The Office of the National Coordinator for Health Information Technology

Synthea™ Module Companion Guide

ACUTE MYELOID LEUKEMIA

March 2022

Prepared by Clinovations Government + Health for the Office of the National Coordinator for Health Information Technology and approved for public release

Contract No. HHSP233201500099I/75P00119F37004

Table of Contents

Introduction

Synthea™ is an open-source, synthetic patient generator, created by MITRE, that models the medical history of synthetic patients. Clinical disease modules are created using a combination of clinical care protocols and publicly available disease incidence and prevalence statistics. Synthea uses these modules to generate individual synthetic patient records, simulating the progression and treatment of disease from birth to death. Synthea Module Companion Guides serve to orient users to a specific Synthea module. The intended audience includes those who are reviewing a module under development and/or interested in utilizing the module to generate synthetic patient data.

This document summarizes the scope and intent of the Acute Myeloid Leukemia module. It provides details of the module states and contains a full list of references and data sources used to develop the module.

This module was developed as part of a Demonstration Study replicating the results detailed in Cost-Effectiveness of Levofloxacin Prophylaxis against Bacterial Infection in Pediatric Patients with Acute Myeloid Leukemia, by McCormick et al., published in Pediatric Blood & Cancer in 2020 (1). Using the McCormick microsimulation study as a model for testing Synthea outcomes, this module was used to test and identify opportunities to improve Synthea's functionality and design to support future microsimulation-based hypothesis testing.

The Acute Myeloid Leukemia module was created for a specific use case dedicated to testing the ability of Synthea to replicate the results of a microsimulation study (McCormick, et. al.). This module is not intended to include all possible clinical issues related to the patient with acute myeloid leukemia (AML) or represent a clinical care guideline of any kind.

Module Description

Table 1: Acute Myeloid Leukemia Module Metadata contains a list of metadata attributes that help describe the module including, but not limited to, module steward, module developer, date of last update, and other descriptive information.

Table 1: Acute Myeloid Leukemia Module Metadata

Metadata	Description
Title	Acute Myeloid Leukemia
Module File Name	acute_myeloid_leukemia
Version Number	1.0
Date Created	August 12, 2021
Module Steward	Office of the National Coordinator for Health Information Technology (ONC)
Module Developer	Clinovations Government + Health
Description	This module models Levofloxacin prophylaxis in patients age <=21 years of age. It is based on a microsimulation study to effectively test the utility of Synthea data for PCOR hypothesis testing. This module was designed with a microsimulation-based hypothesis from a study by McCormick et al., which provides an evaluation of the cost effectiveness of levofloxacin use in children with acute myeloid leukemia (AML). The McCormick study includes a decision-analysis model designed to evaluate the cost-effectiveness of levofloxacin prophylaxis compared to no prophylaxis in patients less than or equal to 21 years of age with AML during a single chemotherapy inpatient visit. The study reports outcomes, including the cost of bacterial infection, cost per ICU admission, and cost per death avoided. In order to replicate the costs within this study, costs within appropriate Synthea cost lookup files were updated. In addition, one city in the default demographics file within Synthea was updated with gender, race, and ethnicity parameters from the McCormick study in order to generate similar population characteristics. This module is not intended to include all possible clinical issues related to the patient with acute myeloid leukemia (AML) or represent a clinical care guideline of any kind.
Disclaimer	Synthea™ is an open-source, synthetic patient generator created by MITRE that models the medical history of synthetic patients. This Synthea module is developed using the Synthea Module Builder and is limited to the capabilities of Synthea and the Synthea Module Builder. This module was created to demonstrate Synthea's ability to replicate the results of a microsimulation study. The module is not intended to represent the care processes of patients with AML or a clinical care guideline. Instead, it is based solely on the parameters of the McCormick study. This Synthea module is not a clinical guideline, does not establish a standard of medical care, and has not been tested for all potential applications. THIS MODULE IS PROVIDED "AS IS" WITHOUT WARRANTY OF ANY KIND.

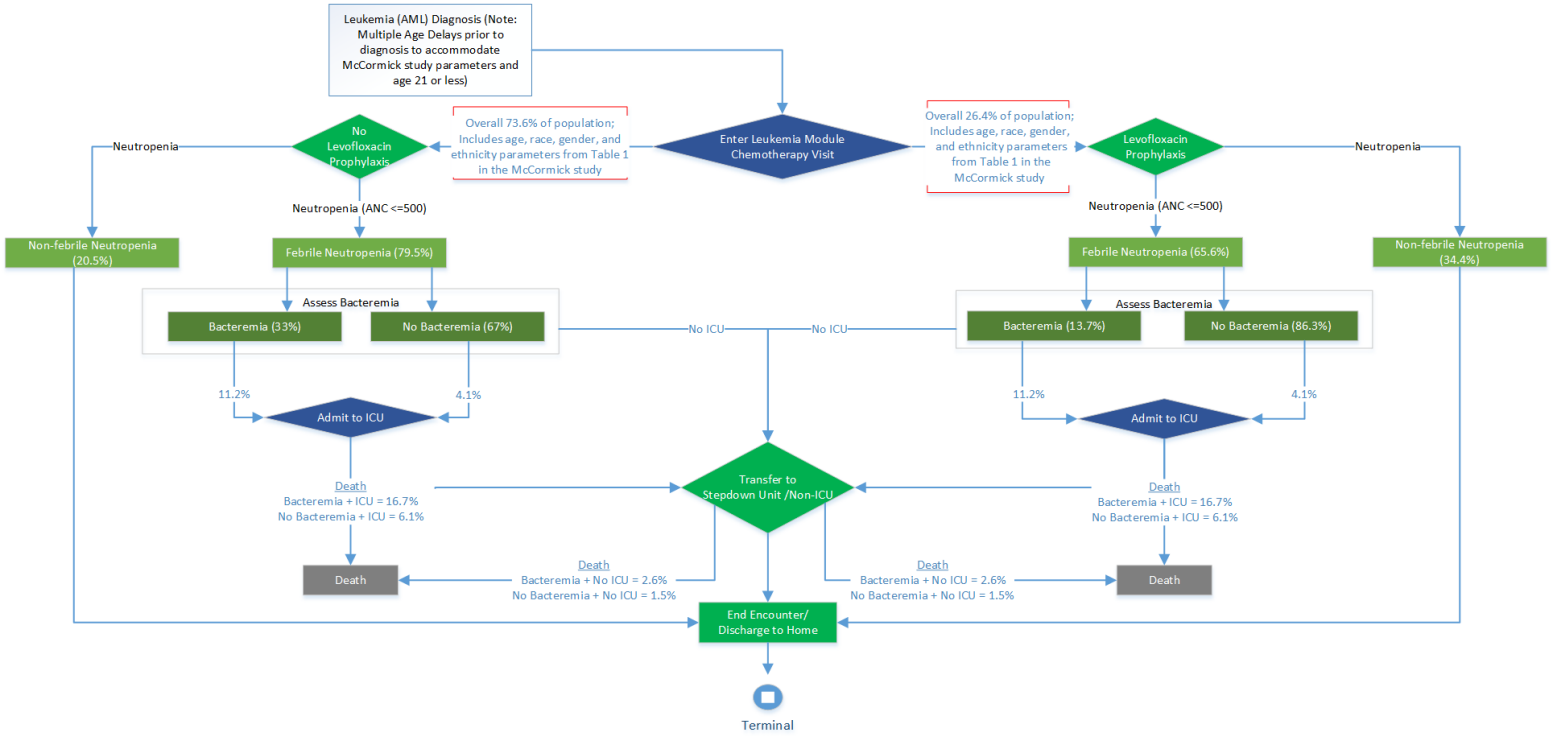
Metadata	Description
Related Module(s)	None
Reference(s)	McCormick M, Friehling E, Kalpatthi R, Siripong N, Smith K. Cost-effectiveness of levofloxacin prophylaxis against bacterial infection in pediatric patients with acute myeloid leukemia. Pediatric Blood & Cancer. 2020 Oct;67(10):e28469 (1)

The Office of the National Coordinator for Health Information Technology

Module Diagram

A Synthea™ module diagram within the Synthea Module Builder is often large and complex to view, as it includes both clinical states and control states. It may be challenging for users to understand and navigate the module within Synthea, especially those who are new to the process. The purpose of the following Visio diagrams is to provide a high-level, simplified view of the module contents and flow so users understand the scope and main components of the module before diving into details.

Figure 1: Acute Myeloid Leukemia Visio Diagram



Module States

Table 2: Acute Myeloid Leukemia Module States provides details about each clinical state modeled within the module. State Names are modeled in the Acute Myeloid Leukemia module. The Type column indicates the Synthea state type used to define the state. State Remarks provide detailed documentation for each state, including notes, references, and data sources used to define probabilities. The Terminology column identifies the standard codes used to model the clinical states.

Table 2: Acute Myeloid Leukemia Module States

State Name	Type	State Remarks	Terminology
Initial	Initial	Initial state of a module required by Synthea™.	n/a
Delay_0	Delay	Delay set for percentage of patients to have no delay after birth before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_1	Delay	Delay set for percentage of patients to have a delay of 1 year after birth before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_2	Delay	Delay set for percentage of patients to have a delay of 2 years after birth before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_3	Delay	Delay set for percentage of patients to have a delay of 3 years after birth before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_4	Delay	Delay set for percentage of patients to have a delay of 4 years after birth before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_5	Delay	Delay set for percentage of patients to have a delay of 5 years after birth before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_6	Delay	Delay set for percentage of patients to have a delay of 6 years after birth before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_7	Delay	Delay set for percentage of patients to have a delay of 7 years before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_8	Delay	Delay set for percentage of patients to have a delay of 8 years after birth before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_9	Delay	Delay set for percentage of patients to have a delay of 9 years before progressing to Acute_Myeloid_Leukemia_AML state.	n/a

State Name	Type	State Remarks	Terminology
Delay_10	Delay	Delay set for percentage of patients to have a delay of 10 years before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_11	Delay	Delay set for percentage of patients to have a delay of 11 years before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_12	Delay	Delay set for percentage of patients to have a delay of 12 years before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_13	Delay	Delay set for percentage of patients to have a delay of 13 years before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_14	Delay	Delay set for percentage of patients to have a delay of 14 years before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_15	Delay	Delay set for percentage of patients to have a delay of 15 years before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_16	Delay	Delay set for percentage of patients to have a delay of 16 years before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_17	Delay	Delay set for percentage of patients to have a delay of 17 years before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_18	Delay	Delay set for percentage of patients to have a delay of 18 years before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_19	Delay	Delay set for percentage of patients to have a delay of 19 years after birth before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_20	Delay	Delay set for percentage of patients to have a delay of 20 years after birth before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Delay_21	Delay	Delay set for percentage of patients to have a delay of 21 years before progressing to Acute_Myeloid_Leukemia_AML state.	n/a
Acute_Myeloid_Leukemia_AML	Condition Onset	Probability set to 100% of the population. All patients are diagnosed with AML. Direct transition to Chemotherapy_Inpatient_Encounter state.	System: SNOMED-CT Code: 91861009 Display: Acute myeloid leukemia, disease (disorder)
Chemotherapy_Inpatient_Encounter	Encounter	Probability set to 100% of the population. All patients enter an initial encounter for chemotherapy. Direct transition to Chemotherapy state.	System: SNOMED-CT Code: 185347001 Display: Encounter for problem (procedure)

State Name	Type	State Remarks	Terminology
Chemotherapy	Procedure	Probability set to 100% of the population. All patients receive chemotherapy. Direct transition to Determine_Levofloxacin_Prophylaxis state.	System: SNOMED-CT Code: 367336001 Display: Chemotherapy (procedure)
Determine_Levofloxacin_Prophylaxis	Simple	This state checks the AML population for levofloxacin prophylaxis using a table transition with specific transition probabilities to match McCormick study parameters for gender, race, and ethnicity. Default probability set to 26.38% of the population to receive levofloxacin (transition to Levofloxacin state) while 73.62% transition to No_Levofloxacin_Prophylaxis state.	n/a
Levofloxacin	MedicationOrder	Probability based on table transition parameters. Default probability set to 26.38% of the AML population. Direct transition to Absolute_Neutrophil_Count_ANC state. Levofloxacin costs were added to the medications lookup table for this coded medication.	System: SNOMED-CT Code: 199885 Display: levofloxacin 500 MG Oral Tablet Attribute: levofloxacin
No_Levofloxacin_Prophylaxis	Simple	This state accommodates the population that does not receive levofloxacin. Direct transition Absolute_Neutrophil_Count_ANC2 state.	n/a
Absolute_Neutrophil_Count_ANC	Observation	AML patients who receive levofloxacin undergo a laboratory test for absolute_neutrophil_count (ANC). Results will be selected from a range of 250-500 mm3. Direct transition to Check_Fever state.	System: LOINC Code: 751-8 Display: Neutrophils [#/volume] in Blood by Automated count Category: laboratory
Absolute_Neutrophil_Count_ANC2	Observation	AML patients who did not receive levofloxacin undergo a laboratory test for ANC. Results will be selected from a range of 250-500 mm3. Direct transition to Check_Fever2 state.	System: LOINC Code: 751-8 Display: Neutrophils [#/volume] in Blood by Automated count Category: laboratory
Check_Fever	Simple	This state checks the Levofloxacin population for fever. A temperature check is performed. A percentage (34.4%) of patients will transition to the Normal_Body_Temp state. The remainder of the Levofloxacin population (65.6%) transitions to the Fever state.	n/a
Check_Fever2	Simple	This state checks the No_Levofloxacin_Prophylaxis population for fever. A temperature check is performed. A percentage (20.5%) of patients will transition to the Normal_Body_Temp state. The remainder of the No_Levofloxacin_Prophylaxis population (79.5%) transitions to the Fever state.	n/a

State Name	Type	State Remarks	Terminology
Normal_Body_Temp	Observation	Patients receive a temperature check and results are within normal limits. Temperature is selected from a range of 96-99 degrees Fahrenheit. Direct transition to Non-Febrile_Neutropenia state.	System: LOINC Code: 8310-5 Display: Body Temperature Category: vital-signs
Fever	Observation	Patients receive a temperature check and results are higher than normal. Temperature is selected from a range of 100.4-103 degrees Fahrenheit. Direct transition to Febrile_Neutropenia state.	System: LOINC Code: 8310-5 Display: Body Temperature Category: vital-signs
Non-Febrile_Neutropenia	ConditionOnset	This state diagnoses the patient with non-febrile neutropenia. Direct transition to Transfer_to_Stepdown state.	System: SNOMED-CT Code: 47318007 Display: Neutropenia (disorder)
Febrile_Neutropenia	ConditionOnset	This state diagnoses the patient with febrile neutropenia. Direct transition to Check_Bacteremia state.	System: SNOMED-CT Code: 409089005 Display: Febrile neutropenia (disorder)
Check_Bacteremia	Simple	All febrile neutropenia patients progress to this state, which evaluates the patient for bacteremia. A certain percentage of patients will progress to the Bacteremia state with the remainder transitioning to the No_Bacteremia state based on McCormick study parameters.	n/a
Bacteremia	ConditionOnset	A certain percentage of febrile neutropenia patients will be diagnosed with bacteremia based on McCormick study parameters. Costs for inpatient encounters were updated in the encounters lookup table in Synthea for this coded event. Patients transition to Transfer_to_ICU, Transfer_to_Stepdown, and Death_Event states based on McCormick study parameters.	System: SNOMED-CT Code: 5758002 Display: Bacteremia (finding) Attribute: bacteremia
No_Bacteremia	Simple	A certain percentage of febrile neutropenia patients will not be diagnosed with bacteremia based on McCormick study parameters. Patients transition to Transfer_to_ICU, Transfer_to_Stepdown, and Death_Event states based on McCormick study parameters.	n/a
Transfer_to_ICU	Procedure	A certain percentage of patients with and without bacteremia will be admitted to the ICU based on McCormick study parameters. ICU admission costs were updated in the encounters lookup table in Synthea for this coded event.	System: SNOMED-CT Code: 305351004 Display: Admit to intensive care unit (ICU)

State Name	Type	State Remarks	Terminology
Transfer_to_Stepdown	Procedure	This state transitions the patient to the Stepdown Unit. All non-febrile neutropenia patients progress to this state. Other patients will progress to this state based on McCormick study parameters (live). Direct transition to End_Levofloxacin state.	System: SNOMED-CT Code: 449214001 Display: Transfer to stepdown unit (procedure)
End_Levofloxacin	MedicationEnd	This state ends levofloxacin for AML patients who receive levofloxacin. Direct transition to End_AML state.	System: SNOMED-CT Code: 199885 Display: levofloxacin 500 MG Oral Tablet
End_AML	ConditionEnd	This state ends the condition of AML. Direct transition to End_Non-Febrile_Neutropenia state.	n/a
End_Non-Febrile_Neutropenia	ConditionEnd	This state ends the condition of non-febrile neutropenia. Direct transition to End_Febrile_Neutropenia state.	n/a
End_Febrile_Neutropenia	ConditionEnd	This state ends the condition of febrile neutropenia. Direct transition to End_Bacteremia state.	n/a
End_Bacteremia	ConditionEnd	This state ends the condition of bacteremia. Direct transition to the End_Encounter state.	n/a
End_Encounter	EncounterEnd	All Transfer_to_Stepdown patients transfer to this state to end the encounter and discharge to home after acute conditions are ended. Direct transition to Terminal state.	System: NUBC Code: 1 Display: Discharge to Home
Death_Event	Procedure	A certain percentage of patients will die in the module based on McCormick study parameters (die). Mortality costs were updated in the procedures lookup table in Synthea for this coded event. Direct transition to Death state.	System: SNOMED-CT Code: 16983000 Display: Death in hospital (event)
Death	Death	Patients who suffer a death event will automatically progress to the death state within the module. Direct transition to End_Encounter2 state.	System: SNOMED-CT Code: 91861009 Display: Acute myeloid leukemia, disease (disorder)
End_Encounter2	EncounterEnd	All death patients transfer to this state to end the encounter. Direct transition to Terminal state.	System: NUBC Code: 41 Display: Expired in medical facility
Terminal	Terminal	Final state of a module required by Synthea™.	n/a

Module Parameters

Table 3: Acute Myeloid Leukemia Module Parameters summarizes the probabilities used to construct distributed module states where branching occurs in the module flow. A value of 1.0 indicates 100%; 0 indicates 0%. All probabilities were based on parameters within the McCormick study.

Table 3: Acute Myeloid Leukemia Module Parameters

Parameter	Value	Notes and References
Probability of age at time of AML diagnosis	1.0	n/a
1. No delay	0.0416	n/a
2. 1-year delay	0.098	n/a
3. 2-year delay	0.1264	n/a
4. 3-year delay	0.1094	n/a
5. 4-year delay	0.0645	n/a
6. 5-year delay	0.0533	n/a
7. 6-year delay	0.0345	n/a
8. 7-year delay	0.0362	n/a
9. 8-year delay	0.0318	n/a
10. 9-year delay	0.0354	n/a
11. 10-year delay	0.0346	n/a
12. 11-year delay	0.0289	n/a
13. 12-year delay	0.0312	n/a
14. 13-year delay	0.033	n/a
15. 14-year delay	0.03	n/a
16. 15-year delay	0.0343	n/a
17. 16-year delay	0.0289	n/a
18. 17-year delay	0.0323	n/a
19. 18-year delay	0.0323	n/a
20. 19-year delay	0.0346	n/a
21. 20-year delay	0.0315	n/a
22. 21-year delay	0.0173	n/a

Parameter	Value	Notes and References
Probability of levofloxacin administration	1.0	n/a
1. Probability of receiving levofloxacin—table distribution with default probability	0.2638	(1)
2. Probability of not receiving levofloxacin—table distribution with default probability	0.7362	(1)
Probability of fever and febrile neutropenia in levofloxacin patients	1.0	n/a
1. Levofloxacin patients with fever (febrile neutropenia)	0.656*	(2) (8) (15-17)
2. Levofloxacin patients with normal temperature (non-febrile neutropenia)	0.344	n/a
Probability of fever and febrile neutropenia in non-levofloxacin patients	1.0	n/a
1. Non-levofloxacin patients with fever (febrile neutropenia)	0.795*	(2) (8) (12-17)
2. Non-levofloxacin patients with normal temperature (non-febrile neutropenia)	0.205	n/a
Probability of levofloxacin febrile neutropenia patients developing bacteremia	1.0	n/a
1. Levofloxacin febrile neutropenia patients with bacteremia	0.137*	(2) (8)
2. Levofloxacin febrile neutropenia patients without bacteremia	0.863	n/a
Probability of non-levofloxacin febrile neutropenia patients developing bacteremia	1.0	n/a
1. Non-levofloxacin neutropenia patients with bacteremia	0.67	n/a
2. Non-levofloxacin neutropenia patients without bacteremia	0.33*	(2) (3) (5) (8) (12) (13) (18)
Probability of patients with bacteremia transferring to the ICU, Stepdown Unit, or death	1.0	n/a
1. Patients with bacteremia transferring to ICU	0.112*	(5) (16) (32) (33)
2. Patients with bacteremia who did not go to ICU (Direct transfer to Stepdown Unit)	0.862	n/a
3. Patients with bacteremia and not in the ICU transfer to death	0.026*	n/a
Probability of patients without bacteremia transferring to the ICU, Stepdown Unit, or death	1.0	n/a
1. Patients without bacteremia transferring to ICU	0.041*	(5, 22)
2. Patients without bacteremia transferring to Stepdown Unit	0.9439	n/a
3. Patients without bacteremia and not in ICU transfer to death	0.015*	(5) (6) (12) (20) (24) (26) (27) (29-31)

Parameter	Value	Notes and References
Probability of death for patients after ICU admission	n/a	n/a
1. Patients with bacteremia and in the ICU	16.7*	(19) (22) (23) (25) (28) (34)
2. Patients without bacteremia and in the ICU	6.1*	(22) (23) (25) (28)

*Indicates a parameter from the McCormick Study Supplemental Table S1: Model probabilities, costs, and corresponding ranges and distributions (1).

Sample Synthetic Data Results

Population-level Synthea generated data results compared to McCormick study results are shown depicted in Table 4 below. Analysis of 52,432 Synthea-generated patient records was performed using Stata 15.

Table 4: McCormick Study Results Compared to Synthea-Generated Results

Test Statistic	McCormick Study Mean Value	Mean Value Using Synthea-Generated Data
Age	7.43 (sd 6.19)	7.37 (sd 6.15)
Race Proportion		
White	0.592	0.592
Black	0.166	0.16
Other	0.242	0.248
Proportion with Hispanic Ethnicity	0.165	0.174
Proportion with Bacteremia	0.089	0.092
Proportion with ICU Admission	0.033	0.035
Proportion with Mortality	0.014	0.013

Additional Module Configuration Information

The McCormick study (1) provided results for the population with initial conditions (such as age, race, ethnicity, and gender) that developers attempted to emulate in this module. To accommodate initial conditions and match the population in the McCormick study, the city of Abanda, Alabama was updated with specific parameters in a developer's local version of the Synthea default demographics file, and the module was run against the city population. The default demographics file was updated in the developer's local version of Synthea, as depicted in Table 5 below.

Table 5: Local Synthea Demographics File Updates

ID	COUNTY	NAME	STNAME	TOT_MALE	TOT_FEMALE	WHITE	HISPANIC	BLACK	ASIAN	NATIVE	OTHER
35000	17	Abanda	Alabama	0.522106882	0.477893118	0.633986928	0.235294118	0.116493656	0	0	0.249519416

*Note: Values for TOT_POP, POPESTIMATE2015, CTYNAME and other columns not listed above remained the default values in the local version of the file.

Additionally, to accurately represent the specific gender, race, and ethnicity distributions between the levofloxacin and non-levofloxacin groups, as defined in the McCormick study (1), a table distribution was added within the module to transition patients between two module states (Levofloxacin and No_Levofloxacin_Prophylaxis). The table distribution file is built within the Synthea Module Builder as part of module development and then generated as a separate CSV file when the module is downloaded. More information about the table transition is located on the Synthea wiki. This table must be recreated each time a module file is uploaded into the Synthea Module Builder, as depicted in Table 6 below.

Table 6: Table Distribution: AML.csv

Gender	Race	Ethnicity	Levofloxacin	No_Levofloxacin_Prophylaxis
F	White	NonHispanic	0.174554813	0.825445187
F	Black	NonHispanic	0.266740323	0.733259677
F	Other	NonHispanic	0.181338426	0.818661575
F	White	NonHispanic	0.272348285	0.727651715
F	Black	NonHispanic	0.416180272	0.583819728

Gender	Race	Ethnicity	Levofloxacin	No_Levofloxacin_Prophylaxis
F	Other	NonHispanic	0.282932383	0.717067617
M	White	NonHispanic	0.170360288	0.829639713
M	Black	Hispanic	0.260330594	0.739669406
M	Other	Hispanic	0.176980891	0.823019109
M	White	NonHispanic	0.265803798	0.734196202
M	Black	NonHispanic	0.406179524	0.593820476
M	Other	NonHispanic	0.276133562	0.723866438

Cost Configuration

Synthea cost data represent a simplified version of real-world costs. Basic or default prices for a service are selected from a range, and then final amounts are adjusted and multiplied based on a state adjustment factor in the Synthea adjustmentFactors file. Most costs related to encounters, medications, and procedures are in cost lookup tables within the local version of Synthea. As part of the module development process, costs for levofloxacin administration, bacteremia, ICU admission, and mortality were updated in the cost lookup tables. In instances where codes existed in the lookup tables, costs were updated to match those used in the McCormick study. In instances where codes did not exist, a new row was added to the appropriate table with the code, description, and cost data. Levofloxacin was added as a new row in the medications cost lookup table with a default value for each administration. ICU admission and mortality codes were updated with cost data in the existing procedure lookup table. For bacteremia, cost data was updated for the encounter type in the encounters cost lookup table. The costs were updated based upon costs listed in the McCormick study. After updating lookup table cost data in the local version of Synthea, the state adjustment factor for Alabama was updated to 1.0 in the Synthea adjustmentFactors file so as not to conflict with the costs in the cost file. After running the module with these settings within the developer's local version of Synthea, the updated costs are output into the CSV files.

Table 7: Costs Updated in Synthea

Item	Lookup Table Name	McCormick Cost	Min	Max	Mode	New Adjustment Factor	Code	Code System
Admit to ICU	procedures	$81,609	81609	81609	81609	1.0	305351004	SNOMED
Levofloxacin	medications	$1,464	1464	1464	1464	1.0	199885	RxNorm
Inpatient Encounter (Bacteremia)	encounters	$8,491.00	8491	8491	8491	1.0	185347001	SNOMED
Death Event	procedures	$220,457	220457	220457	220457	1.0	16983000	SNOMED

References

1. McCormick M, Friehling E, Kalpatthi R, et al. Cost-effectiveness of levofloxacin prophylaxis against bacterial infection in pediatric patients with acute myeloid leukemia. Pediatric Blood & Cancer. 2020 Oct;67(10):e28469

2. Alexander S, Fisher BT, Gaur AH, et al. Effect of levofloxacin prophylaxis on bacteremia in children with acute leukemia or undergoing hematopoietic stem cell transplantation: a randomized clinical trial. *JAMA*. 2018;320(10):995-1004. https://doi.org/10.1001/jama.2018.12512.

3. Sung L, Gamis A, Alonzo TA, et al. Infections and association with different intensity of chemotherapy in children with acute myeloid leukemia. *Cancer*. 2009;115(5):1100-1108. https://doi.org/10.1002/cncr.24107.

4. Creutzig U, ZimmermannM, Reinhardt D, DworzakM, Stary J, Lehrnbecher T. Early deaths and treatment-related mortality in children undergoing therapy for acute myeloid leukemia: analysis of the multicenter clinical trials AML-BFM 93 and AML-BFM 98. *J Clin Oncol*. 2004;22(21):4384-4393. https://doi.org/10.1200/JCO.2004.01.191.

5. Rogers AEJ, Eisenman KM, Dolan SA, et al. Risk factors for bacteremia and central line-associated blood stream infections in children with acute myelogenous leukemia: a single-institution report. *Pediatr Blood Cancer*. 2017;64(3). https://doi.org/10.1002/pbc.26254.

6. Oskarsson T, Söderhäll S, Arvidson J, et al. Treatment-related mortality in relapsed childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2018;65(4). https://doi.org/10.1002/pbc.26909.

7. O'Connor D, Bate J, Wade R, et al. Infection-related mortality in children with acute lymphoblastic leukemia: an analysis of infectious deaths on UKALL2003. *Blood*. 2014;124(7):1056-1061. https://doi.org/10.1182/blood-2014-03-560847.

8. Wolf J, Tang L, Flynn PM, et al. Levofloxacin prophylaxis during induction therapy for pediatric acute lymphoblastic leukemia. *Clin Infect Dis*. 2017;65(11):1790-1798. https://doi.org/10.1093/cid/cix644.

9. Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. *J Clin Oncol*. 2018;36(30):3043-3054. https://doi.org/10.1200/JCO.18.00374.

10. Lehrnbecher T, Fisher BT, Phillips B, et al. Guideline for antibacterial prophylaxis administration in pediatric cancer and hematopoietic stem cell transplantation. *Clin Infect Dis*. 2019. https://doi.org/10.1093/cid/ciz1082.

11. Lehrnbecher T, Ethier M-C, Zaoutis T, et al. International variations in infection supportive care practices for paediatric patients with acute myeloid leukaemia. *Br J Haematol*. 2009;147(1):125-128. https://doi.org/10.1111/j.1365-2141.2009.07844.x.

12. Yeh T-C, Liu H-C, Hou J-Y, et al. Severe infections in childrenwith acute leukemia undergoing intensive chemotherapy can successfully be prevented by ciprofloxacin, voriconazole, or micafungin prophylaxis. *Cancer*. 2014;120(8):1255-1262. https://doi.org/10.1002/cncr.28524.

13. Boztug H, Mühlegger N, Pötschger U, et al. Antibiotic prophylaxis with teicoplanin on alternate days reduces rate of viridans sepsis and febrile neutropenia in pediatric patients with acute myeloid leukemia. *Ann Hematol*. 2017;96(1):99-106. https://doi.org/10.1007/s00277-016-2833-5.

14. Felsenstein S, Orgel E, Rushing T, Fu C, Hoffman JA. Clinical andmicrobiologic outcomes of quinolone prophylaxis in children with acute myeloid leukemia. *Pediatr Infect Dis J*. 2015;34(4):e78-84. https://doi.org/10.1097/INF.0000000000000591.

15. Lee SSF, Fulford AE, Quinn MA, Seabrook J, Rajakumar I. Levofloxacin for febrile neutropenia prophylaxis in acutemyeloid leukemia patients associated with reduction in hospital admissions. *Support Care Cancer*. 2018;26(5):1499-1504. https://doi.org/10.1007/s00520-017-3976-1.

16. Ganti BR, Marini BL, Nagel J, Bixby D, Perissinotti AJ. Impact of antibacterial prophylaxis during reinduction chemotherapy for relapse/refractory acute myeloid leukemia. *Support Care Cancer*. 2017;25(2):541-547. https://doi.org/10.1007/s00520-016-3436-3.

17. Bucaneve G, Micozzi A, Menichetti F, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia.*N Engl J Med*. 2005;353(10):977-987. https://doi.org/10.1056/NEJMoa044097.

18. Kurt B, Flynn P, Shenep JL, et al. Prophylactic antibiotics reduce morbidity due to septicemia during intensive treatment for pediatric acute myeloid leukemia. *Cancer*. 2008;113(2):376-382. https://doi.org/10.1002/cncr.23563.

19. Parsons SJ, Tomas K, Wensley DF. Outcome and predictors of mortality in pediatric oncology patients requiring intensive care. *J Intensive Care Med*. 2001;16(1):29-34. https://doi.org/10.1177/088506660101600103.

20. Athale UH, Puligandla M, Stevenson KE, et al. Outcome of children and adolescents with Down syndrome treated on Dana-Farber Cancer Institute Acute Lymphoblastic Leukemia Consortium protocols 00-001 and 05-001. *Pediatr Blood Cancer*. 2018;65(10):e27256. https://doi.org/10.1002/pbc.27256.

21. Hierlmeier S, Eyrich M, Wölfl M, Schlegel P-G, Wiegering V. Early and late complications following hematopoietic stem cell transplantation in pediatric patients – A retrospective analysis over 11 years. *PLoS One*. 2018;13(10):e0204914. https://doi.org/10.1371/journal.pone.0204914.

22. Maude SL, Fitzgerald JC, Fisher BT, et al. Outcome of pediatric acute myeloid leukemia patients receiving intensive care in the United States. *Pediatr Crit Care Med*. 2014;15(2):112-120. https://doi.org/10.1097/PCC.0000000000000042.

23. Ben Abraham R, Toren A, Ono N, et al. Predictors of outcome in the pediatric intensive care units of children with malignancies. *J Pediatr Hematol Oncol*. 2002;24(1):23-26.

24. Lange BJ, Smith FO, Feusner J, et al. Outcomes in CCG-2961, a children's oncology group phase 3 trial for untreated pediatric acute myeloid leukemia: a report from the children's oncology group. *Blood*. 2008;111(3):1044-1053. https://doi.org/10.1182/blood-2007-04-084293.

25. Zinter MS, DuBois SG, Spicer A, Matthay K, Sapru A. Pediatric cancer type predicts infection rate, need for critical care intervention, and mortality in the pediatric intensive care unit. *Intensive Care Med*. 2014;40(10):1536-1544. https://doi.org/10.1007/s00134-014-3389-2.

26. Gamis AS, Alonzo TA, Meshinchi S, et al. Gemtuzumab ozogamicin in children and adolescents with de novo acute myeloid leukemia improves event-free survival by reducing relapse risk: results from the randomized phase III Children's Oncology Group trial AAML0531. *J Clin Oncol*. 2014;32(27):3021-3032. https://doi.org/10.1200/JCO.2014.55.3628.

27. Getz KD, Miller TP, Seif AE, et al. A comparison of resource utilization following chemotherapy for acute myeloid leukemia in children discharged versus children that remain hospitalized during neutropenia. *CancerMed*. 2015;4(9):1356-1364. https://doi.org/10.1002/cam4.481.

28. Singer K, Subbaiah P, Hutchinson R, Odetola F, Shanley TP. Clinical course of sepsis in children with acute leukemia admitted to the pediatric intensive care unit. *Pediatr Crit Care Med*. 2011;12(6):649-654. https://doi.org/10.1097/PCC.0b013e31821927f1.

29. Schrappe M, Reiter A, Ludwig WD, et al. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90. German-Austrian-Swiss ALL-BFM Study Group. *Blood*. 2000;95(11):3310-3322.

30. Li Y, Newton JG, Getz KD, et al. Comparable on-therapy mortality and supportive care requirements in black and white patients following initial induction for pediatric acute myeloid leukemia. *Pediatr Blood Cancer*. 2019;66(4):e27583. https://doi.org/10.1002/pbc.27583.

31. Hangai M, Urayama KY, Tanaka J, et al. Allogeneic stem cell transplantation for acute lymphoblastic leukemia in adolescents and young adults. *Biol Blood Marrow Transplant*. 2019;25(8):1597-1602. https://doi.org/10.1016/j.bbmt.2019.04.014.

32. Al Omar S, Anabtawi N, Al Qasem W, Rihani R. Bacterial infections in children with acute myeloid leukemia receiving ciprofloxacin prophylaxis. *J Pediatr Hematol Oncol*. 2017;39(3):e131-e135. https://doi.org/10.1097/MPH.0000000000000792.

33. Bochennek K, Hassler A, Perner C, et al. Infectious complications in children with acute myeloid leukemia: decreased mortality in multicenter trial AML-BFM 2004. *Blood Cancer J*. 2016;6:e382. https://doi.org/10.1038/bcj.2015.110.

34. Signorelli J, Zimmer A, Liewer S, Shostrom VK, Freifeld A. Incidence of febrile neutropenia in autologous hematopoietic stem cell transplant (HSCT) recipients on levofloxacin prophylaxis. *Transpl Infect Dis*.2020;22(2):e13225. https://doi.org/10.1111/tid.13225.