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Clinical Prediction Models and the role of Evidence Synthesis

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Prediction

Estimate the absolute risk in individual patients of …

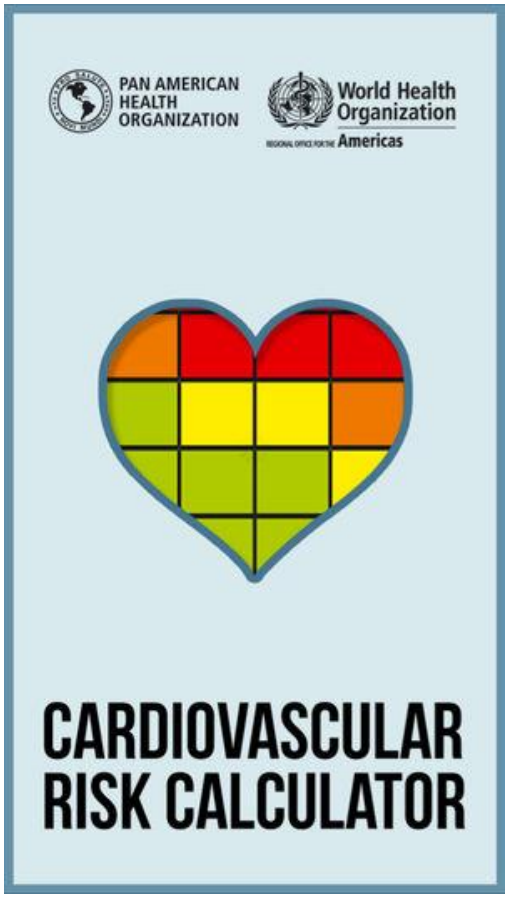
- an outcome's presence (diagnosis)
- an outcome's future occurrence (prognosis)

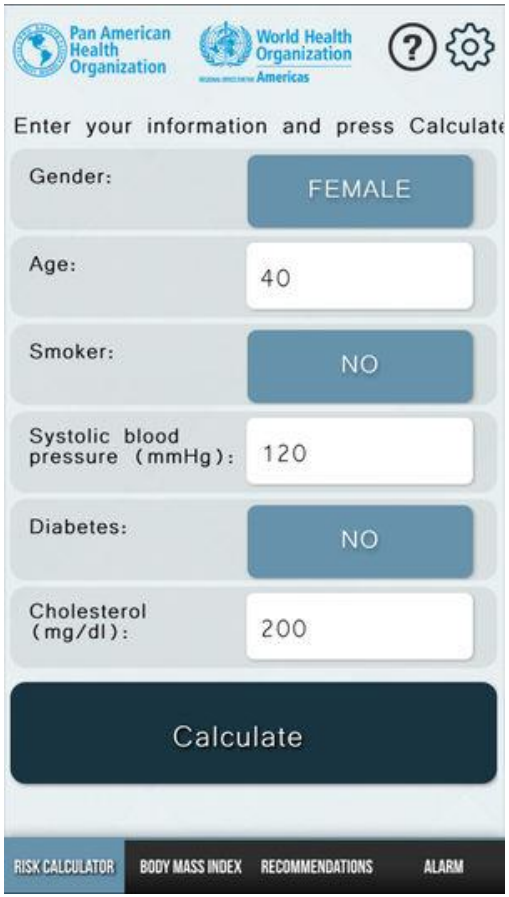
Example

"What is the 10-year risk of cardiovascular disease in a visiting primary care patient?"

Prediction models

Combine information from multiple predictors





Prediction models are abundant

- > 350 models for cardiovascular disease
- > 100 models for brain trauma patients
- > 100 diabetes type 2 models
- > 100 models for prostate cancer
- > 60 models for breast cancer prognosis

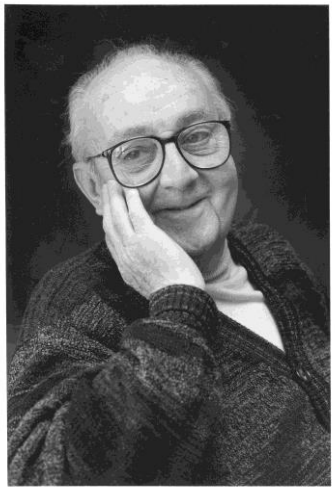
The reality

Poor understanding of

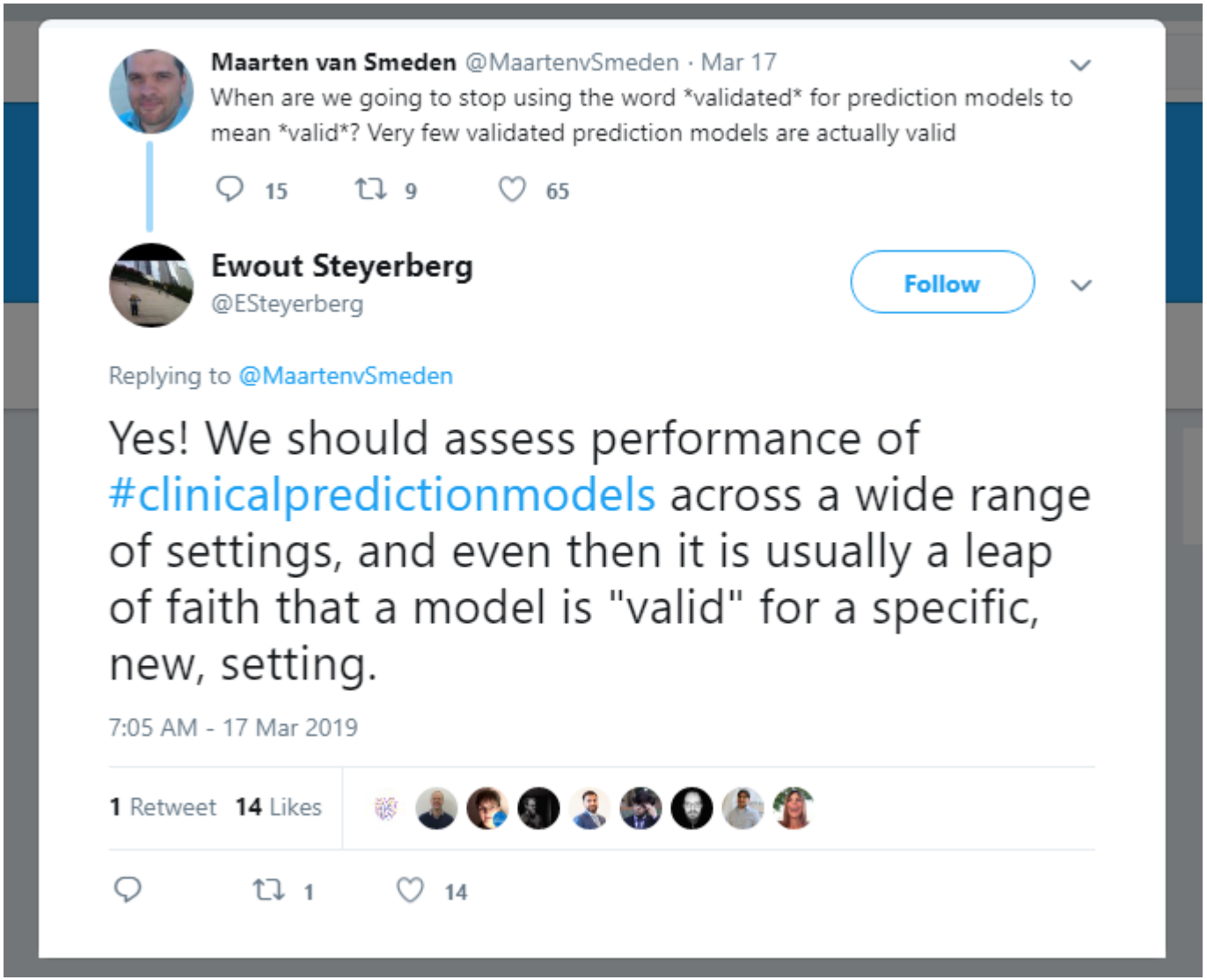
- The validity of model predictions in new patients
- The generalizability of prediction models across different settings and populations
- The comparative performance of prediction models
- The clinical impact of prediction models

“All models are wrong, but some are useful”

George Box



The need for evidence synthesis



Maarten van Smeden @MaartenvSmeden · Mar 17

When are we going to stop using the word *validated* for prediction models to mean *valid*? Very few validated prediction models are actually valid

15 9 65

Ewout Steyerberg
@ESteyerberg

Follow

Replying to @MaartenvSmeden

Yes! We should assess performance of #clinicalpredictionmodels across a wide range of settings, and even then it is usually a leap of faith that a model is "valid" for a specific, new, setting.

7:05 AM - 17 Mar 2019

1 Retweet **14** Likes

1 14

The need for evidence synthesis

Synthesis of published prognosis studies may help

- To identify promising markers
  - By summarizing their (incremental) prognostic value
  - By exploring sources of between-study heterogeneity
- To identify promising prediction models
  - By summarizing their predictive performance
  - By exploring generalizability across different settings and populations
  - By evaluating the need for further improvements
- To improve estimation of prediction models
  - By avoiding overfitting in small samples

The need for evidence synthesis

Commentary | Open Access | Open Peer Review

The increasing need for systematic reviews of prognosis studies: strategies to facilitate review production and improve quality of primary research

Johanna A. A. G. Damen and Lotty Hooft

Diagnostic and Prognostic Research 2019 **3**:2
https://doi.org/10.1186/s41512-019-0049-6
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Cochrane

Summarizing prognosis evidence

Research Methods & Reporting

A guide to systematic review and meta-analysis of prognostic factor studies

BMJ 2019 ; 364 doi: https://doi.org/10.1136/bmj.k4597 (Published 30 January 2019)
Cite this as: *BMJ* 2019;364:k4597

Research Methods & Reporting

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

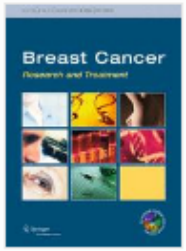
BMJ 2017 ; 356 doi: https://doi.org/10.1136/bmj.i6460 (Published 05 January 2017)
Cite this as: *BMJ* 2017;356:i6460

Summarizing prognosis evidence

Formal review steps and tools

- Defining the review question (PICOTS)
- Defining the search strategy
- Quality appraisal
  - Checklist for prognostic factor studies (QUIPS)
  - Checklist for prognostic model studies (PROBAST)
- Data extraction & meta-analysis
  - Focus on unadjusted and adjusted prognostic effects
  - Focus on model discrimination and calibration
- Interpretation (GRADE)
- Reporting (guidelines: REMARK, PRISMA, TRIPOD)

Summarizing prognosis evidence



Breast Cancer Research and Treatment
April 2012, Volume 132, Issue 2, pp 365–377

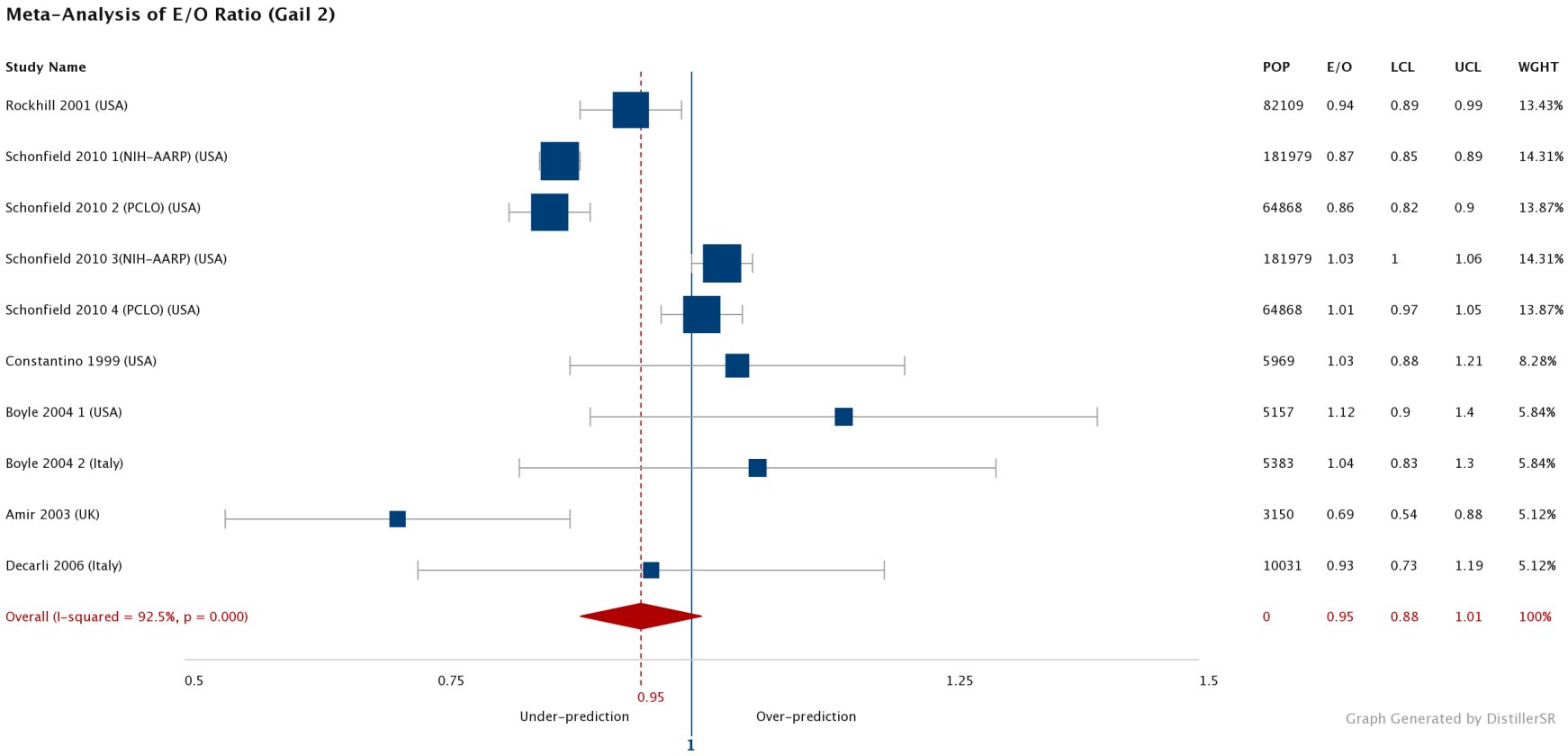
A systematic review of breast cancer incidence risk prediction models with meta-analysis of their performance

Authors | Authors and affiliations

Catherine Meads, Ikhlaaq Ahmed, Richard D. Riley

"There is a need for models with better predictive performance but, given the large amount of work already conducted, further improvement of existing models based on conventional risk factors is perhaps unlikely. Research to identify new risk factors with large additionally predictive ability is therefore needed, alongside clearer reporting and continual validation of new models as they develop."

Summarizing prognosis evidence



Summarizing prognosis evidence

More recent examples (2018)

- Prediction of maternal mortality (10.1371/journal.pone.0208563)
- Prediction of major bleeding events after percutaneous coronary intervention (10.1016/j.amjcard.2018.08.025)
- Prediction of pressure ulcer risk (10.1016/j.ijnurstu.2018.08.005)
- Prediction of food demand (10.1016/j.envint.2018.07.019)
- Prediction of venous thromboembolism following joint replacement (10.1016/j.thromres.2018.06.024)

Summarizing prognosis evidence

Key issues

- Quality and heterogeneity of primary studies
- Selective reporting and publication bias
- Between-study heterogeneity

The way forward

- Publication of study protocols
- Adherence to conduct and reporting guidelines
- Meta-analysis of individual participant data

Meta-analysis of individual participant data

Development of better prediction models

- Reduced risk of overfitting
- Ability to address wider spectrum of patients
- Ability to estimate more complex associations

More extensive testing of model performance, as to establish whether model performance is

- Satisfactory on average
- Consistently good across different settings and (sub)populations

Meta-analysis of individual participant data

Assessing external validity during model development

- Cross-validation with non-random hold-out samples
- Multivariate meta-analysis of performance estimates
- Evaluation of likely performance in new settings

Moderating generalizability during model development

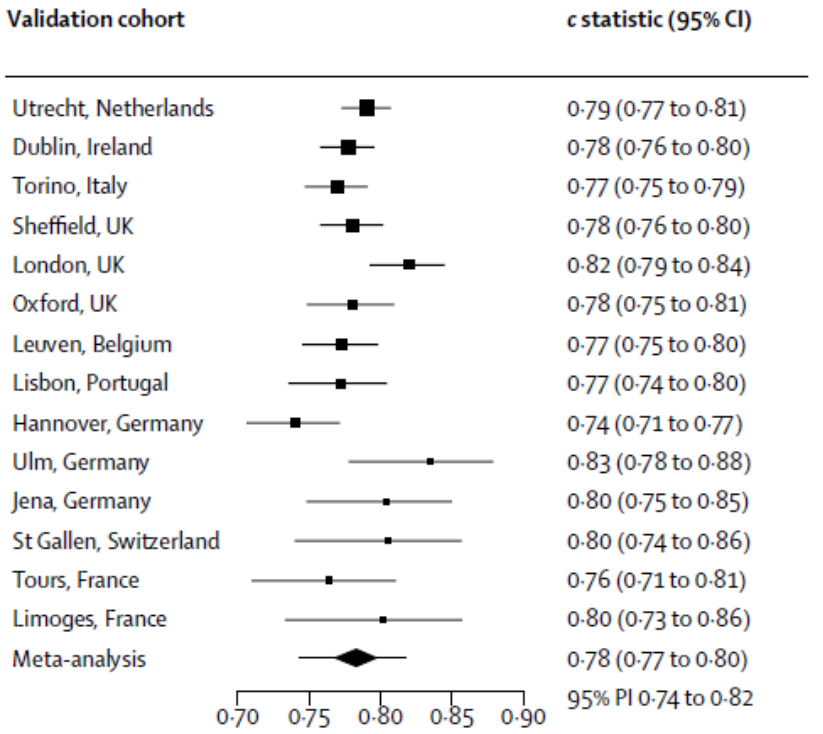
- Testing the need for stratified models
- Adopting loss functions that penalize predictions with poor transportability

[Work in progress]

Meta-analysis of individual participant data

Prediction of unfavorable outcomes in patients with amyotrophic lateral disease (DOI: 10.1016/S1474-4422(18)30089-9)

- Meta-analysis of IPD
  - 14 specialized ALS centres
  - Total sample size =11,475
- Model development
  - Royston-Parmar models
  - Study-specific baseline hazard
  - Common predictor effects
- Generalizability
  - Pr(c-stat>0.70) = 100%
  - Pr(0.8<cal slope < 1.2) = 97.1%



THE LANCET Neurology

Key references

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- A new framework to enhance the interpretation of external validation studies of clinical prediction models.
  Debray TP, et al. J Clin Epidemiol. 2015.
- External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges.
  Riley RD, et al. BMJ. 2016.
- Construction and validation of a prognostic model across several studies, with an application in superficial bladder cancer.
  Royston P, et al. Stat Med. 2004.
- Assessment of heterogeneity in an individual participant data meta-analysis of prediction models: an overview and illustration.
  Steyerberg EW, et al. Stat Med. Under Review.

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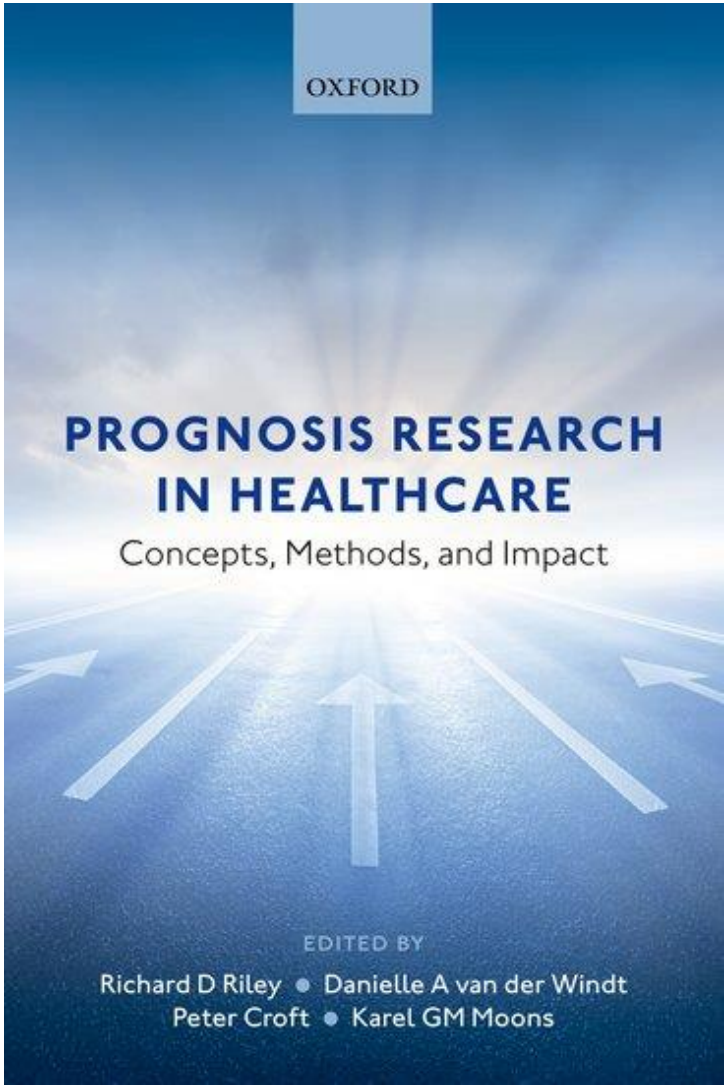

RESEARCH

Meta-analysis in prognosis research

Thomas PA Debray[1,2*†], Valentijn MT de Jong[1†], Karel GM Moons[1,2] and Richard D Riley[3]

BMC Diagnostic and Prognostic Research 2019 (Under Review)

OPEN ACCESS

GUIDELINES AND GUIDANCE

PLOS | MEDICINE

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

Thomas P. A. Debray, Richard D. Riley, Maroeska M. Rovers, Johannes B. Reitsma, Karel G. M. Moons, Cochrane IPD Meta-analysis Methods group

Published: October 13, 2015 • https://doi.org/10.1371/journal.pmed.1001886

metamisc

Diagnostic and Prognostic Meta-Analysis

https://CRAN.R-project.org/package=metamisc

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