

# Title: Predictors of diagnostic transition from major depressive disorder to bipolar disorder: a retrospective observational network study

PRESENTER: Jenna Reys

**AIM:** To develop and externally validate a model that can predict which patients newly diagnosed with major depressive disorder are misdiagnosed and will later be diagnosed with bipolar disorder.

**BACKGROUND:** Bipolar disorder (BD) is a chronic debilitating psychiatric condition characterized by recurrent episodes of mania and depression. About 40% of BD patients are first diagnosed with major depressive disorder (MDD), and there are high prospective diagnosis conversion rates of MDD to BD (20-year rate of 25%<sup>1</sup> and annual rate of 0.8%-3.9%<sup>2,3</sup>). Thus, it is debatable whether MDD is an independent disorder co-occurring in subjects with BD, or it is simply an earlier stage of BD<sup>4</sup>.

**METHODS:** We focus on the prediction problem: In patients newly diagnosed with MDD, predict the risk of being diagnosed with BD 1 day until 365 days after the MDD diagnosis.

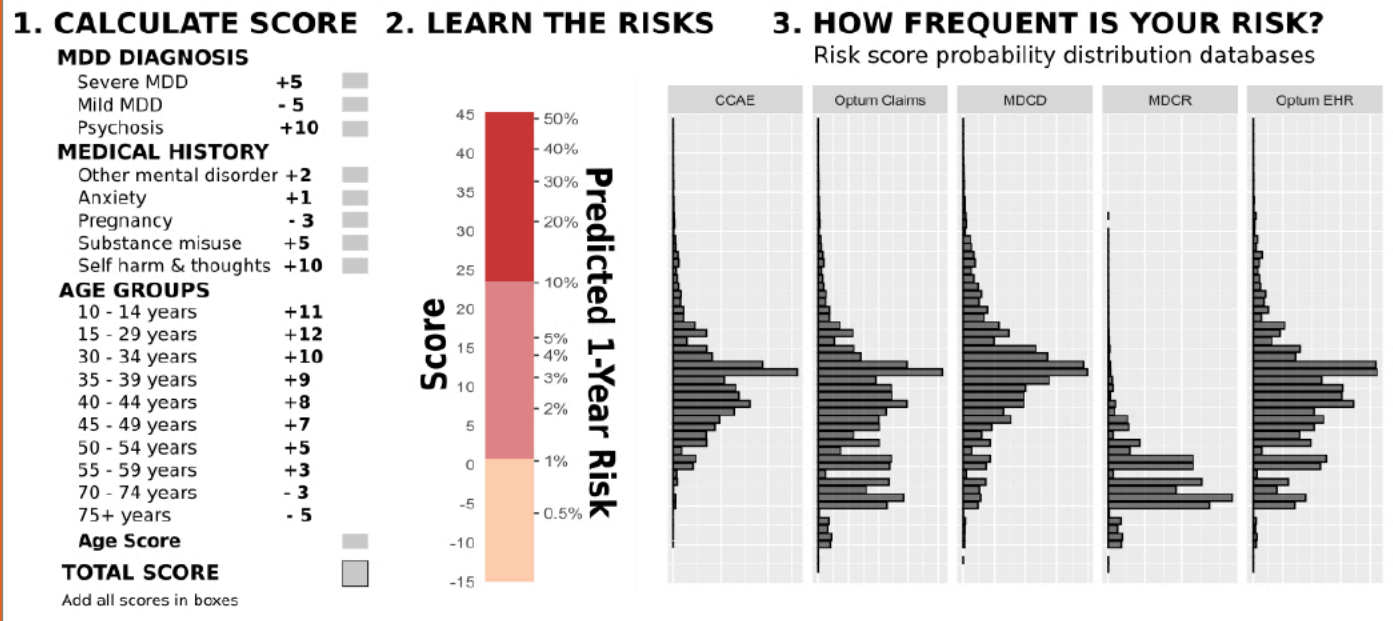
We developed data-driven models using the OHDSI PatientLevelPrediction package as follows: We used data prior to the MDD diagnosis to construct features and trained a LASSO logistic regression model using cross validation to identify the optimal hyper-parameter using 75% of the data. The features consisted of age/gender demographics and MDD diagnosis month in addition to binary indicators (value of 1 or 0) for every diagnoses, drug exposures, and procedures concept id recorded for any patient diagnosed with MDD. The remaining 25% data were used to evaluate the internal validation performances. Data-driven models were developed in CCAE, MDCR, MDCC, Optum Claims and Optum EHR.

After inspecting the data-driven models across the five databases, a simple model was derived by i) a subject matter expert inspecting the predictors and assigning broad labels for predictors considered to indicate the same medical problem (i.e. alcohol abuse and opioid dependence were labeled as "substance misuse"); ii) definitions for each 'broad' label predictor were developed (complete predictor phenotypes), iii) logistic regression models using these predictor phenotypes, age groups (60-69 as reference) and gender were trained, iv) these new models were inspected and predictors with inconsistent directionality across datasets were excluded; v) the remaining predictor's coefficients across the 5 database were averaged, multiplied by 10, and rounded to the nearest integer to create an easily computable score.

We externally validated the simple model across the OHDSI network. We calculated the discrimination in terms of area under the receiver operating characteristic (AUROC) curve. In addition, we investigated the 10-year 'BD free survival' as a function of our simple model predicted 1-year conversion risk.

## We were able to use a data-driven approach across multiple datasets to identify nine key predictors of MDD to BD conversion.

### Our model may be used to identify MDD patients who are at greatest risk for converting to BD



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**DATABASES:**

**Development:** IBM MarketScan® Commercial Database (CCAE), IBM MarketScan® Medicare Supplemental Database (MDCR), IBM MarketScan® Multi-State Medicaid Database (MDCC), Optum® de-identified Electronic Health Record Dataset (EHR), and Optum® De-identified Clinformatics Data Mart Database

**Validation:** Columbia University (CUIMC), Ajou University (AUSOM), Stanford University (STARR), IQVIA, and Japan Medical Data Center database (JMDC), Veterans Health Administration (US EMR)

**RESULTS:**

	AUC	Target size	Outcome count	Outcome %
CCAE	69.03	677233	24325	3.592
MDCR	63.29	46200	591	1.279
MDCC	66.16	253811	15789	6.221
Optum claims	74.49	520406	14297	2.747
Optum EHR	71.63	1118954	24468	2.187

Table 1. Sizes and discriminative perform of simple model on datasets used to develop the model.

	AUC	Target size	Outcome count	Outcome %
CUIMC (US EMR)	57.04	5611	457	8.145
STARR (US EMR)	64.59	27266	290	1.064
AUSOM (Korean EHR)	78.5	2,570	30	1.17
IQVIA AMB (US EMR)	69.09	148343	1548	1.044
IQVIA Belgium (Belgium EHR)	75.7	667	7	1.050
IQVIA DAGER (German EHR)	62.77	127353	315	0.247
IQVIA DAFR (French EHR)	61.54	1910	17	0.890
JMDC (Japanese claims)	61.02	1303	67	5.142
US VA (US EMR)	67	359,449	9,246	2.57

Table 2. Sizes and discriminative perform of simple model on external datasets (not used to develop the model).

The younger patient age, the higher severity of initial depressive episode, as well as the presence of psychotic features and anxiety during the index depression are predictive of MDD diagnostic transition to BD within one year. The older age (over 75), mild baseline depression, and pregnancy are predictors on a lower MDD-BD transition risk within one year.

**IMPORTANT LEARNINGS:**

We were able to use a data-driven approach across multiple datasets to identify nine key predictors of MDD to BD conversion.

The simple model obtained an AUROC ~ 0.60-0.70 across a range of databases in Europe, the US and Asia.

Our model may be used to identify MDD patients who are at greatest risk for converting to BD using the data on or prior to the visit where they are initially diagnosed with MDD.



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