Section VIII. Scientific Studies and Analyses

F. Population Modeling – Effect on the Population as a Whole

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VIII. Scientific Studies and Analyses

F. Effect on the Population as a Whole

1. Summary

A model (Certara USA, Inc. 2018 [pg 20]) was developed to evaluate the impact of introduction of VLN™ on the population. Market research shows that VLN™ cigarettes are not attractive to new potential smokers considering initiating or former smokers relapsing to conventional cigarette smoking. VLN™ has 95% less nicotine than conventional cigarettes on the market. VLN™ is just as hazardous as conventional cigarettes. The risks of consuming VLN™ cigarettes and risks of being exposed to environmental tobacco smoke from VLN™ by non-users are expected to be the same as for conventional cigarettes. That is, the risks are the same irrespective of product, VLN™ or conventional cigarette, and therefore do not need to be considered since the concentrations of toxicants will be the same for the smoker or non-user. For this reason, effects of environmental tobacco smoke are not considered in the model, and different relative risks for VLN™ are considered only in the sensitivity analysis.

The target market for VLN™ is current smokers who wish to reduce their nicotine consumption. Possible consequences of switching to VLN™ cigarettes include reduced cigarette consumption and increased quitting, with corresponding gradual reductions in mortality rates. The model predicts the effect of introducing VLN™ in 2020 on mortality and morbidity over the period 2015 to 2100[1]. The model outputs included cumulative avoided cigarette-attributable deaths and life-years gained after switching to VLN™ cigarettes. Avoided cigarette-attributable

[1] The model predicts smoking rate declines and mortality from 2015 to 2020 using published data. The effect of introducing VLN™ in 2020 is then incorporated into the model's assumptions.

deaths were calculated as the difference in cigarette-attributable deaths with VLN™ cigarettes versus without VLN™ cigarettes, where cigarette-attributable deaths arise from the increase in risk of death for smokers relative to never-smokers. Likewise, life-years gained in each year are calculated as the difference in the annual predicted adult population with versus without VLN™ cigarettes. Under a base-case scenario, the model predicts conventional cigarette smokers who switch to VLN™ cigarettes will avoid about 340,000 smoking-attributable deaths and add about 8.05 million life-years to their lives by the year 2100 (cumulative). Younger adults will experience the greatest long-term benefits, due to their longer opportunity to switch to VLN cigarettes. Under a **optimistic** scenario there will be almost 1 million avoided smoking attributable deaths and almost 19 million life years gained. Morbidity was modeled in terms of health care costs associated with death. Avoiding 340,000 deaths in the base-case scenario was estimated to avoid $178 billion in morbidity costs.

For comparison purposes, a scenario was constructed assuming a 2020 mandated reduction in cigarette nicotine to minimally addictive levels, similar to the recent Apelberg publication (Apelberg et al. 2018 [pg 20]). In this scenario, the model predicts about 8.2 million avoided smoking-attributable deaths and 150 million life-years gained by 2100, similar to Apelberg's base-case (8.5 million and 134 million, respectively).

2. Background

The FDA recommends that applicants submit quantitative estimates of the effect the marketing of the product, as proposed, may have on the health of the population as a whole (U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products, 2012, [pg 20]). The estimates should integrate all of the information regarding the marketing of

the product and its potential effects on health, tobacco use behavior, and tobacco use initiation to provide an overall assessment of the potential effect that the product's introduction to the market may have on overall tobacco-related morbidity and mortality. FDA recommends that the applicant estimate the attributable risk of all of the various health effects for various types of individuals (see bullets below) in the U.S. population, as well as the total number of individuals of each type. The FDA recommends that the applicant quantify the potential changes in mortality of the various types of affected individuals in the U.S. population (see bullets below). This would include, among other things, an estimate of the number of smokers who are likely to switch to the product and the subsequent reduction in the number of lives lost due to tobacco use, the number of smokers who may use the product in conjunction with other tobacco products instead of quitting and the subsequent effect on the number of lives lost due to tobacco use, as well as the number of non-smokers who may initiate use of tobacco with the product and the subsequent increase in the number of lives lost to tobacco use. The FDA recommends that a similar approach be used to assess the potential impact on mortality resulting from other diseases, as well as morbidity in the various types of affected individuals in the U.S. population. The types of individuals may include, but are not limited to, the following:

- Tobacco users who switch from other commercially marketed tobacco products to the proposed product;
- Tobacco users and non-users who, after adopting the proposed product, switch to or switch back to other tobacco products that may present higher levels of individual health risk;
- Tobacco users who opt to use the proposed product rather than cease tobacco use altogether;
- Tobacco users who opt to use the proposed product rather than an FDA approved tobacco cessation medication;
- Non-users who initiate tobacco use with the proposed product, such as youth, never users, former users; Tobacco users who use the product in conjunction with other tobacco products;

- and Non-users who experience health risks from the product.

3. A Simulation Model to Evaluate the Impact of VLN™ Cigarettes on the Population as a Whole

A model was developed (Certara USA, Inc. 2018 [pg 20]) to simulate the impact on the U.S. adult population as a whole of marketing 22nd Century's VLN™ cigarettes. It is a Markov state dynamic population model, similar to the models of Apelberg (Apelberg et al. 2018 [pg 20]) and Warner (Warner and Mendez, 2018 [pg 20]). It tracks the U.S. adult population's smoking status and smoking-related deaths over time, simulating the effects of switching to VLN™ cigarettes on cigarette consumption and cessation. The model considers, among other things, the impact of initiation, switching to VLN™, switching back to conventional cigarettes, sustaining as a VLN™ smoker, and quitting. Figure VIII.F-1. Base Model of Cigarette Smoking shows a model of potential cigarette use behavior without VLN™. Individuals can choose to not smoke (becoming never-smokers), and eventually die. They can choose to smoke, smoke throughout their life, and eventually die. The smokers can choose to quit at some point, and eventually die. Figure VIII.F-2. *Model showing potential VLN™ paths (tan)*. adds the potential paths that VLN™ smokers can choose. Conventional cigarette smokers can make a decision to use VLN™, become sustaining users of VLN™, and eventually die. They can try VLN™ and relapse back to conventional cigarettes. They can use VLN™, potentially reducing their cigarette consumption, and possibly quit smoking. The various transitions between the boxes were modeled to predict the outcome of using VLN™. Published data on U.S. demographic projections, conventional cigarette initiation, CPD, quit rates, and mortality for smokers and never-smokers were used as inputs.

The model considered initiation with VLN™ by new smokers as well as re-initiation by former smokers attracted to VLN™. Market research (M/A/R/C Research, 2018 [pg 20]) indicated

little interest in VLN™ products from non-smokers and former smokers, and therefore these subpopulations were assumed not to initiate or re-initiate with VLN™ cigarettes at a greater rate than the general population. That is, VLN™ cigarettes are not expected to increase total initiation. A small proportion of new smokers may initiate with VLN at rate proportional to overall initiation rate. The model assumes that there is no initiation with VLN at 18 years of age (model entry) but that some of these new smokers switch to VLN™ in the next year. The impact of this assumption is to delay the accrued benefits of VLN™ by one year.

VLN™ has 95% less nicotine than conventional cigarettes on the market but it is just as toxic as conventional cigarettes. The risks of consuming VLN™ cigarettes and risks of being exposed to second-hand VLN™ smoke are expected to be the same as conventional cigarettes. Therefore, effects of second-hand smoke are not considered in the model, and different relative risks for VLN™ are considered only in sensitivity analysis.

Figure VIII.F-1. Base Model of Cigarette Smoking

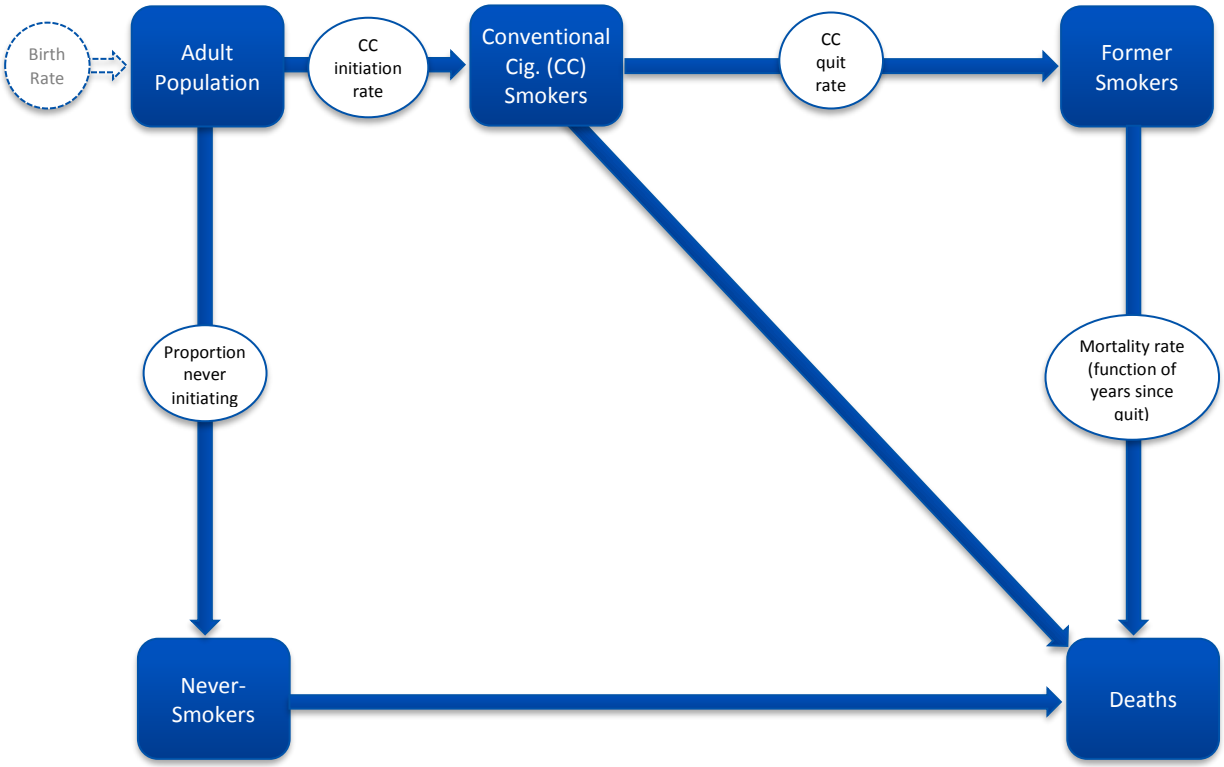
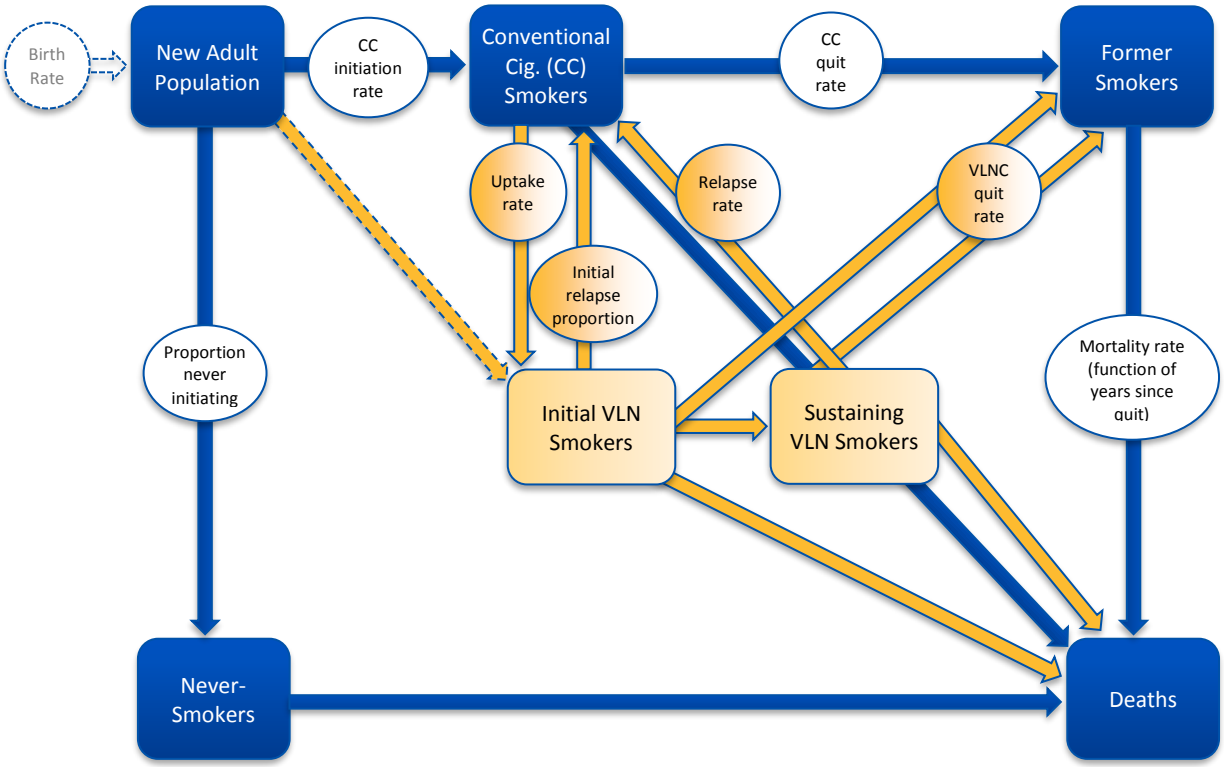


Figure VIII.F-2. Model showing potential VLN™ paths (tan).



The target market for VLN™ is current smokers who wish to reduce their nicotine consumption. Possible consequences of switching to VLN™ cigarettes include reduced cigarette consumption and increased quitting, with corresponding gradual reductions in mortality rates. The model predicts the effect of introducing VLN™ in 2020 on mortality over the period 2015 to 2100[2]. The model outputs included cumulative avoided cigarette-attributable deaths and life-years gained after switching to VLN™ cigarettes. Avoided cigarette-attributable deaths were calculated as the difference in cigarette-attributable deaths with versus without VLN™ cigarettes, where cigarette-attributable deaths arise from the increase in risk of death for smokers relative

[2] The model predicts smoking rate declines and mortality from 2015 to 2020 using published data. The effect of introducing VLN™ in 2020 is then incorporated into the model's assumptions.

to never-smokers. Likewise, life-years gained in each year are calculated as the difference in the annual predicted adult population with versus without VLN™ cigarettes. The base-case has the following assumptions:

- 25% market penetration
- 7.1% annual switching rate of conventional cigarette smokers to VLN™
- 50% of VLN™ smokers sustain smoking VLN™ after 1 year[3]
- 10% of VLN™ smokers relapse back to conventional cigarettes
- 50% reduction in CPD by sustaining VLN™ smokers, except 0 reduction for 20% of this subpopulation, as well as 0 reduction in the first year
- 18% increase over conventional cigarette quit rates (which average 4.5%/year)

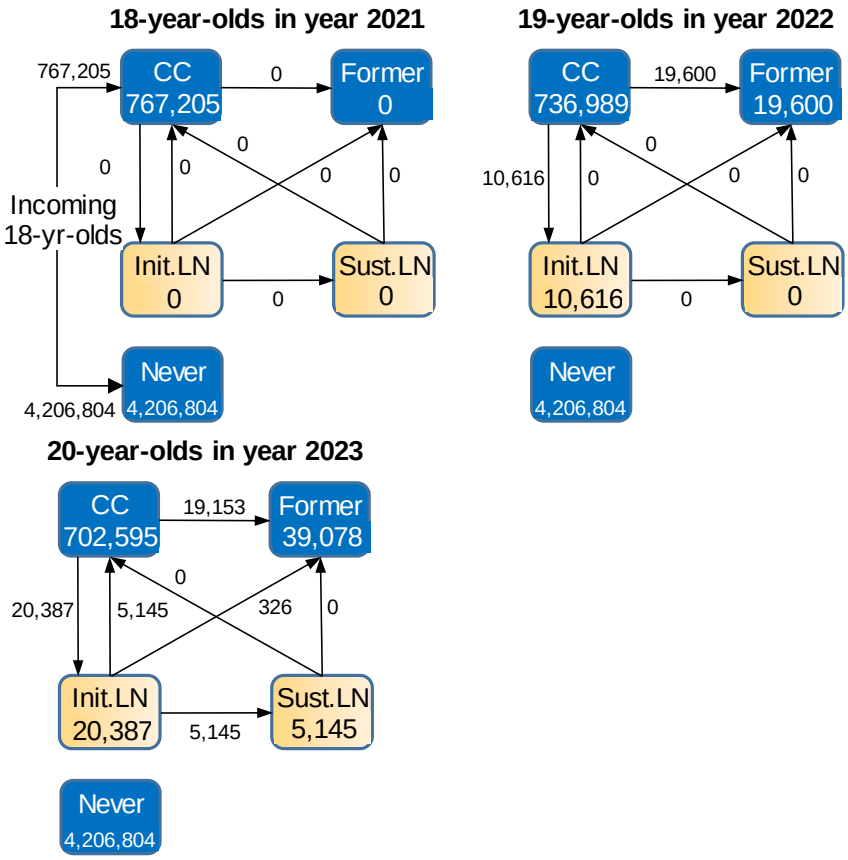
Sensitivity analysis indicated that major determinants of mortality differences in the model were the quit rate and the long-term relapse rate back to conventional cigarettes. The determinants were used in pessimistic and optimistic scenarios to provide a potential measure of variability in the estimates of the overall impact of VLN™. Since the FDA has proposed to reduce the amount of nicotine in cigarettes and Apelberg (Apelberg *et al.* 2018 [pg 20]) has published a model of the impact of this proposed rule, a similar analysis was done. Another analysis looked at the impact of VLN™ on subpopulations: 18 – 24-year-olds, 25 – 64-year-olds, and >64-year-olds.

Figure VIII.F-3 shows what happens to a cohort of 18-year-olds who enter the base-case model in 2021. A majority of the cohort (4,206,804) becomes never-smokers. A total of 767,205 become conventional smokers. None are allowed to initiate with VLN™, nor to quit in the first

[3] These consumers are not addicted to VLN. They just choose to not quit.

year (the model works in one-year increments). In 2022, the 18-year-olds are now 19-year-olds. 19,600 decide to quit smoking, becoming former smokers. 10,616 decide to try VLN™. In 2023, an additional 19,153 smokers decide to quit, becoming former smokers. 20,387 conventional cigarette smokers try VLN™, 5,145 VLN™ smokers relapse back to conventional cigarettes and 326 quit. The model continues following every initial cohort of every age (from 18 to a final category of >99) until they die or reach year 2100. The numbers of individuals of each age and sex in each smoking category (never-smokers, former smokers, current conventional smokers and VLN™ smokers) are summed to determine the total at-risk populations. Subpopulations are broken out by age, sex, and smoking status. Former smokers are tracked by the number of years since quitting. Mortality rates are calculated based on age, sex, smoking status, cigarettes per day, and years since quitting for former smokers.

Figure VIII.F-3. Model sample of incoming cohort of 18-year-olds followed over three years.



Based on recent rapid declines in U.S. smoking initiation, the model predicts U.S. adult smoking prevalence to decline to about 4.4% in 2050 and 0.8% by 2100, even without VLN™ cigarettes (Figure VIII.F-4). Slightly lower prevalence levels are predicted with VLN™ cigarettes, which are assumed not to affect conventional cigarette initiation (Figure VIII.F-5). Assuming a final market penetration rate of 25%, VLN™ cigarettes are predicted to avoid about 340,000 smoking-attributable deaths and add about 8.05 million life-years by year 2100 (Figure VIII.F-6). Younger adults show the greatest long-term benefits (Figure VIII.F-7 and Figure VIII.F-8)[4], due to their longer opportunity to switch to VLN™ cigarettes (Figure VIII.F-9).

[4] New pop. is the inclusion of new smokers into the model each year.

Figure VIII.F-4. Projected smoking prevalence compared to NHIS data.

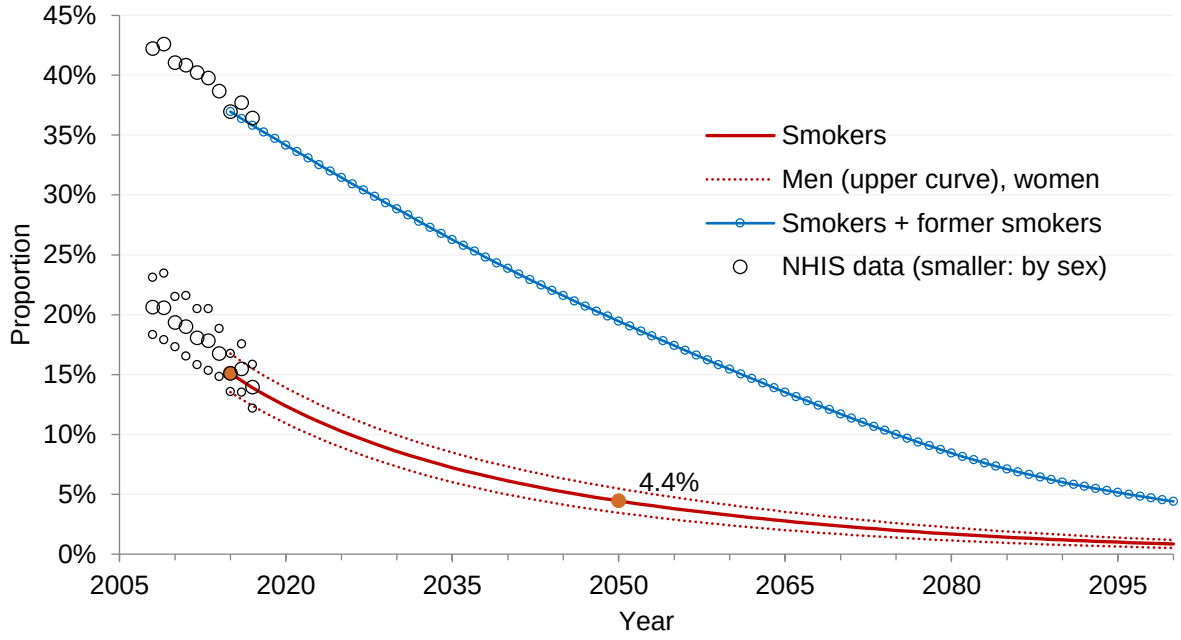


Figure VIII.F-5. Predicted total smoking prevalence by age group and sex with VLN Introduction

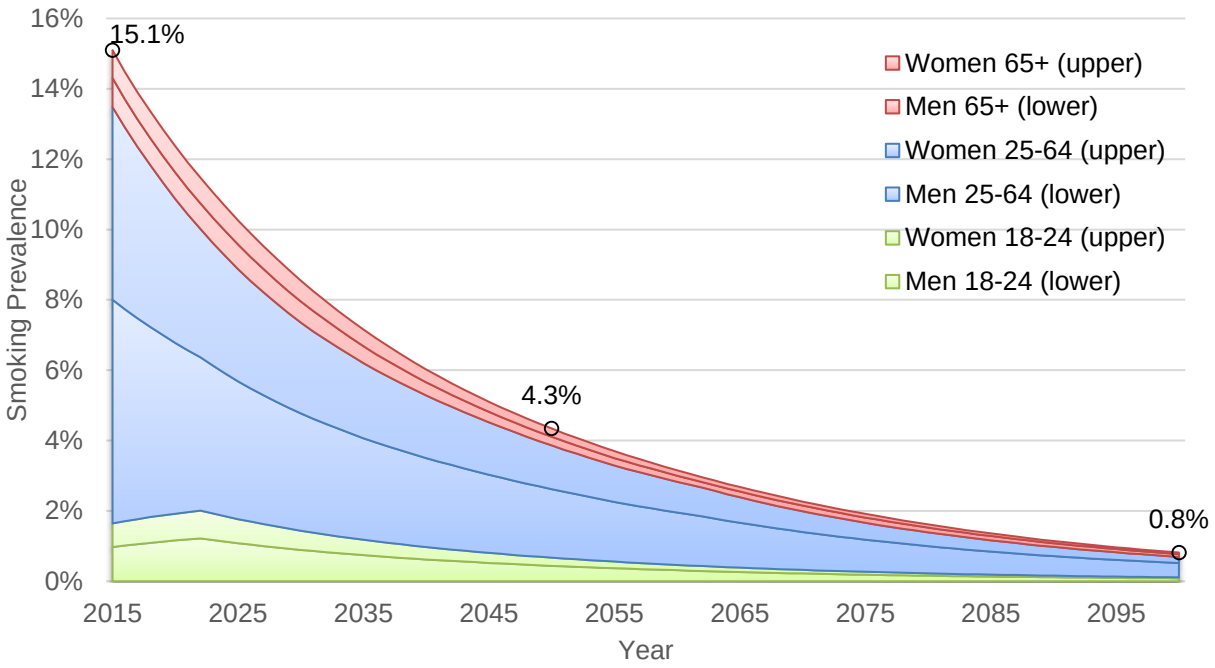


Figure VIII.F-6. Base-case scenario of avoided cigarette-attributable deaths and life-years gained

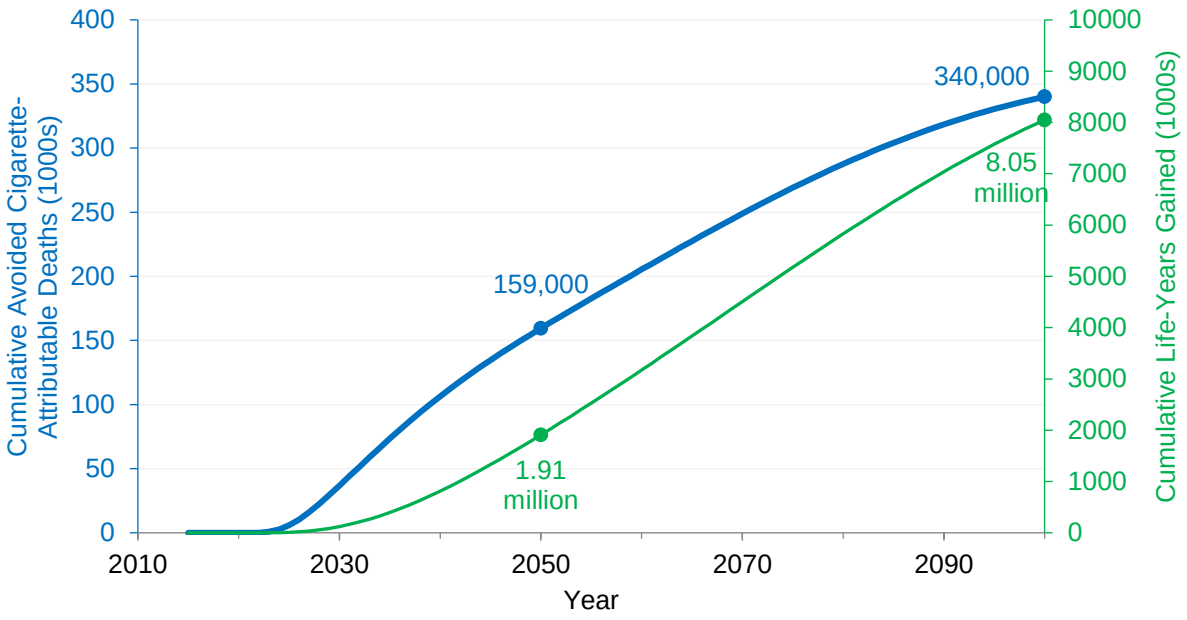


Figure VIII.F-7. Cumulative avoided cigarette-attributable deaths by age group.

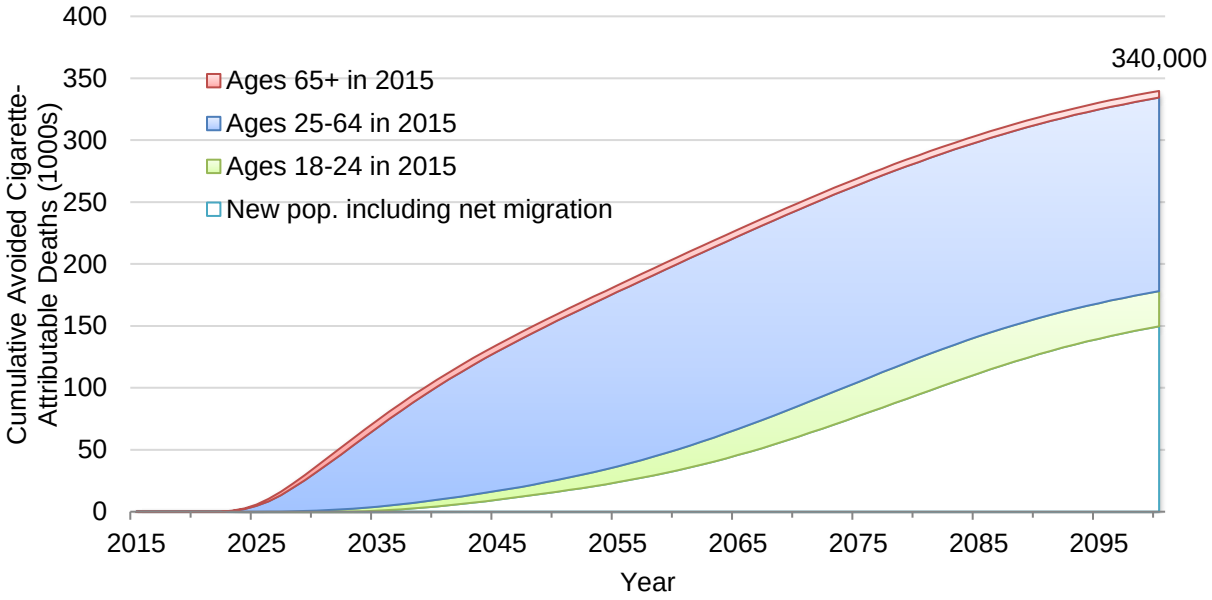


Figure VIII.F-8. Cumulative life-years gained by age group

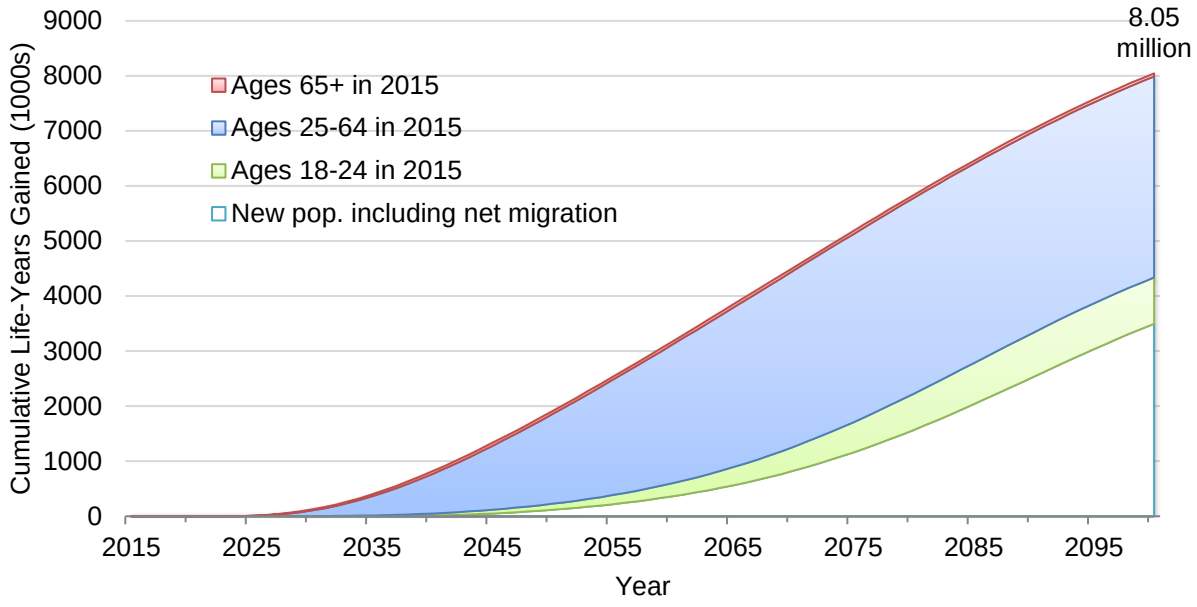
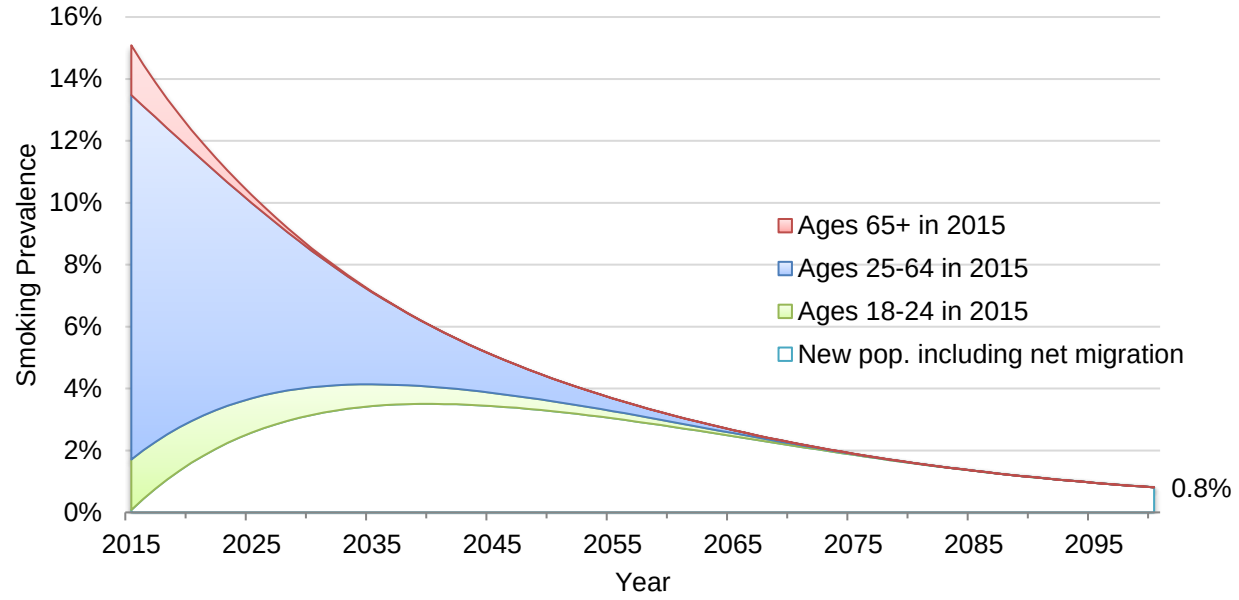


Figure VIII.F-9. Breakdown of smoking prevalence by age group.



An optimistic scenario was defined with VLN™ smokers quitting at 150% of the average conventional cigarette rate of 4.5%, (i.e. 6.75%), (compared to a base-case of 118%, i.e. 5.3%) and not relapsing to conventional cigarettes after the first year. A pessimistic scenario was

defined with VLN™ smokers quitting at 100% of the conventional cigarette quit rate (i.e. VLN™ had no effect on quitting and the user quits at the average historical rate of 4.5%) and relapsing to conventional cigarettes at 20% (compared to a base- case of 10%) per year after the first year. The impact of these scenarios is shown in Figure VIII.F-10 and Figure VIII.F-11. These analyses provide an indication of the potential variability in the estimates of the results.

Table VIII.F-1 shows the results of various scenarios. Under the optimistic scenario, there are almost 1 million avoided smoking attributable deaths and almost 19 million life years gained.

Figure VIII.F-10. Impact of optimistic and pessimistic scenarios on avoided smoking-attributable deaths.

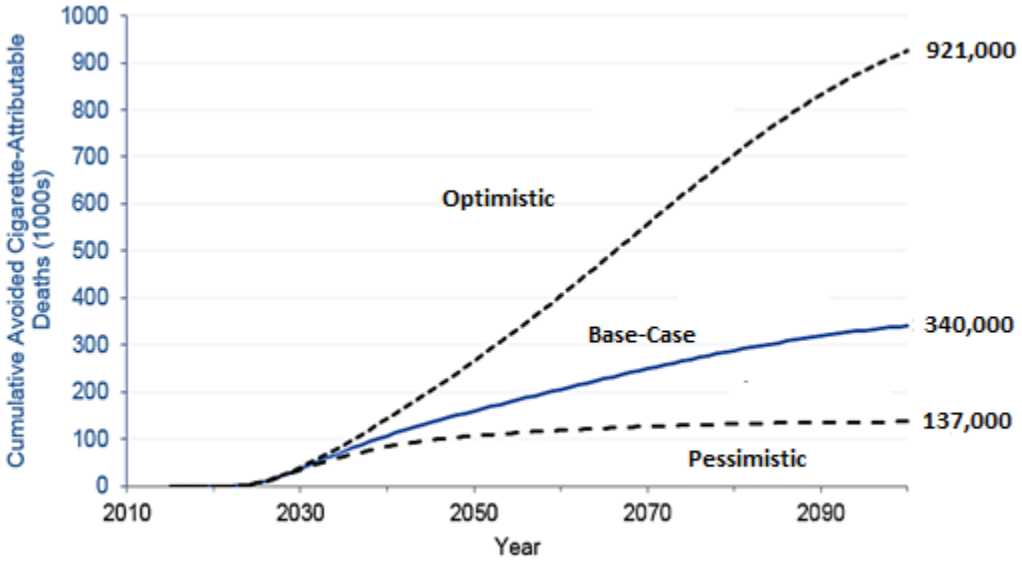


Figure VIII.F-11. Impact of optimistic and pessimistic scenarios on cumulative life-years gained.

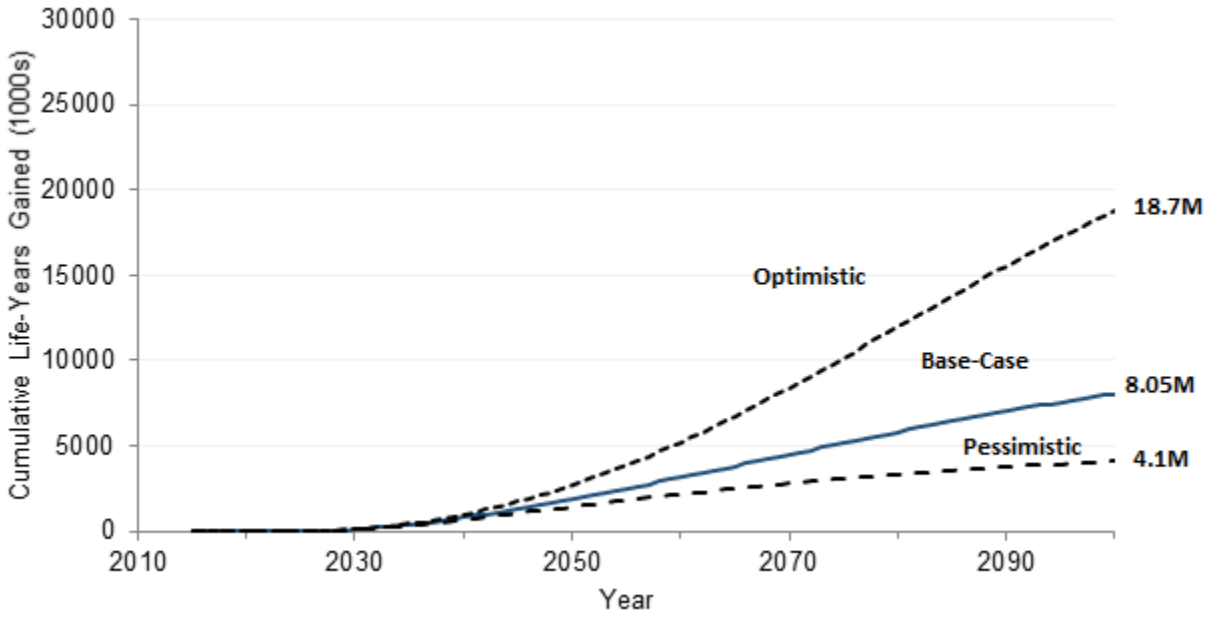


Table VIII.F-1. Effects of optimistic and pessimistic scenarios on estimates of population impact.

Scenario:	**Base**	Pessimistic	Intermediate 1	Intermediate 2	Optimistic	Mandate in 2020
Quit rate relative to CC smokers	118%	100%	100%	150%	150%	100%
Long-term relapse rate to CC	10%	20%	10%	10%	0%	0%
Year 2050						
Total population ≥18 years old (millions)	310.4	310.4	310.4	310.5	310.5	320.7
Cigarette-attributable deaths since 2015 (1000s)						
CC-only case	13934.1	13934.1	13934.1	13934.1	13934.1	9813.3
With new product	13774.6	13827.4	13793.7	13742.4	13669.1	12269.9
Avoided	159.5	106.7	140.4	191.7	265.0	2456.5
Life-years gained since 2015						
vs. CC-only (1000s)	1908.3	1449.8	1795.8	2101.4	2722.7	24196.0
Per avoided cigarette-attributable death	12.0	13.6	12.8	11.0	10.3	9.8
Year 2100						
Total population ≥18 years old (millions)	358.1	358.0	358.1	358.2	358.3	372.3
Cigarette-attributable deaths since 2015 (1000s)						
CC-only case	23364.9	23364.9	23364.9	23364.9	23364.9	17467.1
With new product	23024.8	23228.6	23176.1	22787.9	22443.3	25849.1
Avoided	**340.1**	136.3	188.8	576.9	921.6	8382.1
Life-years gained since 2015						
vs. CC-only (1000s)	**8048.9**	4102.6	5597.4	11957.6	18735.3	157743.2

This analysis was focused on mortality and life years gained. Reduction in morbidity as a result of extended life years and avoided death is also a possible outcome. If morbidity and mortality from cigarette smoking are assumed proportional, the predicted cigarette-attributable deaths avoided with VLN cigarettes can be used to approximate how they might reduce morbidity. Effects on morbidity was modeled by the tracking the impact of VLN™ on the cigarette-attributable fraction of U.S. healthcare expenditures. That is, people who switch to VLN™ are healthier and have reduced health care costs, therefore their quality of life should be improved. The 2014 Surgeon General's report estimated this cost at about $170 billion in year 2010, in 2010 dollars. This becomes $240 billion in 2018 dollars, when inflated at the 4.4% average increase. The report also estimated economic costs of lost productivity attributable to death from cigarette smoking, which almost doubled the total cost estimate, adding $151 billion per year over 2005-2009. These indirect costs will not be considered here since the focus is morbidity.

Under base case assumptions, the model predicts 459,000 cigarette-attributable deaths in 2018 (consistent with the estimate of 480,000 deaths from smoking and secondhand smoke in USDHHS 2014). The cigarette-attributable cost per death in 2018 is then $240 billion/459,000 = $523,000. VLN™ cigarettes were found above to avoid 340,000 cigarette-attributable deaths through year 2100. Thus, a simple approximation of the morbidity impact of VLN cigarettes, measured by potential healthcare cost savings through 2100, is 340,000 times $523,000, or $178 billion, in 2018 dollars.

An additional scenario was evaluated for comparison purposes assuming a 2020 mandated reduction in cigarette nicotine to minimally addictive levels, similar to Apelberg

(Apelberg *et al.*, 2018 [pg 20]) The Apelberg scenario assumed much higher baseline smoking prevalence, around 8% over 2050-2100, but falling to close to 1% with the mandate. Despite substantial model differences, the VLN™ model could be adjusted to give results similar to Apelberg's model, with about 8.2 million avoided smoking-attributable deaths (Figure VIII.F-12) and 150 million life-years gained by 2100 (Figure VIII.F-13).

Additional information about the study and results may be found in the model report (Certara USA, Inc., 2018, [pg 20]).

Figure VIII.F-12. Comparison of Apelberg and VLN models – avoided cigarette-attributable deaths

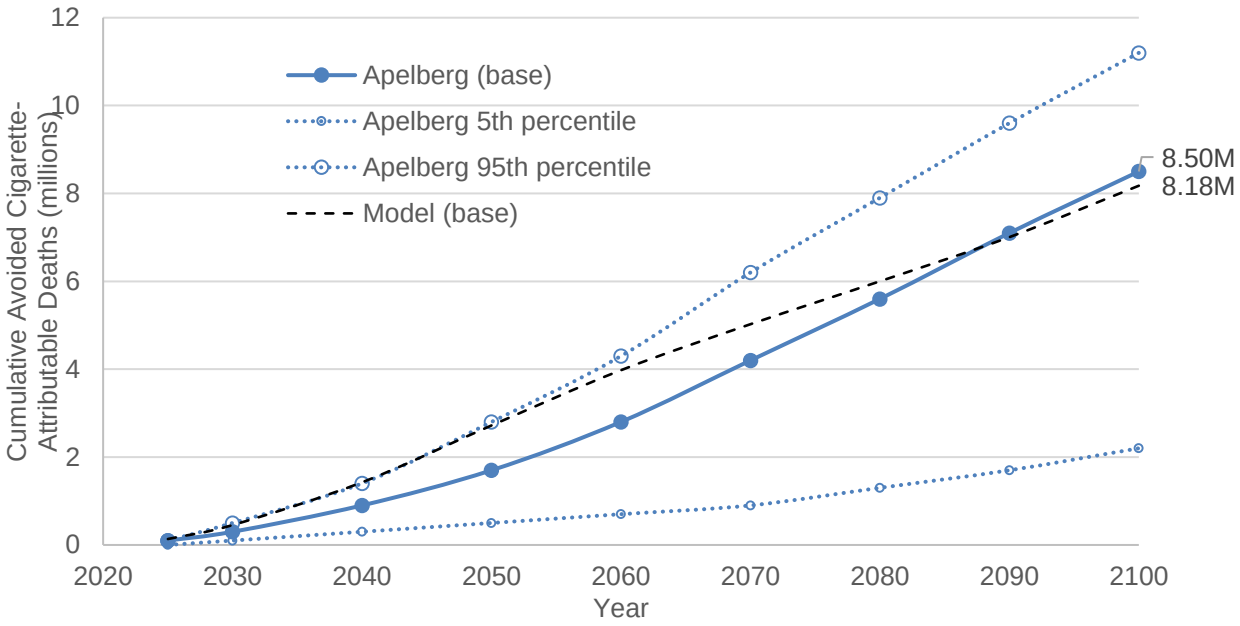
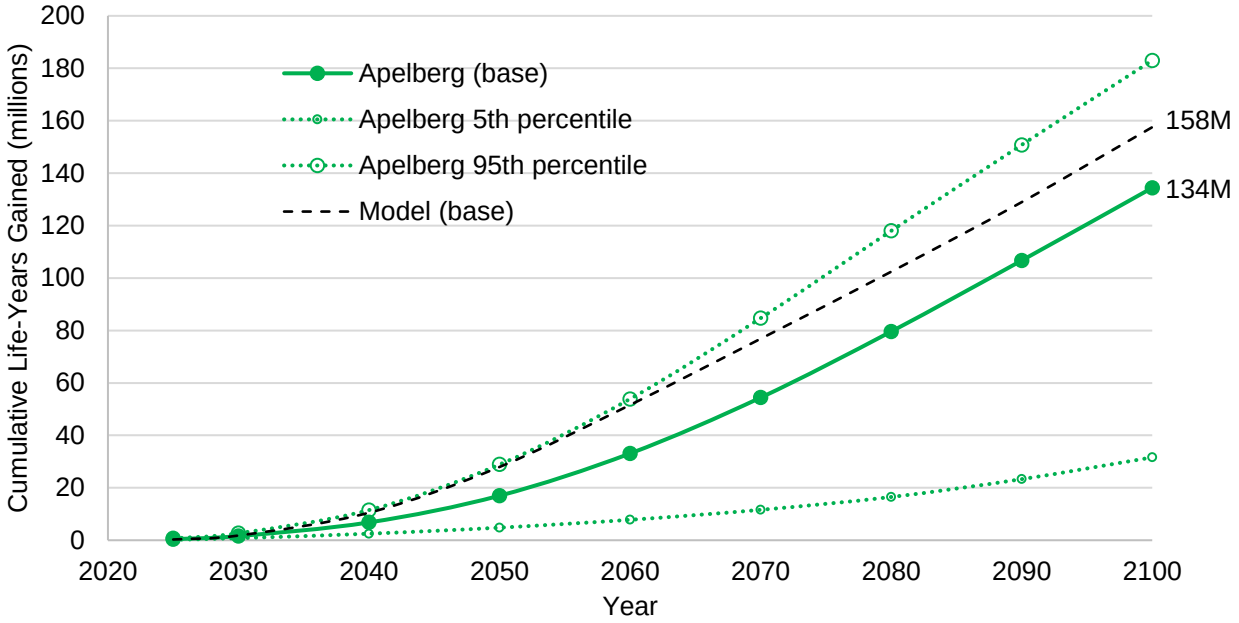


Figure VIII.F-13. Comparison of Apelberg and VLN models - Life years gained.



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