Prostate cancer progression depends in part on the complex interactions between testosterone, its active metabolite DHT, and androgen receptors. In a metastatic setting, the first line of treatment is the elimination of testosterone. However, such interventions are not curative because cancer cells evolve via multiple mechanisms to a castrate-resistant state, allowing progression to a lethal outcome. It is hypothesized that administration of antiandrogen therapy in an intermittent, as opposed to continuous, manner may bestow improved disease control with fewer treatment-related toxicities. The present study develops a biochemically motivated mathematical model of antiandrogen therapy that can be tested prospectively as a predictive tool. The model includes “personalized” parameters, which address the heterogeneity in the predicted course of the disease under various androgen-deprivation schedules. Model simulations are able to capture a variety of clinically observed outcomes for “average” patient data under different intermittent schedules. The model predicts that in the absence of a competitive advantage of androgen-dependent cancer cells over castration-resistant cancer cells, intermittent scheduling can lead to more rapid treatment failure as compared to continuous treatment. However, increasing a competitive advantage for hormone-sensitive cells swings the balance in favor of intermittent scheduling, delaying the acquisition of genetic or epigenetic alterations empowering androgen resistance. Given the near universal prevalence of antiandrogen treatment failure in the absence of competing mortality, such modeling has the potential of developing into a useful tool for incorporation into clinical research trials and ultimately as a prognostic tool for individual patients.

castration resistance | continuous androgen ablation | intermittent androgen ablation | rapid antiandrogen cycling
results suggest that low androgen levels can increase selection for castration-resistant cancer cells with elevated AR expression. We will use this evolutionary concept as the basis for the mathematical progression model proposed here.

The objective of the present paper is to develop a comprehensive mathematical model of CaP progression, focused primarily on antiandrogen therapy of advanced disease, which could be applied to different antiandrogen interventions. We consider the case of a typical patient with advanced prostate cancer. We introduce three primary cell phenotypes—healthy prostatic epithelial cells (E), androgen-dependent CaP cells (N), and castration-resistant CaP cells (M). Here, E, N, and M represent total cell number, in millions. While E cells are limited to the prostate, N and M cells are typically systemic at metastatic sites, allowing for simulation of cases where patients present with metastatic disease or relapsed/recurrent disease post radical prostatectomy or radiation. To avoid overparameterizing our system, N and M represent total CaP burden in the body and are not compartmentalized to specific metastatic sites such as bone or lymph nodes. Driving the behavior of each cell is the intracellular signaling network presented in Fig. 1. Following Eikenberry et al. (20), this is translated into a system of differential equations using the law of mass action, the full details of which are presented in SI Text.

Our model is designed to simulate the response to antiandrogen therapy of prostate cancer up to the emergence of castration resistance, defined as the progression of the disease in the presence of castrate concentrations of serum testosterone.

Mathematical Model

We begin with a description of the equations describing the dynamics of the principle species in our model—namely, healthy epithelial and cancer cells, and intraprostatic and serum PSA concentration.

**Cell Type E.** Healthy epithelial cells proliferate at a rate \( \mu_E \) and have a natural death rate \( \delta_E \) that is in balance and dependent on testosterone- and DHT-activated androgen receptors \( A_{E_L} \) and \( A_E \), respectively; Fig. 24). Competitive inhibition due to the presence of other cells is also incorporated in our model. The equation governing \( E \) is

\[
\frac{dE}{dt} = \mu_E(A_{E_L}A_E)(1 - \frac{E + \epsilon(N + M)}{\eta^C(t)}) - \delta_E(A_{E_L}A_E)E. \tag{1}
\]

Prostate volume increases with age (21) by a process known as benign prostatic hypertrophy. By choosing the carrying capacity \( \eta^C(t) \) in the cell proliferation term to be a function of time, we can capture this variability in prostate size accurately. The parameter \( \epsilon \) is a measure of the competitive interaction between healthy and cancer cells. Because \( N \) and \( M \) include CaP cells from distant metastatic sites, \( \epsilon \) is assumed to have a very small or negligible value in the setting of metastatic disease but could have a role in locally advanced nonmetastatic disease.

**Cell Type N.** Because we are concerned with prostate cancer that has its origins in the epithelia, the proliferation rate \( \mu_N \) and the death rate \( \delta_N \) of androgen-dependent cancer cells are significantly related to androgen-activated androgen receptors \( A_{N_L} \) and \( A_N \), respectively) signaling, as in the case of \( E \). The equation for \( N \) is taken to be

\[
\frac{dN}{dt} = (1 - \alpha_{mut})\text{prolif}_N - \delta_N(A_N A_{N_L})N. \tag{2}
\]

Here, prolif \( N = \mu_N(A_N A_{N_L})N(1 - (\epsilon E + N + M)/\eta^C) \), and \( \eta^C \) is a measure of the maximum carrying capacity of the tissue in the case that the cancer resides. It has been suggested that mutations leading to castration resistance are an early event, independent of androgen ablation (22). This indicates the possibility of mutation acquisition occurring as a result of proliferation of aberrant cancer cells in \( N \), which is accounted for by the parameter \( \alpha_{mut} \), which represents the probability of a cell with androgen-dependent phenotype \( N \) mutating to a castration-resistant phenotype \( M \). This is an important parameter in our model, because it could account for significant heterogeneity, in addition to being a key predictor of treatment outcome. Note that the overall rate of
mutation ($\alpha_{\text{mut}} + \text{prolif}_M$) depends both on the number of proliferating $N$ cells as well as how fast they proliferate.

**Cell Type $M$.** The equation governing the rate of growth of castration-resistant cancer cells is similar to that for $N$ above,

$$\frac{dM}{dt} = \text{prolif}_M - \delta_M(A_M A_M)M + \alpha_{\text{mut}} \text{prolif}_N. \quad [3]$$

Here, $A_{M}$ and $A_M$ are testosterone- and DHT-activated androgen receptors respectively, in $M$ and $\text{prolif}_M = M(MA_M)/(cE + N + M)^2$.

**PSA in Tissue, $P$.** Healthy and cancerous epithelial cells of the prostate produce PSA (23) in response to activated androgen receptors (24). However, in the noncancerous prostate the extra-vasation of the large PSA protein (35 kDa) into the bloodstream is hampered due to the presence of natural barriers, including the basal cell layer, prostatic basement membrane, prostatic stroma, and layers of the capillary walls (25). The equation governing PSA production in tissue is taken to be

$$\frac{dP}{dt} = -\alpha_P P E_{\text{leak}} - \gamma_P P_0 (N + M)^2 K_P + N + M - \lambda_P P + \text{prod}_P. \quad [4]$$

PSA is produced by $E$, $N$ and $M$, in response to activated androgen receptors, at a rate $\text{prod}_P = \sum_i (-E_i N M P_i (A_i + A_{\text{mut}} + p_i) i)$, where $P_i$ is a rate constant. We also account for the possibility of an independent production mechanism, via the constant $\rho_P$. PSA undergoes natural decay at a rate $\lambda_P$ and is assumed to leak into blood serum at a rate dependent on the epithelial volume relative to stromal volume of the prostate. Consequently, this leakage rate is taken to be proportional to the epithelial fraction $E_{\text{leak}}$ in the nonmalignant prostate—that is, the ratio of the epithelial volume to total prostatic volume.

In order to model the breakdown of natural barriers to the leakage of PSA into the blood in the presence of cancer cells, an additional leakage term is incorporated in Eq. 4. It is assumed that this additional leakage is negligible when the number of tumor cells is low, while for high numbers of tumor cells, this leakage is approximately linearly related to the number of tumor cells. This assumption is reasonable because it is to be expected that a comprehensive breakdown of the interstitial PSA barriers is more likely to occur for a higher number of tumor cells.

**Serum PSA, $P_S$.** The equation governing the rate of change of serum PSA concentration is

$$\frac{dP_S}{dt} = \alpha_P P E_{\text{leak}} + \gamma_P P_0 (N + M)^2 K_P + N + M - \lambda_P P. \quad [5]$$

The leakage terms in Eq. 4 correspond to source terms for serum PSA. Serum PSA is cleared from the body at a rate $\lambda_P$.

**Personalized Parameters.** We divide the parameters in our model into three categories: (i) parameter values from the literature, (ii) parameters derived from data fitting, and (iii) personalized parameters. The parameters in classes $i$ and $ii$ are derived from experimental data, humans when possible or experimental animal models as reported in ref. 26, and in vitro data on established CaP cell lines. A detailed description of the estimation of these parameters is presented in SI Text, sections S2 and S3. Data on the development of the human prostate, together with variations in its size and serum androgen levels with age, is taken into account while extrapolating parameter values for the human case.

It is commonly recognized that prostate cancer is a highly heterogeneous disease regarding response to antiandrogen therapy and rate of progression. In addition, serum testosterone and other androgens are known to vary widely from person to person. Furthermore, although PSA within a person is a useful marker of changing tumor burden in response to therapy, PSA is a poor predictor of tumor burden between patients. The model is equipped to deal with this heterogeneity by appropriately adjusting the relevant model parameters to match each patient profile; we refer to these parameters as “personalized parameters.”

Initially, cancer cells are assumed to be androgen-dependent. Following ref. 27, the transformed cells are assumed to differ from healthy epithelial cells in having a higher net turnover rate. This is the first of our personalized parameters, because this doubling rate is estimated from patient treatment data and can vary among individuals. The simulation is allowed to run, until our virtual patient’s PSA levels accumulate, at which time a screening event (screening PSA or digital rectal exam) is assumed to take place. However, in many men not undergoing screening or previously treated with local therapy that was too late, cancer cells

Fig. 2. (A) Androgen-dependent proliferation (DHT, blue and testosterone, green) and death (red) rates for human prostatic epithelial cells estimated from fitting experimental data. Activated AR concentration of 1 in dimensionless terms corresponds to homeostatic levels in the healthy prostate from fitting experimental data. Activated AR concentration of 1 in dimensionless terms corresponds to homeostatic levels in the healthy prostate from fitting experimental data. Activated AR concentration of 1 in dimensionless terms corresponds to homeostatic levels in the healthy prostate from fitting experimental data. Activated AR concentration of 1 in dimensionless terms corresponds to homeostatic levels in the healthy prostate from fitting experimental data. Activated AR concentration of 1 in dimensionless terms corresponds to homeostatic levels in the healthy prostate from fitting experimental data.
have spread via the lymphatics or blood to metastatic sites. At this point antiandrogen therapy is the mainstay of treatment, and the various drugs and their actions are shown in Fig. 1. Because this is a proof-of-concept paper, we do not distinguish between the unique aspects of each drug’s action; instead we assume that the collective effect of the treatment is to reduce the bioavailability of DHT in the prostate by 60%, based upon the literature (14). From this point onward, we may simulate continuous or intermittent therapy. As mentioned earlier, we assume that mutations leading to M phenotype emerge spontaneously as a result of N cell proliferation. The hypothesis that application of androgen ablation therapy selects for these resistant cell lines is then investigated. M cells are allowed to have a different rate of turnover in terms of proliferation and apoptosis rates as compared to N cells. The type of mutation, frequency of mutation acquisition, and mutated-cell doubling time are also designated as personalized parameters. Given that one of the common mutations observed in hormonally refractive tumors is androgen receptor overexpression, we take this example, coupled with an increased stability of the receptors, to be the mutations in M cells. Then, by changing cell doubling time and frequency of mutation acquisition, we can simulate an aggressive versus a milder M phenotype and predict responses to continuous versus intermittent therapy (on various schedules).

Results

Case Study 1: Slow Cycling of Intermittent Therapy. In 1995, Goldenberg et al. (28) published one of the first trials of intermittent androgen ablation therapy in prostate cancer patients. A group of 47 patients represented a wide range of cancer stage and grade and had an average age of 67 years. The mean follow-up time was 120 weeks and two cycles of treatment reported, lasting 73 and 75 weeks, with a mean time off therapy of 30 and 33 weeks, respectively. In seven patients with Stage D2 disease, the cancer was reported to progress to an androgen-independent stage in a mean time of 128 weeks. The treatment consisted of inhibiting pituitary gonadotropins with goserelin and androgen receptor blockade with flutamide. PSA concentrations (averaged across the entire patient dataset) were reported on an eight-week cycle due to dominance of the castration-resistant phenotype. Fig. 2 shows the temporal evolution of the various cell populations corresponding to this schedule. As can be seen, even the application of continuous therapy at this point is unable to contain the rapidly proliferating M cells (red curve). In contrast, application of continuous therapy instead of intermittent therapy from the start of treatment is predicted to result in a disease-free survival period of up to five years; for more details, see SI Text, section 4.

Case Study 2: Rapid Cycling of Intermittent Therapy. Here, we investigate the effect of competition between cells of type N and M on choice of treatment schedule. Both cell types may be competing for space and nutrients; and it is possible that in the process of mutation acquisition, cell type M becomes a poor competitor of cell type N. We quantify the competitive advantage of M over N by a parameter \( \theta > 1 \), replacing \( (1 - (eE + N + M)/\gamma^2) \) by \( (1 - (eE + (1/\theta)(N + M))/\gamma^2) \) in Eq. 2, and by \( (1 - (eE + 6N + M)/\gamma^2) \) in Eq. 3.

In 2006, Feltquate et al. (29) reported on a study conducted to investigate the feasibility of rapid androgen cycling for men with progressive prostate cancer. The schedule included a 12-week induction of androgen deprivation, followed by four-week treatment cycles consisting of a gonadotropin-releasing hormone agonist analogue injection on day 1, coupled with testosterone repletion on days 1 to 7. This cycling was repeated until the cancer progressed to a castration-resistant stage. A number of PSA patterns were observed including patients whose PSA levels declined to an undetectable nadir, as well as PSA decline to a plateau, followed by eventual increase. A large subset of these patients had undergone radical prostatectomy previously and was thus being treated for metastatic disease. Although such a schedule is unlikely to be common in clinical practice we present it here to illustrate the wide scope of our model in terms of its ability to simulate a variety of treatment scenarios.

It is possible to repeat the fitting exercise described earlier for Case 1 for the various PSA patterns reported in ref. 29. This leads

\[ \alpha \]
to results similar to those reported above. While this serves as
good validation of our model—because we are able to reproduce
a number of clinically observed outcomes for a variety of different
treatment strategies—we use the experimental data to test a hy-
thesis of possibly vital importance in determining treatment
strategies for advanced CaP patients. The question we wish to
ask of the model is “What if M cell type is a poor competitor of
N cell type?” This is a natural question to pose; it can be an
important determinant of the success of intermittent therapy
in comparison to continuous treatment in terms of delaying the
onset of a hormonally refractive cancer. Note that under condi-
tions of androgen ablation, N cells have a reduced rate of pro-
iferation and undergo apoptosis at a high rate, thereby losing
their competitive edge over M cells.

Fig. 3A shows a fit of our model to patient PSA data as
reported in ref. 29 (compare to figure 2B in reference) for the
case when PSA levels appear to decline to a stable plateau. Eventu-
ally the PSA levels start to rise again, at which point the patient
is taken off the rapid cycling trial and put on continuous therapy.
Fig. 3B shows corresponding normalized cell numbers. Note that
as we are simulating a case where the patient is likely to have
received a radical prostatectomy before enrollment in the study,
the number of PECs has been set to zero. Prior to fitting, we make
the assumption that the M phenotype has overexpression of
androgen receptors coupled with an increased stability in these,
as in case study 1. The personalized parameters being fit are the
same as earlier.

Taking a value of $\theta = 3$, model simulations predict that the
patient has an expected disease-free survival time of 28 months
post rapid cycling therapy, after which PSA levels begin to rise
again above a minimum threshold (taken to be $4 \text{ ng/mL}$ for the
purposes of illustration), due to emergence of castration resis-
tance. In contrast, had continuous therapy been provided from
the start of treatment, the expected recurrence of disease would
have occurred four months sooner. We now increase the para-
meter $\theta$ and provide rapid cycling therapy for as long as it takes
for PSA levels to start rising again. This is followed by continuous
therapy, as in the therapy protocol reported in ref. 29. The time
lag between disease recurrence in this case, versus providing con-
tinuous therapy from the outset, is predicted to increase exponen-
tially (Fig. 3C). It should be noted that for $\theta \leq 2$, continuous
versus intermittent therapy application is favored.

Discussion
Advanced CaP is treated with drugs that either inhibit androgen
synthesis or block the ability of androgens to interact with its
receptor in prostate cancer cells. It has been hypothesized that
intermittent as opposed to continuous therapy may have advan-
tages for some individuals through limiting impact of treatment
on quality of life and metabolic or functional health outcomes
as well as prolonging the duration of response to antiandrogen
therapy. Intermittent scheduling may also reduce the rate of ac-
quision of mutations that contribute to the castration-resistant
phenotype. Yet, at the present time we lack tools to help us tailor
the appropriate therapy for each individual.

The paper develops a biochemically motivated mathematical
model that begins to address heterogeneity of prostate cancer
progression under different antiandrogen treatment regimes. The
model is formulated by a system of differential equations where
most of the parameters are based on experimental data. Due to
the heterogeneous nature of the disease, several “personalized
parameters” are to be adjusted based upon patient data. By fitting
model predictions of serum PSA levels in response to androgen
ablation therapy, we provide a quantitative confirmation of the
clinically held view (14) that the selective pressure of androgen
blockade is a stimulus for the emergence of hormonally refractive
cancers.

The model was applied to two case studies (28, 29) of inter-
mittent therapy representing two different intermittent treatment
strategies. By adjusting the few personalized parameters, we were
able to fit the model simulations to the “average” patients re-
ported in the corresponding publications for these cases. We
subsequently used the model to predict the future course of the
disease for the next 5–10-year period under either intermittent or
continuous therapy. Which of these two strategies yields a longer
remission period depends on the personalized parameters, which
quantify the competitive advantage of androgen-sensitive cancer
cells over mutated androgen-independent cancer cells and on the
“aggressiveness” of the mutated cancer cells.

The key to a model that is predictive and prognostic is the iden-
tification and quantification of the parameters that contribute to
the variation or heterogeneity that is profound in the prostate
cancer population. We have postulated these to be the following parameters: rate of acquisition of new mutations conferring resistance, competitive advantage of hormone-sensitive cells over androgen-independent cells, and overall sensitivity to androgen deprivation. Having shown that model simulations agree with medical data for the average patients, the model may be used in the future to examine individual cases and clinical trials, to further quantify the contribution of these factors to treatment failure in order to predict which men would benefit from continued therapy or one of many different strategies of intermittent therapy, thus enhancing outcome through personalized therapy.

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Supporting Information

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SI Text

S1 Model Equations. The full system of equations used to model prostate cancer development is presented below, together with notation used.

Notation. \( t \) = Time (days)
\( V_{\text{max}}(t) \) = Maximum Prostate Volume (mm\(^3\))
\( V_c \) = Volume of an Epithelial Cell (mm\(^3\))
\( \eta^2(t) \) = Maximum number of Epithelial Cells in Prostate
\( \eta^2 \) = Maximum number of Cancer Cells in Body
\( T_S \) = Serum Testosterone Concentration (nM)
\( P_S \) = Serum PSA concentration (ng/ml)
\( P \) = Tissue PSA concentration (ng/ml)
\( E \) = Normal Prostatic Epithelial Cell number (millions)
\( N \) = Androgen-dependent Cancer Cell number (millions)
\( M \) = Castrate-resistant Cancer Cell number (millions)
\( T_i \) = Testosterone concentration in cell type \( i \) (nM), \( i = E,N,M \)
\( \eta^2_i \) = Constitutive free Androgen Receptor expression level, in cell type \( i \) (nM), \( i = E,N,M \)
\( R_i \) = Free Androgen Receptor concentration in cell type \( i \) (nM), \( i = E,N,M \)
\( D_i \) = DHT concentration in cell type \( i \) (nM), \( i = E,N,M \)
\( A_i \) = DHT-activated Androgen Receptor concentration in cell type \( i \) (nM), \( i = E,N,M \)
\( A_{\text{ts}} \) = Testosterone-activated Androgen Receptor concentration in cell type \( i \) (nM), \( i = E,N,M \)

Equations.

\[ T_S = a_T t^2 + b_T t + c_T \]  \[ S1 \]
\[ \frac{dE}{dt} = \mu_E (A_E A_{E_t}) E \left( 1 - \frac{eE + N + M}{\eta^2(t)} \right) - \delta (A_E A_{E_t}) E \]  \[ S2 \]
\[ \frac{dN}{dt} = \mu_N (A_N A_N_t) N \left( 1 - \frac{eE + N + M}{\eta^2} \right) - \delta (A_N A_N_t) N - a_{\text{mut prolif}} N \]  \[ S3 \]
\[ \frac{dM}{dt} = \mu_M (A_M A_M_t) M \left( 1 - \frac{eE + N + M}{\eta^2} \right) - \delta (A_M A_M_t) M + a_{\text{mut prolif}} N \]  \[ S4 \]
\[ \mu_i (A_i A_{\text{ts}}) = q_i^1 \frac{(A_i)^2}{(q_i^2)^2 + (A_i)^2} + q_i^1 \frac{(A_{\text{ts}})^2}{(q_i^2)^2 + (A_{\text{ts}})^2} \]  \[ i = E,N,M \]  \[ S5 \]
\[ \delta_i (A_i A_{\text{ts}}) = \frac{q_i^1}{q_i^2 + q_i^1 A_i + q_i^1 A_{\text{ts}}} \]  \[ i = E,N,M \]  \[ S6 \]
\[ \text{prolif}_N = \mu_N (A_N A_N_t) N \left( 1 - \frac{eE + N + M}{\eta^2} \right) \]  \[ S7 \]
\[ \frac{dT_i}{dt} = f(T_S) - \lambda_T T_i - \beta_T \frac{T_i}{K_T + T_i} - k_T^2 R_i T_i + k_T^2 A_{\text{ts}} \]  \[ i = E,N,M \]  \[ S8 \]

\[ f(T_S) = \frac{a_T T_S}{b_T + T_S} + c_T \]  \[ S9 \]
\[ \frac{dR_i}{dt} = a_R - \lambda_R R_i - k_R^2 R_i D_i + k_R^2 A_i - k_T^2 R_i T_i + k_T^2 A_{\text{ts}} \]  \[ i = E,N,M \]  \[ S10 \]
\[ \frac{dD_i}{dt} = \beta_T \frac{T_i}{K_T + T_i} - \lambda_R D_i - k_D^2 R_i D_i + k_D^2 A_i \]  \[ i = E,N,M \]  \[ S11 \]
\[ \frac{dA_i}{dt} = -\lambda_A A_i + k_D^2 R_i D_i - k_D^2 A_i \]  \[ i = E,N,M \]  \[ S12 \]
\[ \frac{dA_{\text{ts}}}{dt} = -\lambda_A A_{\text{ts}} + k_D^2 R_i T_i - k_D^2 A_{\text{ts}} \]  \[ i = E,N,M \]  \[ S13 \]
\[ a_R = \lambda_R (p_i^1 - A_i - A_{\text{ts}}) + \lambda_A A_i + \lambda_A A_{\text{ts}} \]  \[ i = E,N,M \]  \[ S14 \]
\[ \frac{dP}{dt} = \sum \beta_p (A_i + A_{\text{ts}} + p_i) i - \alpha_p P \frac{(N + M)^2}{K_P + N + M} - \lambda_p P \]  \[ i = E,N,M \]  \[ S15 \]
\[ \frac{dP_S}{dt} = \alpha_p P \frac{(N + M)^2}{K_P + N + M} - \lambda_p P_S \]  \[ S16 \]
\[ E_{\text{frac}} = V_c \frac{E}{P_{\text{vol}}} \]  \[ S17 \]
\[ P_{\text{vol}} = \frac{a_V}{b_V^2 + c_V} + c_V \]  \[ S18 \]

S2 Parameter Estimation from Literature Review and Rat Data. The estimation of parameters relating to prostatic growth as a function of androgens is discussed below. Where possible, parameter values were taken from the literature or were fit to experimental data taken from the literature using lsqcurvefit, a nonlinear least squares tool available in Matlab. Care was taken to not fit more than 2-3 parameters at one time, to a give set of data. In all other cases, biologically realistic values for parameters were chosen.

Parameter Values from Literature Review. Table S1 gives a list of parameter values obtained from a literature survey. Here, \( T \) represents testosterone, \( A_R \) represents androgen receptor, and DHT represents dihydrotestosterone.

Parameter Values from Data Fitting (Rat Prostate). Estimating rate of testosterone entry into prostate and healthy cell proliferation and death as a function of testosterone-activated AR concentration in a rat model. The source of experimental data is Wright et al. (1). In the first set of experiments, 55-day-old male Sprague Dawley rats are castrated and treated with subcutaneously implanted testosterone pellets together with finasteride to ensure minimal or no conversion of testosterone to DHT in the prostate and killed four days after castration. Because the pellets ensure a constant
amount of testosterone is released each day, we can assume serum testosterone $T_S$ is approximately constant.

The model Eqs. S1–S18 may be modified as follows to simulate these experiments as follows. The unknown functions and parameters to be estimated are indicated in bold. These are the rate of testosterone entry into the prostatic epithelia $f(T_S)$, the testosterone-activated AR dependent rates of cell proliferation $\mu_E(0,A_{Ei})$ and cell death $\delta_E(0,A_{Ei})$, the maximum carrying capacity of the prostate for epithelial cells $E_0$, the rate of AR production $\alpha_{Re}$, and the rate of testosterone-activated AR decay $\lambda _{AE}$.

$$\frac{dT_E}{dt} = f(T_S) - \lambda_T T_E - k_f^T R_E T_E + k_f^T A_{Ei} \quad [S19]$$

$$\frac{dE}{dt} = \mu_E(0,A_{Ei}) E \left( 1 - \frac{E}{E_0} \right) - \delta(0,A_{Ei}) E \quad [S20]$$

$$\frac{dR_E}{dt} = \alpha_{Re} - \lambda_{Re} R_E - k_f^T R_E T_E + k_f^T A_{Ei} \quad [S21]$$

$$\frac{dA_{Ei}}{dt} = -\lambda_{AE} A_{Ei} + k_f^T R_E T_E - k_f^T A_{Ei} \quad [S22]$$

The experimental data to which we will fit these unknowns is indicated in rows 1–7 in Table S2. Following Eikenberry et al. (2), we suppose that at homeostasis, free AR concentration together with the constitutive level of expression of AR per million epithelial cells is the constitutive level of expression of AR per million epithelial cells, in nM. For the rat prostate, $R_E^{0}$ is taken to have a value of 90 nM, as this gives the best overall fit to the complete set of experimental data.

We first consider a prostate at homeostasis. In experiments described in (1), when a 5-mg pellet was given following castration, ventral prostatic weight was found to be at its normal (homeostatic) value of 0.449 g. The steady states of serum testosterone ($T_S = 11.15 \text{ nM}$) and intraprostatic testosterone ($T_E = 72.03 \text{ nM}$) corresponding to this dose will be referred to as $T_E^h$ and $T_E^r$ respectively. Finally, a healthy ventral prostate in a rat has been estimated to contain $E_0 = 39.42 \times 10^6$ cells (3). We can therefore estimate the volume $V_C$ of a typical prostatic epithelial cell to be epithelial volume $V_C^0$ divided by the number of cells. Denoting homeostatic values of free and testosterone-activated AR by $R_E^h$ and $A_{Ei}^h$ respectively, Eqs. S21 and S22 give the following two equations, at the homeostatic steady state. We will use these to estimate the value of $A_{Ei}^h$.

$$0 = \alpha_{Re} - \lambda_{Re} R_E - k_f^T R_E^h T_E^h + k_f^T A_{Ei}^h \quad [S23]$$

$$0 = -\lambda_{AE} A_{Ei}^h + k_f^T R_E^h T_E^h - k_f^T A_{Ei}^h \quad [S24]$$

Fig. S1A displays total intraprostatic testosterone $T + A_{Ei}$ as a function of serum testosterone $T_S$ (black squares), while Fig. S2A displays total intraprostatic DHT $T_D + A_{Ei}$ as a function of $T_S$ (black squares). From these experimentally derived graphs (1), we can see that $D_T + A_{Ei} \approx T + A_{Ei}$. This suggests that DHT-activated AR are more stable that testosterone-activated AR. Indeed, there is also some experimental evidence for this (4). We conclude that $\lambda_{AE} \ll \lambda_{AE}$, while (by Table S1), $\lambda_{AE} \ll \lambda_{Re}$. It is therefore reasonable to expect that $\lambda_{AE}$ and $\lambda_{Re}$ are close in value; here, we shall assume that they are in fact equal. Note that choosing a marginally lower value for $\lambda_{AE}$ than $\lambda_{Re}$ does not affect the quality of our simulations, but in the absence of experimental data guiding us, we take these to be equal. Solving Eqs. S23 and S24 allows us to determine the value of $A_{Ei}^h = 66.1019 \text{ nM}$, the activated AR concentration at homeostasis. Berges et al. (5) have estimated prostatic epithelial cell proliferation and death rates to be equal (with a value of 0.0083 per hour) at homeostasis. Thus we know that $\mu_E(0,A_{Ei}^h)(1 - E^0/E_0) = 0.0083$, and $\delta_E(0,A_{Ei}^h) = 0.0083$ per hour. Further, because it takes six weeks for a rat to reach sexual maturity (6), we must have from Eq. S20 that $E_0 = 1.4 \times E^0$ (assuming that prostate development starts with a single cell and that it takes six weeks for the ventral prostate to reach its steady state of 39.42 million cells). In this case, $\mu_E(0,A_{Ei}^h) \approx 0.029$.

Next, we estimate the rate of entry of testosterone form the serum into the prostate $f(T_S)$ by observing that the binding of testosterone to its receptors occurs at a very fast time scale in comparison to the rates of proliferation or apoptosis of cells and that from ref. 1 we have estimates of intraprostatic testosterone at day 4, versus serum testosterone levels (in columns 1 and 4 of Table S2), we may solve Eqs. S19, S21, and S22 to their steady state for each given value of $T_S$ and $T$ in order to estimate a value for $f(T_S)$. Taking a Hill function-like form for $f(T_S)$ as given by Eq. S9 provides the best fit. We assume here that the prostate produces testosterone locally at a very low rate. This is corroborated by data from ref. 1, where small amount of testosterone were detected in the prostates of castrated rats that were given no testosterone (see figure 2 in the referenced paper). The fitted parameter values are reported in Table S3.

We finally solve the entire system of Eqs. S19–S22 to estimate the precise functional forms of $\mu_E(0,A_{Ei})$ and $\delta_E(0,A_{Ei})$ by fitting to cell count data as shown in column 5, rows 1–7 of Table S2. The resulting fits are shown in Fig. S1C. The estimated functional form for epithelial cell proliferation is given below.

$$\mu_E(0,A_{Ei}) = q_E^T \left( \frac{(A_{Ei})^2}{(q_E^T)^2} + (A_{Ei})^2 \right) \quad [S25]$$

This functional form is chosen because it is known that activated AR dimerize before translocating to the nucleus and inducing downstream effects (7); indeed the enzymatic process $A_{Ei} + B \rightarrow B \rightarrow E$ where $B$ translocates to the nucleus leads to Hill’s dynamics with exponent 2. From the homeostasis data we can reduce the number of unknowns in this expression by 1 parameter. Note that we get our fit by taking $\delta_E(0,A_{Ei})$ to be constant, at 0.0083 per hour. In other words, the model predicts the best fit if we assume that testosterone primarily induces a proliferative effect, rather than a prosurvival effect in prostatic epithelial cells. The fitted values are shown in Table S3. The proliferation and death rates are plotted versus various values of $A_{Ei}$ in Fig. S1B.

**Estimating rate of testosterone conversion to DHT and cell proliferation and death as a function of DHT-activated AR concentration in a rat model.** In another set of experiments described in Wright et al. (1), the castrated rats as described previously are not treated with finasteride, allowing for the conversion of testosterone to DHT in the prostate. The model Eqs. S1–S18 can be modified to simulate these experiments as in the equations that follow. The unknown functions and parameters to be estimated are indicated in bold. These unknown parameters relating to the rate of conversion of testosterone to DHT mediated by the enzyme 5-α reductase $\beta_T$ and $K_T$, and the DHT-activated AR dependent rates of cell proliferation $\mu_E(A_E,A_{Ei})$ and cell death $\delta_E(A_E,A_{Ei})$.

$$\frac{dT_E}{dt} = f(T_S) - \lambda_T T_E - \beta_T \frac{T_E}{K_T + T_E} - k_f^T R_E T_E + k_f^T A_{Ei} \quad [S26]$$

$$\frac{dE}{dt} = E_t[A_E,A_{Ei}] E \left( 1 - \frac{E}{E_0} \right) - \delta(E_A,A_{Ei}) E \quad [S27]$$

$$\frac{dA_{Ei}}{dt} = \beta_T \frac{T_E}{K_T + T_E} - \lambda_D D - k_f^T R_D E + k_f^T A_{Ei} \quad [S28]$$

Jain et al. www.pnas.org/cgi/doi/10.1073/pnas.1115750108
The experimental data to which we will fit these unknowns is indicated in rows 8–13 of Table S2. We have two reservations about this data. First, note that the twelfth row seems to be in disagreement with all the other rows because it implies that a 4.6-fold increase in serum testosterone leads to only a 1.3-fold increase in DHT levels. In view of these reservations, while per- pared with homeostatic values (row 11) and that these higher DHT values result in a lower prostatic weight. The second reservation is concerned with the testosterone level $T_S = 3.767 \text{nM}$ in row 13. This level is much too high because it implies that a 4.6-fold increase in intraprostatic DHT concentration of 8.20 ng per g prostatic tissue (in columns 1 and 4, rows 8–13 of Table S2), we may solve the above system of equations, barring the cell equation, to its steady state for each given value of $T_S$ and $D_E$ in order to obtain this fit, it is necessary to assume that the epithelial fraction in the human prostate increases with age, and this is taken into account by making serum testosterone $T_S$ a function of time as given by Eq. S1. Note that we are not concerned here with the precise mechanism of testosterone production; hence a phenomenological choice has been made to describe the temporal evolution for this quantity, rather than a detailed biochemical formulation as was done for intraprostatic hormones and proteins. The data being fit is in the form of average serum testosterone values versus age, taken from ref. 11. The resultant fit is shown in Fig. S3A and variable values given in Table S4. Finally, testosterone production in men also falls with age, and this is taken into account by making serum testosterone $T_S$ a function of time as given by Eq. S1. Note that we are not concerned here with the precise mechanism of testosterone production; hence a phenomenological choice has been made to describe the temporal evolution for this quantity, rather than a detailed biochemical formulation as was done for intraprostatic hormones and proteins. The data being fit is in the form of average serum testosterone values versus age, taken from ref. 11. The resultant fit is shown in Fig. S3A and variable values given in Table S4. Further, the doubling time of the prostate has been calculated to be 2.76 years (10). We therefore need to adjust the cell turnover rates as estimated earlier to fit this data. In the absence of evidence to the contrary, we assume that the prostatic epithelial volume to prostate volume ratio is preserved between rats and humans. Then, a fully developed and healthy human prostate must contain approximately 1.86 billion epithelial cells. We further assume that all kinetic parameters and dependence of cell proliferation and death rates on androgens are also preserved between rats and humans. In this case, the only parameters that need to be altered are $q_{1S}^m$ and $q_{1S}^f$, the maximal proliferation rates, and $d_1^T$, the maximal death rate of epithelial cells and the constants $q_{2S}^m$, $d_2^S$ and $d_2^S$, (see Eqs. S5 and S6). Additionally, in order to account for the fact that at least 90% of the androgen in a human prostate is in the form of DHT, the value of AR expression per cell $k_{12}^p$ is adjusted to 180 nM and maximal rate of testosterone conversion to DHT $\beta_T$ is increased fourfold. The values of the scaled variables are given in Table S4.

The natural enlargement of the prostate that occurs over time is accounted for by estimating a functional form for prostate volume $P_{vol}$ as given by Eq. S18. The data being fit is in the form of average prostate volumes versus age, taken from ref. 11. The resultant fit is shown in Fig. S3A and variable values given in Table S4. Finally, testosterone production in men also falls with age, and this is taken into account by making serum testosterone $T_S$ a function of time as given by Eq. S1. Note that we are not concerned here with the precise mechanism of testosterone production; hence a phenomenological choice has been made to describe the temporal evolution for this quantity, rather than a detailed biochemical formulation as was done for intraprostatic hormones and proteins. The data being fit is in the form of average serum testosterone values versus age, taken from ref. 11. The resultant fit is shown in Fig. S3A and variable values given in Table S4.

Estimating PSA production and leakage rates. The equations describing PSA production in the prostate, and its leakage into blood serum has been discussed in Results in the main text. In the absence of cancer, average serum PSA values are observed to increase with age. We account for this heterogeneity by making the rate of PSA leakage dependent on the endothelial fraction of the prostate, as in Eqs. S15 and S16. The data being fit are taken from Richardson and Oesterling (13), with the resultant fit shown in Fig. S3C. In order to obtain this fit, it is necessary to assume that the epithelial fraction in the human prostate increases with age; consequently, the maximal carrying capacity of the prostate for epithelial cells $n^f$ is made a function of age. The unknowns $\beta_{Pc}$ and $\rho_E$ in Eq. S15 relating to intracellular PSA production are assigned arbitrary values, because there is no data available to fit these to. The fitted functional form is given below, and parameters in Table S4.

\[
q^{fE}(t) = a_E \rho^{fE} + \rho_E^p + c_E
\]

S4 Personalized Prostates (Prostate Cancer Progression and Treatment). Fits of parameters relating to $N$ and $M$ cell turnover rates, probability of mutation from $N$ to $M$ phenotype $\phi_{mut}$, and CaP cell-dependent PSA leakage rate parameters ($\gamma_E$ and $\kappa_F$) are fit to the available data. As mentioned in the main text, cancer cell PSA production rate $\beta_P$ is kept fixed throughout the simulations at 30% of the value of $\beta_P$. The mutated cells ($M$) are presumed to have a fourfold receptor overexpression level and fourfold increase in stability of receptors (see Table S1). All other constants relating to intracellular processes in both $N$ and $M$ cell are kept at the same values as for the $E$ cell type. The various parameter values are reported in Table S5 (Case study 1, muta-
tion to average phenotype—rows 1–14 (rows 1–4 are fixed prior to fitting), and Case study 1, mutation to aggressive phenotype—rows 15–18), and Table S6 (Case study 2). Note that for Case study 2, the parameter $\theta$ is a measure of the competitive advantage of $N$-cells over $M$-cells.

Sensitivity Analysis on the Probability of Mutation Acquisition. Given the importance of the parameter $\alpha_{\text{mut}}$ that measures the probability of mutation acquisition by $N$ cells, we conduct a sensitivity analysis on its effect on treatment outcome, in Case Study 2 (see main text). Increasing its value by 100% is predicted to result in rapid androgen cycling treatment failure at 20 months as compared to 26 months in the control simulation case. If the patient is put on continuous treatment at this point, the expected disease free survival time is 25 months as compared to 29 months in the control. Interestingly, increasing $\alpha_{\text{mut}}$ appears to offset the competitive disadvantage of $M$ cells versus $N$ cells to a certain extent; had continuous therapy been provided from the start of treatment, the expected recurrence of disease would have occurred only two months sooner as compared to rapid cycling therapy. In contrast, decreasing $\alpha_{\text{mut}}$ by 50% is predicted to increase the time of rapid cycling therapy efficacy by five months as compared to the control case. If the patient is put on continuous treatment at this point, the expected disease free survival time is three months longer. As in the control case, had continuous therapy been provided from the start of treatment, the expected recurrence of disease would have occurred five months sooner than in the rapid cycling case.

Fig. S1. (A) Male Sprague Dawley rats were castrated as described in ref. 1 and given finasteride + various doses of testosterone for four days, at the end of which intraprostatic testosterone and ventral prostate weights were measured and recorded versus corresponding values of serum testosterone. Experimental data is indicated in black squares, while the best fit is shown in a solid line. The dotted line shows androgen levels in a prostate at homeostasis. (B) Fitted proliferation and death rates (in per hour) of prostatic epithelial cells as a function of testosterone-activated androgen receptor concentration (in nM). (C) The ventral prostate weight values reported in ref. 1 are used to fit proliferation and apoptosis rates for healthy prostatic epithelial cells. The dotted line shows typical epithelial cell numbers in a healthy ventral prostate at homeostasis and black squares represent experimental data.

Fig. S2. (A) Male Sprague Dawley rats were castrated as described in Wright et al. (1) and given various doses of testosterone for four days, at the end of which intraprostatic DHT and ventral prostate weights were measured and recorded versus corresponding values of serum testosterone. Experimental data is indicated in black squares, while the best fit is shown in a solid line. The dotted line shows androgen levels in a prostate at homeostasis. (B) Fitted proliferation and death rates (in per hour), of prostatic epithelial cells as a function of DHT- and testosterone-activated androgen receptor concentration (in nM). (C) The ventral prostate weight values reported in Wright et al. (1) are used to fit proliferation and apoptosis rates for healthy prostatic epithelial cells. The dotted line shows typical epithelial cell numbers in a healthy ventral prostate at homeostasis and black squares represent experimental data.

Fig. S3. (A) Fit to changes in prostatic volume versus age taken from ref. 1. Values represent mean and standard deviation. (B) Fit to changes in serum testosterone versus age, taken from ref. 2. Values represent mean and standard deviation. (C) Fit to average PSA levels versus age, data taken from ref. 3. Values represent mean and standard deviation for men with noncancerous prostate.

Testosterone concentration can be converted from ng/g heavy prostate has been determined by observing that its molecular weight is 288.43 and the density of a prostate is 1.0 g/mL.

The number of cells corresponding to a particular weight of prostate can be estimated by fixing our reference as a rat ventral prostate volume of 219 mm³.

Table S1. Parameter values from literature review

<table>
<thead>
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<th>Parameter</th>
<th>Name</th>
<th>Value</th>
<th>Units</th>
<th>Source</th>
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</thead>
<tbody>
<tr>
<td>$V_C$</td>
<td>epithelial cell volume</td>
<td>$5.56 \times 10^{-6}$</td>
<td>mm³</td>
<td>(1)</td>
</tr>
<tr>
<td>$P_{V}^{n}$</td>
<td>rat ventral prostate volume</td>
<td>600</td>
<td>mm³</td>
<td>(1)</td>
</tr>
<tr>
<td>$E_r^{n}$</td>
<td>rat ventral prostatic epithelial volume</td>
<td>219</td>
<td>mm³</td>
<td>(1)</td>
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<tr>
<td>$k_I$</td>
<td>T:AR association rate</td>
<td>0.14</td>
<td>nM⁻¹·hour⁻¹</td>
<td>(2)</td>
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<tr>
<td>$k_D$</td>
<td>DHT:AR association rate</td>
<td>0.053</td>
<td>nM⁻¹·hour⁻¹</td>
<td>(2)</td>
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<tr>
<td>$\lambda$</td>
<td>AR dissociation rate</td>
<td>0.018</td>
<td>hour⁻¹</td>
<td>(2)</td>
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<tr>
<td>$\lambda_{RN}$</td>
<td>AR decay rate in $E$, $N$ cells</td>
<td>(li/2) /3</td>
<td>hour⁻¹</td>
<td>(3)</td>
</tr>
<tr>
<td>$\lambda_{MN}$</td>
<td>AR decay rate in $M$ cells</td>
<td>(li/2) /6</td>
<td>hour⁻¹</td>
<td>(4)</td>
</tr>
<tr>
<td>$\lambda_{AR}$</td>
<td>DHT-activated AR decay rate in $E$, $N$ cells</td>
<td>(li/2) /12</td>
<td>hour⁻¹</td>
<td>(4, 5)</td>
</tr>
<tr>
<td>$\lambda_{AR}$</td>
<td>DHT-activated AR decay rate in $M$ cells</td>
<td>(li/2) /24*</td>
<td>hour⁻¹</td>
<td>(4, 5)</td>
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<tr>
<td>$\lambda_D$</td>
<td>DHT decay rate</td>
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<td>hour⁻¹</td>
<td>(3)</td>
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<tr>
<td>$\lambda_P$</td>
<td>PSA clearance rate from serum</td>
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<td>hour⁻¹</td>
<td>(6)</td>
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<tr>
<td>$\lambda_P$</td>
<td>PSA decay rate in tissue</td>
<td>(li/2) /12.3</td>
<td>hour⁻¹</td>
<td>(7, 8)</td>
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</table>

*DHT is reported to induce a twofold to sixfold stabilization in androgen receptors, and we take an average value of fourfold greater stability.


Table S2. Experimental data from ref. 1

<table>
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<tr>
<th>$T_4$ (nM)</th>
<th>Prostate weight (g)</th>
<th>Testosterone (ng/g)</th>
<th>Testosterone (nM) *</th>
<th>Number of cells (millions) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.206</td>
<td>0.4</td>
<td>1.37</td>
<td>18.09</td>
</tr>
<tr>
<td>0.345</td>
<td>0.227</td>
<td>1.8</td>
<td>6.12</td>
<td>19.93</td>
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<tr>
<td>1.379</td>
<td>0.314</td>
<td>7.2</td>
<td>24.46</td>
<td>27.57</td>
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<tr>
<td>4.103</td>
<td>0.343</td>
<td>10.0</td>
<td>33.98</td>
<td>30.11</td>
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<tr>
<td>6.138</td>
<td>0.382</td>
<td>13.8</td>
<td>46.89</td>
<td>33.53</td>
</tr>
<tr>
<td>12.100</td>
<td>0.449</td>
<td>21.2</td>
<td>72.03</td>
<td>39.42</td>
</tr>
<tr>
<td>15.448</td>
<td>0.470</td>
<td>26.0</td>
<td>88.34</td>
<td>41.26</td>
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</table>

<table>
<thead>
<tr>
<th>$T_4$ (nM)</th>
<th>Prostate weight (g)</th>
<th>DHT (ng/g)</th>
<th>DHT (nM) *</th>
<th>Number of cells (millions) *</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>0.217</td>
<td>0.45</td>
<td>1.69</td>
<td>19.14</td>
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<td>0.110</td>
<td>0.277</td>
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<td>7.76</td>
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<tr>
<td>0.683</td>
<td>0.418</td>
<td>6.9</td>
<td>23.28</td>
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<td>0.828</td>
<td>0.449</td>
<td>8.2</td>
<td>27.66</td>
<td>39.42</td>
</tr>
<tr>
<td>0.814</td>
<td>0.413</td>
<td>9.9</td>
<td>33.40</td>
<td>36.27</td>
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<tr>
<td>3.767</td>
<td>0.541</td>
<td>12.7</td>
<td>42.85</td>
<td>47.50</td>
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</table>

*Testosterone concentration can be converted from ng/g to nM by observing that its molecular weight is 288.43 and the density of a prostate is 0.98 g/mL (1).

The number of cells corresponding to a particular weight of prostate can be estimated by fixing our reference as a 0.449 g heavy prostate has 39.42 x 10⁶ cells.

The method of lines is used to estimate the volume of $T_4$ needed to maintain a prostate at homeostasis, from the data in ref. 2.

Table S3. Estimated parameter values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Units</th>
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<tbody>
<tr>
<td>r₀</td>
<td>90</td>
<td>nM</td>
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<tr>
<td>a₀TS</td>
<td>49.13</td>
<td>nM Testosterone per hour</td>
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<tr>
<td>b₀TS</td>
<td>22.23</td>
<td>nM Testosterone</td>
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<tr>
<td>c₀TS</td>
<td>0.23</td>
<td>nM Testosterone per hour</td>
</tr>
<tr>
<td>q₁ET</td>
<td>0.01</td>
<td>per hour</td>
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<tr>
<td>q₂ET</td>
<td>30.26</td>
<td>nM Activated AR</td>
</tr>
<tr>
<td>q₆E</td>
<td>0</td>
<td>dimensionless</td>
</tr>
<tr>
<td>q₇E/q₈E</td>
<td>0.0083</td>
<td>per hour</td>
</tr>
<tr>
<td>λ₄AET</td>
<td>ln(2)/3</td>
<td>per hour</td>
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<tr>
<td>E₀</td>
<td>55.12</td>
<td>million cells</td>
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<tr>
<td>β₇T</td>
<td>4.569</td>
<td>nM Testosterone/DHT per hour</td>
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<tr>
<td>K₇T</td>
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<td>nM Testosterone</td>
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<tr>
<td>q₉₁</td>
<td>0.009</td>
<td>per hour</td>
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<tr>
<td>q₉₂</td>
<td>8.789</td>
<td>nM Activated AR</td>
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<tr>
<td>q₉₃</td>
<td>0.925</td>
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</tr>
<tr>
<td>q₉₄</td>
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Table S4. Estimated parameter values

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<tr>
<td>q₂ET</td>
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<tr>
<td>q₃ET</td>
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<td>q₅ET</td>
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<td>q₆ET</td>
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<td>q₇ET</td>
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<tr>
<td>aᵥ</td>
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<td>bᵥ</td>
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<td>cᵥ</td>
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<td>cm³</td>
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<td>dᵥ</td>
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<td>cₑ</td>
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Table S5. Estimated personalized parameter values for case study 1

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<td>$r_M^0$</td>
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<tr>
<td>$\beta_{PM}$</td>
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<td>per nM per hour</td>
</tr>
<tr>
<td>$q_C^N$</td>
<td>22.4</td>
<td>cell number in billions</td>
</tr>
<tr>
<td>$q_N^1$</td>
<td>$10.480 \times 10^{-4}$</td>
<td>per hour</td>
</tr>
<tr>
<td>$q_M^1$</td>
<td>$11.100 \times 10^{-4}$</td>
<td>per hour</td>
</tr>
<tr>
<td>$q_C^N$</td>
<td>0.150</td>
<td>nM activated AR per hour</td>
</tr>
</tbody>
</table>

Parameters for Mutant Cell with Average Phenotype:
- $q_M^1$ : $0.980 \times 10^{-4}$ per hour
- $q_M^3$ : $0.010$ nM activated AR per hour
- $\alpha_{mut}$ : $1 \times 10^{-4}$ dimensionless
- $\gamma_P$ : $3.125 \times 10^{-4}$ per million cells per hour
- $K_P$ : 800 cell number in billions

Parameters for Mutant Cell with Aggressive Phenotype:
- $q_M^1$ : $1.696 \times 10^{-4}$ per hour
- $q_M^3$ : $4.821 \times 10^{-4}$ per hour
- $\alpha_{mut}$ : $1 \times 10^{-7}$ dimensionless

Table S6. Estimated personalized parameter values for case study 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_{PN}$</td>
<td>0.002</td>
<td>per nM per hour</td>
</tr>
<tr>
<td>$\beta_{PM}$</td>
<td>0.003</td>
<td>per nM per hour</td>
</tr>
<tr>
<td>$q_N^3$</td>
<td>0.105</td>
<td>nM activated AR per hour</td>
</tr>
<tr>
<td>$q_M^1$</td>
<td>$2.266 \times 10^{-4}$</td>
<td>per hour</td>
</tr>
<tr>
<td>$q_M^3$</td>
<td>$6.6445 \times 10^{-4}$</td>
<td>per hour</td>
</tr>
<tr>
<td>$q_C^N$</td>
<td>0.009</td>
<td>nM activated AR per hour</td>
</tr>
<tr>
<td>$\alpha_{mut}$</td>
<td>$1 \times 10^{-3}$</td>
<td>dimensionless</td>
</tr>
<tr>
<td>$\gamma_P$</td>
<td>$0.6 \times 10^{-4}$</td>
<td>per million cells per hour</td>
</tr>
<tr>
<td>$K_P$</td>
<td>7</td>
<td>cell number in billions</td>
</tr>
<tr>
<td>$\theta$</td>
<td>3</td>
<td>dimensionless</td>
</tr>
</tbody>
</table>