The TCA's Population Impact Standard for New Products and Health Claims: How does Population Modeling Actually Work?

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Moderated by **Saul Shiffman**, Professor of Psychology, University of Pittsburgh and Senior Scientific Advisor, Pinney Associates, Inc.

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Introduction to Population Modeling

Saul Shiffman, Ph.D.

Professor of Psychology, University of Pittsburgh
& Senior Scientific Advisor, Pinney Associates

Consult to JUUL Labs, previously to RAI (RJ Reynolds) & BAT
on smoking cessation, e-cigarettes, harm reduction

Considered This?

vs.

Sage smoked for 23 years, and switched to JUUL in 2018.

"I hadn't planned to switch. But after about a week of having the JUUL in my hand, I started reaching for it over my pack of cigarettes."
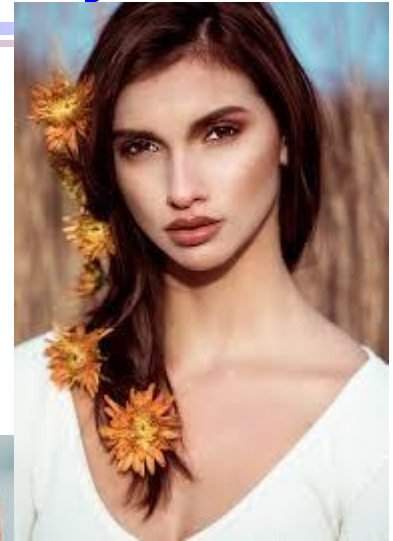
Make the Switch

3

Everybody Models

Some do it Systematically

Why Model?

- *Integrate effects of multiple influences*
- *Predict effect of changes in policy or products*
- Identify key drivers of outcomes
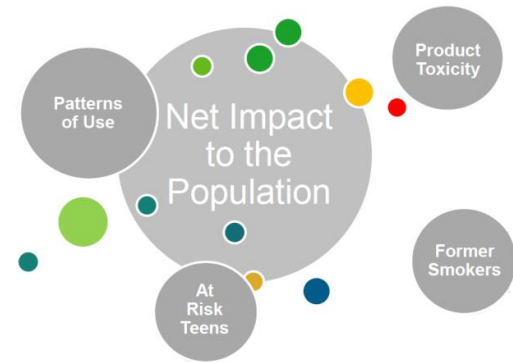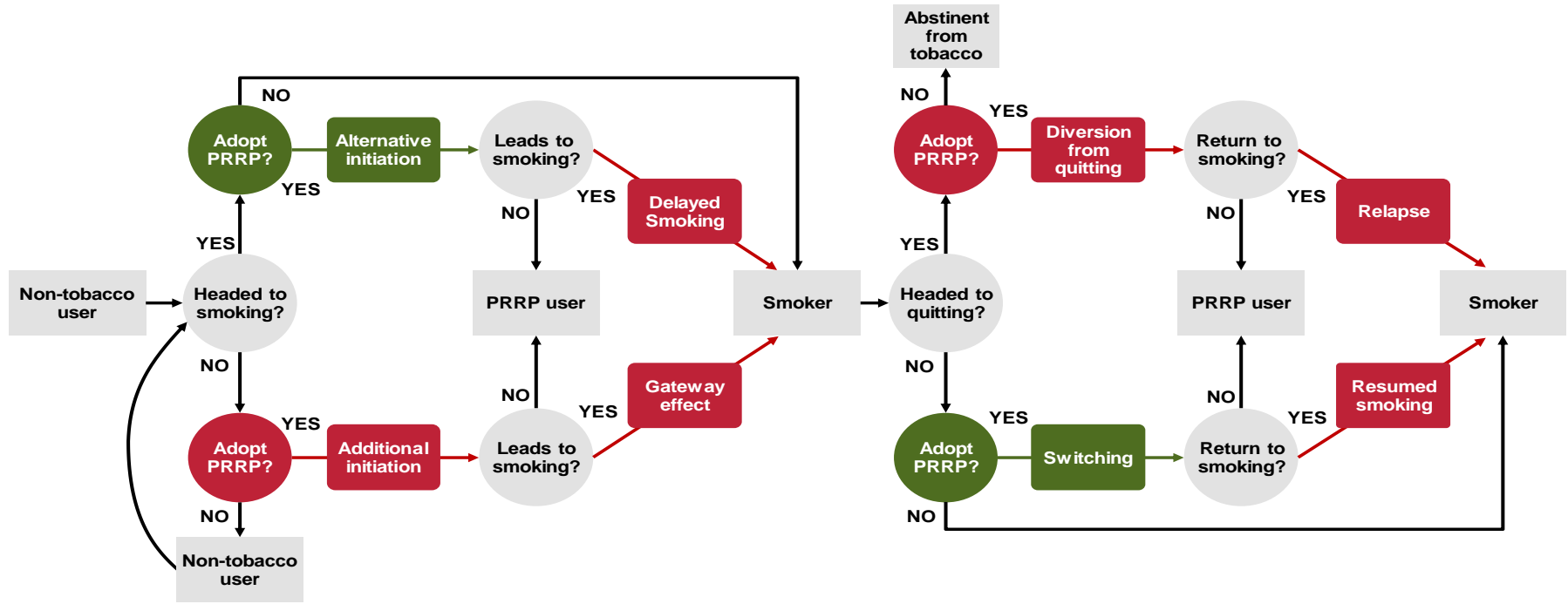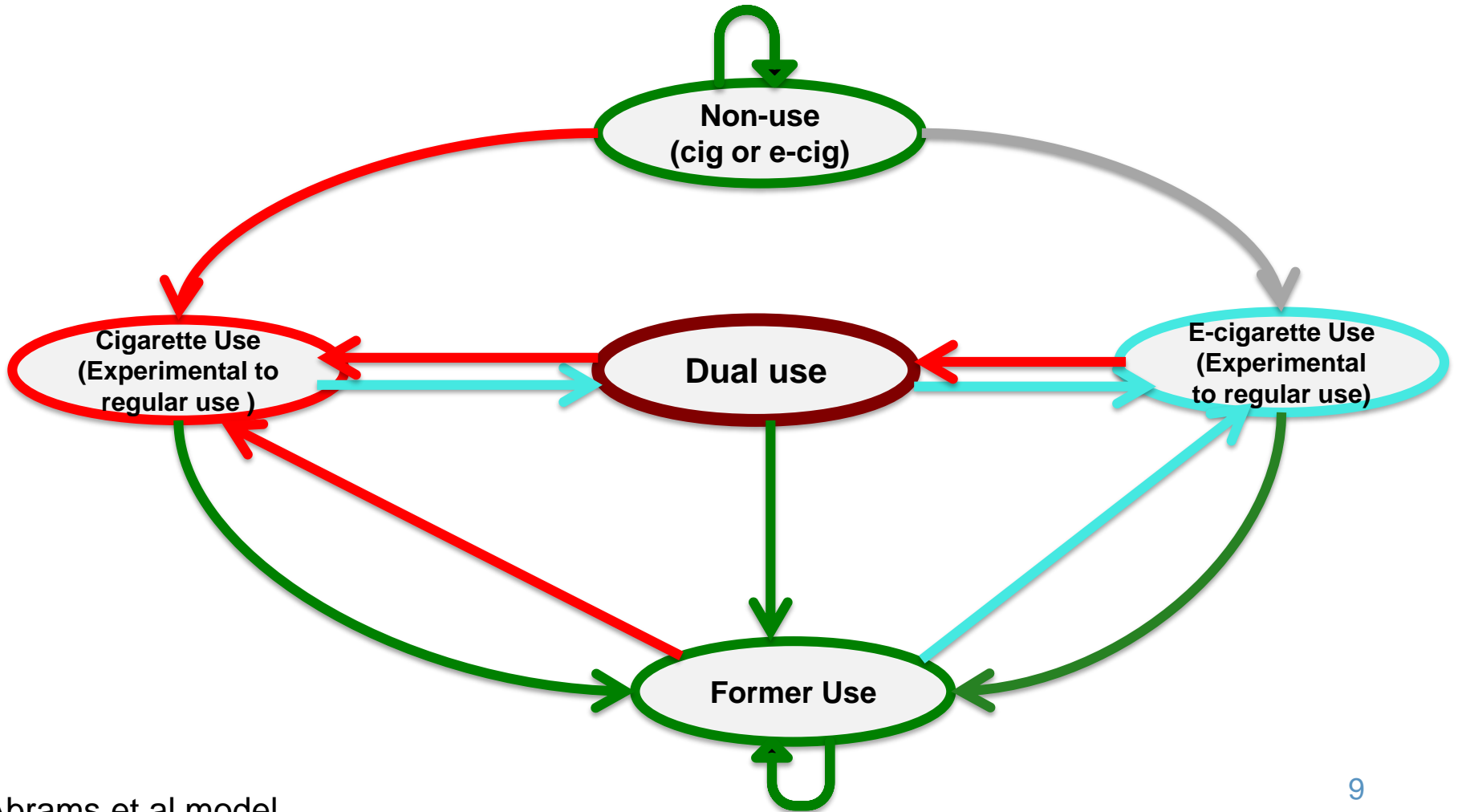- Prioritize data collection

US FDA
Population Health Standards

- New products (PMTAs):
  "appropriate for the protection of the public health" (910(c)(4), FD&C Act)
- Modified-risk claims (MRTPAs):
  "will benefit the health of the population as a whole" (2(36),Tobacco Control Act)
- Inherently invoke balancing of harms and benefits
- Inherently involve considering a different world

ASSESSING OVERALL IMPACT TO PUBLIC HEALTH

Net Impact to the Population

Patterns of Use

Product Toxicity

At Risk Teens

Former Smokers

Bachand et al model

8

Abrams et al model

9

Appelberg et al model

10
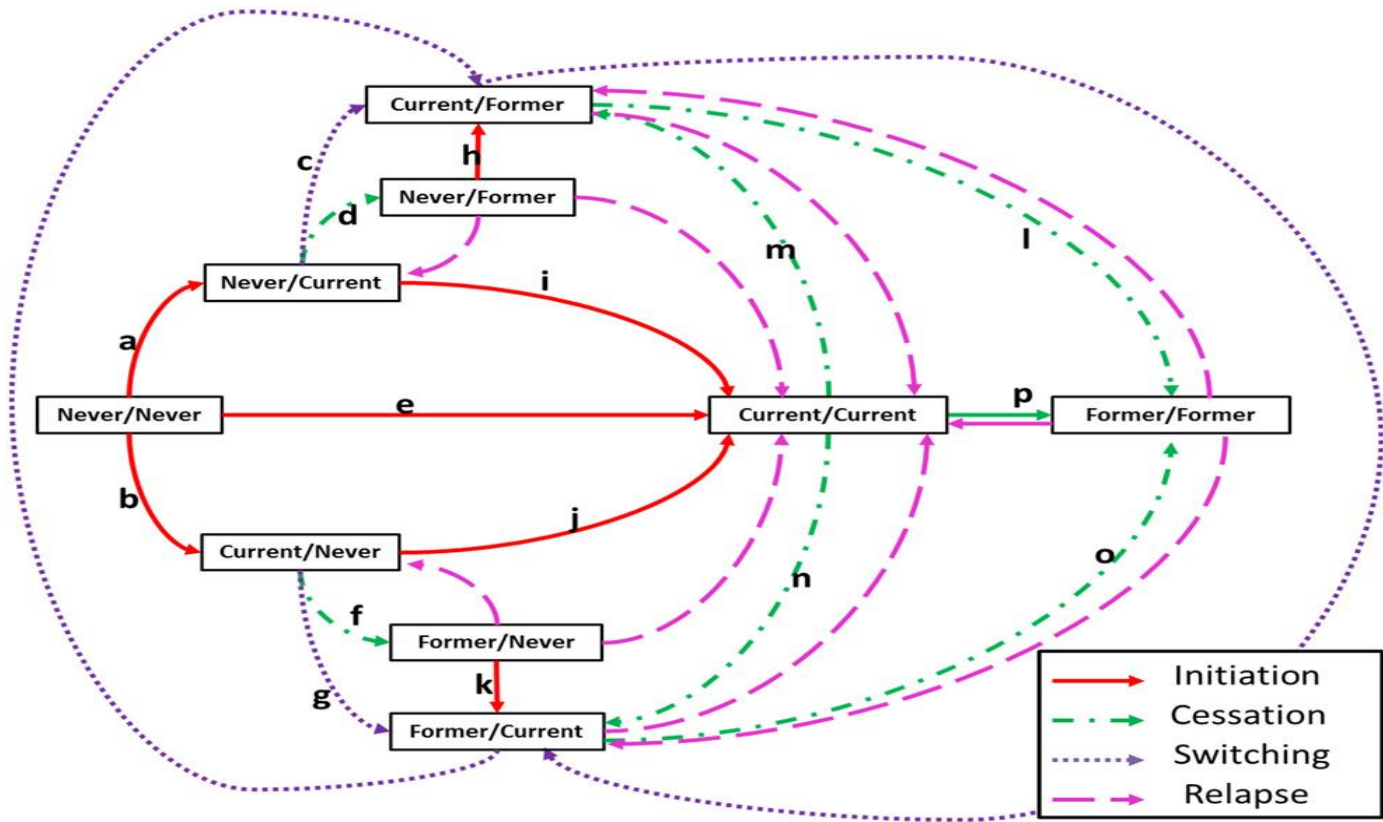
Outcomes

- Ultimate outcome: Population health
  - Longevity/survival
  - Burden of disease
  - Quality-Adjusted Life-Years (QALYs)
- Intermediate outcomes
  - Prevalence
  - Initiation
  - Age distribution
  - Etc.

All Lives Matter….

OK, maybe [e-cigarettes] can help five currently addicted adult smokers quit. But for every five adult smokers that quit, one kid's going to become addicted to nicotine. And we might say on balance, that's not a trade that we would be willing to make from a regulatory standpoint.

- Scott Gottlieb, as FDA Commissioner

Inputs Based on Observation

- Defining the **base case**… the current world
- Profiles of the population
  - Including 'stocks' of smokers, ex-smokers, non-smokers
- Existing, observed transition/flow rates
- Health impact of smoking (i.e., base-case product)
- Base-case model can be verified by seeing if it 'predicts' actual observed data

Inputs that May Need to be Inferred

- Health impact of alternative product
  - Often expressed as a proportion of the risk of smoking
- New transitions introduced in the ***counterfactual***… the new world
  - Consumer research
  - Assumptions, extreme values
- Typically assume "all else being equal"
  - Population dynamics getting less and less 'equal'

Prediction is very difficult…

Especially about the future

- Niels Bohr, Nobel Prize Physicist

Sensitivity Testing

- Inputs and assumptions not known with certainty
- Test sensitivity / robustness of outputs to variation in inputs
- Define range of uncertainty
- Build confidence in conclusions

Tipping Point Analysis

- Directed form of sensitivity testing
- What combination of inputs, boundary conditions, reverses the conclusions?
  - When can harm reduction be harmful?
- Reductio ad absurdum – are such boundary conditions plausible?

Simple, Heuristic Model:
The Risk/Use Equilibrium

Amount by which prevalence would need to increase to counteract benefit, based on posited product's risk-reduction

Kozlowski et al model
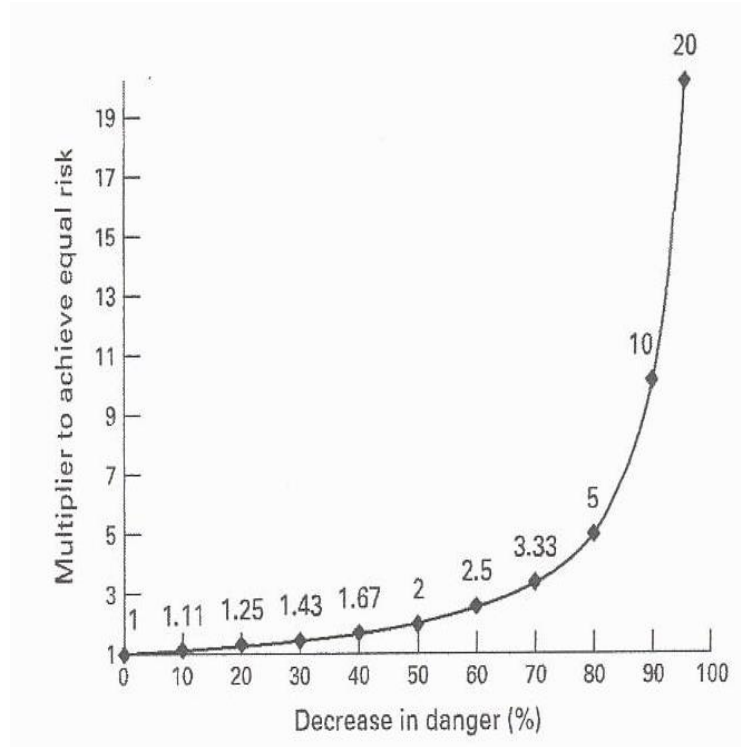
A Modeling Consumer's Guide

- Modeling frameworks differ
- Assumptions and inputs are key
- Look for sensitivity and tipping-point analyses

FDA: Public health standard

"Public health standard" calls for the review of the scientific evidence regarding

1. Risks and benefits of the tobacco product standard to the population as a whole, including both triers and non-triers of tobacco products;

2. Whether there is an increased or decreased likelihood that those who do not currently use tobacco products, most notably youth, will start to use tobacco products; and

3. Whether there is an increased or decreased likelihood that existing triers of tobacco products will stop using such products

Computational Models

- Simulation models (macro or micro) models are used in other fields, but are increasingly common in public health, especially in the fields of tobacco control and obesity

- Models are especially useful where there are dynamic systems with many stages (e.g., policy -> environment -> behaviors -> health outcomes) and where the effects unfold over time.

- Models attempt to make the connections between stages, across stages and over time explicit, focusing on the movement of whole system rather than an isolated part
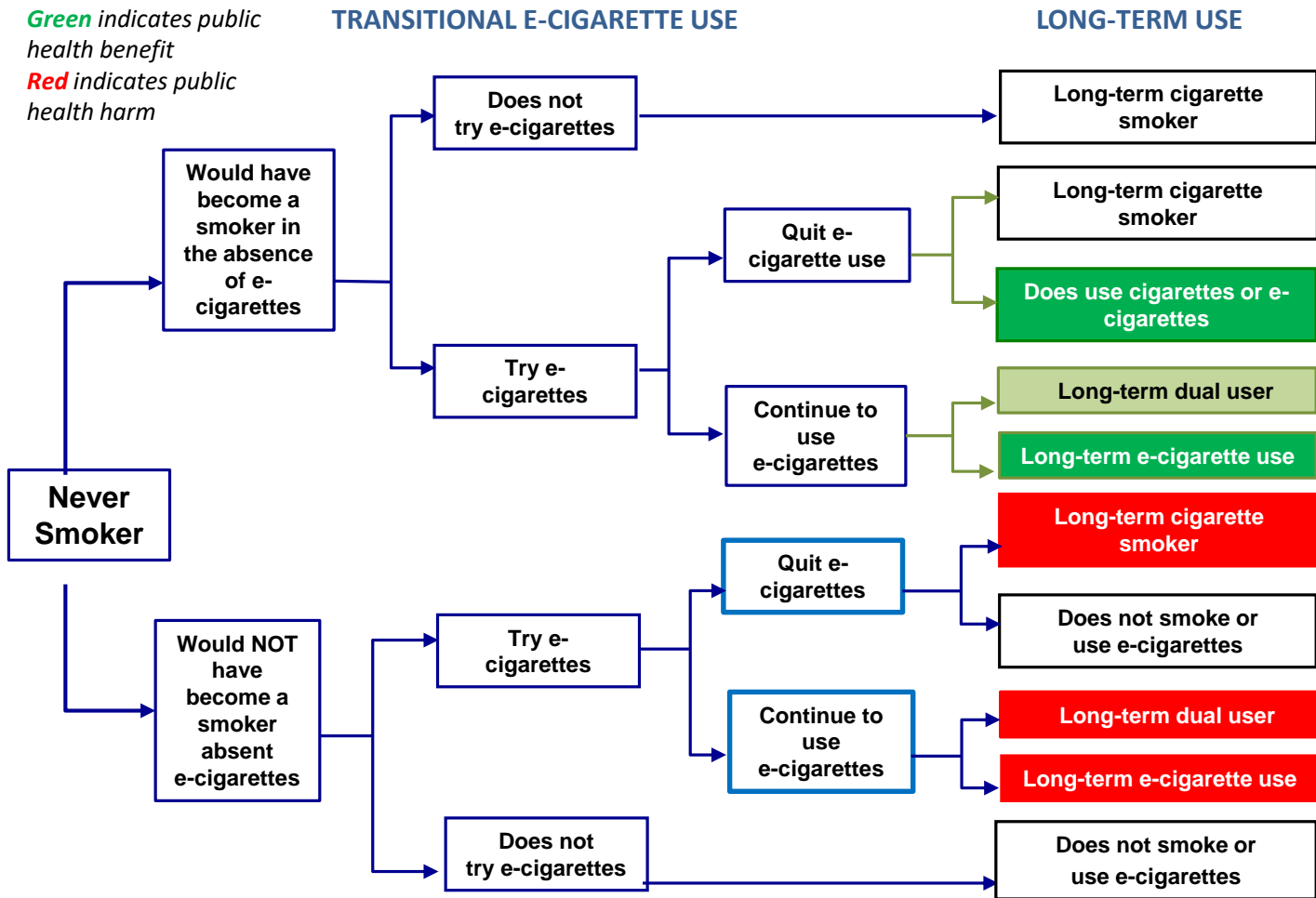
Purposes of Modeling

- Predictive: Examining Past and Predicting Future Behavior:

  Past Policies-> Past and Future Smoking and E-cigarette Use -> Health Outcomes

- Hypothetical Policies:

  Potential Future Policies (given current policies) ->

  E-Cigarette and Cigarette Use Patterns -> Health Outcomes

- Heuristic: Understanding system aspects, helping to determine the information needed to evaluate public health impacts

Predictive, But Heuristic: The Public Health Impact of E-cigarette Use Among Never Smokers
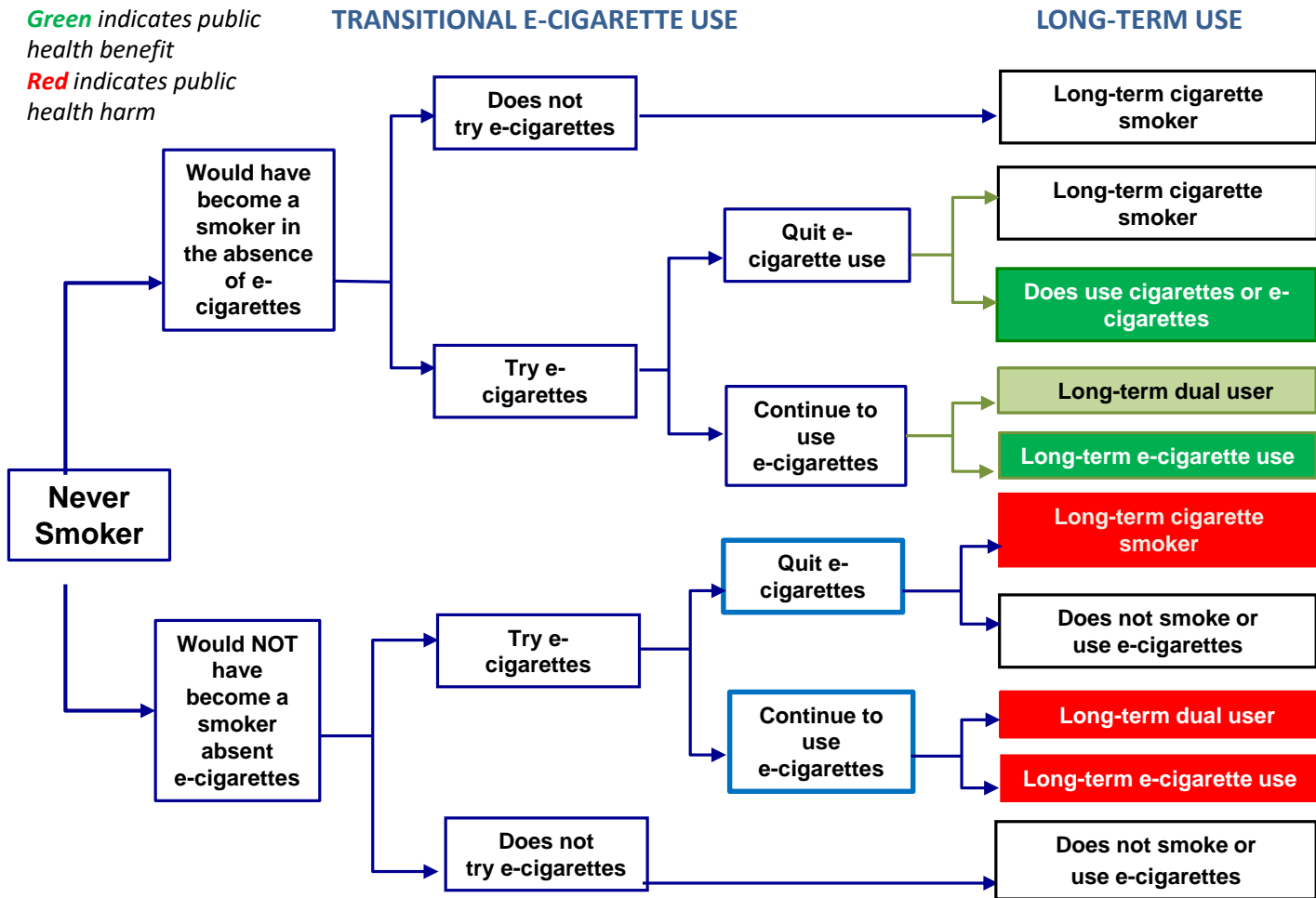
Predictive: Levy et al. Initiation Model (2017, Nic Tob Res)

- ❖ Unlike other models, focuses on a representative single cohort: age 15 in 2012

- ❖ Applies a decision-theoretic framework (Levy et al. 2017, Addiction) grounded in a public health approach to examine the effect of transitions to final states of established use.

- ❖ Distinguishes trial use from established e-cigarette use

- ❖ With trial use, individuals may transition to: 1) exclusive e-cigarette use, 2) dual (cig and e-cig) use, 3) exclusive cigarette use, or 4) no use (e-cigarettes as transition to quitting both).

- ❖ Public health implications depend on the counterfactual of what would have happened in the absence of e-cigarette use
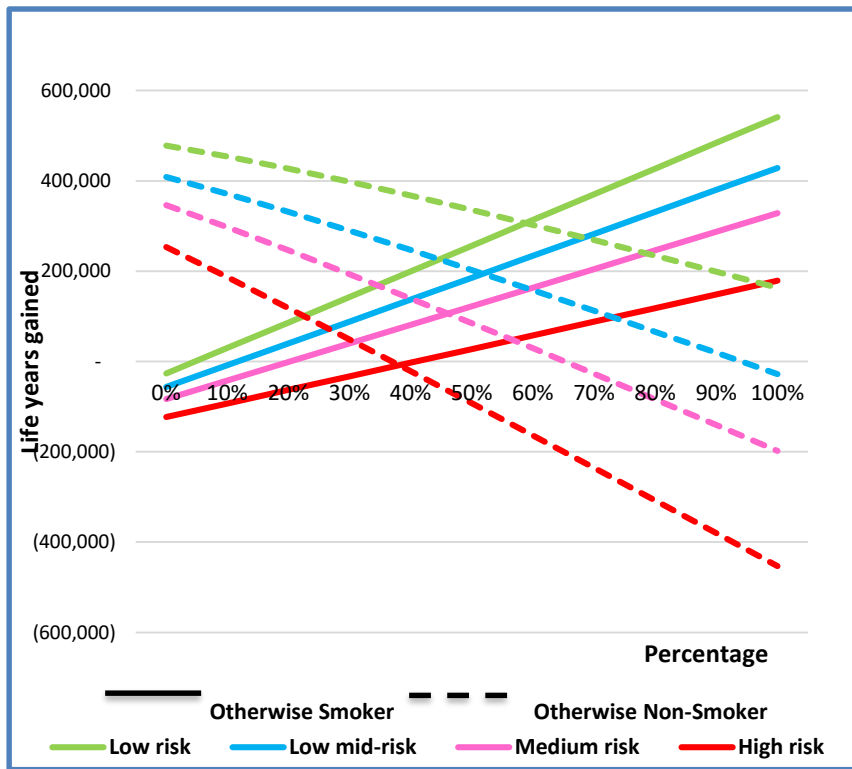
Predictive, But Heuristic: The Public Health Impact of E-cigarette Use Among Never Smokers

Trial Use Sensitivity Analysis: Male
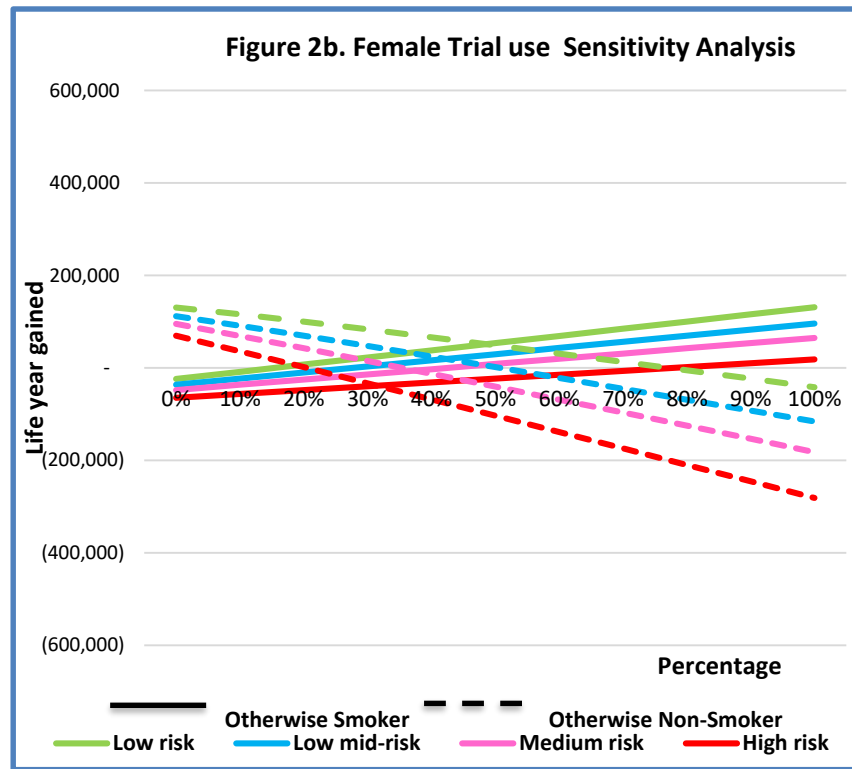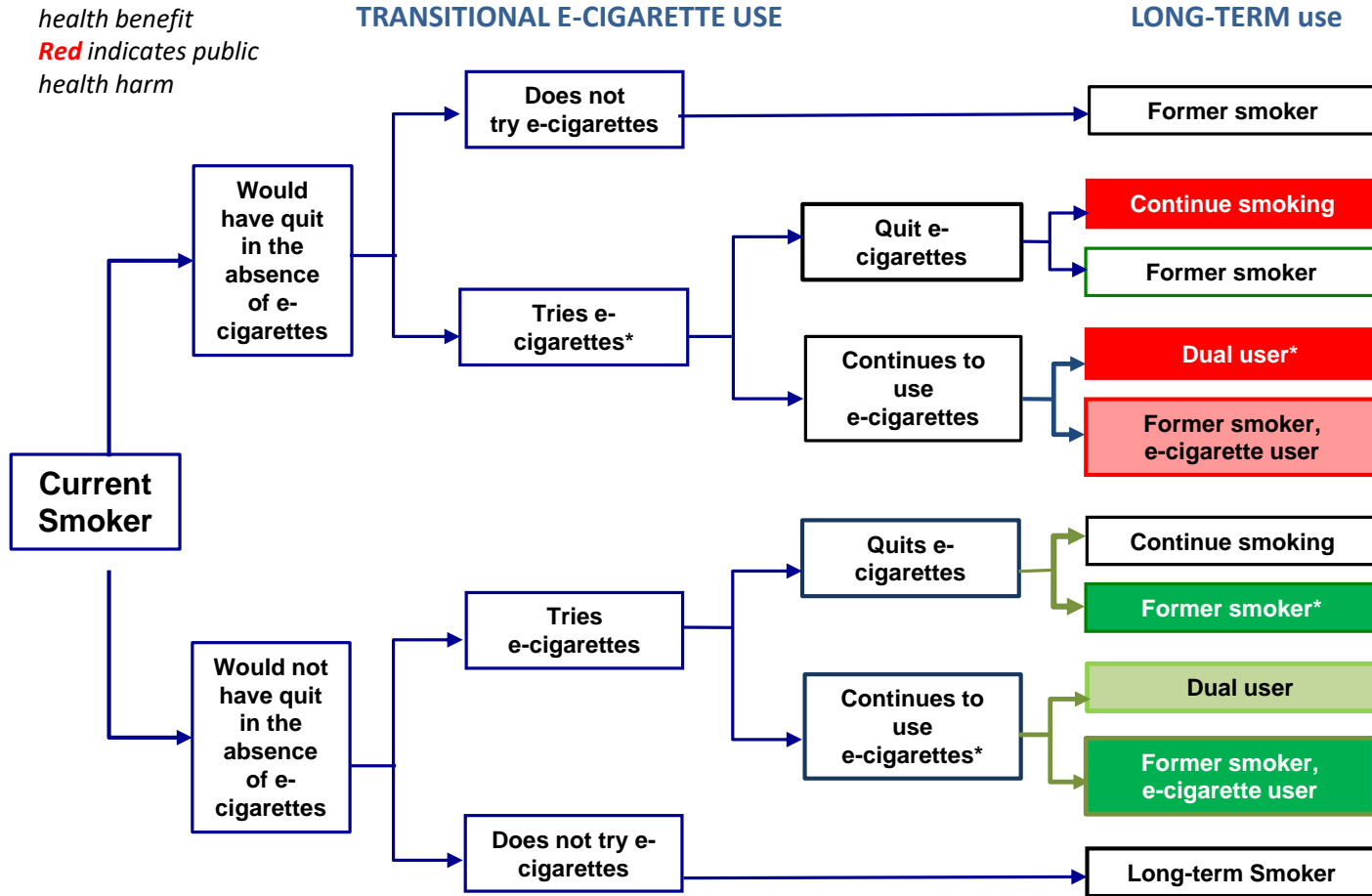
Trial Use Sensitivity Analysis: Female

Figure 2b. Female Trial use Sensitivity Analysis

The Public Health Impact Of E-cigarette Use Among Current Smokers

Green indicates public health benefit
Red indicates public health harm

TRANSITIONAL E-CIGARETTE USE

LONG-TERM use

Current Smoker

Would have quit in the absence of e-cigarettes
- Does not try e-cigarettes → Former smoker
- Tries e-cigarettes*
  - Quit e-cigarettes
    - Continue smoking
    - Former smoker
  - Continues to use e-cigarettes
    - Dual user*
    - Former smoker, e-cigarette user

Would not have quit in the absence of e-cigarettes
- Tries e-cigarettes
  - Quits e-cigarettes
    - Continue smoking
    - Former smoker*
  - Continues to use e-cigarettes*
    - Dual user
    - Former smoker, e-cigarette user
- Does not try e-cigarettes → Long-term Smoker

Hypothetic Impacts of Switching to NVPs: Structure

- Begin with a Status Quo- in this case no vaping, includes current and former smokers, developed applying age-period cohort analysis(NHIS) survey using data up until 2012 (before e-cigarettes widely used)- ignores other tobacco use

- Allow switching from cigarettes to e-cigarettes over a ten year period to the residual cigarette prevalence- will consider two scenarios, specifying basic parameters of risk and use rates

- Public health implications depend on the counterfactual of what would have happened in the absence of e-cigarette use

Levy et al. 2017, Tobacco Control

The Two Scenarios

ASSUMPTIONS

OPTIMISTIC
1. Excess mortality risk of e-cigarettes at 5% that of cigarettes
2. Cessation from cigarettes and e-cigarettes at the 100% the rate of cigarette cessation pre-strategy
3. Initiation at the 100% the rate of cigarette initiation pre-strategy
4. Residual cigarette prevalence of 5% after 10 years

PESSIMISTIC
1. Excess mortality risk of e-cigarettes at 40% that of cigarettes
2. Cessation from cigarettes and e-cigarettes at the 50% the rate cigarette cessation pre-strategy
3. Initiation at the 150% the rate of cigarette initiation pre-strategy
4. Residual cigarette prevalence of 10% after 10 years

Hypothetic Impacts: Two Scenarios

METHODS

- Project from 2016 to 2100 current and former cigarette prevalence, attributable deaths and life years lost by age and gender under the status quo

- Project current and former smokers and vaper prevalence and attributable deaths from 2016 to 2100 by age and gender for US under the status quo current and former cigarette prevalence and attributable death

- Compare results of each vaping scenario to the status quo

Status Quo and E-Cigarette Substitution, Premature Deaths and Life Years Lost For All US Cohorts, Males and Females Combined
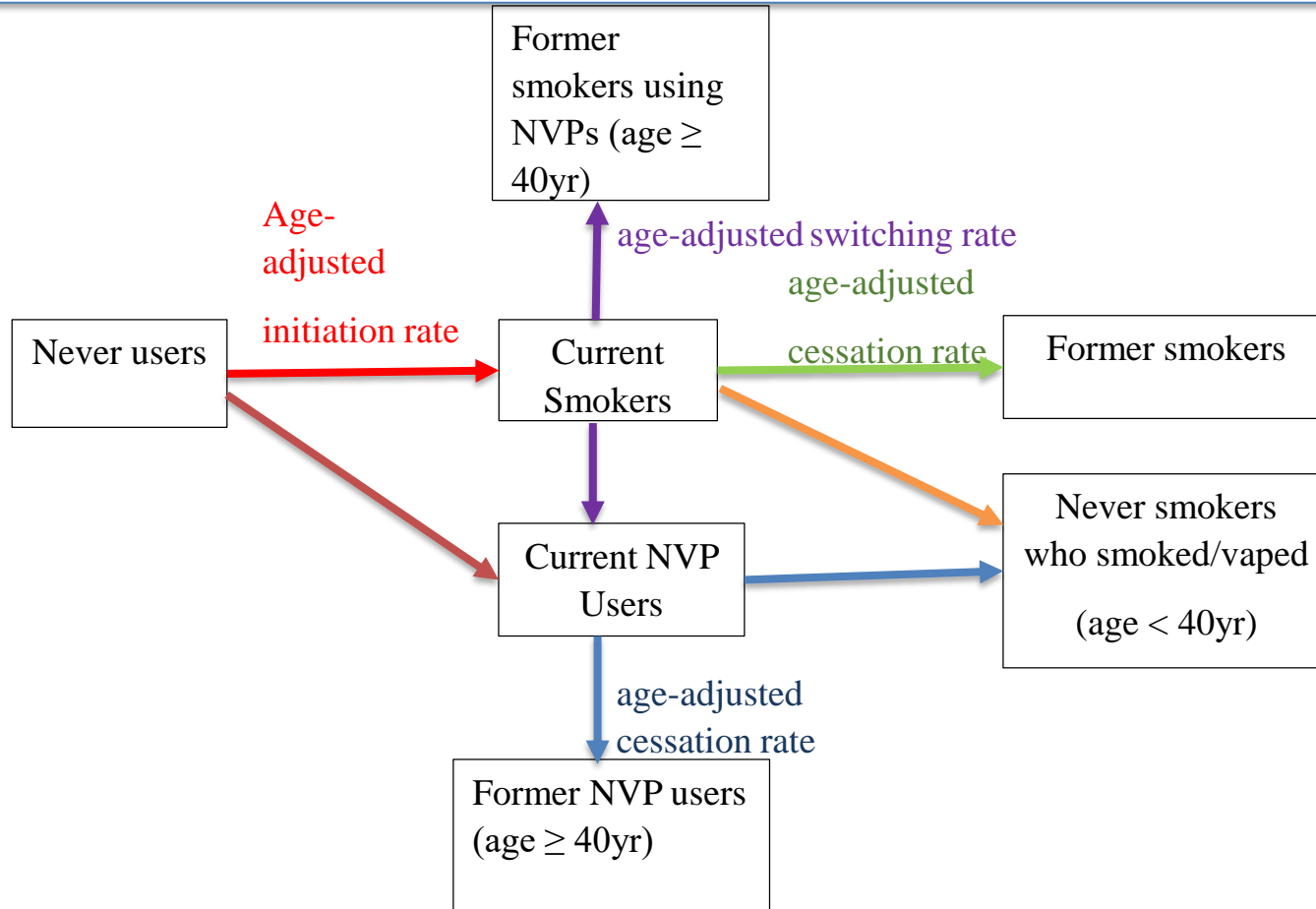
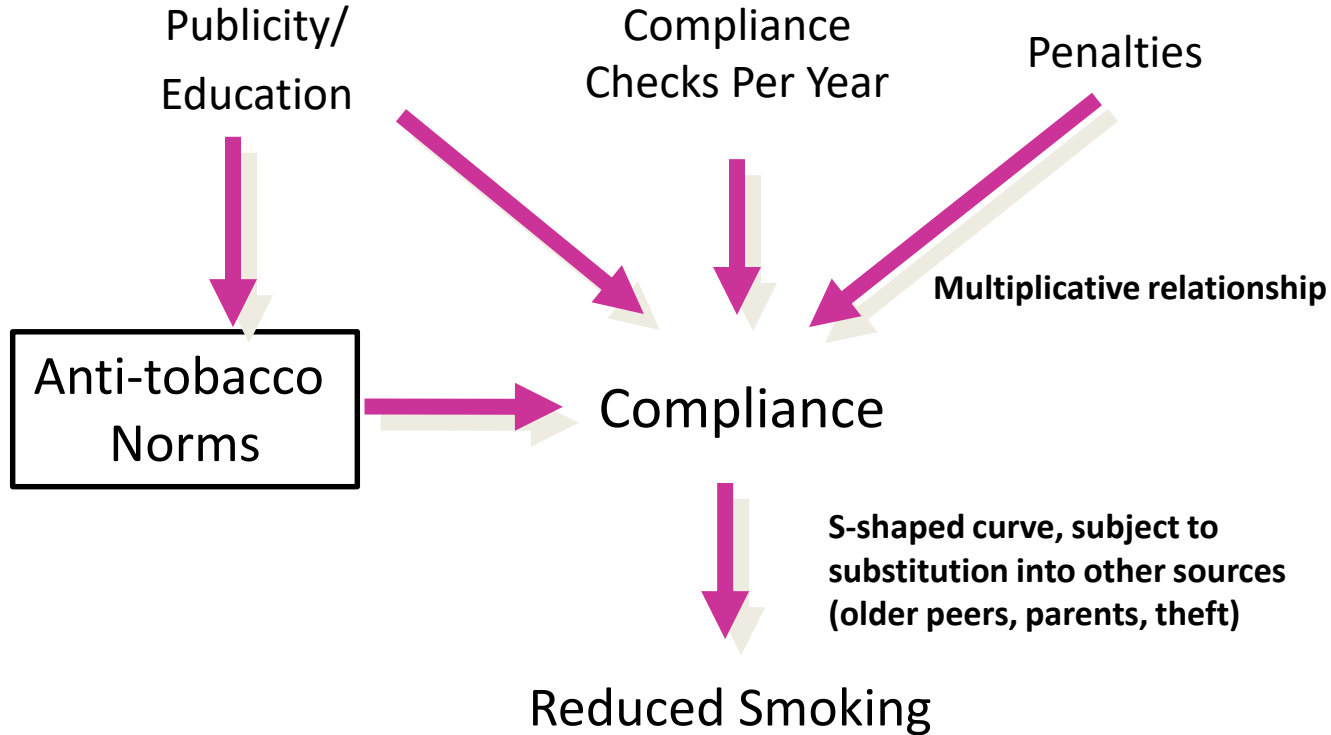| OUTCOME	Year 2016	2026	2060	2080	2100	Cumulative (2016-2100)	Deaths Prevented/ Life Years Gained*	% Change relative to status quo
Status Quo Scenario								
Premature Deaths	461,588	470,743	316,556	167,037	2,905	26,065,448		
Life Years Lost	5,689,458	5,625,286	2,626,503	685,593	1,852	248,639,532		
Optimistic Scenario								
Premature Deaths	461,588	380,832	233,243	56,399	459	19,484,289	**6,581,159**	**-25.2%**
Life Years Lost	5,689,458	3,839,765	1,345,385	183,297	294	161,905,579	**86,733,953**	**-34.9%**
Pessimistic Scenario								
Premature Deaths	461,588	456,297	298,689	127,706	2,188	24,432,065	**1,633,383**	**-6.3%**
Life Years Lost	5,689,458	5,261,398	2,319,388	528,926	1,396	227,835,203	**20,804,329**	**-8.4%**
* Life Years gained = Life years lost in Status Quo - Life years lost in E-cigarette Substitution Scenario								

Results and Implications

- Potential for major gains in optimistic scenario

- Even under pessimistic (worst case scenario), there are gains from a strategy of encouraging switching from cigarettes to e-cigarettes

- Can compare parameters, including how use rates and risks vary over time

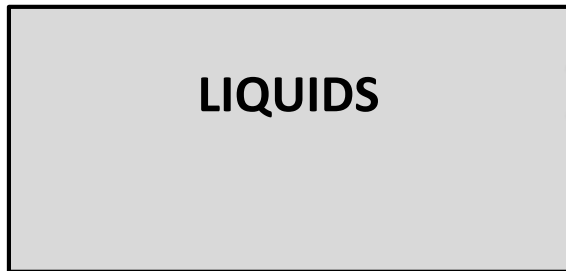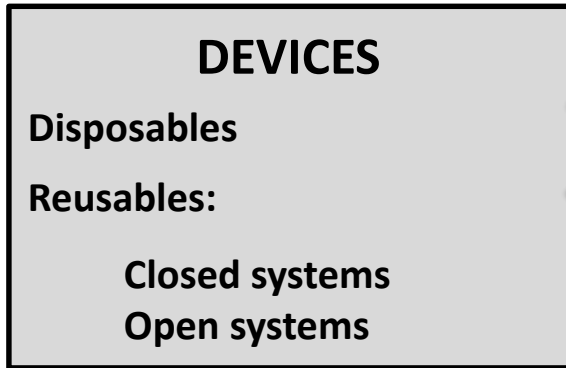Schema for New User Friendly More Flexible Nicotine Vaping Model

Heuristic: Policy Components Affecting Youth Access Enforcement

Publicity/Education

Compliance Checks Per Year

Penalties

Multiplicative relationship

Anti-tobacco Norms

Compliance

S-shaped curve, subject to substitution into other sources (older peers, parents, theft)

Reduced Smoking

Originally applied to youth access, but applies to marketing restrictions and smoke-free air laws

Conclusions

- **Cohort analysis is central, i.e., Circumstances at early ages affect later ages (past experiences)**
  - **Awareness and perceived risk**
  - **Previous experience: Available products with differing appeal, ability to satisfy cravings**
- **Need to determine useful measures of experimental and regular use and perhaps even long-term use, allowing for all transitions (e.g., exclusive and dual)**
- **Much will depend on products available (esp HNB)**
- **Government regulation and industry structure may play an important role**

Modeling the impact of an existing Tobacco product with a Modified-Risk Claim on Population Health

Ryan Black
Assoc. Fellow
Altria Client Services

FDLI

MRTPA Statutory Requirements (§ 911(g)(1))

- The candidate product, as it is actually used by consumers, will:

1. Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and

2. Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

"**FDA encourages** the development and application of innovative analytical methods to make preliminary estimates of the potential effects of some change in the marketplace. Methods ….include secondary data analyses and **computational modeling**."

Source: Food and Drug Administration Center for Tobacco Products, 2012: Guidance for Industry - Modified Risk Tobacco Product Applications: Draft Guidance. Center for Tobacco Products.

Copenhagen® Snuff Fine Cut – Proposed Claim

1 — **Draws the attention of adult smokers**

2 — **Single disease focus**
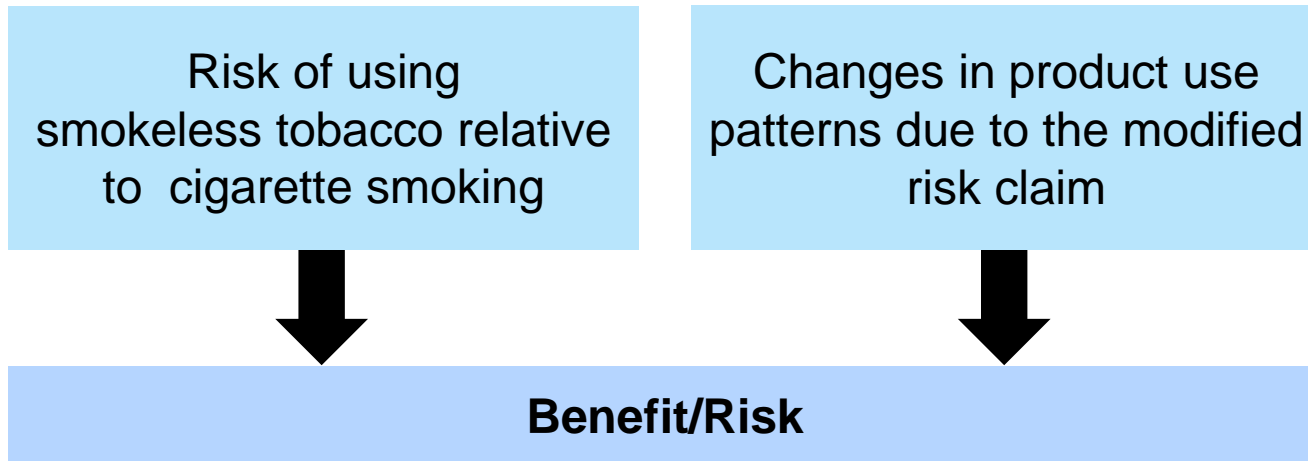Neither states nor implies that the product presents no risk of lung cancer or other disease

3 — **Desired single use behavior**

Modeling the Impact of the Claim

| Risk of using smokeless tobacco relative to cigarette smoking | Changes in product use patterns due to the modified risk claim |

Benefit/Risk

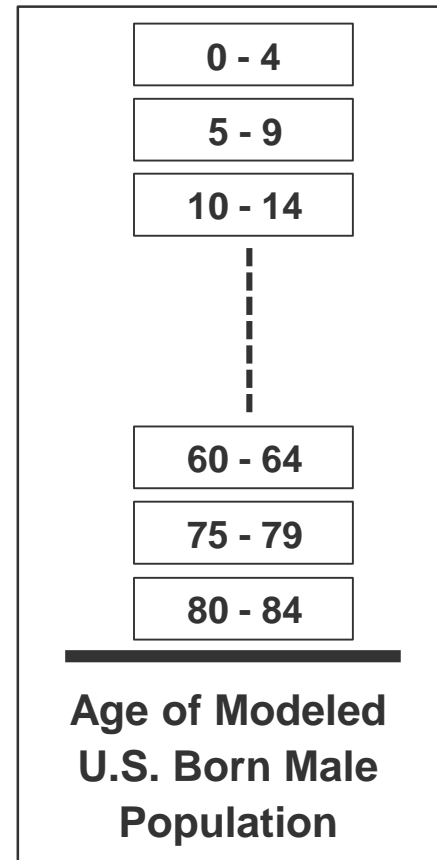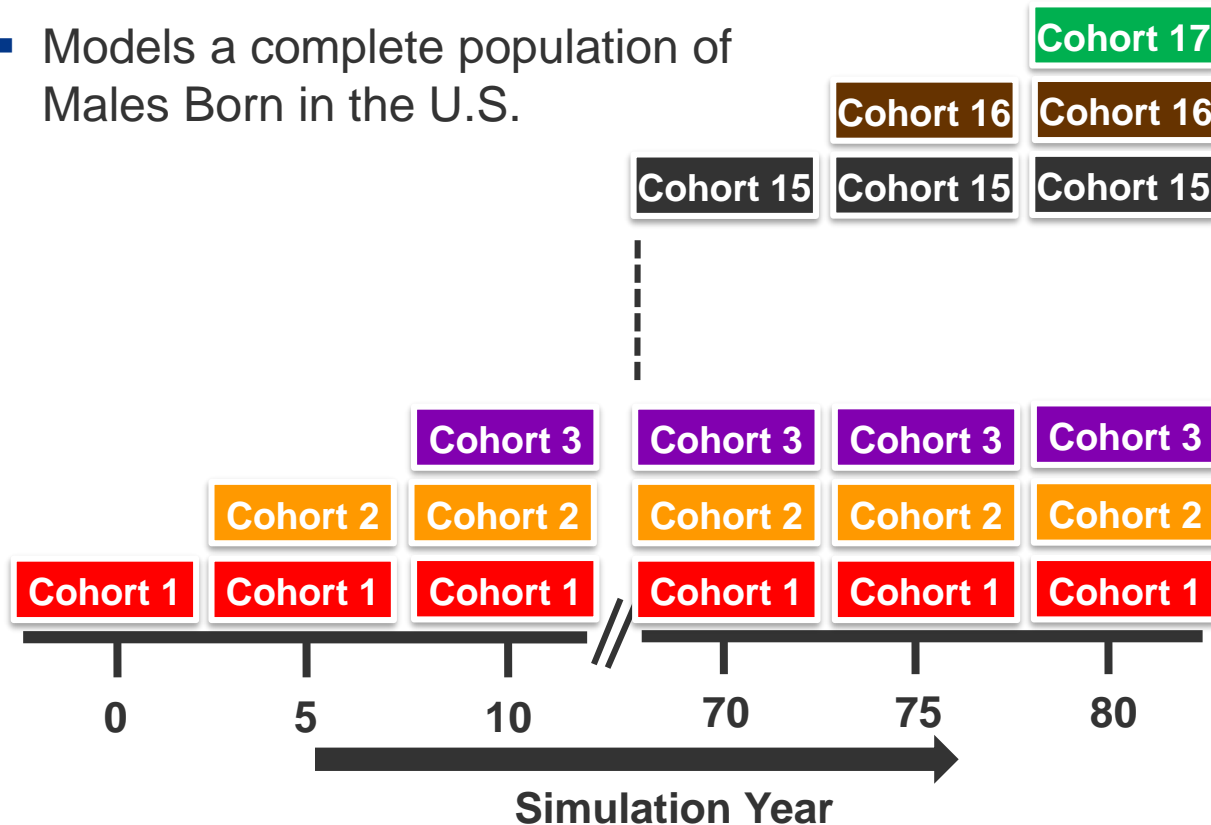# Modeling Framework

Base Case – World As Is Today

Modified Case – Future World
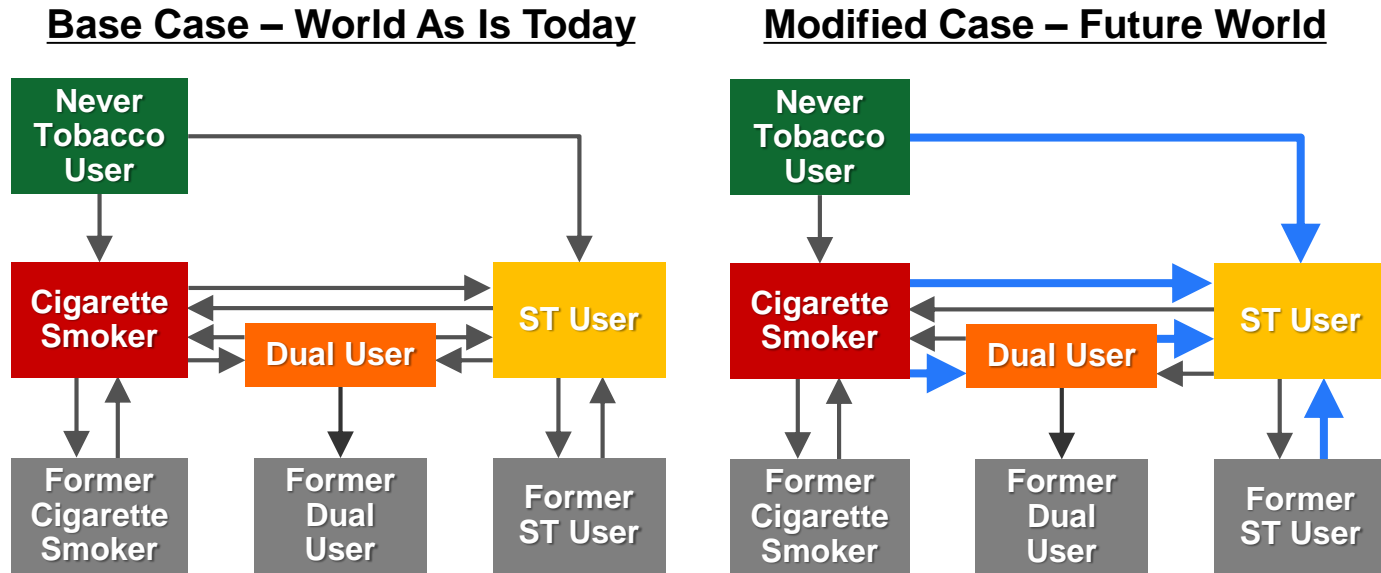
Estimate population benefit/risk by comparing the difference in All-cause Mortality between the Base Case and Modified Case
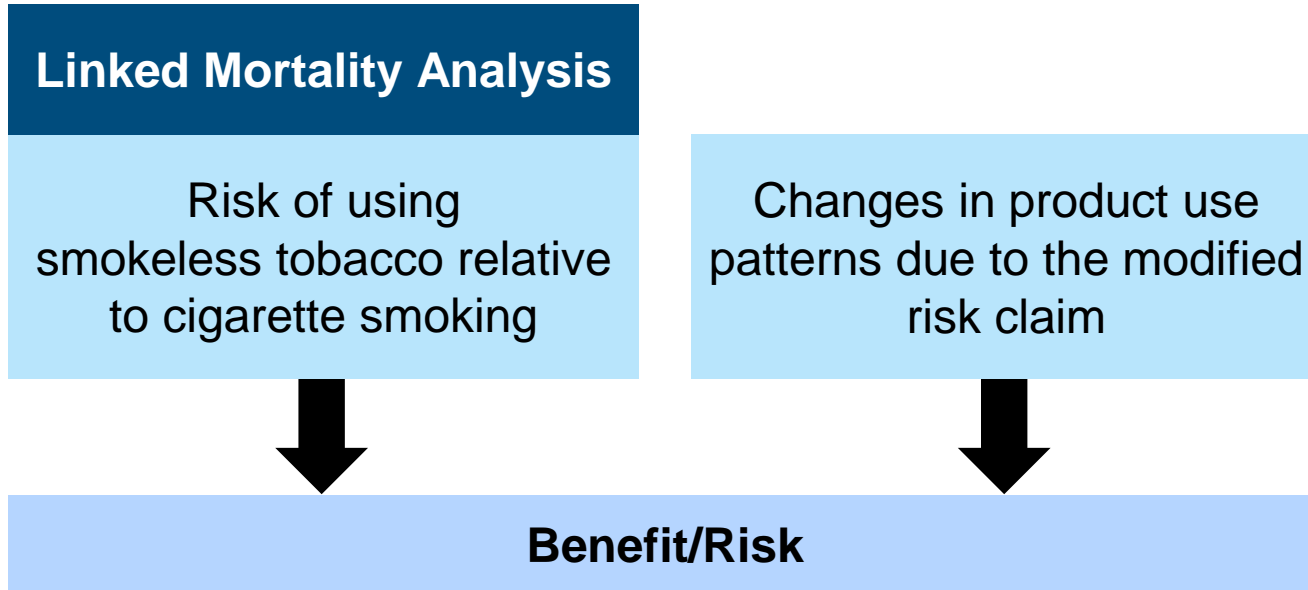
Time-Staggered Multiple Cohort Approach

- Models a complete population of Males Born in the U.S.

Single Cohort Approach based on: Bachand, Annette M.; Sulsky, Sandra I., (**2013**) A dynamic population model for estimating all-cause mortality due to lifetime exposure history. Regul. Toxicol. Pharmacol. 67;2

Modeling the Impact of the Claim

Linked Mortality Analysis
Risk of using smokeless tobacco relative to cigarette smoking

Changes in product use patterns due to the modified risk claim

Benefit/Risk

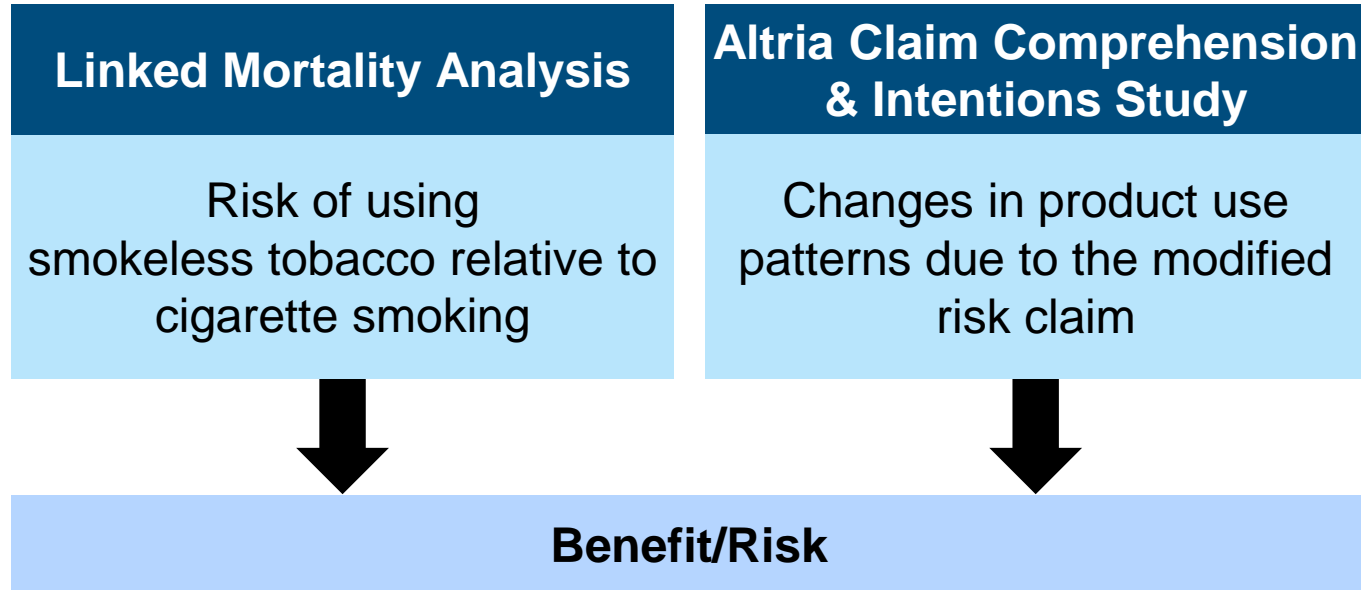# Risk of Smokeless Tobacco (ST) Use Relative to Cigarette Smoking

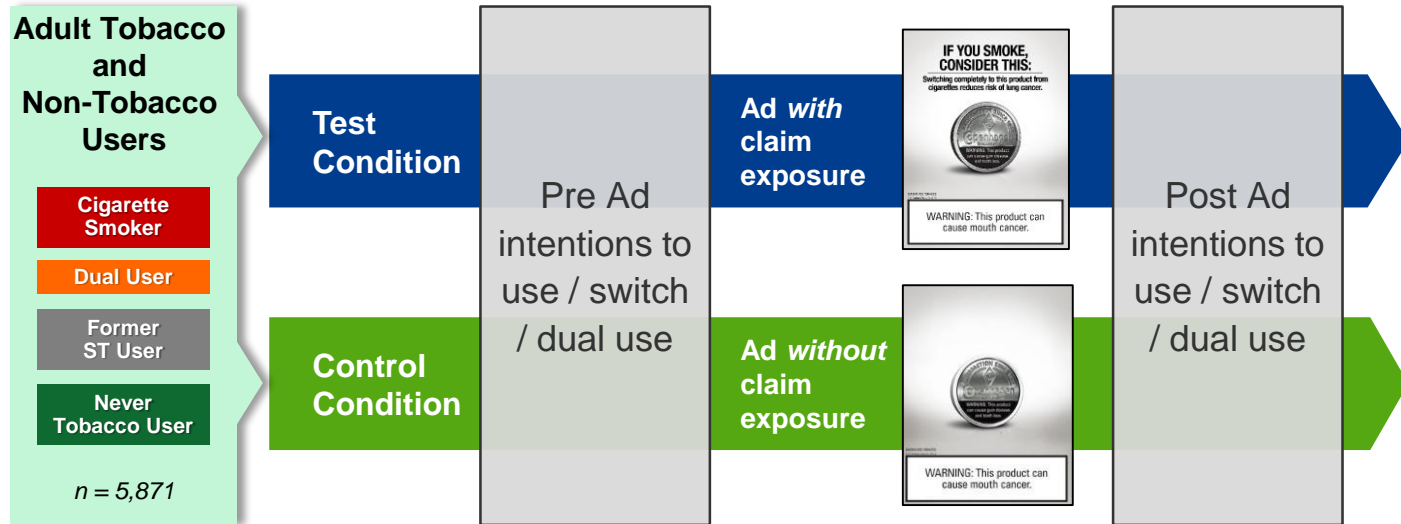- The increased likelihood of all-cause mortality estimated from ALCS Linked Mortality Analysis*

- We estimated the risk for Smokeless Tobacco Use to be 9% of Cigarette Smoking

*Fisher, M.T.; Tan-Torres, S.M.; Gaworski, C.L.; Black, R.A.; Sarkar, M., (**2019**) Smokeless tobacco mortality risks: An analysis of two contemporary nationally representative longitudinal mortality studies. Harm Reduct. J. 16;27

Modeling the Impact of the Claim

Linked Mortality Analysis	Altria Claim Comprehension & Intentions Study
Risk of using smokeless tobacco relative to cigarette smoking	Changes in product use patterns due to the modified risk claim

Benefit/Risk

Altria Claim Comprehension & Intentions Study (CCIS)

- Estimate relative percent difference between response of Test and Control group

- Applied the estimated relative percent differences to Base Case transition rates to generate the Modified Case transition rates

Relative Impact

Adult Tobacco Use Behavior	Change in Likelihood of Behavior* (Relative Impact Factor)
1 **Cigarette Smokers Switching to Copenhagen® Snuff**	**1.21**
2 **Cigarette Smokers Transitioning to Dual Use**	**1.25**
3 **Dual Users Switching to Copenhagen® Snuff**	**1.06**
4 **Former Smokeless Tobacco Users Relapsing to Copenhagen® Snuff**	**1.00**
5 **Never Users Initiating with Copenhagen® Snuff**	**0.94**

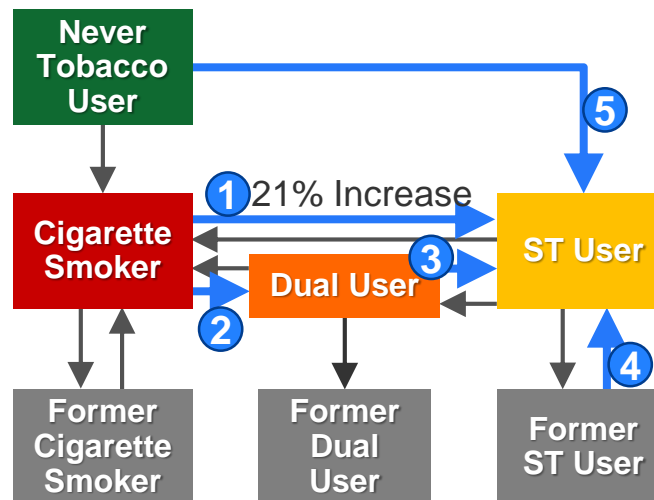*Results not statistically significant.

Modeling Framework

Base Case – World As Is Today
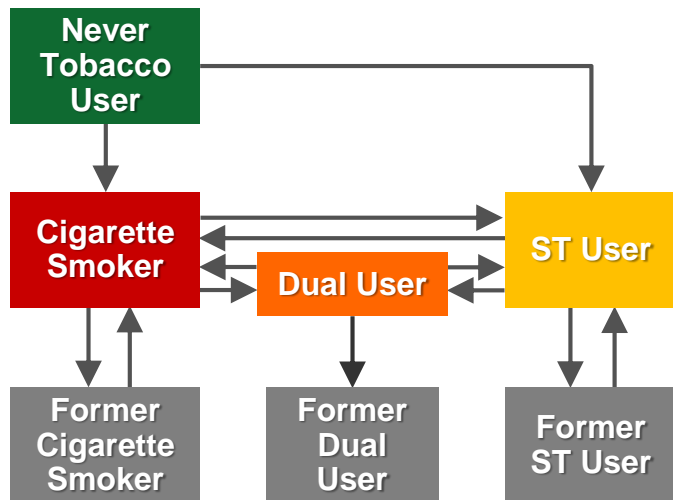
Modified Case – Future World

Adult Male Transition Rates

| Tobacco Use Transition	Base Case Transitions* (From the Literature)	Modified Case Transitions* (Adjusted from CCI Study)
1 **Current smoker → ST**	1.4%	**21% Increase** 1.7%
2 **Current smoker → Dual user (ST + cigarettes)**	3.2%	4.0%
3 **Dual user → ST**	17.4%	18.4%
4 **Former ST → ST**	1.8%	1.8%
5 **Never user → ST**	1.6%	1.5%

*Five year transition rates
Base case transition rates largely informed by Tam J., Day H.R., Rostron B.L., Apelberg B.J. A systematic review of transitions between cigarette and smokeless tobacco product use in the United States. BMC Public Health. 2015;15:258

Modeling Framework

Base Case – World As Is Today
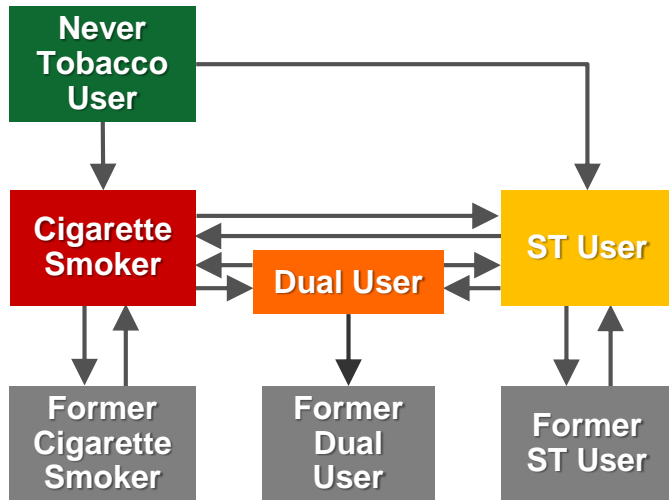
Modified Case – Future World
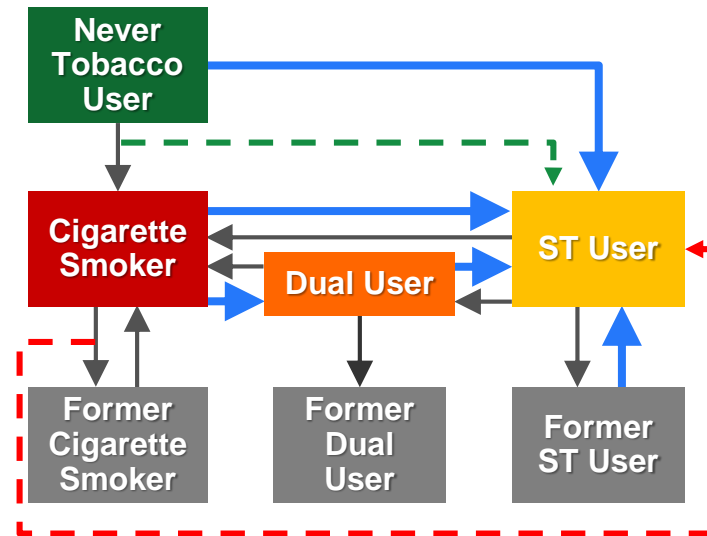
Approximately 93,000 premature deaths prevented over 60 years following claim authorization

Sensitivity Analysis

- Concurrently vary:
  - Change in rate of Never Tobacco Users initiating on smokeless tobacco (*Initiation*)
  - Change in rate of Cigarette Smokers switching to smokeless tobacco (*Switching*)

- All other transition rates kept the same as those in the Modified Case scenario
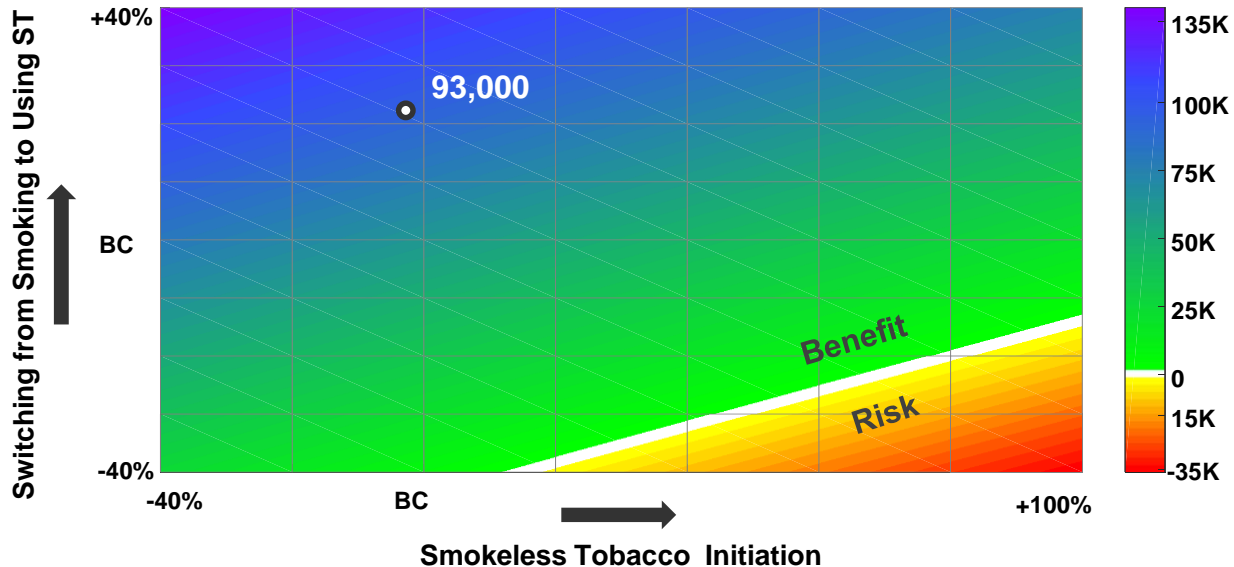
Summary

- Models can serve as important tools for evaluating population health impact

- Sensitivity Analysis is important in examining the robustness of model projected outcomes

FDA Remarks on Population Health Benefit

FDA: "Computational modeling estimated a relatively small net population health benefit from market authorization of Copenhagen Snuff Fine Cut with the proposed modified risk claim."

Source: FDA TPSAC presentation slide 49.

A Computational Model for Assessing the Population Health Impact of Introducing a Modified Risk Claim on an Existing Smokeless Tobacco Product

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Michael A. Jones** [1]**, Ryan A. Black** [1]**, Thomas M. Bryan** [1] **and Mohamadi A. Sarkar** [1]

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check for
updates

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