MATHEMATICAL ONCOLOGY

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MOFFITT CANCER CENTER

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IASLC INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
Conquering Thoracic Cancers Worldwide

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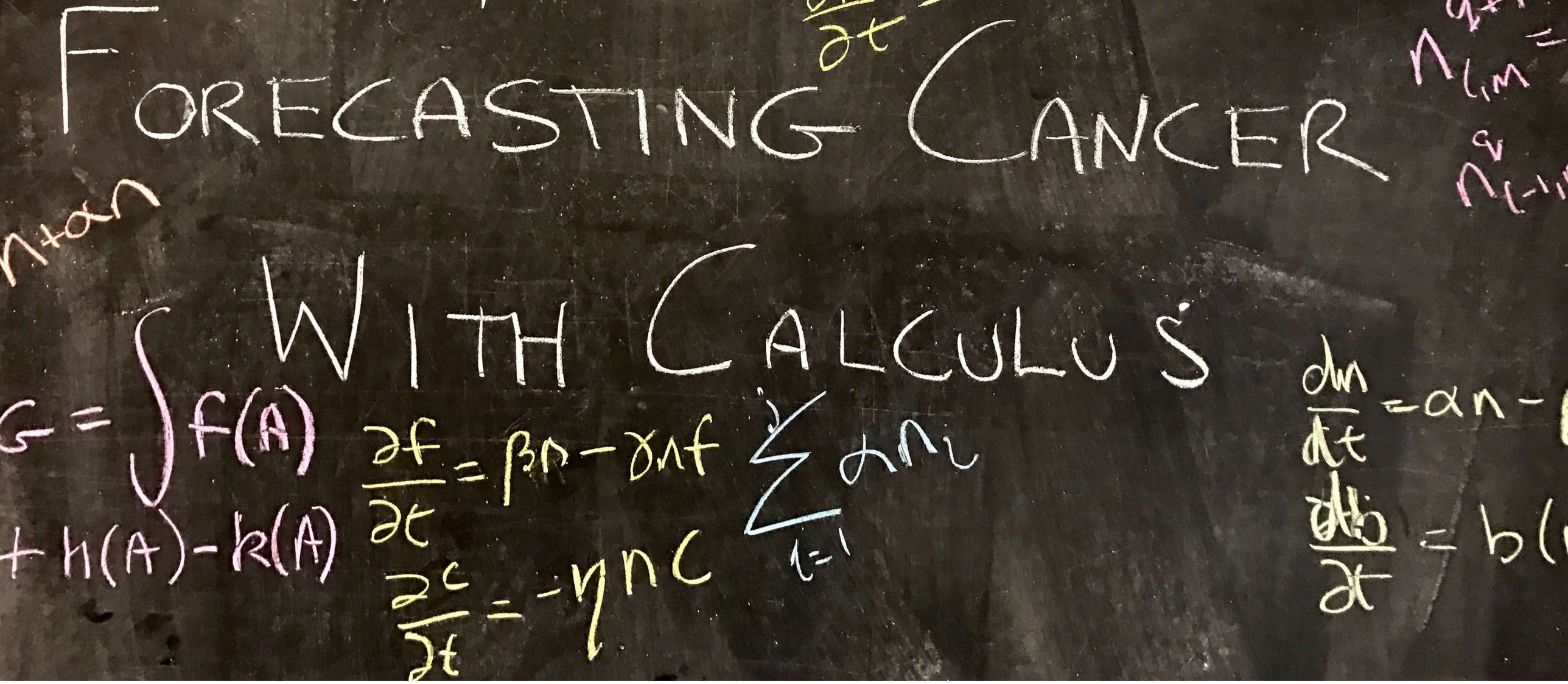
Creating Aha! Moments In Healthcare



@ARA_ANDERSON

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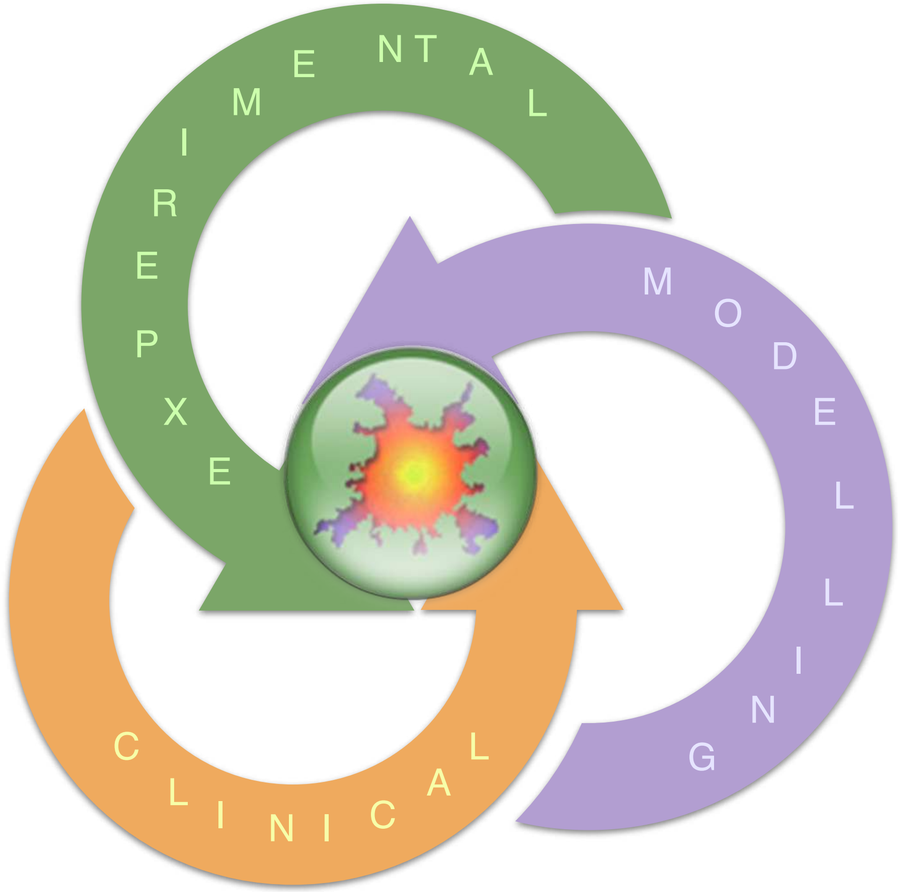
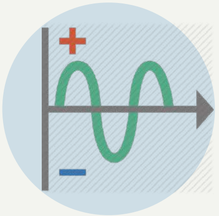
IMO Integrated Mathematical Oncology



Unified goal: To better understand, predict and treat cancer

I AM A MODELER:

- Make predictions
- Answer questions
- Generate hypothesis



YOU ARE A MODELER:

- Biological (e.g. Cell culture)
- Mathematical (e.g. Differential equations)
- Clinical (e.g. Imaging)

Preclinical = Homogeneity

- Experimental systems: in vitro & in vivo
- Error bars should minimized
- Reproducibility is central to research

Clinical = Heterogeneity

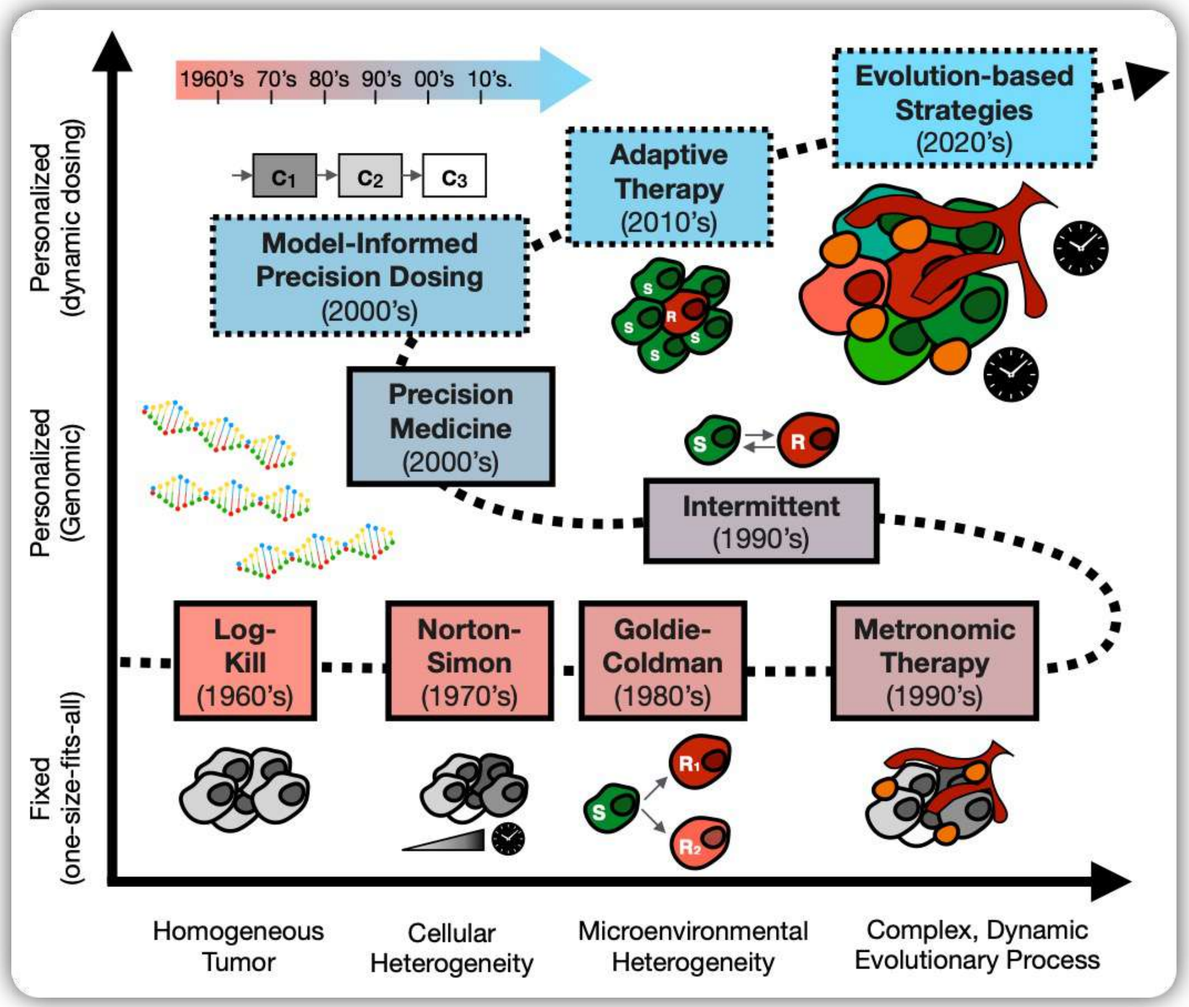
- Within individual tumours
- Across patients with the same cancer
- Diversity in age, stage, health & history etc


ATLANTIC HURRICANE TRACKS

MATHEMATICAL MODELS CAN PREDICT THE FUTURE

ADVANCES IN TREATMENT SCHEDULING

- Over the last 60 years treatment scheduling has evolved significantly
- You might not know that mathematical modeling played an important role in much of it
- With ever increasing drug options, dosing, timing and combination needs modeling more than ever.



MAXIMUM TOLERATED DOSE THERAPIES FAIL BECAUSE OF RESISTANCE

Sandy Anderson

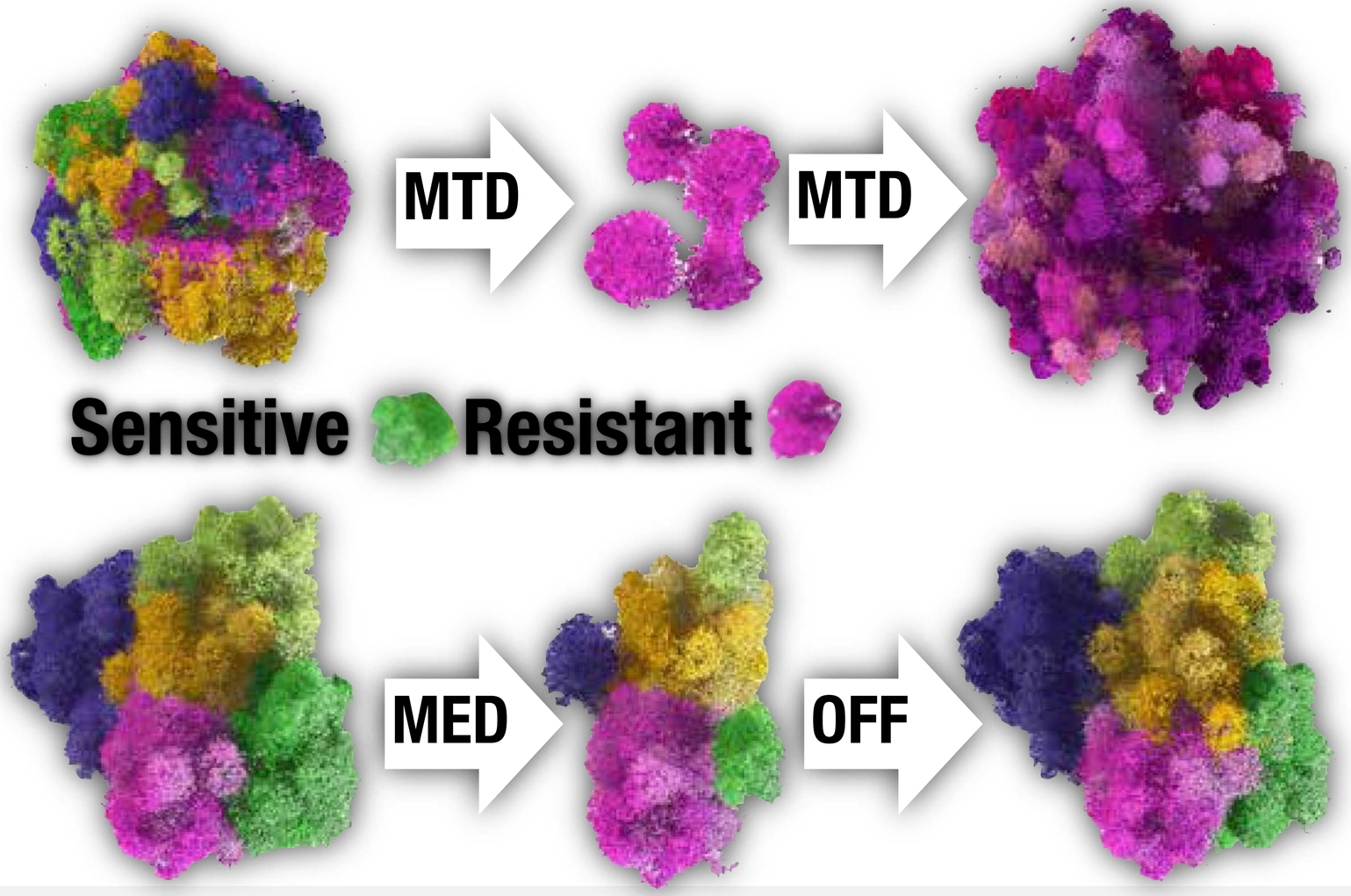
Bob Gatenby

Damon Reed

Evolutionary Therapy

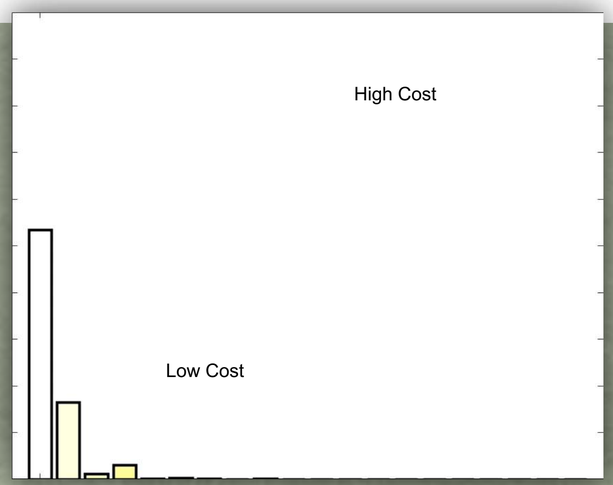
“To develop and deploy the next generation of truly personalized cancer therapy, through the integration of predictive mathematical models, patient data and evolutionary principles”

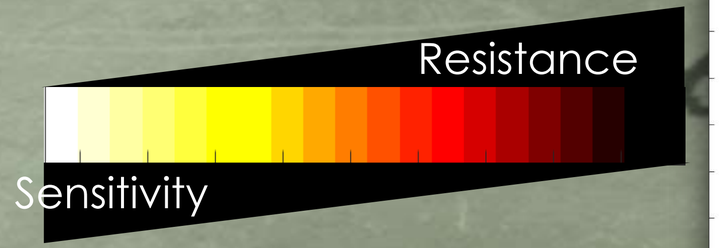
PRINCIPLES OF ADAPTIVE THERAPY

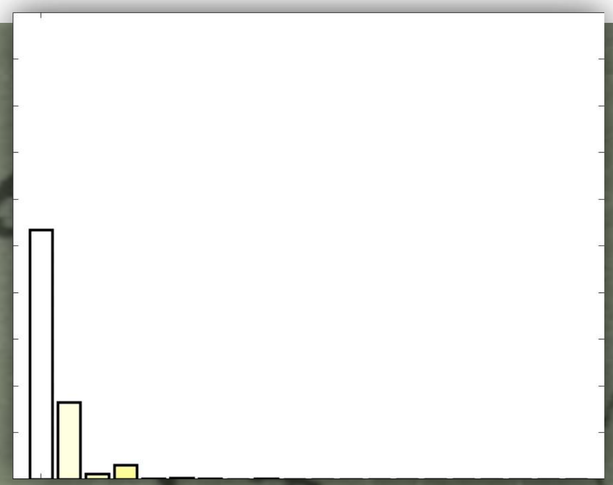


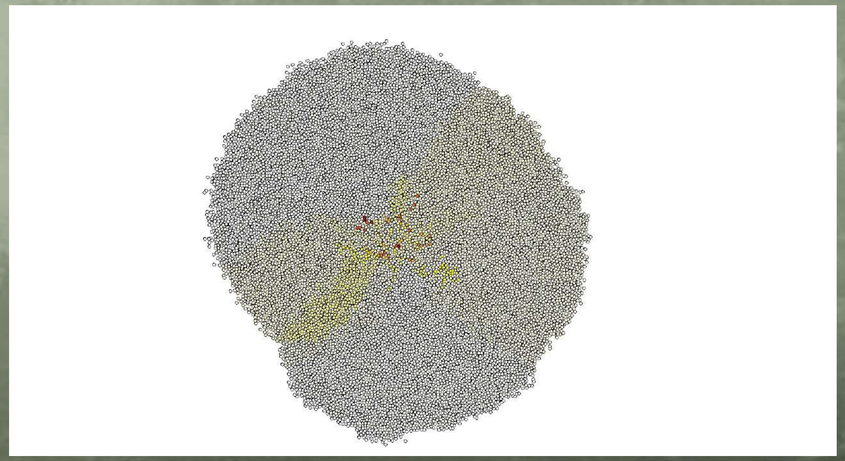
Evolution of resistance is inevitable with MTD
Sensitive cells suppress growth of resistant clones

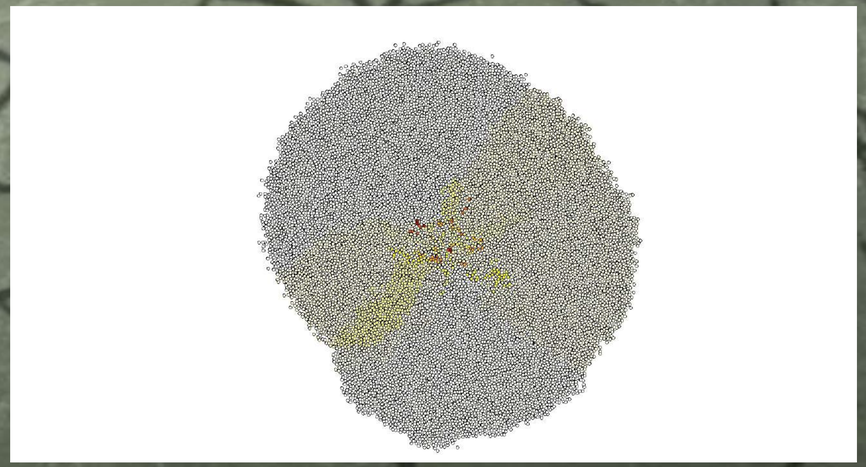
CONTINOUS vs ADAPTIVE THERAPY
MEDIUM HETEROGENEITY







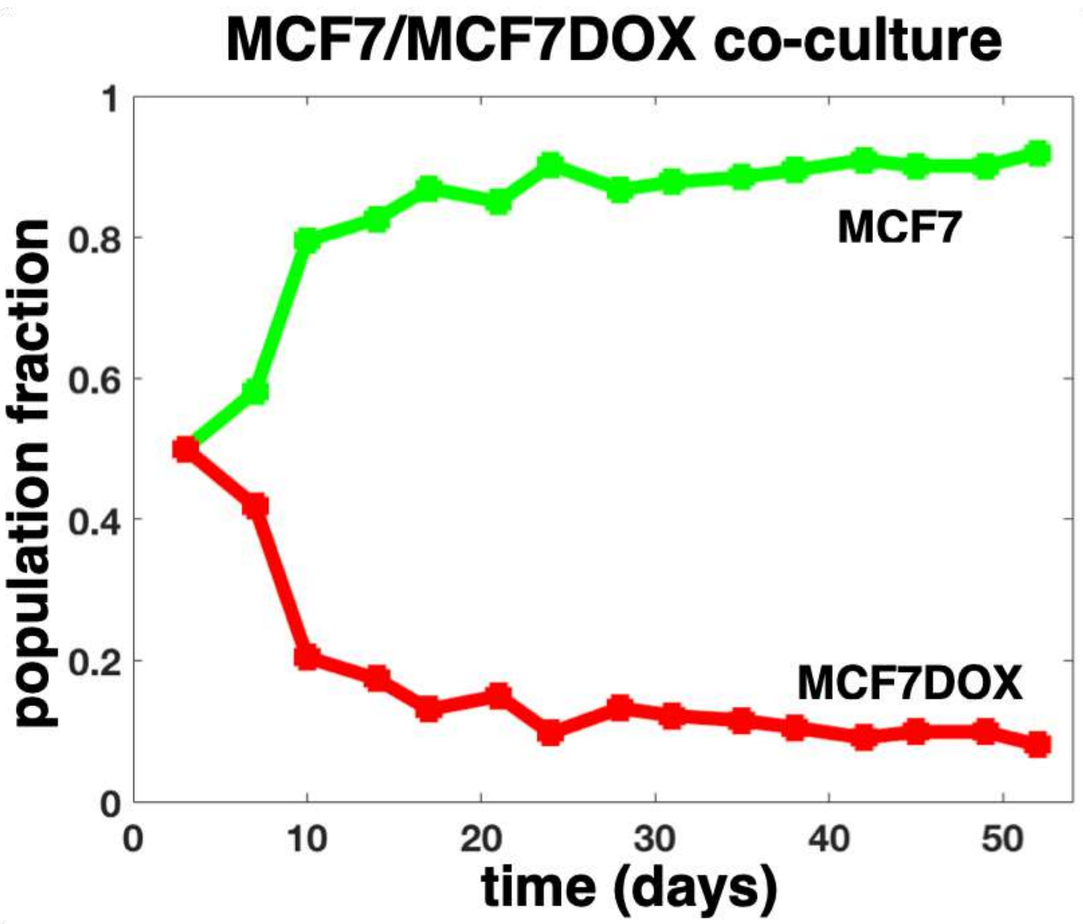


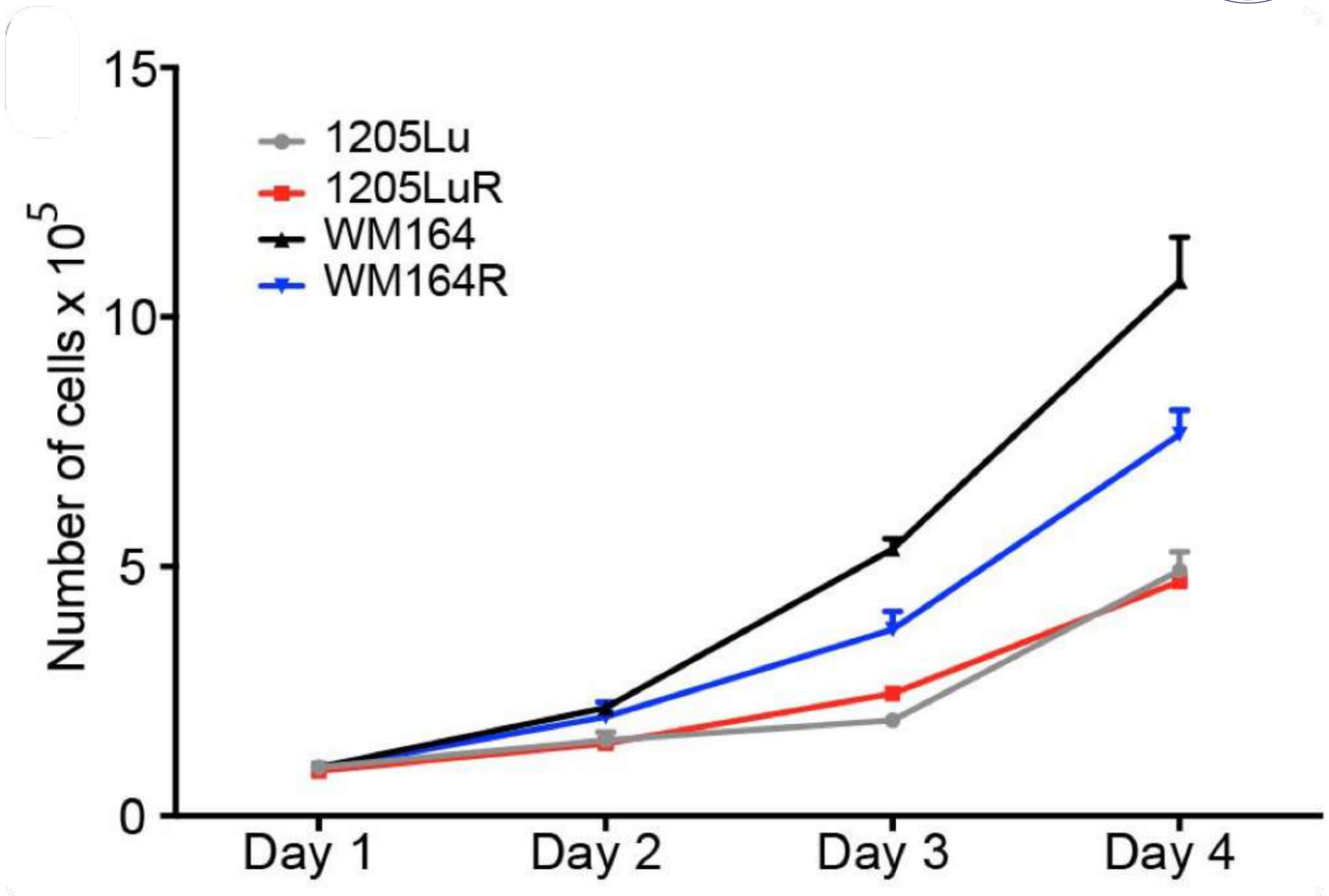


Cancer Research 2018, doi: 10.1158/0008-5472.CAN-17-2649.

https://jillagal.github.io/CTvsAT/

RESISTANCE MAY HAVE A COST

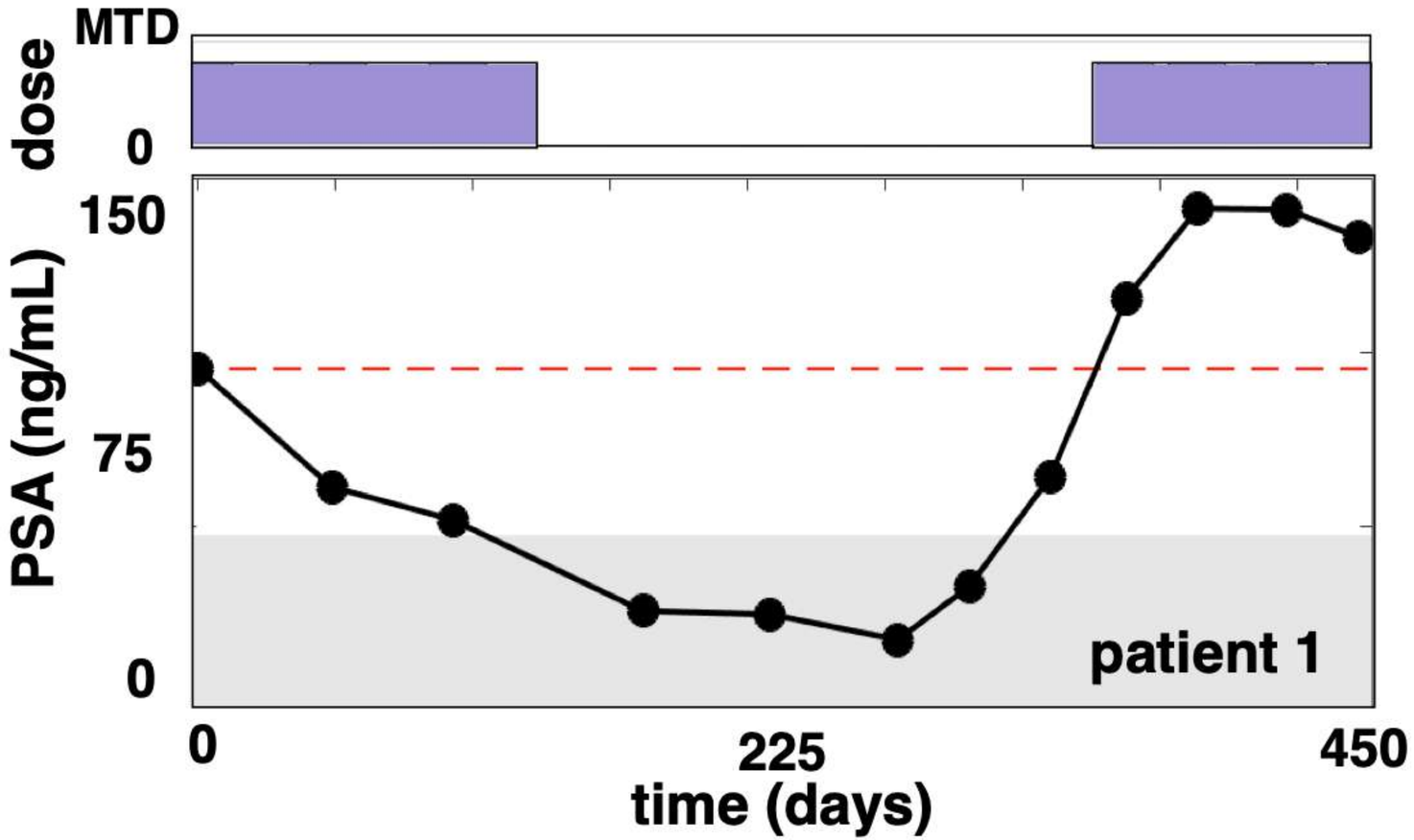




Different cell lines exhibit different costs of resistance

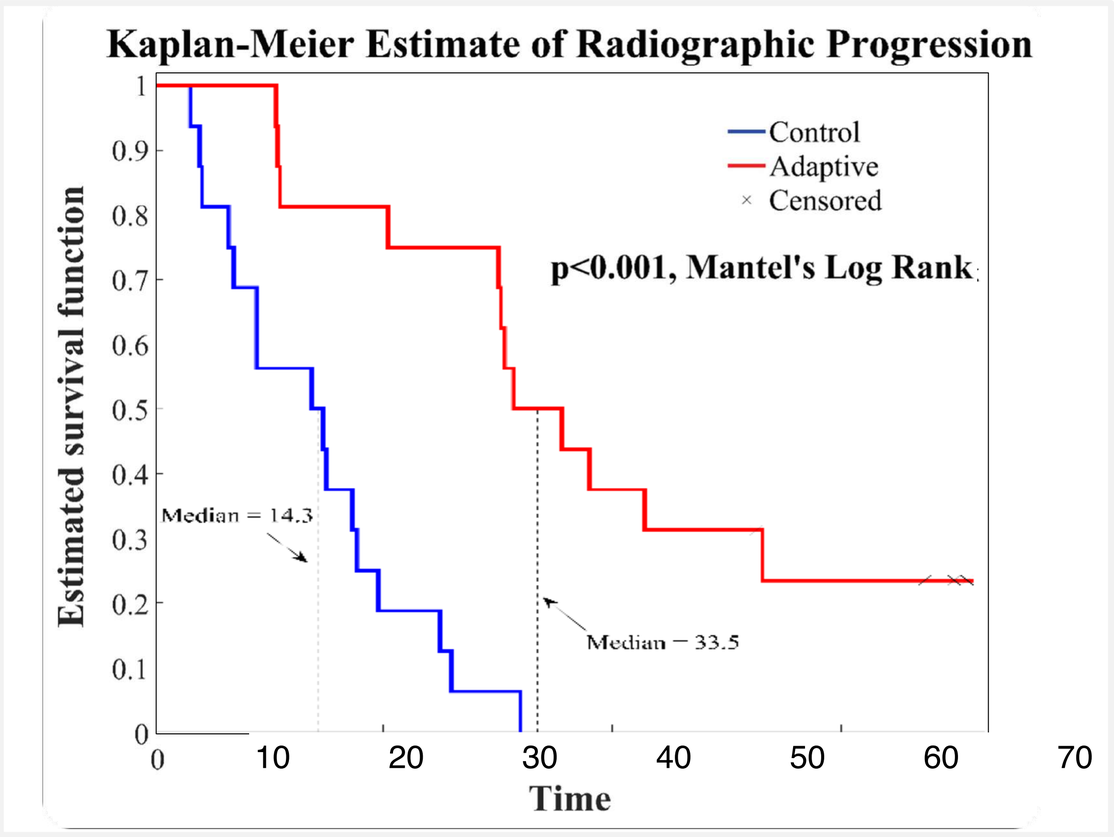
ADAPTIVE PROSTATE CANCER TRIAL (NCT02415621)

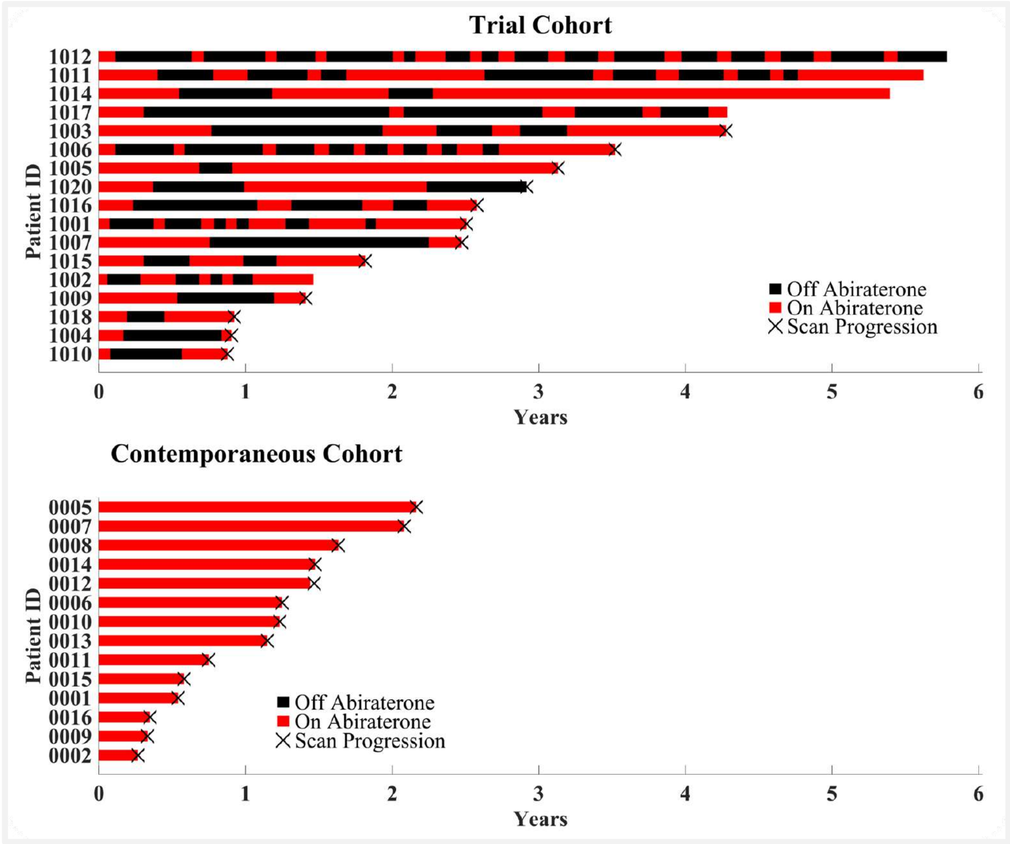
If response exceeds >50% reduction in PSA, withdraw therapy until PSA reaches pre-treatment level



ABIRATERONE TRIAL RESULTS

- Improved median TTP (33.5 months) and median OS (58.5 months) (Hazard ratio, 0.20)
- Subjects received no abiraterone during 46% of time on trial
- 4 patients remain on trial with stably cycling disease (53-70 months)



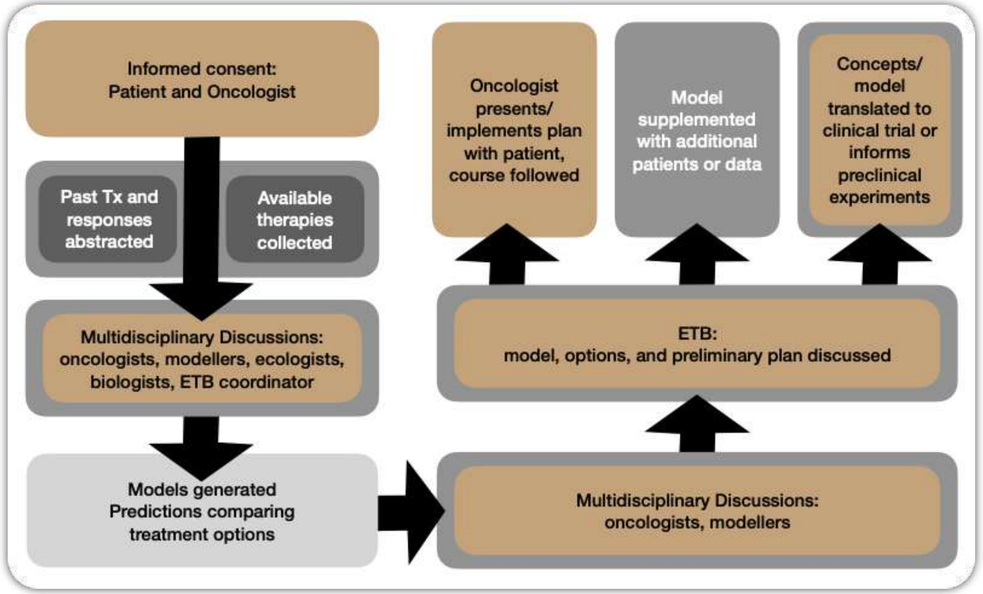


Nat Comms. 2017, doi.org/10.1038/s41467-017-01968-5

EVOLUTIONARY CLINICAL TRIALS

NCI TRIAL	TITLE
NCT05651828	Adaptive vismodegib in advanced basal cell carcinoma
NCT05189457	1st Strike, 2nd Strike Therapies for High Risk Metastatic Castration Sensitive Prostate Cancer
NCT02415621	Adaptive Abiraterone Therapy for Metastatic Castration Resistant Prostate Cancer
NCT03511196	Intermittent Androgen Deprivation Therapy for Stage IV Castration Sensitive Prostate Cancer
NCT03543969	Adaptive BRAF-MEK Inhibitor Therapy for Advanced BRAF Mutant Melanoma
NCT04388839	Evolutionary Therapy for Rhabdomyosarcoma
NCT04343365	Generating Novel Therapeutic Strategies Based on Evolutionary Tumor Board

EVOLUTIONARY TUMOR BOARD (ETB)



Christine Chung

Damon Reed

Clinical trial to implement the ETB (NCT04343365)

- Different patients from different cancers every month
- Pre-board discussion with IMO 1-2 weeks before ETB
- Multi-model approach driven by eco-evolutionary principles
- Integrated decision making process

PATIENT ETB-003 (HEAD AND NECK)

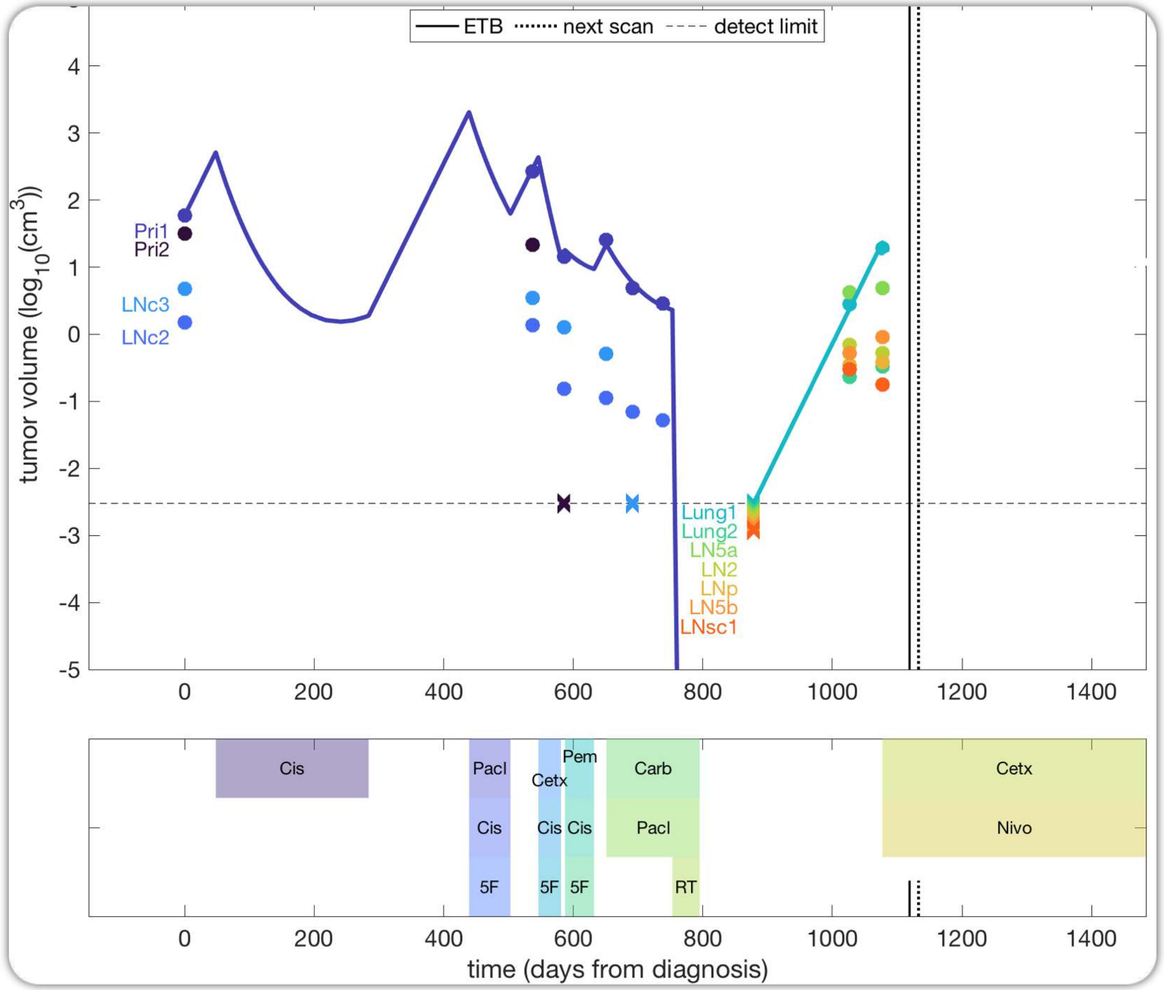
$$\dot{T}_i = \left(\overbrace{\tilde{\gamma}_i}^{Growth} - \overbrace{\sum_j \delta_j E_j D_j}^{Death} \right) T_i$$

$$\dot{E}_j = \left(\overbrace{s_j(1-E_j)(1-D_j)}^{Sensitization} - \overbrace{r_j D_j}^{Resistance} \right) E_j$$

$$D_j = D_j(t)$$

Approach

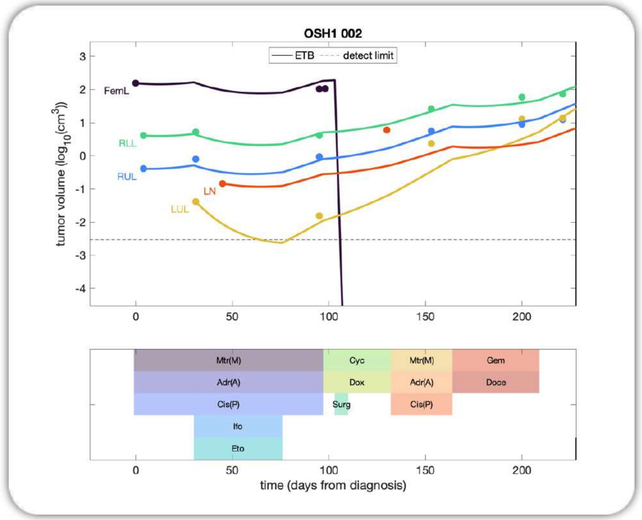
- Fit base growth rate (γ_i) from target lesions
- Drug efficacy (∂_j) fit under therapy
- Rate of resistance (r_j) fit in combo with efficacy
- Resensitization rates (s_j) will mostly come from historical data

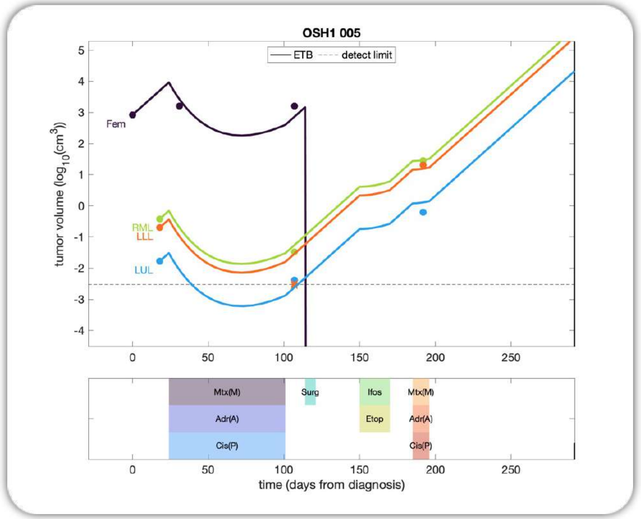


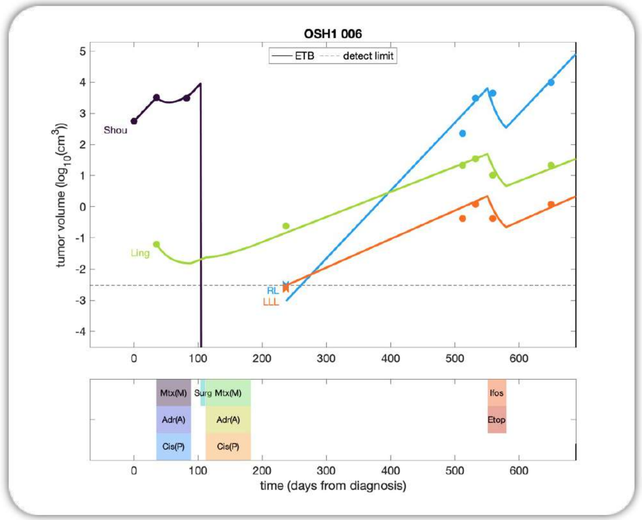
HISTORICAL PATIENTS CONSTRAIN MODEL

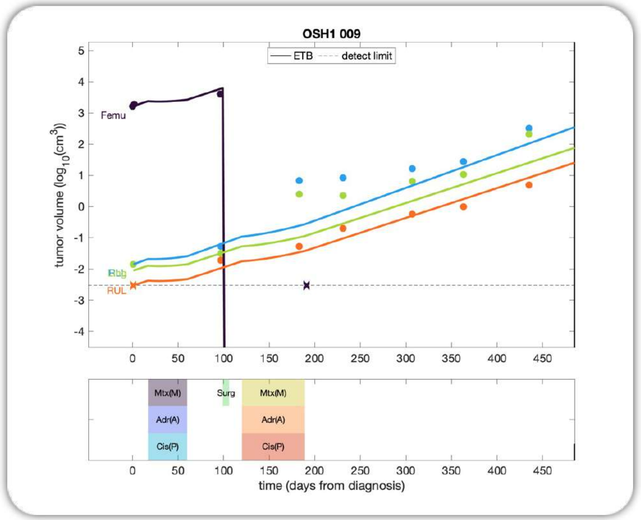
Approach

- Retrospectively apply ETB workflow to historical cohorts in the same disease
- Collect parameter ranges for growth rates, drug efficacy, rates of resistance and sensitization
- Use these ranges prospectively for new patients on the ETB



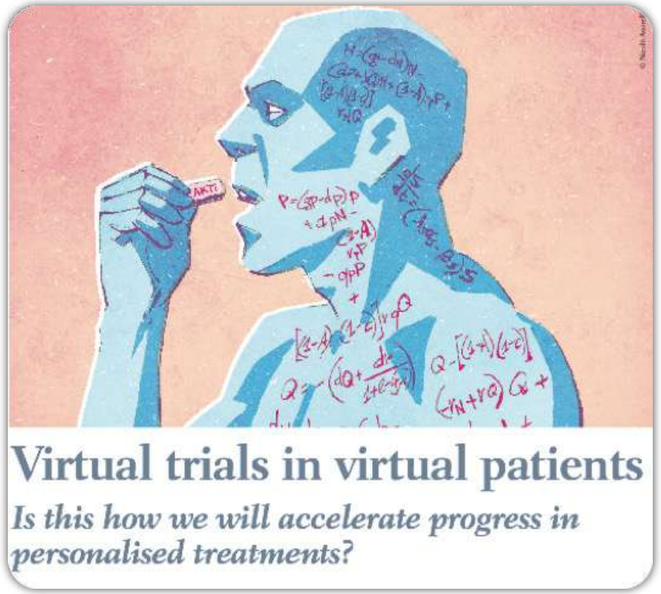


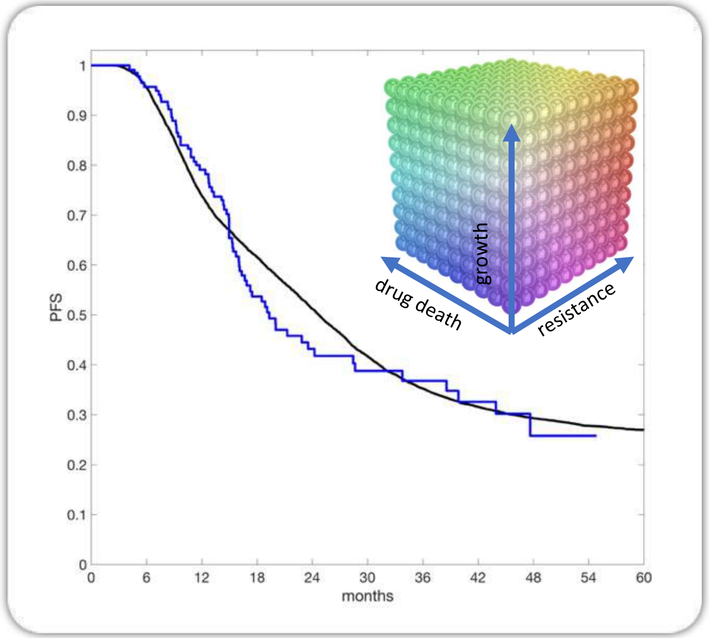




PHASE I TRIALS

- Phase I for imaginary number
- Use historic trial data
- Calibrate model to outcomes
- Uses Kaplan-Meier & waterfall plots
- Generate a Cohort of virtual patients
- Captures uncertainty
- Ideal for testing & optimization

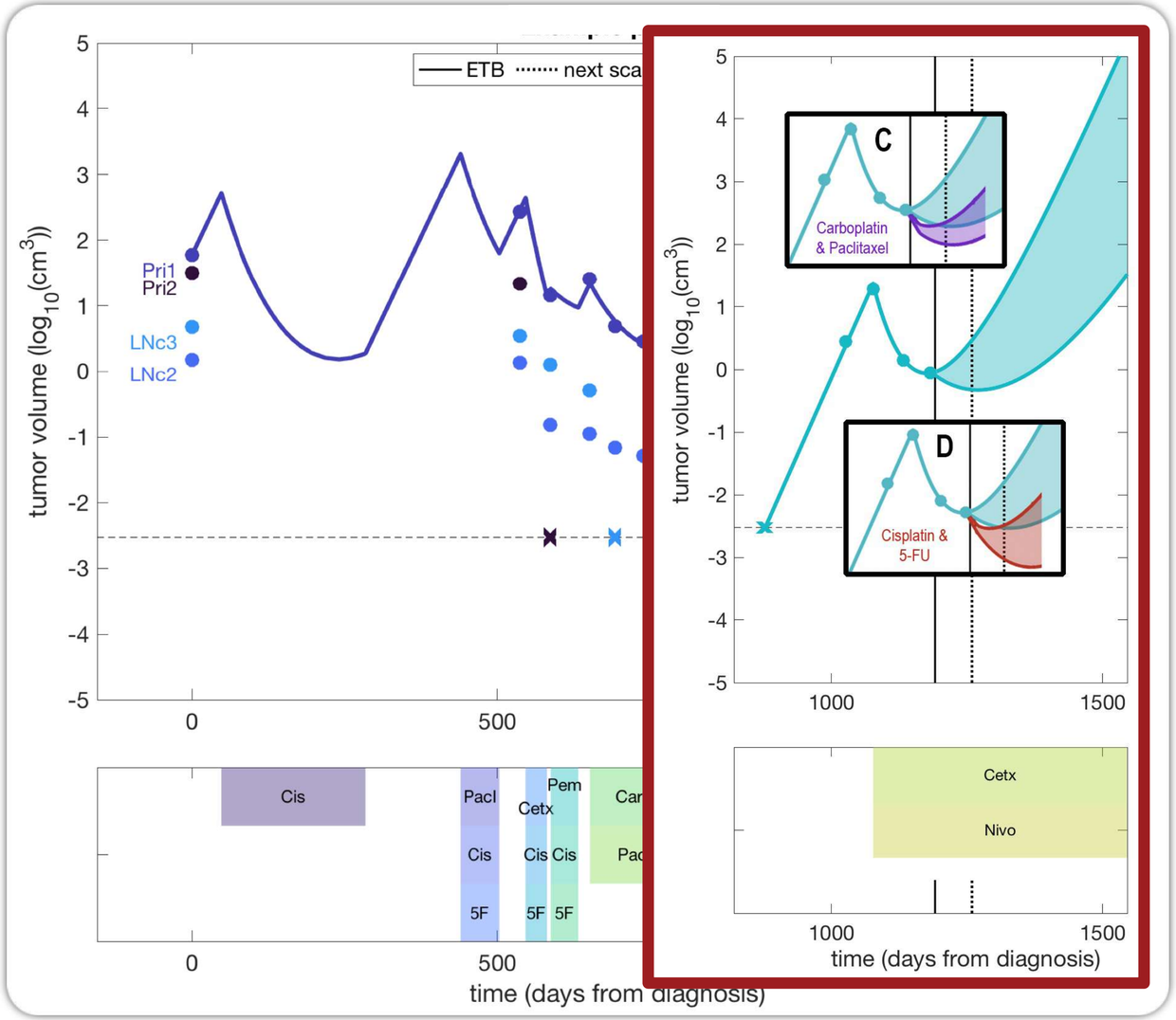




Kim E. et al. Eur J Cancer. 2016 Nov;67:213-222. doi: 10.1016/j.ejca.2016.07.024.

DECISION SUPPORT FOR ALL THERAPIES

- Comparison of different therapies based on historical precedent can suggest outcome ranges
- In this case, both chemotherapy options are not expected to improve outcomes over continuation of targeted therapy
- After third scan, despite continued response, model suggests switching to chemotherapy soon



MedRxiv 2023, doi: 10.1101/2023.01.18.23284628

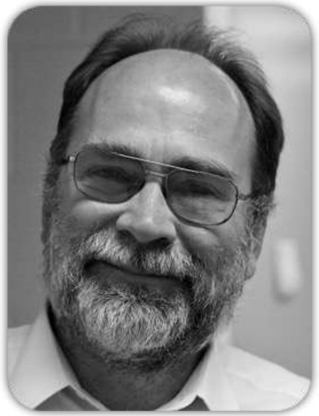
CONCLUSIONS

- Treatment selects for resistant phenotypes
- Timing matters but so does space
- Smart sequential therapies can exploit evolution
- Resistant phenotypes may have a cost
- Dynamic measures of burden are critical
- Patients should be their own control
- Evolutionary therapies: new use for old drugs


Jill Gallaher


Mark Robertson-Tessi


Robert Gatenby


Joel Brown


Damon Reed


Christine Chung

PSOC
CSBC

“In the long history of humankind those who learned to collaborate and improvise most effectively have prevailed”