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Use of multiple IPDs in developing prediction models

Thomas Debray, PhD

Julius Center for Health Sciences and Primary Care
Utrecht, The Netherlands


Stratenum

Prediction

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

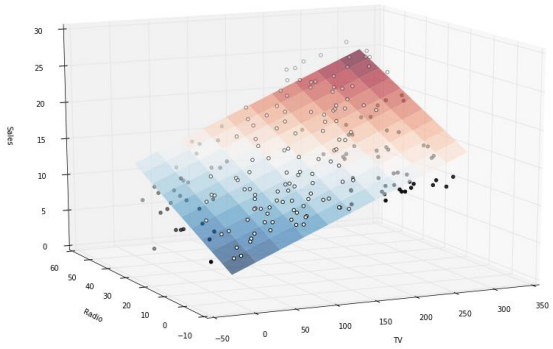
- Turn available information (predictors) into a statement about the probability:
  … of having a particular disease -> **diagnosis**
  … of developing a particular event -> **prognosis**

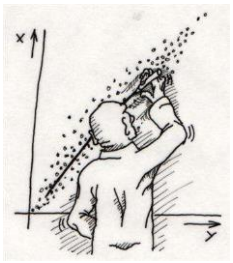
- Use of prognostic information:
  - to inform patients and their families
  - to guide treatment and other clinical decisions
  - to create risk groups
  - …

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, …)





Prediction

What is a good model?

- Generates accurate predictions in individuals from potential population(s) for clinical use
- Ability to discriminate between different risk groups
- Improves patient outcomes by informing treatment decisions

Common pitfalls

Most models are not as good as we think

- Poor quality of prognostic modelling studies
  - Limited sample size
  - Incomplete registrations & reporting
  - Absent study protocols
- Poor transportability
  - Case-mix variation across populations
  - Differences in measurement methods
  - Time-varying predictor effects
  - Changes in standards of care and treatment strategies
- Lack of external validation

Use of multiple IPDs

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Prediction research using IPD-MA

Potential advantages of multiple IPDs

- Development of better prediction models
  - Reduced risk of overfitting
  - Ability to address wider spectrum of patients
  - Ability to investigate more complex associations
  - Ability to "borrow strength" (e.g. in case of missing data)

- More extensive testing of model performance
  - Ability to externally validate across multiple settings (also upon model development)
  - Ability to investigate sources of poor or inconsistent model performance
  - Ability to assess usability of prediction models across different situations

IPD-MA prediction studies (general)

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

PLoS Med 12(10): e1001886. doi:10.1371/journal.

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[¶]

Individual participant data meta-analysis of prognostic factor studies: *state of the art?*

BMC Medical Research Methodology 2012, **12**:56

Ghada Abo-Zaid[1], Willi Sauerbrei[2] and Richard D Riley[3]

Developing and validating risk prediction models in an individual participant data meta-analysis

BMC Medical Research Methodology 2014, **14**:3

Ikhlaaq Ahmed[1], Thomas PA Debray[2], Karel GM Moons[2] and Richard D Riley[3]

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

BMJ 2016;353:i3140

Richard D Riley,[1] Joie Ensor,[1] Kym I E Snell,[2] Thomas P A Debray,[3,4] Doug G Altman,[5] Karel G M Moons,[3,4] Gary S Collins[5]

Big differences with intervention research

	Intervention Research	Diagnostic/Prognostic Modeling Research
General Issues		
Primary aim	Estimation of therapeutic effect of a specific treatment	Estimation of the probability of the presence (diagnosis) or future occurrence (prognosis) based on combinations of two or more predictors
Secondary aims	Treatment effect in study subgroups	Evaluate accuracy of model predictions across subgroups, settings, or countries
Estimates of interest	(Adjusted) treatment-outcome associations	(Distribution of) individual outcome probabilities/risks; discrimination and calibration of estimated model probabilities
Association measures	Relative risk estimates: risk ratio, hazard ratio, risk difference, and odds ratio	Absolute probability or risk estimates of the outcome at interest
Study design	Randomized studies	Observational research (randomized study data sometimes also used)

The presence of heterogeneity between IPD sets may substantially affect the transportability of developed models!

Model development in IPD-MA

Need to identify whether aggregation of IPD is justifiable, and how to adjust for heterogeneity.

- **Allow for different baseline risks in each of the IPD studies**
  - Account for differences in outcome prevalence (or incidence) across studies
  - Examine between-study heterogeneity in predictor effects and prioritize inclusion of (weakly) homogeneous predictors
  - Appropriate intercept for a new study can be selected using information on outcome prevalence (or incidence)
- **Implement a framework that uses internal-external cross-validation**

Internal-external cross-validation (IECV)

Statistics in Medicine

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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

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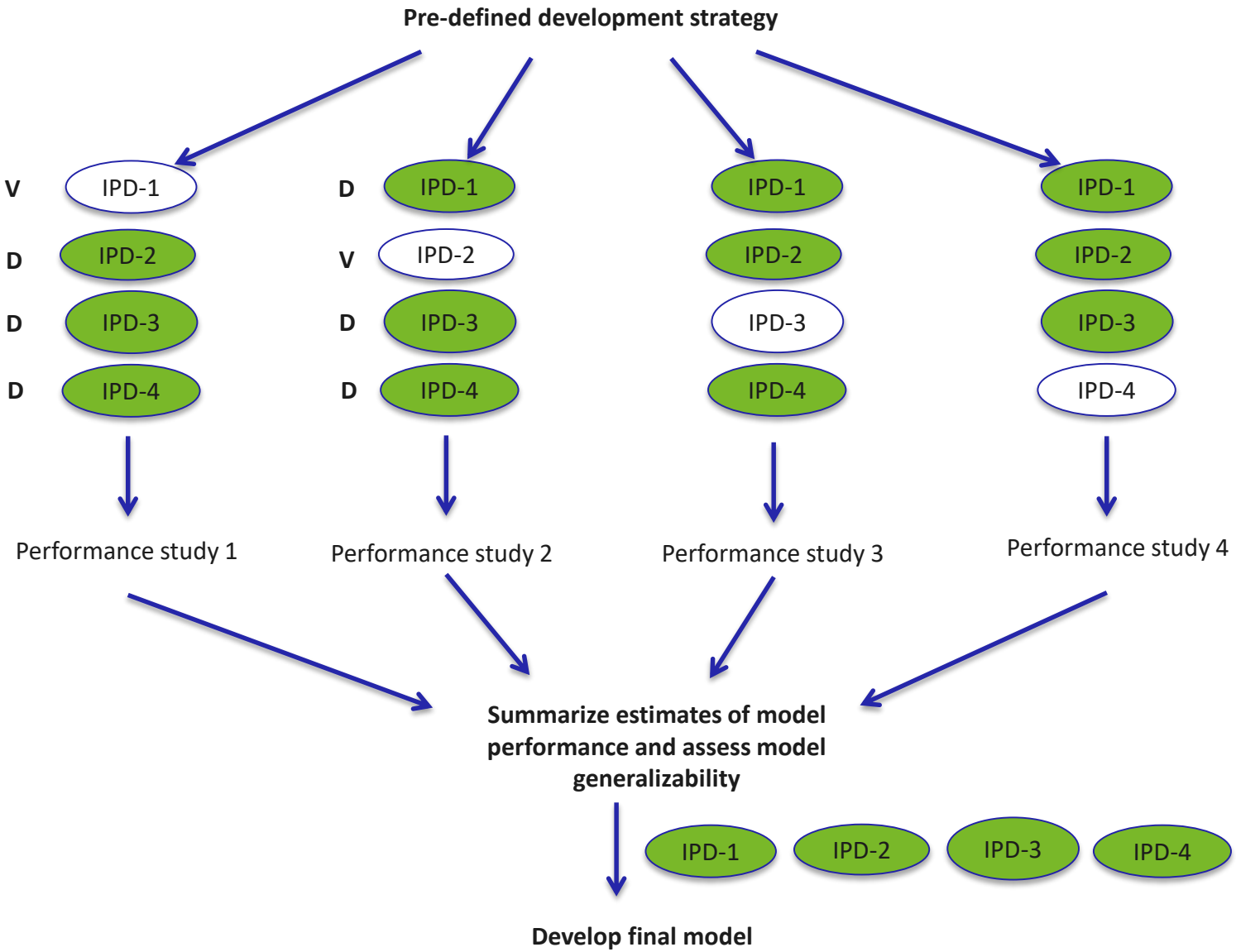
Am score 5

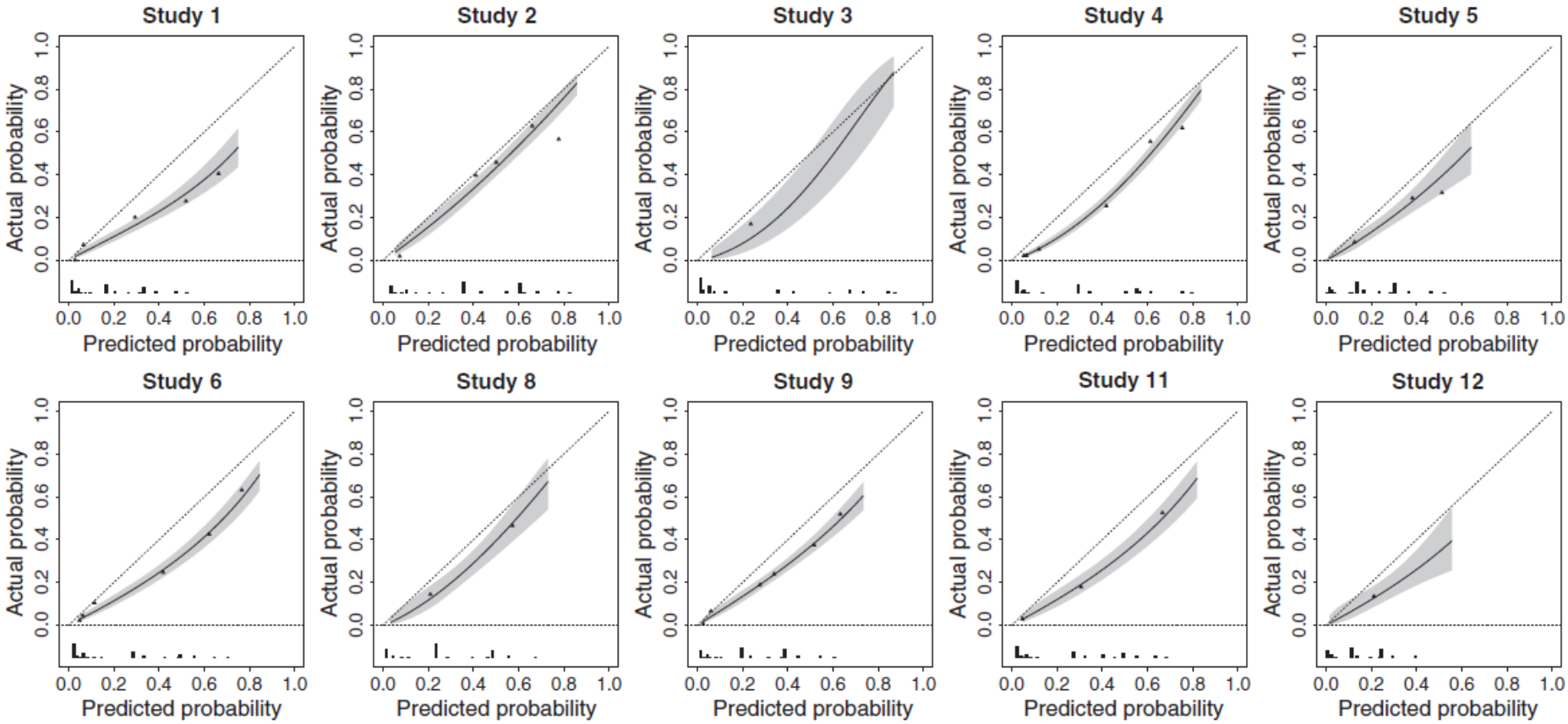
✉ Correspondence to: Thomas P. A. Debray, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Stratenum 6.131, PO Box 85500, 3508GA Utrecht, The Netherlands.
E-mail: T.Debray@umcutrecht.nl

Internal-external cross-validation (IECV)



Internal-external cross-validation (IECV)

The IECV approach allows for many external validations



Assessing model performance

Meta-analysis of performance estimates

- A ‘good’ prediction model will have
  - satisfactory performance on average
  - little or no between-study heterogeneity in performance

- Need to summarize estimates of model performance…
  - To estimate likely performance in new studies
  - To calculate probability of “good” performance
  - To evaluate sources of between-study heterogeneity

Meta-analysis of performance estimates

ELSEVIER

CrossMark

Journal of Clinical Epidemiology 69 (2016) 40–50

Journal of Clinical Epidemiology

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,*]

[a]*Public Health, Epidemiology and Biostatistics, School of Health and Population Sciences, Public Health Building, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK*

[b]*School of Mathematics, Watson Building, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK*

[c]*Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Str. 6.131, PO Box 85500, 3508 GA Utrecht, The Netherlands*

[d]*Dutch Cochrane Centre, University Medical Center Utrecht, Str. 6.131, PO Box 85500, 3508 GA Utrecht, The Netherlands*

[e]*Research Institute for Primary Care and Health Sciences, Keele University, Staffordshire ST5 5BG, UK*

[f]*Department of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands*

Accepted 8 May 2015; Published online 16 May 2015

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[1], Joie Ensor[1], Thomas PA Debray[2,3], Karel GM Moons[2,3], Richard D Riley[1]

RESEARCH METHODS AND REPORTING

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click for updates

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]

Meta-analysis of performance estimates

Compare competing modeling strategies

- Choice of predictors
- Dealing with heterogeneity
- Non-linear effects
- Interaction terms

Table 2. Joint predicted probability of "good" discrimination and calibration performance of the DVT model for each of the three implementation strategies, derived using the multivariate meta-analysis results for the C statistic and calibration slope shown in Table 1

		Joint predicted probability of meeting criteria in new population		
Calibration slope required	Minimum C statistic required	Strategy (1): Develop using logistic regression and implement with intercept estimated in external validation study	Strategy (2): Develop using logistic regression and implement with average study intercept taken from developed model	Strategy (3): Develop using logistic regression and implement with intercept taken from a study used in development data with a similar prevalence
0.9–1.1	0.70	0.027	0.037	0.037
0.8–1.2	0.70	0.146	0.158	0.156
0.9–1.1	0.65	0.427	0.413	0.409
0.8–1.2	0.65	0.728	0.712	0.707

Abbreviation: DVT, deep vein thrombosis.

Meta-analysis of performance estimates

Identify & address sources of heterogeneity

- Differences in patient spectrum
- Differences in baseline risk
- Differences in predictor effects

Facilitate tailoring of developed models!

ORIGINAL ARTICLE

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]

[a]*Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Str. 6.131, PO Box 85500, 3508GA Utrecht, The Netherlands*

[b]*Department of Public Health, Erasmus Medical Center, Rotterdam, The Netherlands*

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Further research

- Dealing with differences in variable definitions
- Assessing data quality
- Imputation of missing data
- Variable selection
- Addressing heterogeneity
- Reporting
- …