Assessing Cancer Treatment Efficacy: The Past, the Present, and the Future!

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Conflicts of Interest

None

Potter Stewart

Associate Justice of the Supreme Court of the United States

Nominated by Dwight D. Eisenhower / Served from 10/14/58 – 6/3/81

In the obscenity case of Jacobellis v. Ohio (1964), Stewart wrote in his short concurrence that "hard-core pornography" was hard to define, but that "I know it when I see it"

Where did the definitions of response come from?

Charles Moertel, MD

12 spheres
1.8 - 14.5 cm
[5 = 6 and 7 = 8]
16 hematologists
1920
measurements

Where did the definition of partial response (PR) come from?

Twelve solid spheres were selected, measuring from 1.8 to 14.5 cm in diameter. It was assumed that this size range would cover the sizes usually encountered in measurable clinical masses such as subcutaneous, lymph node, and intra-abdominal tumors. These masses were then arranged in random size order on a soft mattress and covered with a layer of foam rubber. This layer measured 0.5 in. in thickness for the six smaller masses to approximate skin and subcutaneous tissue and 1.5 in. for the six larger masses to approximate abdominal wall. Each of 16 experienced physicians practicing in oncology was then asked to measure the diameter of each sphere using the usual technique and equipment (ruler or caliper) he employed in clinical practice.

Where did the definition of partial response (PR) come from?

The actual "tumor" diameters are shown in Table 1. The participants were unaware that "tumors" 5 and 6 were designed to have the same diameter and so to provide an estimate of the reproducibility of each physician's measurements of tumor size. Tumors 7 and 8 were also designed for this purpose (the slight difference in true diameters 5 and 6 and in 7 and 8 reflect variations in the manufacturing process).

Where did the definition of PR come from?

How often did **two investigators** think the same tumor was different? Very often!

TABLE 3. Erroneously Declared Objective Responses and Objective Progressions When Two *Different* Investigators Measure Tumor Which Has Remained the Same Size

Baseline tumor	Tumor measured subsequently	Number of different investigator pairings	No. of pairings who report objective responses ≥ 25% shrinkage	No. of pairings who report objective responses ≥ 50% shrinkage	No. of pairings who report objective progression ≥ 25% growth	No. of pairings who report objective progression ≥ 50% growth
#5	#5	240	29	6	64	23
#5	#6	240	70	26	83	48
#6	#5	240	60	8	94	58
#6	#6	240	83	39	95	70
#7	#7	240	57	7	67	37
#7	#8	240	64	18	67	31
#8	#7	240	51	7	66	38
#8	#8	240	65	19	68	37
TOTAL		1920	479 (24.9%)	130 (6.8%)	604 (31.5%)	342 (17.8%)

↓50%
6.8%

Where did the definition of PR come from?

How often did **the same investigator** think the same tumor was different? Very often!

TABLE 2. Erroneously Declared Objective Response and Objective Progressions When the Same Investigator Repeats a Measurement on a Tumor Which Has Remained the Same Size

Baseline tumor	Tumor measured subsequently	No. of same-investigator evaluations	No. of investigators who reported objective responses ≥ 25% shrinkage	No. of investigators who reported objective responses ≥ 50% shrinkage	No. of pairings who report objective progression ≥ 25% growth	No. of pairings who report objective progression ≥ 50% growth
#5	#6	16	4	4	2	2
#6	#5	16	2	0	4	4
#7	#8	16	3	1	3	3
#8	#7	16	3	0	3	3
TOTAL		64	12 (18.8%)	5 (7.8%)	12 (18.8%)	12 (18.8%)

↓50%
7.8%

Where did the definitions of response come from?

How often did **two different investigators** think the same tumor was different?

No. of pairings who report objective responses	
≥ 25% shrinkage	≥ 50% shrinkage
29	6
70	26
60	8
83	39
57	7
64	18
51	7
65	19
479 (24.9%)	130 (6.8%)

How often did **the same investigator** think the same tumor was different?

No. of investigators who reported objective responses	
≥ 25% shrinkage	≥ 50% shrinkage
4	4
2	0
3	1
3	0
12 (18.8%)	5 (7.8%)

THE EFFECT OF MEASURING ERROR ON THE RESULTS OF THERAPEUTIC TRIALS IN ADVANCED CANCER

CHARLES G. MOERTEL, MD,* AND JAMES A. HANLEY, PHD†

In this study, 16 experienced oncologists each measured 12 simulated tumor masses employing their usual clinical methods. Unknown to the oncologists, two pairs of these tumors were identical in size. This permitted a total of 64 measurement comparisons of the same investigator measuring the same size mass and 1920 comparisons of different investigators measuring the same size mass. If a 50% reduction in the product of perpendicular diameters is accepted as a criterion, the objective response rate due to measuring error alone was 7.8% by the same investigator and 6.8%by different investigators. If a 25% reduction criterion is used, the respective "placebo" response rates were 19% and 25%. In the clinical setting it is recommended that the 50% reduction criterion be employed and that the investigator should anticipate an objective response rate of 5 to 10% due to human error in tumor measurement.

Cancer 38:388–394, 1976.

From these humble beginnings….from cutoffs chosen for "operational reasons" not for "efficacy"….we evolved to assessment of efficacy

Moertel was primarily thinking about / dealing with lymphomas

1. CNS Tumors [RANO]
2. Mesothelioma
3. Ovarian Cancer
4. Breast Cancer
5. Prostate Cancer

From these humble beginnings….from cutoffs chosen for "operational reasons" not for "efficacy"….we evolved to assessment of efficacy

WHO then "codified" the definition of response And RECIST "immortalized it"

WHO
(**W**orld **H**ealth **O**rganization)
versus
RECIST
(**R**esponse **E**valuation **C**riteria **I**n **S**olid **T**umors)

	WHO	RECIST
Measurability	Measurable, bidimensional	Measurable, unidimensional: Conventional method ≥20 mm; Spiral CT ≥10 mm; Target versus non-target lesion
	Non-measurable/evaluable	Non-measurable
Objective response		
Complete response (CR)	Disappearance of all known lesion(s); confirmed at 4 weeks	Disappearance of all known lesion(s); confirmed at 4 weeks
Partial response (PR)	At least 50% decrease; confirmed at 4 weeks	At least 30% decrease; confirmed at 4 weeks
Stable disease (SD)	Neither PR nor PD criteria met	Neither PR nor PD criteria met
Progressive disease (PD)	25% increase; no CR, PR or SD documented before increased disease, or new lesion(s)	20% increase; no CR, PR, or SD documented before increased disease, or new lesion(s)

Appendix II, Table 2. Relationship between change in diameter, product, and volume*

Appendix II, Table 2. Relationship between change in diameter, product, and volume*

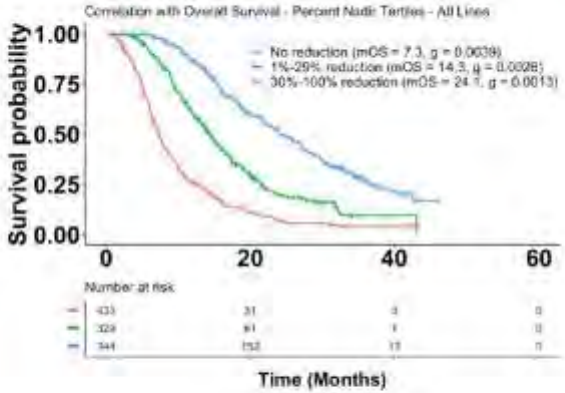
RECIST WHO

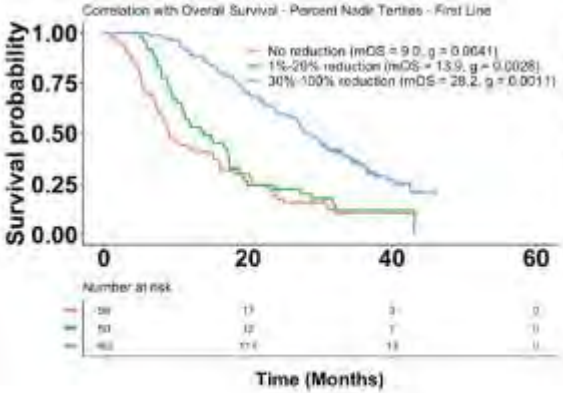
	Diameter, $2r$	Product, $(2r)^2$	Volume, $4/3\pi r^3$
Response	Decrease	Decrease	Decrease
	30%	50%	65%
	50%	75%	87%
Disease progression	Increase	Increase	Increase
	12%	25%	40%
	20%	44%	73%
	25%	56%	95%
	30%	69%	120%

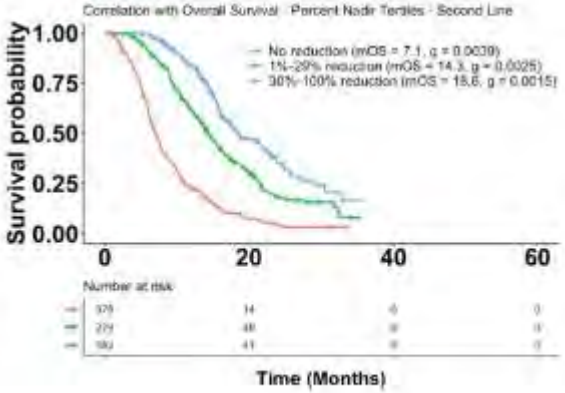
*Shaded areas represent the response evaluation criteria in solid tumors (diameter) and World Health Organization (product) criteria for change in tumor size to meet response and disease progression definitions.

Colon Cancer, Data: PRIME/VELOUR/MK646, Uni-Dimensional – 0/30/100

Kaplan Meier







Why do we need new methods to assess response?

Endpoints supporting early and late clinical development programs in oncology are fundamentally different

The development of new treatments in oncology is a long, costly, and too often unsuccessful process

Currently, the gold standard is overall survival

Tumor growth and regression rate

CANCER RESEARCH

VOLUME 24 SEPTEMBER 1964 NUMBER 8

Perspectives in Cancer Chemotherapy: Therapeutic Design*

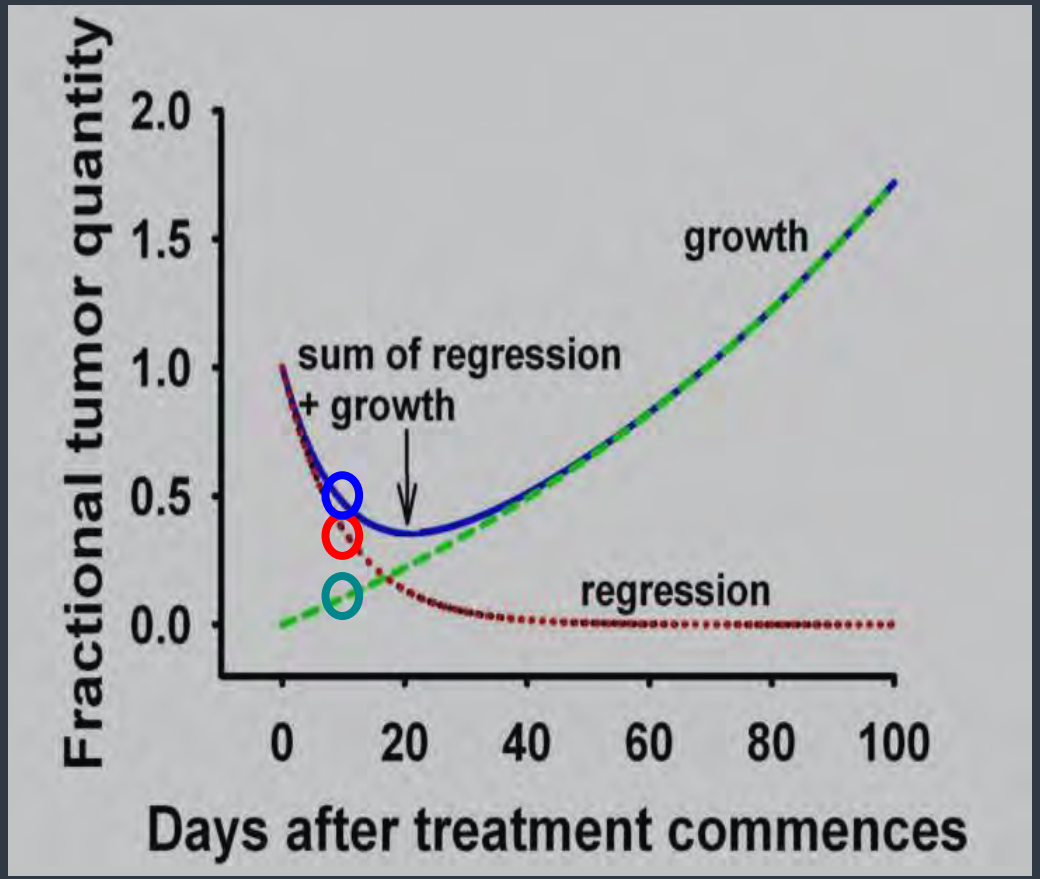
HOWARD E. SKIPPER

(*Kettering-Meyer Laboratories (Affiliated with the Sloan-Kettering Institute), Southern Research Institute Birmingham, Alabama*)

THE KINETIC BEHAVIOR OF L1210 LEUKEMIA CELLS IN THE UNTREATED HOST

Chart 1 shows the relationship between the number of leukemic cells inoculated and the average life span of the host. From these and supporting data (3), it may be deduced that there is about a 2-day lag period following inoculation of L1210 cells, after which they go into log phase, doubling every 0.55 days until such proliferation has produced a lethal number (*ca.* 1.5 billion leukemic cells).

Theory for regression and growth



$$F(t) = e^{(g \cdot t)} + e^{(-d \cdot t)} - 1$$

Where

f = tumor measurement in t days

g = growth rate constant

d = regression rate constant

Statistical package for R to calculate *g* and *d*

We developed a package in R software , designated as tumgr

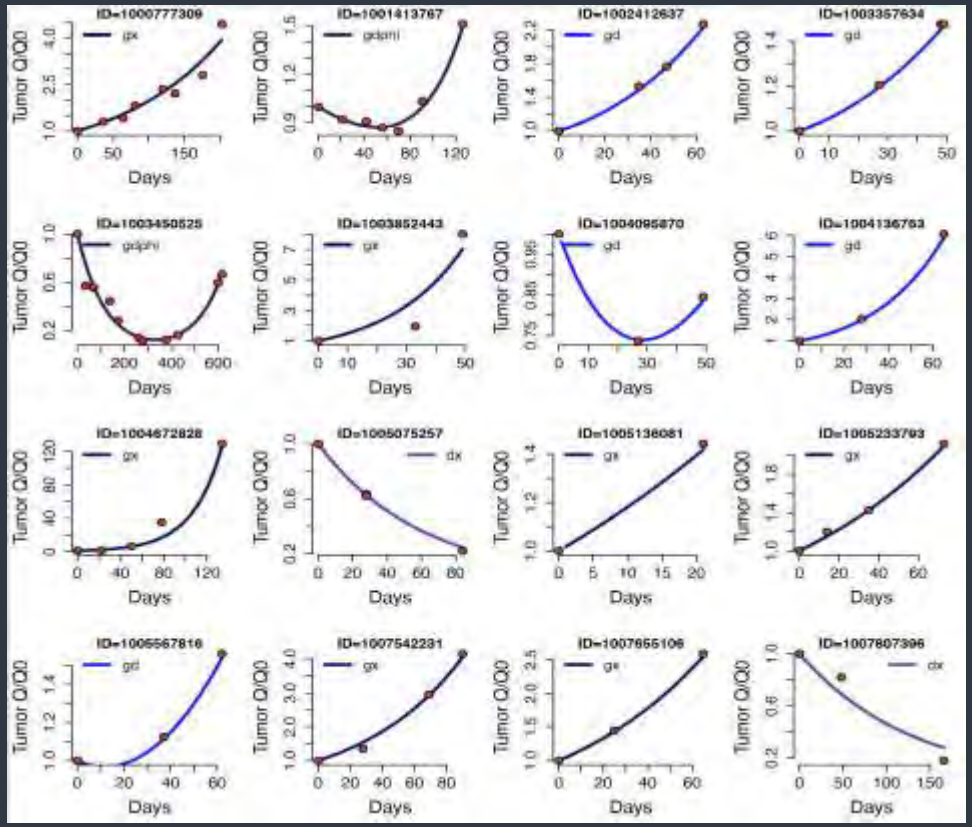
This allows us to obtain tumor growth rates using the models above

In cases where all parameters were significant predictors of tumor quantity (quantity at time t/quantity at time 0, given the specified cutoff value of 0.10) in more than one model, the model that minimized the Akaike Information Criterion (AIC) is selected.

Input

name	date	size
2	0	169.1
2	14	176
2	33	190.8
2	75	47.3
3	0	0.39
3	6	0.27
3	56	0.18
3	84	0.2
3	112	0.27
3	140	0.29
3	168	0.49
10	0	178.8
10	3	177
10	31	248.3
10	59	339.3
10	88	265.9
10	115	74.8

Output



Parameter	N	Median	IQR
g	539	0.00368	(0.001243, 0.008576)
d	462	0.014835	(0.00778, 0.026884)
phi	92	0.992159	(0.960662, 0.998713)

- Note that the curves are not drawn to fit the data but rather *are described by the fixed rate constants for **g, d** or both* that are estimated by an iterative process that assesses the fit of the data to each of four basic equations.

Relation of *g* value with tumor doubling time

The parameter ***g*** is related to the halving time of doubling (Td) by the formula **Td=0.693/g**, in which 0.693 is the natural logarithm (ie, log e) of 2

The formula for the relation between the time for the size of the tumor to decrease by half (T1/2) and the parameter ***d*** is the analogous
T1/2=0.693/***d***

g of 0.0024/day means a tumor doubling time of 288 days

Why calculate *g*-rate?

Prostate Cancer: Prednisone / Mitoxantrone / Docetaxel
Survival of *g* quartiles

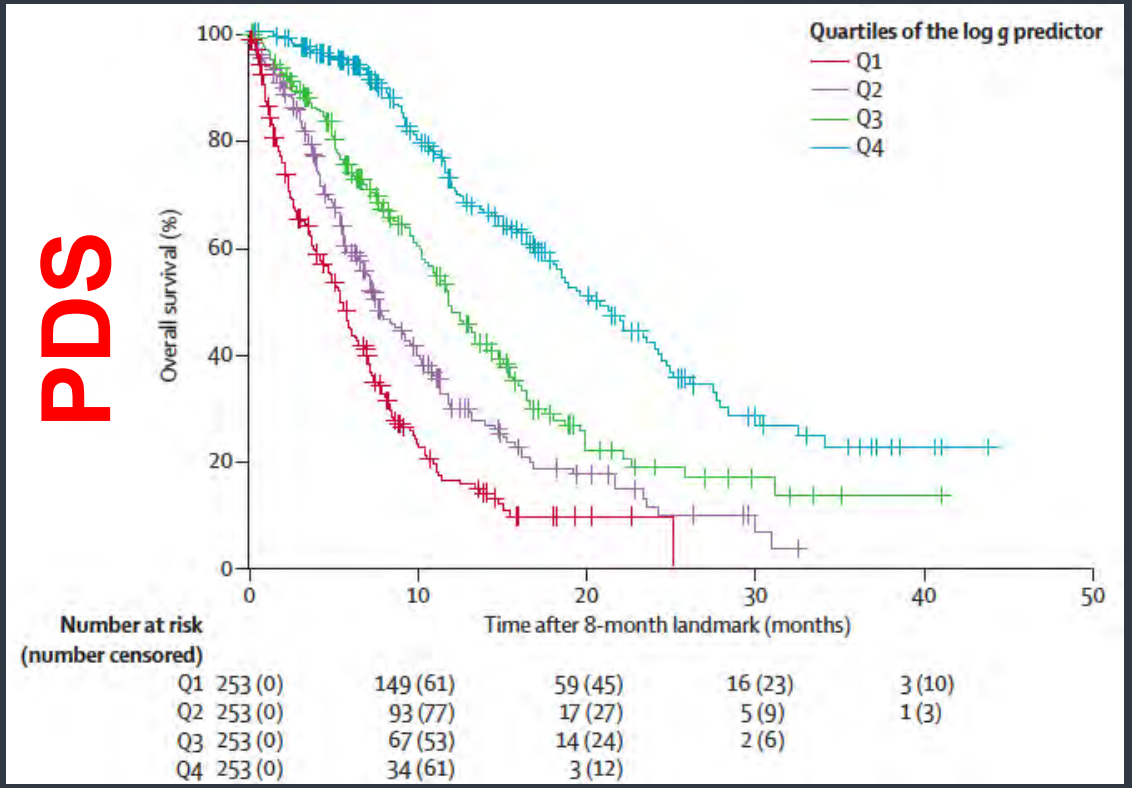
Estimation of tumour regression and growth rates during treatment in patients with advanced prostate cancer: a retrospective analysis

Julia Wilkerson, Kald Abdallah, Charles Hugh-Jones, Greg Curt, Mace Rothenberg, Ronit Simantov, Martin Murphy, Joseph Morrell, Joel Beetsch, Daniel J Sargent†, Howard I Scher, Peter Lebowitz, Richard Simon, Wilfred D Stein, Susan E Bates, Tito Fojo*

Wilkerson J,. Lancet Oncol. 2017 Jan;18(1):143-154.

Correlation of OS with *g* quartiles using clinical trial data

PDS



VA Informatics and Computing Infrastructure (VINCI)

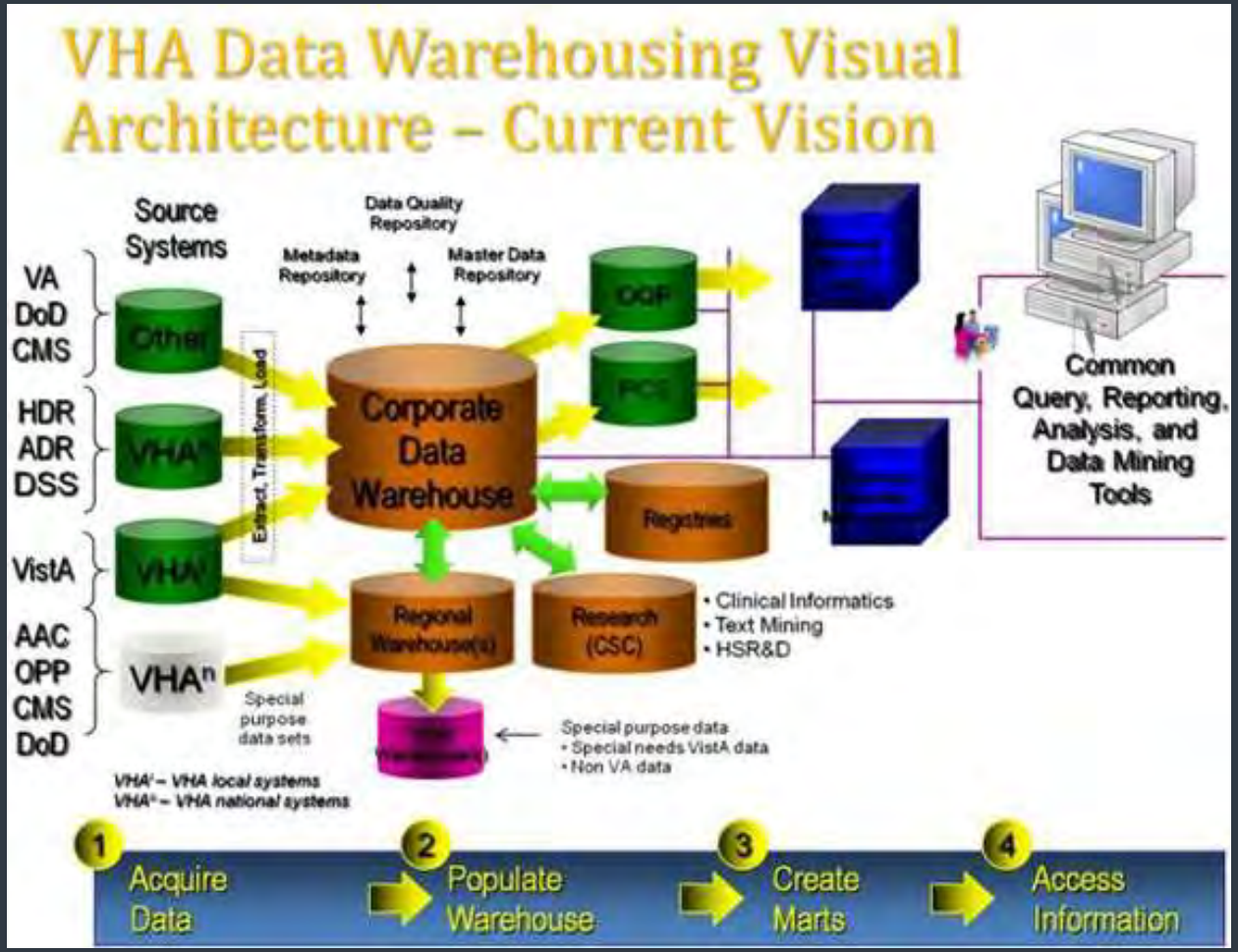
VA has the oldest electronic medical record system

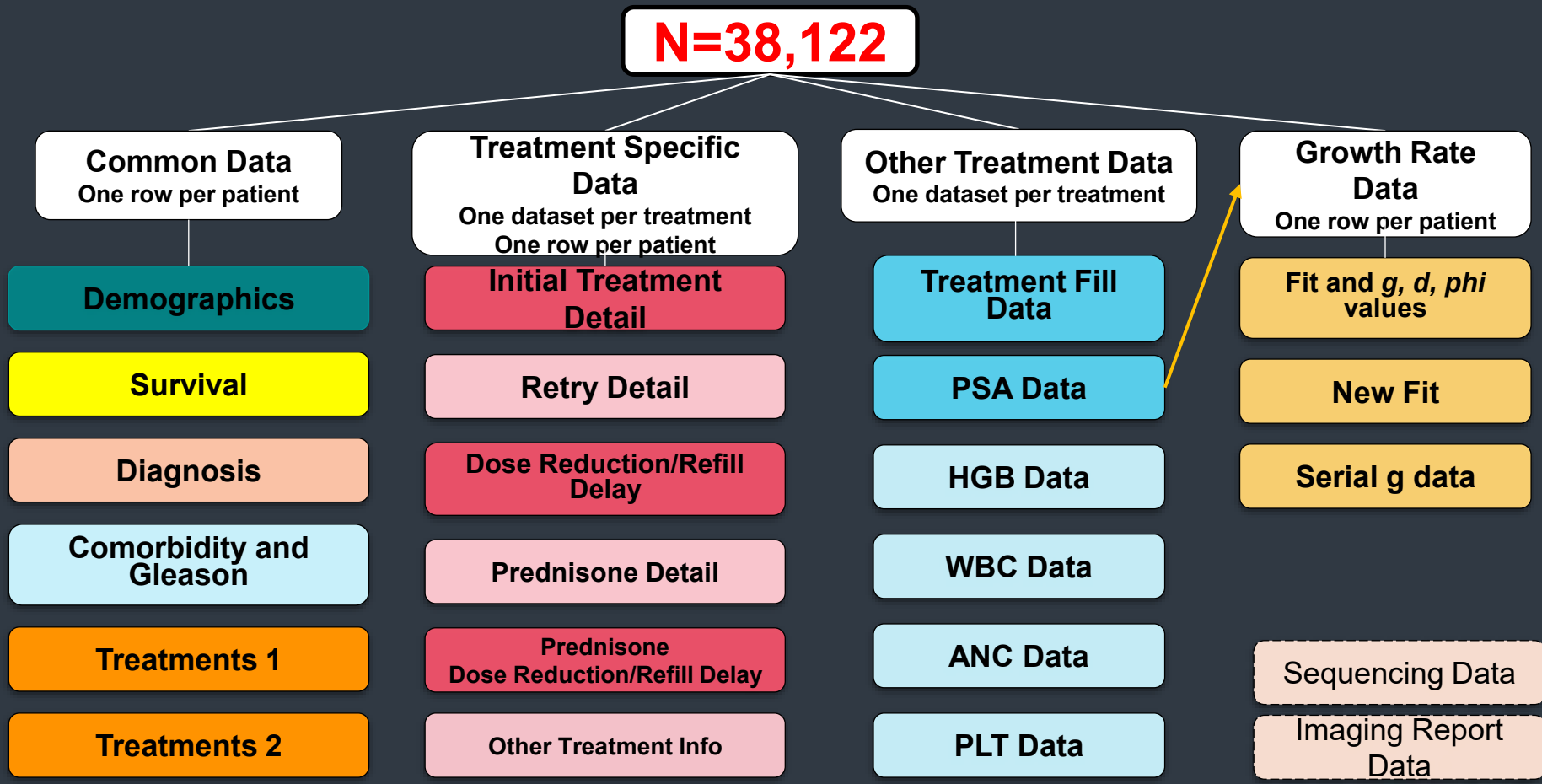
VINCI is an initiative to improve researchers' access to VA data and to facilitate the analysis of those data while ensuring Veterans' privacy and data security

Infrastructure connects all VHA data at a national level

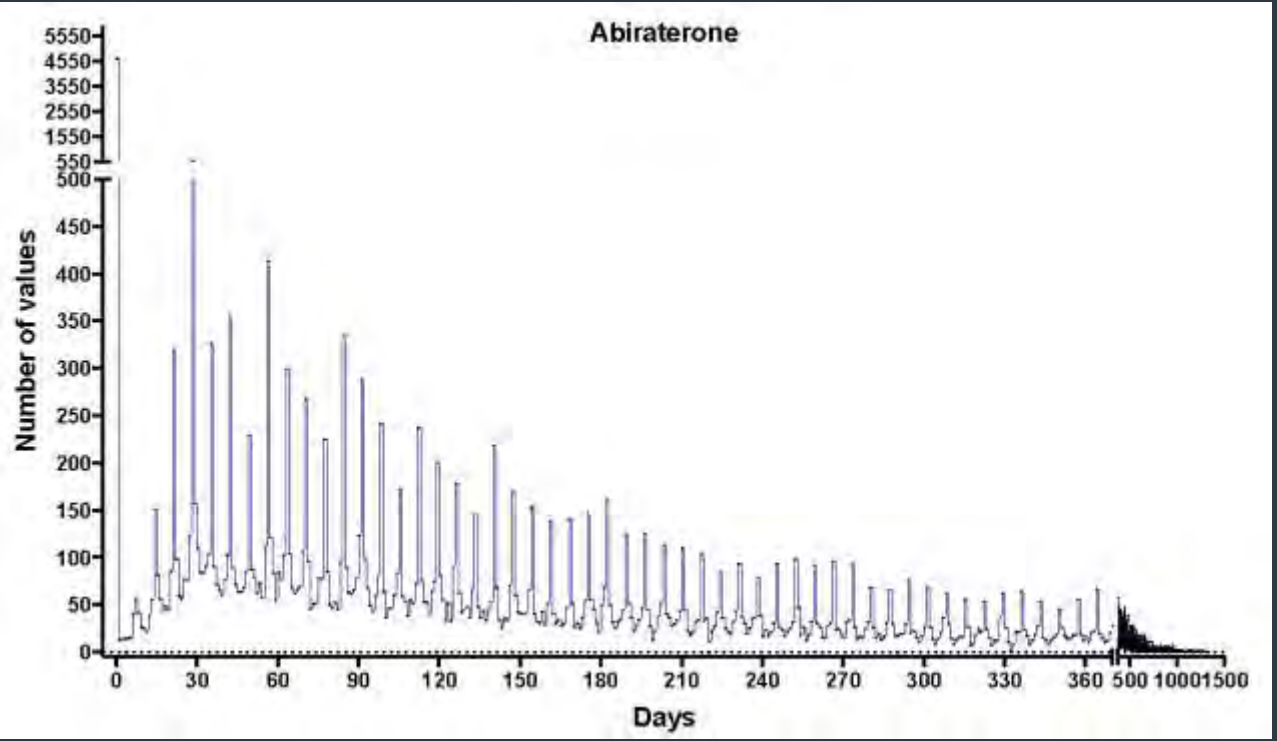
One of richest real world data source available

VHA Data Warehousing Visual Architecture – Current Vision



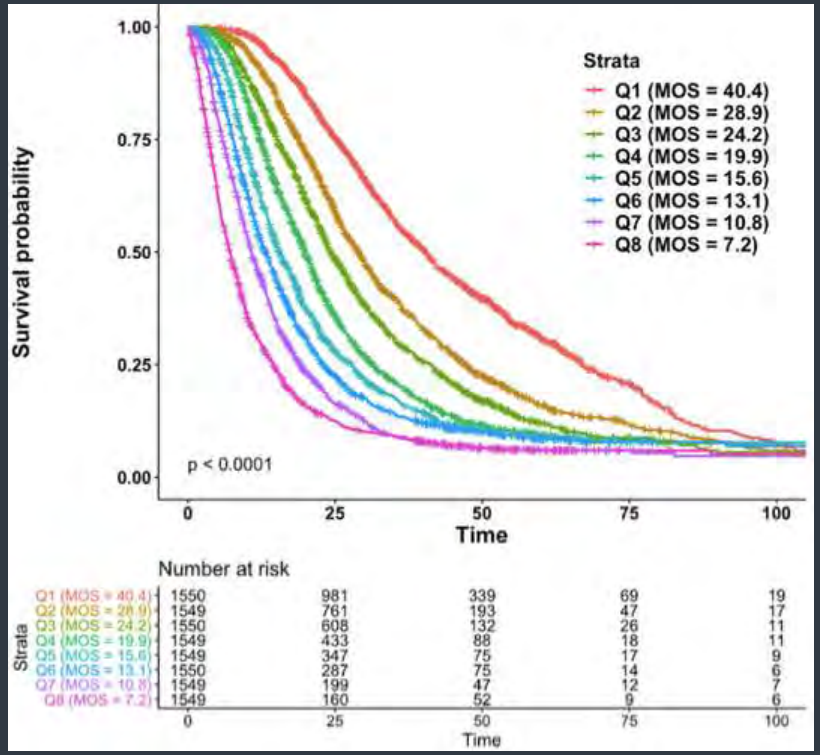

N=38,122
Common Data
One row per patient
Demographics
Survival
Diagnosis
Comorbidity and Gleason
Treatments 1
Treatments 2
Treatment Specific Data
One dataset per treatment
One row per patient
Initial Treatment Detail
Retry Detail
Dose Reduction/Refill Delay
Prednisone Detail
Prednisone Dose Reduction/Refill Delay
Other Treatment Info
Other Treatment Data
One dataset per treatment
Treatment Fill Data
PSA Data
HGB Data
WBC Data
ANC Data
PLT Data
Growth Rate Data
One row per patient
Fit and g, d, phi values
New Fit
Serial g data
Sequencing Data
Imaging Report Data
-15 before START to +15 after END

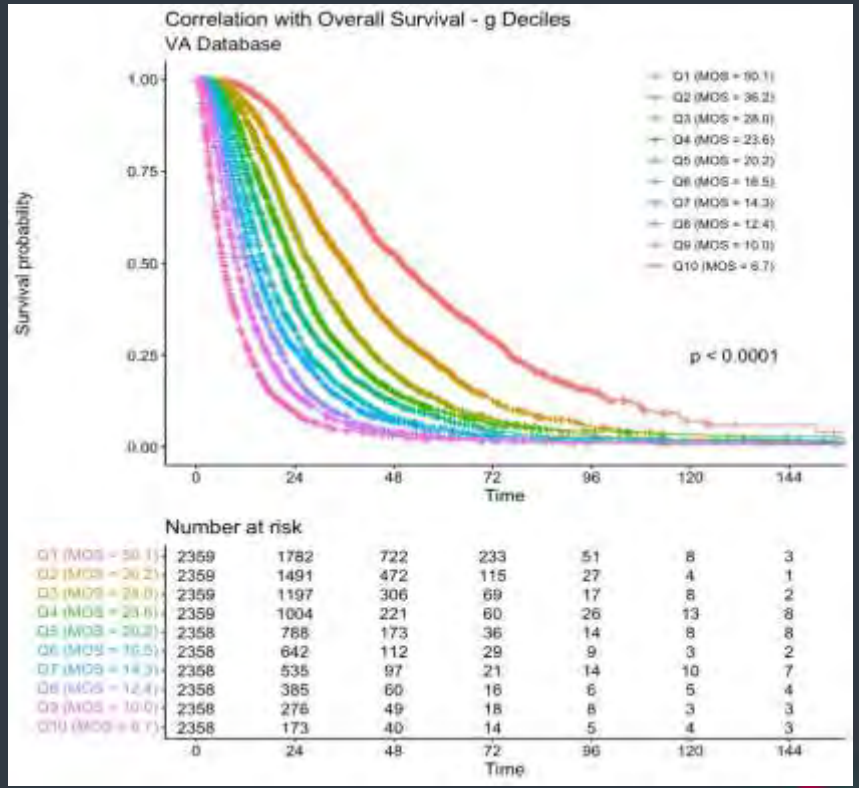
Most patient had monthly PSA assessments



Leuva et al 2019

g is a biomarker of OS even when combining real-world data and clinical trial data





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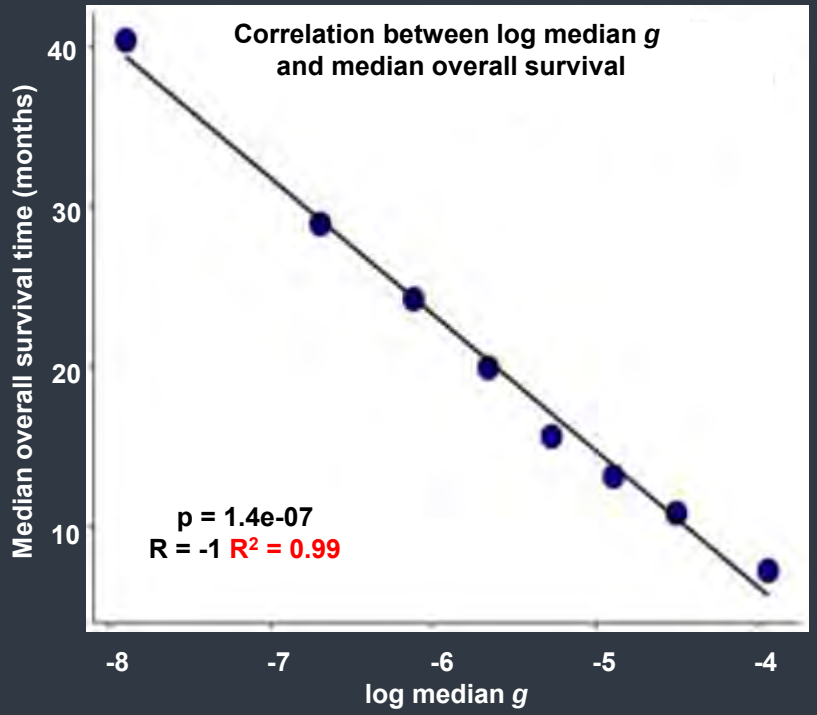
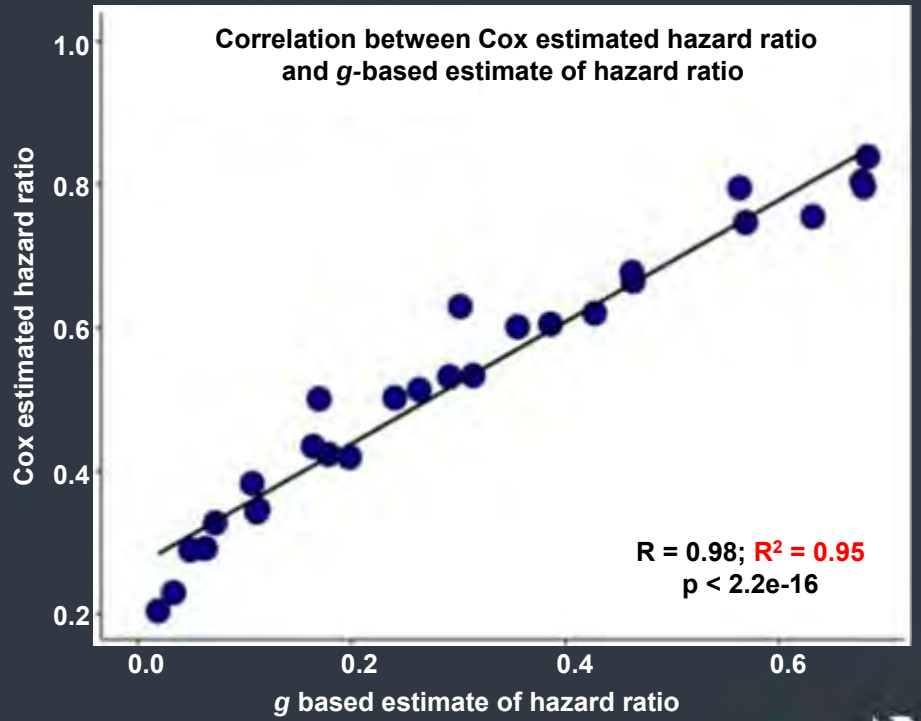
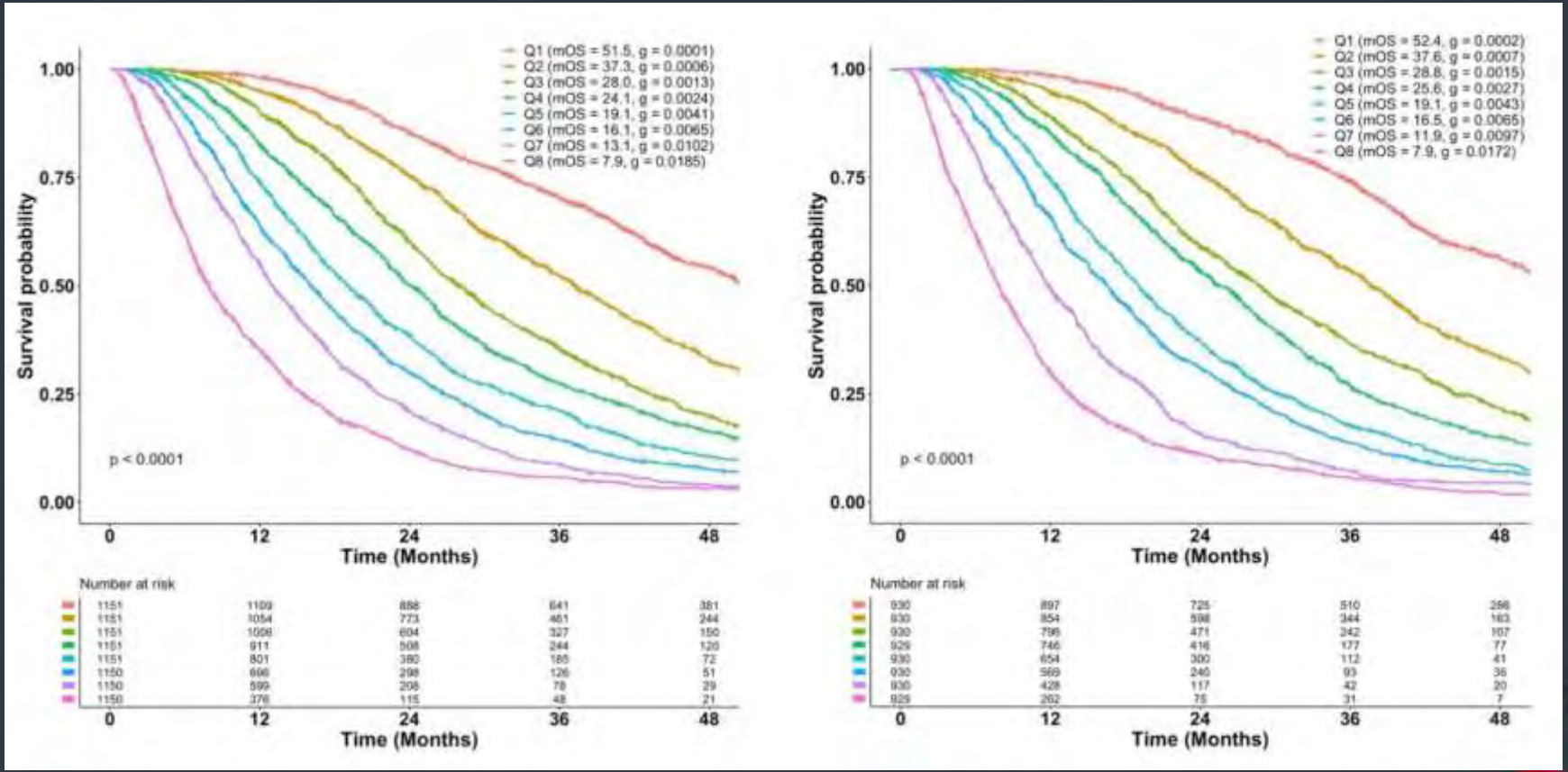




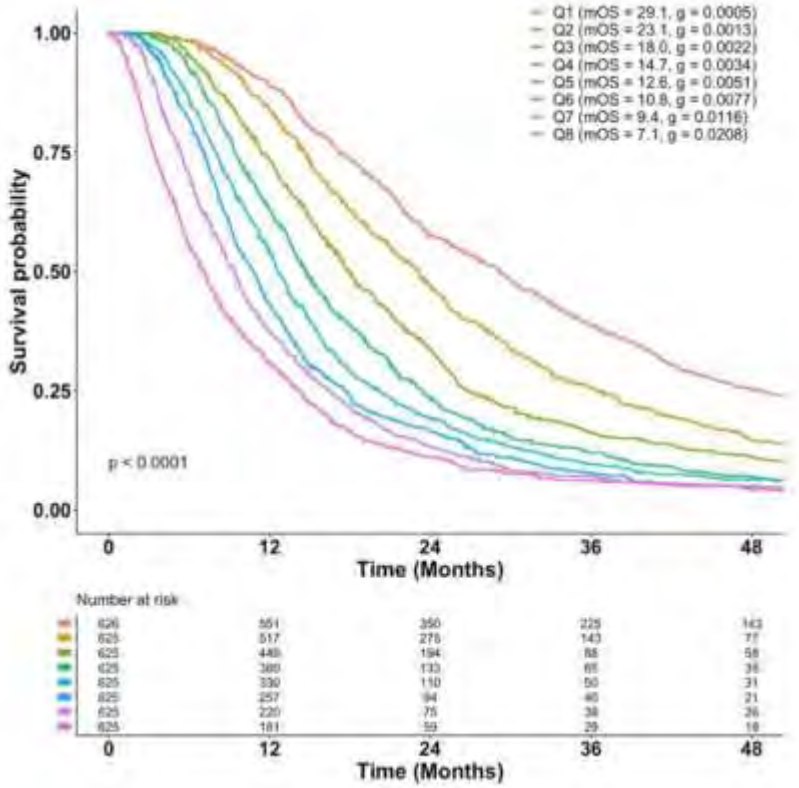
Correlation of *g* values with OS - hormonal therapy

Abiraterone [9205] Enzalutamide [7438]

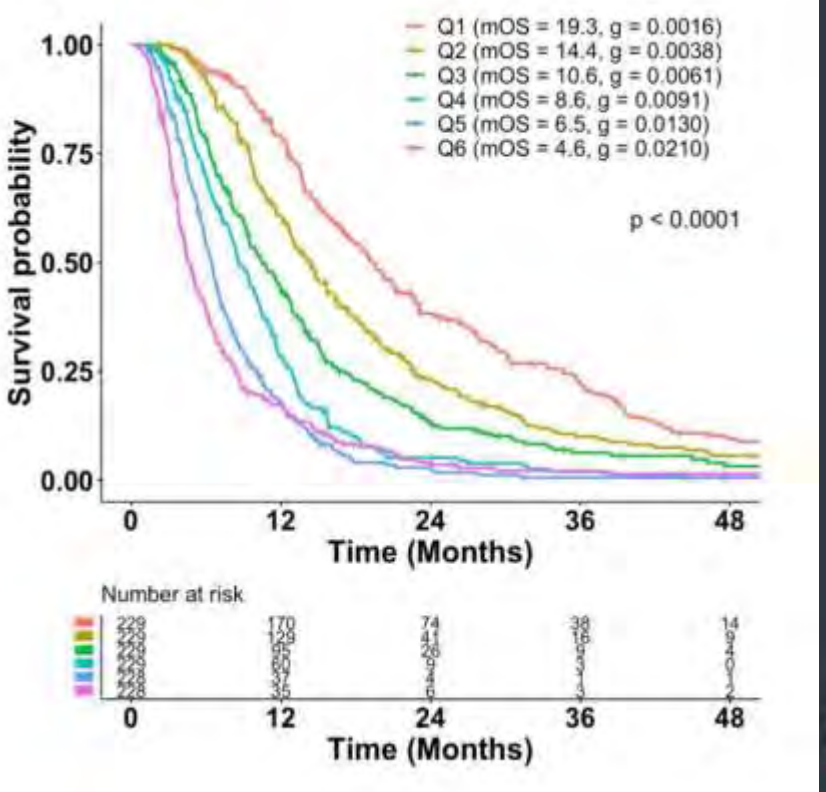


Correlation of *g* values with OS - chemotherapy

Docetaxel [5001]

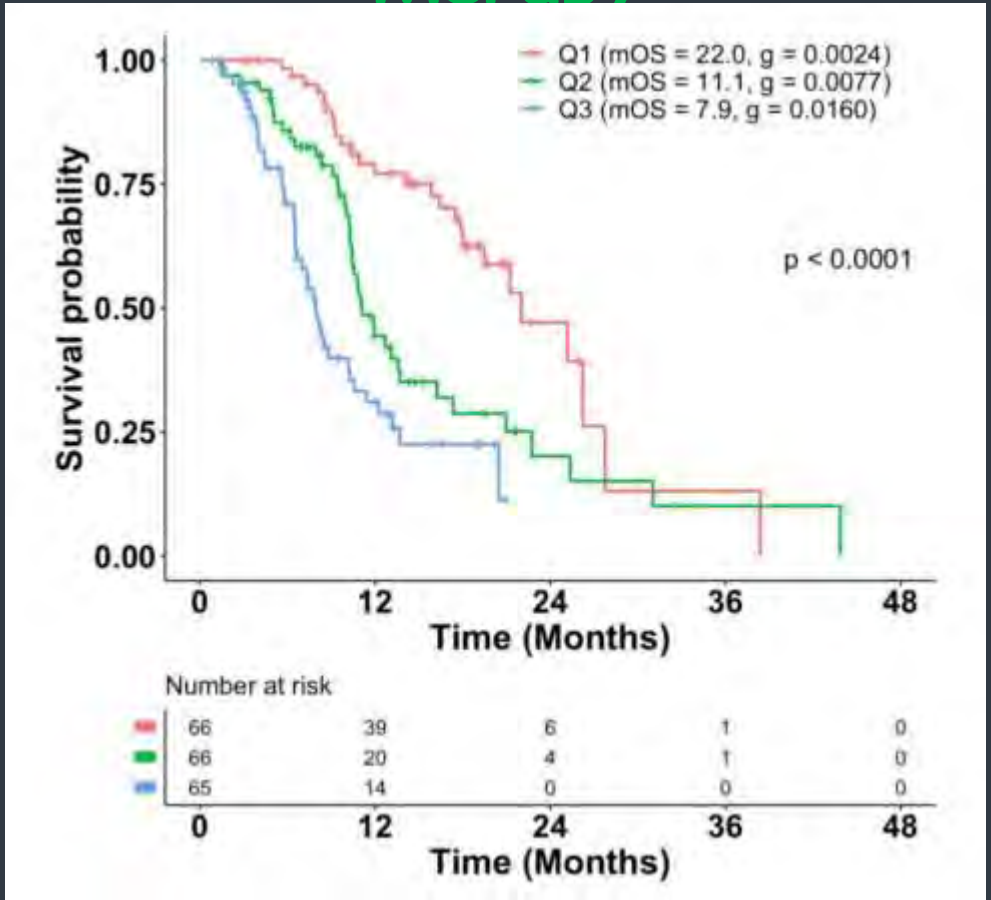


Cabazitaxel [1372]

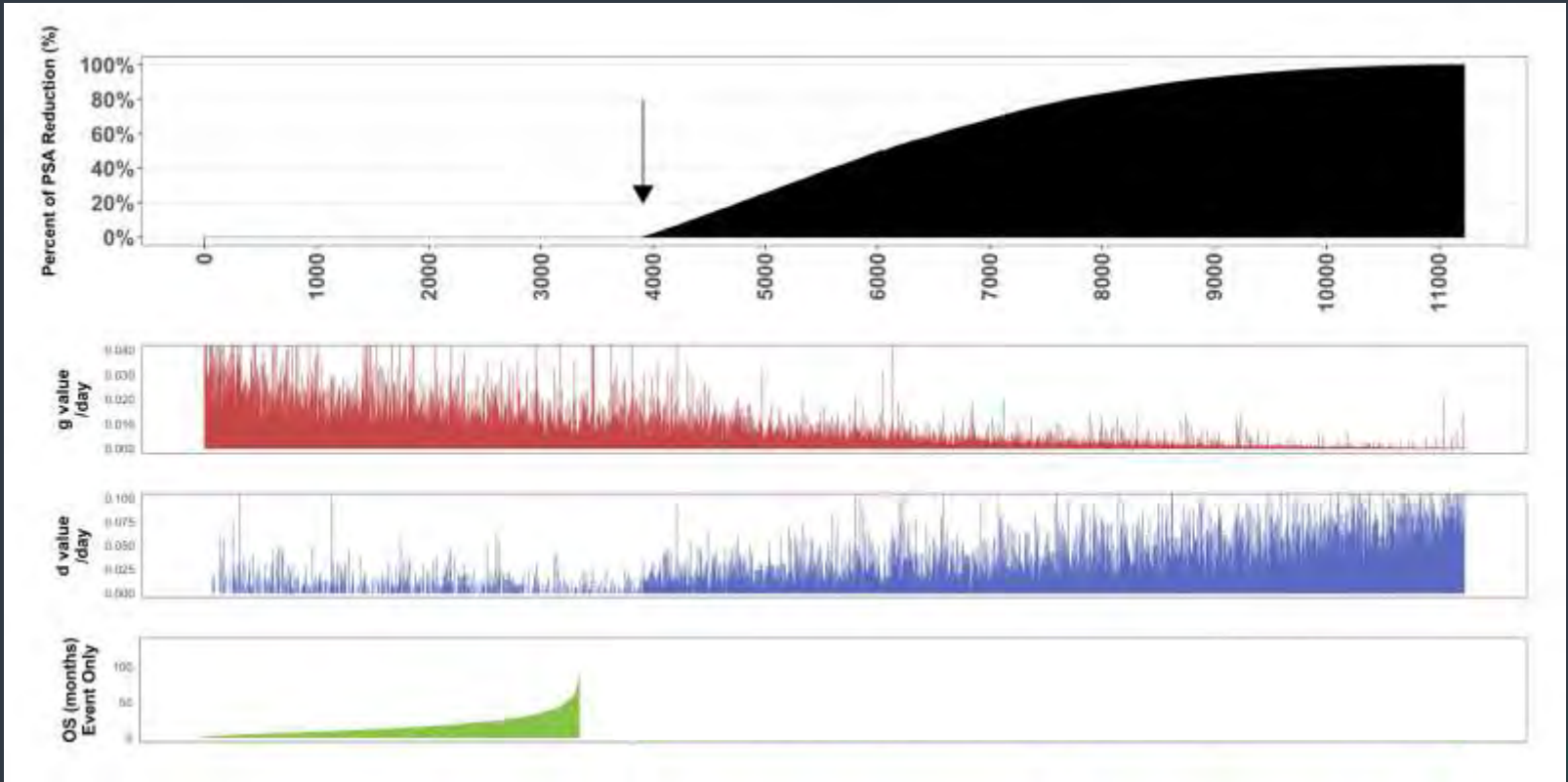


Correlation of *g* values with OS – targeted therapy

Olaparib [197]



g-rate method can identify patient who benefit despite no PSA decline



g-rate based Doubling time (DT)

Von Hoff's paradigm for targeted therapy

Progression Free Survival

PFS ratio =PFS on MP-selected therapy/PFS on prior therapy

The molecular profiling(MP) approach was deemed of clinical benefit for the individual patient who had a PFS ratio(PFS on MP-selected therapy/PFS on prior therapy) of ≧1.3.

D. D. Von Hoff et al. *Journal of Clinical Oncology*(2010)

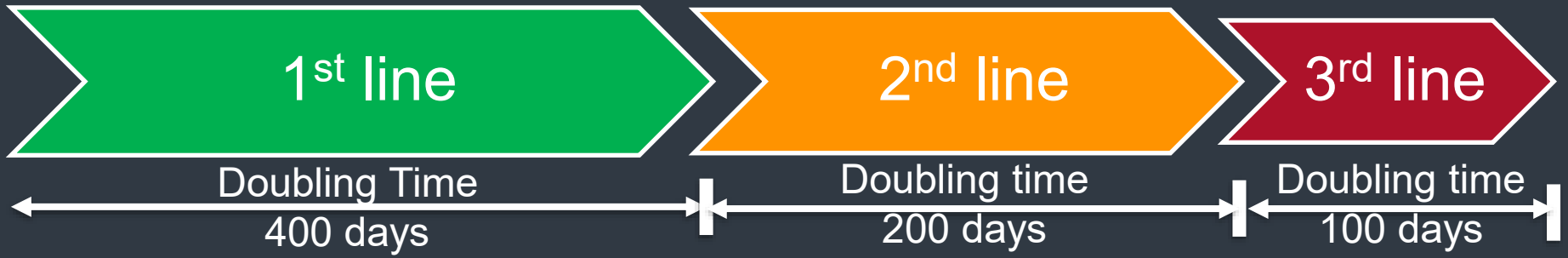
Relation of *g* value with tumor doubling time (DT)

The parameter g is related to the halving time of doubling (DT) by the formula **DT=0.693/g**, in which 0.693 is the natural logarithm (ie, log e) of 2

The formula for the relation between the time for the size of the tumor to decrease by half (T1/2) and the parameter d is the analogous
T1/2=0.693/d

g of 0.0024/day means a tumor doubling time of 288 days

g-rate doubling time (DT) based on line of therapy



Doubling Time (DT) ratio calculation

$$\frac{\text{g-rate based DT on current medication}}{\text{g-rate based DT on medication Just before current medication}} \geq 1 = \text{Benefit}$$

olaparib efficacy in U.S. Veterans with metastatic prostate cancer (mPC)

Veterans had

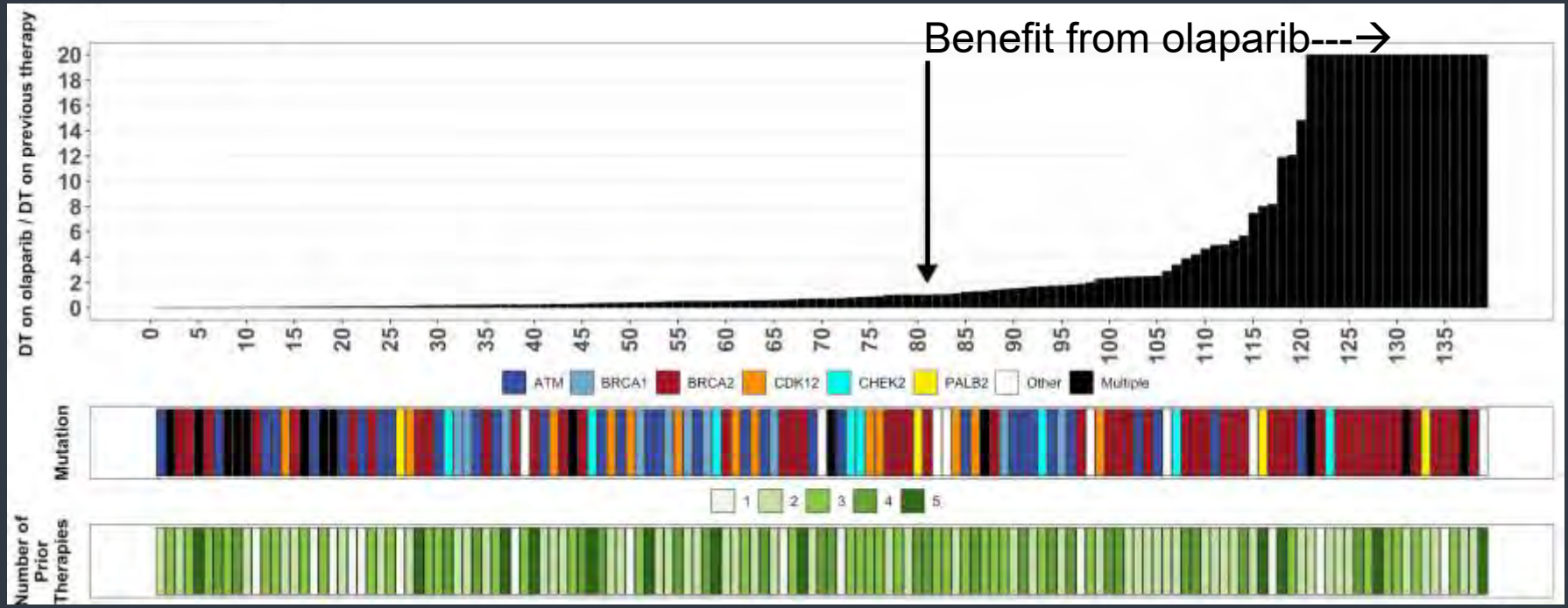
1) mPC with somatic or germline alterations/mutations in genes involved in homologous repair recombination (HRR),
2) received olaparib (PARP inhibitor) and a novel hormonal therapy or chemotherapy, and
3) estimable rates of tumor growth (***g*-**rate) using PSA values obtained while receiving treatments

Identified 139 Veterans which met above criteria

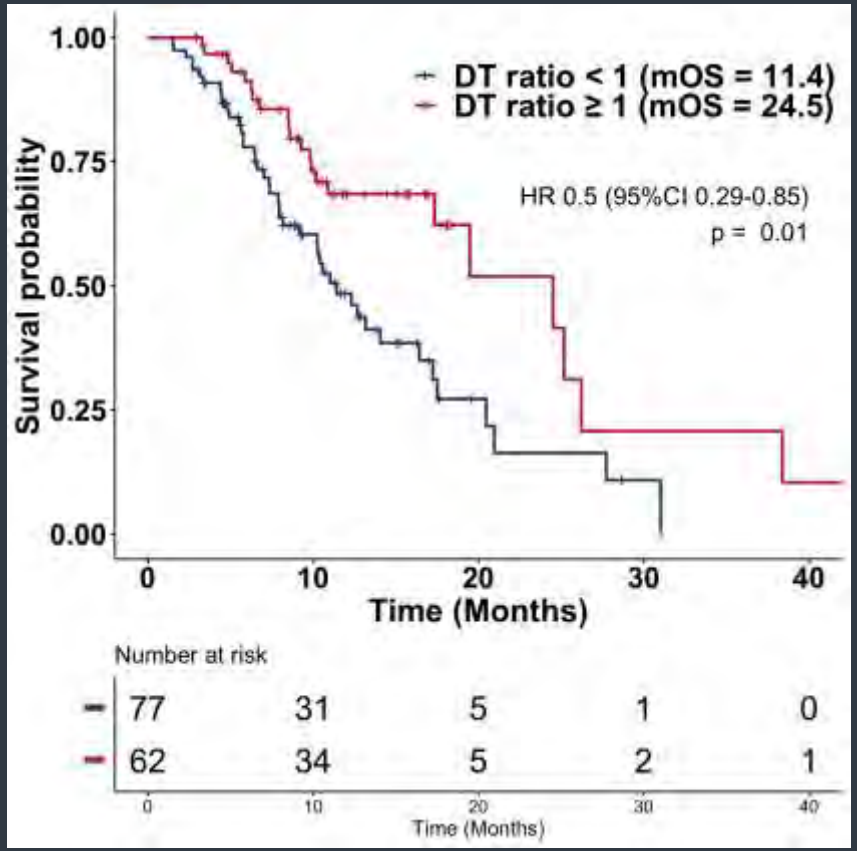
Doubling Time (DT) ratio calculation

$$\frac{\text{g-rate based DT on olaparib}}{\text{g-rate based DT on medication Just before olaparib}} \geq 1 = \text{Benefit}$$

62 of 139(45%) postulated to have benefit

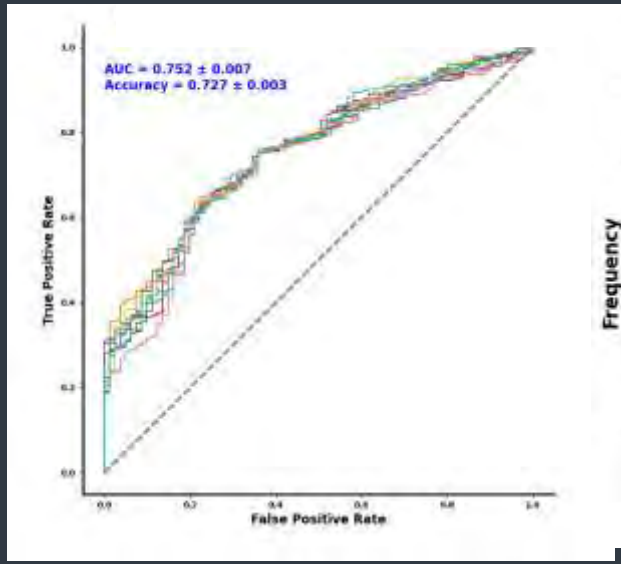


DT ratio ≥ 1 correlated with improved survival



g-rate based Machine learning / AI model

g-rate based machine learning model



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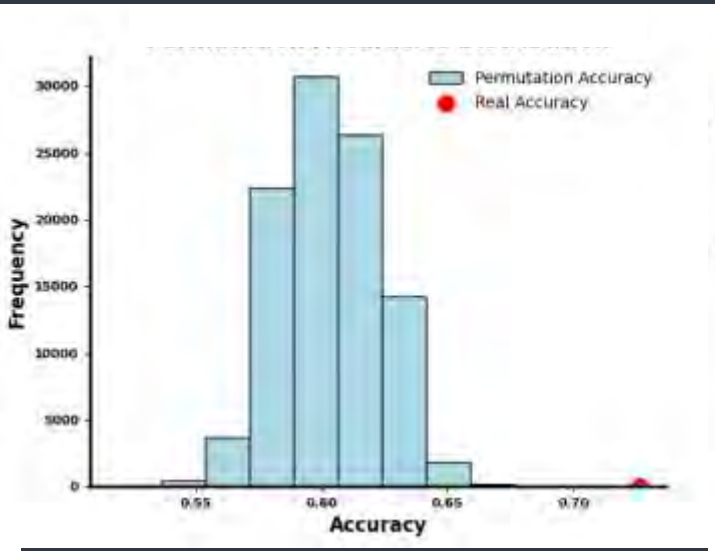

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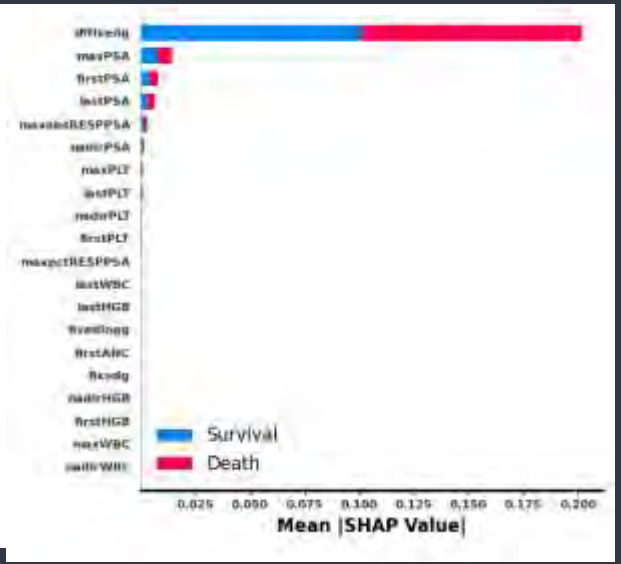


C

Take home points

Estimate of g values and tumor doubling times(DT) correlate with overall survival, the FDA gold standard

Ideal way to analyze real world data as it is not affected by assessment intervals

It has wide applicability – so far studied in RCC, prostate, lung cancer, colorectal cancer, medullary thyroid cancer, breast cancer, neuroendocrine cancer, pancreatic cancer, melanoma

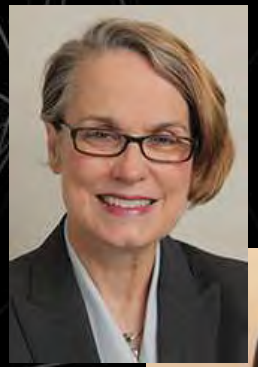
As a rule, successive therapies result in faster rates of growth. By using each Veteran (patient) as his own control, one can confidently assess the value of a therapy by comparing the g value of the experimental therapy to the g value of the therapy just before.

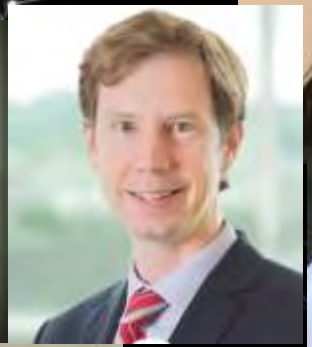
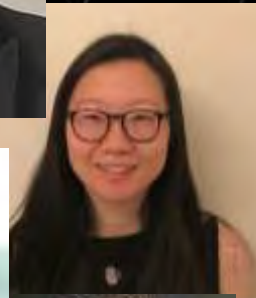
g-rate based machine learning model seems to be performing excellently in predicting survival in prostate cancer in early feasibility study

Thank you

Dr. Tito Fojo
Mengxi Zhou
Dr. Susan Bates
Dr. Jieqiong Wang
Dr. Raymond Bergan
Dr. Benjamin Teply
Dr. Carol Luhrs
Dr. Anna Park
Melody Rosenberg





Mengxi Zhou

University of Nebraska Medical Center

Nebraska Medicine