Appendix B. Model Validation

To ensure that SiMMDep was functioning correctly and producing results as expected, we carried out several forms of model validation (face, internal, cross-validity) and numerous checks within each facet.

Face validity

Table B1. Face validity assessments in the SiMMDep model

Module	Item
Disease progression	The number of patients who are alive at the beginning of each year was equal to the sum of patients in different health states
Cost & QALY	Total cost is equal to the sum of components Setting utility and disutility to zero, resulted in zero QALY Setting utility to one and disutility to zero, resulted in equal LY and QALY Setting discount and mortality to zero, resulted in LY to be equal to the number of patients at the beginning of the year Increasing the value of health utility index values resulted in higher QALY
Mortality	Setting mortality risk ratios to 1.00 and ensuring mortality matched the background mortality by age and sex

Internal validity

We conducted internal validation in 1) patient and 2) cohort base levels. In the patient level, we followed patients with different characteristics individually and assessed whether the model assigned the correct input parameters to them (e.g., health utility index values, costs, mortality probability). At the cohort level, we extracted different outcomes from the model and examined whether the model produced results that matched the patterns observed in input data sources.

Table B2. Internal validity assessments in the SiMMDep model

Module	Item	Target for Validation	Note
Entry Cohort	Number of newly diagnosed and prevalent patients (eligible for pharmacotherapy) entering model	MSP[1], DAD[2] (2015-2020)	Slightly higher than the target from 2020, considering the population growth
Demographic	The number of patients with	Ferrari et al., 2013[3] and	

different MDD severity was consistent with the input parameters	Kessing et al., 2008[4]
Distribution of current age of entry cohort by sex (newly diagnosed and prevalent patients)	MSP[1], DAD[2], and MSP Consolidation File[5] (2015-2020)
Distribution of age of onset of prevalent patients in the entry cohort by sex	MSP[1], DAD[2], and MSP Consolidation File[5] (2015-2020)
Ratio of female patients in the incident and prevalent cohort	MSP[1], DAD[2], and MSP Consolidation File[5] (2015-2020)
Ratio of MDD patients (prevalent and newly diagnosed) with psychiatric comorbidities at the entry cohort	MSP[1] and DAD[2] (2015-2020)
Ratio of prevalent MDD patients with a history of previous severe MDD episodes	Kessing et al., 2008[4]
Distribution of geographic ancestry	Statistics Canada[6]
Distribution of metabolizer phenotypes (CYP2C19) by geographic ancestry	Bousman et. al, 2021[7] and PharmGKB[8-10]
Distribution of metabolizer phenotypes (CYP2D6) by geographic ancestry	Bousman et. al, 2021[7] and PharmGKB[8-10]

Treatment and adverse effect module	Distribution of treatment trials for prevalent MDD patients at the time of entering model	PharmaNet[11] (2015-2020)
	Medication selection based on CYP2C19 metabolizer phenotypes	Sequence2Script tool[12]
	Medication selection based on CYP2D6 metabolizer phenotypes	Sequence2Script tool[12]
	Distribution of medications for newly diagnosed and prevalent patients at the first medication trial	PharmaNet[11] (2015-2020)
	Distribution of medications for prevalent patients at the third medication trial	PharmaNet[11] (2015-2020)
	Medication-medication interaction	Lexi-Interact Database[13]
	Number of recurrences of untreated patients at week 52 and distribution of MDD severity level	Calculated based on Hardeveld et al., 2013[14]
	Risk of recurrence for newly diagnosed patients with low risk of recurrence at week 52	Calculated based on Hardeveld et al., 2013[14]
	Risk of recurrence for prevalent patients with low risk of recurrence at week 52	Calculated based on Hardeveld et al., 2013[14]

	Risk of recurrence for high risk prevalent patients at week 116	Calculated based on Hardeveld et al., 2013[14]	
	Recurrence rate in the "Well" health state	Hardeveld et al., 2013[14]	
	Probability of full remission with and without PGx testing	Cipriani et al., 2018[15] and Bunka et al., 2023[16]	
	Probability of discontinuation with and without PGx testing	Cipriani et al., 2018[15] and Bunka et al., 2023[16]	
	Number of patients in the "Well" health state who are on medication	Clinical experts	
	Number of PGx tests in the intervention arm	Calculation based on number of patients who are eligible to receive PGx testing in different branches of the treatment trials based on the base-case scenario	
Hospitalization	Rate of hospitalization (incidence, prevalence, "Well" state, refractory)	DAD[2] (2015-2020)	Number of hospital admissions divided by number of patients (incidence, prevalence, well state, refractory) at the beginning of year and the number matched the input parameters

Cost and QALY	Direct medical cost of death due to suicide	Vasiliadis et al., 2015[17]	Cost of direct medical cost of death due to suicide divided by number of death due to suicide was equal to the unit cost in each calendar year
	Cost of hospitalization for incidence, prevalence, "Well" and refractory patients	DAD[2] (2015-2020) and Estimated using CIHI 2021[18]	Cost of hospitalization divided by the number of hospital admissions was equal to the unit cost for incidence, prevalence, "Well" and refractory patients in each calendar year
	Cost of ECT	CIHI[19]	
	Cost of PGx testing	Maruf 2020[20] and MSC Payment schedule, 2020[21]	Cost of PGx divided by number of PGx tests done in each calendar year was equal to the unit cost of PGx
	Cost of assessment and monitoring	Micro-costing approach based on expert opinions, the MSC payment schedule[21], and average salary of health care professionals in BC[22]	Total cost of monitoring and assessment divided by patients was equal to the average cost of assessment across different groups

Mortality	Rate of mortality by sex	Statistics Canada[23]

Note: MSP = Medical Service Plan; DAD = Discharge Abstract Database.

Cross-validity

We compared the model's cost-effectiveness outcome of PGx testing for MDD with a recent Canadian health technology assessment (HTA).[24] In the cross-validation, we ran the model for a shorter time horizon and tried to make similar assumptions (e.g., population, PGx testing price, some of the health utility values, and scenario for delivering PGx). Although we achieved similar results in this cross-validation, our assumptions are well-justified and we contend that it is essential to model long-term outcomes with this type of recurrent mental health condition.

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