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# Supplementary Material

**Article Title:** A New Prediction Model for Evaluating Treatment-Resistant Depression

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## List of Supplementary Material for the article



## Disclaimer

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| Baseline Characteristics | Study Sample (n=480) | | *Excluded Sample* (n=317) |
|---|---|---|---|
| | Training Sample (n=400) | Test Sample (n=80) | |
| Resistance/Non-Resistance (n) | 153 / 247 | 30 / 50 | 114 / 203 |
| % Resistance | 38% | 37.5% | 36% |
| Remission/Non-Remission | 118/282 | 22/58 | 92/225 |
| % Remission | 29.5% | 27.5% | 29% |
| Mean Age (SD) | 49.74 (14.49) | 49.02 (13.26) | 49.64 (13.79) |
| Sex (% Female) | 67.75% | 72.5% | 69.89% |
| Ethnicity (% Caucasian) | 98% | 100% | 99% |

**Supplementary eTable 1.** Baseline characteristics of the study sample and the excluded sample. For the study sample, distinctive characteristics for the training sample (n=400) and the test sample (n=80) for the machine learning classification algorithm are provided. None of the three patient samples significantly differed from each other.

| Predictor | Type & Levels | **Resistance** (n=183) *vs* **Non-Resistance** (n=297) | **Remission** (n=140) *vs* **Non-Remission** (n=340)) |
|---|---|---|---|
| **Sociodemographic Predictors** | | | |
| **Age** | Metric *(mean)* | 49.0 / 49.9 | 50.2 / 49.0 |
| **Gender** | Binomial *(female)* | 125 / 204 | 92 / 237 |
| **Ethnicity** | Binomial *(caucasian)* | 179 / 293 | 138 /334 |
| **Psychosocial Predictors** | | | |
| **Occupation** | High<br>Medium<br>Low<br>Other | 22 / 44<br>35 / 115<br>26 / 51<br>70 / 87 | 23 / 43<br>59 / 121<br>23 / 54<br>35 / 122 |
| **Education** | Legal School<br>No Legal School<br>Secondary Inferior<br>Secondary Superior<br>University | 49 / 64<br>11 / 32<br>47 / 64<br>37 / 64<br>39 / 73 | 82 / 31<br>16 / 27<br>75 / 36<br>24 / 77<br>33 / 79 |
| **Marital Status** | Single<br>Living With<br>Married<br>Divorced<br>Widowed | 30 / 50<br>9 / 16<br>106 / 163<br>26 / 40<br>12 / 28 | 23 / 57<br>7 / 18<br>84 / 185<br>15 / 51<br>11 / 29 |
| **Number of Children** | Metric *(mean)* | 1.6 / 1.9 | 2.2 / 1.6 |
| **Cinical Features** | | | |
| **Severity** | Moderate<br>Severe<br>Severe with Psychsis | 120 / 151<br>60 / 128<br>3 / 18 | 74 / 197<br>53 / 135<br>13 / 8 |
| **Suicididality** | Binomial *(yes)* | 41 / 150 | 81 / 110 |
| **Melancholia** | Binomial *(yes)* | 35 / 109 | 41 / 103 |
| **Psychotic Features currently** | Binomial *(yes)* | 23 / 34 | 16 / 41 |
| **Psychotic Features lifetime** | Binomial *(yes)* | 14 / 42 | 26 / 30 |
| **Change of Appetite** | Binomial *(yes)* | 129 / 227 | 114 / 242 |
| **Change of Sleep** | Binomial *(yes)* | 156 / 232 | 114 / 274 |
| **Unrest** | Binomial *(yes)* | 162 / 227 | 121 / 268 |
| **Fatigue** | Binomial *(yes)* | 175 / 281 | 136 / 320 |

| | | | |
|---|---|---|---|
| **Feelings of Guilt** | Binomial *(yes)* | 142 / 203 | 110 / 235 |
| **Decision Making impaired** | Binomial *(yes)* | 172 / 263 | 130 / 305 |
| **Autoaggressive Thoughts** | Binomial *(yes)* | 121 / 181 | 95 / 207 |
| **Social Disfunctioning** | Binomial *(yes)* | 178 / 286 | 136 / 328 |
| **Personal MDD History** | | | |
| **Number of MDE** | Metric *(mean)* | 4.4 / 4.6 | 4.2 / 4.9 |
| **Timespan 1st to last MDE** | Metric *(mean)* | 12.2 / 11.2 | 11.8 / 11.5 |
| **Age first AD** | Metric *(mean)* | 39.3 / 40.4 | 40.8 / 39.6 |
| **Response 1st AD** | Good<br>Mediocre<br>Little | 88 / 192<br>65 / 68<br>30 / 37 | 104 / 176<br>21 / 112<br>15 / 52 |
| **Subsyndromal Bipolarity** | Binomial *(yes)* | 45 / 86 | 35 / 96 |
| **Axis II Comorbidity** | | | |
| **PD** | Binomial *(yes)* | 53 / 39 | 10 / 82 |
| **Agoraphobia** | Binomial *(yes)* | 17 / 13 | 3 / 27 |
| **Social Phobia** | Binomial *(yes)* | 24 / 19 | 5 / 38 |
| **OCD** | Binomial *(yes)* | 6 / 7 | 1 / 12 |
| **PTSD** | Binomial *(yes)* | 9 / 6 | 2 / 13 |
| **GAD** | Binomial *(yes)* | 18 / 10 | 2 / 26 |
| Addiction & Substance Use | | | |
| **History of Drug Abuse** | Binomial *(yes)* | 12 / 18 | 6 / 24 |
| **Smoking** | Binomial *(yes)* | 71 / 107 | 47 / 131 |
| **Alcohol Abuse** | Binomial *(yes)* | 7 / 15 | 8 / 14 |
| **Alcohol Addiction** | Binomial *(yes)* | 9 / 10 | 2 / 17 |
| **Any Substance Use** | Binomial *(yes)* | 11 / 16 | 6 / 21 |
| **Drug Abuse** | Binomial *(yes)* | 6 / 5 | 2 / 9 |
| **Drug Addiction** | Binomial *(yes)* | 7 / 2 | 1 / 8 |
| **Axis III Comorbidities** | | | |
| **Diabetes** | Binomial *(yes)* | 25 / 62 | 49 / 38 |
| **Thyroid Disorder** | Binomial *(yes)* | 22 / 86 | 56 / 52 |
| **Family History** | | | |
| **MDD 1° Relatives** | Binomial *(yes)* | 78 / 116 | 59 / 135 |

| | | | |
|---|---|---|---|
| **MDD 2° Relatives** | Binomial *(yes)* | 30 / 46 | 24 / 52 |
| **BD 1° Relatives** | Binomial *(yes)* | 12 / 26 | 13 / 25 |
| **BD 2° Relatives** | Binomial *(yes)* | 7 / 9 | 5 / 11 |
| **Number of Relatives MDD** | Metric *(mean)* | 0.6 / 0.6 | 0.6 / 0.6 |
| **Number of Relatives BD** | Metric *(mean)* | 0.1 / 0.1 | 0.1 / 0.1 |
| **Other Predictors** | | | |
| **In- or Outpatient** | Binomial *(inpatient)* | 116 / 156 | 64 / 218 |
| **Psychotherapie** | Binomial *(yes)* | 39 / 73 | 28 / 84 |

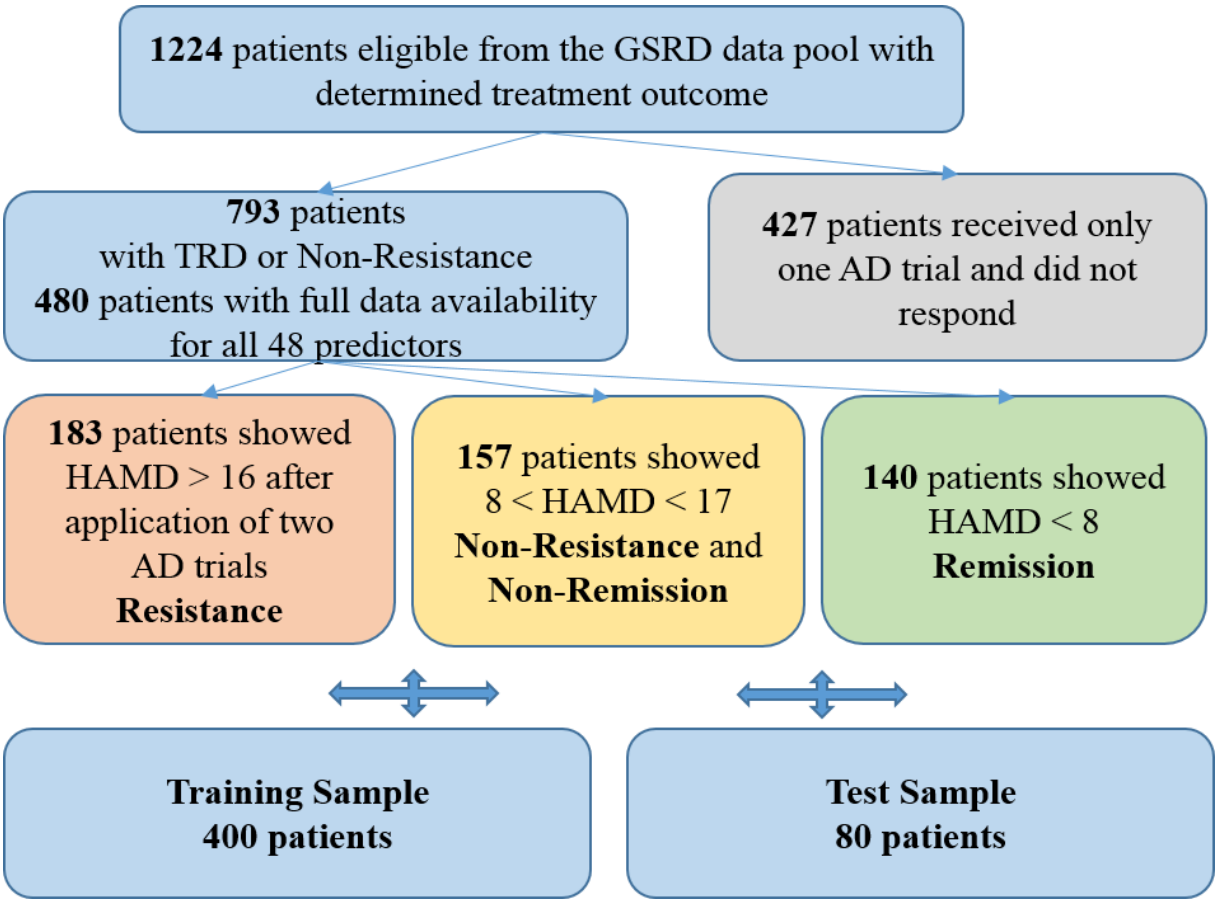
**Supplementary eTable 2.** List of all 48 predictors featured in the analysis ordered by groups. The second row explains the quality of the predictor and provides predictor levels. The third row shows means for the predictors among resistant and non-resistant patients. The last row shows means for the predictors among patients showing remission and non-remission. Abbreviations: MDD = major depressive disorder; MDE = major depressive episode; BD = bipolar disorder; AD = antidepressant; PTSD = posttraumatic stress disorder; GAD = generalized anxiety disorder; OCD = obstructive compulsive disorder.

| **Predictor** | | **Resistance** *(n=183)* Vs **Non-Resistance** *(n=297)* | **p =** | **Remission** *(n=140)* Vs **Non-Remission** *(n=340)* | **p =** |
|---|---|---|---|---|---|
| Thyroid Disorder | *(no)* | 161 / 211 | **<0.0001** | 84 / 288 | **>0.0001** |
| Panic Disorder | *(no)* | 130 / 258 | **<0.0001** | 130 / 258 | **>0.0001** |
| Suicidality | *(yes)* | 41 / 150 | **<0.0001** | 81 / 110 | **0.0001** |
| In- or Outpatient | *(inpatient)* | 116 / 156 | **0.0029** | 64 / 218 | **0.0002** |
| Response to 1st AD | *(good)*<br>*(mediocre)*<br>*(little)* | 88 / 192<br>65 / 68<br>30 / 37 | **0.0119** | 104 / 176<br>21 / 112<br>15 / 15 | **0.0006** |
| Number of Children | *(mean)* | 1.6 / 1.9 | **0.0339** | 2.2 / 1.6 | **0.0016** |
| Melancholia | *(no)* | 35 / 109 | **0.0001** | 41 / 103 | *n.s.* |
| Occupation | *(high)*<br>*(medium)*<br>*(low)*<br>*(other)* | 22 / 44<br>65 / 115<br>26 / 51<br>70 / 87 | *n.s.* | 23 / 43<br>53 / 97<br>59 / 121<br>35 / 122 | **0.0382** |
| Diabetes | *(no)* | 168 / 235 | *n.s.* | 91 / 312 | **0.0027** |

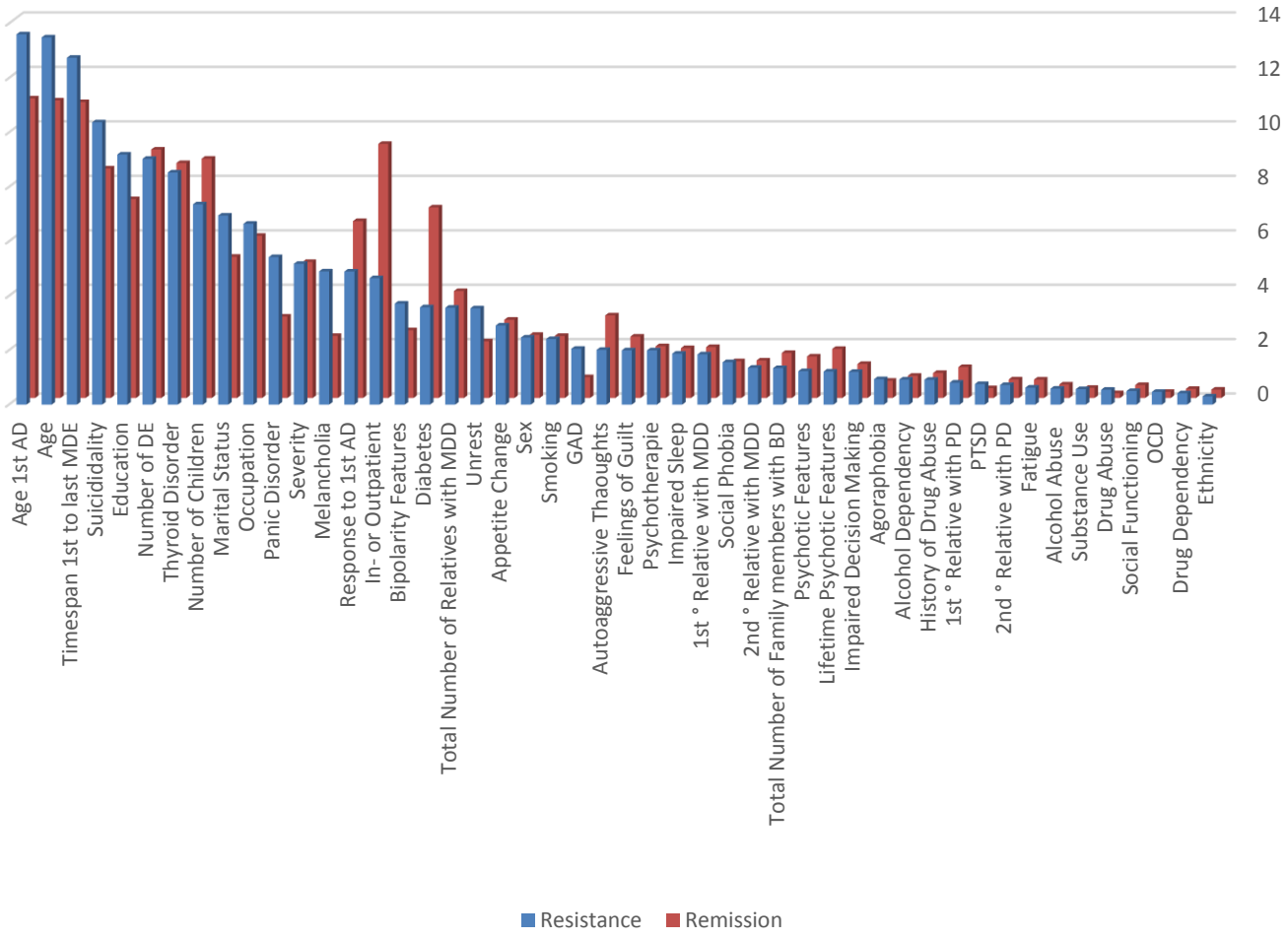
**Supplementary eTable 3.** Logistic regression model using the 15 most important factors for remission and resistance according to RandomForests. Predictors are ordered by p-value, Only predictors, that reached significance for either remission or resistance, are listed below. In the second and forth row, the counts for predictor levels are listed for remission and non-remission as well as resistance and non-resistance. For metric predictors, the means for are stated. Suicidality, thyroid disorder and panic disorder showed the strongest association, followed by in- or outpatient status, the response to the 1st AD administered and number of children. Melancholic depression was only significant for resistance while occupation status and diabetes were only relevant for remission. Age, education, severity, number of major depressive episodes, marital status, timespan between 1st and last depressive episode and age of 1st antidepressant treatment did not show significant associations and are not listed. Abbreviations: p = p-value for chi-square test, AD = antidepressant.

| Set | Treatment Resistance | Remission |
|---|---|---|
| **Top 5** | Age 1st AD, Timespan, Age, Suicidality, Education | Age 1st AD, Timespan, Age, In- or Outpatient, Number of MDE |
| **Top 10** | + Number of MDE, Thyroid Disorder, Number of Children, Marital Status, Occupation | + Thyroid Disorder, Number of Children, Suicidality, Diabetes, Education |
| **Top 15** | + Severity, Melancholia, Response to 1st AD, Panic Disorder, In- or Outpatient | + Response to 1st AD, Occupation, Marital Status, Severity, Total Number of Relatives with MDD |
| **Top25** | + Subsyndromal Bipolarity, Total Number of Relatives with MDD, Unrest, Diabetes, Appetite Change, Smoking, GAD, Autoaggressive Thoughts, Feelings of Guilt, Psychotherapy | + Panic Disorder, Melancholia, Total Number of Relatives with PD, Impaired Sleep, Appetite Change, Smoking, Lifetime Psychotic Features, Autoaggressive Thoughts, Feelings of Guilt, Psychotherapy |
| **Top 35** | + Sex, Impaired Sleep, ° Relatives with MDD, Social Phobia, 2° Relatives with MDD, Lifetime Psychotic Features, Current Psychotic Features, Impaired Decision Making, Total Number of Relatives with PD, Agoraphobia | + Sex, ° Relatives with MDD, Social Phobia, 2° Relatives with MDD, Current Psychotic Features, Impaired Decision Making, Agoraphobia, GAD, Subsyndromal Bipolarity, Unrest |
| **All 48** | + Alcohol Dependency, History of Drug Abuse, 1° Relatives with PD, PTSD, 2° Relatives with PD, Fatigue, Alcohol Abuse, Substance Use, Drug Abuse, Social Functioning, OCD, Drug Dependency, Ethnicity | + Alcohol Dependency, History of Drug Abuse, 1° Relatives with PD, PTSD, 2° Relatives with PD, Fatigue, Alcohol Abuse, Substance Use, Drug Abuse, Social Functioning, OCD, Drug Dependency, Ethnicity |

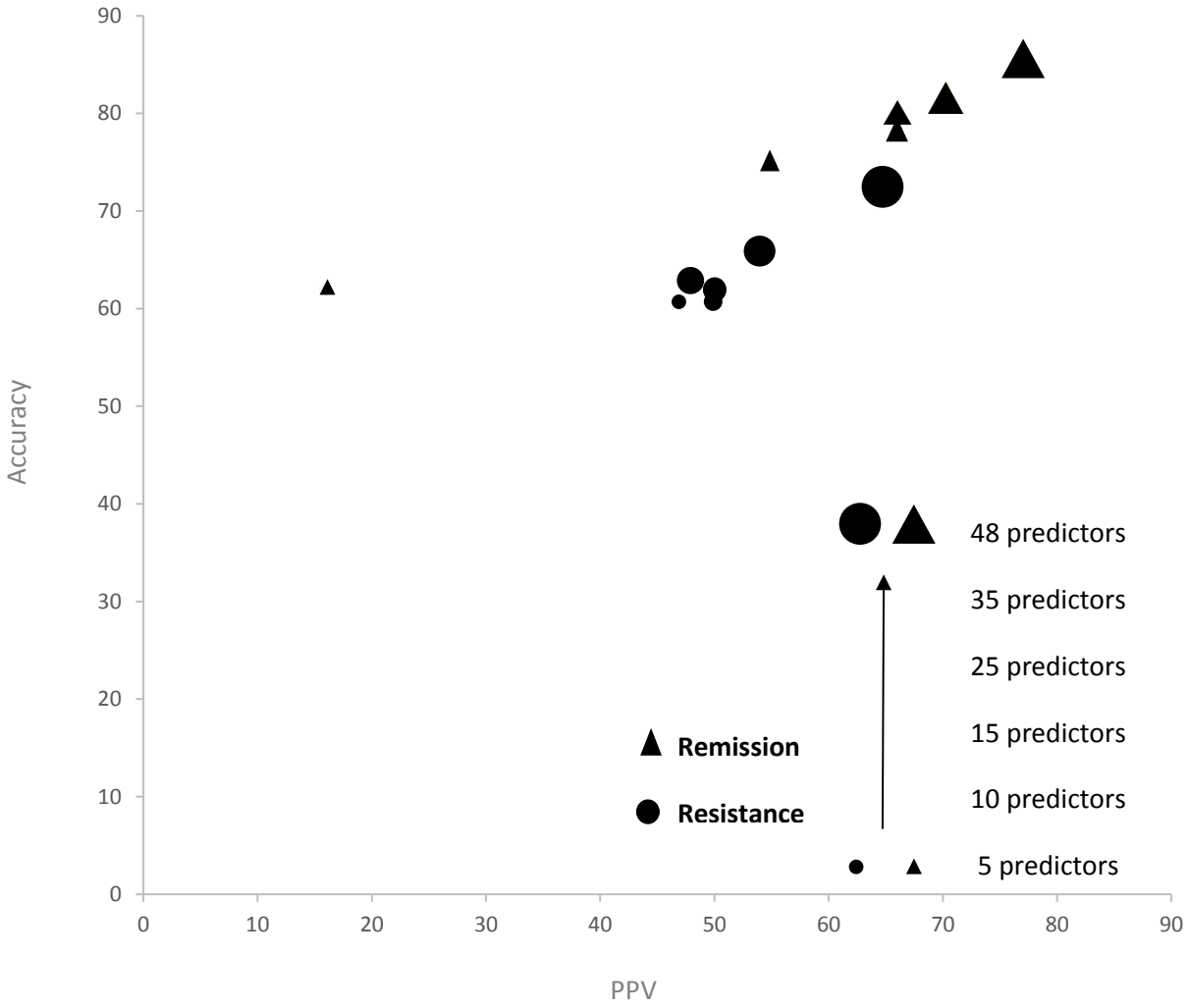
**Supplementary eTable 4.** Sets of predictors used for predicting resistance and remission respectively. Predictors were ordered by their importance measures for the prediction model.




**Supplementary eFigure 1.** Patient allocation diagram. 1224 patients of the GSRD data pool with determined treatment outcome were available. 427 of these were excluded for being non-responders indicating that they had received only one antidepressant trial to which they did not respond. Of the remaining 793 patients 480 showed full data availability, 183 of those were resistant to two antidepressant trials and 140 showed remission while 157 patients were not resistant but did not show remission. Subsequently these 480 patients were randomly assigned to the training and the test sample for the RandomForest algorithm on a quota of 5:1. Abbreviations: TRD = treatment resistant depression, HAMD = 17-item Hamilton Depression Scale; GSRD = European Group for the Study of Resistant Depression; AD = antidepressant.




**Supplementary eFigure 2.** Importance values measured by mean decrease in Gini for all predictors, listed on the x-axis starting with the least important. Results are shown for remission and for resistance. Mean decrease in Gini is shown on the y-axis. A higher value indicates higher usefulness for classification decisions in the prediction model. Abbreviations: MDD = major depressive disorder; MDE = depressive episode; BD = bipolar disorder; AD = antidepressant; PTSD = postraumatic stress disorder; GAD = generalized anxiety disorder; OCD = obstructive compulsive disorder.




**Supplementary eFigure 3.** Accuracy and negative predictive value (NPV) for the different sets of predictors. The accuracy is illustrated on the y-axis and the PPV on the x-axis. Using all 48 predictors enabled an accuracy of 0.737 for predicting resistance and 0.825 for remission. Thereby two thirds of patients predicted to stay resistant and three quarters of patients predicted to show remission can be expected to actually do so. Reducing the number of predictors subsequently weakens the performance of the prediction model and using only the 5 most important predictors leads to an accuracy of 0.612 for resistance and 0.7 for remission and about half of the predictions for resistance and most (0.84) of the predictions for remissions are wrong.