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

Yale University

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Version Table

Version	Date	Notes
1.0.00	2025-09-30	Initial release

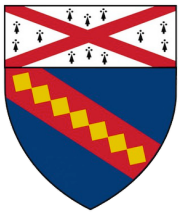
Other Publications

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

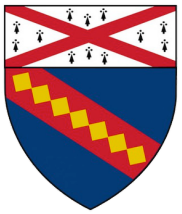
Definitions and methodologies for the basic model outputs.

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.

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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.

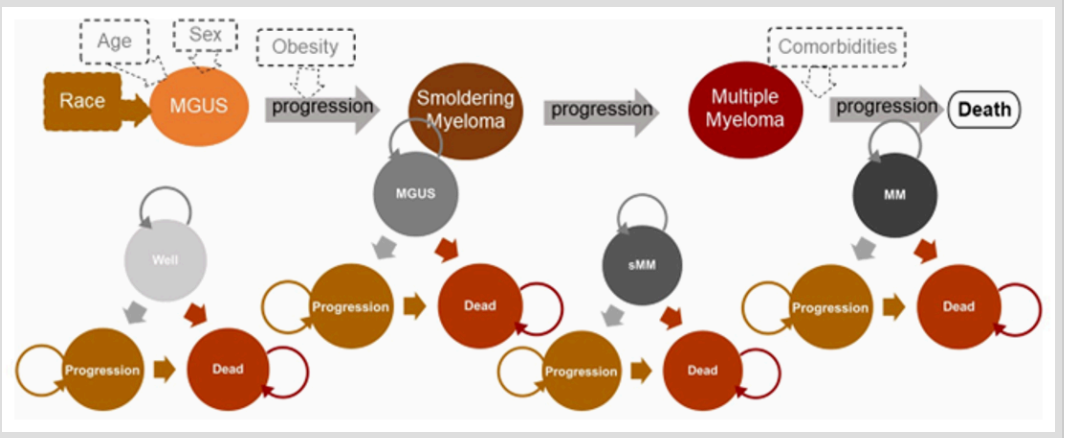
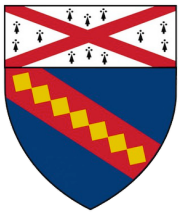


***Figure 1**. YUMM Model Scheme*

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.

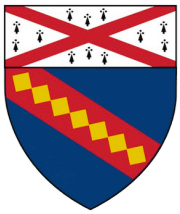
Assumption Listing

- 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**.

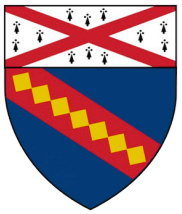
Parameter	Description	Source/Reference
MGUS prevalence	2003 MGUS prevalence, by age, gender, and race	1999-2004 NHANES
BMI distribution	The percentage of population by BMI (normal weight, overweight, and obese), by age, gender, and race in 2003	2003 NHANES
MGUS incidence	Annual transition probabilities 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.

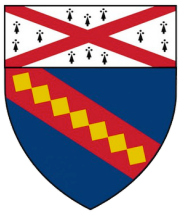
2. Calibration Overview

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.

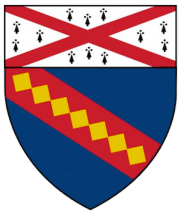
$$Inc_i = \frac{\#\ of\ people\ with\ MM\ onset\ between\ age\ [i, i+4)}{Total\ \#\ of\ people\ at\ risk,\ age\ [i,\ i+4]},\ \ i = 55,\ 60,\ \ \ldots,\ 75$$

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

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

References

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.

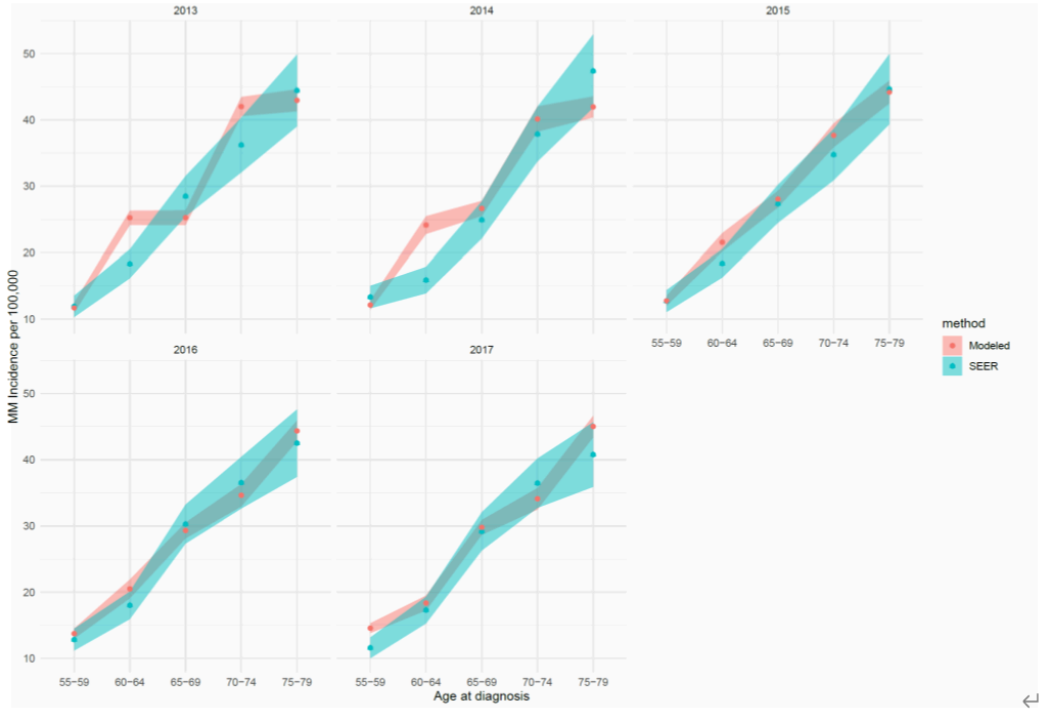


***Figure 2**. MM incidence in the US: simulated results and 95% CI versus data obtained from SEER 2013-2017*

MGUS screening

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

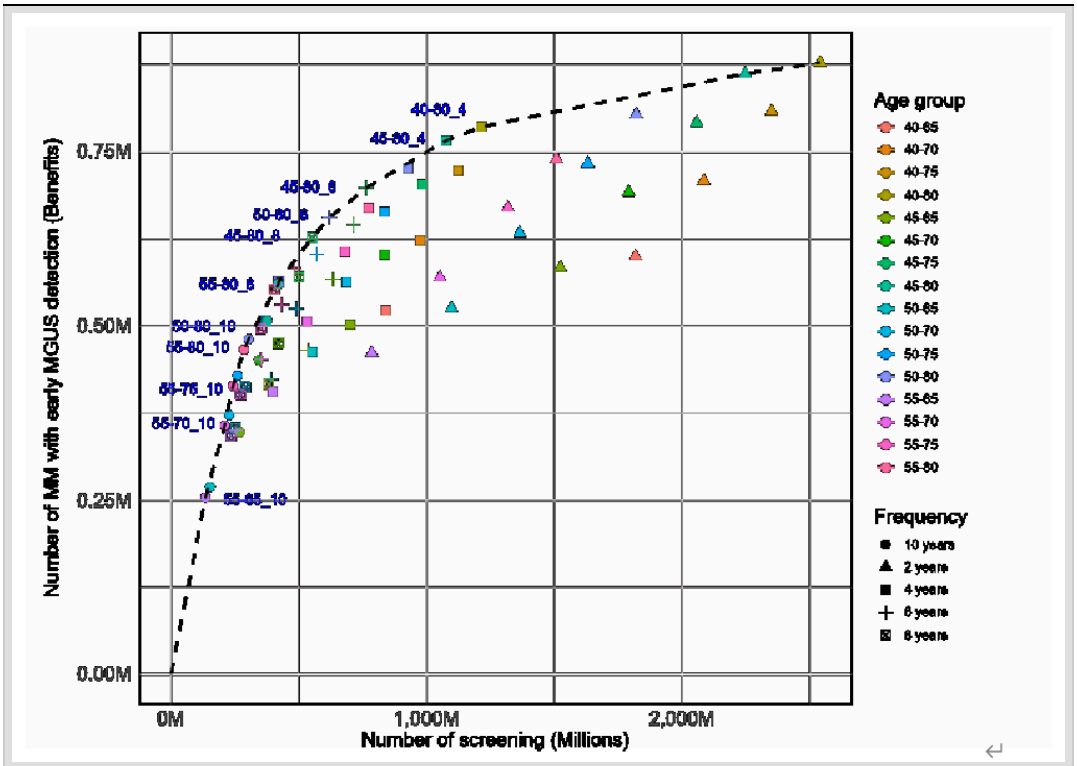
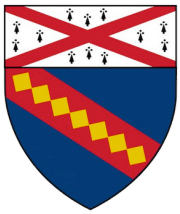


***Figure 3**. MM incidence in the US: simulated results and 95% CI versus data obtained from SEER 2013-2017*



Key References

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