A framework for evaluating and distinguishing validity and generalization of prediction models

TPA Debray[1], H Koffijberg[1], Y Vergouwe[12], D Nieboer[2], EW Steyerberg[2], KGM Moons[1]

[1]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands
[2]Center for Medical Decision Sciences, Eramsus Medical Center Rotterdam, The Netherlands

University Medical Center Utrecht

Introduction

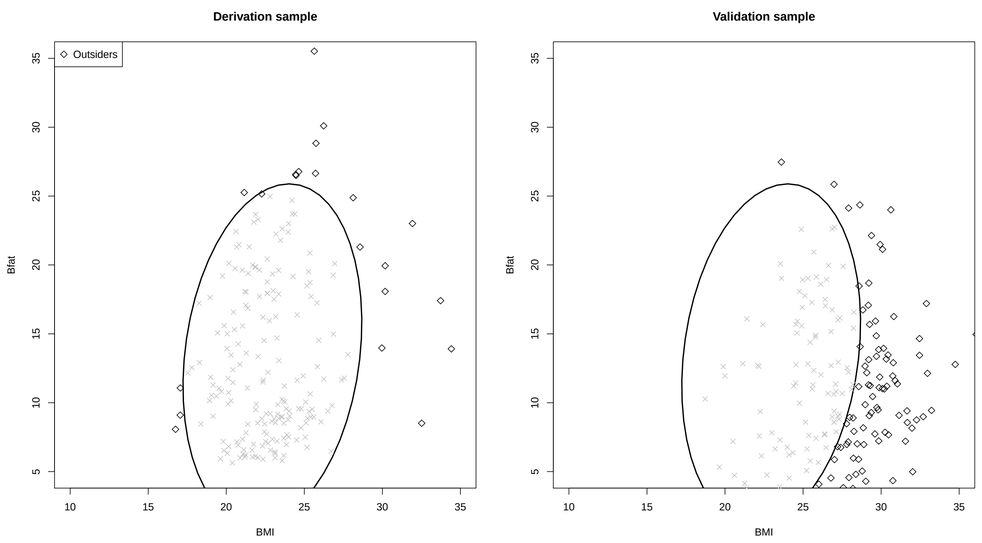
It is widely acknowledged that newly developed diagnostic or prognostic prediction models should be validated in samples with different (i.e. not included in the sample from which the model was developed) but related (i.e. similar characteristics or case mix) individuals [1]. However, criteria for 'different but related' are lacking, compromising structured model validation studies. Based on previous recommendations we describe a framework of methodological steps for analyzing and interpreting the results of prediction model validation studies, to enhance inferences about the model's generalizability across populations, clinical practices and settings.

Proposed Framework

- Extension of framework proposed by Justice *et al* [2]
- Three steps; each step may consider alternative statistics which keeps the overall structure of the framework intact.
- Gradually build the model's credibility through iterative comparison to and consistency with empirical studies as they become available

Step 1

Quantify to what extent the derivation sample and validation sample are related



- Weighted Mahalanobis distance
  - Quantify relatedness of subject characteristics
  - Compare amount of *outsiders*: subjects with atypical combination of characteristics
- Spread of the linear predictor
  - Identify case mix homogeneity
  - Reveal potential for good discrimination [3]
- Mean of the linear predictor
  - Identify case mix severity
  - Reveal potential for good calibration-in-the-large

Step 2

Assessment of the model performance in the validation sample

- Discrimination
  - Apparent and case mix corrected concordance (c-) statistic
  - Does model discrimination deteriorates due to differences in case mix heterogeneity?
- Calibration
  - Calibration-in-the-large and calibration slope
  - Summary measures for validity of predictive mechanisms

Step 3

Inferences on the model's generalizability

- Distinguish between reproducibility (requires the model to perform well in individuals who were not included during its derivation but who are from the same underlying population) and transportability (requires the model to perform well in individuals from a different but plausibly related population)
- Reproducibility is good (or poor) if derivation and validation sample are similar and the performance is good (or poor) in the validation sample.
- Transportability is good (or poor) if derivation and validation sample have a different case mix and the performance remains adequate (or deteriorates).

Case Study

- Prediction of Deep Vein Thrombosis (DVT) in patients with suspected DVT
- Prediction model with 7 patient characteristics and the result of a D-dimer test
- Individual participant data available from the derivation and 3 validation populations

	Derivation	Validation 1	Validation 2	Validation 3
N	**1,295**	791	1,028	1,756
Incidence DVT	**22%**	16%	13%	23%
Male gender	**36%**	38%	37%	37%
Oral contraceptive use	**10%**	10%	10%	5%
Presence of malignancy	**6%**	5%	5%	13%
Recent surgery	**14%**	13%	8%	11%
Absence of leg trauma	**85%**	82%	72%	85%
Vein distension	**20%**	20%	15%	16%
Calf difference $\geq$ 3cm	**43%**	41%	30%	24%
D-dimer abnormal	**70%**	72%	46%	52%
Outsiders	**10%**	9%	14%	9%
SD (LP)	**1.68**	1.65	1.79	1.81
Mean (LP)	**-1.93**	-1.88	-2.97	-2.70
c statistic	**0.79**	0.77	0.82	0.86
c statistic (case mix corrected)	**0.79**	0.79	0.80	0.84
Calibration-in-the-large	**0.00**	-0.48	0.02	0.73
Calibration slope	**1.00**	0.90	0.80	1.02

Table: Baseline table for 4 primary care DVT datasets.

Results

- Validation 1
  - Step 1: similar case mix
  - Step 2: predictive mechanisms not comprised
  - Step 3: prediction model reproduces adequately
  - Model intercept should be updated when applied in new subjects
- Validation 2
  - Step 1: different (and more heterogeneous) case mix
  - Step 2: predictive mechanisms somewhat comprised
  - Step 3: prediction model transports moderately
  - Model predictions remain accurate on the population level
- Validation 3
  - Step 1: similar (although more heterogeneous) case mix
  - Step 2: predictive mechanisms not comprised
  - Step 3: prediction model reproduces adequately
  - Model intercept should be updated when applied in new subjects

Summary

- Framework for evaluating the generalizability of a prediction model
- Interpret model performance according to differences in case mix
- Distinguish between reproducibility and transportability
- Quantify prediction accuracy
- Pin-point inadequate predictive mechanisms

References

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Contact

Thomas Debray, MSc
Julius Center for Health Sciences and Primary Care
University Medical Center Utrecht
Tel: +31 (0) 88 75 68640
Email: t.debray@umcutrecht.nl

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