Combined Model Profile
Version: 1.0.00
Released: 2025-09-30

Myeloma Combined Model Profile

Individual Model Profiles

Washington University Multiple Myeloma Model-Compartmental Model (WUMM-CM): Model Profile
Washington University
Version: 1.0.00
Released: 2025-09-30

Washington University Multiple Myeloma-Discrete Event Simulation Model (WUMM-DES): Model Profile
Washington University
Version: 1.0.00
Released: 2025-09-30

Yale University Natural History of Multiple Myeloma Model (YUMM): Model Profile
Yale University
Version: 1.0.00
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Combined Model Profile Version Table

Version	Date	Notes
1.0.00	2025-09-30	Initial release

Washington University
Version: 1.0.00
Released: 2025-09-30

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

Washington University

Contact

Su-Hsin Chang (chang.su-hsin@wustl.edu)

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Suggested Citation

Huber JH, Ji M, Shih YH, Wang M, Colditz G, Chang SH. Washington University Multiple Myeloma Model-Compartmental Model (WUMM-CM): Model Profile. [Internet] Sep 30, 2025. Cancer Intervention and Surveillance Modeling Network (CISNET). Available from: https://cisnet.cancer.gov/resources/files/mpd/myeloma/CISNET-myeloma-wumm-cm-model-profile-1.0.00-2025-09-30.pdf

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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

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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.

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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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8. Jagat Singh, Alden W Dudley, Kimberly A Kulig. Increased incidence of monoclonal gammopathy of undetermined significance in blacks and its age-related differences with whites on the basis of a study of 397 men and one woman in a hospital setting. The Journal of laboratory and clinical medicine. Elsevier; 1990;116(6):785–789.

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.

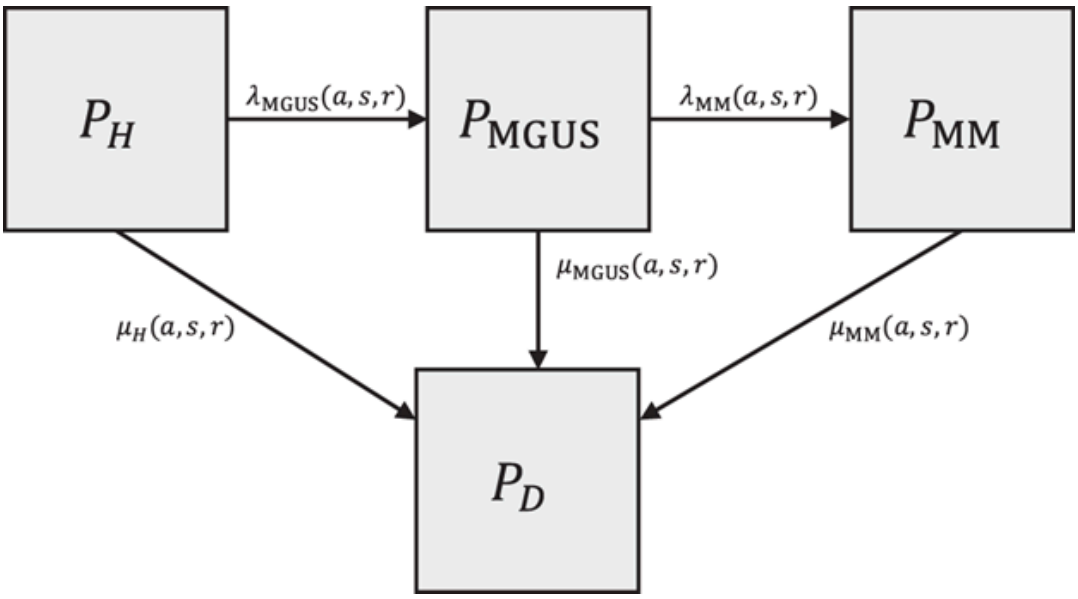

Figure 1. Model Schematic. Borrowed with permission from Huber et al. (2023)

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.

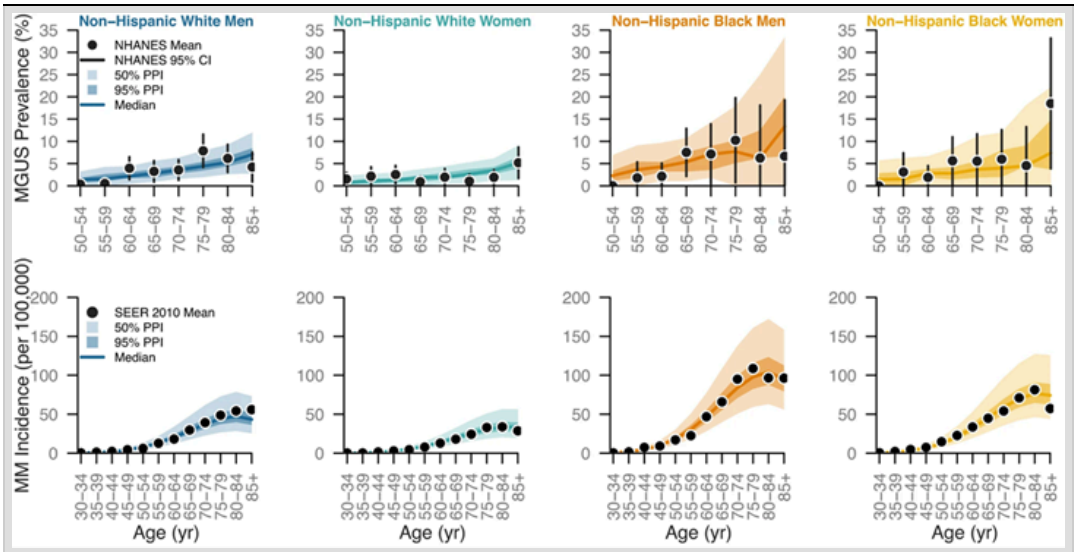

Figure 2. Comparison of Fitted Model to NHANES and SEER Data. Reproduced with permission from Huber et al. (2023).

Key References

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Harvey Jay Cohen, Jeffrey Crawford, Murali K Rao, Carl F Pieper, Mark S Currie. Racial differences in the prevalence of monoclonal gammopathy in a community-based sample of the elderly. The American journal of medicine. Elsevier; 1998;104(5):439–444.

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Washington University

Contact

Su-Hsin Chang (chang.su-hsin@wustl.edu)

Funding

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Shih YH, Ji M, Huber J, Wang M, Schoen MW, Thomas TS, Colditz GA, Li J-S, Michaud TL, Chang S-H. Burden of Monoclonal Gammopathy of Undetermined Significance and multiple myeloma: A discrete-event simulation modeling study (in preparation)

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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

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5. Reference not found for key: ncicancerstatfacts2024@greenberg2012disparities.
6. Harvey Jay Cohen, Jeffrey Crawford, Murali K Rao, Carl F Pieper, Mark S Currie. Racial differences in the prevalence of monoclonal gammopathy in a community-based sample of the elderly. The American journal of medicine. Elsevier; 1998;104(5):439–444.
7. Jagat Singh, Alden W Dudley, Kimberly A Kulig. Increased incidence of monoclonal gammopathy of undetermined significance in blacks and its age-related differences with whites on the basis of a study of 397 men and one woman in a hospital setting. The Journal of laboratory and clinical medicine. Elsevier; 1990;116(6):785–789.

Washington University
Model Overview

Model Overview

Summary

In the CISNET Multiple Myeloma incubator program, the Washington University modeling group has constructed and calibrated a discrete event simulation (DES) model tailored to model the natural history of MM, from no MGUS/MM, MGUS development, progression to MM, and death for the U.S. population aged 20 years or older (WUMM-DES).

Purpose

The long-term goal of this WUMM-DES model is to fill the gap in setting and prioritizing policy goals for MM prevention and control. To achieve this goal, we constructed a discrete event simulation (DES) model to simulate the natural history of MM from the development of MGUS to MM, followed by survivorship for the U.S. population. Using this model, we will then evaluate whether promising intervention strategies throughout the continuum of care will effectively prevent the devastating malignancy or improve MM survival with great value.

Background

In the CISNET Multiple Myeloma incubator program, the Washington University modeling group has constructed and calibrated a DES model tailored to model the natural history of MM, from no MGUS/MM, MGUS development, progression to MM, and death for the U.S. population aged 20 years or older (WUMM-DES), stratified by race/ethnicity and sex.

The WUMM-DES model is a stochastic model informed by real-world data to simulate the natural history of MM progression. DES models the operation of a system as a discrete sequence of well-defined events in time. It is usually a preferred model, due to its simplicity, efficiency, and flexibility, (e.g., no fixed cycle length, ability to manage multiple events simultaneously and to allow interactions between individuals).[1-4]The parameters will vary based on the characteristics of each individual, and thus the model is agent-based. Due to the long progression of asymptomatic MGUS to symptomatic MM (a feature that makes Markov models inefficient) and the unknown functional form of a mathematical equation for progression (a feature that precludes the use of system dynamics models), DES is an appropriate modeling for MGUS-MM progression.

The developed simulation modeling can be tailored to set research priorities and design clinical trials, including assessing sample sizes and power, evaluating the impact of treatment adherence of the participants, and determining the optimal treatment strategies. It can also be used to predict trial results and set policy goals.

Model Description

The theoretical model builds on natural history of MM (**Figure 1**). The WUMM-DES model targets at the U.S. general population aged over 20 years since the prevalence of MGUS for the population aged below 20 years is nearly 0%.[5] The model currently integrates three demographic factors, age, sex, and race/ethnicity and simulates the natural history of MM for four U.S. populations, including non-Hispanic white (NHW) men and women, as well as non-Hispanic Black (NHB) men and women.

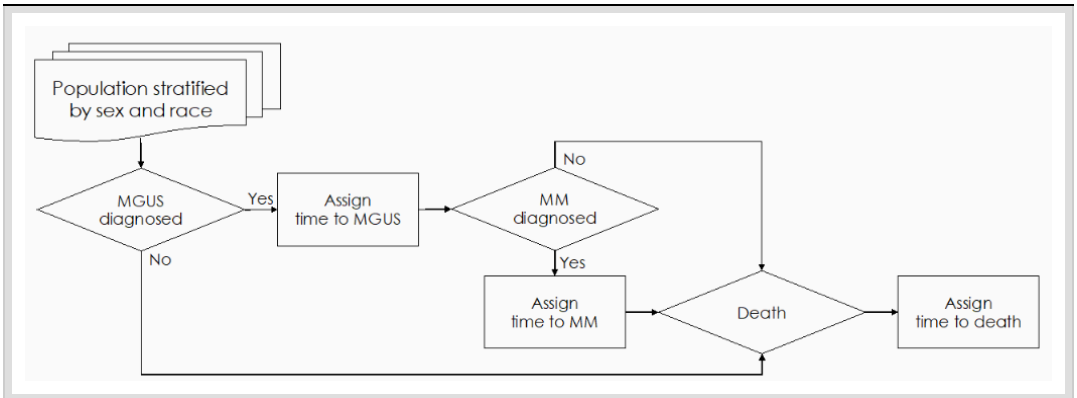

Figure 1. *WUMM-DES Model Schemepace*

Stratified by sex and race, this model starts with the population at age 20 without disease. For each population, some individuals develop MGUS, while the others do not. Some patients with MGUS progress to MM with varied time to progression depending on their characteristics, while others do not progress. All individuals, with or without MGUS and/or MM will be assigned time to all-cause death with time depending on their disease path and their individual characteristics.

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Assumption Overview

Summary

Model assumptions are based on the availability of secondary data and/or evidence supported by the literature. We made assumptions on the following aspects: risk factors, disease stages, diagnosis, MM treatment, access to care, and parametric assumptions.

Background

Model assumptions are based on the availability of secondary data and/or evidence published by the literature. The etiology of MGUS and MM is poorly known. Henceforth, only known risk factors with sufficient evidence and available data will be included in the model. Previous studies reported that risk factors for MGUS/MM include older age, black race, male sex, family history, radiation, and pesticide exposure. Among these reported risk factors, older age, black race, male sex, and family history are of sufficient evidence. Therefore, we included all but family history because data on family history are either unavailable or poorly captured. Another known and established clinical risk factors for MM -- obesity (defined as body mass index (BMI $\geq$30 kg/m^2)), will be included in the future model.

Furthermore, the disease etiology is complex. Our model currently only includes four disease stages, including no MGUS/MM, MGUS, MM, and death. Also, unlike full-blown MM, which is symptomatic, since MGUS is asymptomatic and a diagnosis does not warrant treatment, time of diagnosis of MGUS is incidental. Finally, novel (and costly) treatment regimens for MM management have emerged frequently for the past decade, improving MM survival with unknown impact on MM health disparities. We made the following assumptions.

Assumption Listing

- Only known risk factors with available data were integrated into the model, including age, race/ethnicity, sex, and obesity (with the first three already integrated in the current model and the last to be expanded).
- Smoldering MM (sMM) is a more advanced pre-malignant disease than MGUS. sMM disease stage is currently not included in the WUMM-DES.
- Data on MGUS/MM diagnosis were used to proxy MGUS/MM development. For MM, since MM is symptomatic, we assumed that the time for MM development should be sufficiently close to the time for MM diagnosis. For MGUS, since it is asymptomatic and the diagnosis is incidental, we used calibration to correct the bias.
- MM survival only depends on the characteristics of population based on the data without considering treatment regimens.
- Health insurance status,and thus access to care, is not currently considered in the model.
- Because the WUMM-DES is a lifetime horizon model, the lifetime probability of death for all individuals is equal to 1. In addition, the maximum life expectancy for the simulated individuals is 100 years.
- The probabilities and time-to-event distributions for disease progression depend on individual demographics, recognizing the inherent heterogeneity among individuals. Details can be found in Parameter Overview.

Parameter Overview

Summary

The WUMM-DES has several key parameters, including probabilities of an event and distributional parameters for time to events. These events include MGUS, MM, death. Several databases were used to estimate the parameters, including the National Health and Nutrition Examination Study (NHANES), National Health Interview Survey (NHIS), Medical Expenditure Panel Survey (MEPS), Surveillance, Epidemiology, and End Results (SEER), Veteran Health Administration (VHA), and the Centers for Disease Control and Prevention (CDC).

Background

The parameters for a DES model include the probability of an event and distributional parameters for the time to this event. The current WUMM-DES has three events: MGUS, MM, and death.

Data Sources

To ensure that our models are evidence-based and generalizable to the studied subpopulations, we populated our model using estimates derived via data from several databases representing different U.S. populations. Secondary data analyses were performed to estimate the parameters in the models. These data were also used to calibrate and validate the evidence-based models. Each database is briefly described below.

1.Three national databases that are nationally representative samples of the U.S. general population: the National Health and Nutrition Examination Study (NHANES), 1971-, the National Health Interview Survey (NHIS), 1963-, and its linked mortality data files (with mortality follow-up until end of 2015), the Medical Expenditure Panel Survey (MEPS), 1996-.

2.Surveillance, Epidemiology, and End Results (SEER) and related software, 1975-: When combined with the use of the Complete Prevalence (ComPrev) and Projected Prevalence (ProjPrev) Software, we will be able to obtain annual prevalence of MM based on the limited-duration prevalence obtained from SEER*Stat.

3.Veteran Health Administration (VHA), 1998-: VHA contains electronic health record (EHR) data for veterans utilizing the Veteran Affairs (VA) healthcare system in the entire nation and can be linked to other data, e.g., Department of Defense and Medicare. VA healthcare system provides access to all eligible veterans for a lifetime, and therefore captures the most complete longitudinal data among all databases.

4.The Centers for Disease Control and Prevention (CDC), 1999-: CDC life tables provide data on mortality and life expectancy for the U.S. generally population stratified by age, sex, and race.

Parameters

Parameters are listed in **Table 1**.

Table 1: Parameters and data sources

Parameter	Event	Source	Year
Probability			
P_G	No MGUS to MGUS	VHA	2000-2022
P_{M1}	MGUS to MM for MGUS at [20,50)		
P_{M2}	MGUS to MM for MGUS at [50,65)		
P_{M3}	MGUS to MM for MGUS at [65,75)		

P_{M4}	MGUS to MM for MGUS at [75,100)		
Time-to-event distribution			
$F_G(t)$	No MGUS to MGUS	VHA	2000-2022
$F_{M1}(t)$	MGUS to MM for MGUS <50		
$F_{M2}(t)$	MGUS to MM for MGUS at [50,65)		
$F_{M3}(t)$	MGUS to MM for MGUS at [65,75)		
$F_{M4}(t)$	MGUS to MM for MGUS at [75,100)		
$F_{D,H}(t)$	No MGUS to death	CDC Life Table	2002
$F_{D,G}(t)$	MGUS to death	CDC Life Table, Ji et al., 2023	2002, 1999-2004
$F_{D,M}(t)$	MM to death	CDC Life Table, SEER	2002, 2000-2019

1. Parameters were initially estimated from the VHA data, including the probability of no MGUS to MGUS (P_G) and its corresponding time-to-event distribution (F_G). To account for age-specific progression rates, the progression of MGUS to MM was stratified into four age groups based on the age at which MGUS was diagnosed: 20-49, 50-64, 65-74, and 75-100 years. The probabilities of MGUS progression to MM for these age groups are represented as P_{Mi}, $i = 1, 2, 3, 4$, respectively, along with their corresponding time-to-event distributions $F_{M1}(t)$, $i = 1, 2, 3, 4$,respectively.[1]

   Due to the imbalanced sample sizes for gender in the VHA data, these parameters were obtainedsolely based on race. To ensure parameters are representative of for each subpopulation, calibration was conducted. The parameters obtained from the VHA data were served as the starting values and were calibrated using both national estimates of MGUS prevalence and MM incidence for each subpopulation. The time-to-event distributions were presented as cumulative density functions (CDFs).

   The distribution for time (from age 20)-to-MGUS, $F_G(t)$, were assumed to be piece-wise linear with five parameters based on empirical CDF curves.

$$F_G(t) = \begin{cases} \frac{p_1 \cdot (t-20)}{30} & \text{if } t \in [20, 50] \\ \frac{(p_2 - p_1) \cdot (t-50)}{15} + p_1 & \text{if } t \in [50, 65] \\ \frac{(p_3 - p_2) \cdot (t-65)}{15} + p_2 & \text{if } t \in [65, 75] \\ \frac{(p_4 - p_3) \cdot (t-75)}{15} + p_3 & \text{if } t \in [75, 85] \\ \frac{(p_5 - p_4) \cdot (t-85)}{15} + p_4 & \text{if } t \in [85, 100] \end{cases}$$

   The distributions for time-from-MGUS-to-MM, F_{Mi}, were estimated by Gamma distribution,

   $F_{Mi}(t) = \frac{\gamma(a_{Mi}, b_{Mi} t)}{\Gamma(a_{Mi})}$,

   $\gamma(s, x) = \int_0^x t^{s-1} e^{-t} dt$,

$\Gamma(s) = \int_0^\infty t^{s-1}e^{-t}dt$,

where $i = 1, 2, 3, 4$ for the five age groups, $\Gamma(a_{Mi})$ is the gamma function, and $\gamma(a_{Mi}, b_{Mi}t)$ is the incomplete gamma function. Therefore, the mean and variance of time from MGUS to MM are $\frac{a_{Mi}}{b_{Mi}}$ and $\frac{a_{Mi}}{b_{Mi}^2}$, respectively.

2. Parameters for mortality include time to death for (a) no MGUS $F_{D,H}(t)$, (b) MGUS $F_{D,G}(t)$, and (c) MM $F_{D,M}(t)$.
Because the WUMM-DES is a lifetime horizon model, the lifetime probability of death for all individuals is equal to 1.

   a. For each subpopulation, $F_{D,H}(t)$ were estimated from the CDC life tables, reflecting the mortality rates of the general population.

   b. We obtained estimates for $F_{D,G}(t)$ from a published study by our team: hazard ratios (HR) for death comparing MGUS population to no MGUS population in the United States: 1.21, 1.17, and 1.16 for MGUS at age 50 to 69, 70 to 79, and ≥80 years, respectively[1] Assuming theevent times in each age interval is an exponential distribution, the probability to death can be expressed as $1 - e^{-\lambda}$, where λ is the mortality rate. Therefore, the probability from MGUS diagnosis to death at time t is, $p_{D,G}(t) = 1 - (1 - p_{D,H}(t))^{HR(t)}$, where $P_{D,H}$(t) is the probability of death among general population at time t. Therefore,

$F_{D,G}(t) = 1 - \exp\left(\int_0^t \frac{HR(t)f_{D,H}(t)}{F_{D,H-1}}dt\right)$, where $f_{D,G}(t) = \frac{dF_{D,H}(t)}{dt}$
$F_{D,M}(t) = 1 - RS(t)$

Derivation of $F_{D,G}(t)$:

Let $T_{D,G}$ be the random variable denoting the time of death from MGUS and $f_{D,G}$ and $F_{D,G}$ be the probability density and cumulative distribution functions of $T_{D,G}$, respectively, then the hazard rate of death from MGUS is defined by $h_{D,G}(t) = -\frac{f_{D,G}(t)}{1-F_{D,G}(t)}$. Hence, it satisfies $h_{D,G}(t) = \frac{d}{dt}\log(1 - F_{D,G}(t))$, which also holds for the hazard rate of death from health $h_{D,H}(t)$ with $F_{D,G}(t)$ replaced by $F_{D,H}(t)$, the cumulative distribution function of the time of death from health. The hazard ratio is then defined by $HR(t) = \frac{h_{D,G}(t)}{h_{D,H}(t)}$, so that

$\frac{d}{dt}\log(1 - F_{D,G}(t)) = HR(t)\left(-\frac{f_{D,G}(t)}{1-F_{D,G}(t)}\right)$, which yields
$F_{D,G}(t) = 1 - \exp\left(-\int_0^t \frac{HR(t)f_{D,G}(t)}{F_{D,G}(t)-1}dt\right)$.

Derivation of $F_{D,M}(t)$:

Let $T_{D,M}$ be the random variable characterizing the time of death after MM is diagnosed, then its cumulative distribution function $F_{D,M}(t)$ gives the probability of death from MM in t years or less. By the definition of $RS(t)$ as the percentage of patients surviving MM for t years or more (from the SEER database), we obtain $RS(t) = 1 - F_{D,M}(t)$.

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Component Overview

1. Simulation Overview

Summary

We describe microsimulation/Monte Carlo simulation and detail for each component/step of the simulation of the constructed WUMM-DES model.

Overview

We performed Monte Carlo simulations using a hypothetical subpopulation aged 20 years with a size of 100,000. For each subpopulation, we first determined whether an individual in this population has an event by comparing the probability P with a random number ($\widehat{P}$), drawn from a uniform distribution $U[0,1]$. If $\widehat{P} < P$, the individual experiences an event; otherwise, the individual does not experience the event. For individuals experiencing an event, their time to such event was determined by another random number from $U[0,1]$ to compare to the CDF for the time-to-event (F) to identify the time corresponding to the random number.

Component Listing

- Progression from no MGUS/MM to MGUS: Within a hypothetical subpopulation aged 20 years without MGUS/MM (n=100,000), we first determined whether an individual in this population develops MGUS by comparing the probability P_G with a random number ($\widehat{P}_G$) drawn from $U[0,1]$. If $\widehat{P}_G < P_G$, the individual develops MGUS; otherwise, the individual dies without MGUS or MM (see below for time to death). For individuals who were determined to develop MGUS, their time to MGUS was determined by another random number, $\widehat{F}_G$, drawn from $U[0,1]$ to compare to F_G to identify T_G, where $T_G = F_G^{-1}(\widehat{F}_G)$. The age at MGUS was then determined by $A_G = 20 + T_G$.

- Progression of MGUS to MM: For those with MGUS, whether an individual develops MM was determined by comparing the probability P_M, where P_M varies with age at MGUS (20-50, 50-64, 65-74, and 75-100), with a random number ($\widehat{P}_M$) drawn from $U[0,1]$. If $\widehat{P}_M < P_M$, the individual develops MM; otherwise, the individual dies without MM (see below for time to death). For individuals who were determined to develop MM, their time to MM was further determined by another random number, $\widehat{F}_M$, drawn from $U[0,1]$ to compare to F_M to identify T_M, where $T_M = F_M^{-1}(\widehat{F}_M)$. The age at MM was then determined by $A_M = A_G + T_M$.

- Death: Age at death was determined by $F_{D,H}$, $F_{D,G}$, and $F_{D,M}$.
  - For individuals without MGUS/MM, their life expectancy was determined by a random number, $\widehat{F}_{D,H}$, drawn from $U[0,1]$ to compare to $F_{D,H}$ to identify $T_{D,H}$, where $T_{D,H} = F_{D,H}^{-1}(\widehat{F}_{D,H})$. The age at death was then determined by $A_H = 20 + T_{D,H}$.
  - For individuals with MGUS without progressing to MM, their life expectancy was determined by a random number, $\widehat{F}_{D,G}$, drawn from $U[0,1]$ to compare to $F_{D,G}$ to identify $T_{D,G}$, where $T_{D,G} = F_{D,G}^{-1}(\widehat{F}_{D,G})$. The age at death for individuals with MGUS without progressing to MM was then determined by $A_{DG} = A_G + T_{D,G}$.
  - For individuals with MM, their life expectancy was determined by a random number, $\widehat{F}_{D,M}$, drawn from $U[0,1]$ to compare to $F_{D,M}$ to identify $T_{D,M}$, where $T_{D,M} = F_{D,M}^{-1}(\widehat{F}_{D,M})$. The age at death for individuals with was then determined by $A_{DM} = A_M + T_{D,M}$.

- The aforementioned process was repeated for each of the four subpopulations. For each subpopulation, we obtained model outputs including prevalence of MGUS, incidence of MM, median age at MGUS/MM, and life expectancy for no MGUS/MM, MGUS without MM, and MM.
- For each subpopulation, the process was repeated for 1,000 times to compute the means, standard errors, and 95% confidence intervals.

2. Calibration Overview

Summary

We provide an overview of the calibration process employed to ensure the accuracy and reliability of the WUMM-DES model. In this process, we fine-tuned the model parameters, including the probability of no MGUS to MGUS, MGUS to MM, and corresponding time-to-event distribution parameters, with the objective to minimize the difference between the simulated outcomes and the real-world data, thus ensuring the model validity.

Overview

For each subpopulation, we targeted the following key parameters for calibration:

1. Probability of developing MGUS in individuals without MGUS/MM (P_G)
2. Parameters for the CDF of time from no MGUS/MM to MGUS (F_G)
3. Probability of developing MM in individuals with MGUS for each of the four age groups: 20-49, 50-64, 65-74, and 75-100 (P_{Mi}, $i = 1, 2, 3, 4$)
4. Parameters for the CDF of time from MGUS to MM (F_{Mi}, $i = 1, 2, 3, 4$)

The calibrated parameters and their corresponding intervals are outlined in **Table 2**.

Table 2: Uncertain parameters for calibration

Symbol	Description	Interval
P_G	Probability of no MGUS to MGUS	$(0, 0.5]$
$a_{G1}, a_{G2}, a_{G3}, a_{G4}, a_{G5}$	Fitting parameters for no MGUS to MGUS (F_G)	$(20, 100]$
$P_{M1}, P_{M2}, P_{M3}, P_{M4}$	Probability of MGUS to MM	$(0, 0.5]$
$a_{M1}, a_{M2}, a_{M3}, a_{M4}$	Fitting parameters for MGUS to MM	$(0, 5]$
$b_{M1}, b_{M2}, b_{M3}, b_{M4}$	($F_{M1}, F_{M2}, F_{M3}, F_{M4}$)	$(0, 3]$

We used age-specific MGUS prevalence and MM incidence for calibration. Age-specific MGUS prevalence with one-year age intervals from age 54 to 80 was estimated from the NHANES 1999 to 2004. Age-specific MM incidence with five-year age intervals from age 20 to 80 were obtained from SEER 2013 to 2018.

These data were compared to the same outputs, i.e., age-specific MGUS prevalence with one-year age intervals from age 54 to 80 ($M = 37$), and age-specific MM incidence with five-year age intervals from age 20 to 80 ($N = 12$), from the simulation. We then performed an optimization to minimize the sum of the squared errors (SS) with respect to the target parameters listed in **Table 2**. The error was defined as the differences between the simulated prevalence/incidence outputs or the prevalence/incidence data.

$$\min_{\substack{P_G, a_{G1}, \cdots, a_{G5}, \\ P_{M1}, \cdots, P_{M4}, \\ a_{M1}, \cdots, a_{M4}, \\ b_{M1}, \cdots, b_{M5},}} SS = \sum_{i=1}^{M} \left| \text{Pre}_{\text{Model},i} - \text{Pre}_{\text{NHANES},i} \right|^2 + \sum_{i=1}^{N} \left| \text{Inc}_{\text{Model},i} - \text{Inc}_{\text{SEER},i} \right|^2$$

subject to:

$$0 < P_G \leq 0.5$$

$$20 \leq a_{G1} \leq a_{G2} \leq a_{G3} \leq a_{G4} \leq a_{G5} \leq 100$$

$$0 < P_{Mi} \leq 0.5, \;\; i = 1, 2, 3, 4$$

$$0 < a_{Mi} \leq 5, \;\; i = 1, 2, 3, 4$$

$$0 < b_{Mi} \leq 3, \;\; i = 1, 2, 3, 4$$

The upper bounds for the constraints were informed by empirical data.

The calibration results can be found in Results Overview.

Output Overview

Summary

We define the outputs generated by MM-DES model, including MGUS prevalence, MM incidence, life expectancy, and life years lost.

Overview

- MGUS prevalence: Prevalence is defined as the proportion of a population who have a specific characteristic in a given time period.[1] In the WUMM-DES model, we evaluated age-specific MGUS prevalence with one-year age intervals from age 54 to 80,

$$Pre_i = \frac{\#\ of\ people\ with\ MGUS\ at\ age\ i}{Total\ \#\ of\ people\ alive},\ \ i = 54,\ 55, \cdots, 80.$$

- MM incidence: Incidence is defined as the number of cases of disease having their onset during a prescribed period of time, which is often expressed as a rate.[2] In the WUMM-DES model, we evaluated age-specific MM incidence with five-year age intervals from age 20 to 80,

$$Inc_i = \frac{\#\ of\ people\ with\ MM\ onset\ between\ age\ [i, i+5)}{Total\ \#\ of\ people\ at\ risk},\ \ i = 20, 25, \cdots, 80.$$

- Life Expectancy (LE): Life expectancy is defined as the average number of years of life a person who has attended a given age can expect to live.[3] In the WUMM-DES model, we evaluate life expectancy with 10-year age group across three different conditions for each subpopulation: people without MGUS/MM, those with MGUS onset but no MM development, and those with MM onset.

- Life Years Lost (LYL): Life years lost, or years of life lost, estimates the number of years that individuals who died would have lived if they had not experienced a specific condition. It provides a measure of the impact of premature mortality on a population. [4] In the WUMM-DES model, we defined as LE without MGUS/MM minus LE at MGUS/MM.

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Results Overview

Summary

We summarize the key results generated from the WUMM-DES model. Furthermore, it quantifies the differences across various demographic subpopulation in terms of life expectancy (LE) and life years lost (LYL).

Results List

Calibration

We conducted 1,000 simulations for each subpopulation using the calibrated parameters outlined in the Calibration Overview. In each simulation, the model output was compared to the national data to obtain the difference. We then computed the mean squared errors (MSEs) across the 1,000 simulations. We plotted MGUS prevalence (**Figure 2**) and MM incidence (**Figure 3**) to visually present the calibration results in comparison to the data from the NHANES (1999-2004) and SEER (2013-2018) data. The calibrated results closely approximate both the MGUS prevalence and MM incidence. **Table 3** presents the MSEs of the simulated MGUS prevalence and MM incidence compared to NHANES and SEER data.

Table 3: Mean squared errors (MSE) for NHB men and women, NHW men and women

	NHW men	NHB men	NHW women	NHB women
MGUS prevalence MSE (%)	1.64	11.8	0.88	3.52
MM incidence MSE (cases per 100,000)	19.6	3.17	12.7	22.0

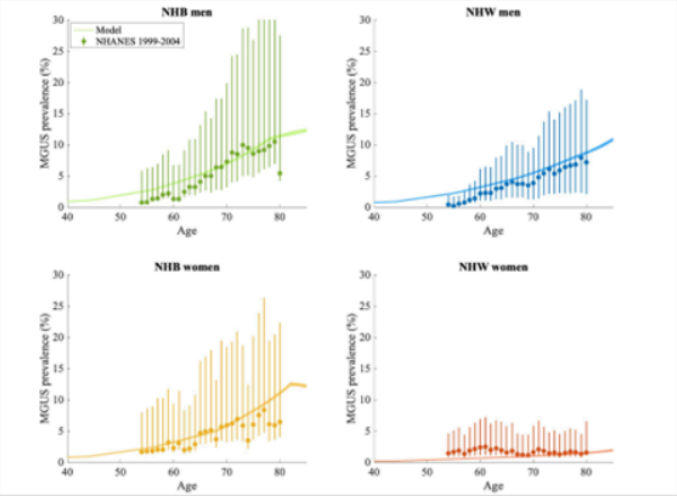

Figure 2. MGUS prevalence for NHB men and women, NHW men and women: calibrated data and 95% CI versus data estimated from NHANES 1999-2004

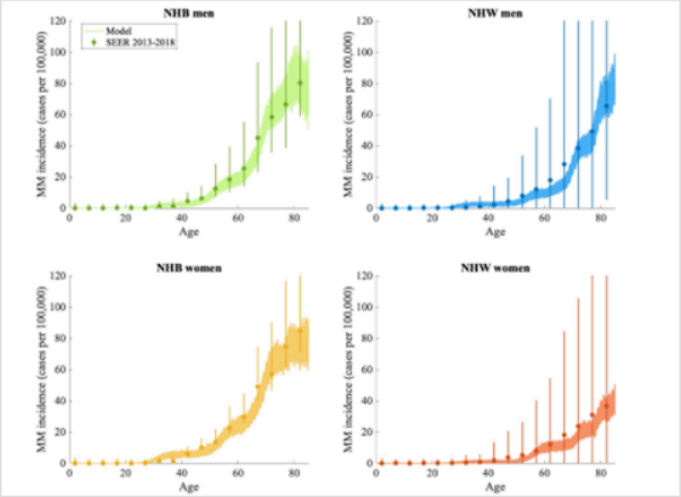

Figure 3. MM incidence for NHB men and women, NHW men and women: calibrated data and 95% CI versus data obtained from SEER 2013-2018

Simulation

The simulation was conducted on the calibrated model 1,000 times for each subpopulation and the means, standard errors, and 95% confidence intervals from these simulations.

We present age-specific incidence (**Figure 2**), LE at MGUS/MM, and LYL associated with MGUS/MM (see **Figure 2** and **Figure 3**). Results show that NHW men and women exhibited longer LEs compared to their NHB counterparts for those diagnosed with MGUS/MM. For both NHW and NHB patients, women exhibited higher LYL after MM diagnosis compared to men.

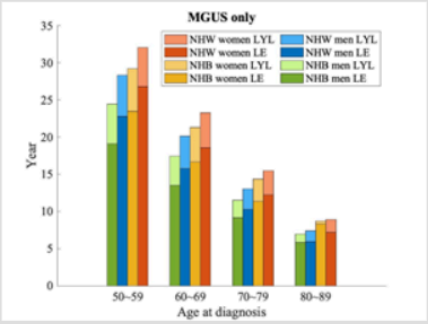

Figure 4. Life expectancy (LE) and life years lost (LYL) for NHB men and women, NHW men and women after MGUS diagnosis.

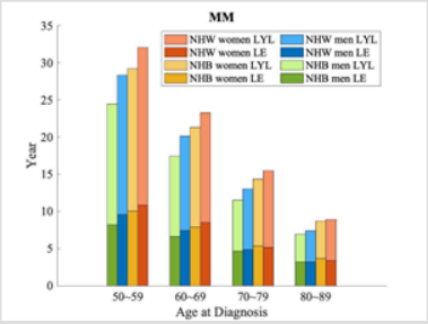

Figure 5. Life expectancy (LE) and life years lost (LYL) for NHB men and women, NHW men and women after MM diagnosis.

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Yale University
Version: 1.0.00
Released: 2025-09-30

Yale University Natural History of Multiple Myeloma Model (YUMM): Model Profile

Yale University

Contact

Shi-Yi Wang (shiyi.wang@yale.edu)

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Suggested Citation

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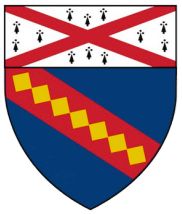
Version Table

Version	Date	Notes
1.0.00	2025-09-30	Initial release

Other Publications

Ahmad I, Wang R, Neparidze N, Lange J, Wang SY. Potential benefits and harms of monoclonal gammopathy of undetermined significance screening strategies in the US: A simulation study. (in preparation)

Yale 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

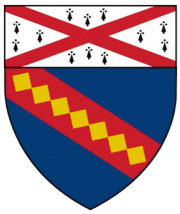
Definitions and methodologies for the basic model outputs.

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 Yale University modeling group is to construct an evidence-based, calibrated, validated natural history of multiple myeloma (MM) model to evaluate MM prevention and control interventions/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.[5-7]

The long-term goal of the models developed by the CISNET Multiple Myeloma Incubator Program is to guide MM prevention and control interventions/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 YUMM 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.
2. April Teitelbaum, Abbie Ba-Mancini, Hui Huang, Henry J Henk. Health care costs and resource utilization, including patient burden, associated with novel-agent-based treatment versus other therapies for multiple myeloma: findings using real-world claims data. The oncologist. Oxford University Press; 2013;18(1):37–45.
3. Eric M Maiese, Kristin A Evans, Bong-Chul Chu, Debra E Irwin. Temporal trends in survival and healthcare costs in patients with multiple myeloma in the United States. American Health & Drug Benefits. Engage Healthcare Communications, LLC; 2018;11(1):39.
4. Claire de Oliveira, Reka Pataky, Karen E Bremner, Jagadish Rangrej, Kelvin KW Chan, Winson Y Cheung, et al. Phase-specific and lifetime costs of cancer care in Ontario, Canada. BMC cancer. Springer; 2016;16:1–12.
5. Reference not found for key: ncicancerstatfacts2024@greenberg2012disparities.
6. Harvey Jay Cohen, Jeffrey Crawford, Murali K Rao, Carl F Pieper, Mark S Currie. Racial differences in the prevalence of monoclonal gammopathy in a community-based sample of the elderly. The American journal of medicine. Elsevier; 1998;104(5):439–444.
7. Jagat Singh, Alden W Dudley, Kimberly A Kulig. Increased incidence of monoclonal gammopathy of undetermined significance in blacks and its age-related differences with whites on the basis of a study of 397 men and one woman in a hospital setting. The Journal of laboratory and clinical medicine. Elsevier; 1990;116(6):785–789.

Yale University
Model Overview

Model Overview

Summary

The Yale University Multiple Myeloma modeling group has constructed and validated an individual-based, stage-dependent, state-transition microsimulation model tailored to model the natural history of MM, from no MGUS/MM, MGUS development, progression to MM, and death for the U.S. population aged 40 years or older (YUMM).

Purpose

The long-term goal of this YUMM model is to fill the gap in setting and prioritizing policy goals for MM prevention and control. To achieve this goal, we constructed a microsimulation model to simulate the natural history of MM from the development of MGUS to MM, followed by survivorship for the U.S. population. Using this model, we will then evaluate whether promising intervention strategies throughout the continuum of care will effectively prevent the devastating malignancy or improve MM survival with great value. Ongoing work is aimed at capturing longitudinal changes in body mass index (BMI).

Background

In the CISNET Multiple Myeloma incubator program, the Yale University modeling group has constructed and validated a microsimulation model tailored to model the natural history of MM, from no MGUS/MM, MGUS development, progression to MM, and death for the U.S. population aged 40 years or older (YUMM), stratified by race (blacks and whites) and gender.

The YUMM model is an individual-based, stage-dependent, state-transition microsimulation model informed by real-world data to simulate the natural history of MM progression. The parameters vary based on the characteristics of each individual, accounting for risk factors of MGUS/MM development and progression, such as age, race, gender and BMI.

The developed simulation modeling can be tailored to set research priorities and design clinical trials, including assessing sample sizes and power, evaluating the impact of treatment adherence of the participants, and determining the optimal treatment strategies. It can also be used to predict trial results and set policy goals.

Model Description

The theoretical model builds on natural history of MM (**Figure 1**). The YUMM model targets at the U.S. general population aged over 40 years since the prevalence of MGUS for the population aged below 40 years is very small.[1] The model currently integrates three demographic factors, age, sex, and race and simulates the natural history of MM for four U.S. populations, including non-Hispanic white (NHW) men and women, as well as non-Hispanic Black (NHB) men and women.

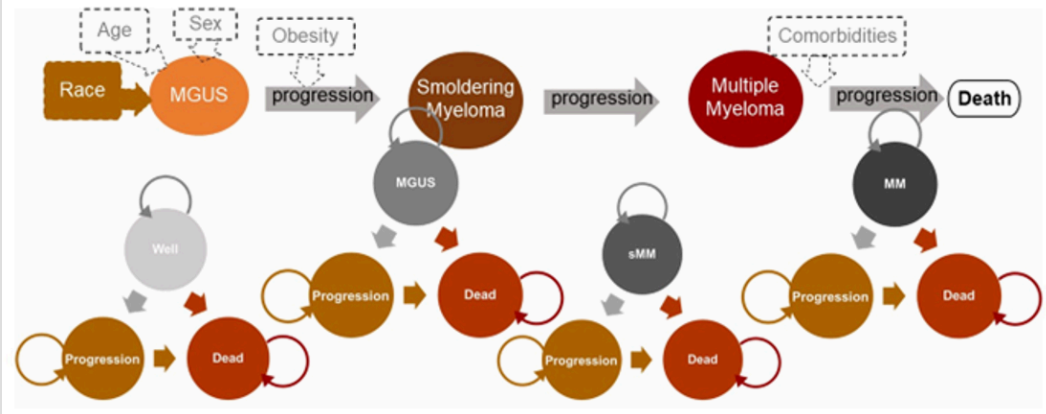
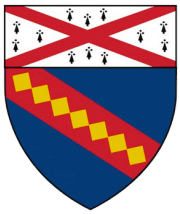


***Figure 1**. YUMM Model Scheme*

Stratified by sex and race, this model starts with the population at age 40 without multiple myeloma. For each population, some individuals develop MGUS, while the others do not. Some patients with MGUS progress to MM with varied probabilities to progression depending on their characteristics. All individuals, with or without MGUS and/or MM may die due to other diseases or multiple myeloma, depending on their disease path and their individual characteristics.

References

1. O Landgren, B I Graubard, S Kumar, R A Kyle, J A Katzmann, K Murata, et al. Prevalence of myeloma precursor state monoclonal gammopathy of undetermined significance in 12372 individuals 10-49 years old: a population-based study from the National Health and Nutrition Examination Survey. Blood Cancer J. 2017 Oct;7(10):e618.



Assumption Overview

Summary

Model assumptions are based on the availability of secondary data and/or evidence supported by the literature. We made assumptions on the following aspects: risk factors, disease stages, diagnosis, MM treatment, and parametric assumptions.

Background

Model assumptions are based on the availability of secondary data and/or evidence published by the literature. The etiology of MGUS and MM is poorly known. Henceforth, only known risk factors with sufficient evidence and available data will be included in the model.

MGUS Development

Previous studies reported that risk factors for MGUS development include older age, black race, male sex, family history, radiation, and pesticide exposure. Among these reported risk factors, older age, black race, male sex, and family history are of sufficient evidence. Therefore, we included all but family history because data on family history are either unavailable or poorly captured.

MGUS Progression to MM

The progression from MGUS to MM is understudied. While one systematic review found old age, female gender, and high BMI were associated with an increased risk of MGUS-MM progression,[1] the results were subject to publication bias. We thus used results derived from analyses of the Veterans Health Administration data to estimate risks of MGUS-MM progression, which varied by age, race, gender, and BMI.

Finally, the disease etiology is complex. Our model currently only includes four disease stages, including healthy (no MGUS/MM), MGUS, MM, and death. Also, unlike full-blown MM, which is symptomatic, since MGUS is asymptomatic and a diagnosis does not warrant treatment, time of diagnosis of MGUS is incidental. Finally, novel (and costly) treatment regimens for MM management have emerged frequently for the past decade, improving MM survival with unknown impact on MM health disparities.
We made the following assumptions.

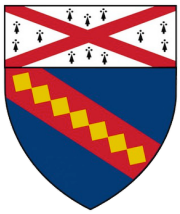
Assumption Listing

- Only known risk factors with available data were integrated into the model, including age, race, gender, and obesity (with the first three already integrated in the current model and the last to be expanded).
- Smoldering MM (sMM) is a more advanced pre-malignant disease than MGUS. sMM was not modeled as an intermediate state between MGUS and MM at this time in the YUMM, due to the lack of available data.
- Data on MGUS/MM diagnosis were used to proxy MGUS/MM development. For MM, since MM is symptomatic, we assumed that the time for MM development should be sufficiently close to the time for MM diagnosis. While MGUS is asymptomatic and the diagnosis is incidental, we assumed no difference in risk of MGUS-MM progression between MGUS patients with and without diagnosis.
- MM survival only depends on the characteristics of population and whether or not they received treatments. We did not consider survival difference between treatment regimens, yet allowed improved survival over time.
- Health insurance status is not currently considered in the model.
- Because the YUMM is a lifetime horizon model, the lifetime probability of death for all individuals is equal to 1. The cycle length is one year. In addition, the maximum life expectancy for the simulated individuals is 100 years.

- The probabilities for disease progression are contingent upon individual demographics, recognizing the inherent heterogeneity among individuals. Details can be found in Parameter Overview.
- Ongoing work is aimed at capturing the trend of body mass index (BMI) in the US, as BMI is a well-established risk factor for MGUS/MM.

References

1. Yimeng Li, Sylvia H Hsu, Rong Wang, Poy Theprungsirikul, Natalia Neparidze, Su-Hsin Chang, et al. Associations between patient characteristics and progression to multiple myeloma among patients with monoclonal gammopathy of undetermined significance: A systematic review. Clin Lymphoma Myeloma Leuk. Elsevier BV; 2024 Dec;



Parameter Overview

Summary

The YUMM included has several key parameters, including 2003 MGUS prevalence and transition probabilities between states. Several databases were used to estimate the parameters, including the National Health and Nutrition Examination Study (NHANES), National Health Interview Survey (NHIS), Medical Expenditure Panel Survey (MEPS), Surveillance, Epidemiology, and End Results (SEER), Veteran Health Administration (VHA), and the Centers for Disease Control and Prevention (CDC).

Background

The YUMM simulated US healthy and MGUS (excluding individuals with MM) population of 40--80 years of age, starting from 2003. The model included four health states, Healthy, MGUS, MM, and Death.

Data Resource

To ensure that our models are evidence-based and generalizable to the studied subpopulations, we populated our model using estimates derived via data from several databases representing different U.S. populations. Secondary data analyses and simulated results were used to estimate the parameters in the models. These data were also used to validate the evidence-based models. Each database is briefly described below.

1. Three national databases that are nationally representative samples of the U.S. general population: the National Health and Nutrition Examination Study (NHANES), 1971-, the National Health Interview Survey (NHIS), 1963-, and its linked mortality data files (with mortality follow-up until end of 2015), the Medical Expenditure Panel Survey (MEPS), 1996-.

2. Surveillance, Epidemiology, and End Results (SEER) and related software, 1975-: When combined with the use of the Complete Prevalence (ComPrev) and Projected Prevalence (ProjPrev) Software, we will be able to obtain annual prevalence of MM based on the limited-duration prevalence obtained from SEER*Stat.

3. Veteran Health Administration (VHA), 1998-: VHA contains electronic health record (EHR) data for veterans utilizing the Veteran Affairs (VA) healthcare system in the entire nation and can be linked to other data, e.g., Department of Defense and Medicare. VA healthcare system provides access to all eligible veterans for a lifetime, and therefore captures the most complete longitudinal data among all databases.

4. The Centers for Disease Control and Prevention (CDC), 1999-: CDC life tables provide data on mortality and life expectancy for the U.S. generally population stratified by age, sex, and race.

Parameters

Parameters are listed in **Table 1**.

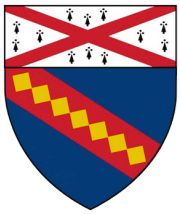
Parameter	Description	Source/Reference
MGUS prevalence	2003 MGUS prevalence, by age, gender, and race	1999-2004 NHANES
BMI distribution	The percentage of population by BMI (normal weight, overweight, and obese), by age, gender, and race in 2003	2003 NHANES
MGUS incidence	Annual transition probabilities from Healthy to MGUS, by age, gender and race	Simulated estimates[1]
Background mortality	Annual background mortality from Healthy to Death, by age, gender, race, and year	CDC Life Table, 2003-2020
MGUS->MM	Annual transition probability from MGUS to MM, by age, gender, race, and BMI	VHA data analysis
MGUS->Death	MGUS->Death Adjusted hazard ratio (MGUS vs Healthy) and background mortality	NHANES analysis[2]
Proportion of MM patients who received treatment	The percentage of MM patients who received treatment, by age, gender, and race	SEER-Medicare and BCBS data analysis

MM->Death	Annual transition probability from MM to Death, by age, gender, race, treatment received, and year SEER-Medicare and SEER	SEER-Medicare and SEER

Table 1: Parameters and data sources

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. Nat Commun. Springer Science; 2023 Sep;14(1):5768.
2. Mengmeng Ji, John H Huber, Martin W Schoen, Kristen M Sanfilippo, Graham A Colditz, Shi-Yi Wang, et al. Mortality in the US populations with monoclonal gammopathy of undetermined significance. JAMA Oncol. 2023 Sep;9(9):1293–1295.



Component Overview

1. Simulation Overview

Summary

We describe microsimulation and detail for each component/step of the simulation of the constructed YUMM model.

Overview

We use a stochastic, stage-dependent, state-transition micro-simulation model targeting the US healthy and MGUS (excluding individuals with MM) population of 40–80 years of age, starting from 2003. New populations of age 40 after 2003 are added annually and simulated through age 100 or until death. For each subpopulation (by age, sex, and race), we simulated the proportion of individuals who transitioned to MGUS, MM, and Death over time. The model includes a natural history component and a treatment component. Initially, the natural history component tracks the MGUS-MM development sequence as a function of age, sex, race, and risk factors such as obesity. Secondly, the treatment component accounts for new treatment dissemination. The probability that a simulated person with a new diagnosis of MM receives treatment is modeled as a function of age, sex, race, and calendar year. These treatment patterns were based on analyses of the SEER—Medicare linked dataset for patients aged ≥65, and analyses of the Blue Cross Blue Shield Axis data for patients aged <65 years at diagnosis. As the probabilities for disease progression depend on individual demographics, risk factors, treatment received, and duration within state, individual-based microsimulation models address many of the limitations of traditional cohort-based models, because of their capability to reflect individual clinical pathways and incorporate the impact of history on future events.

Component Listing

- Progression from Healthy to MGUS: Our simulation captured the proportion of individuals who transition across different states, and the timing of such transition. We are able to calculate the prevalence of MGUS as $p_{MGUS}(a,s,r) = \frac{P_{MGUS}(a,s,r)}{1-P_D(a,s,r)}$ and the incidence of MGUS (newly diagnosed MGUS at a certain calendar year).
- Progression from MGUS to MM: Similarly, we calculated the prevalence of MM as $p_{MM}(a,s,r) = \frac{P_{MM}(a,s,r)}{1-P_D(a,s,r)}$ and the incidence of MM (newly diagnosed MM at a certain calendar year).
- Progression from MM to Death: We calculated the proportion of individuals who died after MM.
- For each subpopulation, the process was repeated for 100 times to compute the means, standard errors, and 95% confidence intervals.

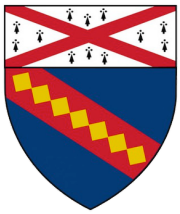
2. Calibration Overview

Summary

We provide an overview of the calibration process employed to ensure the accuracy and reliability of the YUMM model. Model calibration will be performed, and the parameters will be adjusted using the Nelder-Mead algorithm[1]. Our ongoing work aims at adding sMM into our natural history modeling and capturing the trend in increasing BMI in the US. In this process, we will fine-tune the model parameters, including the probability of Healthy to MGUS, MGUS to sMM, and sMM to MM, with the objective to minimize the difference between the simulated outcomes and the real-world data, thus ensuring the model validity.

References

1. Douglas C A Taylor, Vivek Pawar, Denise Kruzikas, Kristen E Gilmore, Ankur Pandya, Rowan Iskandar, et al. Calibrating longitudinal models to cross-sectional data: the effect of temporal changes in health practices. Value Health. Elsevier BV; 2011 Jul;14(5):700–704.



Output Overview

Summary

We define the outputs generated by the YUMM model, including MGUS prevalence, MM incidence, and MM mortality.

Overview

- MGUS prevalence: Prevalence is defined as the proportion of a population who have a specific characteristic in a given time period.[1] In the YUMMS model, we evaluated age-specific MGUS prevalence with five-year age intervals from age 55-59, 60-64, ..., 75-79.

$$Pre_i = \frac{\#\ of\ people\ with\ MGUS\ at\ age\ [i,\ \ i+4]}{Total\ \#\ of\ people\ alive\ at\ age\ [i,\ i+4]},\ i = 55,\ 60,\ \ \ldots,\ 75$$

- MM incidence: Incidence is defined as the number of cases of disease having their onset during a prescribed period of time, which is often expressed as a rate.[2] In the YUMM model, we evaluated age-specific MM incidence with five-year age intervals from age 55-59, 60-64, ..., 75-79.

$$Inc_i = \frac{\#\ of\ people\ with\ MM\ onset\ between\ age\ [i, i+4)}{Total\ \#\ of\ people\ at\ risk,\ age\ [i,\ i+4]},\ \ i = 55,\ 60,\ \ \ldots,\ 75$$

- MM mortality: We evaluated age-specific MM mortality with five-year age intervals from age 55-59, 60-64, ..., 75-79.

$$Mortality_i = \frac{\#\ of\ people\ with\ MM\ died\ at\ age\ [i,\ \ i+4]}{Total\ \#\ of\ people\ alive\ at\ age\ [i,\ i+4]},\ i = 55,\ 60,\ \ \ldots,\ 75$$

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1. National Cancer Institute. Mental Health information Statistics, what is prevalence . 2024.
2. National Center for Health Statistics, Division of analysis and epidemiology. CDC: Centers for Disease Control and Prevention. . 2024.

Results Overview

Summary

This section describes the results of our model validation to data from SEER. We also examined 80 MGUS screening strategies, varying in terms of the starting age of screening (40, 45, 50, or 55), the ending age (60, 65, 70, or 75), and the frequency of screening (every 2, 4, 6, 8, or 10 years). We projected the number of early MGUS-MM detection per 100 000 screenings across 80 strategies.

Results List

Validation

We validated our simulated MM incidence, age 55-79, year 2013 through 2017. We plotted age-specific MM incidence (**Figure 2**) to visually present the results in comparison to the data from SEER (2013-2017) data. The results closely approximate the MM incidence.

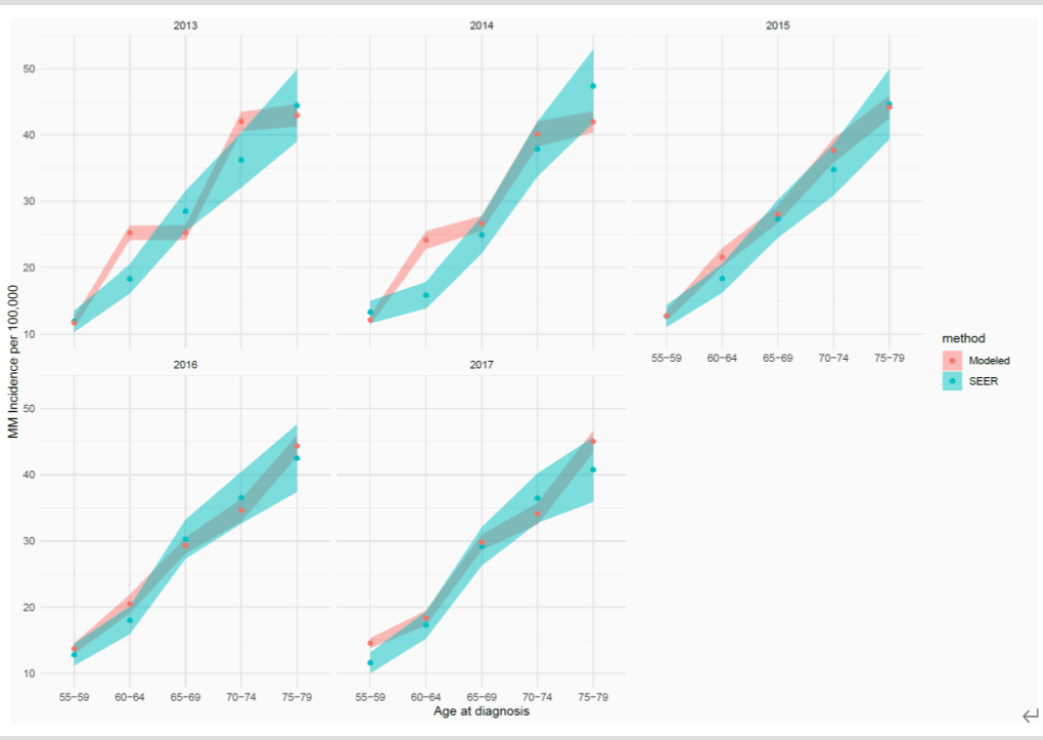


***Figure 2**. MM incidence in the US: simulated results and 95% CI versus data obtained from SEER 2013-2017*

MGUS screening

We generated a "screening-effective frontier," stressing the need to optimize screening strategies for maximal benefits at a given screening level (**Figure3**).

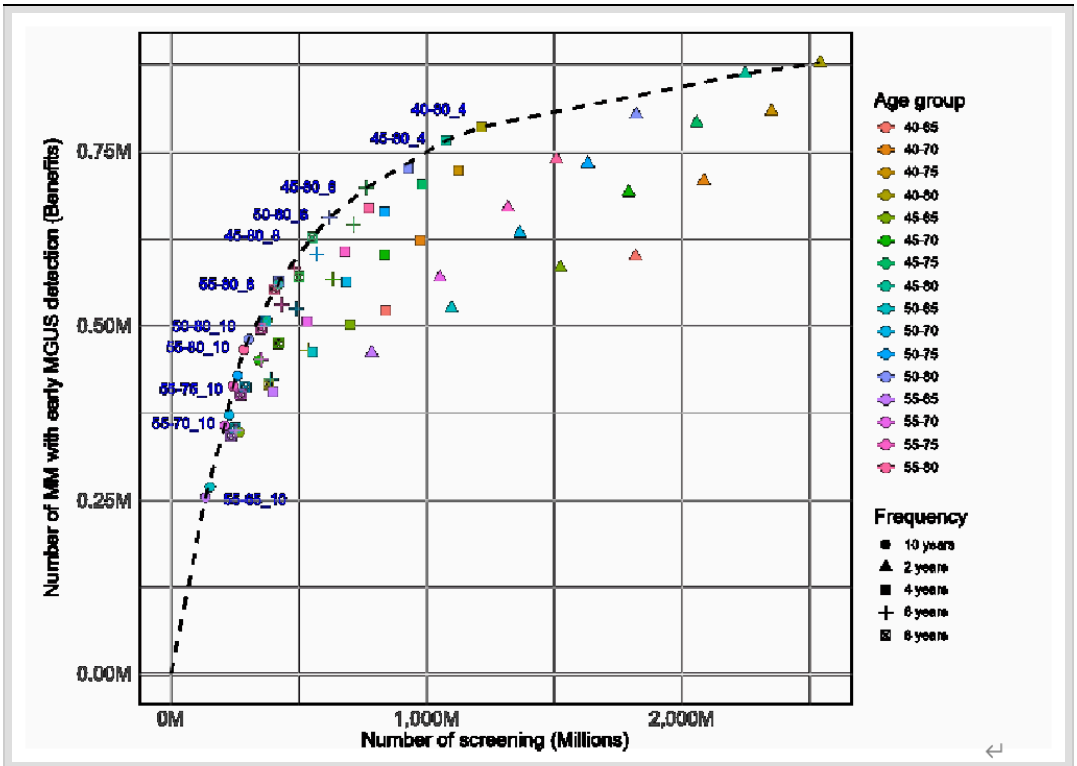
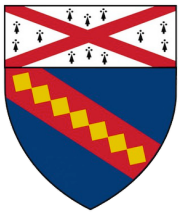


Figure 3. *MM incidence in the US: simulated results and 95% CI versus data obtained from SEER 2013-2017*



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