**PROBAST**

Study:

Predicting the Risk of Developing Type 1 Diabetes Using a One-Week Continuous Glucose Monitoring Home Test With Classification Enhanced by Machine-Learning: An Exploratory Study

Step 2: Type of prediction study

**Is the study a diagnostic or a prognostic study?**

Diagnostic

**Is the study a development only, development and validation or validation only study?**

Development only

**What is the model of interest?**

Support vector machine

**What is the outcome of interest?**

Prediction of Diabetes risk

Step 3: Assess risk of bias

**Domain 1: Participants**

**Describe the sources of data and criteria for participant selection**

The study enrolled healthy relatives of individuals with T1D with zero and two or more islet Ab, who were recruited from the TrialNet Pathway to Prevention study (https://www.trialnet.org/our-research/risk-screening). Participants were those aged 12 to 45 years and who had a brother, sister, child, or parent with T1D, or were individuals aged 12 to 20 years and who had a cousin, aunt, uncle, niece, nephew, half brother, half sister, or grandparent with T1D. Among the major exclusion criteria were diagnosis of diabetes, a relevant medical condition, or being treated with medications that might interfere with the study.

**1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?**

Y

**1.2 Were all inclusions and exclusions of participants appropriate?**

N

**Risk of bias introduced by selection of participants:**

High

**Rationale of bias rating**

Criteria target participants at risk of developing T1D. Hard to generalize to general population.

**Domain 2: Predictors**

**List and describe predictors included in the final model, e.g. definition and timing of assessment**

After the hospital visit, the participants were given a blinded Dexcom G4 Platinum CGM, which they wore for the next seven days at home. The CGM traces from the participants were collected and glycemic features/metrics were extracted and computed.

**2.1 Were predictors defined and assessed in a similar way for all participants?**

Y

**2.2 Were predictor assessments made without knowledge of outcome data?**

Y

**2.3 Are all predictors available at the time the model intended to be used?**

Y

**Risk of bias introduced by predictors or their assessment**

Low

**Rationale of bias rating**

Predictors are assessed similar for every patient due to same CGM device.

**Domain 3: Outcome**

**Describe the outcome, how it was defined and determined, and the time interval between predictor assessment and outcome determination:**

Diabetes disease risk as defined by amount of participants’ autoantibody status (0 vs 2+) at time of study inclusion

**3.1 Was the outcome determined appropriately?**

Y

**3.2 Was a pre-specified or standard outcome definition used?**

PN

**3.3 Were predictors excluded from the outcome definition?**

Y

**3.4 Was the outcome defined and determined in a similar way for all participants?**

Y

**3.5 Was the outcome determined without knowledge of predictor information?**

Y

**3.6 Was the time interval between predictor assessment and outcome determination appropriate?**

U

**Risk of bias introduced by the outcome or its determination**

Unclear

**Rationale of bias rating**

Unclear exactly how and when the autoantibody status was defined. If this was done at start of study inclusion there is the risk that the amount of autoantibodies changed. Also relying only on autoantibodies may not be reliable for estimating T1D disease risk.

**Domain 4: Analysis**

**Describe number of participants, number of candidate predictors, outcome events and events per candidate predictor**

A total of 42 participants completed the CGM study and were included in the analysis. Twenty-one participants had zero (low-risk group) and the other 21 participants had two or more islet Ab (high-risk group).

**Describe how the model was developed, predictor selection and risk group definition**

Recursive Feature Elimination with Cross-Validation (RFECV) was used as the feature selection method for this analysis to address the dimensionality issues.

Four different classification models were used to develop an Ab classifier and define the best classifier model, namely, linear discriminant analysis (LDA), SVM, LR, and K-nearest neighbors (KNN).

**Describe whether and how the model was validated, either internally (cross validation, random split sample) or externally (e.g. temporal validation, geographical validation, different setting, different type of participants)**

A 10-fold cross-validation technique was implemented in this analysis.

**Describe the performance measures of the model, e.g. calibration, discrimination, classification, net benefit, and whether they were adjusted for optimism**

AUC

**Describe any participants who were excluded from the analysis**

Four participants were excluded from the analysis (three participants from the negative group, low risk, and one participant from ≥2 Ab group, high risk): three of them had breakfast after all SLMM, and one had breakfast 30 minutes before all SLMM.

**Describe missing data on predictors and outcomes as well as methods used for missing data**

Not described

**4.1 Were there a reasonable number of participants with the outcome?**

N

**4.2 Were continuous and categorical predictors handled appropriately?**

Y

**4.3 Were all enrolled participants included in the analysis?**

N

**4.4 Were participants with missing data handled appropriately?**

U

**4.5 Was selection of predictors based on univariable analysis avoided?**

Y

**4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of controls)**

**accounted for appropriately?**

Y

**4.7 Were relevant model performance measures evaluated appropriately?**

Y

**4.8 Were model overfitting and optimism in model performance accounted for?**

Y

**4.9 Do predictors and their assigned weights in the final model correspond to the results**

**from multivariable analysis?**

Y

**Risk of bias introduced by the analysis**

High

**Rationale of bias rating**

Small amount of outcomes. Some patients were excluded.

**Overall Risk of bias**

High