 2014)



Siontis et al (J Clin Epidemiol 2014)

Most models are not as good as we think

Lack of generalizability across settings & (sub)populations

- Poor reproducibility
  - Overfitting to the data at hand
- Poor transportability
  - Differences in patient spectrum
  - Differences in measurement methods
  - Changes in standards of care and treatment strategies
  - …

Use of large, clustered, datasets

Research partially funded by my VENI grant (91617050)
"Better predictions using big data sets"

UNIVERSITY OF OXFORD

Keele University

Cochrane

UMC Utrecht Julius Center

Use of large clustered data sets

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Research Methods & Reporting

External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges

BMJ 2016 ; 353 doi: https://doi.org/10.1136/bmj.i3140 (Published 22 June 2016)
Cite this as: *BMJ* 2016;353:i3140

PLOS | MEDICINE

GUIDELINES AND GUIDANCE

Individual Participant Data (IPD) Meta-analyses of Diagnostic and Prognostic Modeling Studies: Guidance on Their Use

Thomas P. A. Debray[1,2]*, Richard D. Riley[3], Maroeska M. Rovers[4], Johannes B. Reitsma[1,2], Karel G. M. Moons[1,2], Cochrane IPD Meta-analysis Methods group[¶]

Use of large clustered data sets

Potential advantages

- Development of better prediction models
  - Reduced risk of overfitting
  - Ability to address wider spectrum of patients
  - Ability to investigate more complex associations
- More extensive testing of model performance
  - Ability to externally validate across multiple settings
  - Ability to investigate sources of heterogeneity
  - Ability to improve or tailor the model

Model development

- Need to identify whether aggregation of multiple data sources is justifiable
  - Differences in included populations
  - Differences in measurement methods
  - Differences in treatment standards

- Need to account for heterogeneity across settings
  - Differences in outcome prevalence (or incidence)
  - Differences in predictor effects
  - Failing to account for clustering may cause prediction models to yield poor performance across different (sub)populations!

Implement a framework that uses internal-external cross-validation

Internal-external cross-validation (IECV)

PDF

Info

Statistics in Medicine

Explore this journal >

Research Article

A framework for developing, implementing, and evaluating clinical prediction models in an individual participant data meta-analysis

Thomas P.A. Debray ✉, Karel G.M. Moons, Ikhlaaq Ahmed, Hendrik Koffijberg, Richard David Riley

First published: 11 January 2013 Full publication history

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ELSEVIER

Journal of Clinical Epidemiology

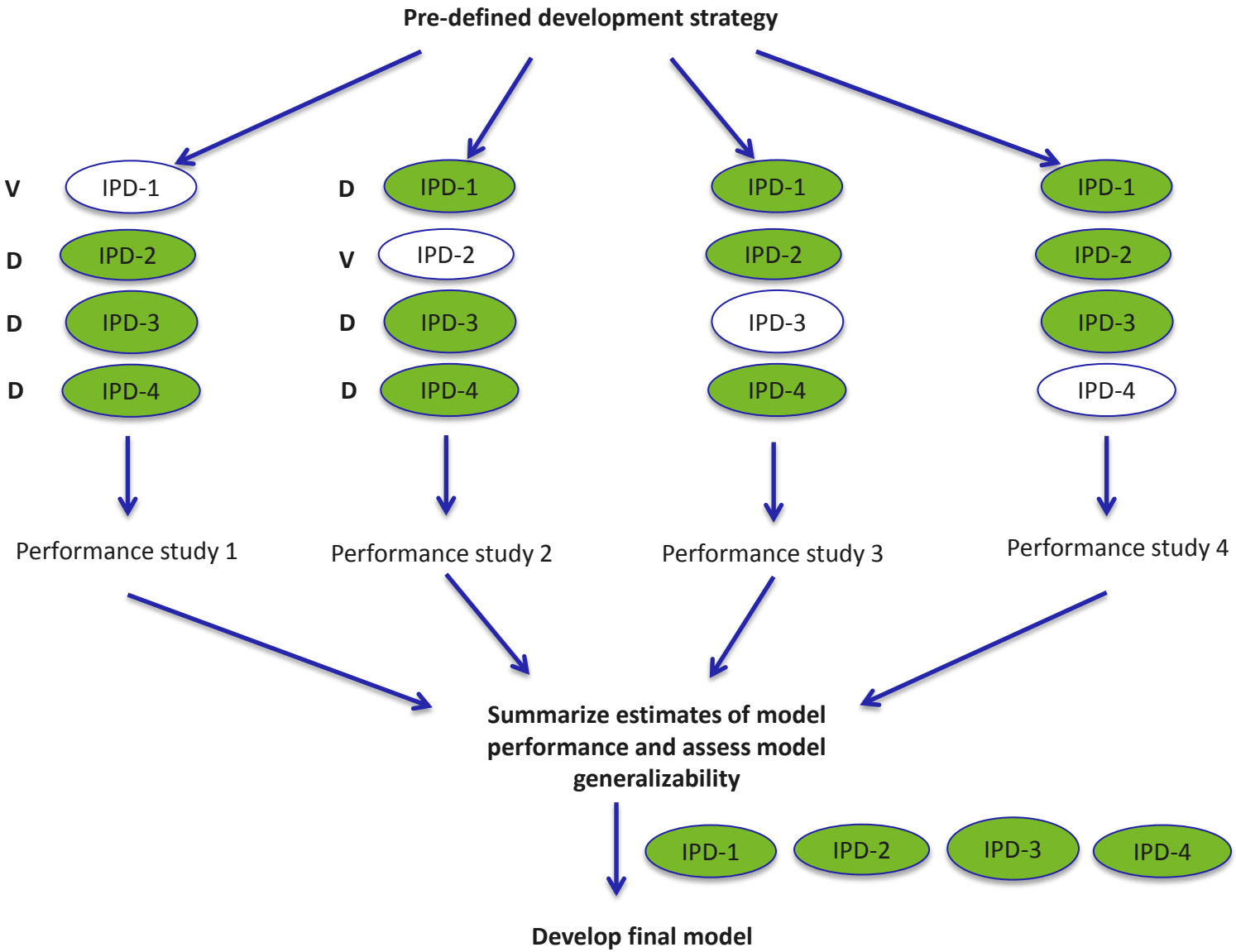
Volume 69, January 2016, Pages 245-247

Commentary

Prediction models need appropriate internal, internal–external, and external validation

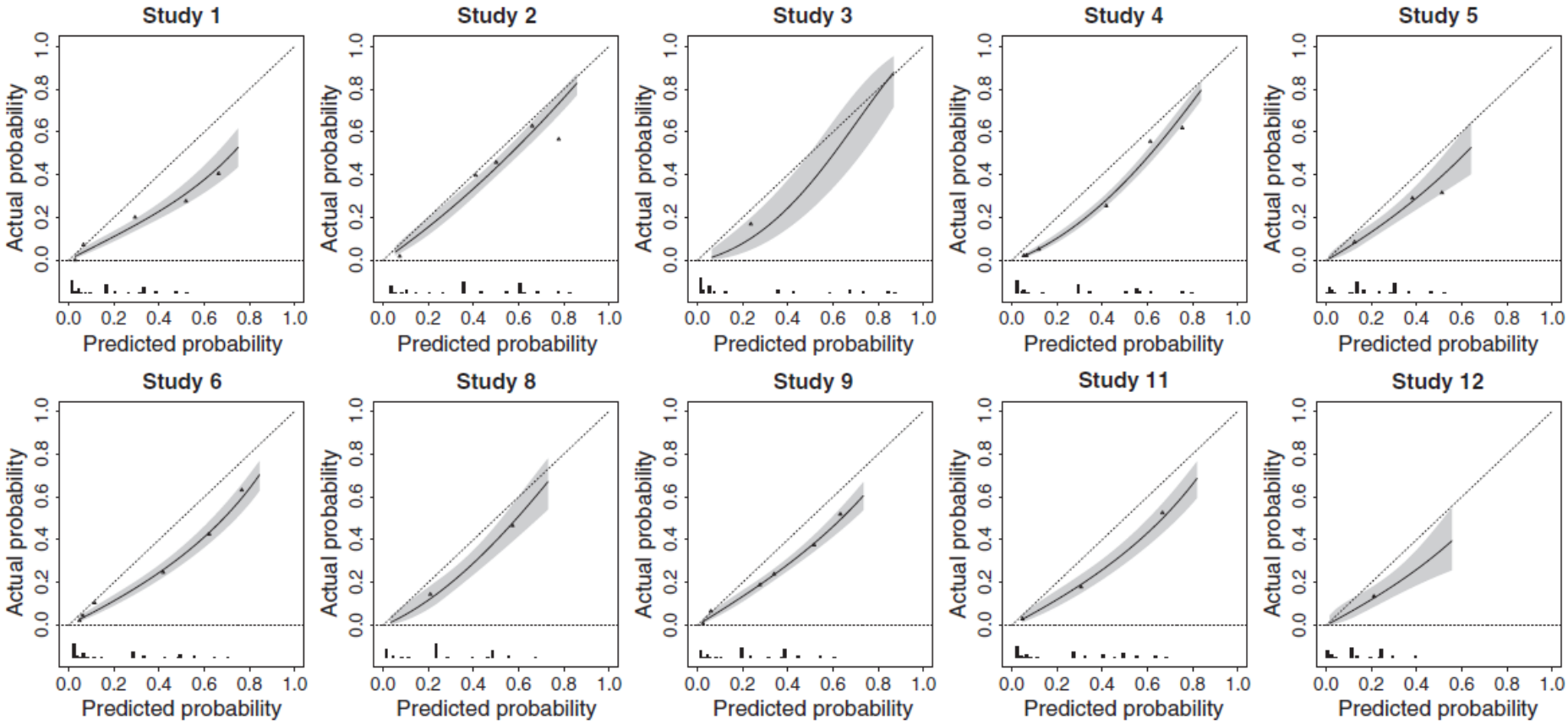
Ewout W. Steyerberg ✉ [a], Frank E. Harrell Jr. [b]

Internal-external cross-validation (IECV)



Internal-external cross-validation (IECV)

The IECV approach allows for many external validations



Assessing model performance

Synthesis of performance estimates

- A 'good' prediction model should have
  - satisfactory performance on average
  - little or no between-study heterogeneity in performance

- Meta-analysis may help …
  - To estimate likely performance in new studies
  - To identify sources of heterogeneity
  - To evaluate different modeling strategies
  - To distinguish between reproducibility and transportability
  - To identify "boundaries" of model generalizability

Assessing model performance

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A new framework to enhance the interpretation of external validation studies of clinical prediction models

Thomas P.A. Debray[a,*], Yvonne Vergouwe[b], Hendrik Koffijberg[a], Daan Nieboer[b], Ewout W. Steyerberg[b,1], Karel G.M. Moons[a,1]

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Multivariate meta-analysis of individual participant data helped externally validate the performance and implementation of a prediction model

Kym I.E. Snell[a], Harry Hua[b], Thomas P.A. Debray[c,d], Joie Ensor[e], Maxime P. Look[f], Karel G.M. Moons[c,d], Richard D. Riley[e,*]

SMMR STATISTICAL METHODS IN MEDICAL RESEARCH

Meta-analysis of prediction model performance across multiple studies: Which scale helps ensure between-study normality for the *C*-statistic and calibration measures?

Kym IE Snell, Joie Ensor, Thomas PA Debray, ... Show all authors

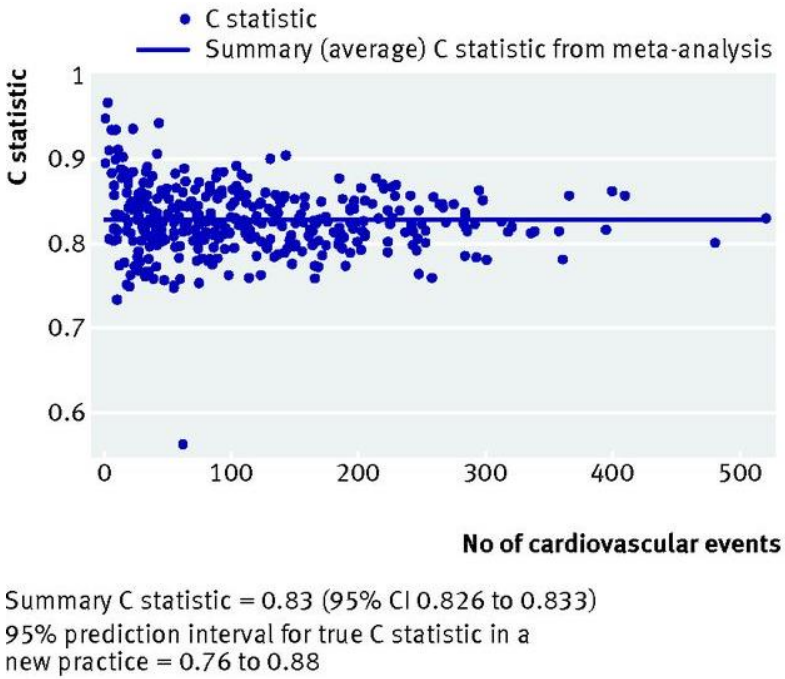
thebmj

A guide to systematic review and meta-analysis of prediction model performance

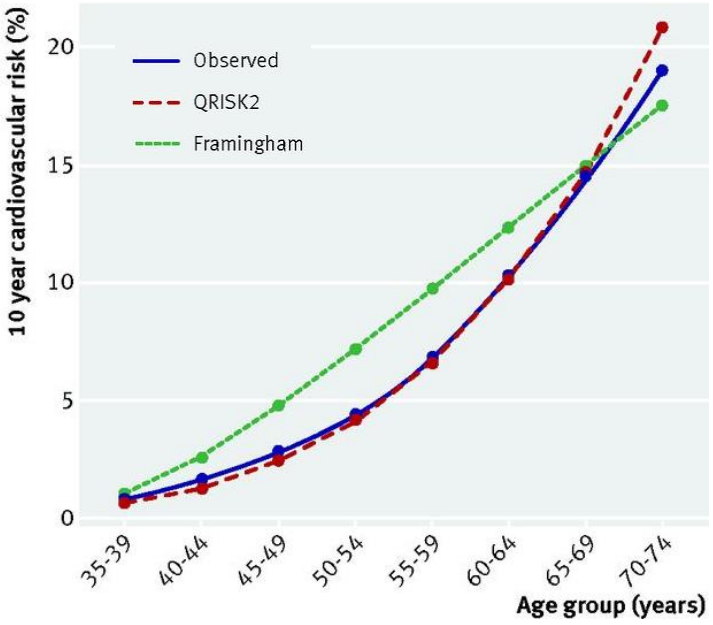
Thomas P A Debray,[1,2] Johanna A A G Damen,[1,2] Kym I E Snell,[3] Joie Ensor,[3] Lotty Hooft,[1,2] Johannes B Reitsma,[1,2] Richard D Riley,[3] Karel G M Moons[1,2]

Assessing model performance

Investigation of heterogeneity across settings

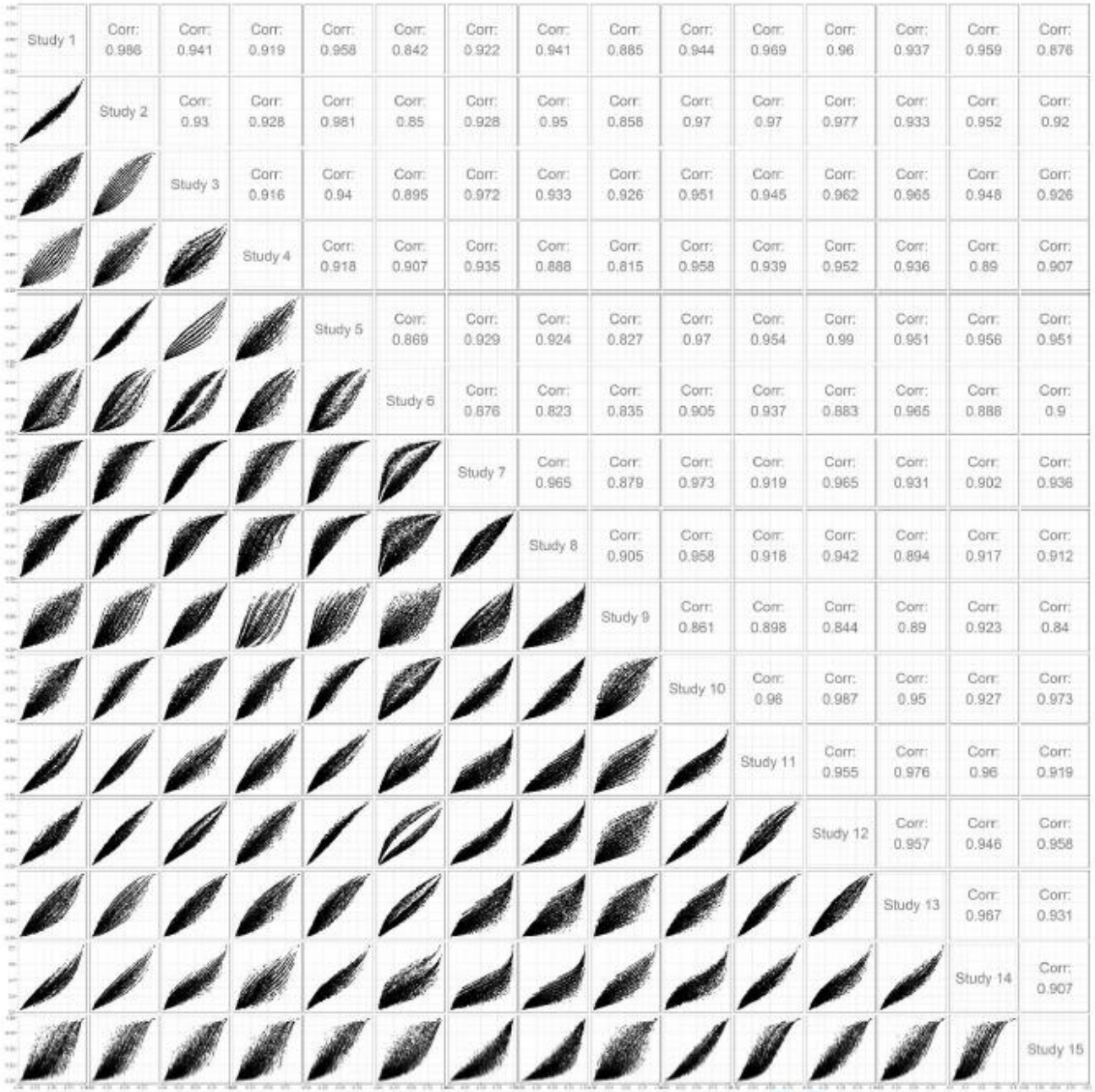


Concordance statistic for QRISK2, for each of the 364 included general practices (N ≈ 2,000,000)



Calibration of QRISK2 and the Framingham risk score in women aged 35 to 74 years

Riley RD, et al. External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges. BMJ. 2016;353:i3140.


Study 1
Corr: 0.986
Corr: 0.941
Corr: 0.919
Corr: 0.958
Corr: 0.842
Corr: 0.922
Corr: 0.941
Corr: 0.885
Corr: 0.944
Corr: 0.969
Corr: 0.96
Corr: 0.937
Corr: 0.959
Corr: 0.876
Study 2
Corr: 0.93
Corr: 0.928
Corr: 0.981
Corr: 0.85
Corr: 0.928
Corr: 0.95
Corr: 0.858
Corr: 0.97
Corr: 0.97
Corr: 0.977
Corr: 0.933
Corr: 0.952
Corr: 0.92
Study 3
Corr: 0.916
Corr: 0.94
Corr: 0.895
Corr: 0.972
Corr: 0.933
Corr: 0.926
Corr: 0.951
Corr: 0.945
Corr: 0.962
Corr: 0.965
Corr: 0.948
Corr: 0.926
Study 4
Corr: 0.918
Corr: 0.907
Corr: 0.935
Corr: 0.888
Corr: 0.815
Corr: 0.958
Corr: 0.939
Corr: 0.952
Corr: 0.936
Corr: 0.89
Corr: 0.907
Study 5
Corr: 0.869
Corr: 0.929
Corr: 0.924
Corr: 0.827
Corr: 0.97
Corr: 0.954
Corr: 0.99
Corr: 0.951
Corr: 0.956
Corr: 0.951
Study 6
Corr: 0.876
Corr: 0.823
Corr: 0.835
Corr: 0.905
Corr: 0.937
Corr: 0.883
Corr: 0.965
Corr: 0.888
Corr: 0.9
Study 7
Corr: 0.965
Corr: 0.879
Corr: 0.973
Corr: 0.919
Corr: 0.965
Corr: 0.931
Corr: 0.902
Corr: 0.936
Study 8
Corr: 0.905
Corr: 0.958
Corr: 0.918
Corr: 0.942
Corr: 0.894
Corr: 0.917
Corr: 0.912
Study 9
Corr: 0.861
Corr: 0.898
Corr: 0.844
Corr: 0.89
Corr: 0.923
Corr: 0.84
Study 10
Corr: 0.98
Corr: 0.987
Corr: 0.95
Corr: 0.927
Corr: 0.973
Study 11
Corr: 0.955
Corr: 0.976
Corr: 0.96
Corr: 0.919
Study 12
Corr: 0.957
Corr: 0.946
Corr: 0.958
Study 13
Corr: 0.967
Corr: 0.931
Study 14
Corr: 0.907
Study 15

More guidance underway!

- Future book chapters
  - Collins GS, Moons KGM, Debray TPA, Altman DG, Riley RD. **Systematic reviews of prediction models.** Systematic Reviews in Health Care: Meta-Analysis in Context (Wiley)
  - Riley TD, Debray TPA, Moons KGM. **Individual Participant Data Meta-analysis of Prognosis Studies.** Evidence synthesis using individual participant data: concepts, methods, and guidance for clinical research (CRC Press)
  - Steyerberg EW, Nieboer D, Debray TPA, van Houwelingen H. **Meta-analysis of prediction models.** Handbook of Meta-analysis (CRC Press)

- Courses
  - MSc Epidemiology
  - Elevate
  - Cochrane

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