Appendix A. Model Design

Model components

We developed a microsimulation policy model (https://bit.ly/3qvEJkC) of care pathways for people with MDD. A detailed description of the model and how it was developed (evidence base, source data and analyses) is under review.[1] In brief, the simulation model of major depression (SiMMDep) was developed with targeted inputs from key stakeholders including patient partners (LR, GL) and clinicians (one family physician (MP), one psychiatrist (CS), and one psychologist (DE)).

To populate the model, we analyzed BC administrative data for the years 2015 to 2020 for individuals in BC aged 19–99 years old who satisfied the criteria for depression.[2] Several data sets, including Medical Service Plan (MSP)[3], Discharge Abstract Database (DAD)[4], MSP Consolidation File[5], Vital Statistics Deaths records[6], PharmaNet[7], and National Ambulatory Care (NACRS)[8] were linked. Using a recently validated case definition for depression (at least one hospitalization with the diagnosis of MDD, or at least two diagnoses in the physician claims within a year)[2], we established an MDD cohort (newly diagnosed and prevalent MDD patients). We excluded from the cohort any patients who satisfied the diagnostic criteria for bipolar disorder, schizophrenia, and schizoaffective disorder since their treatment are very different from those for major depressive disorder (MDD).

SiMMDep was intentionally designed with a modular approach (8 different interconnected modules) to enhance flexibility (Figure A1). Each module can be revised independently of the others and tailored for different contexts. An overview of the modules is as follows:

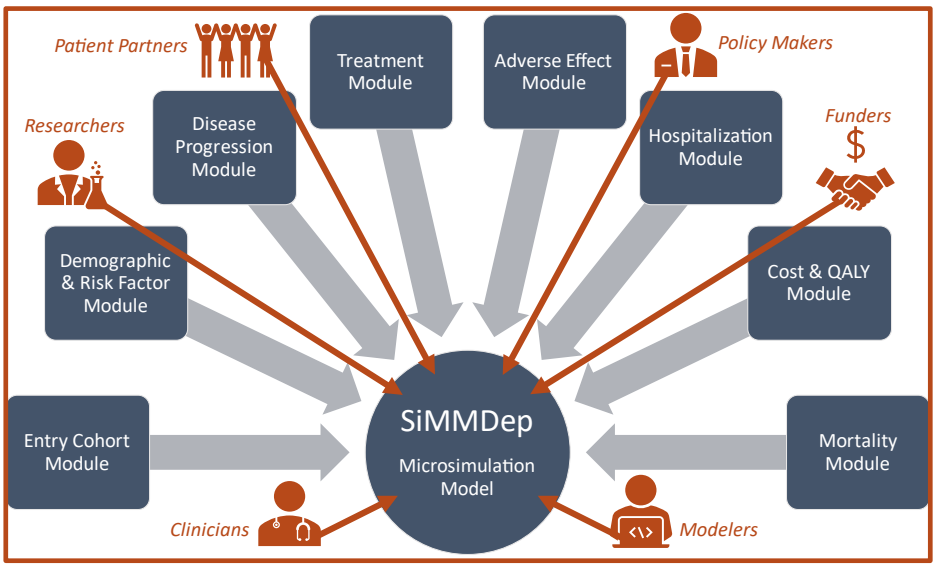

Figure A1: SiMMDep modules and contributors

1) **Entry Cohort Module** determines the target population represented in the model. It calculates the number of incident and prevalent cases of MDD by multiplying the incidence and prevalence rate by the size of the at-risk adult (19+) population in BC

(Table A1). The model includes the entire 2021 cohort of BC adults (age 19-99 years) with MDD eligible for pharmacological treatment (N = 194,149, mean age = 45.6).

2) **Demographics Module** assigns a unique set of variables to each patient. Some of the key input parameters such as current age, age of onset, sex, psychiatric comorbidity, as well as MDD history status (incident and prevalent) were estimated according to BC administrative data.[3-8] Condition severity for newly diagnosed and prevalent patients was extracted from Ferrari et al.[9] and Kessing et al.[10], respectively.

   Because pharmacogenetic variants can occur more or less frequently among different ancestry groups[11, 12], the model assigns each patient to one of the nine geographic ancestry categories listed in the Pharmacogenomics Knowledgebase (PharmGKB)[13-16] (i.e., European, East Asian, Central/South Asian, American, Near Eastern, Latino, Sub-Saharan African, Oceanian, African-American/Afro-Caribbean). We utilized these nine categories, leveraging the reported prevalence of CYP2C19 and CYP2D6 metabolizer phenotypes within these geographic ancestry groups from PharmGKB and in Bousman et al.[47]

   To establish the prevalence of each geographic ancestry group in BC, we utilized Statistics Canada data (2016 Canadian Census results)[17], after matching to the PharmGKB categories (Table A1 and A2). Once the geographic ancestry group was assigned to each patient, metabolizer phenotypes for CYP2C19 and CYP2D6 were attributed accordingly (Figure A2 and Figure A3).

3) **Disease Progression Module** captures the patient's transition between the three different health states over time (MDD, Well, and Death). The duration of each cycle in the model is one week. Event probabilities sourced from the literature were converted to a one-week time frame by transforming the probabilities to a rate (prob=1-exp(-rate)), adjusting the rate to the relevant time window, and then back-calculating the probability from the rate.

Table A1: Model input parameters for entry cohort (N. newly diagnosed = 33,104 and N. prevalent patients = 161,045) and demographic modules

Model Parameters	Mean	Source
MDD history status		
Prevalence rate	0.0472	MSP[3], DAD[4], and MSP Consolidation File[5] (2015-2020)
Incidence rate	0.0132	
Female (%)		
Prevalent patients	68%	
Newly diagnosed patients	58%	
Age (year)		
Prevalent patients		
Female	Beta distribution ($\alpha = 2.16$, $\beta = 2.96$)	
Male	Beta distribution ($\alpha = 2.36$, $\beta = 3.24$)	
Newly diagnosed patients		

Female	Beta distribution ($\alpha = 0.36$, $\beta = 1.77$)	
Male	Beta distribution ($\alpha = 0.99$, $\beta = 2.24$)	
Age of onset of prevalent patients		
Female	Normal distribution (-3.77 + 0.94 × age, 3.56)	
Male	Normal distribution (-3.21 + 0.94 × age, 3.68)	
Patients with other psychiatric comorbidities (excluding schizophrenia, schizoaffective and bipolar)		
Prevalent patients	Logit (P(comorbidity = 1)) = -0.88 + 0.06 × age - 0.34 × (sex = female) - 0.065 × age at onset	
Newly diagnosed patients	Logit (P(comorbidity = 1)) = -2.17 + 0.02 × age -0.38 × (sex = female)	
N. previous episode Prevalent patients	Median = 2	Hardeveld et al., 2013[18]
History of a previous severe episode (%) Prevalent patients	34%	Kessing et al., 2008[10]
Severity of MDD episode, newly diagnosed patients (%)		Ferrari et al., 2013[9]
Mild	68%	
Moderate	19%	
Severe	13%	
Severity of MDD episode, prevalent patients (%)		Kessing et al., 2008[10]
Mild	17%	
Moderate	49%	
Severe	34%	
Geographic ancestry (%)		Statistics Canada[17]
European	67.50%	
East Asian	15.29%	
Central/South Asian	6.51%	
American[a]	5.40%	
Near Eastern	1.95%	
Latino	1.25%	
Sub-Saharan African	0.92%	
Oceanian	0.73%	
African-American/Afro-Caribbean	0.45%	

[a] The 'American' category includes pre-colonial populations from North and South America; namely, American Indian, Alaska Native, First Nations, Inuit, and Métis in Canada, and Indigenous peoples of Central and South America.[19] MSP = Medical Service Plan; DAD = Discharge Abstract Database.

Table A2: Matching geographic ancestry groups between PharmGKB (used in the model) and Statistics Canada

Geographic ancestry categories in PharmGKB (used in the model)	Description	Geographic ancestry categories in Statistics Canada	Description
European	The European genetic ancestry group includes populations of primarily European descent, including European Americans. We define the European region as extending west from the Ural Mountains and south to the Turkish and Bulgarian border.	**European**	British Isles origins, French origins, Western European origins, Northern European origins, Eastern European origins, Southern European origins, Other European origins
		Other North American*	Acadian, American, Canadian, New Brunswicker, Newfoundlander, Nova Scotian, Ontarian, Quebecois, Other North American origins
East Asian	The East Asian genetic ancestry group includes populations from Japan, Korea, and China, and stretches from mainland Southeast Asia through the islands of Southeast Asia. In addition, it includes portions of central Asia and Russia east of the Ural Mountains.	**East and Southeast Asian origins**	Burmese, Cambodian, Chinese, Filipino, Hmong, Indonesian, Japanese, Korean, Laotian, Malaysian, Mongolian, Singaporean, Taiwanese, Thai, Tibetan, Vietnamese, East and Southeast Asian origins
Central/South Asian	The Central and South Asian genetic ancestry group includes populations from Pakistan, Sri Lanka, Bangladesh, India, and ranges from Afghanistan to the western border of China.	**South Asian**	Bangladeshi, Bengali, Bhutanese, East Indian, Goan, Gujarati, Kashmiri, Nepali, Pakistani, Punjabi, Sinhalese, Sri Lankan, Tamil, south Asian origins

Appendix 1, as submitted by the authors. Appendix to: Ghanbarian S, Wong GWK, Bunka M, et al. Cost-effectiveness of pharmacogenomic-guided treatment for major depression. *CMAJ* 2023. doi: 10.1503/cmaj.221785.

American	American Indian, Alaska Native, First Nations, Inuit, and Métis in Canada, and Indigenous peoples of Central and South America.	**North American Aboriginal**	First Nations (North American Indian), Inuit, Metis
Near Eastern	The Near Eastern genetic ancestry group encompasses populations from northern Africa, the Middle East, and the Caucasus. It includes Turkey and African nations north of the Saharan Desert.	**West Central Asian and Middle Eastern**	Afghan, Arab, Armenian, Assyrian, Azerbaijani, Georgian, Hazara, Iranian, Iraqi, Israeli, Jordanian, Kazah, Kurd, Kuwaiti, Kyrgyz, Lebanese, Palestinian, Pashtun, Saudi Arabian, Syrian, Tajik, Tatar, Turk, Turkmen, Uighur, Uzbek, Yemeni
		North African[**]	Algerian, Berber, Coptic, Egyptian, Libyan, Maure, Moroccan, Tunisian,
Latino	The Latino genetic ancestry group is not defined by an exclusive geographic region, but includes individuals of Mestizo descent, individuals from Latin America, and self-identified Latino individuals in the United States. Like the African American/Afro-Caribbean group, the admixture in this population creates a unique genetic pattern compared to any of the discrete geographic regions, with individuals reflecting mixed Native and Indigenous American, European, and African ancestry.	**Latin; Central and South American**	Arawak, Argentinian, Belizean, Bolivian, Brazilian, Chilean, Colombian, Costa Rican, Ecuadorian, Guatemalan, Guyanese, Hispanic, Honduran, Maya, Mexican, Nicaraguan, Panamanian, Paraguayan, Peruvian, Salvadorian,

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Sub-Saharan African	The Sub-Saharan African genetic ancestry group includes individuals from all regions in Sub-Saharan Africa, including Madagascar.	**Sub-Saharan African**	Central and West African origins, Sub-Saharan African origins (including Sudanese and Dinka), Southern and East African origins, other African origins
Oceanian	The Oceanian genetic ancestry group includes pre-colonial populations of the Pacific Islands, including Hawaii, Australia, New Zealand and Papua New Guinea.	**Oceanian**	Australian, New Zealander, Pacific Islands origin
African American/Afro-Caribbean	Individuals in the African American/Afro-Caribbean genetic ancestry group reflect the extensive admixture between African, European, and Indigenous ancestries and, as such, display a unique genetic profile compared to individuals from each of those regions alone.	**Caribbean**	Antiguan, Bahamian, Barbadian, Bermudan, Carib, Cuban, Dominican, Grenadian, Guadeloupean, Haitian, Jamaican, Kittitian/Nevisian, Martinican, Montserratian, Puerto Rican, St. Lucian, Trinidadian, Vincentian, West Indian, Caribbean origin

* The number for other North American origins was added to European category. ** The count for individuals of North African origin, excluding those from Sudan and the Dinka populations (as these regions fall under the sub-Saharan category), was included in the Near Eastern category.

Statistics Canada (2016 Canadian Census results)[17] included an extra category named "other Asian," and the figures within this category were distributed equally among three other Asian categories (i.e., East Asian, South Asian, and West Central/Middle Eastern).

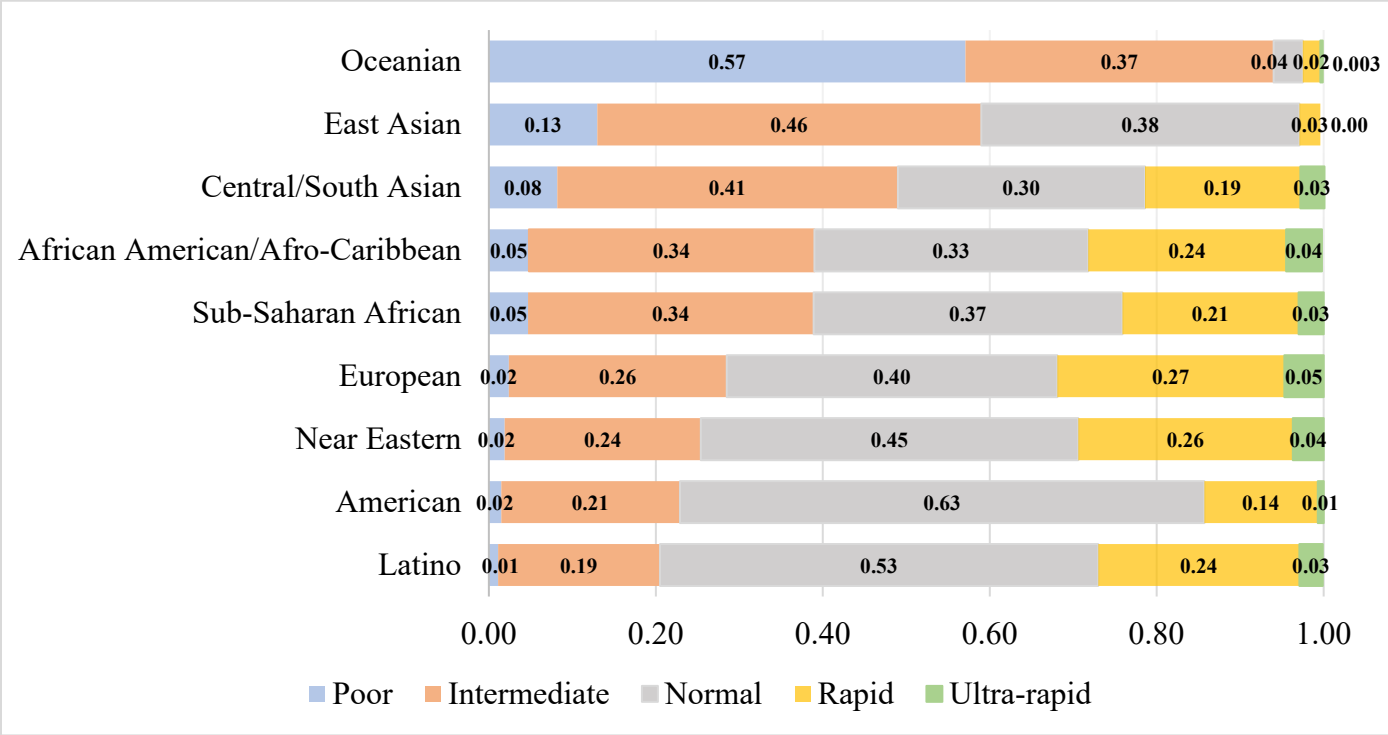

Figure A2: CYP2C19 metabolizer phenotype frequencies for the different ethnographic groups, sourced from published litrature[12] and PharmGKB.[13-16] Note: The 'American' category includes pre-colonial populations from North and South America; namely, American Indian, Alaska Native, First Nations, Inuit, and Métis in Canada, and Indigenous peoples of Central and South America.[19]

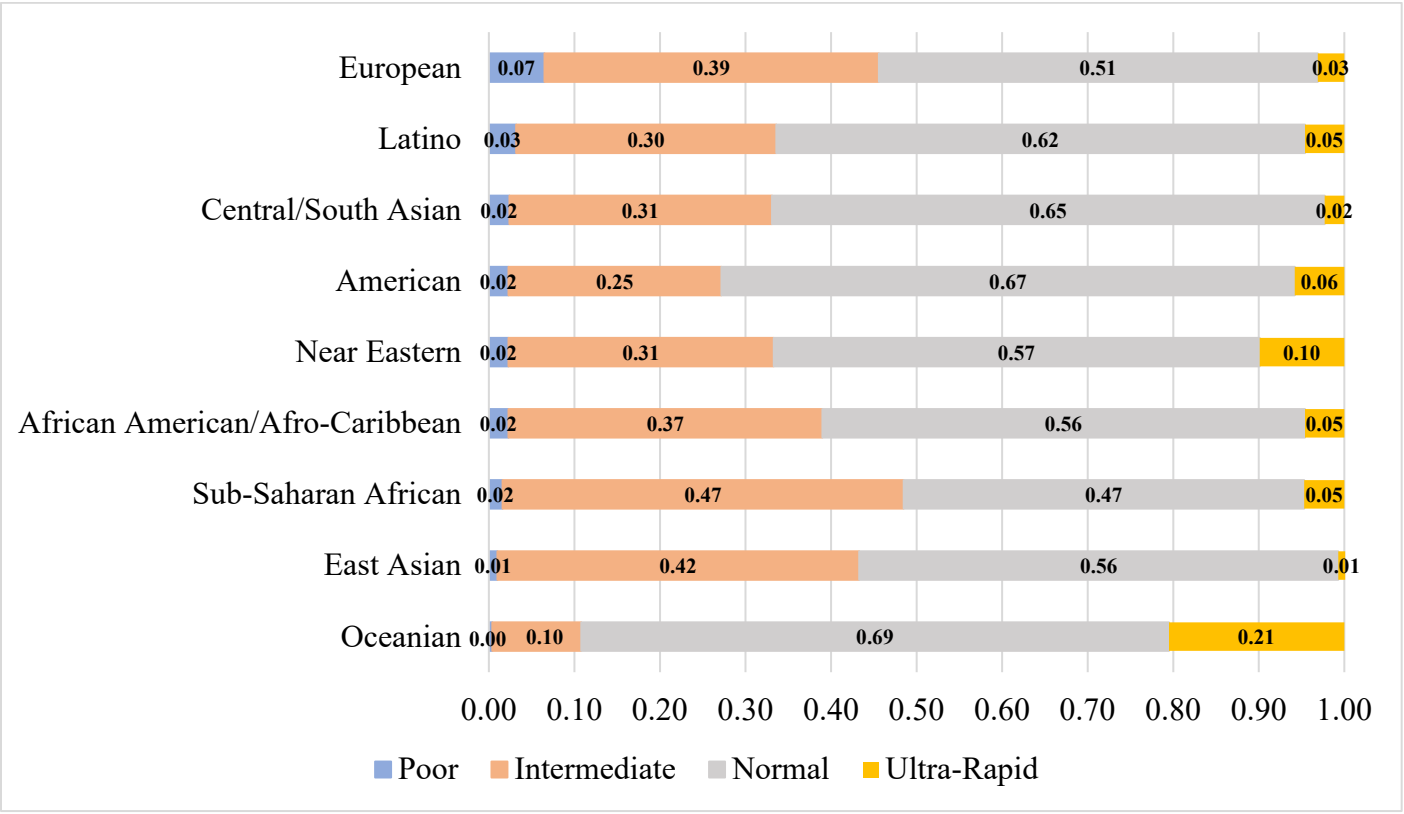

Figure A3: CYP2D6 metabolizer phenotype frequencies for the different ethnographic groups, sourced from published litrature[12] and PharmGKB.[13-16] Note: The 'American' category includes pre-colonial populations from North and South America; namely, American Indian, Alaska Native, First Nations, Inuit, and Métis in Canada, and Indigenous peoples of Central and South America.[19]

4) **Treatment Module** includes five different treatment pathways for patients with MDD in BC (Figure 2). These pathways were designed based on a combination of the CANMAT 2016 guidelines[20] and several meetings with clinical experts and patient partners.[21] Each pathway includes various treatment options. In total, each patient has up to six different treatment options: 1) Mono-pharmacotherapy, 2) Double pharmacotherapy, 3) Combination of mono-pharmacotherapy and psychotherapy, 4) Combination of double pharmacotherapy and psychotherapy, 5) Combination of mono-pharmacotherapy and electroconvulsive therapy (ECT), 6) Combination of double-pharmacotherapy and ECT (Table A3).

   In each pharmacological treatment, the model selects medication for each patient based on 1) CANMAT 2016 guidelines[20], 2) the patient's antidepressant history, which is recorded in the model, and 3) the patient's PGx test results (if available) using "Sequence 2 Script" tool.[22] A frequency distribution of antidepressant prescriptions for prevalent and newly diagnosed patients was created from BC administrative data, and then this distribution was fitted for each treatment pathway (Table A4). When assigning a new medication, the model excludes medications that have previously caused an adverse effect or did not result in full symptom remission for the patient (i.e., ineffective). Then,

the model re-normalizes the medication distribution based on the antidepressants that can still be prescribed, and selects one based on the distribution of antidepressant prescriptions in BC. The model also considers and avoids medication-medication interactions. For individuals who undergo PGx testing, the model implements prescribing recommendations based on their CYP2D6 and CYP2C19 metabolizer phenotypes. We established a compilation of suitable medications for each patient, guided by Clinical Pharmacogenomics Implementation Consortium (CPIC) guidelines[23-25] and the Sequence2Script tool.[22] To encompass all feasible combinations of CYP2D6 and CYP2C19 metabolizer phenotypes, the model excludes medications contraindicated for both phenotypes separately, subsequently assembling a selection of viable treatment options. Ultimately, the model assigns a medication from this refined list, using a normalized probability distribution to accommodate any eliminated medications.

Table A3: Model input parameters for treatment and adverse event modules

Parameters	Mean	Source
Probability of full remission		
Mono-pharmacotherapy	Drug-specific 0.23-0.37	Cipriani et al., 2018[26]
Double-pharmacotherapy	Drug-specific 0.16-0.42	Komossa et al., 2010[27]
Pharmacotherapy & psychotherapy	0.28	Wiles et al., 2013[28]
Pharmacotherapy & ECT	0.39	Ontario HTA (ECT)[29]
Probability of partial remission		
Mono-pharmacotherapy	Drug-specific 0.17-0.25	Calculated based on Cipriani et al., 2018[26]
Pharmacotherapy & psychotherapy	0.18	Calculated based on Wiles et al., 2013[28]
Probability of total discontinuation		
Mono-pharmacotherapy	Drug-specific 0.26-0.4	Cipriani et al., 2018[26]
Double-pharmacotherapy	Drug-specific 0.14-0.23	Komossa et al., 2010[27]
Pharmacotherapy & psychotherapy	Drug-specific 0.14-0.4	Cipriani et al., 2018[26] & Komossa et al., 2010[27]
Pharmacotherapy & ECT	Drug-specific 0.14-0.4	Cipriani et al., 2018[26] & Komossa et al., 2010[27]
Probability of discontinuation due to adverse event		
Mono-pharmacotherapy	Drug-specific 0.05-0.2	Cipriani et al., 2018[26]
Double-pharmacotherapy	Drug-specific 0.02-0.12	Komossa et al., 2010[27]
Pharmacotherapy & psychotherapy	Drug-specific	Cipriani et al., 2018[26] &

	0.02-0.2	Komossa et al., 2010[27]
Pharmacotherapy & ECT	Drug-specific 0.02-0.2	Cipriani et al., 2018[26] & Komossa et al., 2010[27]
Recurrence		
Baseline probability of recurrence in maintenance phase (9 months after remission)	0.158	Calculated based on Hardeveld et al., 2013[18]
Baseline probability of recurrence in "Well" state		
Year 1	0.014	
Year 2	0.012	
Year 3-5	0.017	
Year 6-10	0.012	
Year 11-20	0.011	
Risk modifier	$0.96^{(age-age_{onset})} \times 1.68^{MDD\_history} \times 1.91^{history\_severe\_MDD}$	Hardeveld et al., 2013[18]
Clinical efficacy of PGx testing (Intervention vs. current SoC)		
Risk ratio of full remission	1.46 (1.02; 2.08)	Bunka et al., 2023[30]
Risk ratio of partial remission	1.2 (0.96; 1.51)	Calculated based on Bunka et al., 2023[30]
Risk ratio of total discontinuation	0.89 (0.78; 1.01)	Bunka et al., 2023[30]
Risk ratio of discontinuation due to adverse effect	0.43 (0.16; 1.17)	Calculated based on Bunka et al., 2023[30]

Note: SoC = Standard of care

Table A4: Medications included in the model and their prescription frequency distributions for newly diagnosed and prevalent patients, based on BC administrative data (MSP[3], DAD[4], PharmaNet[7]).

	Medication	Medication Class	Prevalent patients (%)	Newly diagnosed patients (1st year after diagnosis; %)
1st line	Agomelatine	MT1 and MT2 agonist; 5-HT2 antagonist	0.00	0.00
	Bupropion	NDRI	6.56	5.68
	Citalopram	SSRI	9.19	8.72
	Desvenlafaxine	SNRI	1.89	1.00

	Duloxetine	SNRI	3.10	2.08
	Escitalopram	SSRI	24.04	32.33
	Fluoxetine	SSRI	5.51	4.57
	Fluvoxamine	SSRI	0.4	0.30
	Mianserin	a2-Adrenergic agonist; 5-HT2 antagonist	0.00	0.00
	Milnacipran	SNRI	0.00	0.00
	Mirtazapine	a2-Adrenergic agonist; 5-HT2 antagonist	3.73	5.28
	Paroxetine	SSRI	3.29	2.06
	Sertraline	SSRI	12.01	14.16
	Venlafaxine	SNRI	12.29	7.49
	Vortioxetine	SMS	1.73	1.72
2nd line	Amitriptyline	TCA	3.57	2.90
	Clomipramine	SNRI	0.23	0.06
	Levomilnacipran	Reversible inhibitor of MAO-A	0.10	0.06
	Moclobemide	Atypical antipsychotic	0.00	0.00
	Quetiapine	Irreversible MAO-B inhibitor	2.82	2.68
	Selegiline	Serotonin reuptake inhibitor; 5-HT2 antagonist	0.00	0.00
	Trazodone	Serotonin reuptake inhibitor; 5-HT1A partial agonist	9.43	8.84
	Vilazodone	TCA	0.08	0.07
3rd line	Phenelzine	Irreversible MAO inhibitor	0.00	0.00
	Reboxetine	Noradrenaline reuptake inhibitor	0.00	0.00
	Tranylcypromine	TCA	0.00	0.00
	Adjunctive Agent		Prevalent patients	Newly diagnosed patients (1st year after diagnosis)
1st line	Aripiprazole	2nd-generation antipsychotic	6.60	4.06
	Quetiapine	Atypical antipsychotic	31.03	39.30
	Risperidone	2nd-generation antipsychotic	6.08	8.03
2nd line	Brexpiprazole	2nd-generation antipsychotic	0.00	0.00
	Bupropion	NDRI	35.44	25.02
	Lithium	Mood stabilizer	1.06	0.76
	Mianserin	a2-Adrenergic agonist; 5-HT2 antagonist	0.00	0.00

	Mirtazapine	a2-Adrenergic agonist; 5-HT2 antagonist	16.44	19.30
	Modafinil	Stimulant	0.00	0.00
	Olanzapine	Antipsychotic	1.89	2.91
	Liothyronine	Thyroid hormone	1.29	0.63
3rd line	Ziprasidone	Antipsychotic	0.00	0.00
	Ketamine	Anesthetic	0.00	0.00
	Desipramine	TCA	0.17	0.00

Note: MT= Melatonin receptor; NDRI= norepinephrine–dopamine reuptake inhibitor; SSRI= selective serotonin reuptake inhibitor; SNRI= serotonin and norepinephrine reuptake inhibitor; SMS= serotonin modulator and simulator; TCA= tricyclic antidepressant; MAO= monoamine oxidase; MSP = Medical Service Plan; DAD = Discharge Abstract Database.

Table A1: Medication selection based on CYP2C19 metabolizer phenotypes

	Medication	Poor	Intermediate	Normal	Rapid	Ultrarapid
1st line	Agomelatine	1	1	1	1	1
	Bupropion	1	1	1	1	1
	Citalopram	0	1	1	0	0
	Desvenlafaxine	1	1	1	1	1
	Duloxetine	1	1	1	1	1
	Escitalopram	0	1	1	0	0
	Fluoxetine	1	1	1	1	1
	Fluvoxamine	1	1	1	1	1
	Mianserin	1	1	1	1	1
	Milnacipran	1	1	1	1	1
	Mirtazapine	1	1	1	1	1
	Paroxetine	1	1	1	1	1
	Sertraline	0	1	1	1	1
	Venlafaxine	1	1	1	1	1
	Vortioxetine	1	1	1	1	1
2nd line	Amitriptyline	0	1	1	0	0
	Clomipramine	0	1	1	0	0
	Levomilnacipran	1	1	1	1	1
	Moclobemide	1	1	1	1	1
	Quetiapine	1	1	1	1	1
	Selegiline	1	1	1	1	1
	Trazodone	1	1	1	1	1
	Vilazodone	1	1	1	1	1
3rd line	Phenelzine	1	1	1	1	1
	Reboxetine	1	1	1	1	1
	Tranylcypromine	1	1	1	1	1

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	Adjunctive Agent	Poor	Intermediate	Normal	Rapid	Ultrarapid
1st line	Aripiprazole	1	1	1	1	1
	Quetiapine	1	1	1	1	1
	Risperidone	1	1	1	1	1
2nd line	Brexpiprazole	1	1	1	1	1
	Bupropion	1	1	1	1	1
	Lithium	1	1	1	1	1
	Mianserin	1	1	1	1	1
	Mirtazapine	1	1	1	1	1
	Modafinil	1	1	1	1	1
	Olanzapine	1	1	1	1	1
	Liothyronine	1	1	1	1	1
3rd line	Ziprasidone	1	1	1	1	1
	Ketamine	1	1	1	1	1
	Desipramine	1	1	1	1	1

Note: Value of "1" indicates the suitability of the medication for the corresponding metabolizer phenotype, while a value of "0" indicates the medication's inappropriateness.

Table A6: Medication selection based on CYP2D6 metabolizer phenotypes

	Medication	Poor	Intermediate	Normal	Ultrarapid
1st line	Agomelatine	1	1	1	1
	Bupropion	1	1	1	1
	Citalopram	1	1	1	1
	Desvenlafaxine	1	1	1	1
	Duloxetine	1	1	1	1
	Escitalopram	1	1	1	1
	Fluoxetine	1	1	1	1
	Fluvoxamine	0	1	1	1
	Mianserin	1	1	1	1
	Milnacipran	1	1	1	1
	Mirtazapine	1	1	1	1
	Paroxetine	0	1	1	0
	Sertraline	1	1	1	1
	Venlafaxine	0	0	1	1
	Vortioxetine	0	1	1	1
2nd line	Amitriptyline	0	0	1	0
	Clomipramine	0	0	1	0
	Levomilnacipran	1	1	1	1
	Moclobemide	1	1	1	1
	Quetiapine	1	1	1	1

	Selegiline	1	1	1	1
	Trazodone	1	1	1	1
	Vilazodone	1	1	1	1
3rd line	Phenelzine	1	1	1	1
	Reboxetine	1	1	1	1
	Tranylcypromine	1	1	1	1
	Adjunctive Agent	Poor	Intermediate	Normal	Ultrarapid
1st line	Aripiprazole	0	1	1	1
	Quetiapine	1	1	1	1
	Risperidone	0	1	1	0
2nd line	Brexpiprazole	0	1	1	1
	Bupropion	1	1	1	1
	Lithium	1	1	1	1
	Mianserine	1	1	1	1
	Mirtazapine	1	1	1	1
	Modafinil	1	1	1	1
	Olanzapine	1	1	1	1
	Liothyronine	1	1	1	1
3rd line	Ziprasidone	1	1	1	1
	Ketamine	1	1	1	1
	Desipramine	0	0	1	0

Note: Value of "1" indicates the suitability of the medication for the corresponding metabolizer phenotype, while a value of "0" indicates the medication's inappropriateness.

5) **Adverse Effect Module** assigns treatment discontinuation due to a cause, such as medication side effects. This module is flexibly coded to allow for discontinuation due to "other cause" to be modeled if/when data becomes available (e.g. discontinuation due to out-of-pocket costs, stigma, etc.; Table A3).

6) **Hospitalization Module** assigns the weekly probability of hospitalization to patients and counts the number of all-cause hospital admissions (Table A7).

Table A7: All-cause hospitalization rate (per 100 patient-years)

	Rate of all-cause hospitalization (per 100 patient-years)	**Source**
Newly diagnosed patients	17.00	MSP[3], DAD[4], PharmaNet[7]
Prevalent Patients	14.24	(2015-2020)
Patients with refractory MDD	17.81	
General population	7.00	CIHI 2021[31]

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

7) **Cost and QALY Module** captures all treatment-related costs and benefits from the public payer perspective.

- **Cost**
  As patients go through different health states and events in the model, we estimate the costs and resources associated with them (Table A8).
- **Utility**
  All patients enter the model with an MDD-specific utility value that is associated with their illness, stratified by their health state, the severity of MDD, and remission status (Table A9).

8) **Mortality Module** tabulates death due to any cause, including those specific to MDD. We applied a weekly age- and sex-specific mortality rate based on the annual rate we sourced from Statistics Canada and risk ratios that we sourced from the literature[32-35](Table A10).

Table A8: Costs used in the economic model (2020 CAD)

Model input parameters	Mean	Note	Source
Pharmacogenomic test	$738	Including appointments for test request and results review	Maruf 2020[36] and MSC Payment schedule, 2020[37]
MDD treatment			
Psychotherapy Individual Cognitive Behavioral therapy (ICBT)	$236.5	Weekly for 12 weeks	MSC payment schedule[37] and average salary of healthcare professionals in BC[38]
Pharmacotherapy	Drug-specific $0-$17	Weekly medication-specific costs paid by pharma care	PharmaNet[7] (2015-2020)
Electroconvulsive therapy (ECT)	$3,748.14	Weekly for 7 weeks	CIHI[39]
Refractory MDD care	$102	Weekly costs including all MDD and non-MDD treatment costs, inpatient and outpatients' costs	MSP[3], DAD[4], PharmaNet[7] and NACRS[8] (2015-2020)
All-cause hospitalization			
Newly diagnosed patients	$11,838		DAD[4] (2015-2020)
Prevalent Patients	$10,241		
General population	$8,153		Estimated using CIHI 2021[31] and DAD[4] (2015-2020)
Monitoring and assessment			
Drug management costs	$4.10-$15.94	Weekly for 12-weeks	Micro-costing approach based on expert opinions,

Referral costs	$68	At the beginning of any episode	the MSC payment schedule[37], and average salary of healthcare professionals in BC[38]
Monitoring after discontinuation of treatment, no adverse event	$6.66-$12.04	Weekly for 48 weeks	
Monitoring after remission	$7.03-$62.50	Weekly for 40-104 weeks	
Monitoring after no remission	$20.47-$441.24	One-time cost before stepping up care	
Assessment to step up care	$340-$538	One-time cost before stepping up care	
Follow up in the 'Well' health state			
Patients on antidepressant	$7.13-$22.26	Weekly	
Patients no longer on antidepressant	$1.47-$10.16	Weekly for 52 weeks	

Note: MSP = Medical Service Plan; DAD = Discharge Abstract Database; NACRS = National Ambulatory Care.

Table A9: Health utility index for different health states and treatment phases

Health state	Utility	Mean	95% CI lb	95% CI ub	Source
MDD (episodic)	Acute phase				
	Mild MDD	0.57	0.54	0.61	Kolovos et al., 2017[40]
	Moderate MDD	0.52	0.49	0.56	
	Severe MDD	0.39	0.35	0.43	
	Maintenance Phase	0.70	0.67	0.73	
MDD (refractory)		0.57	0.52	0.6	Sobocki et al., 2006[41]
Well		0.80 (SE: 0.01)			Bansback et al., 2012[42]

Note: The observational period for the treatment trial is divided into two phases. The acute phase lasts three months and the maintenance phase could last 6 to 24 months.[20] In the model, the maintenance phase was assumed to last 9 months for the patients with a low risk of recurrence and 24 months for patients with a high risk of recurrence.

Table A10: Input parameters used in the mortality module

Parameter	Mean	Source
All-cause mortality rate in "Well" health state	Age- and sex-dependent background mortality in BC	Statistics Canada[34]
Risk ratio of mortality with episodic MDD compared with the general population	1.58	Cuijper et al., 2013[32]
Hazard ratio of mortality with refractory MDD compared with episodic MDD	1.29	Li et al., 2019[33]

Percentage of death due to suicide among all deaths in patients with MDD history	4% (2%-7%)	Zivin et al., 2007[35]

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