A Computational Model Assessing Population Impact of a New Tobacco Product

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Abstract

Objectives
We developed and validated a computational model to assess the potential health impact of a new tobacco product in the U.S. market.

Methods
An Agent-Based Model (ABM) framework was used to estimate changes in tobacco use prevalence and premature deaths based on the difference between modified (counterfactual) and base case (status quo) scenarios. The hypothetical population transitions between different tobacco-use states based on their attributes and transition probabilities over the simulation period. A transition sub-model coupled with mortality sub-models and excess relative risk (ERR) ratio estimates determine survival probability over time. To demonstrate the functionality and capability of our ABM, we modeled a scenario to simulate the population health impact a new tobacco product on the U.S. market. We also demonstrated sensitivity analyses by adjusting key input parameters.

Results
Our simulation, based on modified- and base-case hypothetical populations using reliable and publicly available input sources, predicts a net benefit to the population with a decrease in premature deaths and cigarette smoking prevalence.

Conclusion
Our computational model, leveraging ABM to assess population impact, is a fit-for-purpose tool for predicting public health outcomes.

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harm reduction, tobacco modeling.

Declarations

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Introduction

Computational models can be used to assess whether authorization of a new tobacco product (NP) will result in a net benefit the health of the population as a whole. (See, e.g., FSPTCA, Section 911(g)). Many computational models have been used to assess the impact of tobacco polices on population health,[1] but the integral details of the majority of these models are not available in peer-review journals. In this paper, we describe the development and validation of a computational model, a summary of which was published previously in a review comparing population models,[2] using a novel approach leveraging agent-based modeling (ABM) to assess the population impact of introducing a new tobacco product (NP), specifically an e-cigarette, into the U.S. market.

Although other researchers have used computational models to simulate the impact of e-cigarettes on the U.S. population, none of these models leverage ABM to assess the change in all-cause mortality.[1][3][4][5][6][7][8][9][10][11][12] Cherng et al.[13] applied ABM techniques within a hypothetical population to examine scenarios of e-cigarette use by smoking status and the effect on smoking initiation and cessation resulting from e-cigarettes’ introduction into the marketplace; however, mortality measures were not assessed in this article.

ABMs allow for each individual agent within the model to have autonomy to make decisions and maintain its own history. In comparison to other modeling techniques, this allows ABMs to have high levels of heterogeneity (i.e., mirroring the real population, each individual within the model is unique in terms of his or her age, gender, tobacco use history, choices made, mortality probability, etc.). When presented with a stimulus, each agent makes a decision based on their individual history and defined probabilities. ABMs can be used to make inferences based on summaries taken from the population of agents, and ABMs easily allow for population- and cohort-level inferences and predictions, as well as for accounting for uncertainty. The ABM approach, while computationally more intensive, follows individuals in the population over the entire simulation timeframe. An ABM can be more advantageous approach because it can account for more complex individual-level interactions over time, in contrast to the standard compartmental models used to assess the impact of a tobacco product on a population.[1][3][4][5][6][7][8][9][10][11][12]
Our model (henceforth referred to as the ALCS ABM) was developed based on guidelines for developing mathematical models for use in health care and public health decision-making, published by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM). These guidelines propose best practices in conceptualizing models; development and implementation of various types of models; dealing with parameter estimation; and uncertainty and on model transparency and validation.

Methods

Our ALCS ABM makes comparisons between a base case (i.e., status quo) and a modified case scenario (i.e., introduction of an NP) to assess the overall difference in tobacco use prevalence and all-cause mortality. There are two main components of the ALCS ABM: a transition sub-model which moves agents through the various tobacco use states over the simulation period and a mortality sub-model used to determine the survival probability of an agent at the end of each time step of the simulation.

In the transition sub-model each agent in the simulation is presented with a stimulus at each time point, which allows agents to change some of their attributes as the simulation progresses. Agents form a hypothetical population that can transition between different tobacco-use states based on transition probabilities. These transition probabilities are used to propagate the population through the various tobacco-use states over the simulation period. The attributes associated with each individual agent are listed in Table 1. At each time point (one-year interval) within the simulation, agents are provided with an option to switch or maintain their current tobacco-use state. The pathway an agent takes is governed by the attributes listed in Table 1 and the associated age and gender specific transition probabilities.

Other attributes may also be included in an ABM, for example, a specific value or a set of values, a probability distribution, and social networks to other agents. As NPs gain authorization and enter the market, product-category specific data on the influence of social networks will become available over time. This then provides the input data needed to activate the interacting component of our ALCS ABM.

<table>
<thead>
<tr>
<th>Table 1. Agent Attributes Tracked Within the ALCS ABM and Associated Descriptions</th>
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</table>

Qeios ID: TVND4Q · https://doi.org/10.32388/TVND4Q
### Agent Attribute Description

<table>
<thead>
<tr>
<th>Agent Attribute</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent ID Number</strong></td>
<td>A unique identification number associated with a particular agent that allows for that agent and their demographic and tobacco use history to be tracked throughout the simulation.</td>
</tr>
<tr>
<td><strong>Alive</strong></td>
<td>This attribute can have a value of 1=Alive or 0=Dead for each agent to indicate whether that agent is alive or dead at that particular time point. Once changed to zero, the agent exits the simulation.</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>This attribute can take a value of 1=Male or 2=Female to indicate the agent’s gender. This attribute is assigned when an agent enters the simulation and remains constant throughout.</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>The numerical value of this attribute indicates the agent’s age at a particular time point within the simulation. This variable is incremented on a yearly basis as the agent survives in the simulation.</td>
</tr>
<tr>
<td><strong>Tobacco-Use State</strong></td>
<td>This attribute describes the tobacco-use state in which the agent resides at a particular time point during the simulation. Any agent can exist in only one tobacco-use state at any one particular point in time but can exist in different tobacco-use states at different time points. The nine tobacco-use states within the simulation are:</td>
</tr>
<tr>
<td></td>
<td>NT = Never user of tobacco</td>
</tr>
<tr>
<td></td>
<td>CS = Current cigarette smoker</td>
</tr>
<tr>
<td></td>
<td>NPU = Current new tobacco product user</td>
</tr>
<tr>
<td></td>
<td>DU = Current dual user of cigarettes and new tobacco product</td>
</tr>
<tr>
<td></td>
<td>FS = Former cigarette smoker</td>
</tr>
<tr>
<td></td>
<td>FNPU = Former new tobacco product user</td>
</tr>
<tr>
<td></td>
<td>FDU = Former user of both cigarettes and new tobacco product</td>
</tr>
<tr>
<td></td>
<td>CS-FNPU = Current cigarette smoker who is a former new tobacco product user</td>
</tr>
<tr>
<td></td>
<td>NPU-FS = Current new tobacco product user who is a former cigarette smoker</td>
</tr>
<tr>
<td><strong>Years of Cigarette Smoking (YSM)</strong></td>
<td>At any time point in the simulation, this attribute accounts for the number of years the agent has been a cigarette smoker. This attribute is incremented for every year the agent smokes as long as the agent is alive.</td>
</tr>
<tr>
<td><strong>Years since Quit Cigarette Smoking (YQSM)</strong></td>
<td>Similarly, the number of years since an agent quit smoking is incremented every year the agent has quit smoking.</td>
</tr>
<tr>
<td><strong>Years of New Tobacco Product Use (YNPU)</strong></td>
<td>This attribute accounts for the number of years an agent has used the NP and incremented every year the agent uses the NP.</td>
</tr>
<tr>
<td><strong>Years since Quit New Tobacco Product Use (YQNPU)</strong></td>
<td>Similarly, the number of years since an agent quit using the NP is incremented every year the agent quit using the NP.</td>
</tr>
<tr>
<td><strong>Years of Dual Use</strong></td>
<td>At any time point in the simulation, this attribute accounts for the number of years an agent has concurrently used cigarettes and the NP. Increments and decrements to this attribute may be varied depending on assumptions used in modeling mortality risk for agents who have dual used.</td>
</tr>
</tbody>
</table>

The mortality sub-model is coupled with the transition sub-model. The mortality sub-model was developed using data from a Kaiser Permanente Medical Care Program Cohort study (KP Study)\(^{[15]}\) and adjusted to the U.S. population using U.S. mortality rates from the Human Mortality Database (HMD). In order to estimate the survival probability associated with NP use, the mortality sub-model is combined with the excess relative risk (ERR) ratio of the NP compared to cigarette use.
We implemented the ALCS ABM in MATLAB® version 9.2 (MathWorks, Inc.). MATLAB® is a high-performance, matrix-based language for technical computing and is an efficient tool for performing operations which involve the use of matrices and vectors.

ALCS ABM Overall Structure

The ALCS ABM involves four main steps. See Figure 1.

1. Generate the initial population

The process starts by establishing a starting population that reflects the population of interest at a particular time frame in terms of age, sex, and smoking status. The model for each simulation run presented used 2,814,219 agents in the starting population, which is approximately 1% of the actual U.S. population of 281,421,906 in the year 2000, allowing 100 computationally feasible runs of the simulation to capture the larger population. Supplementary Data File, Section 1.1 provides details including data sources and assignment of each agent's gender, age and smoking state within the starting population.
2. Estimate mortality

The mortality sub-model is used to determine the survival probability of agents. We developed this sub-model using data from the KP Study data set,\cite{15} and adjusted for U.S. mortality rates in the particular year of interest (2000 in this work) using data from the HMD.\cite{17} To account for age-specific changes in mortality over the simulation timeframe, mortality rates are adjusted using Lee-Carter methodology.\cite{18}\cite{19}\cite{20} The Lee-Carter method adjusts prospective mortality changes across time starting from the baseline mortality year, 2000 in this work, based on historical trends. To estimate mortality probabilities within a modified case scenario (i.e., introduction of an NP into the market), the excess relative risk (ERR) ratio between cigarette smoking and NP use is used. Muhammad-Kah et al.\cite{8} provides a description of how ERR ratios are estimated and applied in population models. Depending on their lifetime tobacco-use histories, the mortality risk for each agent at any time point within the simulation is calculated using a Gompertz hazard function\cite{21}\cite{22} that is dependent on the agent’s attained age, years smoked (YSM), years since cessation from cigarettes (YQSM), years of NP use (YNPU) and years since cessation from the NP (YQNPU). The survival probability of an agent is calculated from the hazard rate as:
\[ P(\text{Survival}) = e^{-h(\text{age}, \text{YSM}, \text{YQSM}, \text{YNPU}, \text{YQNPU})} \]

which translates to probability of mortality by applying the equation below

\[ P(\text{Mortality}) = 1 - e^{-h(\text{age}, \text{YSM}, \text{YQSM}, \text{YNPU}, \text{YQNPU})} \]

Supplementary Data File, Section 1.2 provides details on the mortality model. Simplified equations for the hazard rate calculation for each of the possible tobacco-use states in which an agent may exist in the ALCS ABM at the end of each yearly time interval based on an agent’s specific pathway are shown in Table 2.

<table>
<thead>
<tr>
<th>Agent State</th>
<th>Hazard Rate Calculation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT</td>
<td>( h_{\text{NT}(\text{Age})} = e^{\beta_1 \cdot \text{Age}} )</td>
<td>The hazard function for an NT is calculated using only the age covariate. All other coefficients are set to zero.</td>
</tr>
<tr>
<td>CS</td>
<td>( h_{\text{CS}(\text{Age})} = e^{\beta_1 \cdot \text{Age} + \beta_2 \cdot \text{YSM} + \beta_3 \cdot \text{YSM} \cdot \text{Age}} )</td>
<td>The hazard rate (HR) for a CS. In addition to age, years smoked (YSM) and YSM*age interaction covariates are used.</td>
</tr>
<tr>
<td>FS</td>
<td>( h_{\text{FS}(\text{Age})} = e^{\beta_2 \cdot \text{YSM} + \beta_3 \cdot \text{YSM} \cdot \text{Age} + \beta_4 \cdot \text{YSM} \cdot \text{Age} + \beta_5 \cdot \text{YSM} \cdot \text{Age}} )</td>
<td>HR for an FS expands to include the years quit smoking (YQSM) covariate.</td>
</tr>
<tr>
<td>NPU</td>
<td>( h_{\text{NPU}(\text{Age})} = e^{\beta_2 \cdot \text{YSM} + \beta_3 \cdot \text{YSM} \cdot \text{Age} + \beta_4 \cdot \text{YSM} \cdot \text{Age} + \beta_5 \cdot \text{YSM} \cdot \text{Age}} )</td>
<td>HR for an NPU is based on the ERR of the NPU relative to that of an FS. Years of new tobacco product use (YNPU) is included.</td>
</tr>
<tr>
<td>FNPU</td>
<td>( h_{\text{FNPU}(\text{Age})} = e^{\beta_2 \cdot \text{YSM} + \beta_3 \cdot \text{YSM} \cdot \text{Age} + \beta_4 \cdot \text{YSM} \cdot \text{Age} + \beta_5 \cdot \text{YSM} \cdot \text{Age}} )</td>
<td>HR for an FNPU is calculated by adding the ERR of a FNPU relative to that of an FS. Years quit new tobacco product (YQNP) is added.</td>
</tr>
<tr>
<td>DU</td>
<td>( h_{\text{DU}(\text{Age})} = e^{\beta_2 \cdot \text{YSM} + \beta_3 \cdot \text{YSM} \cdot \text{Age} + \beta_4 \cdot \text{YSM} \cdot \text{Age} + \beta_5 \cdot \text{YSM} \cdot \text{Age}} )</td>
<td>HR for DUs will depend on their YSM and YNPU. If the DU has prior periods of cessation in either product, the YQSM and the YQNP are included to minimize the risk.</td>
</tr>
<tr>
<td>FDU</td>
<td>( h_{\text{FDU}(\text{Age})} = e^{\beta_2 \cdot \text{YSM} + \beta_3 \cdot \text{YSM} \cdot \text{Age} + \beta_4 \cdot \text{YSM} \cdot \text{Age} + \beta_5 \cdot \text{YSM} \cdot \text{Age}} )</td>
<td>HR for FDU will depend on YSM and YNPU, as well as YQSM and YQNP.</td>
</tr>
<tr>
<td>CS-FNPU</td>
<td>( h_{\text{CS-FNPU}(\text{Age})} = e^{\beta_2 \cdot \text{YSM} + \beta_3 \cdot \text{YSM} \cdot \text{Age} + \beta_4 \cdot \text{YSM} \cdot \text{Age}} )</td>
<td>HR for an agent that initiates smoking from the NPU state is expected to be greater than that of an agent that initiates smoking from the NT state. As such, these agents have an aggregated risk that is derived from their CS and FNPU states.</td>
</tr>
<tr>
<td>NPU-FS</td>
<td>( h_{\text{NPU-FS}(\text{Age})} = e^{\beta_2 \cdot \text{YSM} + \beta_3 \cdot \text{YSM} \cdot \text{Age} + \beta_4 \cdot \text{YSM} \cdot \text{Age}} )</td>
<td>Use of the new tobacco product is expected to have a risk less than that of a CS but greater than the risk of a FS, who has completely quit all tobacco use. These agents have a risk that is a combination of their current and former state.</td>
</tr>
</tbody>
</table>
Note: NT = never user of tobacco, CS = current cigarette smoker, NPU = current new tobacco product user, DU = current dual user of cigarettes and NP (new tobacco product), FS = former cigarette smoker, FNPU = former NP user, FDU = former user of both cigarettes and NP, CS-FNPU = current cigarette smoker who was a former NP user, NPU-FS = current NPU user who was a former cigarette smoker.

In Figure 2, we provide an example of lifetime cumulative survival probability curves for: (1) an NT (2) an CS who started smoking cigarettes at age 18 and continues smoking only or smoking without using other tobacco products considered in this study throughout their lifetime; and (3) an NPU that started using the NP with a set ERR ratio = 0.05 at age 18 years and continued use of the only new tobacco product throughout their lifetime. In this case, an ERR ratio of 0.05 indicates that the all-cause mortality risks to an individual who uses the lower risk new tobacco product is 5% of the all-cause mortality risks the individual would carry, if they were to be a cigarette smoker. NT has the highest survival probability followed by NPU which is close to NT survivorship due to the low ERR ratio of the NPU. As expected, CS has a lower survival probability compared to NT and NPU.

![Figure 2. Example of Cumulative Survival Curves](image)

Note: NT = never user of tobacco, CS = current cigarette smoker, NPU = current new tobacco product user; ERR (NPU/CS) = excess relative risk. Ratio is set at 0.05.
3. Transition

Surviving agents as determined from the mortality sub-model enter the transition sub-model. This sub-model determines whether the agents maintain or change their current tobacco-use state: agents are presented with a stimulus that allows them either to stay in their current tobacco-use state or change their tobacco-use state by either initiating or switching to a different tobacco product and/or quitting the tobacco product that they are currently using. The transitions between states are governed by the agent’s defined current tobacco-use state, age, and gender-specific transition probabilities (e.g., initiation rates, cessation rates, switching rates). The transition probabilities can be set to stay constant or change over the simulation. The stimulus presented and transition opportunities available depends on the tobacco-use state in which an agent currently exists at a given time point within the simulation and whether the simulation is being run in the base or modified case format.

Figure 3 depicts the nine possible tobacco-use states and all transitions possible within the ALCS ABM. The transition probabilities \( P_x \) employed within the model are annotated. The state in which an agent resides at the end of each 1-year time step depends on the corresponding transition probabilities.

![Figure 3. The ALCS ABM Tobacco-Use States and Transitions](#)
Note: NT = never user of tobacco, CS = current cigarette smoker, NPU = current new tobacco product user, DU = current dual user of cigarettes and new tobacco product, FS = former cigarette smoker, FNPU = former new tobacco product user, FDU = former user of both cigarettes and new tobacco product, CS-FNPU = current cigarette smoker who was a former new tobacco product user, NPU-FS = NPU who was a former cigarette smoker.

**Green states** = base case states. **Blue states** = modified case states. The red dotted lines indicate the possibility to relapse back to the product an agent previously used.

In Figure 3, the green circles represent the base case (i.e., status quo) tobacco use states; NT, CS and FS. In the base case scenario, agents can make three possible transitions at each time point within the simulation:

a. An NT agent can transition from NT to CS; (illustrated by P1, the probability of smoking initiation) or stay in NT.

b. A CS agent can transition from the CS to FS; the probability of quitting cigarette smoking represented by P2 or stay in the CS state.

c. Once in the FS state, an agent can relapse to cigarette smoking, P21, going back into the CS state or remain in the FS state.

In a modified case scenario, we add six additional states represented in blue which includes the introduction of an NP. In this scenario, the nine possible tobacco-use states have 27 transition probabilities. The breakdown of all the states and the conditions under which each of the transitions may occur are described in the Supplementary Data File, Section 1.3.

As an example, agents in the NT state (see Figure 3) can make one of four possible transitions. They can initiate cigarette smoking and go to a CS state. In this scenario, the initiation probability for transitioning from the NT state to CS state is dependent on the scenario being modeled and may or may not be equal to the initiation probability assigned in the base case scenario. Alternately, agents in the NT state can initiate tobacco use by using the new tobacco product (moving to the NPU state), move to the DU state, or remain in the NT state.

4. Update agent age, immigration and birth projections

In the last step, the age of all surviving agents in the population is increased by 1-year increments after they exit the transition sub-model. New agents are introduced into the population each year due to birth and net immigration, based on U.S. census projections. More details on this step can be found in the Supplementary Data File, Section 1.4. Our modeling scenarios employed time steps of one year and steps 2 - 4 are repeated in annual increments throughout the entire simulation.

Model assumptions

As with all models, the ALCS ABM depends on a variety of explicit and implicit assumptions. The explicit assumptions are made when identifying input parameters such as transition probabilities and the ERR ratio addressed later in the paper.
In terms of the implicit assumptions, the KP Study data set used to create the mortality models may not be representative of the general population since the study participants had health insurance and short follow-up periods and their age-specific mortality rates were lower than those for the U.S. population. However, we have taken appropriate steps of adjusting the data set using data from the HMD to assign weights that reflect mortality rates in the U.S. population for our initial population of interest. Apart from the KP Study data set, there are very limited publicly available data with the attribute of number of years smoked and number of years since cessation. Our mortality model currently does not account for cigarette use frequency (number of days smoked) or amount (number of cigarettes per day). We assume that the average mortality risks of current cigarette smoking are the same irrespective of smoking frequency or amount.

We made an implicit assumption that smoking initiation and cessation rates will remain constant throughout the simulation period. This is similar to the assumption made by Vurgin et al. and others. We also assume that new agents introduced into the model via net immigration will have the same distribution of agent attributes as the starting population. Incorporation of these new agents based on age, gender, smoking status and associated years smoked or years of cessation allows for a more robust estimation of a U.S. population in the future.

Our model also assumes that no new regulatory policies were introduced over the simulation period and other attributes were not considered as limitations.

Model validation

We validated the ALCS ABM model to ensure fit for purpose and predictive ability by comparing results from the base case scenario with published population projections from U.S. Census and smoking prevalence estimates reported by Centers for Disease Control and Prevention based on the National Health Interview Survey (NHIS). The base case scenario assumes that cigarette smoking will continue to be the predominant tobacco use behavior in the U.S. over the entire simulation timeframe (2000-2050). We chose this scenario to validate our model as information about cigarette smoking behavior is readily available from multiple national data sources which have been established over several decades. As shown in Figures 4a and 4b, the ALCS ABM projections for both the U.S. population growth and annual mortality under the base case scenario were similar to U.S. Census Bureau projections. Figure 4c compares the model predicted overall adult smoking prevalence (age 18 and older) for each year from 2000 to 2016, to estimates reported by the Centers for Disease Control (CDC) based on NHIS data. The model predictions from 2000-2014 compare well with the published CDC data.
Figure 4. (a) Comparison of U.S. Census Projections and ALCS ABM Projected Population Growth (b) Comparison of U.S. Census Mortality Projection and ALCS ABM Projected Annual Mortality (c) Comparison of ALCS ABM Projections and CDC Reported Prevalence of Current Adult Cigarette Smokers

In addition, the agreement of gender specific population growth, mortality and age and gender specific prevalence predictions to U.S. Census Bureau and CDC estimates allows us to demonstrate that the model predictions are reasonable and consistent with other published models. The validation results provide affirmation that the model can predict the impact of introducing an NP into the U.S. market, under a variety of use behaviors and relative-risk conditions.
Example of a Model scenario

To demonstrate the applicability of our model to estimate a population health impact (premature deaths prevented), we provide a hypothetical example in which we assessed the impact of introducing an NP into the U.S. market using e-cigarette transition rates estimated from the Population Assessment of Tobacco and Health (PATH). The PATH study was designed to generate longitudinal epidemiologic data on tobacco-use behavior for various tobacco products including e-cigarettes and health in the U.S. We define the number of premature deaths prevented as the difference in predicted cumulative deaths between two hypothetical populations (a base case and modified case) over a 60-year period beginning in the year 2000.

Base Case: status quo scenario

In the status quo scenario (illustrated by green circles in Figure 3), cigarette smoking continues to be the dominant tobacco-use behavior in the marketplace, over the entire simulation timeframe. Under these conditions, an agent within the model can exist in only one of three product use states: NT, CS or FS. Our initial population reflects the U.S. population in the year 2000 in terms of age, sex, and smoking status (i.e., never-user of tobacco, current cigarette smoker, and former cigarette smoker). The base case scenario’s initial population distribution, population updates for birth and immigration, mortality estimations, and transition probabilities (i.e., cigarette initiation and cessation) will be governed by parameters obtained from the sources described in Table 1.1-1 in the Supplementary Data File, Section 1.1.

Modified Case (MC): Introduction of a NP to the Base Case

The MC scenario which illustrates the introduction of a NP in a population relies on key input parameters which include: ERR ratio estimates for exclusive e-cigarette users and dual users relative to cigarette smoking and estimation of transition probabilities between different tobacco use states. A key limitation in modeling the impact of introducing a NP in a population is the lack of input data on both the long-term potential risk and usage pattern of the NP. The MC scenario begins in the year 2000, with the same starting population as the base case. In 2009, e-cigarette products are introduced into the market and are then available as an alternative to cigarette smoking for the remaining years of the simulation, which extends to the year 2060.

Estimation of Excess Relative Risk (ERR) Ratio for exclusive NP use compared to cigarette smoking

We set our ERR ratio to 5% since we chose e-cigarettes to demonstrate the utility of our model and it has been endorsed by other researchers. This ERR ratio assumption is also consistent with other published models. We assigned the ERR of 1.0 for dual use, indicating that they have the same mortality risk as an exclusive cigarette smokers, an assumption that has been adopted by other researchers. We performed sensitivity analyses over a wide range of ERR ratio values to understand the impact of the ERR ratio on model predictions. See Section 3 of the Supplementary Data File.
Transition Probabilities Between Tobacco-Use States

Transition probabilities between different tobacco-use states illustrated by the solid lines in Figure 3 are inputs needed to simulate the changes in cigarette smoking and e-cigarette use behaviors, leading to changes in all-cause mortality and prevalence projections.

We obtained transition probabilities from the Cancer Intervention and Surveillance Modeling Network (CISNET) and an analysis of the PATH Wave 1 (2013-2014) and Wave 2 (2014-2015) study data[31] to demonstrate the use of the ALCS ABM. We obtained our base case cigarette initiation and cessation probabilities from the CISNET database, where the smoking history of U.S. birth cohorts is reported using NHIS data.[32] The cessation probabilities in CISNET are based on at least two years of successful smoking cessation. This is an important consideration since minimal relapse is assumed after a period of 2 years, which allows us to simplify our model by eliminating relapse transitions (indicated by red dotted lines in Figure 3). We also assumed the following transition probabilities are equal:

i. Cessation of e-cigarette use and cigarette smoking (i.e., \( R_b \), \( P_{17} \), and \( P_{19} \) in Figure 3, use the same value as \( P_2 \))

ii. Cessation from dual use of e-cigarettes and conventional cigarettes to either exclusive use state (\( R_1 \), \( P_{12} \) in Figure 3, use the same value as \( P_2 \)).

In this scenario, we assume that the smoking-cessation probabilities reported in CISNET are representative of long-term tobacco cessation outcomes. Therefore, we assign the same cessation probabilities for e-cigarette products. Table 2.7 in Section 2 of the Supplementary Data File summarizes the input parameters that we used to demonstrate our model.

Results of Hypothetical Modeling Scenarios

The results of the MC scenario show a decrease in premature deaths and cigarette smoking prevalence over a 50-year timeframe, following an introduction of the NP. In the modified case modeling scenarios, we introduced the NP based on (PATH Wave 1- Wave 2 e-cigarette rates), into the model starting in the year 2009 and increased initiation rates uniformly over a 5-year period, to achieve the initiation rates estimated from PATH Wave 1 to Wave 2 analysis (see Table 2.7 in the Supplementary Data File) for 2014.

Figures 5 and 6 show the modeling predictions for adult tobacco-use prevalence (18+ years of age) and the cumulative differences in all-cause mortality (ages 35-85) between the base case and the MC scenario (based on PATH Wave 1-Wave 2 e-cigarette rates). Figure 5 (a) shows projected prevalence of overall cigarette smoking and e-cigarette use. With the introduction of e-cigarettes, over time, prevalence of cigarette smoking declines in the model, while prevalence for e-cigarette use increases. A recent publication by Levy et al.[33] compares e-cigarette prevalence estimates reported from eight online and 16 traditional survey datasets, which leverage data from national surveys such as NHIS, PATH, National Health and Nutrition Examination Survey (NHANES), National Adult Tobacco Survey (NATS), etc. in the 2010-2017 timeframe. Though considerable variations were reported within outcomes of the traditional surveys, even within a specific year, our model predictions for the 2013-2016 were well within the range of e-cigarette prevalence estimated from the
different datasets.

Figure 5. Total (a) and Exclusive (b) Adult Cigarette Smoking and E-Cigarette Use Prevalence for the MC and Base Case.
Scenarios

Note: MC = Modified Case.

Figure 6. Impact of the Introduction of E-Cigarette Products on All-Cause Mortality Between the Base Case and MC Scenarios

Our modeling results demonstrate that total cigarette smoking (including exclusive cigarette smokers and dual users) prevalence will reduce to 10.4% by year 2040 and remain approximately constant till the end of the simulation in year 2060. This is a 3.6 percentage point decline from the 14% predicted value for cigarette smoking prevalence in the base case in year 2040 [see Figure 5 (a)]. Total adult e-cigarette prevalence (including exclusive e-cigarette use and dual users) would increase to 8.4%, indicating a shift in tobacco usage from cigarettes to the potentially reduced-risk e-cigarette products. Figure 5 (b) shows projected adult prevalence of exclusive and dual use of cigarette smoking and e-cigarette use. As shown in Figure 5 (b), exclusive adult cigarette prevalence will drop further to 7.3% by 2040 and remain approximately constant till the end of the simulation in year 2060; while exclusive e-cigarette prevalence will increase to 5.3% with dual use contributing 3.1% to the total prevalence for each product. Although the combined total tobacco prevalence (i.e., exclusive use of both products and dual use) of 15.7% in the MC is higher than in the base case (i.e., 14%), the overall net benefit is realized from shifting significant portions of individuals from cigarette smoking to exclusive e-cigarette use (i.e., from a higher to a potentially reduced-risk product).
Along with a decline in adult cigarette smoking prevalence, the results of the cumulative difference in all-cause mortality between the MC and base case scenarios depicted in Figure 6, show a reduction in cumulative number of deaths over the simulation timeframe. To set context, if there is no difference in the number of deaths between the two scenarios, the expected results would fall on the dotted line that depicts no difference. If the results are above this dotted line, the introduction of e-cigarettes would translate to an increase in the number of deaths in the MC scenario compared to the base case (i.e., net risk to the population), and if the outcomes are below the zero line, it would translate to a net benefit to the population. Under the MC, the model predicts ~629,000 premature deaths will be prevented by 2060, compared to the base case, resulting in an overall net benefit.

While the estimated transition rates and ERR values employed in modeling the MC e-cigarette introduction scenario are based on analysis of the most reliable datasets available at that time point, they are point-in-time estimates; thus, they are uncertain. We acknowledge that the e-vapor category is dynamically evolving within the U.S. tobacco landscape; therefore, we conduct sensitivity analysis using a series of modified case scenarios to better understand how each input parameter influences the results of the MC, thereby identifying which inputs have the greatest impact on the predicted outcomes (See Supplementary Data File, Section 3). Based on the sensitivity analyses we conducted for several key transition pathways the greatest impact on the outcomes of the MC scenario were the initiation of cigarette smoking by NT (P1), cigarette smoking cessation (P2 and P17), switching from exclusive cigarette smoking directly to exclusive e-cigarette use (P5) or from DU (P11) to exclusive e-cigarette use.

To better understand the benefit-risk balance at the population level for the MC scenario we conducted a bivariate sensitivity analysis by comparing the outcomes from a large number of MC scenarios, in which we concurrently varied the transition probabilities for a potential risk variable (e-cigarette initiation, P3) and potential beneficial variable (switching from smoking to e-cigarette use, P5).

Figure 7 shows the impact on number of premature deaths prevented, by concurrently varying transition probabilities of e-cigarette initiation (never-tobacco users initiating e-cigarette use) and switching (cigarette smokers quitting smoking and switching to exclusive e-cigarette use), while holding all other inputs transition probabilities the same as those in the MC scenario. Figure 7 displays the average transition rates for the combined age groups from e-cigarette initiation (x axis) and switching from smoking to exclusive e-cigarette use (y axis). The weighted average e-cigarette initiation rate and switching from cigarettes to e-cigarettes in the MC scenario was 1.5% (age 12-24) and 1.4% (age 12-64) respectively. Figure 7 illustrates that a relatively small change in the rate of switching from cigarettes to e-cigarettes has a much larger impact on net benefit than changes in e-cigarette initiation rates. If the rate of switching increases to 2.3% e-cigarette initiation rates would have to increase to relatively high levels of greater than 9.5% compared to the current rate of 1.5%, for the benefit to be negated. The reason is because there is a much larger differential in risk in moving from smoking to e-cigarette use (95% reduction in risk relative to smoking) versus moving from never tobacco use to e-cigarette use (5% risk relative to smoking). A risk–benefit analysis provides insights into how combinations of key input parameters impact population level outcomes.
Discussion and Conclusions

In this paper, we demonstrated how an agent-based modeling approach can be integrated with a mortality sub-model to predict population health outcomes associated with changes in use behaviors of individual tobacco product users in the U.S. The ALCS ABM is based on a well-established methodology using inputs founded on validated measures and executed using extensive quality controls and model verification procedures. The ALCS ABM was verified and validated to accurately estimate public health outcomes (i.e., prevalence and all-cause mortality) on the U.S. population. Our predictions of population growth and mortality in a single-product environment were validated by comparing model outcomes against U.S. Census projections through the year 2050. In addition, the ALCS ABM’s ability to predict smoking prevalence was validated by comparing model predictions against actual prevalence reported by the CDC. These validations demonstrated the suitability of our model to predict tobacco product usage patterns, and the associated impact on public health, from the introduction of a new tobacco product, under a variety of use behaviors and relative risk conditions.

Our MC scenario used estimated e-cigarette transitions from PATH indicated that the introduction of e-cigarettes in

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Note: The white line represents the net neutral line (i.e., no difference in premature deaths between base and modified case scenarios), while the purple /blue /green and orange/red areas represent the benefit and risk areas, respectively.
U.S. market has the potential to prevent premature deaths within 50 years of introduction, compared to continuing with the status quo (i.e., cigarette smoking remaining the predominant tobacco use behavior). We also conducted sensitivity analyses on various input parameters to showcase the impact of uncertainty and variation of the inputs on model projections. To examine the potential population health risk arising from never-tobacco users initiating tobacco use via using e-cigarettes, we conducted a bivariate sensitivity analysis to understand the benefit-risk relationship between initiation of e-cigarettes and switching (i.e., from cigarette smoking to exclusive e-cigarette use), holding all other transitions as they were set in the MC. As with any modeling exercise, we acknowledge that there is the opportunity to update input data as more recent data becomes available.

As with all models there are limitations. A key limitation is that models are constrained by gaps in the current state of the data/science and rely on some assumptions. It is worth noting that estimated transition probabilities may vary due to the many ways in which tobacco user groups are defined.\textsuperscript{[34][35][36]} Most models are built with a specific objective in mind and therefore, may not capture unforeseen events which may trigger major model revisions. Modeling is an iterative process; therefore, as patterns change over time, model scenarios are rerun to assess possible changes in the model outcomes.

In conclusion, our computational ALCS ABM model comparing well-defined modified and base case scenarios is a validated and reliable tool for predicting public health outcomes, arising from the introduction of a new tobacco product such as a modified risk product into the U.S. market.

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Ethical Statement

Funding: This work was supported by Altria Client Services, LLC and all authors are employees of Altria Client Services, LLC. This work is based on data from the Population Assessment of Tobacco and Health study, which is available in the public domain with identifying information removed, and therefore, no ethical clearance was required.

Supplementary Data File

Please see the Supplementary Data File for more information on model development, analysis of the transition probabilities and sensitivity analysis for the Modified Case.

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• Figure 1.1-2. Age Dependent Probabilities of Agent Being Assigned Female or Male Gender within the Initial Population.
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• Figure 3-3. Cumulative difference in all-cause mortality for ages 35-85 between the base case and extreme modified case scenarios.
References


