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Washington University Multiple Myeloma Model-Compartmental Model (WUMM-CM): Model Profile

Washington University

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Version Table

Version	Date	Notes
1.0.00	2025-09-30	Initial release

Other Publications

Huber JH, Ji M, Shih YH, Wang M, Colditz G, Chang SH. Disentangling age, sex, and racial disparities in multiple myeloma burden: a modeling study. Nature Communications. 2023 Sep 20;14(1):5768. PubMed PMID: 37730703; PMCID: PMC10511740.

Washington University
Readers Guide

Reader's Guide

Core Profile Documentation

These topics will provide an overview of the model without the burden of detail. Each can be read in about 5-10 minutes. Each contains links to more detailed information if required.

Model Purpose

This document describes the primary purpose of the model.

Model Overview

This document describes the primary aims and general purposes of this modeling effort.

Assumption Overview

An overview of the basic assumptions inherent in this model.

Parameter Overview

Describes the basic parameter set used to inform the model, more detailed information is available for each specific parameter.

Component Overview

A description of the basic computational building blocks (components) and the calibration procedure of the model.

Output Overview

Definitions and methodologies for the basic model outputs.

Results Overview

A guide to the results obtained from the model.

Key References

A list of references used in the development of the model.

Model Purpose

Summary

The CISNET Multiple Myeloma Incubator Program Washington University modeling group is to construct an evidence-based, calibrated, validated natural history of multiple myeloma (MM) model to evaluate MM prevention and control policies.

Purpose

Multiple myeloma (MM) is a common hematologic cancer and consistently preceded by an asymptomatic premalignant condition – monoclonal gammopathy of undetermined significance (MGUS). [1] MM incurs a significant health and economic burden to patients, family, and the entire healthcare system. [2-4] In addition, MM health disparities are well established. [5-8]

The long-term goal of the models developed by the CISNET Multiple Myeloma Incubator Program is to guide MM prevention and control policies and shift the current clinical paradigm in the management of MGUS and MM toward reducing MM burden and health disparities. We plan to comparatively model the natural disease history of MM from the development of MGUS to MM, followed by survivorship through two modeling groups (Washington University and Yale University modeling groups) under the current clinical practice: Washington University Multiple Myeloma Model (WUMM) and Yale University Multiple Myeloma Model (YUMM).

The WUMM plans to construct an evidence-based, calibrated, validated natural MM history model, which can be utilized to assess (1) the impacts of novel intervention strategies on MM prevention in high-risk patients diagnosed with MGUS, in terms of number of prevented MM cases, costs, and life years saved in high-risk MGUS patients; (2) the impacts of innovative treatment regimens on survival outcomes as well as the value of the guideline recommend therapies in MM patients; and (3) whether, under what conditions, and in which ways the goal of eliminating racial disparities can be achieved through these novel intervention strategies and treatment regimens.

References

1. Ola Landgren. Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma: biological insights and early treatment strategies. Hematology 2013, the American Society of Hematology Education Program Book. American Society of Hematology Washington, DC; 2013;2013(1):478–487.
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Washington University
Model Overview

Model Overview

Summary

In the CISNET Multiple Myeloma Incubator Program, the Washington University modeling group has constructed a discrete-time, multi-state compartmental model to describe the natural history of multiple myeloma (wumm-cm). This model has previously been calibrated and published to characterize disparities in multiple myeloma incidence by age, gender, and race/ethnicity.[1]

Purpose

The purpose of the model is to provide a mathematical framework for describing the natural history of multiple myeloma. Robust mathematical descriptions of the natural history of multiple myeloma are lacking. By rigorously developing and calibrating a mathematical model to multiple, nationally representative data streams, we provide a detailed characterization of this disease process and have already answered fundamental epidemiological questions concerning racial and gender disparities.[1] Ongoing work is aimed at capturing longitudinal changes in MM incidence and incorporating the effects of body mass index (BMI).

Background

The model leverages a compartmental model design to describe the prevalence and incidence of monoclonal gammopathy of undetermined significance (MGUS), a precursor state to MM, and MM. Compartmental models offer a convenient framework for modeling the flow of populations through different disease states (i.e., compartments). One specific advantage of compartmental models is that their deterministic formulation allows for computational speed-ups for model fitting over traditional, stochastic microsimulation models. Furthermore, compartmental models can be easily translated into a corresponding stochastic, microsimulation model, allowing for computational benefits during calibration with greater detail in simulation during subsequent analyses.

Model Description

Briefly, the model is a discrete time, multi-state compartmental model consisting of four health states: Healthy (H), Monoclonal Gammopathy (MGUS), Multiple Myeloma (MM), and Death (D) (Figure 1). The compartment model models the proportion P of a birth cohort that exists in each health state at any given point in time. Flow from one compartment to another is governed by rates that depend upon age a, gender s, and race/ethnicity r. Specifically, $\lambda_{MGUS}(a, s, r)$ is the rate that healthy individuals develop MGUS, and $\lambda_{MM}(a, s, r)$ is the rate that individuals with MGUS develop MM. The rates $\mu_H(a, s, r)$, $\mu_{MGUS}(a, s, r)$, and $\mu_{MM}(a, s, r)$ denote the mortality rates of healthy individuals, individuals with MGUS, and individuals with MM, respectively. For a complete description of the methods, please refer to the detailed methods and supplementary materials in our previously published work.

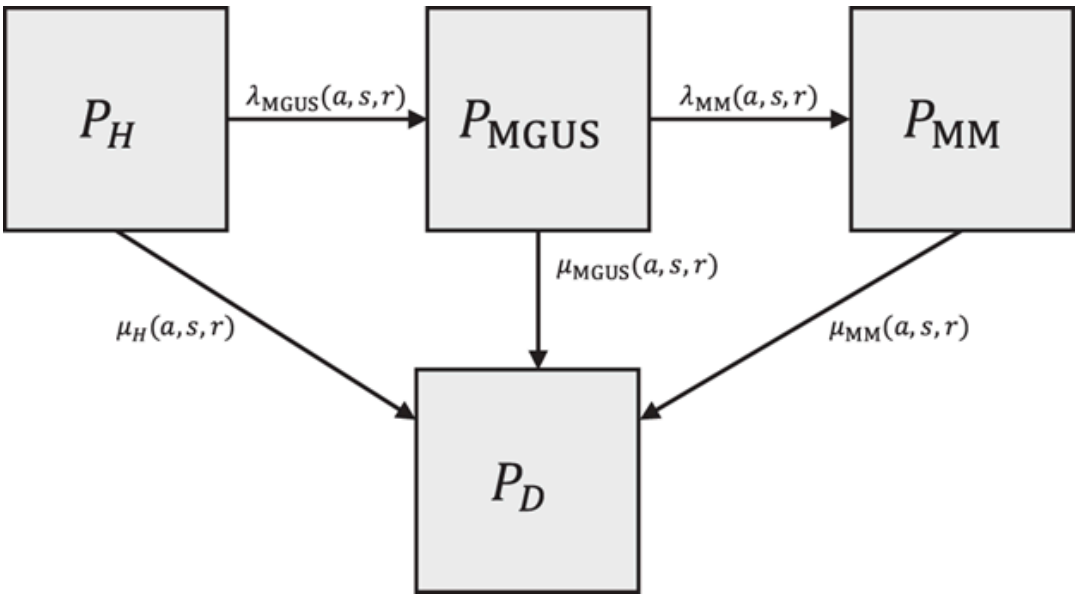

Figure 1. Model Schematic. Borrowed with permission from Huber et al. (2023)

References

1. John H Huber, Mengmeng Ji, Yi-Hsuan Shih, Mei Wang, Graham Colditz, Su-Hsin Chang. Disentangling age, gender, and racial/ethnic disparities in multiple myeloma burden: a modeling study. Nature communications. Nature Publishing Group UK London; 2023;14(1):5768.

Assumption Overview

Summary

Assumptions were made regarding the natural history of multiple myeloma for the purpose of this modeling exercise. All assumptions made during this work were based upon previously published literature.

Background

Data on MGUS and its epidemiology are not well-characterized, because this precursor state is frequently asymptomatic. Accordingly, we made multiple assumptions about the natural history of MGUS and MM that relied upon previously published literature.

Assumption Listing

- In this model, the rate at which a healthy individual develops MGUS depends only upon their age, their gender, and their race/ethnicity. No other covariates, including BMI, were considered in the model at this time.
- Individuals with MGUS develop MM at a rate that depends only upon age, gender, and race/ethnicity.
- Smoldering multiple myeloma was not modeled as an intermediate state between MGUS and MM, due to the lack of available data at this time.
- We assumed that mortality in MGUS-positive individuals was 1.25 times greater than the baseline age- and race/ethnicity-specific mortality rate for men and 1.11 times greater than the baseline age- and race/ethnicity-specific mortality rate for women. [1]
- We assumed that all data on MGUS prevalence and MM incidence used to calibrate the model was nationally representative.

References

1. Terry M Therneau, Robert A Kyle, L Joseph Melton III, Dirk R Larson, Joanne T Benson, Colin L Colby, et al. Incidence of monoclonal gammopathy of undetermined significance and estimation of duration before first clinical recognition. Mayo Clinic Proceedings. Elsevier; 2012. p. 1071–1079.

Parameter Overview

Summary

Multiple model parameters were estimated from data sources on MGUS prevalence and MM incidence. A description of these parameters and their estimates with uncertainty are provided in this section along with a description of the data sources used.

Background

We calibrated our model to data sources on MGUS prevalence and MM incidence to estimate parameters that governed the rate of flow from healthy to MGUS and from MGUS to MM.

Data Resource

Continuous NHANES: We used the continuous NHANES data from 1999-2004 to obtain empirical estimates of MGUS prevalence among 4,355 individuals ages 50 and older. This data was stratified by age, gender, and race/ethnicity. [1]

SEER: We used MM incidence from 2010 that was stratified by age, gender, and race/ethnicity. [2] As can be found in our previously published work,[3] our parameter estimates were robust to the choice of year of MM incidence.

Parameters

A description of the parameters and their corresponding estimates can be found in Table 1.

Table 1: Model parameters, descriptions, and estimates

Parameter	Description	Estimate (95% CI)
γ_{MGUS}	Interception for rate of MGUS development	-9.7 (-11.0 - -8.9)
$\beta_{(MGUS,a)}$	Age coefficient for rate of MGUS development	0.051 (0.036 – 0.065)
$\beta_{(MGUS,s)}$	Gender coefficient for rate of MGUS development	-0.54 (-0.84 - -0.24)
$\beta_{(MGUS,r)}$	Race/ethnicity coefficient for rate of MGUS development	0.68 (0.34 – 1.00)
γ_{MM}	Intercept for rate of MM development	-13 (-15 - -12)
$\beta_{(MM,a)}$	Age coefficient for rate of MM development	0.25 (0.22 – 0.28)
$\beta_{(MM,a^2)}$	Quadratic age coefficient for rate of MM development	-0.0017 (-0.0020 - -0.0015)
$\beta_{(MM,s)}$	Gender coefficient for rate of MM development	0.14 (-0.20 – 0.49)
$\beta_{(MM,r)}$	Race/ethnicity coefficient for rate of MM development	0.20 (-0.17 – 0.58)

References

1. Centers for Disease Control and Prevention (CDC). National Health and Nutrition Examination Survey Data [Internet]. 1999. Available from: <a href=https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=1999>https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=1999
2. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Data, Nov 2021 Sub (1975-2019) - Linked To County Attributes - Time Dependent (1990-2019) Income/Rurality, 1969-2020 Counties [Internet]. 2022. Available from: https://www.seer.cancer.gov
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Component Overview

1. Simulation Overview

Summary

We briefly describe the simulation of our compartmental model and a calculation for the prevalence and incidence of MGUS and MM.

Overview

For the discrete-time, multi-state compartmental model, birth cohorts are simulated forward in time from age 0 to age 100. We assume that, at birth, all individuals are healthy, and no individuals are dead, have MGUS, or have MM. The rate of flow between compartments is governed by the age *a* of the birth cohort, its gender *s*, and the race/ethnicity *r*. Relevant outputs from the model include prevalence and incidence of MGUS and MM.

Component Listing

Simulation of our compartmental model provides us with $P_H(a,s,r)$, $P_{MGUS}(a,s,r)$, $P_{MM}(a,s,r)$, and $P_{MM}(a,s,r)$. Each of these quantities represents the proportion of the birth cohort of individuals of gender *s* and race/ethnicity *r* that occupies that health state at age *a*. We use these model outputs to calculate prevalence and incidence.

Prevalence: To calculate prevalence, we conditioned upon the proportion of the birth cohort that was alive at age *a*. Accordingly, the prevalence of MGUS and MM can be represented as:

$$p_{MGUS}(a,s,r) = \frac{P_{MGUS}(a,s,r)}{1 - P_D(a,s,r)}, \quad (1)$$

$$p_{MM}(a,s,r) = \frac{P_{MM}(a,s,r)}{1 - P_D(a,s,r)}. \quad (2)$$

Incidence: We calculated age-stratified incidence of MGUS and MM among individuals of gender *s* and race/ethnicity *r* by conditioning upon the proportion of the birth cohort that was alive at age *a*. Accordingly, the prevalence of MGUS and MM can be represented as:

$$i_{MGUS}(a,s,r) = \lambda_{MGUS}(a,s,r) p_H(a,s,r), \quad (3)$$

$$i_{MM}(a,s,r) = \lambda_{MM}(a,s,r) p_{MGUS}(a,s,r). \quad (4)$$

In equation (3), $p_H(a,s,r)$ is the prevalence of healthy individuals of age *a*, gender *s*, and race/ethnicity *r*, which we calculated as $1 - p_{MGUS}(a,s,r) - p_{MM}(a,s,r)$ from equations (1-2).

2. Calibration Overview

Summary

The below section describes the methodology for calibrating the model to the NHANES and SEER data.

Overview

We used a Markov chain Monte Carlo (MCMC) algorithm to estimate the parameters of our model. We ran 5 independent chains in parallel. Each chain was run for 1,000,000 samples with a burn-in period of 500,000 samples and thinned every 50 samples to reduce autocorrelation. Convergence of parameters was assessed using the Gelman-Rubin statistics with values less than 1.1 providing statistical support for convergence. After assessing for convergence, the chains were pooled to obtain a final posterior distribution of 50,000 samples. For a complete description of the calibration methodology and the likelihoods used to fit the model to the NHANES MGUS prevalence and SEEER MM incidence, please refer to our previously published work. [1]

References

1. John H Huber, Mengmeng Ji, Yi-Hsuan Shih, Mei Wang, Graham Colditz, Su-Hsin Chang. Disentangling age, gender, and racial/ethnic disparities in multiple myeloma burden: a modeling study. Nature communications. Nature Publishing Group UK London; 2023;14(1):5768.

Output Overview

Summary

We define the outputs generated by our compartmental model.

Overview

Briefly, the compartmental model can generate estimates of prevalence and incidence for MGUS and MM. Prevalence can be stratified by age *a*, gender *s*, and race/ethnicity *r*. Equations to calculate prevalence and incidence of MGUS and MM from the model can be found in the Component Listing section of the Simulation Overview.

Results Overview

Summary

This section describes the results of our model calibration to data from NHANES and SEER.

Result Listing

Our model was calibrated to data on MGUS prevalence from NHANES during 1999-2004 and MM incidence from SEER during 2010. The five independent MCMC chains were well-mixed, and the Gelman-Rubin statistics were 1.0 for each parameter, indicating convergence. As evidenced in Figure 2, the fitted model captured the trends in MGUS prevalence and MM incidence across age, gender, and race/ethnicity. The fitted model was able to reproduce the data with appropriate levels of uncertainty. The 95% posterior prediction interval contained all but two data points with most data points falling close to the median posterior prediction.

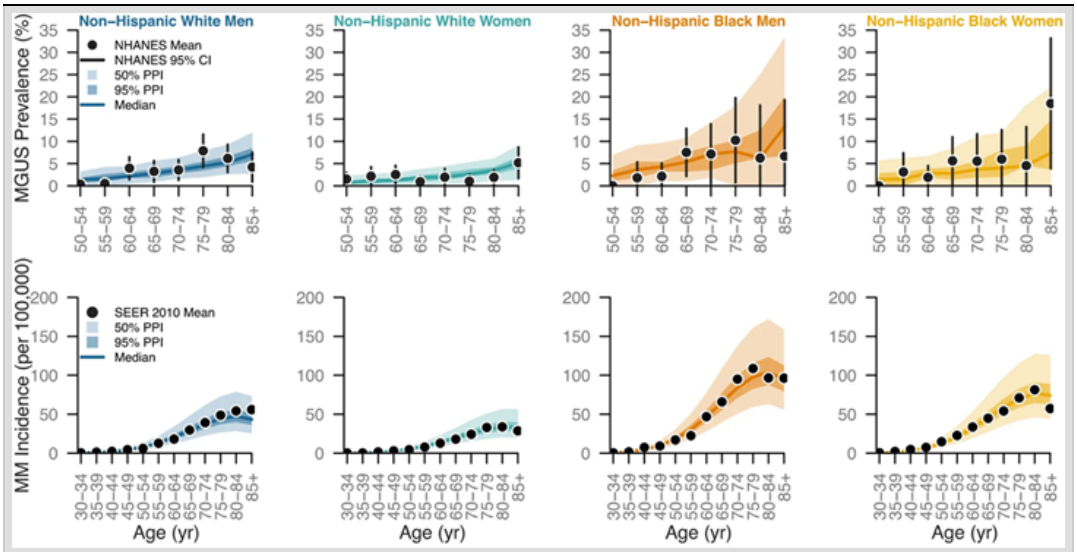

Figure 2. Comparison of Fitted Model to NHANES and SEER Data. Reproduced with permission from Huber et al. (2023).

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