Description of the PSA Model

This section describes the extended case study model for PSA screening, which consists of six fundamental sectors including the population and natural history of disease; screening and clinical detection; treatment; screening dissemination; harm reduction technology; and the PSA screening harms and benefits. The fundamental approach and assumptions for each sector will be explained with critical formulations. The various assumptions and propositions are supported by reference to the modeling and medical literature discussed earlier. The chapter concludes by listing important model parameters with information sources.

Population and Natural History of Disease

Population Increase and Aging: The target population of interest is U.S. male (all races) 50-80-year-olds; however, we also model younger ages (35-50-year-olds) to improve the quality of model calibration to target population trends. We define nine age groups by five-year intervals starting from 35, and another age group that represents the 80+ male population. Different age groupings are used to represent simulation results, including the most commonly used 50+ or 65+ populations. Other subpopulations include the 35 to 44, 45 to 54, 55 to 64, 65 to 75, and 75+ year-old age groups, for which mortality data and population counts were made available by the National Center for Health Statistics (NCHS) at the CDC.

The aging structure comprises one inflow (age_i^{enter}) that indicates the rate of entering for the indicated age category, for 9 age groups, and one outflow (age_i^{leave}) that indicates the rate of leaving the age category. The inflow-of-male-population-turning-35 time series is provided exogenously for the years 1980-2040, based on U.S. Census data history and future projections:

$$age_{i+1}^{enter} = age_i^{leave} \quad \text{for i=1, 2... 9, else 0 for} \quad \text{i=0}$$

The age cohort-specific all-cause death rates, and projections for the decrease in all-cause-mortality were derived from sex- and age-specific U.S. Life Tables. The all-cause death rates for all age groups are then compared to the death counts specified by the CDC WONDER-Compressed mortality file.

Net Immigration (migration to and from a country) is another component that influences the historical and future population counts in the U.S. This study uses the U.S. Census Bureau past data and projections for immigration as an input time series, as a certain fraction of the population that ranges between 0.001 and 0.0049 for the simulated time horizon of 1980-2040. Data were not available by age group. Cumulative net migration between 1980 and 2040 accounts for over 11 million people in the base case simulation for the 35+ U.S. male population.

Natural History of Disease: Figures in the main text illustrate the natural history of prostate cancer and its diagnosis, including the health states and transitions, the asymptomatic onset of screen-detectable cancer, and disease progression through stages. The model design (onset and progression through disease stages) and assumptions were inspired by the prostate cancer natural history diagnosis and history models developed by the CISNET group and other modeling studies published previously.

In this model, screen-detectable cancers progress from loco-regional (M0) to distant-metastatic stage (M1). Cancers are localized at onset and may be either low-grade (Gleason score 2-7), high-grade (Gleason score 8-10), or indolent (any Gleason). High- and low-grade cancers represent those which are of progressive type and may get metastasized, while the indolent class tumors represent the non-progressive, or latent tumors, including regressive tumors which are, by definition, destined to stay confined to the prostate and not metastasize or kill the patient. The model assumes stage durations to be distributed independently according to exponential distributions and not correlated with each other. The disease progression rates are independent

of patient age or disease onset, as with other studies. The model also assumes that indolent and progressive tumors cannot be distinguished at diagnosis and will be treated similarly.

Finding an indolent cancer is not necessarily harmful. However, because there is no way to definitively distinguish an indolent cancer from a progressive one, some screen-detected cancers are treated aggressively. While there is an increasing trend to treat loco-regional cancer with watchful waiting, men are usually dissatisfied with it, as it provides only palliative therapy.

Asymptomatic onset used in the model (Ox_i) is estimated from autopsy studies and previously published models. This model assumes that these adequately reflect the real prevalence of disease in the U.S, although that may be an underestimation of the true amount of latent disease in the population. Biopsy studies using better techniques find a higher age-specific prevalence. The present model assumes a constant secular trend in incidence, in line with other modeling studies. The probabilities of tumor grade at onset (p_j^{Ox}) determine the fraction of disease in each grade category (high, low, indolent) at onset, and add up to one. The equation for the asymptomatic incidence rate (asxInci) is given below.

The metastasis hazard for men with cancer depends on grade, and the hazard of transition to metastatic disease from loco-regional to distant stage (Mx) is selected based on literature review. The metastasis rate (mx) from loco-regional to distant disease is given by the following equation. Mortality of prostate cancer from loco-regional and distant disease stages is represented with death fractions defined by grade (df_j^{M0} and df_j^{M1}). The death fraction and metastasis hazard of indolent tumors are zero by definition.

$$asxInci = AtRisk_i * Ox_i * p_j^{Ox} \quad (2) \qquad mxM0 = UxM0_{i,j} * Mx_j * M_s$$

A comparison of high-level features across different CISNET models and this model (PSA-SD) is presented in Table 1 below. Important parameters are listed in Table 2, at the end of this section.

PSA screening and biopsy follow-up: Existing studies generally superimpose population screening and biopsy patterns on the underlying disease progression process. The model in this study endogenizes the adoption and diffusion of the screening process, and defines the different components of screen detection explicitly. These include the fraction of population that receives the screening test, sensitivity of the test, biopsy compliance, and biopsy detection. Test sensitivity and current screened fraction are endogenous to the model, while biopsy compliance and detection are exogenous. Subjects are eligible to receive regular screenings if their doctor adopted the PSA screening test at the time, and if they are around the age-eligible range for the test.

Screening and Clinical Detection

Subjects who are at risk and never screened may get an initial screening test with a true negative test result or a false positive test result. The subjects with a false positive test result may then have a follow-up test, or get a biopsy to confirm that they do not have the disease. Existing modeling studies do not explicitly define these population stocks of people with a true negative or a false positive test result. In this study we use the flexibility of the system dynamics modeling stock-flow structure and add these stocks to keep track of their values. The value of the false positive stock relative to the healthy population may be an important indicator for policy making.

Subjects in all the three at-risk stocks (at-risk never screened, screened TN, or screened FP) may develop disease based on their age-specific incidence and continue to receive screening tests. People with undiagnosed disease may get screen- or clinical detection, or progress to metastatic disease before being diagnosed. The model estimates an effective test sensitivity ($Sens^{eff}$) that has separate components including test sensitivity (Sens), biopsy compliance (BiopComp), and biopsy detection rate (BiopDetect). The endogenous sensitivity of loco-regional, stage M0 disease is determined by the core model structure. The sensitivity of stage M1 disease is assumed to be

100% accurate, as the test sensitivity increases substantially when disease has progressed beyond the loco-regional stage. The standard for biopsy referral in the U.S. from 1990 to 2005 was a PSA level greater than 4ng/mL, yet lower thresholds were suggested and used in the 1990's, including 3 ng/ml and 2.5 ng/ml. In this model men are eligible for biopsy after screening if their PSA exceeds the endogenous threshold.

Screen detection rate (sx) of disease is given by age and grade. T^{sx} represents the average time between two consecutive screening tests; a testing interval of 2 years is found to be reasonably consistent with observed incidence. S^{s} is the on-off switch for PSA screening:

$$sxM0_{i,j} = \frac{UxM0_{i,j} * F_i * SensM0^{eff} * S^{S}}{T^{sx}}$$

Not all men with a positive test result submit to a follow-up biopsy. The model base biopsy compliance rate following a positive PSA test is taken as 0.5, which is lower than in Europe, where estimates range around 0.8-0.9.

Biopsy detection rate (or biopsy accuracy) represents the ability of biopsy to detect men with existing disease. Its value has increased with the dissemination of extended biopsy schemes over time. 4-core biopsies were standard before 1990, 6-core biopsies by 1995, and 8- to 12-core biopsies were standard by the early 2000's. A 6-core biopsy is 80% accurate, 4-core biopsy accuracy is 2/3 of this amount, and extended core biopsies, which are presently used, are 100% accurate. The biopsy detection rate varied from 0.6 to 1, based on estimates provided in previous studies.

Clinical Detection: Disease can also be clinically detected at any stage and the clinical detection hazard by grade (Cx_j) is assumed to be much higher after metastasis of disease. We do not model digital rectal exam (DRE) testing explicitly, and assume that the clinical detection hazard stays constant after the PSA era. This is an important assumption that may lead to overestimation of the value of the PSA test, since we do not capture any possible increases in the frequency of DRE test rate. In fact, DRE detections are also likely to increase because of disease awareness, which has increased over the years.

The clinical diagnosis rate (cx) for undiagnosed (Ux) loco-regional disease is given as follows:

$$cxM0 = UxM0_{i,j} * Cx_j * C_s$$

Treatment Sector

The treatment sector diagram is shown in Figure 1. Accordingly, patients who are diagnosed with prostate cancer by either screen-detection (Sx patients) or clinical detection (Cx patients) are assigned to one of the three primary treatments, classified as radical prostatectomy (RP), radiation therapy (RT), and active surveillance (AS). Initial treatment choice is classified based on the most aggressive treatment patient has received within 6 months after diagnosis (time to act=0.5 years). For example, anyone who had an RP is classified under surgical treatment even if he also received other treatments. RT and AS may also include androgen deprivation, and AS includes watchful waiting, and no treatment for simplicity.

In this setting, patients may also choose to change the initial course of treatment according to some probability (pChgTx). Patient deaths due to treatment-related procedures are ignored, assuming that they will not have a big effect on population counts. These may reach considerable numbers at lower disease thresholds, however.

Primary treatment choice (pTx) is exogenous to the model, based on the stage of the disease at screen or clinical detection, and treatment choice is not affected by the type of detection. Stock variables represent the treated patients (Tx), categorized by age, grade, and treatment type. The yearly treatment rate (tx) of screen-detected, stage M0 cancer is given as follows:

$$txSxM\ 0 = \frac{SxM\ 0_{i,j} * p^{txM\ 0} * T_s}{\tau}$$

The treatment efficacy parameters for the three primary treatment options are chosen based on previously published studies. Loco-regional disease can still metastasize after treatment, yet the metastasis rate is assumed to be slowed down after treatment. I multiplied the initial hazard of metastasis with some fraction (relMxTx) that is subscripted by treatment choice, denoting the efficacy of treatment to prevent metastasis of early-stage disease. Tx SxM0M1 and Tx CxM0M1 represent subjects who are diagnosed either by screening or clinical detection during early-stage disease and have received treatment for early-stage cancer, yet have already metastasized to distant disease.

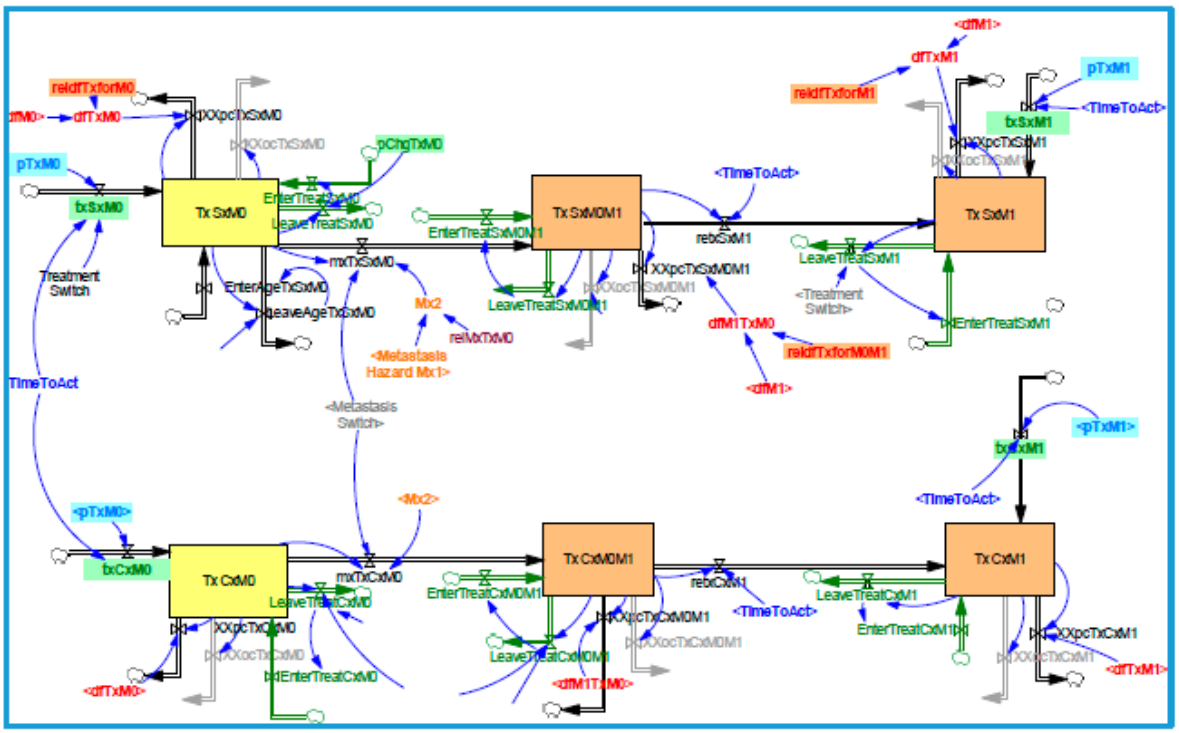

Figure S1 Treatment Sector Stock-Flow Diagram

Screening Dissemination Sector

PSA testing became widespread in the late 1980's before data supported the benefit of screening or aggressively treating diagnosed cancer. In our model, the doctor's adoption of PSA screening is modeled as a fraction that ranges between 0 and the maximum adoption fraction. Screening dissemination takes place after 1985, the year PSA screening is introduced, and rapidly diffuses in the medical community after that. The screening dissemination sector stock/flow structure is given in Figure 3. The equation for the adoption fraction (A) is given as follows, where alpha and beta represent the dissemination parameters:

$$\frac{dA}{dt} = S_s(\alpha + \beta A(A^{\max} - A))\_ifA < A^{\max}, else\ 0$$

The current screened fraction of the population is defined as the product of the adoption fraction (A) and the screen eligible fraction (F). Screen eligibility is determined by the formal recommended starting and stopping ages in the PSA screening guidelines and the standard eligibility fraction, which indicates the maximum eligibility or the reference market for the PSA practice:

$$F = F_{std} * eff_{sa} * eff_{sa}$$

The effects of starting and stopping ages on the screening-eligible fraction are modeled by using graphical functions for an S-shaped curve. Accordingly, the screen-eligible fraction F is closer to maximum between the recommended ages for starting and stopping to screen; yet it fails to reach its maximum within this range, and also extends beyond the formal ranges. Both the screen-eligible fraction and the current screened fraction are given for 5-year age groups between the defined age ranges of 35-80+.

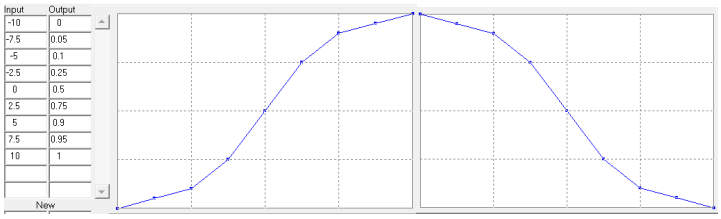

Figure S2 Tables representing the effect of starting and stopping age on screen-eligible fraction

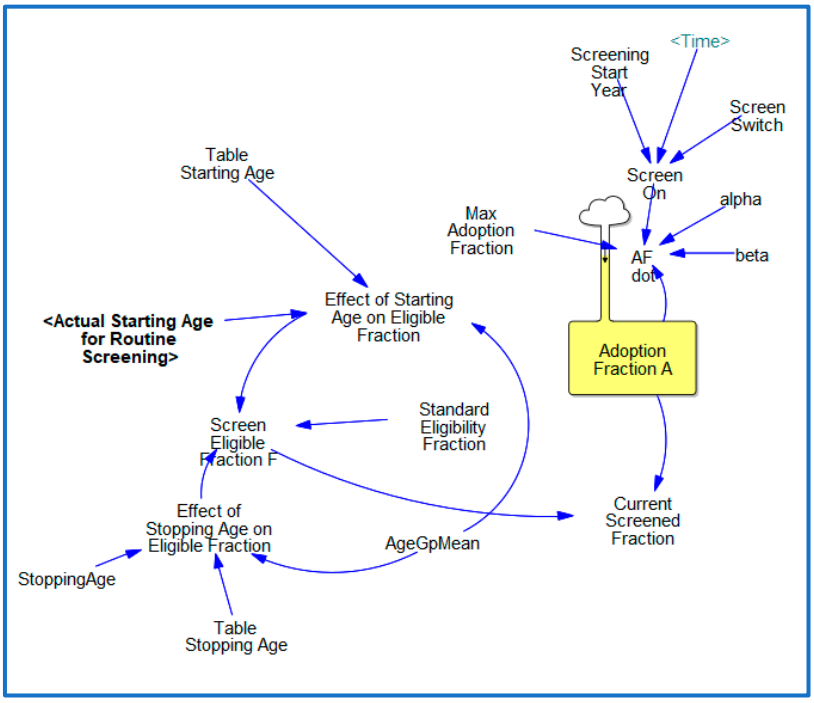

Figure S3 Screening Dissemination Sector

Harm Reduction Technology (HRT) Sector

Figure 4 presents the main stock-flow structure for the harm reduction technology (HRT) sector built for this study.

The HRT sector narrates an economic story in which the firms engaged in harm reduction look at the return to their research and development (R&D) expenditure. In this framework, the level of the HRT is defined as the fraction of the population harmed by treatment that can be treated effectively with HR technology, where T=0 means there is no HRT or treatment available, and T=1 means everyone can benefit from the available technology. As the HRT for prostate cancer improves, the remaining improvement declines, and with it the expected return to a dollar of new R&D. As the expected return to investment goes down, R&D will fall, causing the HRT to saturate below its theoretical maximum level (T^{max}). The rate of change in T (innovation to reduce harms) is modeled with a logistic function where γ represents the fractional improvement in technology:

$$\frac{dT}{dt} = T(T^{\max} - T) * \gamma$$

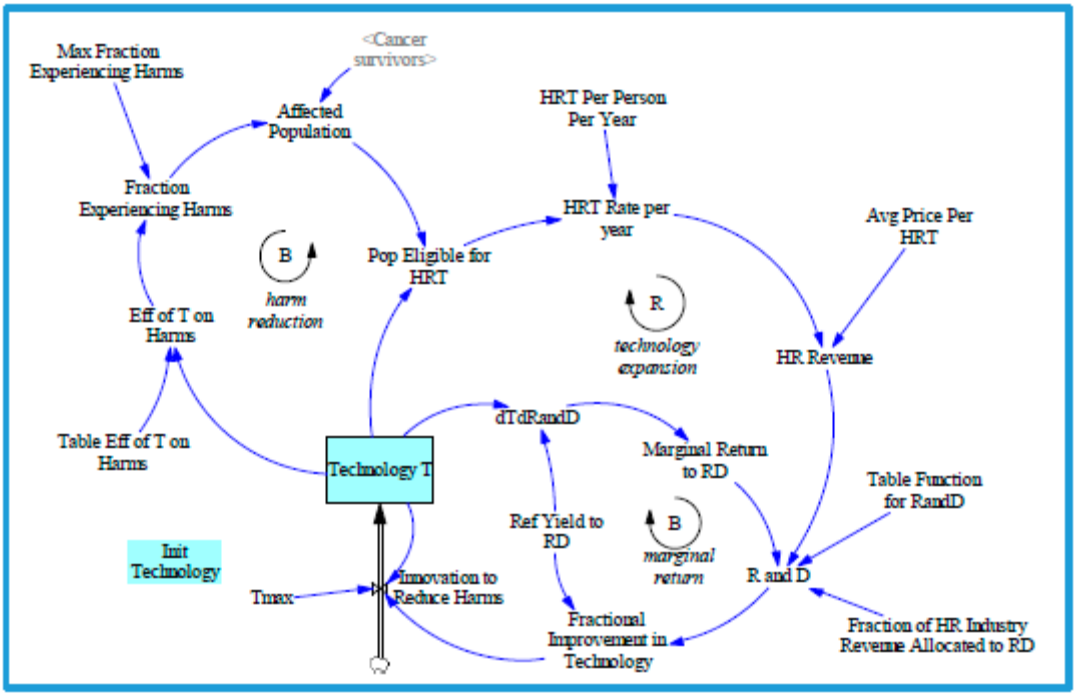

Figure S4 Harm-Reduction Technology Sector

The revenue of the HR industry equals the product of the average price of each harm reduction treatment and the treatment rate per year. Harm reduction treatment rate is defined as the population eligible for harm reduction treatment multiplied by the harm reduction treatments per person per year. Average price per HRT, and the number of HR treatments per person per year are exogenous constants. The eligible population for HRT is defined as the product of affected population and the T, where the affected population represents people who experience the side effects of treatment, including urinary incontinence, bowel problems, and erectile dysfunction. The fraction experiencing harms is equal to the maximum fraction experiencing harms multiplied by the effect of HRT on harms, which is a decreasing function of T. Figure 5 gives the table of the effect of T on harms:[1]

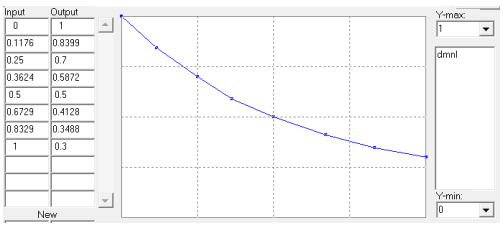

Figure S5 Table of Effect of Technology on Harms

Research and development (R&D) is defined as a fraction of the HR industry revenue, which itself is a function of expected profit per dollar of R&D. I estimate this by looking at the marginal revenue from an increase in HR Technology (T) and comparing it to the marginal cost. The fraction of the HR industry revenue allocated to R&D falls with the reduction in the marginal return to R&D. We take it as linear since no data is available on this relationship.

[1] In this formulation as HRT reaches its maximum level its effect on treatment harms reaches a lower bound. An alternative conceptualization would be to allow investing in HRT until its effects on treatment harms become zero.

Historical Data

Figures give the correspondence of the model to historical data and future projections for the population stocks, including the total population, percent of population above 65 years old, and for various age groups. It should be noted that the mean age of the population decreases first until the end of the 1990's, and then it starts to increase with a decreasing rate till the end of the simulation time horizon. Aging of the population and increase in life expectancy has serious implications for chronic disease incidence and prevalence. Prostate cancer is an age-related disease and aging of the male population implies more prostate cancer survivors in the future, especially if the current trends of screening continue at the current pace.

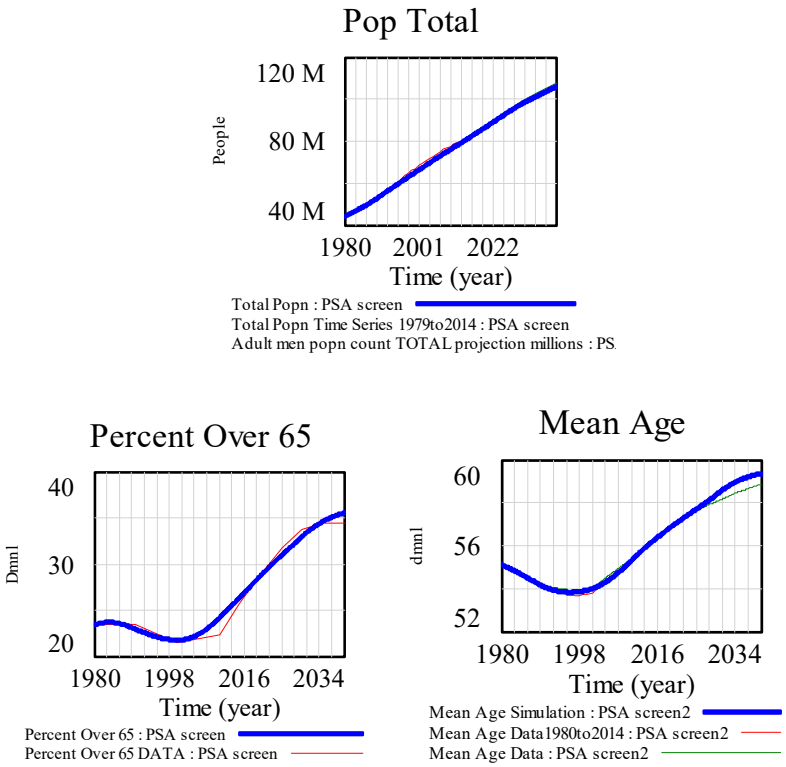

Figure S6 Total population and percent of men over 65 years and older

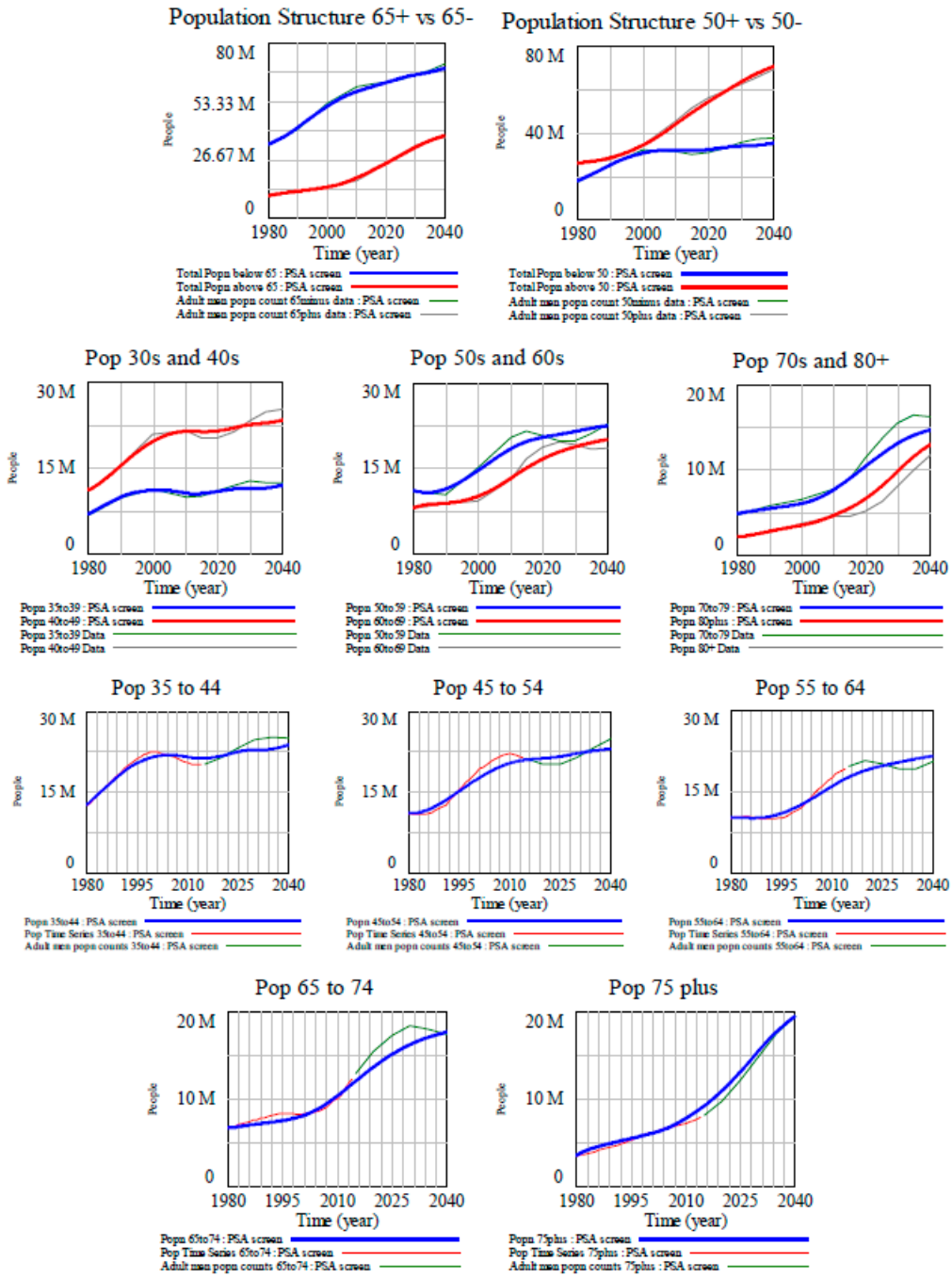

Figure S7 Population counts history and projection for various age groups

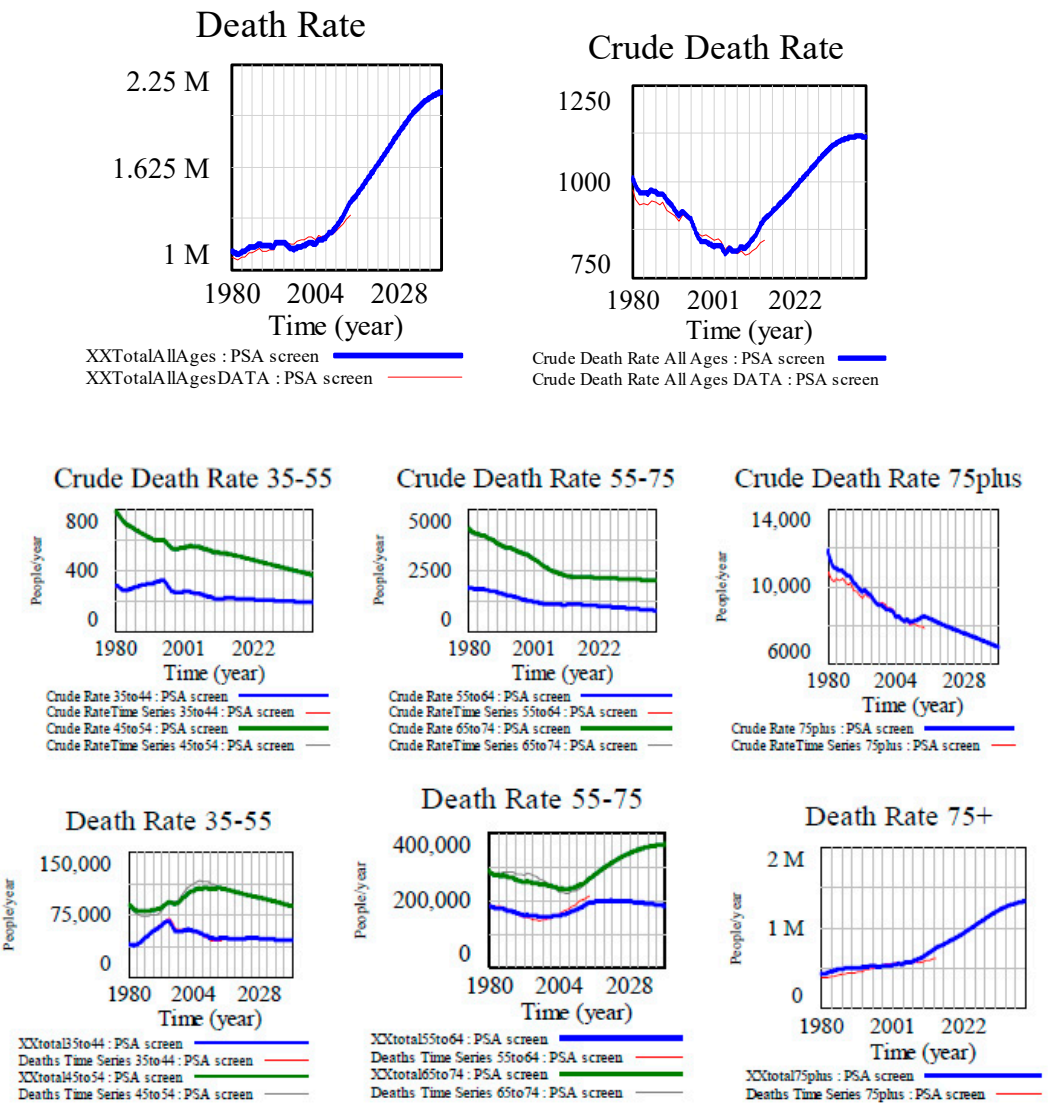

Figure S8 Death rate and crude death rate counts history and projection for various age groups

The death rate is given both in terms of millions of deaths per year, and also as a crude death rate, expressed as the number of deaths reported each calendar year per factor selected. The default factor at the CDC compressed mortality file is per 100,000 population, reporting the death rate per 100,000 persons. Rates are also given for three age groups, 35-55 year olds, 55-75 year olds, and 75+ year olds. Model behavior shows reasonable correspondence to historical behavior of the total population counts and deaths.

Crude Rate = Count / Population * 100,000