Quantitative Personalized Oncology

Heiko Enderling, Ph.D.

Associate Professor

Department of Integrated Mathematical Oncology
Department of Radiation Oncology

H. Lee Moffitt Cancer Center & Research Institute
Tampa, FL USA

heiko.enderling@moffitt.org
http://lab.moffitt.org/enderling

@EnderlingLab

OK to share

Conflicts of interest

No financial conflict of interest to disclose.

I will be discussing research for which provisional patent applications have been filed on which I am listed inventor.

- U.S. Patent 62/944,804: Methods for prostate cancer intermittent adaptive therapy (provisional)
- U.S. Patent 63/010,327: Forecasting individual patient response to radiotherapy with a dynamic carrying capacity model (provisional)

Quantitative Personalized Oncology

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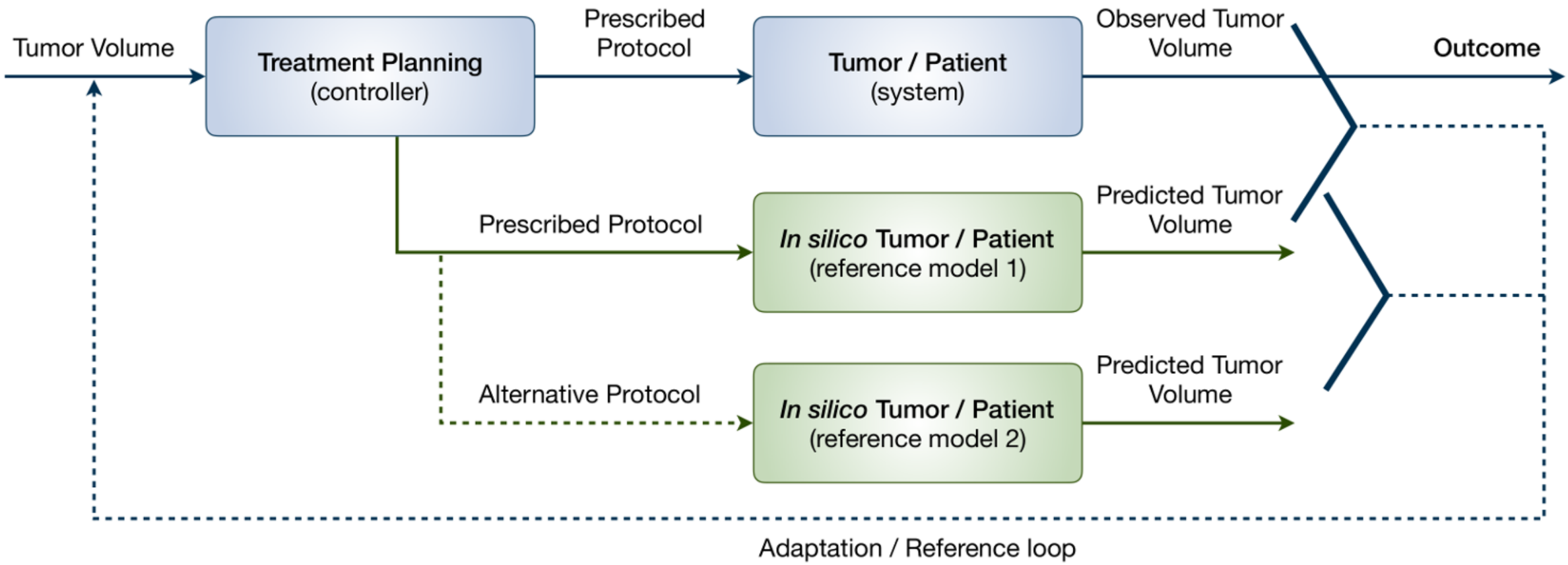
Mission: To integrate quantitative modeling into oncology decision making

Vision: Optimal adaptive cancer therapy for each patient

Strategy: - understand clinical needs
- foster synergistic collaborations
- build calibrated and validated mathematical models of cancer dynamics that provide
    - dynamic biomarkers *and*
    - actionable triggers for treatment personalization

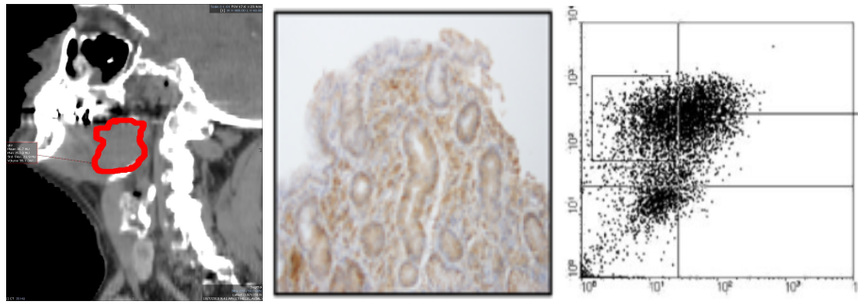
Treatment pipeline



Enderling et al., Trends In Cancer, 2019

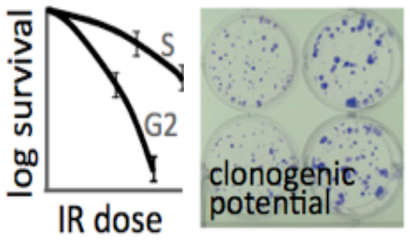
Quantitative Personalized Oncology

Patient-specific clinical data

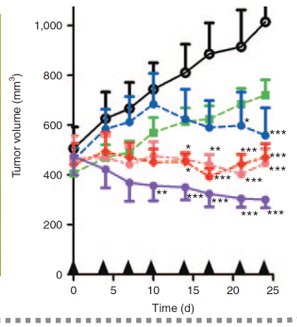


Preclinical studies

in vitro



in vivo



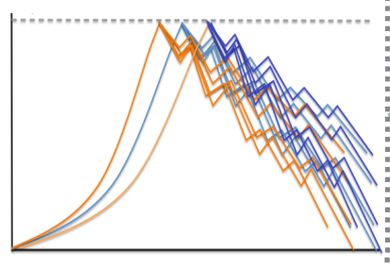
develop

calibrate

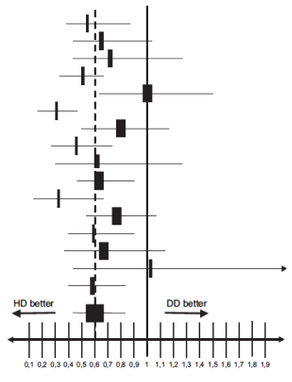
validate

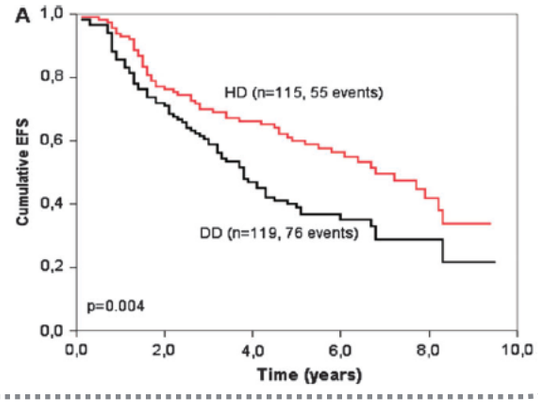
Mathematical model

$$dV = -kV\,dt$$
$$\int \frac{1}{V}\,dV = \int -k\,dt$$



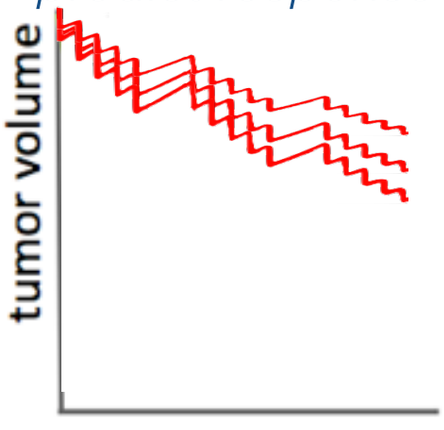
Historic clinical data



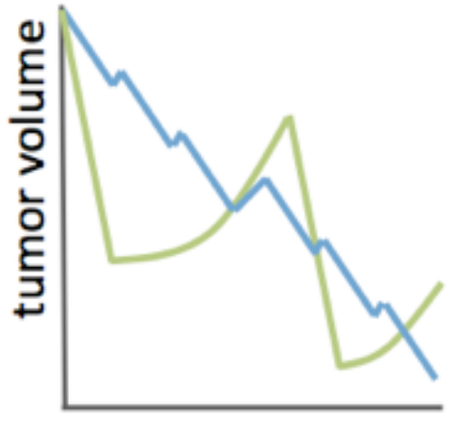


Virtual patient

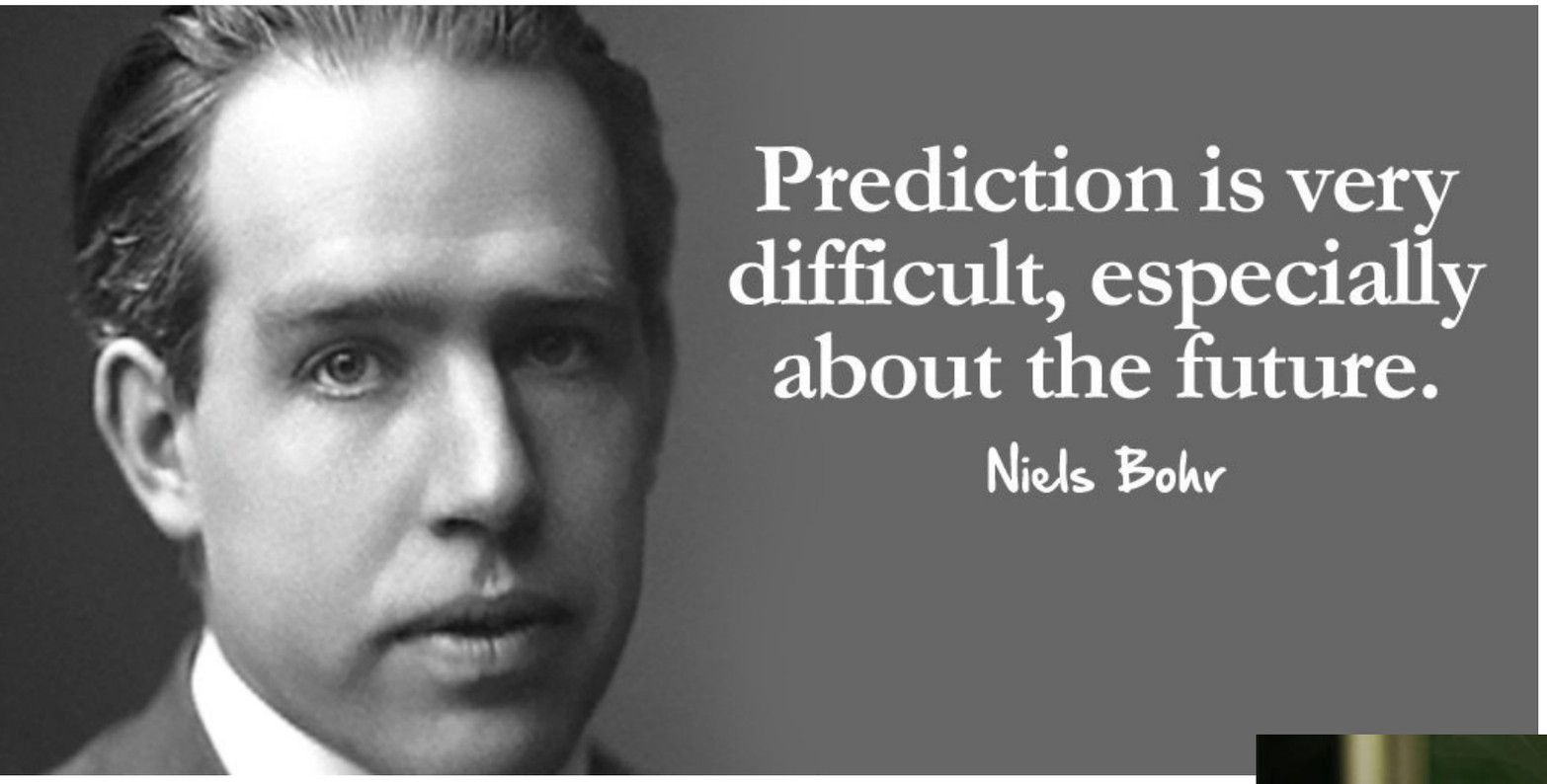
predict response



in silico trials



Aherne et al. (Enderling), Oral Oncol, 2020

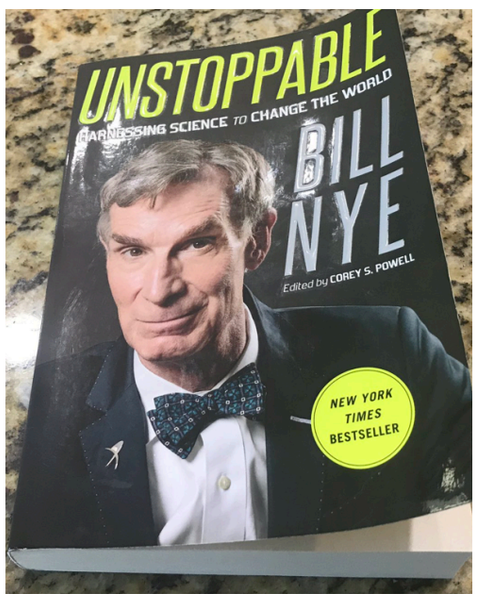


..our ability to predict the future is severely limited by the complexity of the equations…

Stephen Hawking

Predictive modeling standard

identify putative biomarker → develop mechanistic model → calibrate model with existing data → validate model with untrained data → evaluate predictive performance for known treatment → simulate and predict unknown treatment

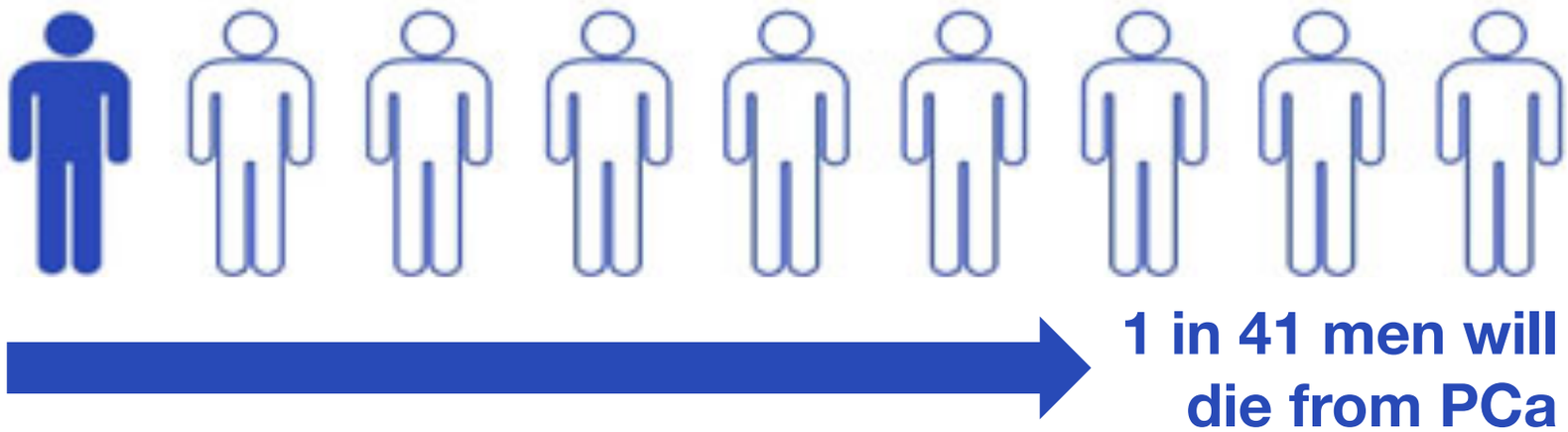


- "A climate computer model is not trusted unless it can predict the past."
- "Any proposed set of statistics is not considered to be of any value unless it can be used to show outcomes of a past [baseball] season".

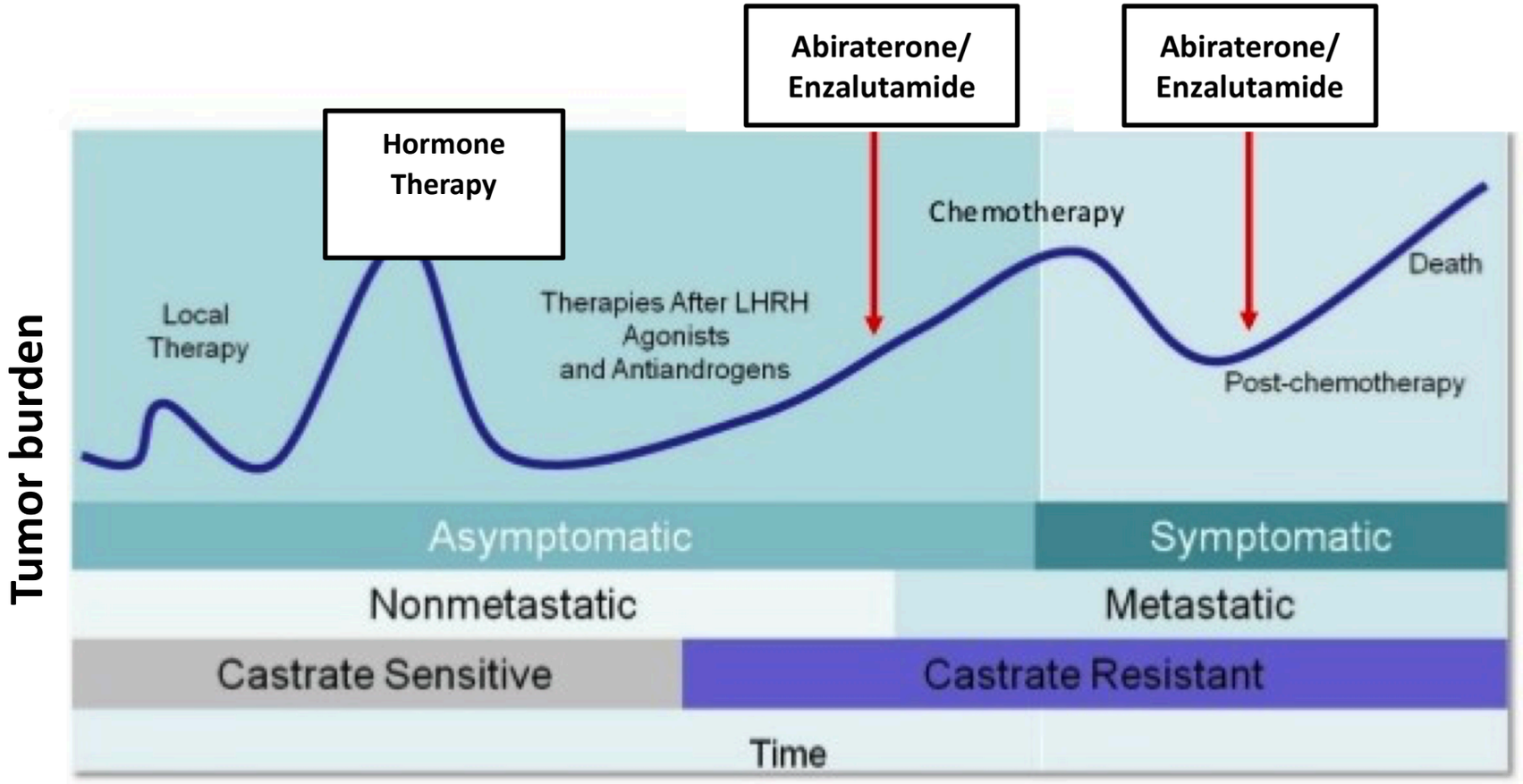
Brady & Enderling, Bull. Math. Biol., 2019

Prostate Cancer

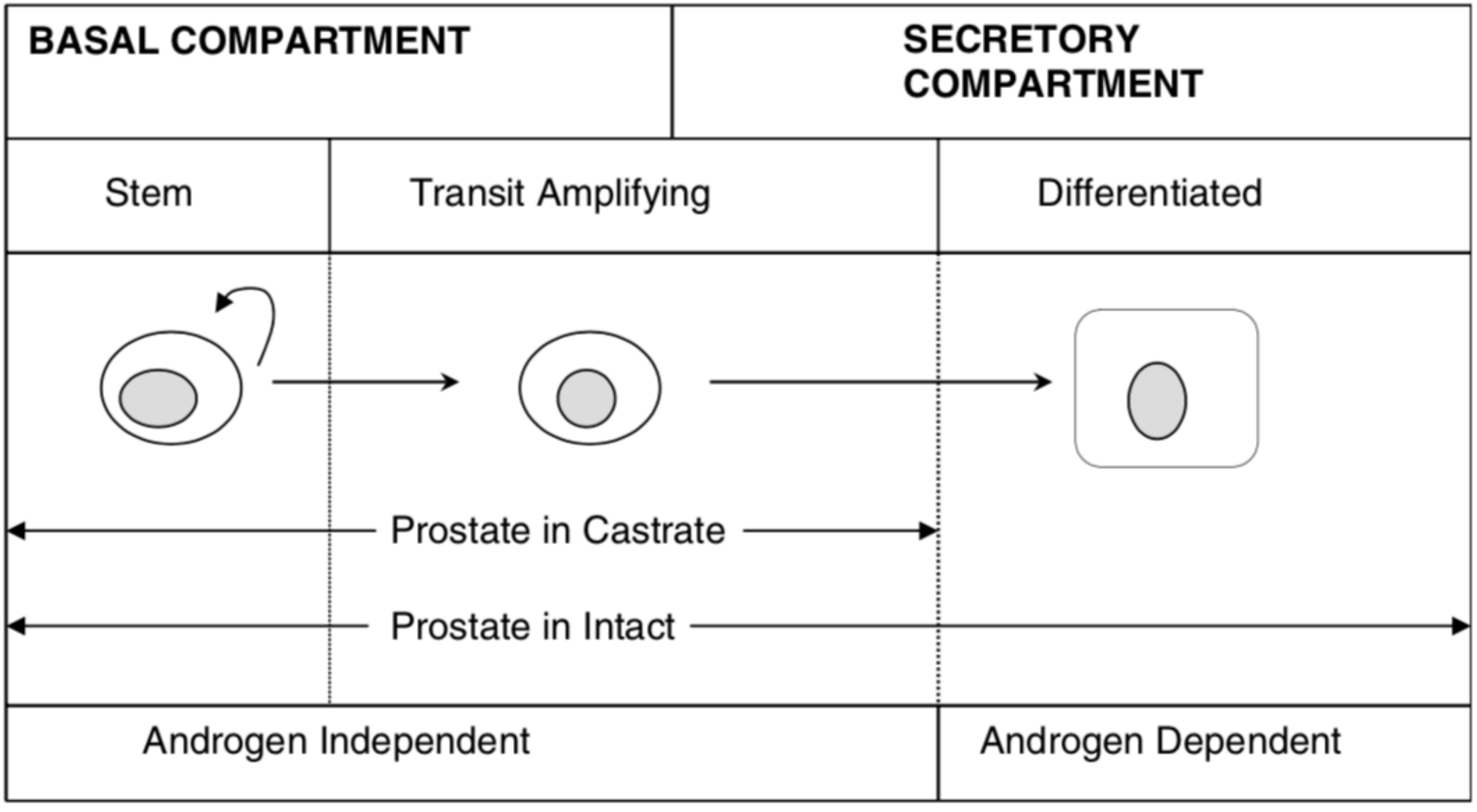
1 in 9 men diagnosed with PCa



1 in 41 men will die from PCa



Prostate Architecture

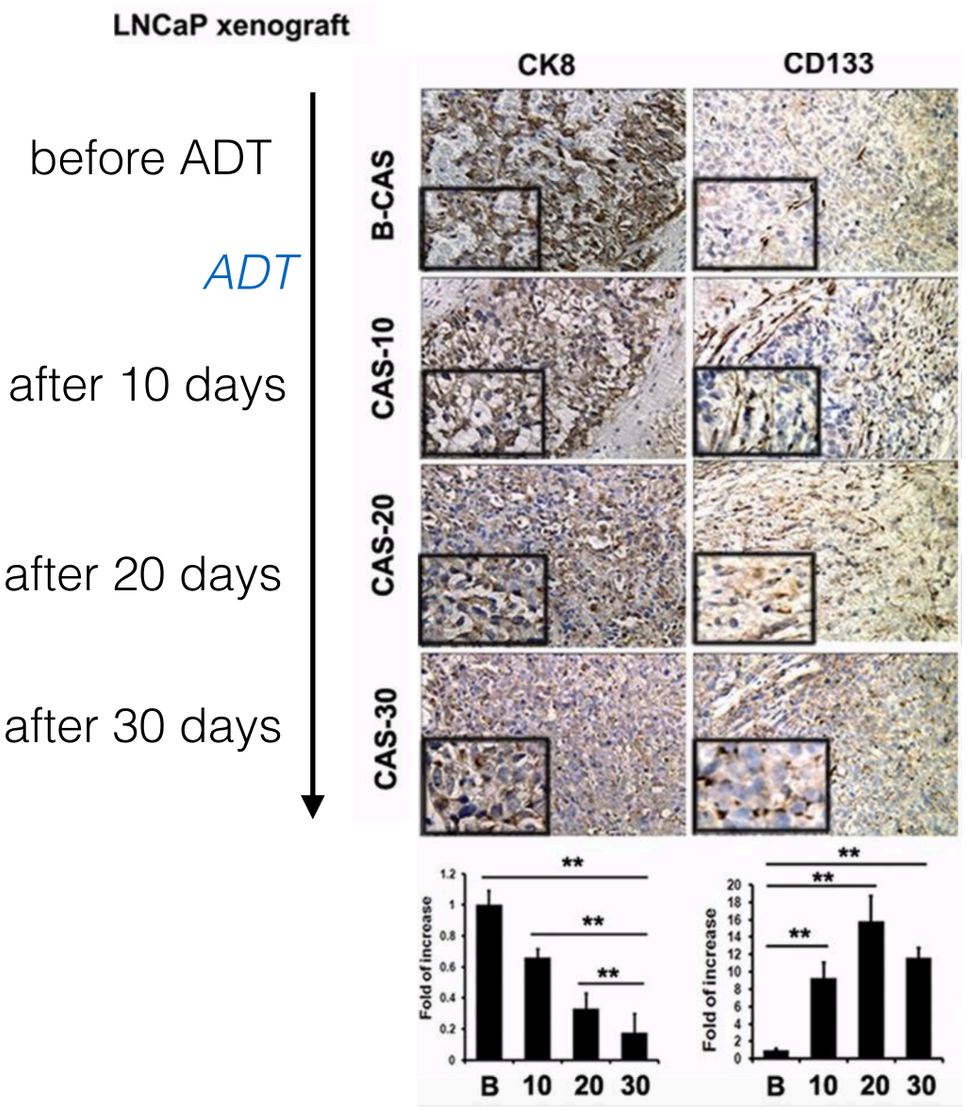


Isaacs & Coffey, Prostate, 1989

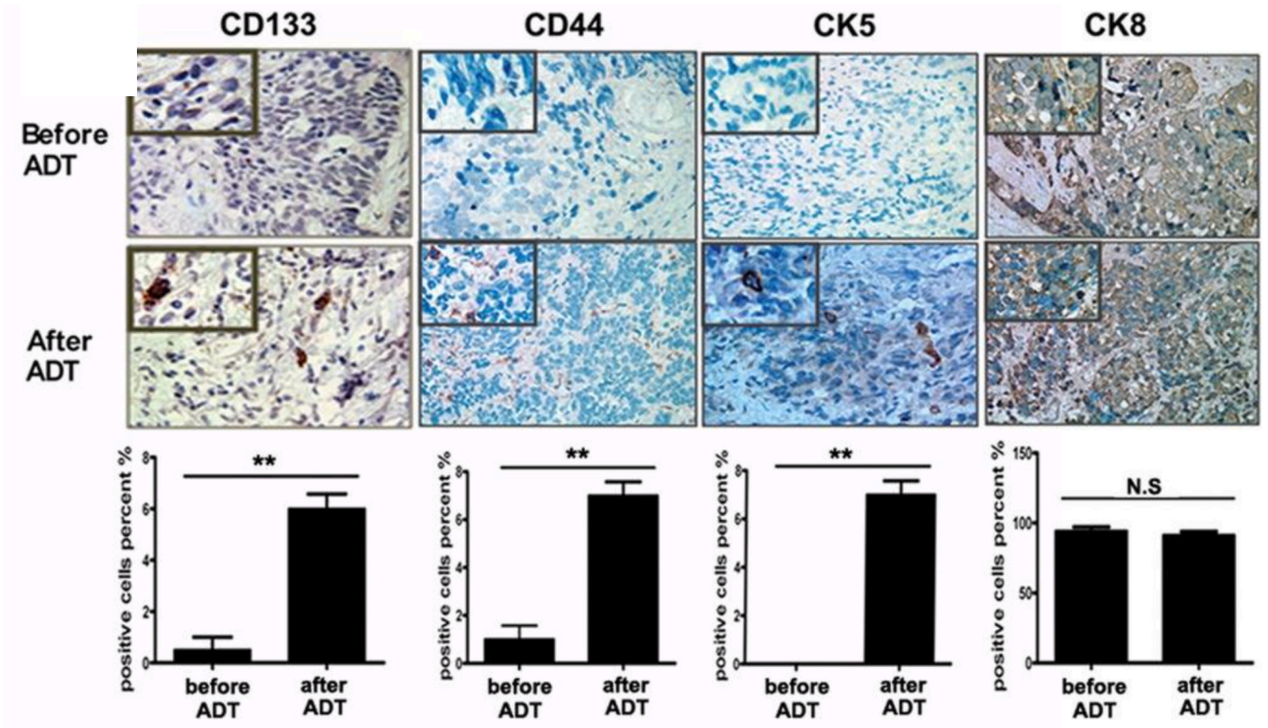
Prostate Cancer stem cells are treatment resistant

ADT: androgen deprivation therapy - chemical castration

mouse tissues

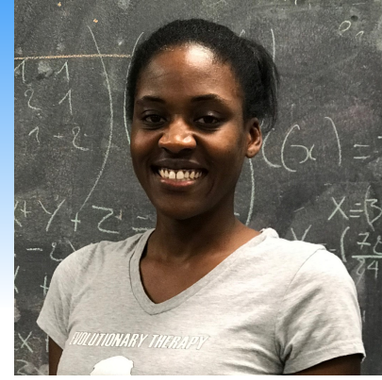


human tissues



Lee et al., J. Mol. Cell Biol., 2013

Research Questions



Dr. Renee Brady-Nicholls

- Does a PCaSC model fit clinical data ?
- Can early treatment response predict outcomes ?
- Can the model predict alternative treatment that would improve outcomes?

Intermittent Hormone Therapy

Cancer

Final Results of the Canadian Prospective Phase II Trial of Intermittent Androgen Suppression for Men in Biochemical Recurrence after Radiotherapy for Locally Advanced Prostate Cancer

Clinical Parameters

Nicholas Bruchovsky, MD, PhD[1]
Laurence Klotz, MD[2]
Juanita Crook, MD[3]
Shawn Malone, MD[4]
Charles Ludgate, MD[5]
W. James Morris, MD[5]
Martin E. Gleave, MD[1]
S. Larry Goldenberg, MD[1]

BACKGROUND. This prospective Phase II study was undertaken to evaluate intermittent androgen suppression as a form of therapy in men with localized prostate cancer who failed after they received external beam irradiation.

METHODS. Patients who demonstrated a rising serum prostate-specific antigen (PSA) level after they received radiotherapy and who were without evidence of distant metastasis were accepted into the study. Treatment in each cycle consisted of cyproterone acetate given as lead-in therapy for 4 weeks, followed by a combination of leuprolide acetate and cyproterone acetate, which ended after a total of 36 weeks.

Cancer **2006;107:389–95.**

- 103 patients with intermittent ADT
- PSA measurements every four weeks

PSA dynamics during ADT

identify putative biomarker

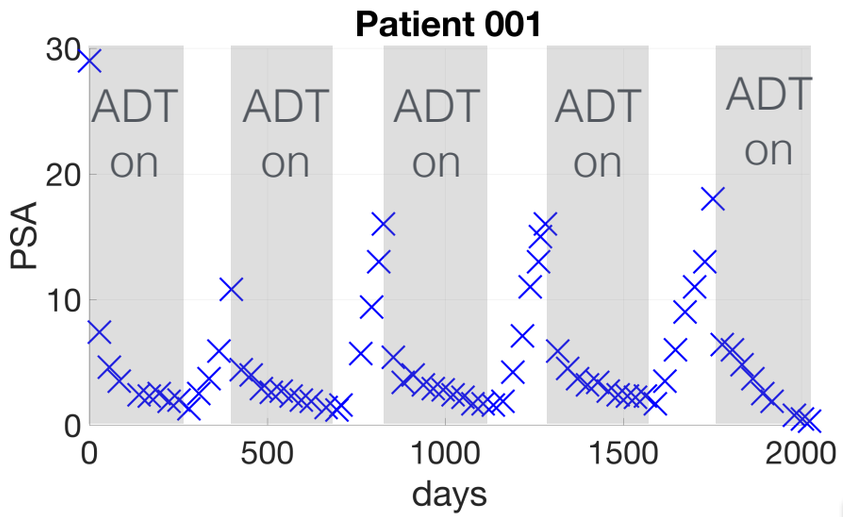
develop mechanistic model

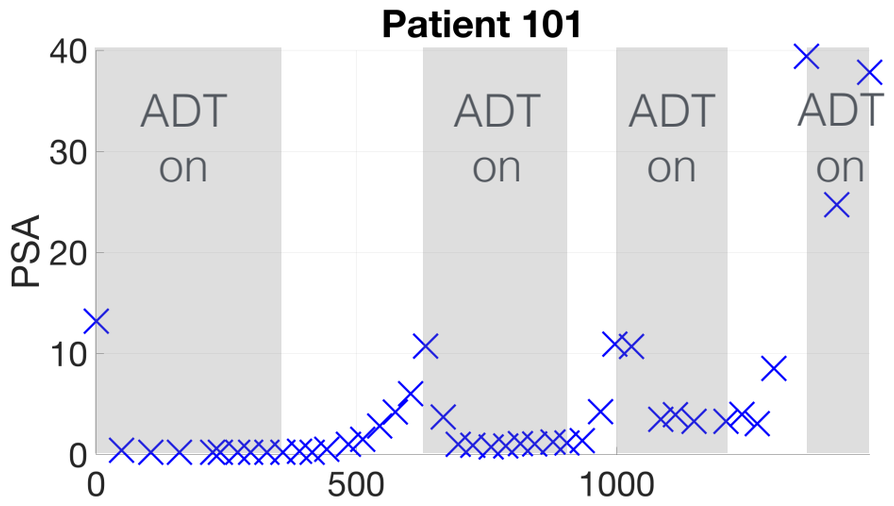
calibrate model with existing data

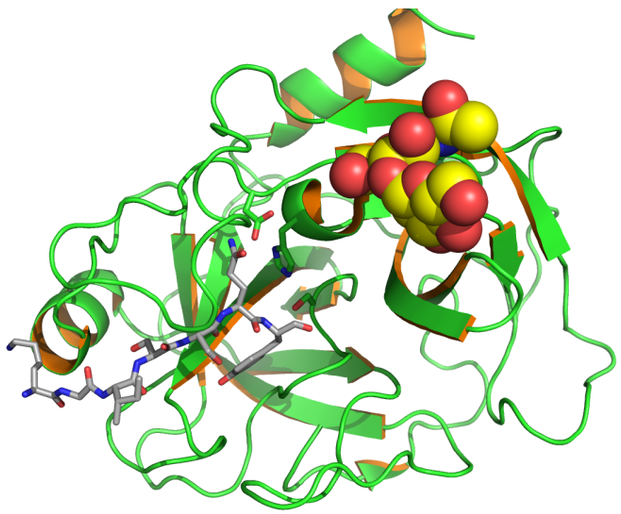
validate model with untrained data

evaluate predictive performance for known treatment

simulate and predict unknown treatment







Prostate specific antigen (PSA) wikipedia

COMMENTARY

J. STEPHEN JONES, MD
Vice Chairman, Glickman Urological and Kidney Institute, Cleveland Clinic

ERIC KLEIN, MD
Head, Section of Urological Oncology, Glickman Urological and Kidney Institute, Cleveland Clinic

Four no more: The 'PSA cutoff era' is over

PROSTATE-SPECIFIC ANTIGEN (PSA) testing has been mired in controversy throughout the short time it has been a clinical tool for detecting prostate cancer. During the first decade after it was approved for prostate cancer screening, the dogma prevailed that the upper limit of normal was 4.0 µg/L. Healthy patients with values above this cutoff were believed to be at risk of prostate cancer and were usually advised to undergo biopsy. Patients with levels below this threshold were told they had normal readings and were reassured that they did not have prostate cancer.

See related editorial, page 33

shown that many men with "normal" PSA values harbor prostate cancer. The most definitive was the Prostate Cancer Prevention Trial,[3,4] which found no PSA level below which prostate cancer can be ruled out, and no level above which prostate cancer is certain (FIGURE 1).

An individual patient's PSA value is only part of the equation. Other risk factors need to be considered, such as his age, race, family history, findings on digital rectal examination, prostate size, results of earlier prostate biopsies, percent free PSA ratio, and whether he takes a 5-alpha reductase inhibitor. Moreover, PSA levels in men who have undergone treatment for prostate cancer are completely independent of the reference ranges in widespread laboratory use, making such references and thresholds even more meaningless in this setting.

PSA is only one of the risk factors for prostate cancer

NO PSA VALUE RULES CANCER IN OR OUT

identify putative biomarker

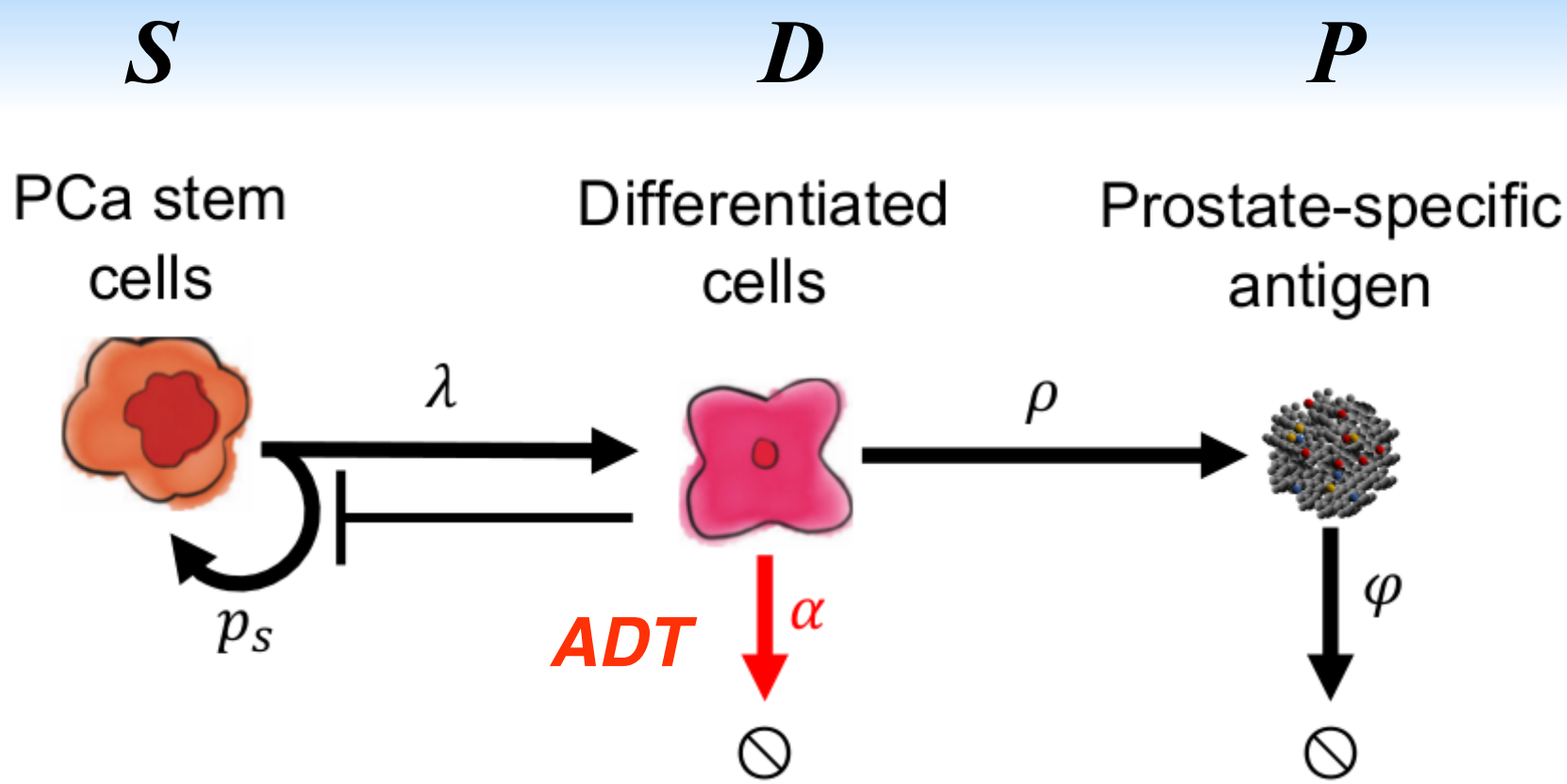
develop mechanistic model

calibrate model with existing data

validate model with untrained data

evaluate predictive performance for known treatment

simulate and predict unknown treatment



$$\frac{dS}{dt} = \left(\frac{S}{S+D}\right) p_s \lambda S$$

$$\frac{dD}{dt} = \left(1 - \frac{S}{S+D} p_s\right) \lambda S - \alpha T_x D$$

$$\frac{dP}{dt} = \rho D - \varphi P$$

5 parameters (p_s, λ, ρ, α, φ) that we can tune to fit the **model PSA dynamics** to **clinical PSA dynamics**

Brady-Nicholls et al., Nat. Commun. 2020

Intermittent Androgen Deprivation

identify putative biomarker

develop mechanistic model

calibrate model with existing data

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Final Results of the Canadian Prospective Phase II Trial of Intermittent Androgen Suppression for Men in Biochemical Recurrence after Radiotherapy for Locally Advanced Prostate Cancer

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Cancer

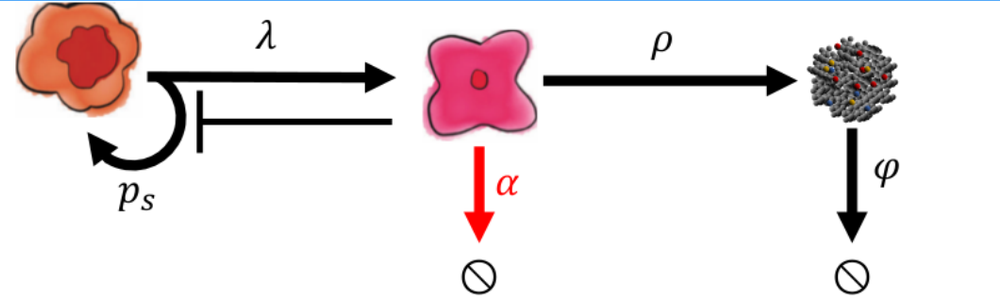
107(2), 389-395, 2006

Number of patients:	70
Total data points:	3,101
Avg. data points / patient:	43

Training Set

Test Set

Model training



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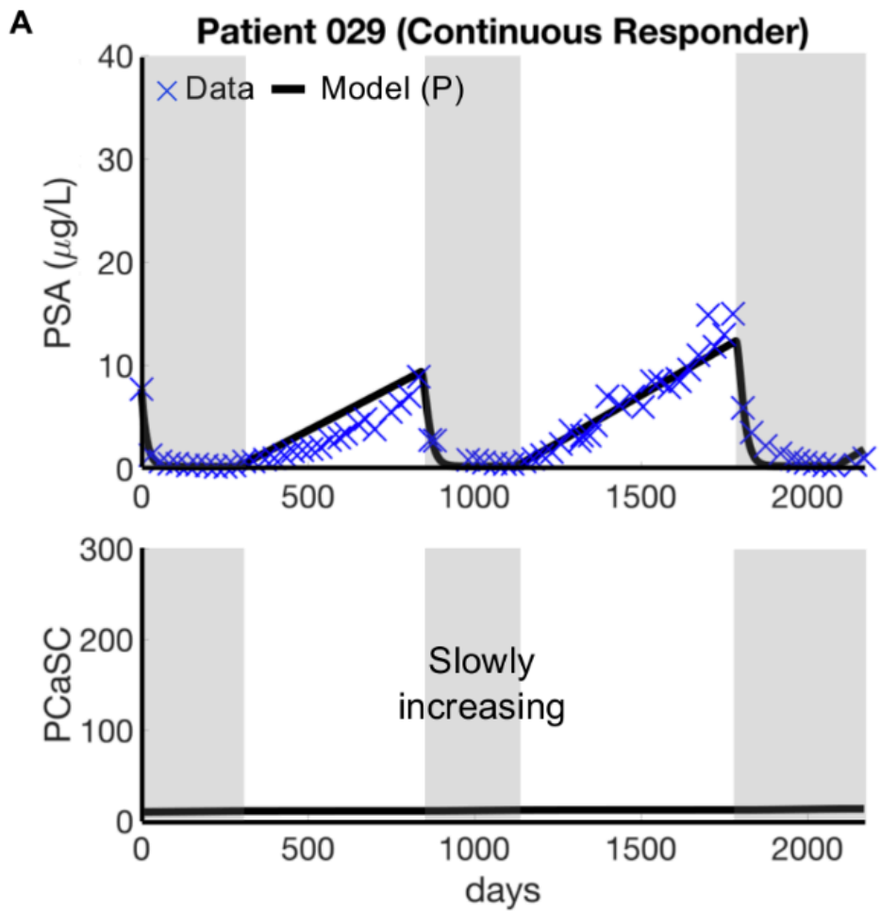
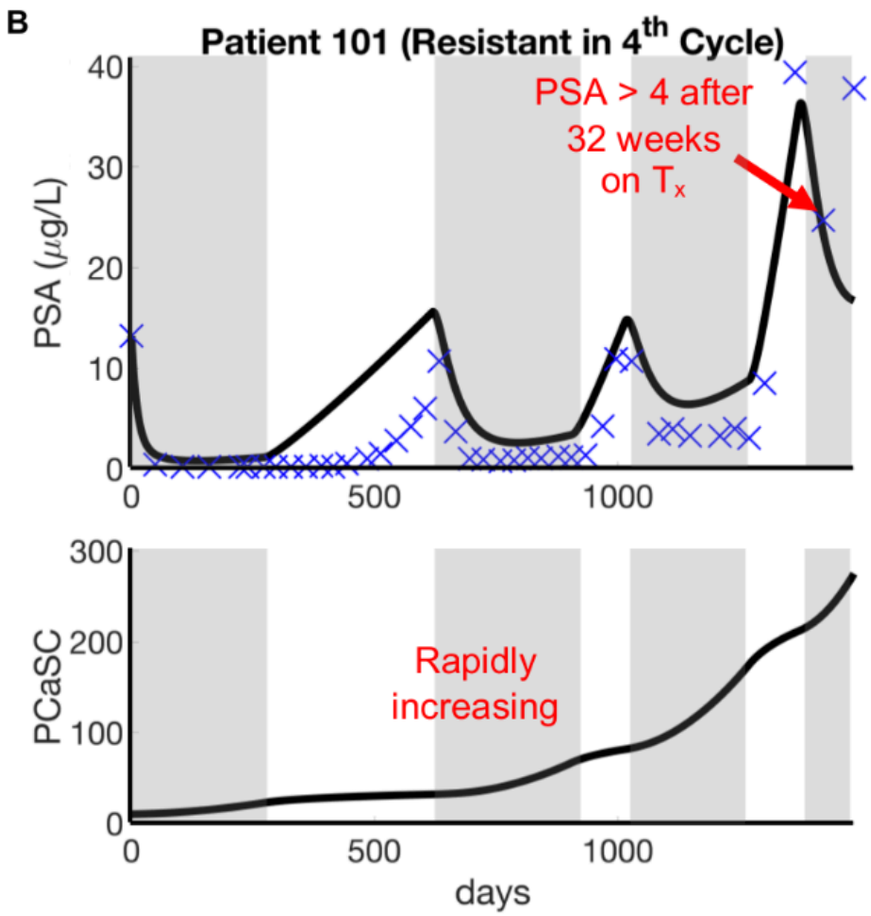
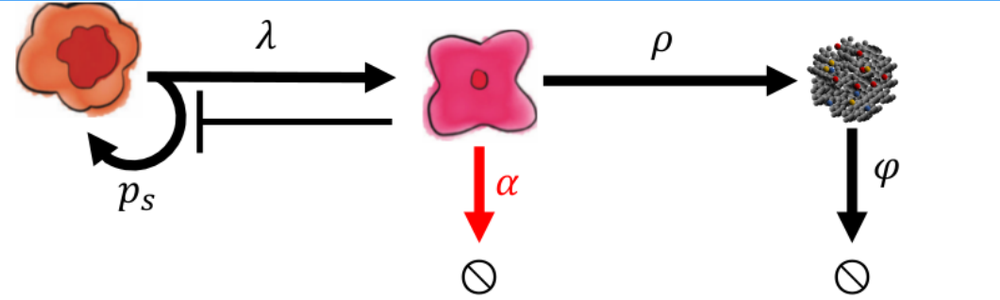




Brady-Nicholls et al., Nat. Commun. 2020

Model training



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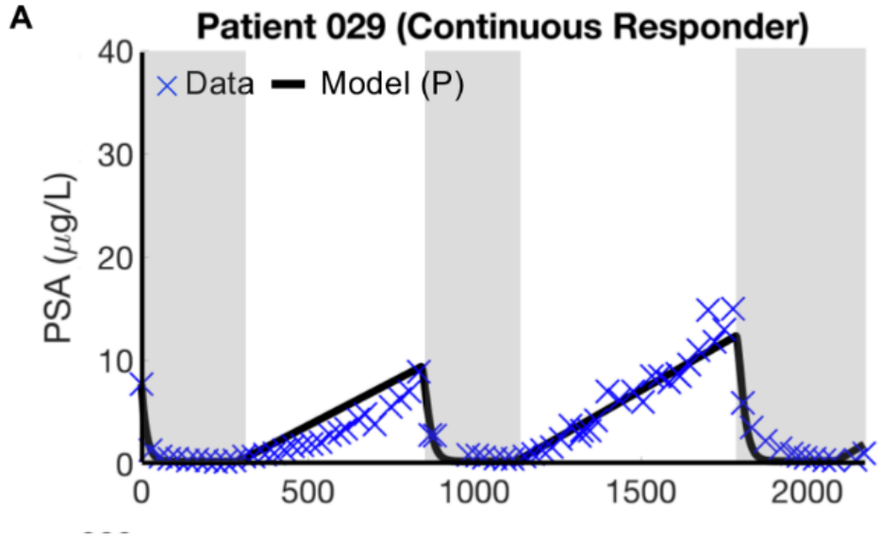
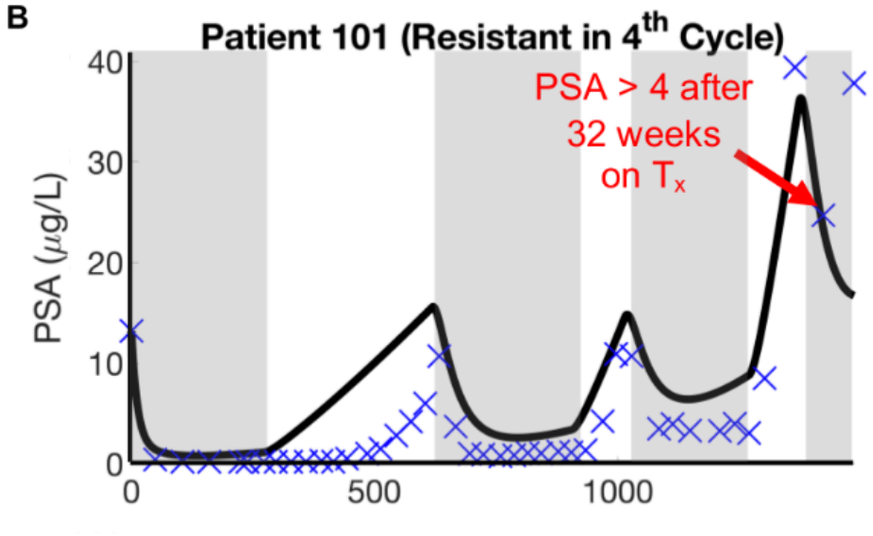
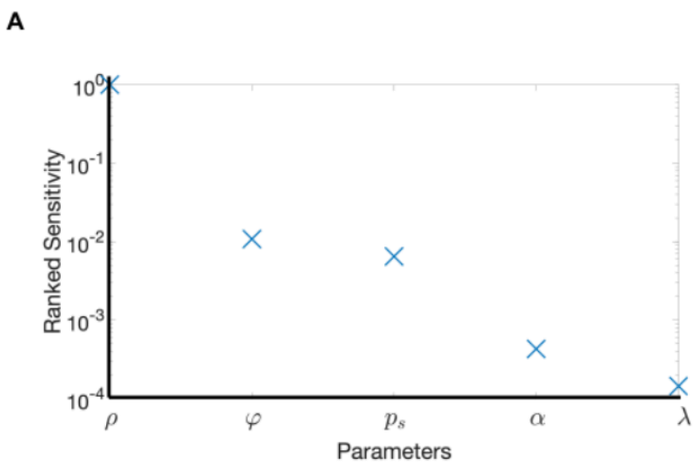
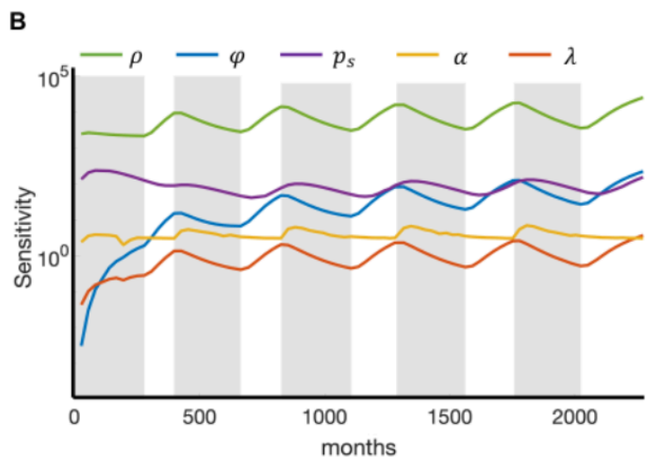
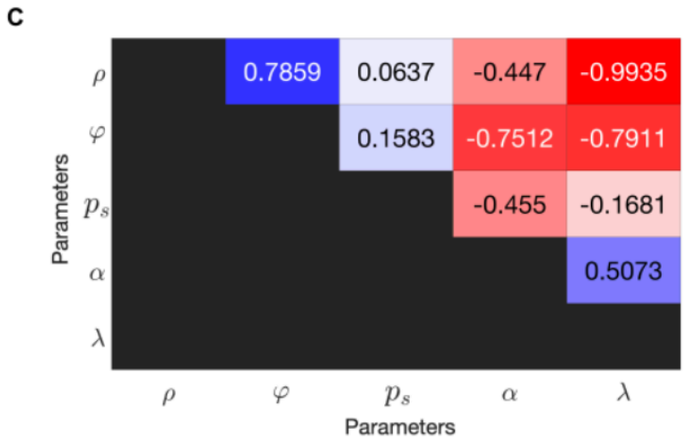
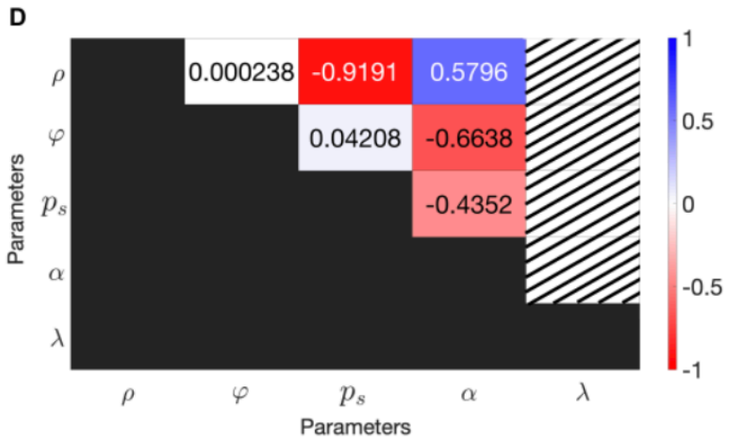


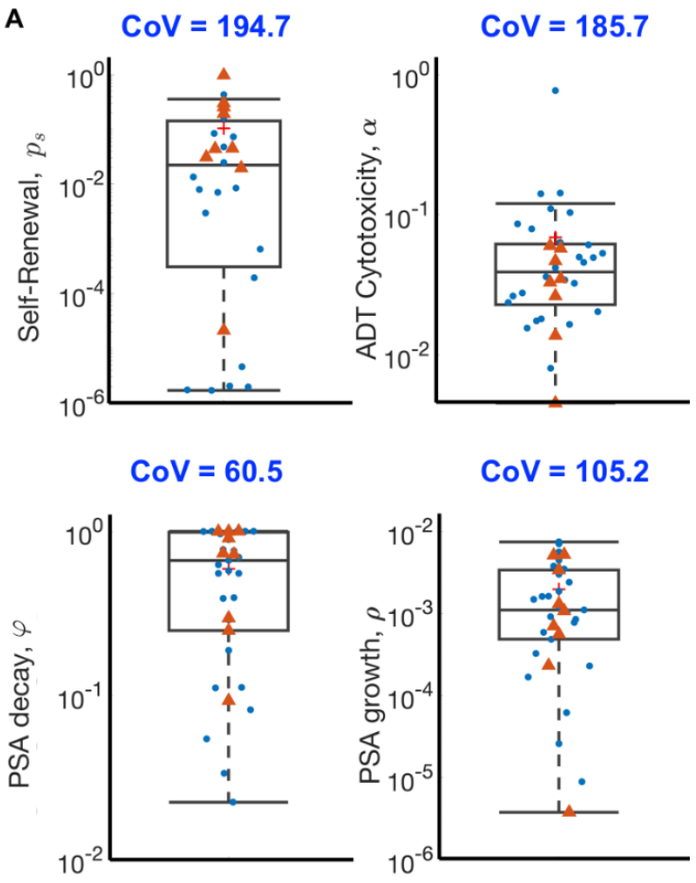








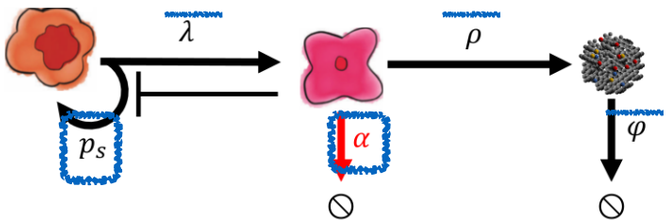


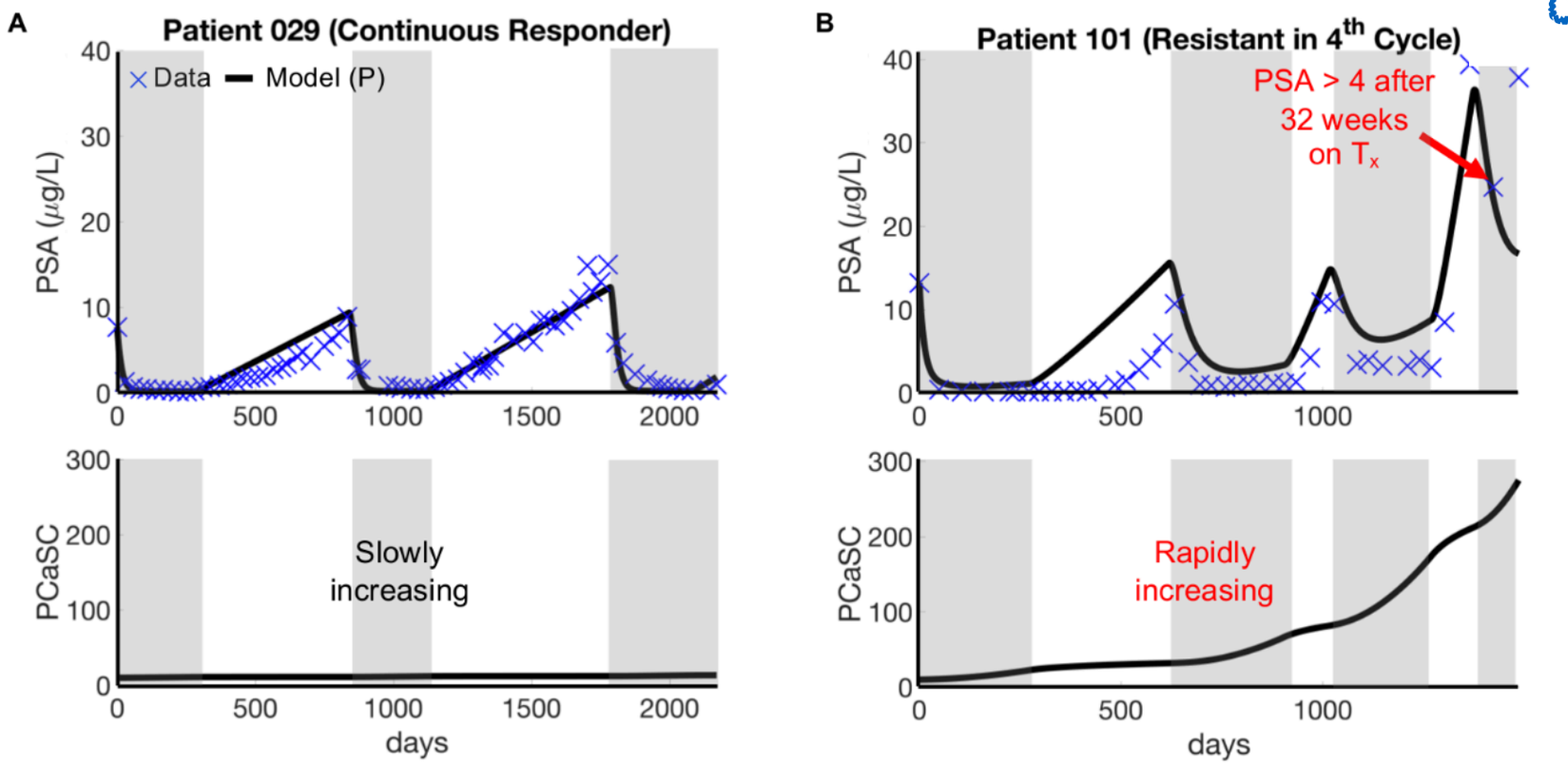


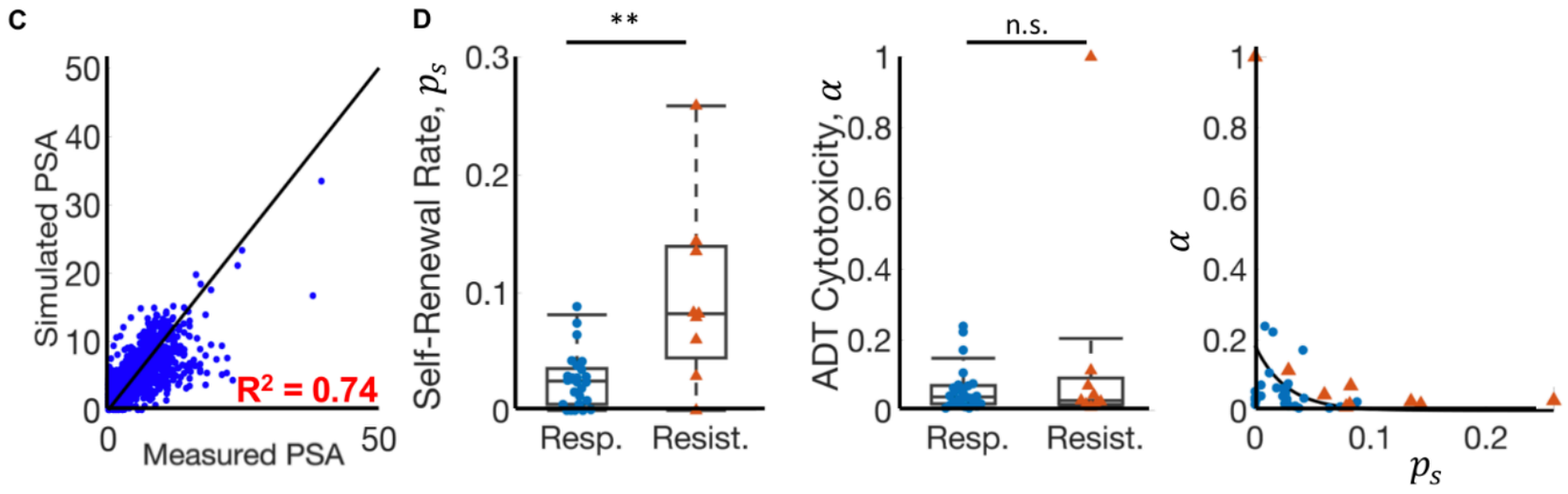
Brady-Nicholls et al., Nat. Commun. 2020

Simultaneous model training

- identify putative biomarker
- develop mechanistic model
- calibrate model with existing data
- validate model with untrained data
- evaluate predictive performance for known treatment
- simulate and predict unknown treatment







Brady-Nicholls et al., Nat. Commun. 2020

Model validation

- identify putative biomarker
- develop mechanistic model
- calibrate model with existing data
- validate model with untrained data
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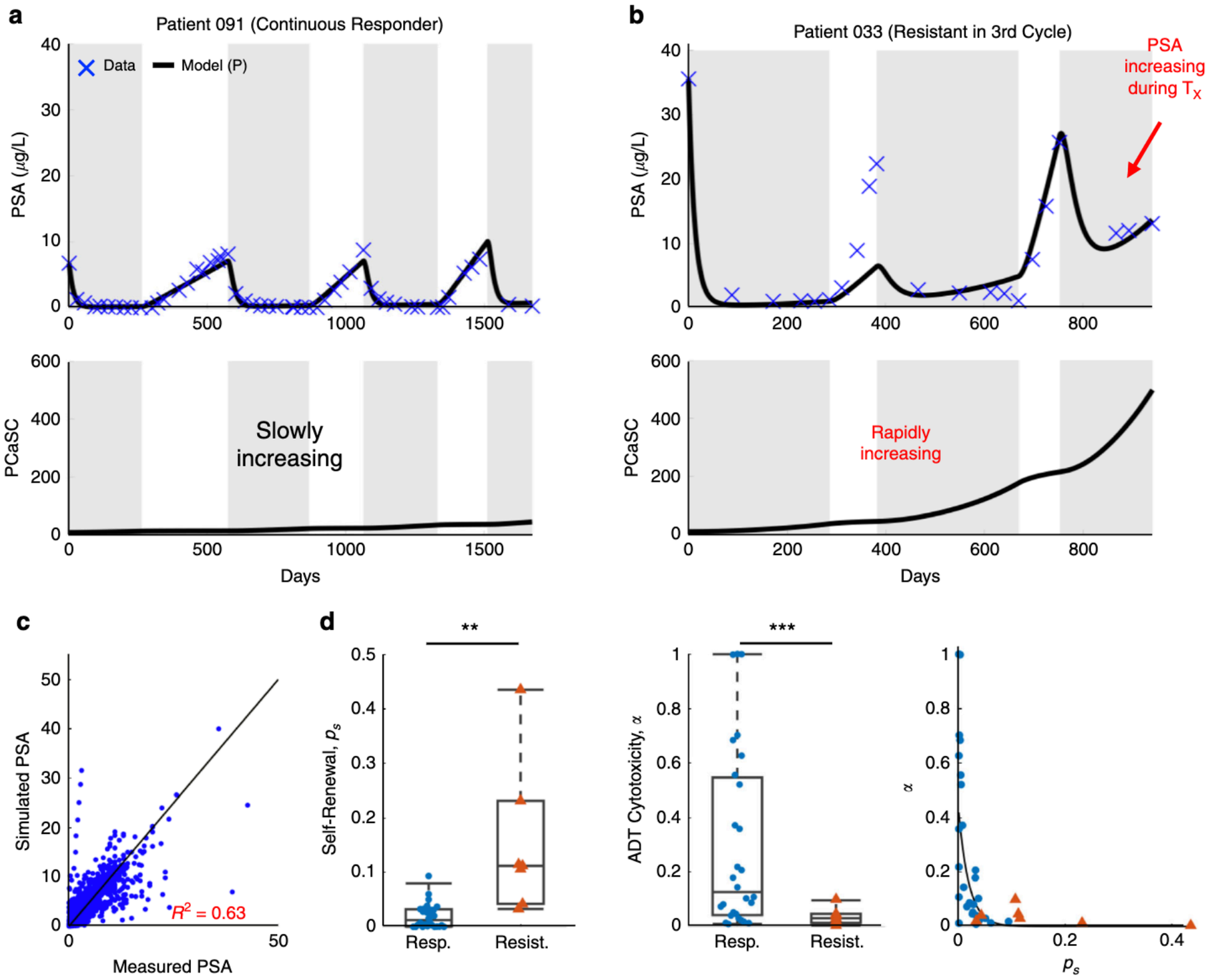

Brady-Nicholls et al., Nat. Commun. 2020

Research Questions

- Does a PCaSC model fit the data ?

- Can early treatment response predict outcomes ?
- Can the model predict alternative treatment that would improve outcomes?

‘Hurricane prediction model’

- identify putative biomarker
- develop mechanistic model
- calibrate model with existing data
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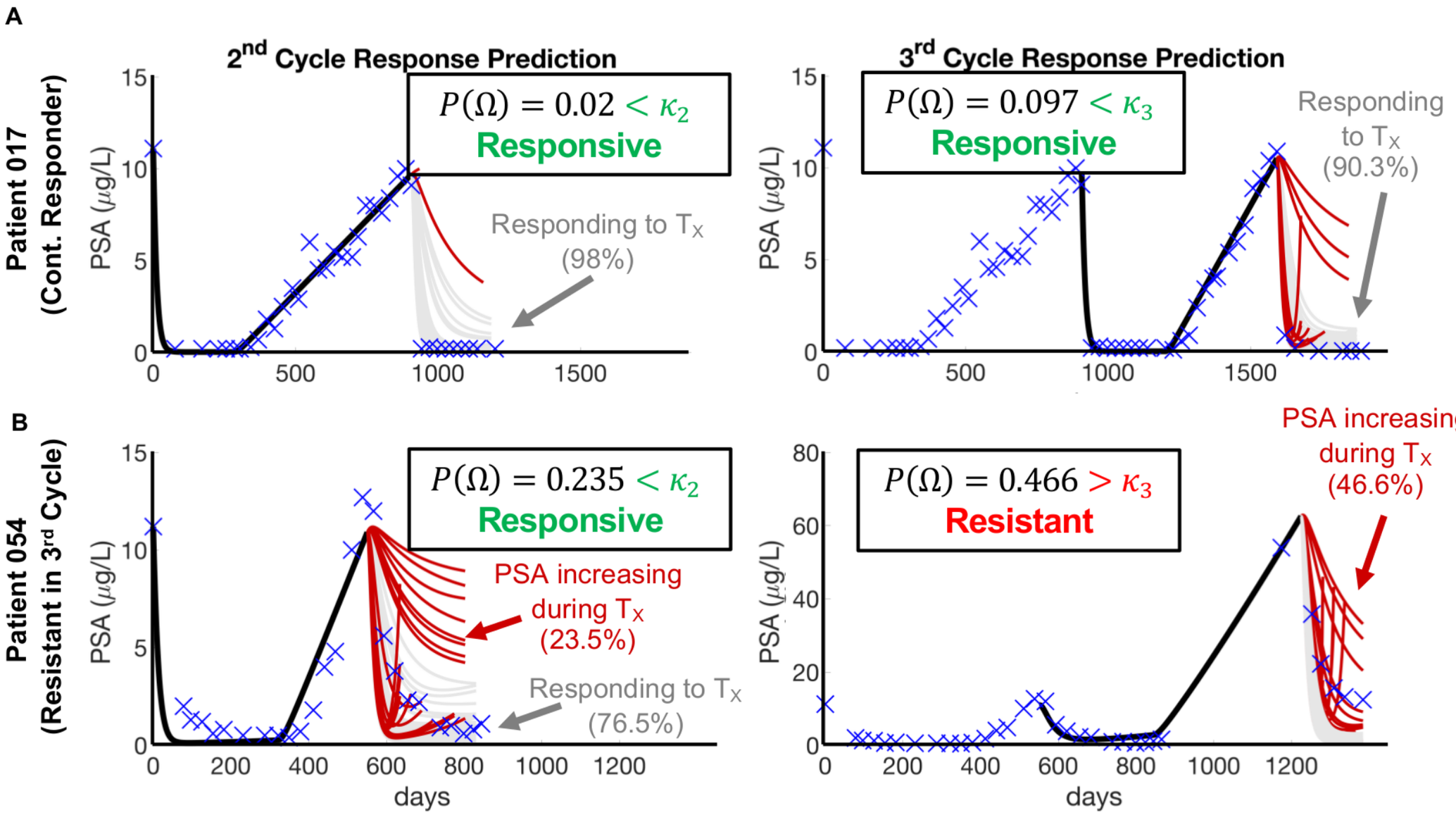

91% Predictive Power!

Research Questions

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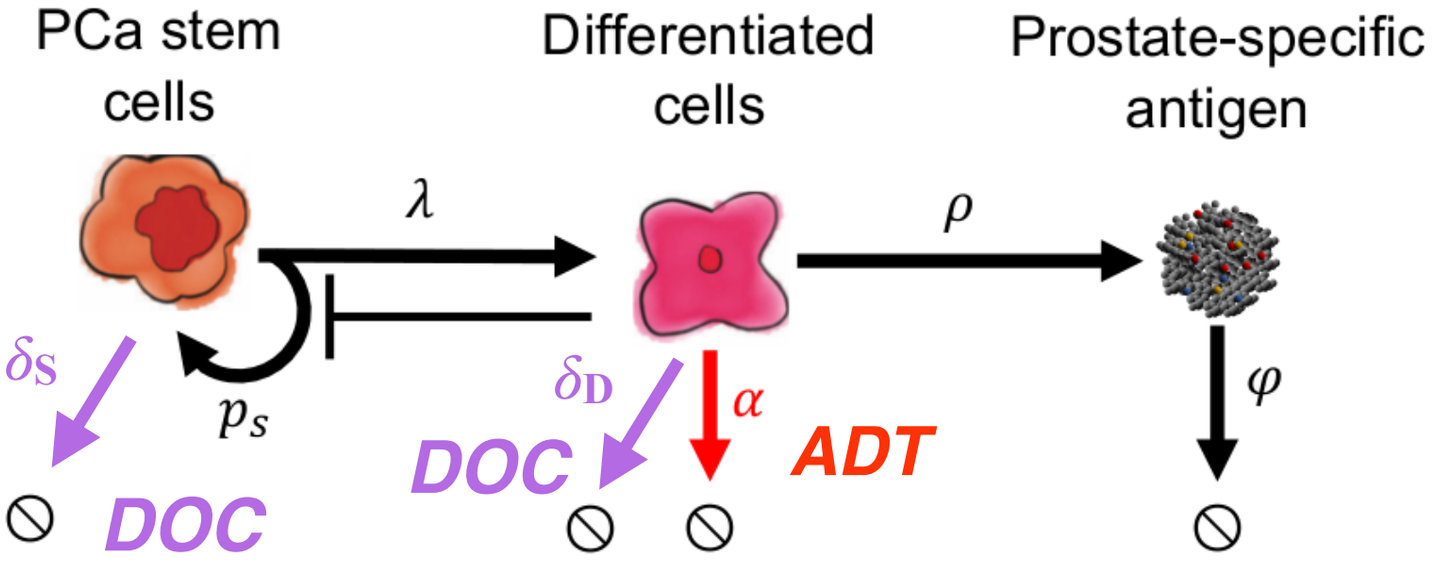
Should we give concurrent chemotherapy early (castration naive) or late (castration resistant)?



Added Docetaxel improves outcomes
Trend toward early DOC for castration naive pts

identify putative biomarker

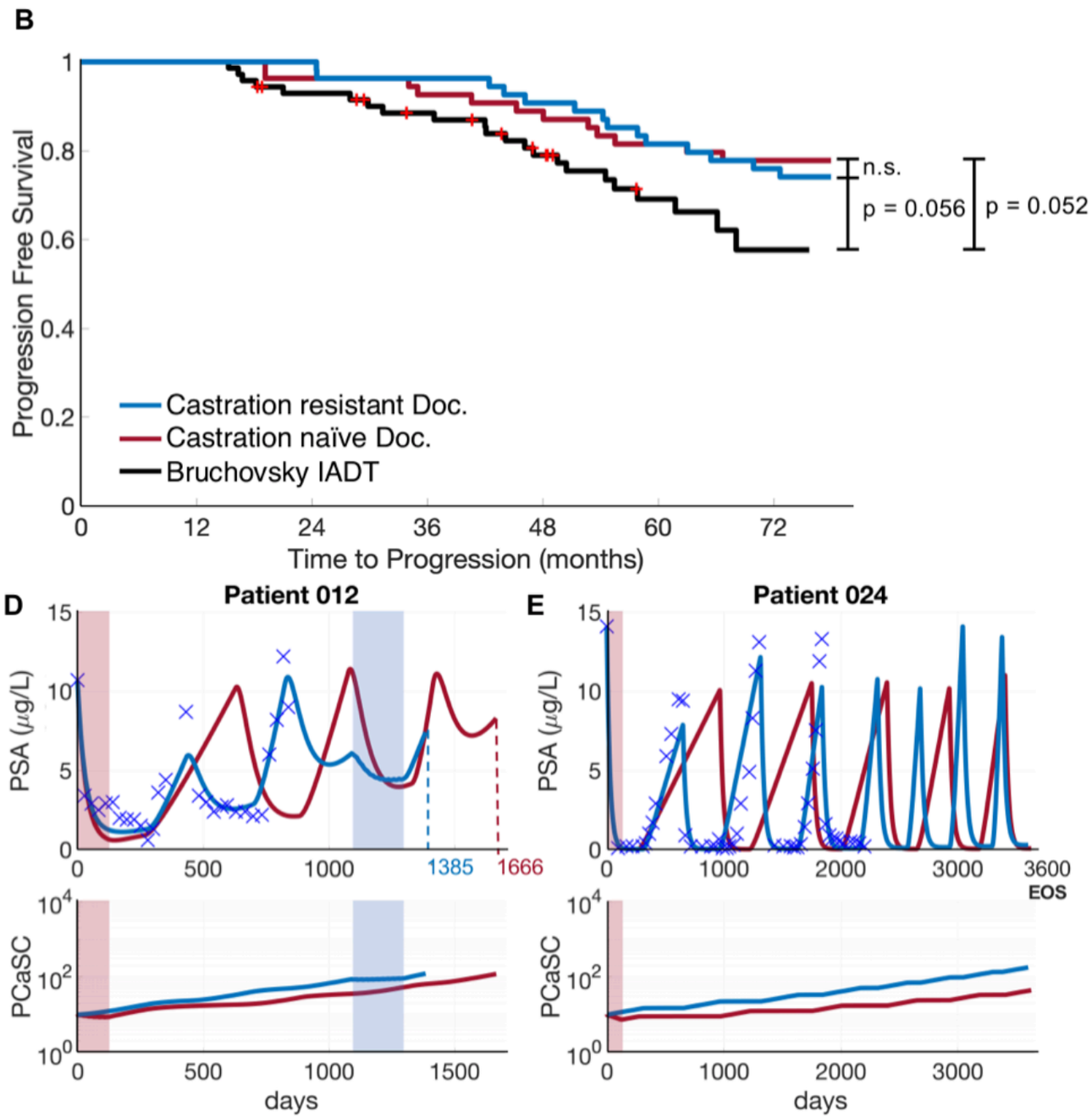
develop mechanistic model

calibrate model with existing data

validate model with untrained data

evaluate predictive performance for known treatment

simulate and predict unknown treatment



Brady-Nicholls et al., Nat. Commun. 2020

Can we predict who'd benefit from added chemo ?

Early Docetaxel benefits patients with higher PCaSC self-renewal rates

identify putative biomarker

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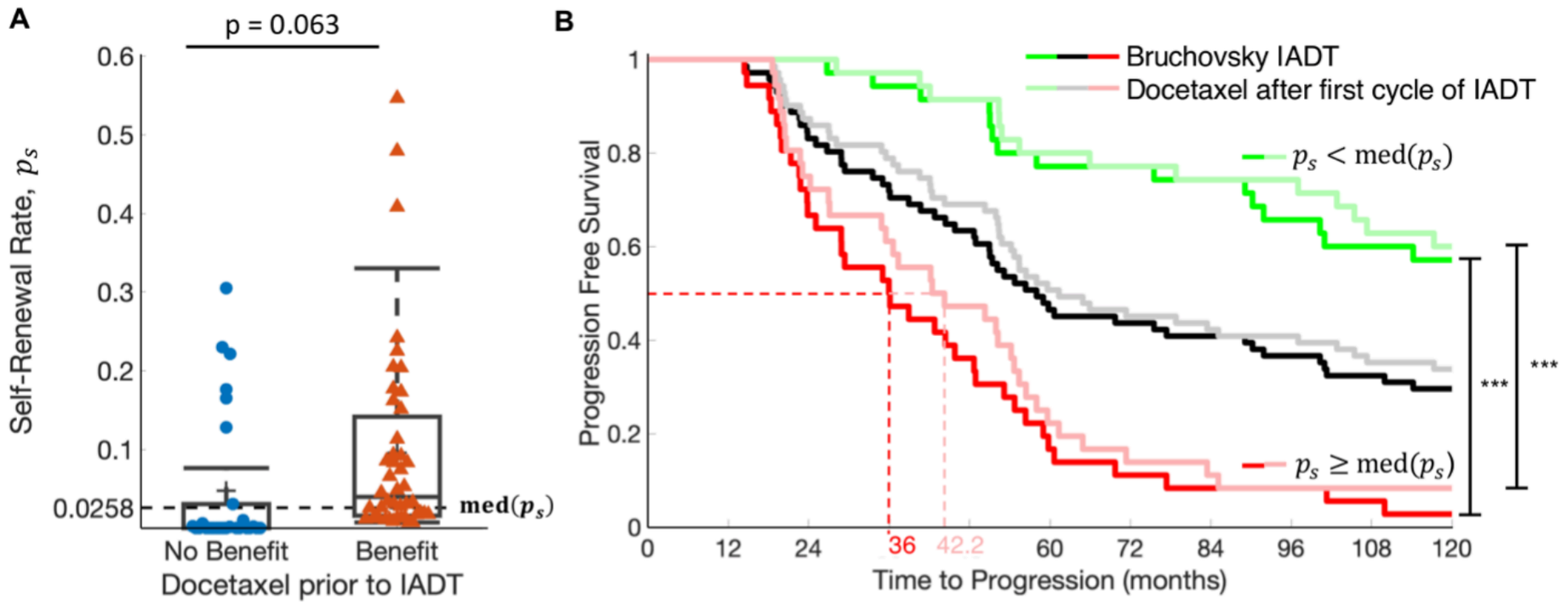

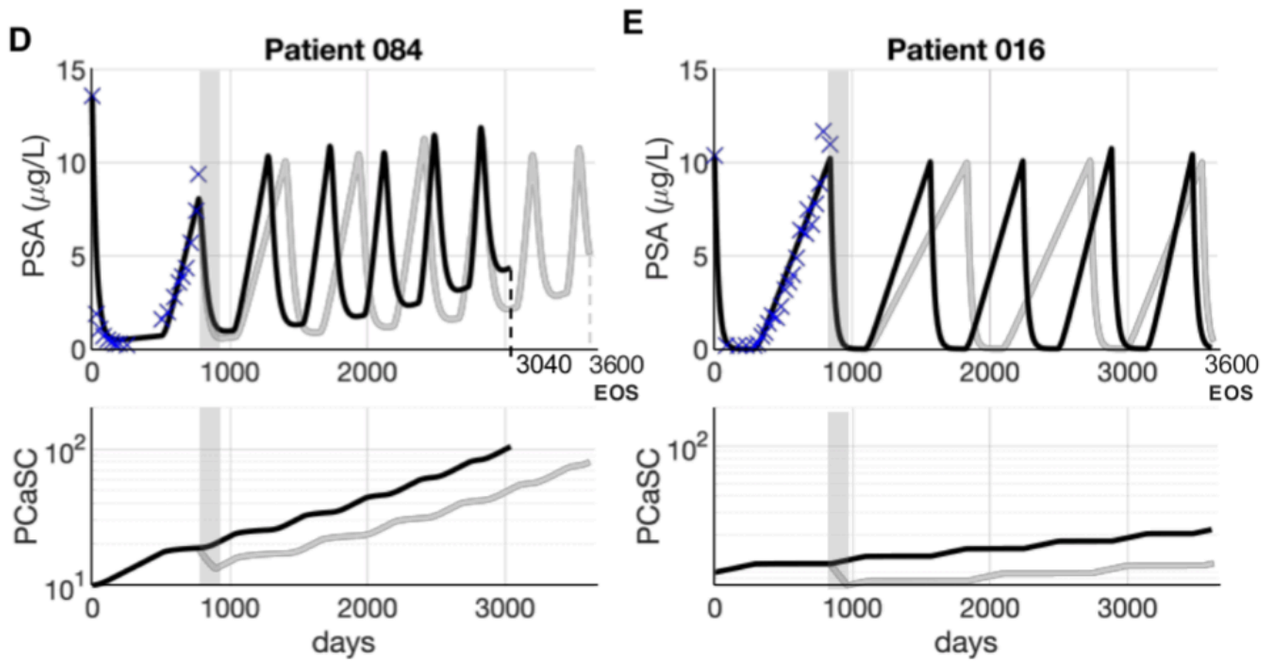

$p_s >$ med (p_s)

$p_s <$ med (p_s)

Brady-Nicholls et al., Nat. Commun. 2020

Research Questions

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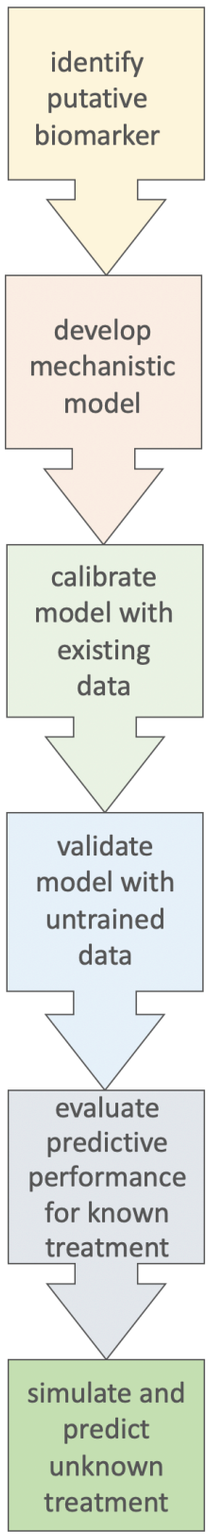
Summary

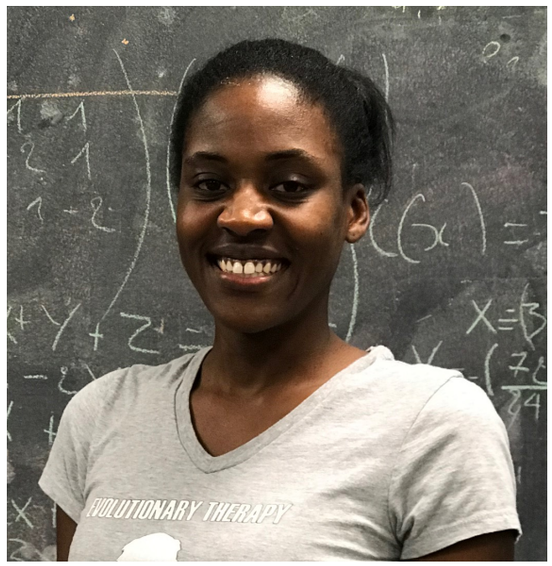


- evaluated PSA dynamics as dynamic biomarker
- PCaSC mathematical model of ADT response/resistance
- trained for PCa patient cohort and individual patients
- validated on untrained data set
- predict response to given therapy with 91% accuracy
- makes testable predictions of alternative treatment protocols

Collaborators

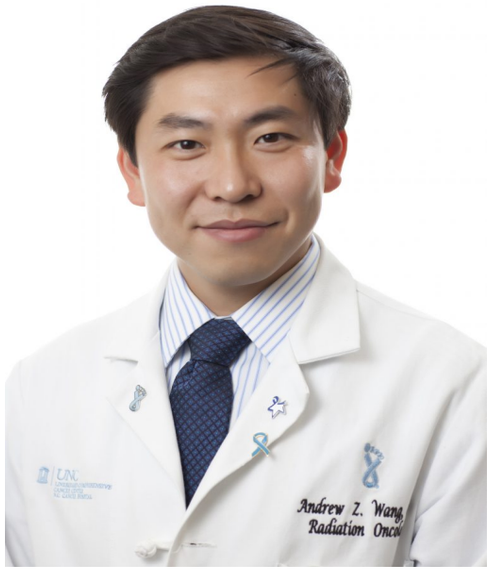
Dr. John Nagy, ASU

@jdnagy96



Dr. Renee Brady-Nicholls

@ReneeBradyPhD



Dr. Andrew Wang, UNC

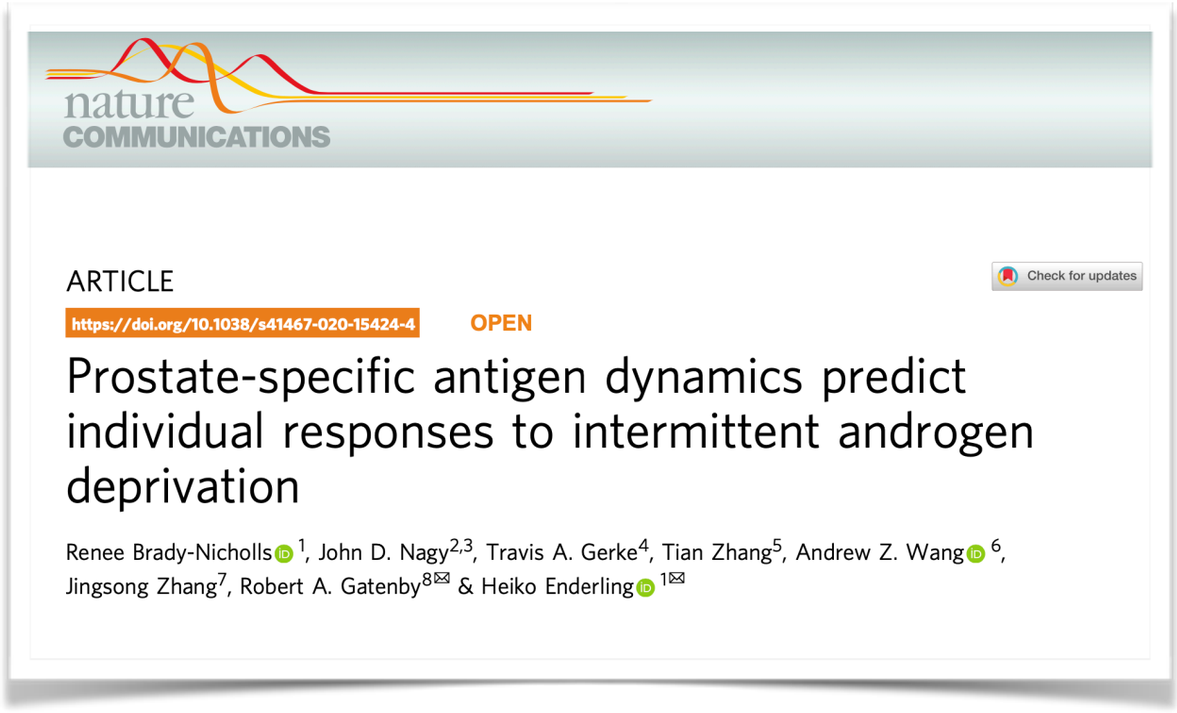
@andyzwang

Dr. Tian Zhang, Duke

@TiangsterZhang

Dr. Jingsong Zhang

Dr. Robert Gatenby

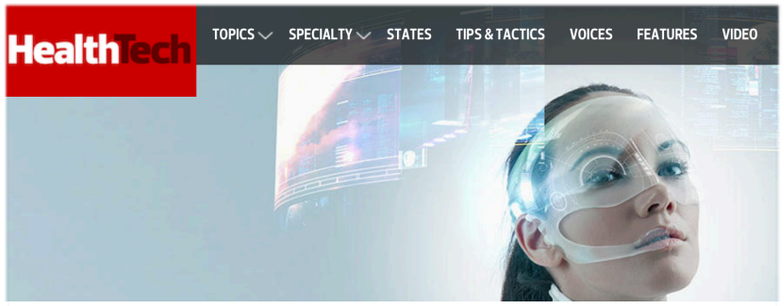


U.S. Patent 62/944,804 (provisional)

Reality check

- All models are wrong - some are useful [George Box]
- As simple as possible (given sparse data), but not simpler than necessary [Albert Einstein]
- Model can only proof ideas wrong, but never right (plausible at best)
- Many models may explain data equally well, but may predict different outcomes
  - VALIDATION VALIDATION VALIDATION !

Reality check



Will Doctors Fear Being Replaced by AI in the Hospital Settling?

Last updated on April 29, 2018 by Kumba Sennaar

- Quantitative approaches will <u>not</u> replace the oncologist !

- The oncologist who uses quantitative approaches <u>may</u> replace the oncologist who does not.

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Funding

Active

NIH NATIONAL CANCER INSTITUTE

1 U01 CA244100-01 (Enderling/SPT)
1 R21 CA234787-01A1 (Enderling/RG)
1 U54 CA193489-01 (Gatenby, EOC)

JAYNE KOSKINAS TED GIOVANIS Foundation for Health and Policy

ocala Royal Dames for cancer research, inc.

FLORIDA BREAST CANCER FOUNDATION Saving Lives

Richard O. Jacobson Foundation

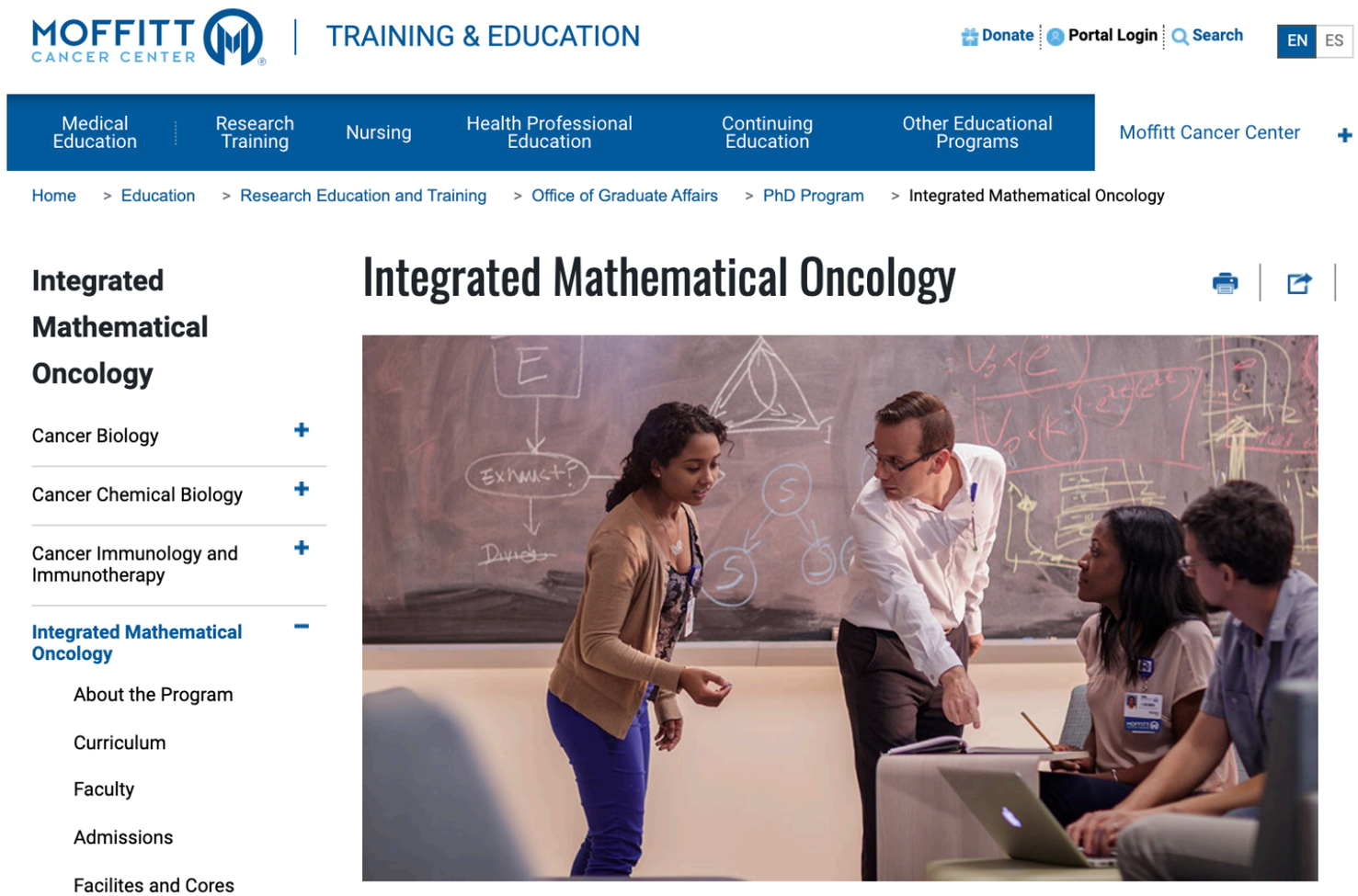
Completed

MOFFITT CANCER CENTER

Miles for Moffitt
DeBartolo Personalized Medicine (x2)
ACS-IRG
IMO workshop (x3)
CoE Evolutionary Therapy

PhD program in Mathematical Oncology

http://moffitt.org/CancerPhd/IMO



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