Computational Approaches to the Optimization of Dose and Schedule: Computational Science in Immuno-Oncology

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Disclosure

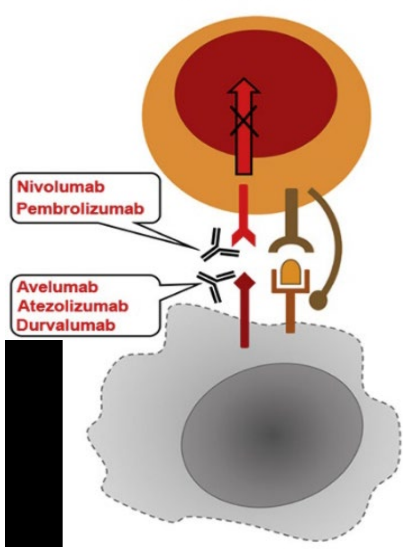
- Founder and CSO of AIQ Solutions

Incredible success of immunotherapy – but it comes with the price!

- Immune checkpoint inhibitors (ICI) prevent cancer cells from suppressing immune response (Weber *et al.* 2010)
  - “Take the brakes off” the immune system
- ICI improve survival in multiple cancers…

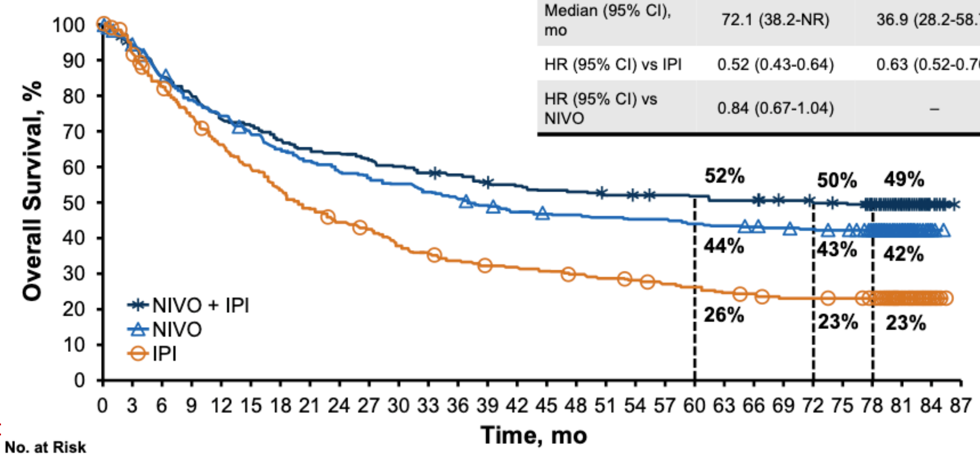
…but also lead to significant adverse events

Inhibition of the PD-1 immune checkpoint protein (Hargadon *et. al.* 2018)



Metastatic melanoma

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	72.1 (38.2-NR)	36.9 (28.2-58.7)	19.9 (16.8-24.6)
HR (95% CI) vs IPI	0.52 (0.43-0.64)	0.63 (0.52-0.76)	–
HR (95% CI) vs NIVO	0.84 (0.67-1.04)	–	–



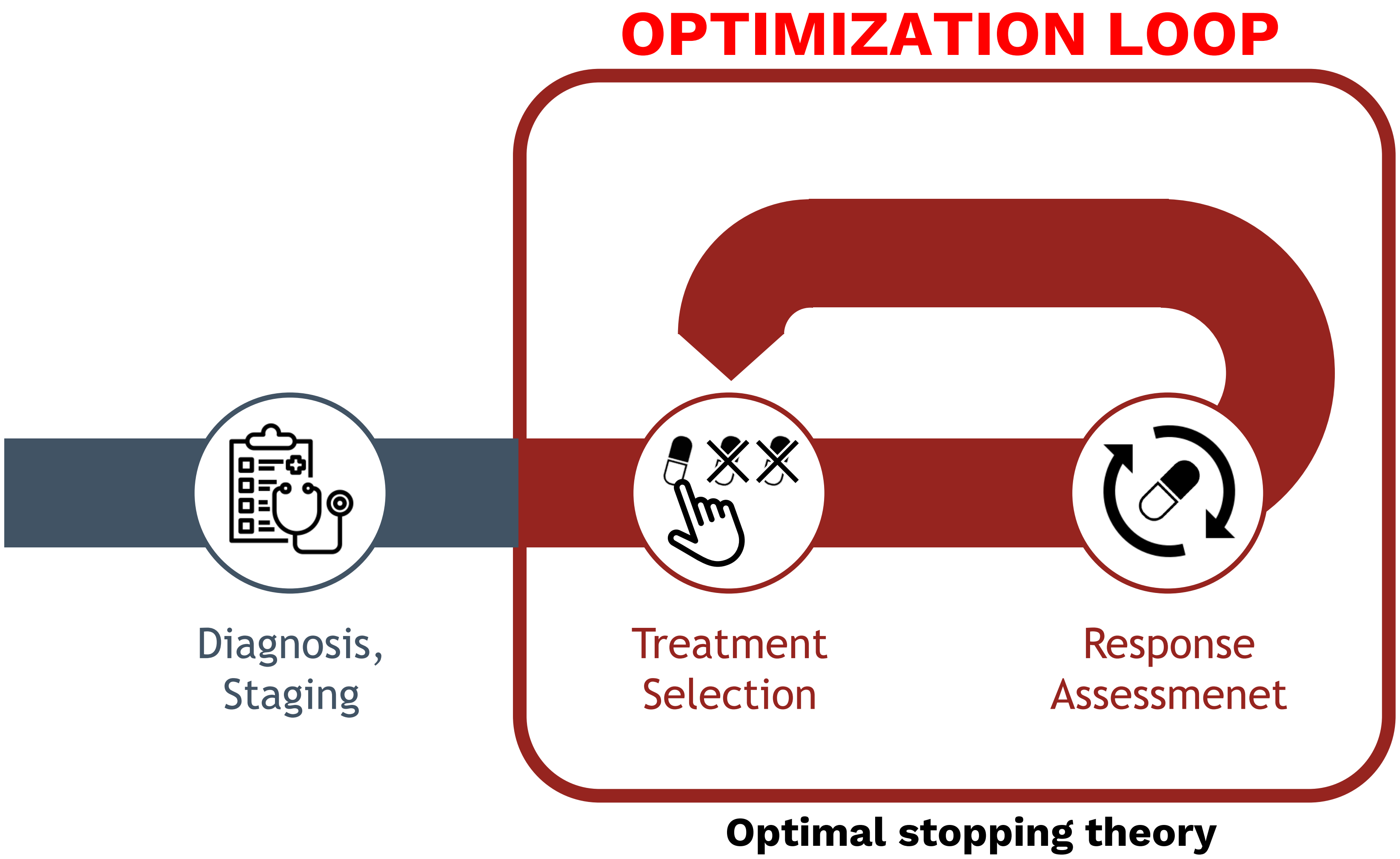
Schc
and
OF WISCONSIN–MADISON

CHECKMATE-067 Trial 6.5 yr outcomes:

- Ipilimumab/Nivolumab vs Nivolumab vs Ipilimumab
- Median Overall Survival (Adverse Events):
  - **Ipi/Nivo** **72.1 months** **(59%)**
  - **Nivo** **36.9 months** **(28%)**
  - **Ipi** **19.9 months** **(19%)**
  - **No ICI** **~6 months**

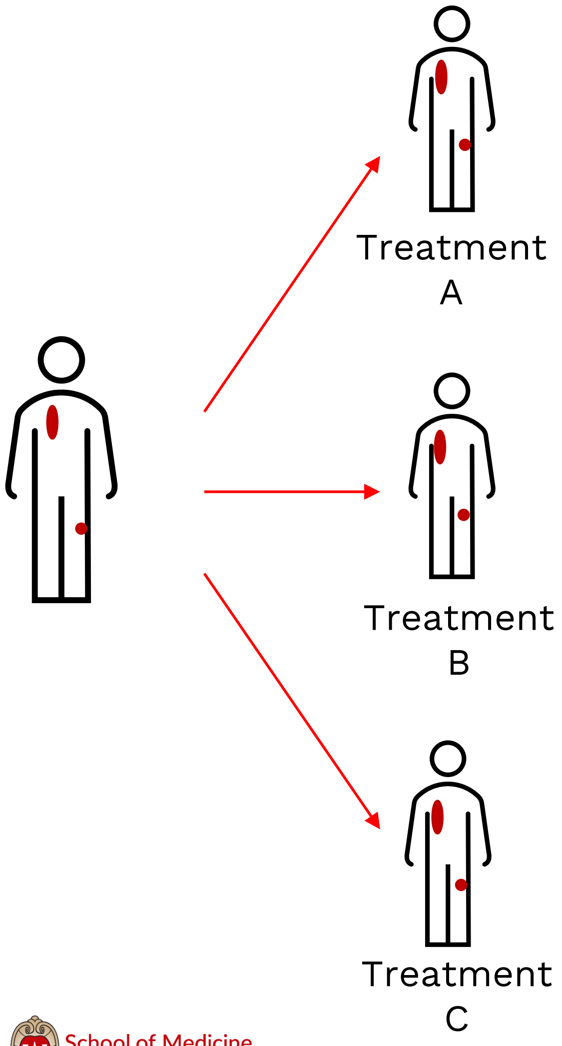
Wolchok *et al*, 2017, N Engl J Med; 377: 1345
Wolchok *et al*, 2022, J Clin Oncol 40(2):127

Optimizing dose and schedule - “optimizing patient treatment journey”

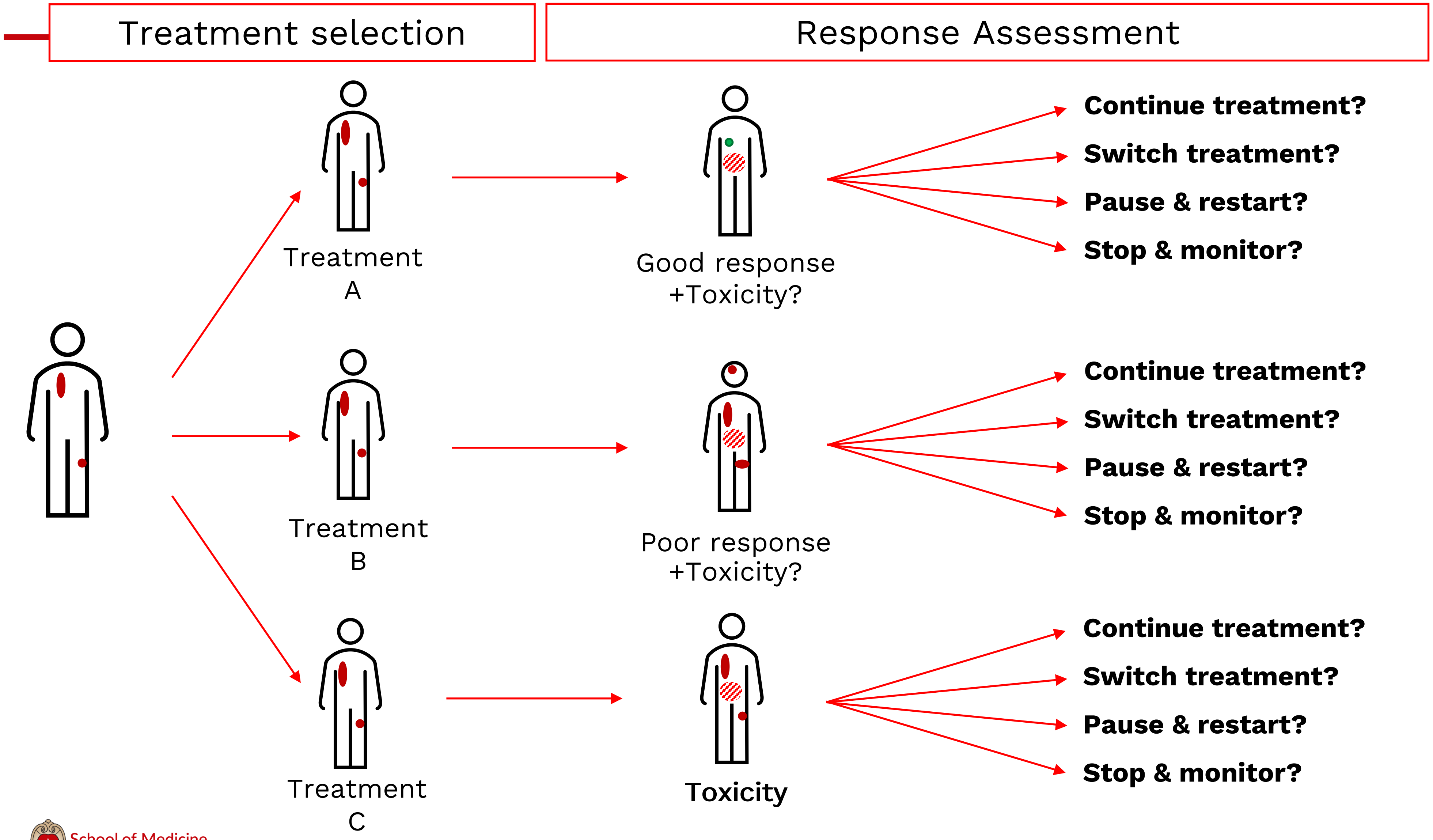


Optimizing treatment schedules

Treatment selection | Response Assessment



Optimizing treatment schedules



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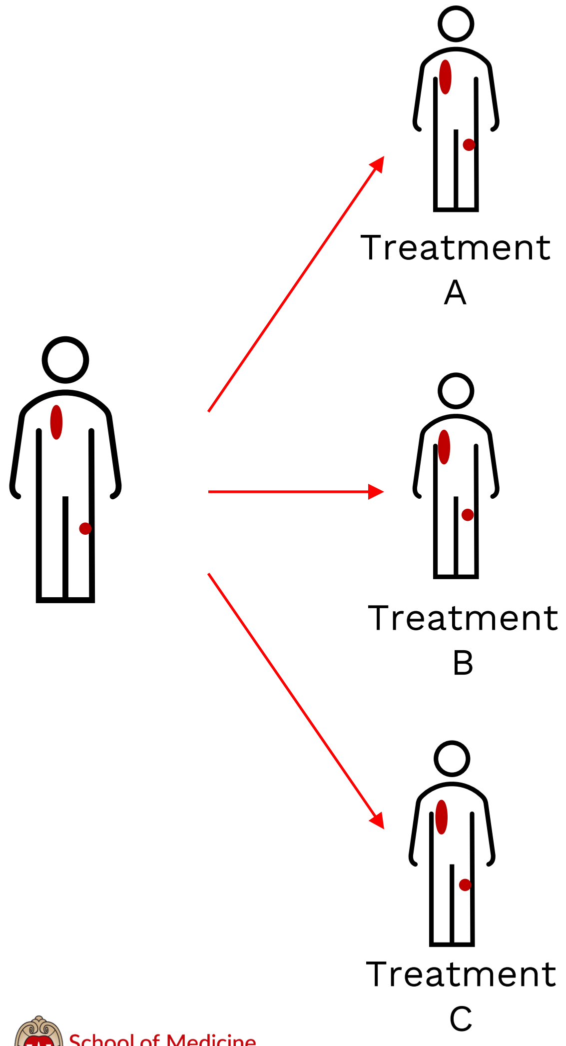
Balancing risks and benefit

Treatment selection

Response Assessment

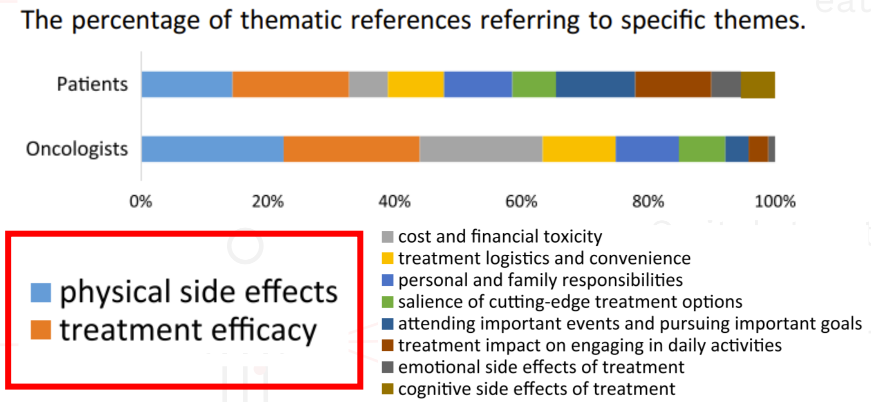


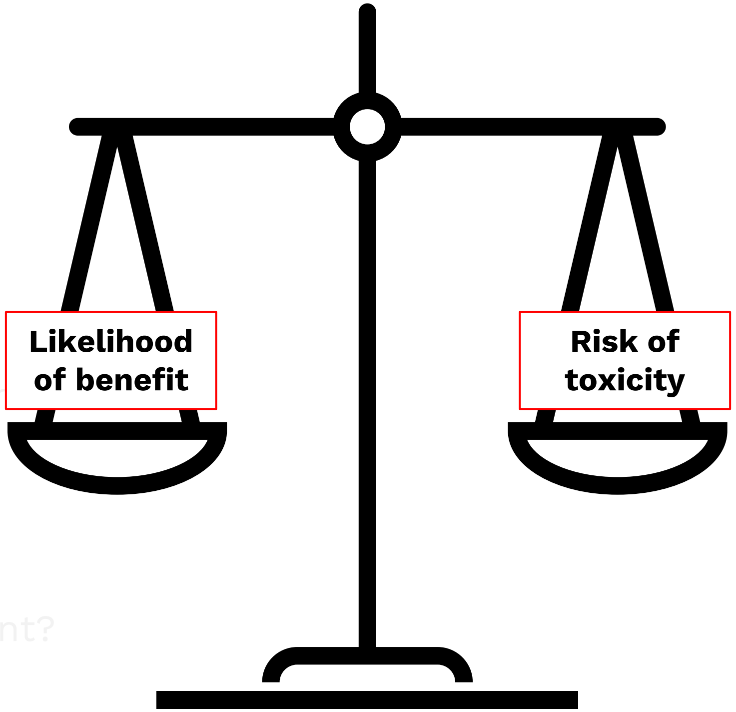
The Oncologist

Breast Cancer

What Is Important When Making Treatment Decisions in Metastatic Breast Cancer? A Qualitative Analysis of Decision-Making in Patients and Oncologists

Gabrielle B. Rocque,[a,b,c] Aysha Rasool,[d] Beverly R. Williams,[c] Audrey S. Wallace,[e] Soumya J. Niranjan,[a] Karina I. Halilova,[b] Yasemin E. Turkman,[f] Stacey A. Ingram,[b] Courtney P. Williams,[b] Andres Forero-Torres,[a,b] Tom Smith,[i] Smita Bhatia,[g] Sara J. Knight[h]





(Rocque *et. al.*, 2019)

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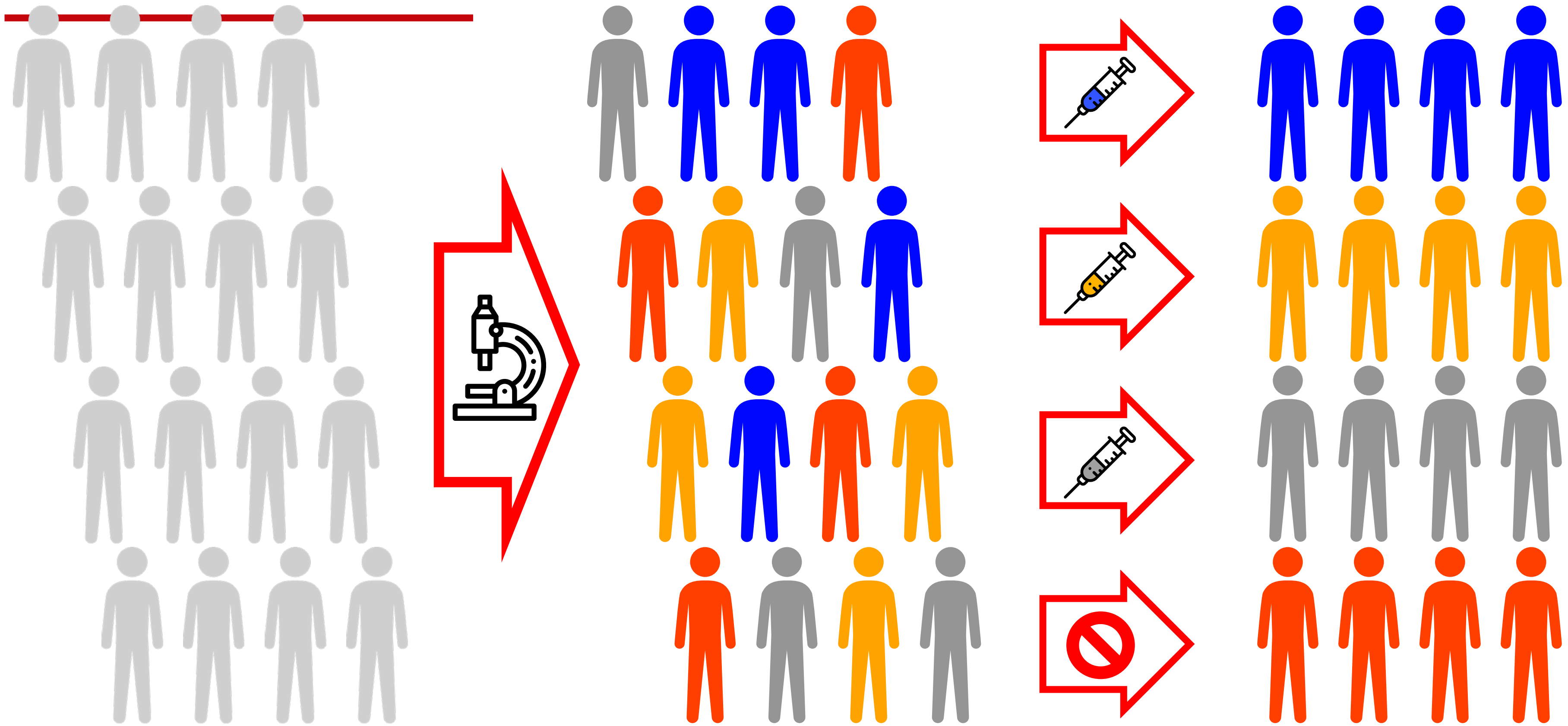
PRECISION MEDICINE

- The problem of response heterogeneity
- The problem of treatment resistance

Precision medicine aims for this...



Not all patients respond the same to any given therapy, therefore different treatments need to be chosen

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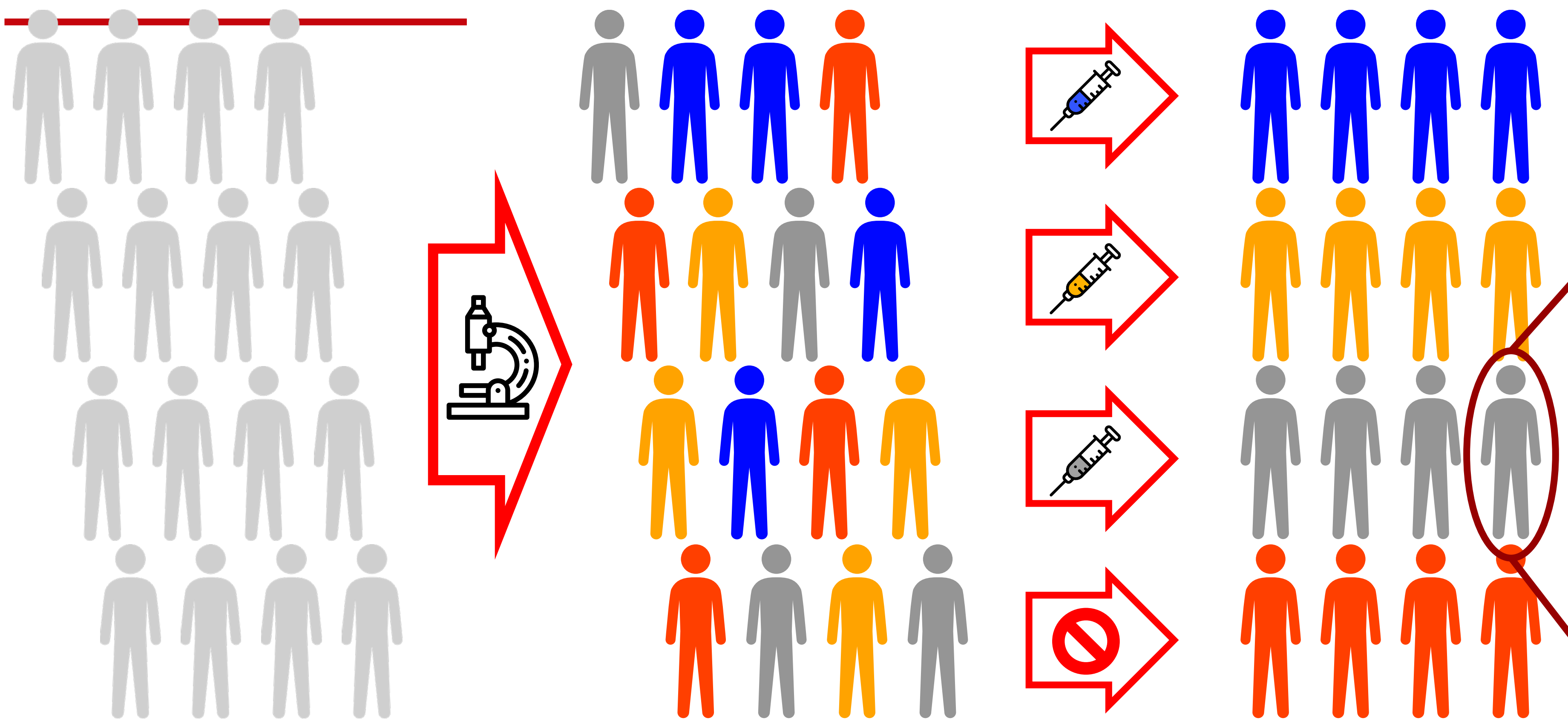
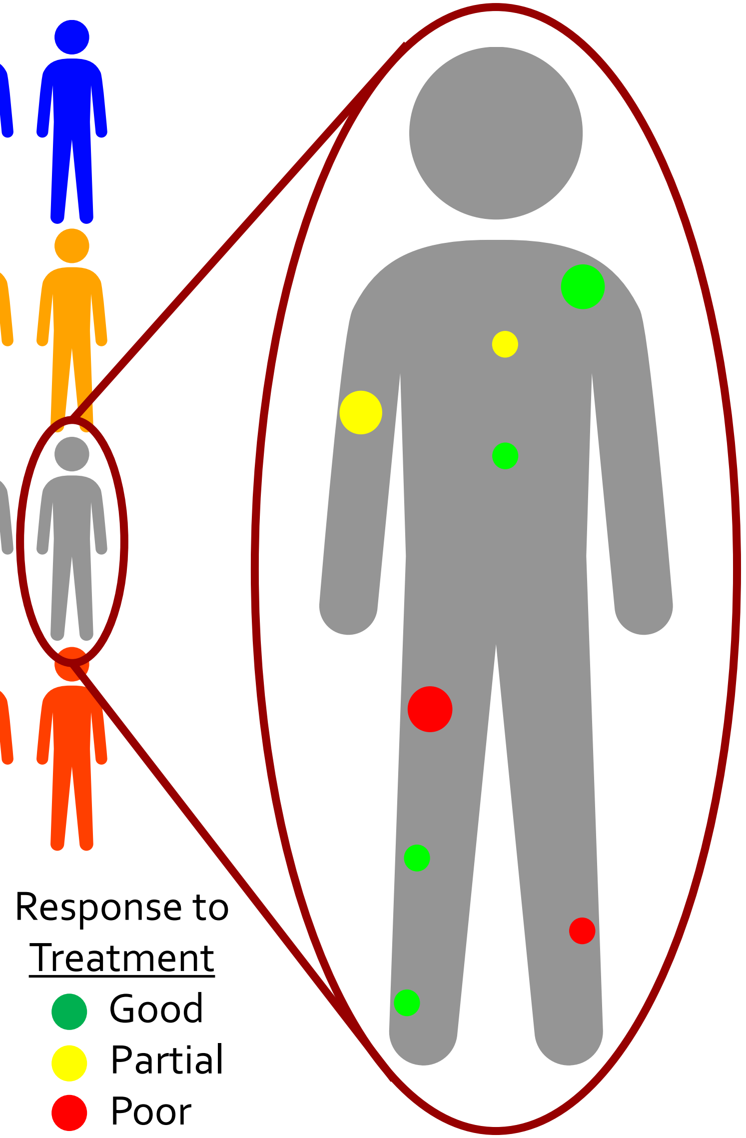
Icons made by Freepik from www.flaticon.com

...but there is a big problem!





Just as not all patients respond the same to any given therapy, not all disease sites within a given patient respond the same.

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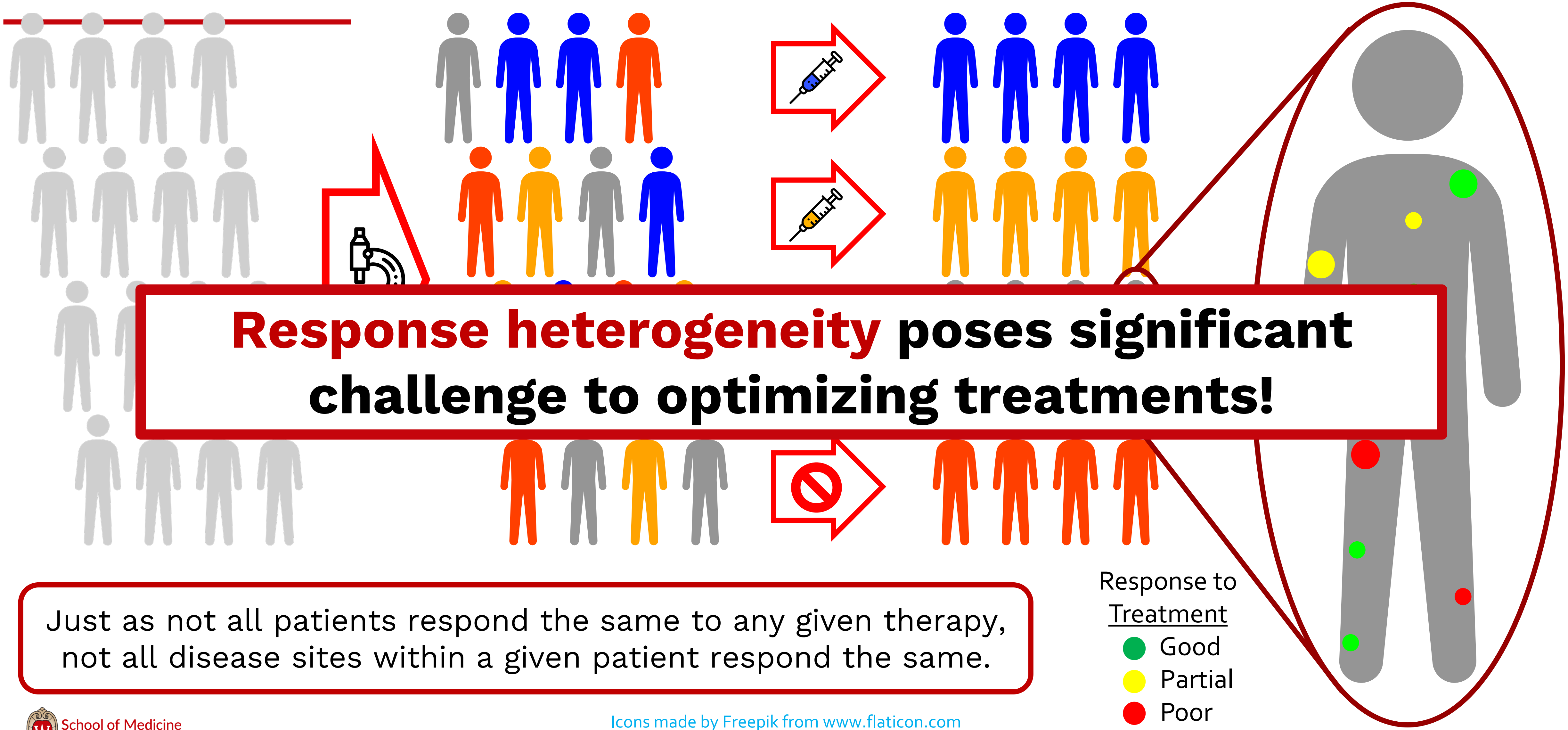
...but there is a big problem!



Response heterogeneity poses significant challenge to optimizing treatments!

Just as not all patients respond the same to any given therapy, not all disease sites within a given patient respond the same.

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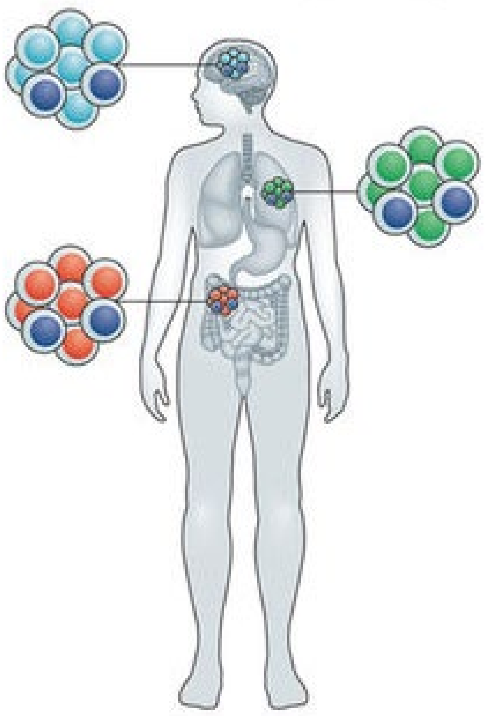
Why heterogeneity?

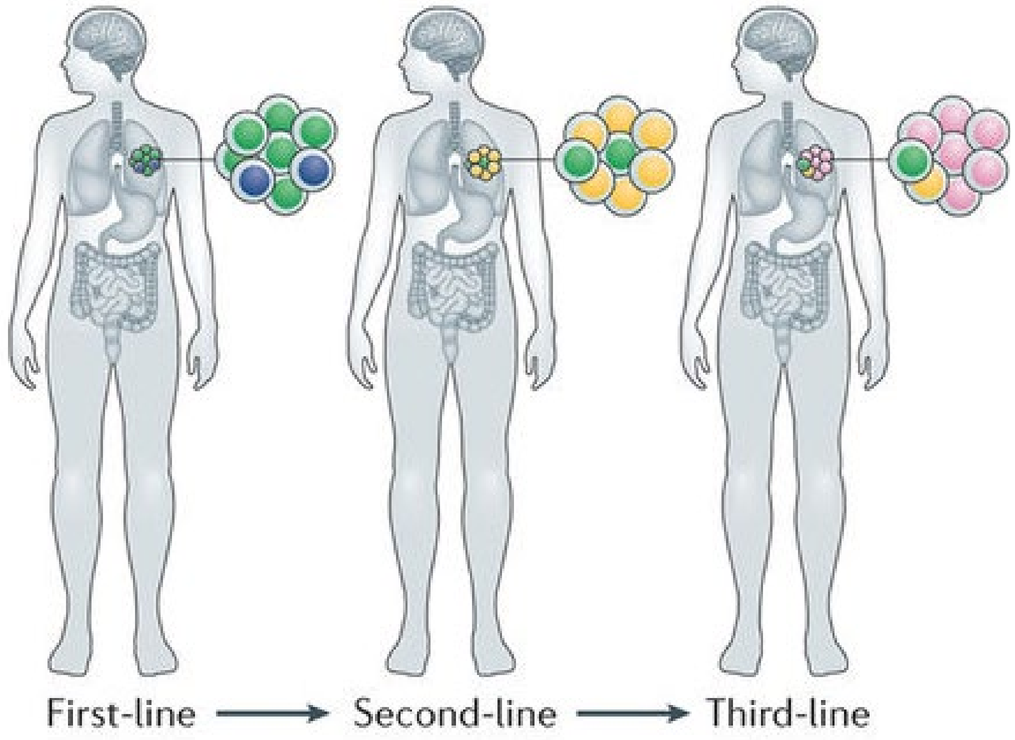
Spatial Heterogeneity

Different disease sites have different responses to therapy at a given point in time



Temporal Heterogeneity

The same disease site may respond differently at different points in time

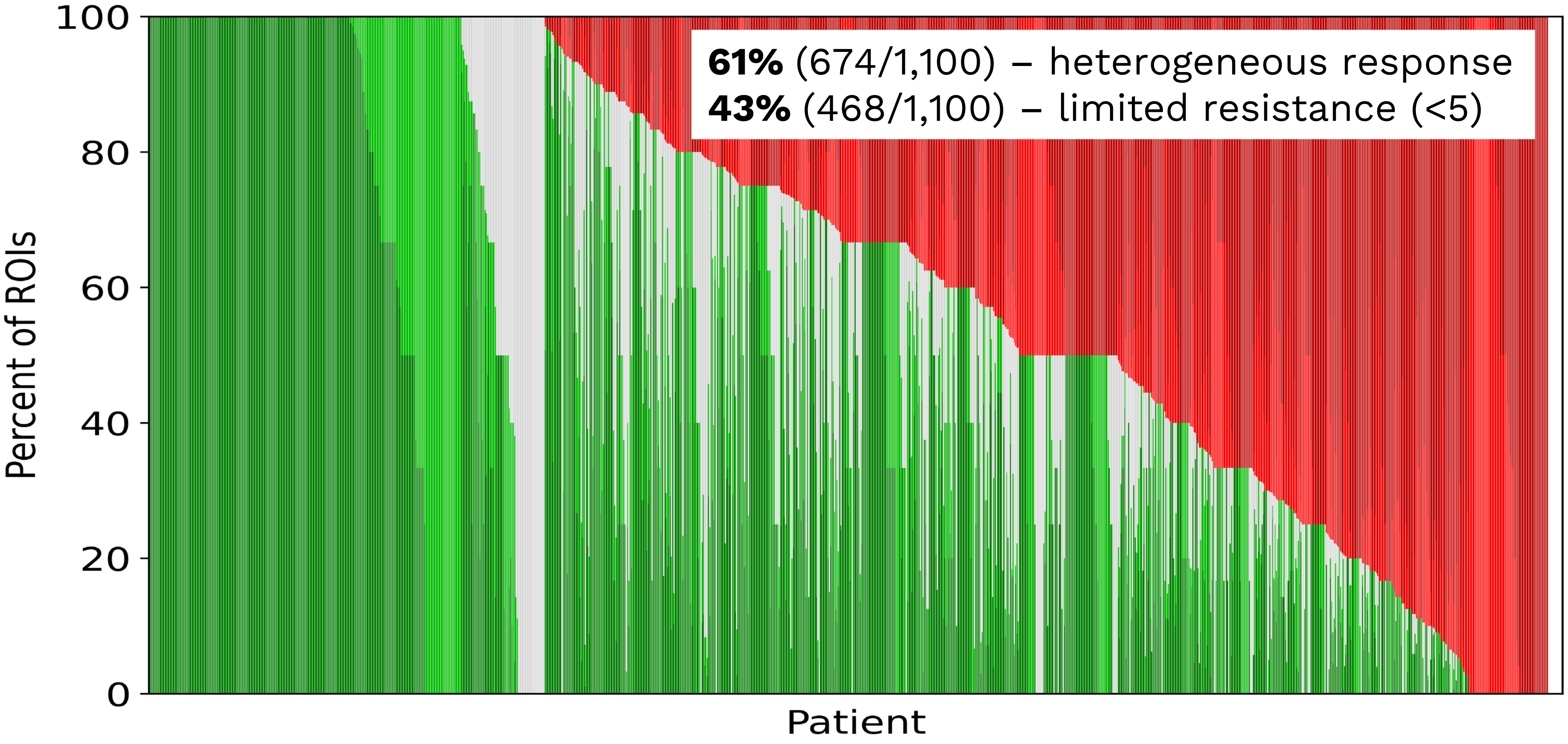


Nature Reviews | Clinical Oncology

Treatment response heterogeneity
Spatial heterogeneity

Within each patient, fraction of lesions in each response category

- New
- Increasing
- Stable
- Decreasing
- Disappeared



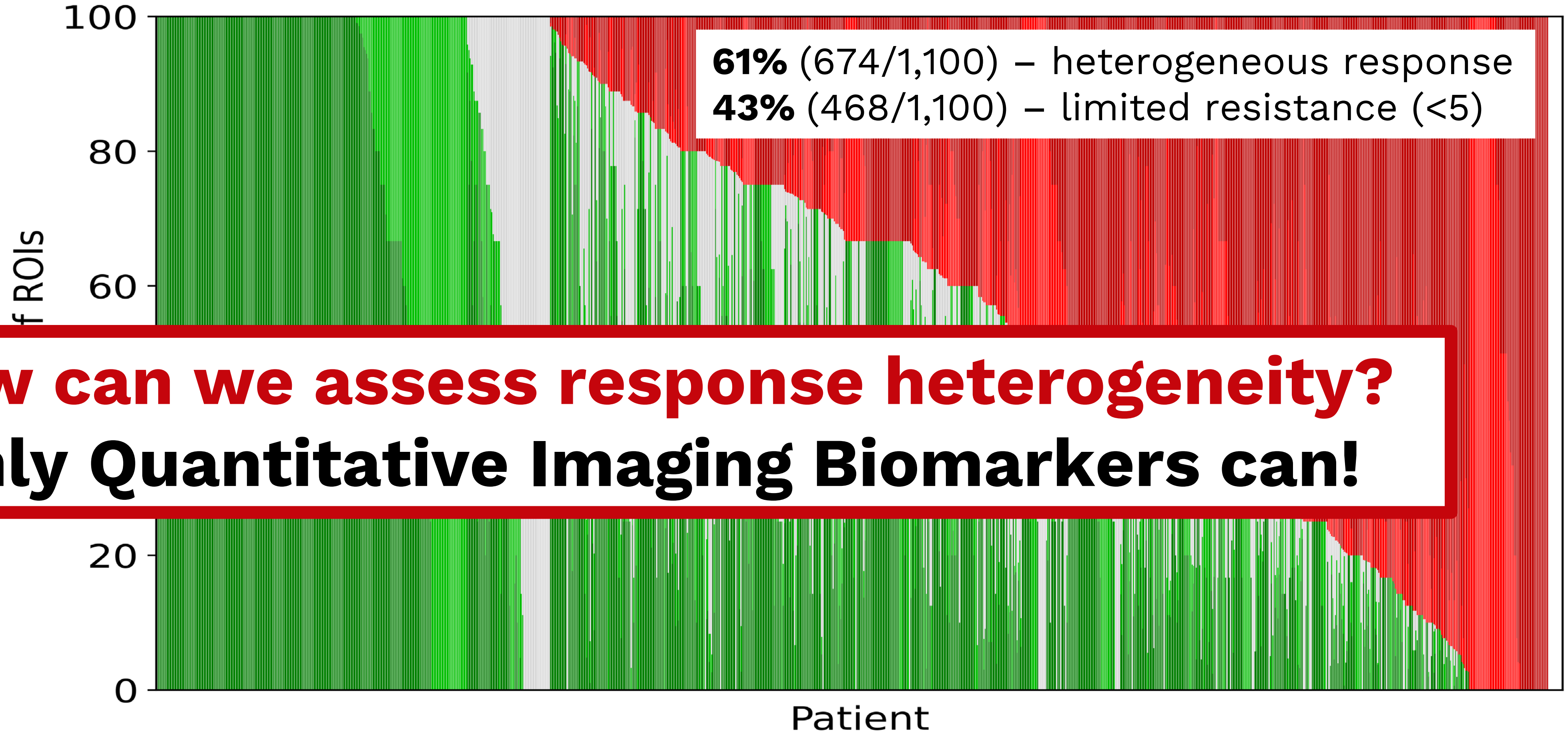
Each bar represents an individual patient (n=1,100)

Cancers included: prostate, GU-bladder, renal, testicular, penile
H&N, NSCLC, GI-NET, melanoma, ACC

Courtesy of AIQ Solutions

Treatment response heterogeneity
Spatial heterogeneity

Within each patient, fraction of lesions in ea respo categ



New
Increasing
Stable
Decreasing
Disappeared

How can we assess response heterogeneity?
Only Quantitative Imaging Biomarkers can!

Each bar represents an individual patient (**n=1,100**)
Cancers included: prostate, GU-bladder, renal, testicular, penile
H&N, NSCLC, GI-NET, melanoma, ACC

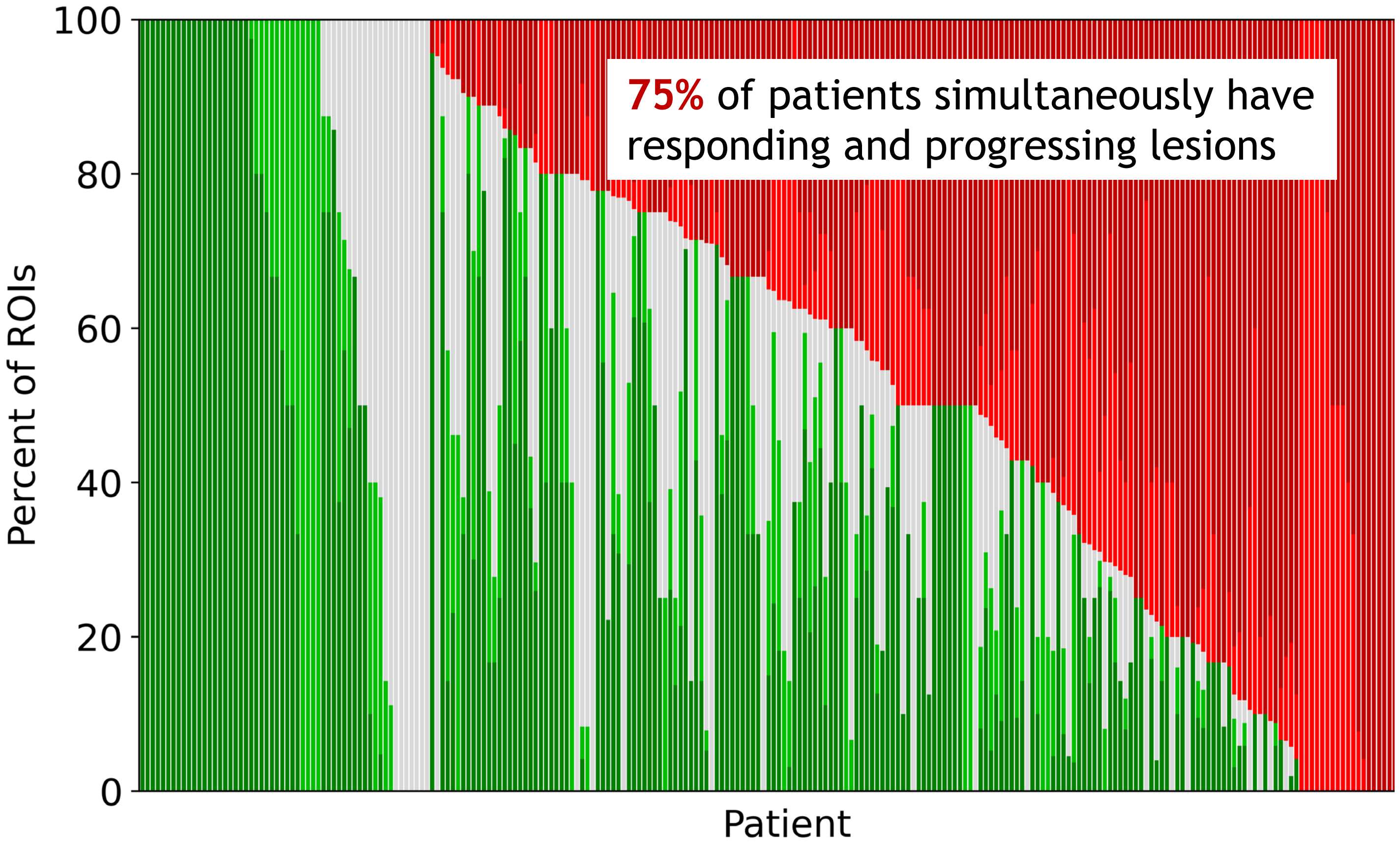
Courtesy of AIQ Solutions

Treatment response heterogeneity (immuno)

Spatial heterogeneity

Within each patient, fraction of lesions in each response category

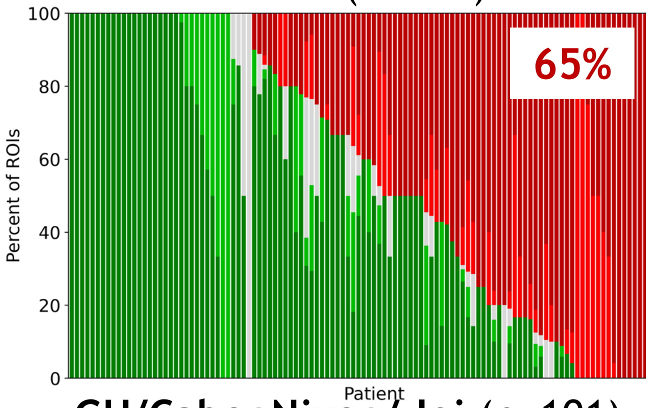
New
Increasing
Stable
Decreasing
Disappeared



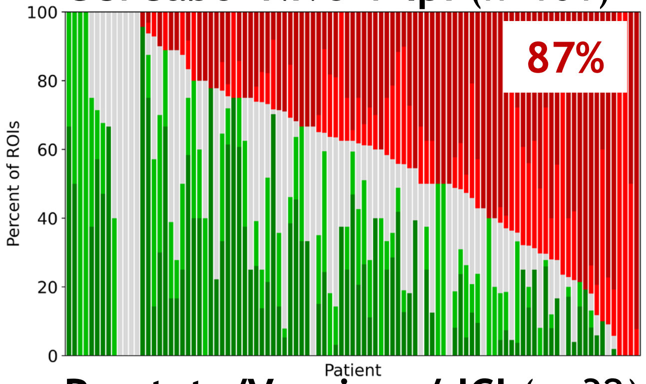
Each bar represents an individual patient (n=250)

Treatment included: Immunotherapy or combination

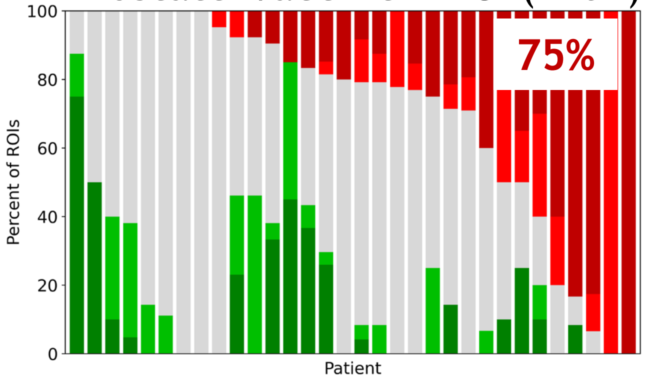
Melanoma/ICI (n=117)



GU/Cabo+Nivo+/-Ipi (n=101)



Prostate/Vaccine+/-ICI (n=32)



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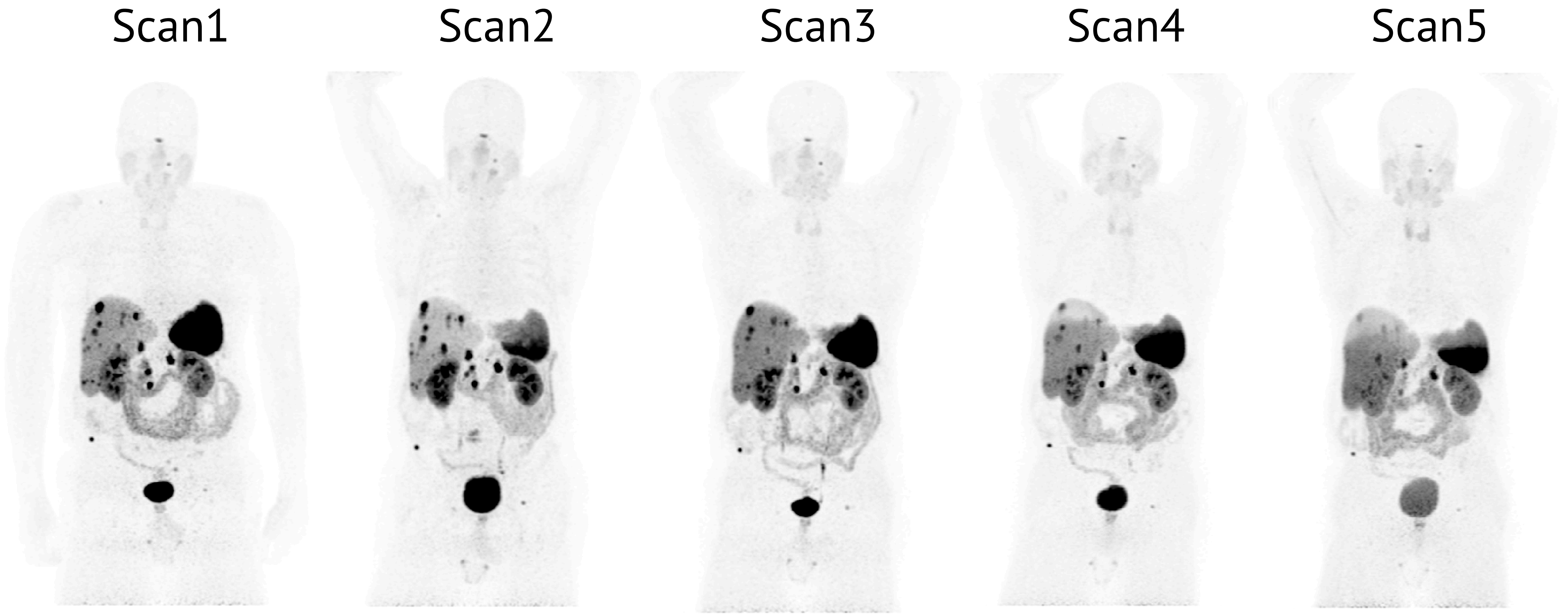
Courtesy of AIQ Solutions

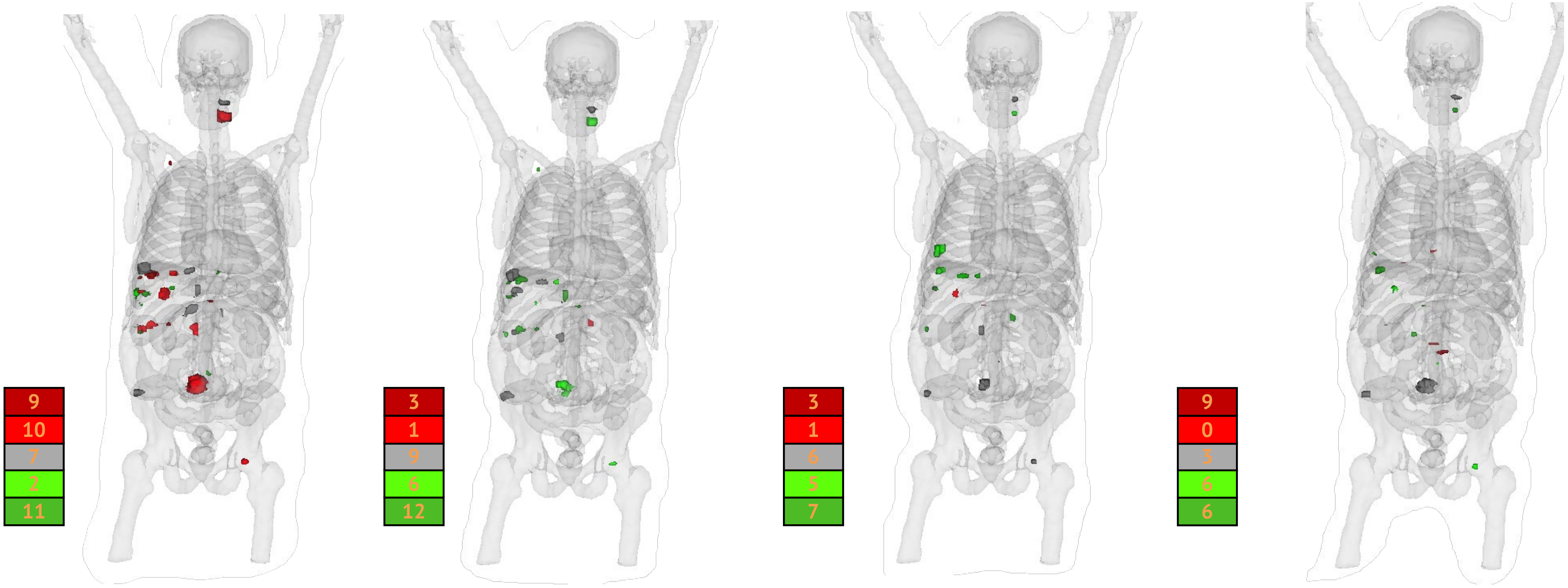
Treatment response heterogeneity
Temporal heterogeneity



Sequential ^{68}Ga-DOTATATE PET/CT imaging during Lutathera therapy

Treatment response heterogeneity
Temporal heterogeneity

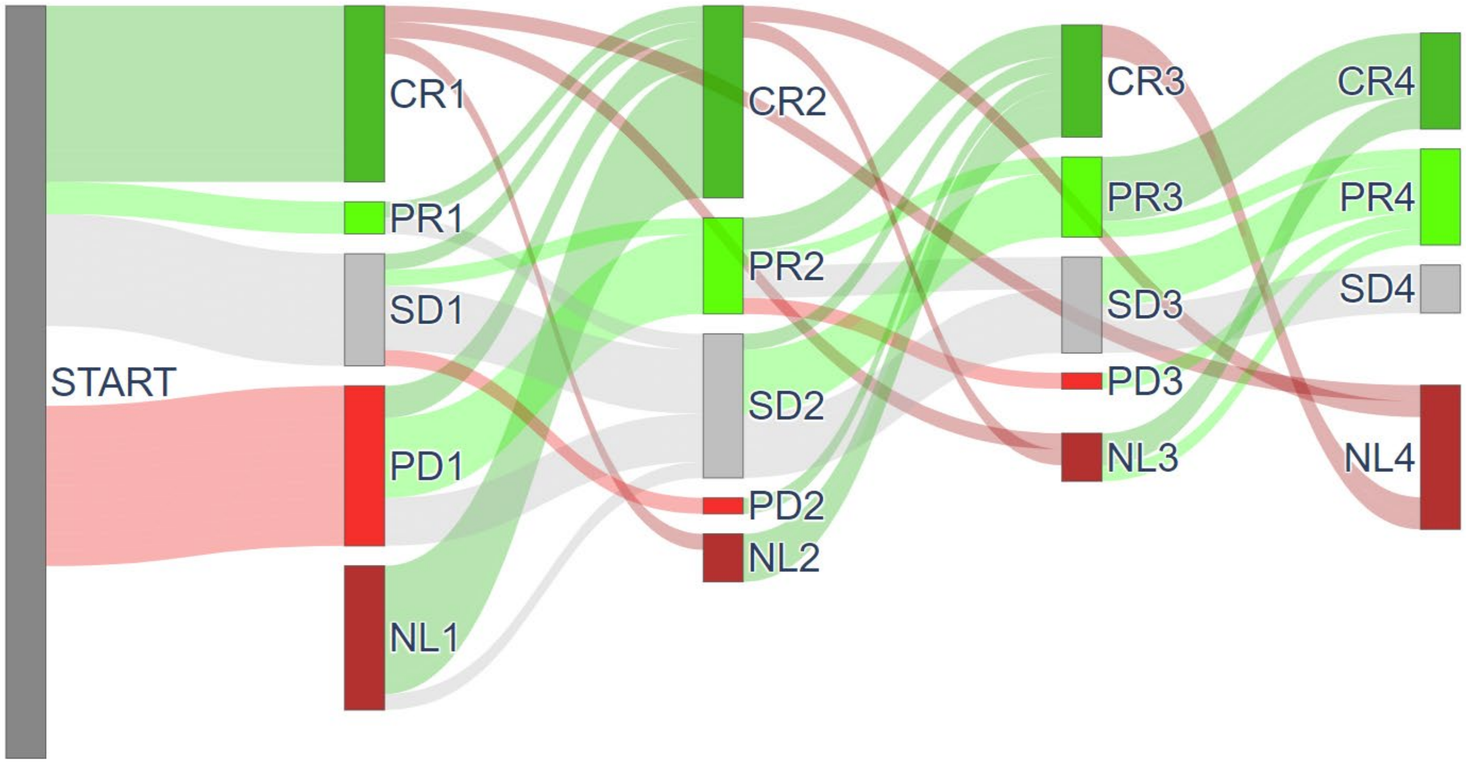
Scan1 to Scan2 Response | Scan2 to Scan3 Response | Scan3 to Scan4 Response | Scan4 to Scan5 Response



Sequential ^{68}Ga-DOTATATE PET/CT imaging during Lutathera therapy

Treatment response heterogeneity

Temporal heterogeneity



Proportion Favorable	0.33	0.58	0.55	0.50
Proportion Unfavorable	0.49	0.13	0.18	0.38

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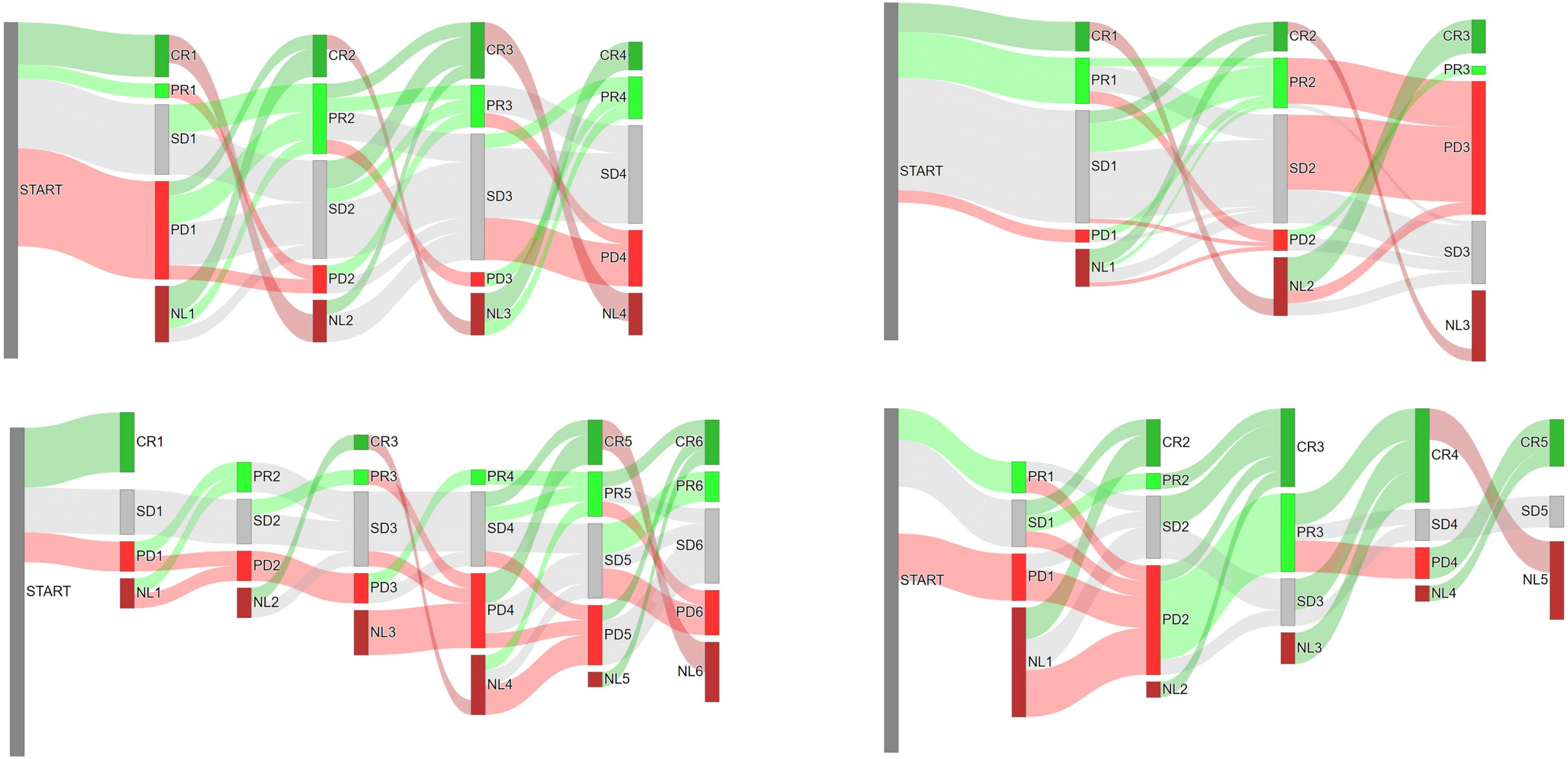
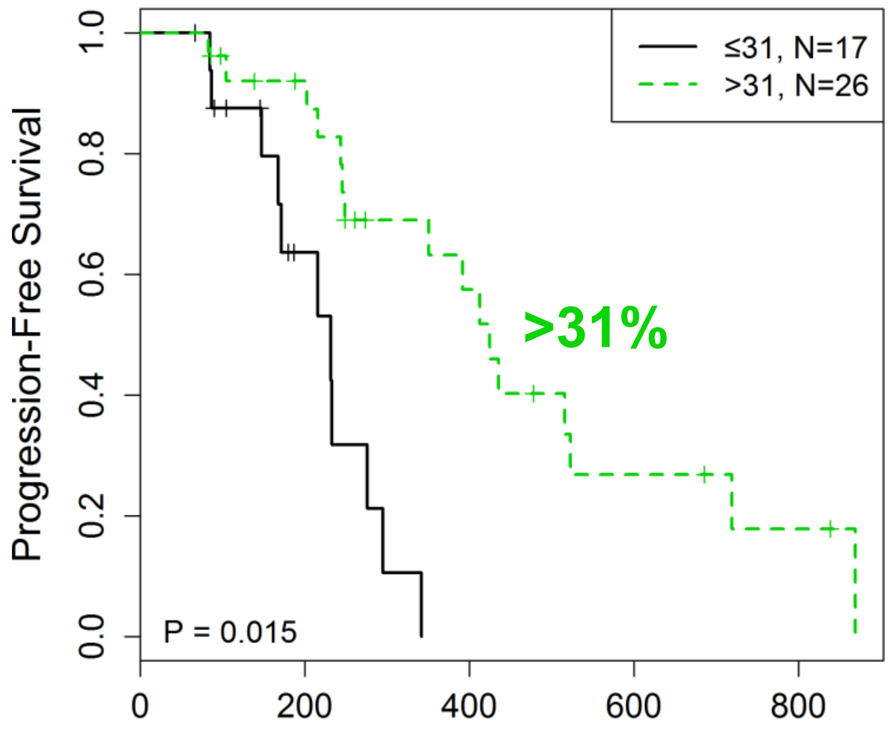
Treatment response heterogeneity
Temporal heterogeneity

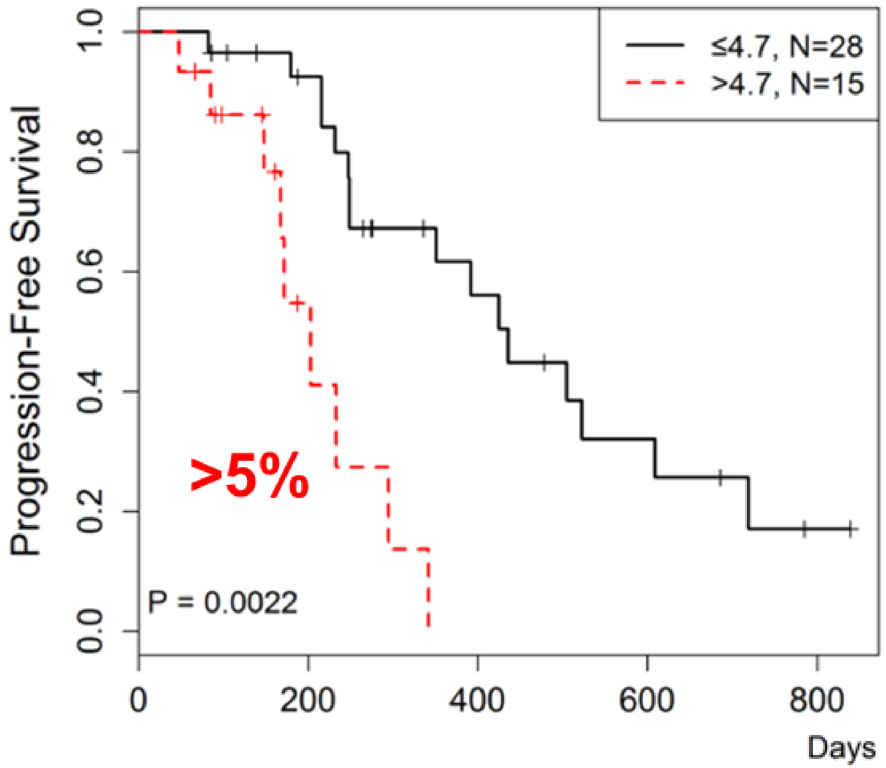


The problem of treatment resistance

Proportion of Favorably Responding Lesions



Proportion of Non-Favorably Responding Lesions



Although favorable response improves outcome,
overall outcome is predominantly driven by resistance

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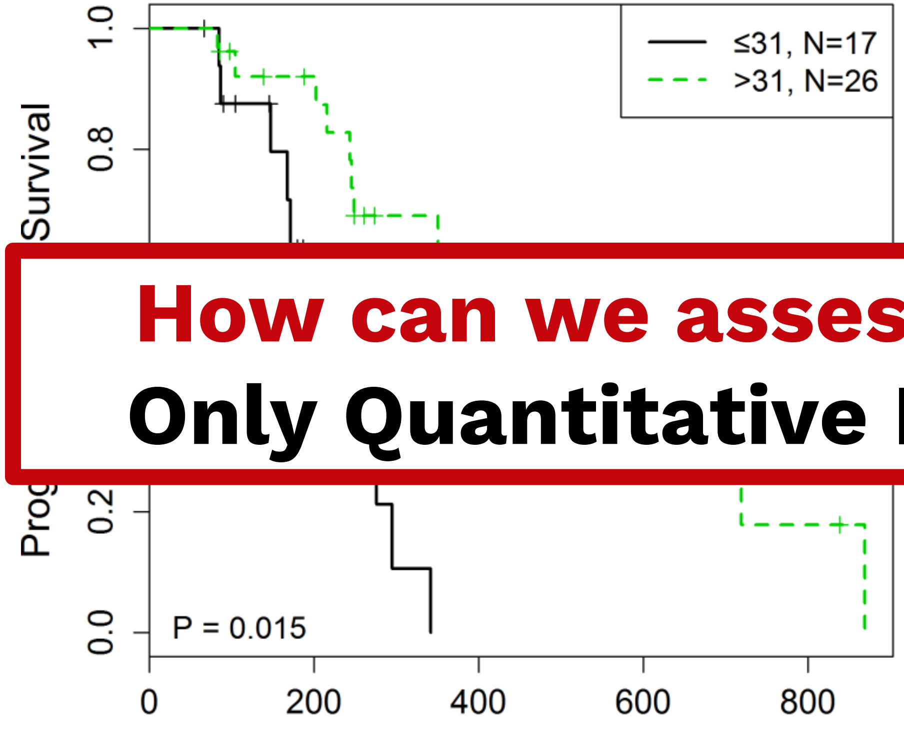
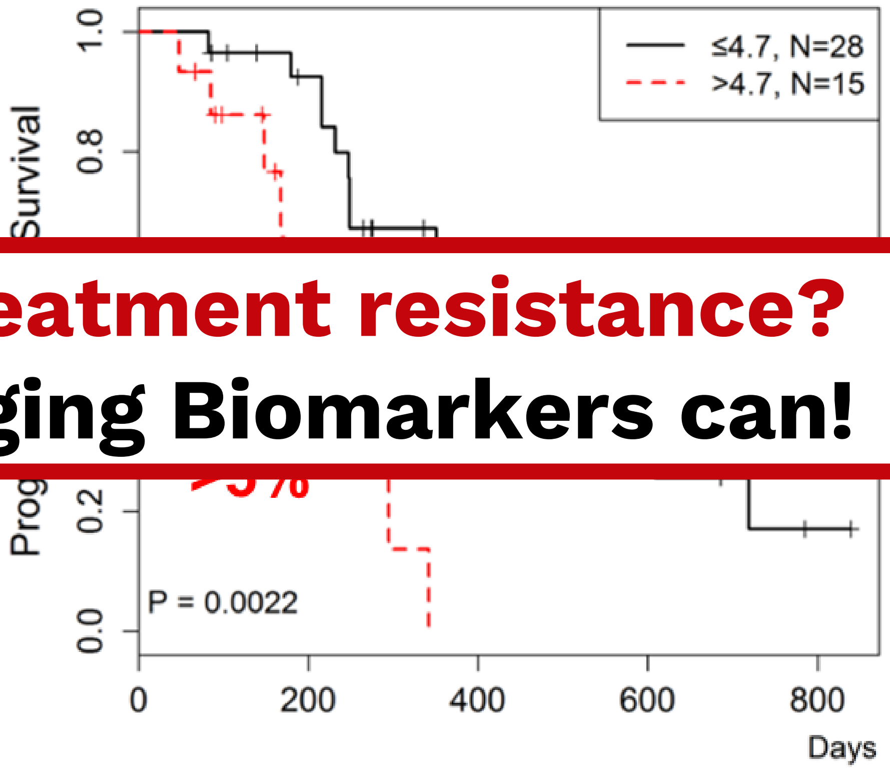
Harmon et al 2017, J Clin Oncol, 35(24): 2829

The problem of treatment resistance

Proportion of Favorably Responding Lesions



Proportion of Non-Favorably Responding Lesions



How can we assess treatment resistance?

Only Quantitative Imaging Biomarkers can!

Although favorable response improves outcome,
overall outcome is predominantly driven by resistance

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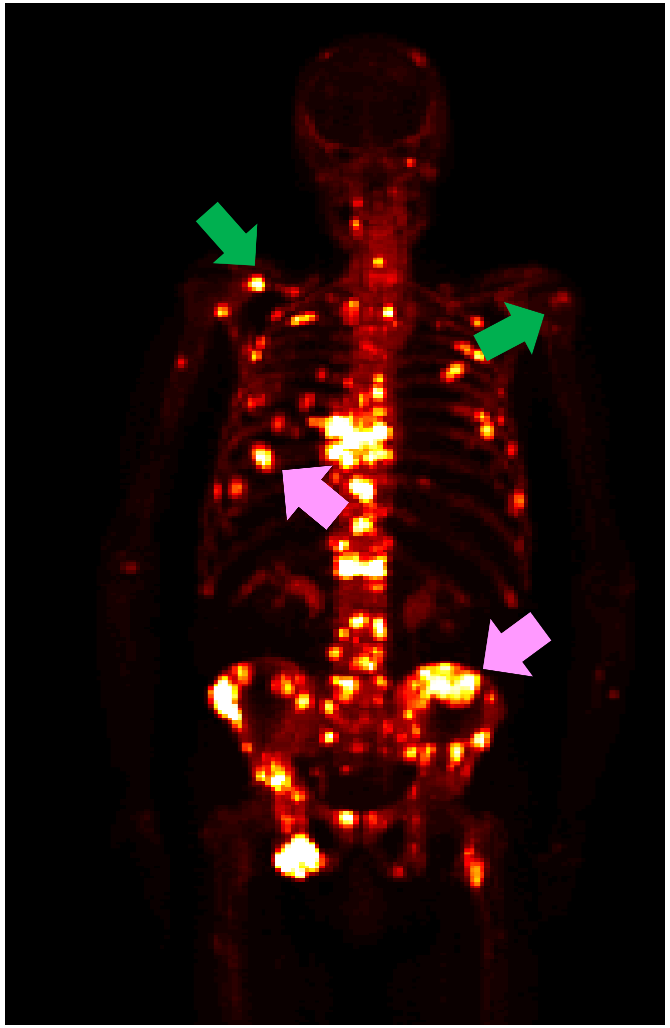
Harmon et al 2017, J Clin Oncol, 35(24): 2829

Treatment response assessment - Current practice

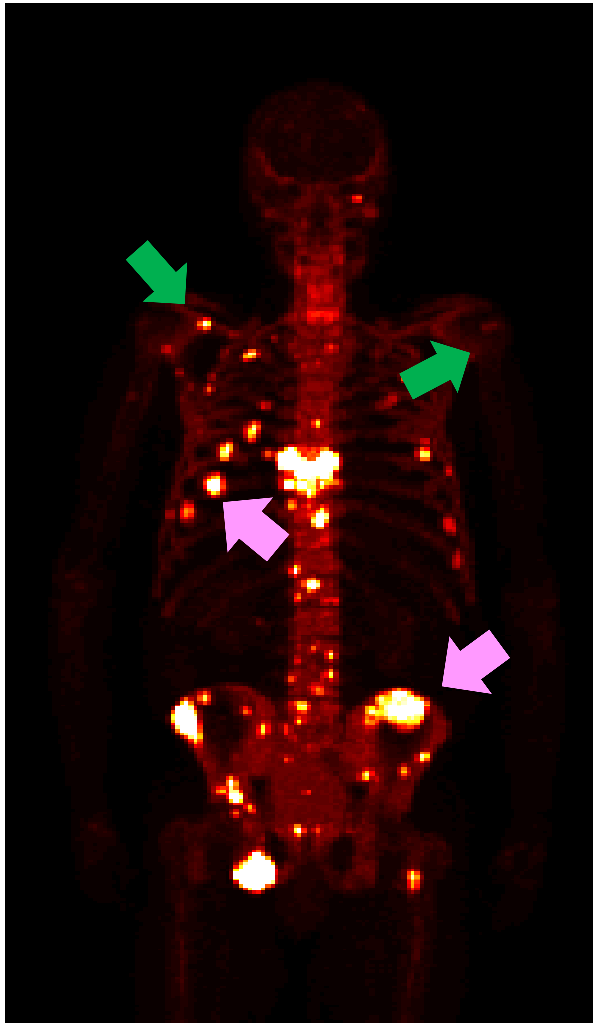
Manual and Qualitative Assessment

Radiologists/nuc med physicians manually identify subset of lesions for treatment evaluation

Time point 1



Time point 2



What information do we want to extract from imaging data?

Number of lesions?

Total disease burden?

Inter-lesion heterogeneity?

……

How do you capture useful intelligence efficiently and objectively?

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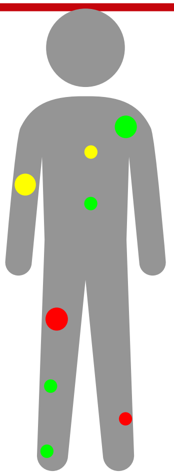
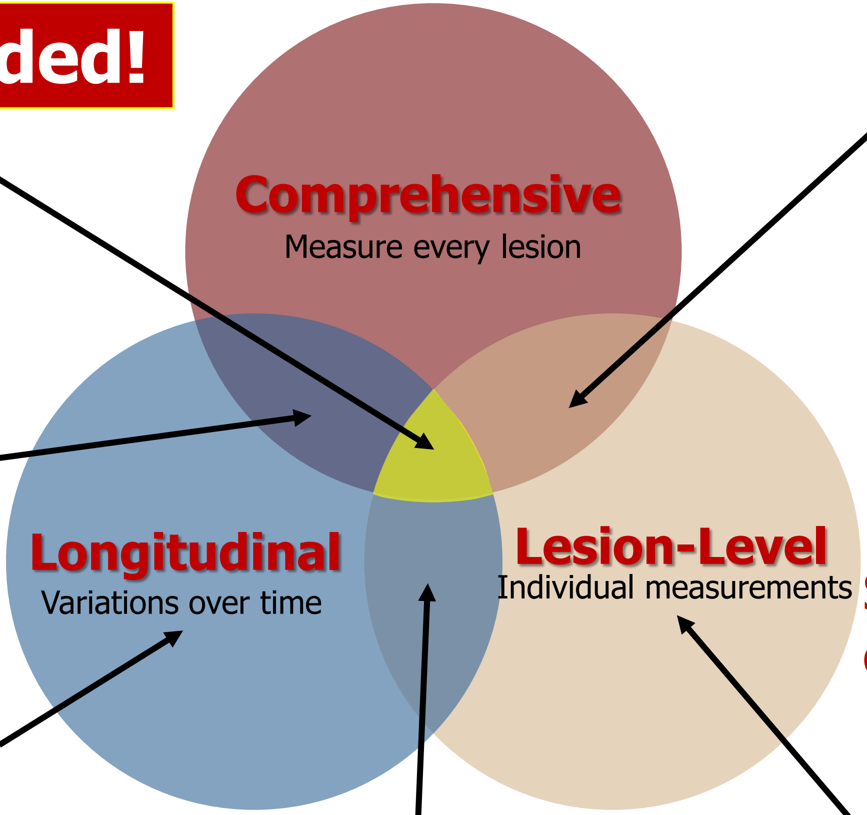
Treatment response assessment –
State-of-the-art



This is needed!



Segment all lesions on baseline
Ohlendorf, F. (2020) QJNMMI
Carlsen, E. (2021) J Nuc. Med.

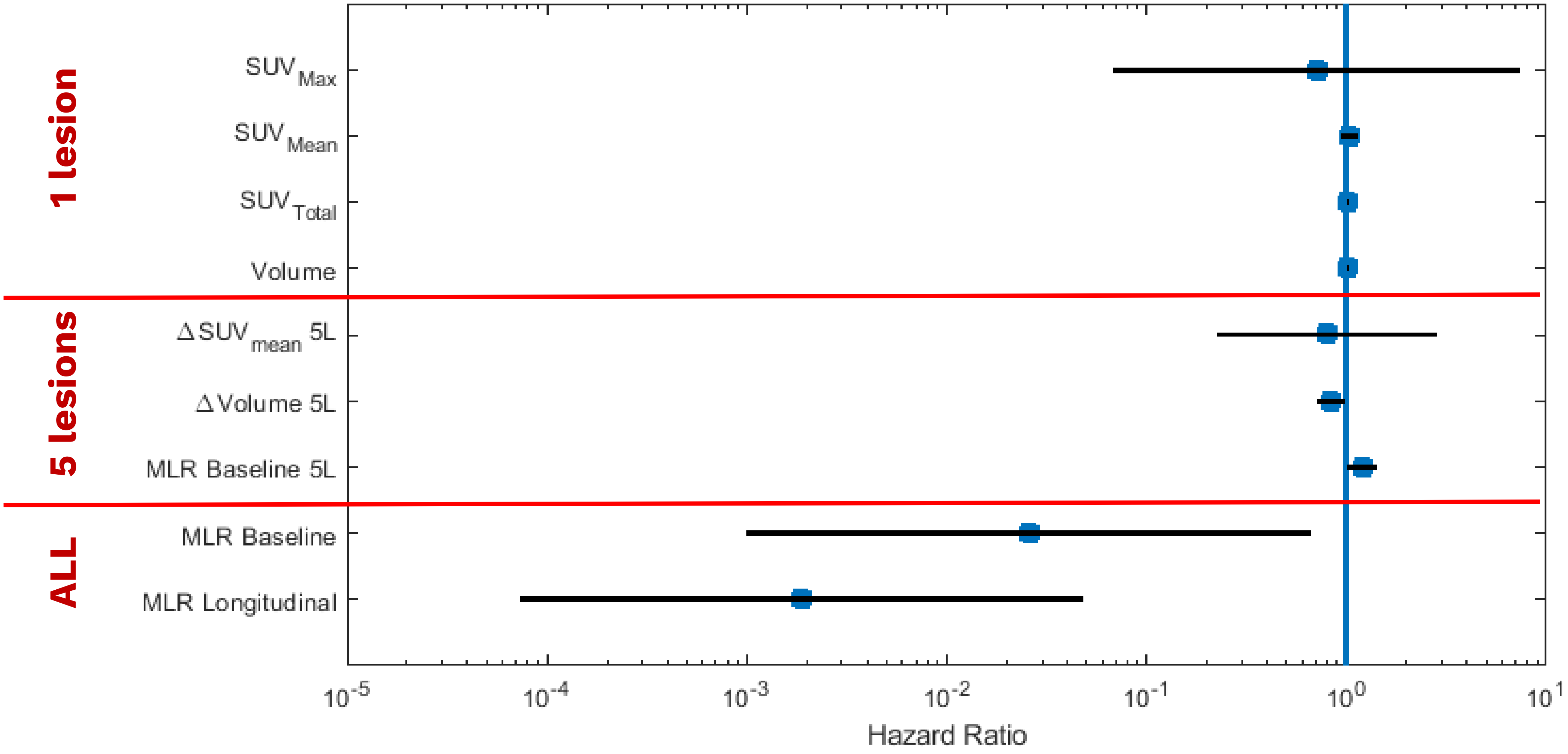
Segment all lesions
Batched longitudinal metrics
Pauwels, E. (2020) J Nuc. Med.

Segment 5 lesions
Batched longitudinal metrics
Kratochwil, C. (2015) Molec. Imag. and Biol.
Sharma, R. (2019) RT and Onc.
Ortega, C. (2021) J Nuc. Med.
Urso, L. (2023) Diagnostics

One lesion!
Gabriel, M. (2009) J Nuc. Med.
Haug, A. (2010) J Nuc. Med.

Segment some lesions on baseline images
Campana, D. (2010) J Nuc. Med.
Ambrosini, V. (2015) J Nuc. Med.
Werner, R. (2017) Oncotarget
Werner, R. (2019) Molec. Imag. And Biol.
Graf, J. (2020) Eur. J Nuc. Med. Molec. Imag.
Zwirtz, K. (2022) Pharmaceutics

Why we need to assess EVERY lesion?



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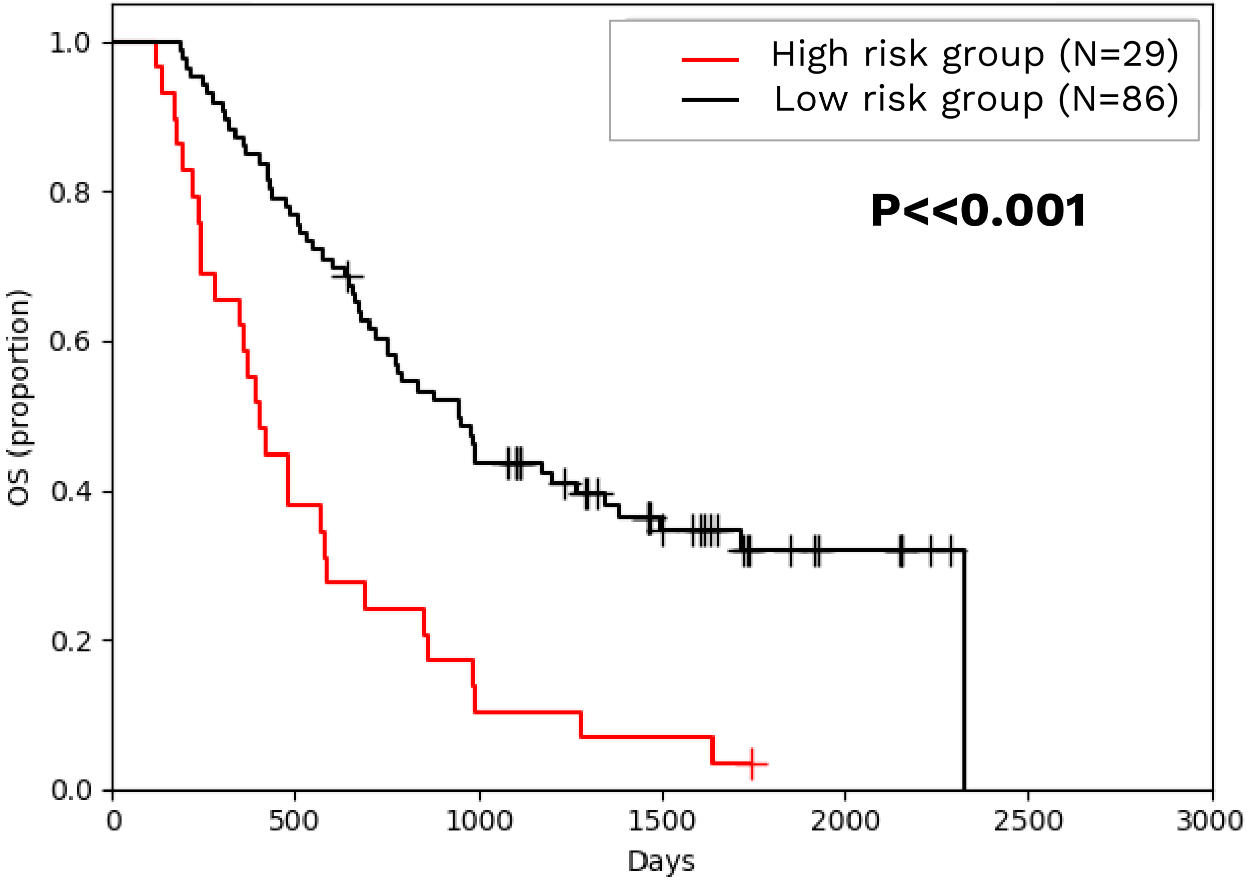
Fernandes et al 2023, ESNM meeting

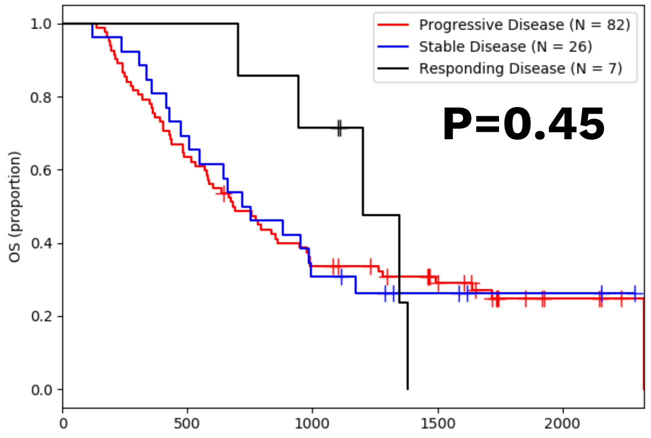
Why we need to assess EVERY lesion?

Assessment of ALL lesions

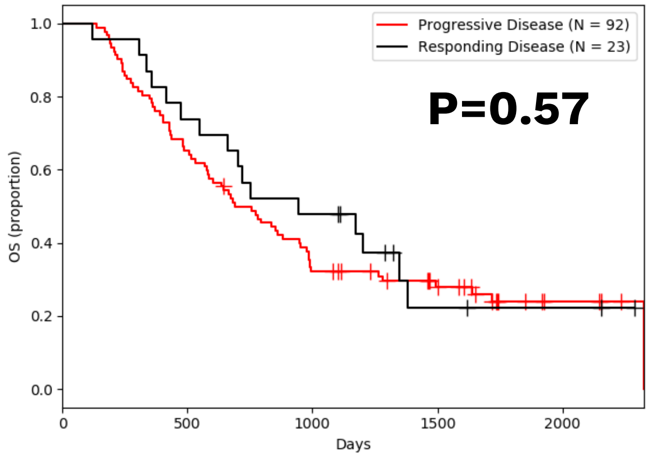


Assessment of FEW lesions

RECIST



PERCIST



Liu et al 2022, ESMO Annual meeting

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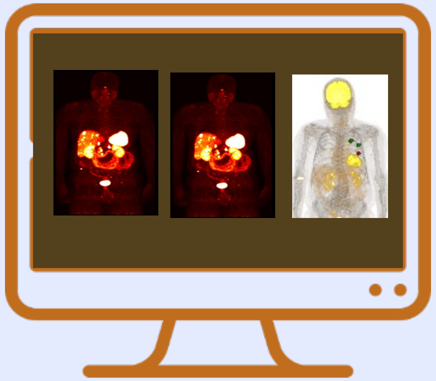
HOW CAN WE GET SUCH DATA?

- AI-based Treatment Response Assessment

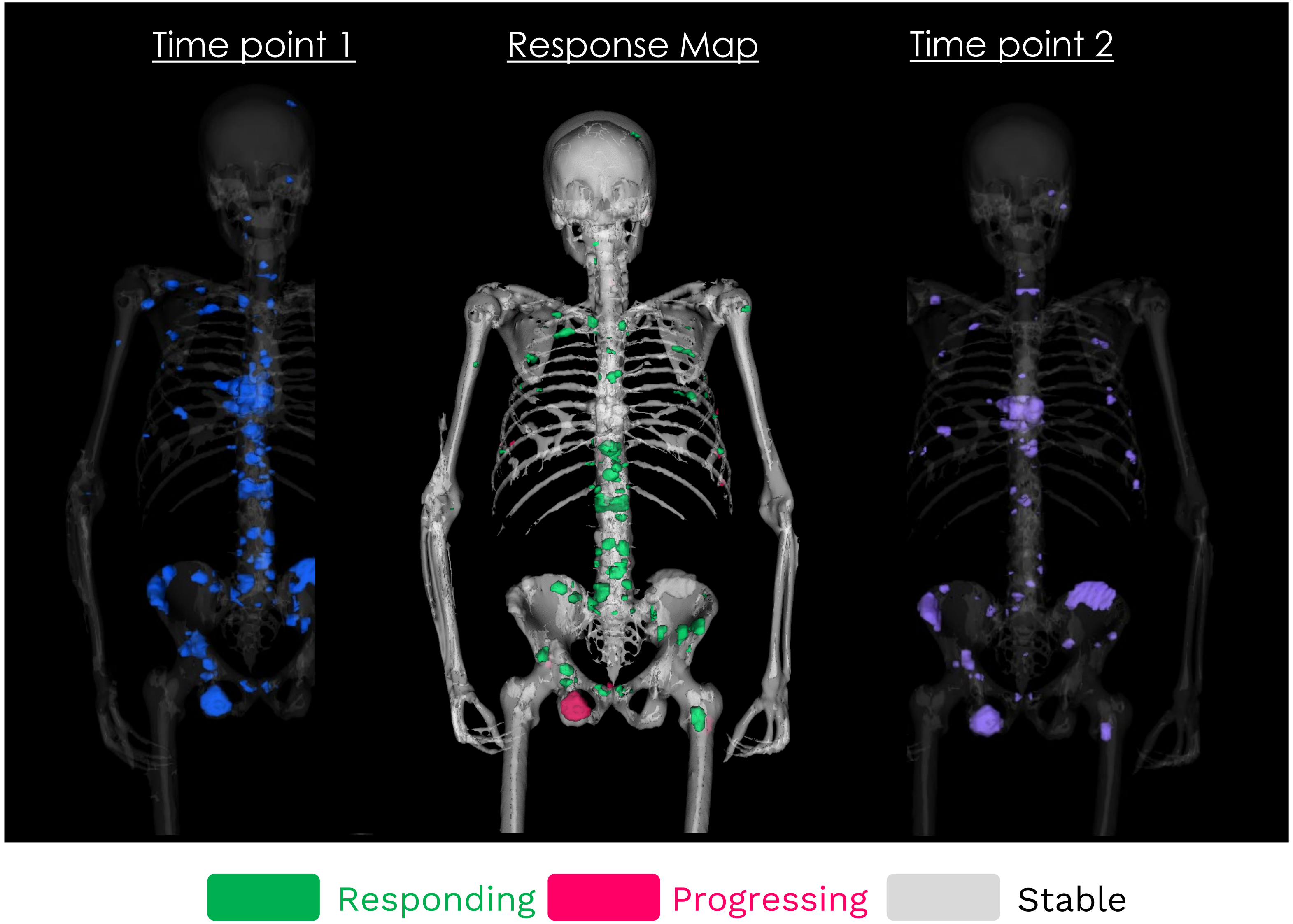
Treatment response assessment –
AI-based approach

Automatic and Quantitative Assessment



Our software automatically detects and classifies all lesions

US Patents 9603567, 10445878
Licensed to our spin-off:
AIQ Solutions



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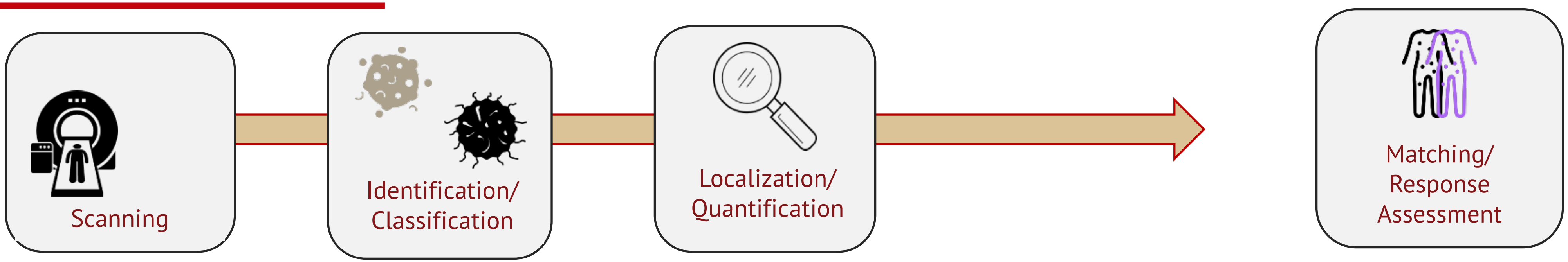
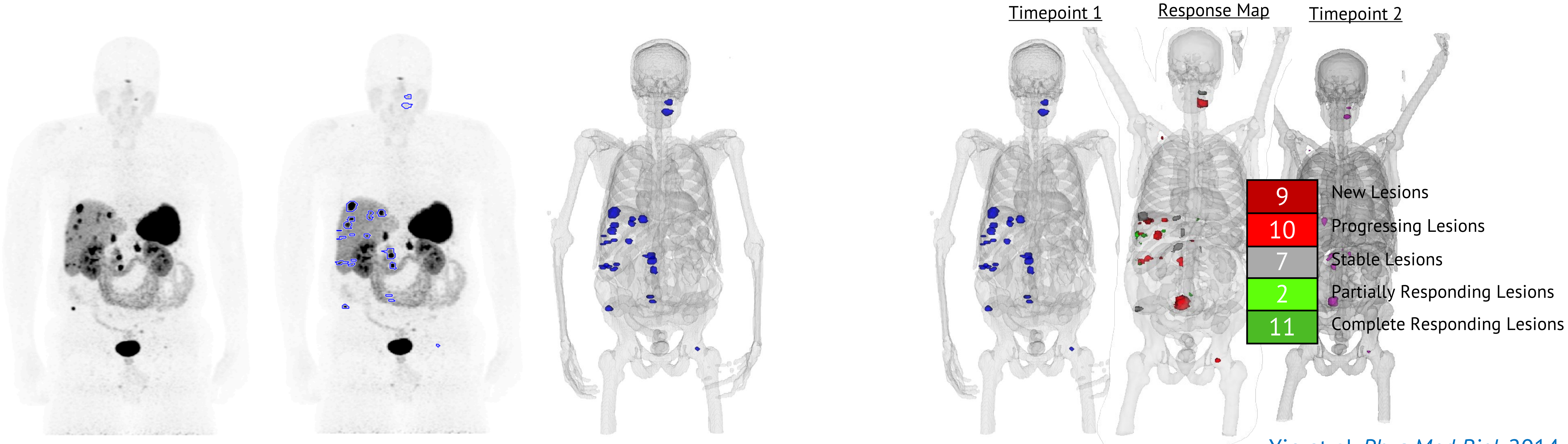
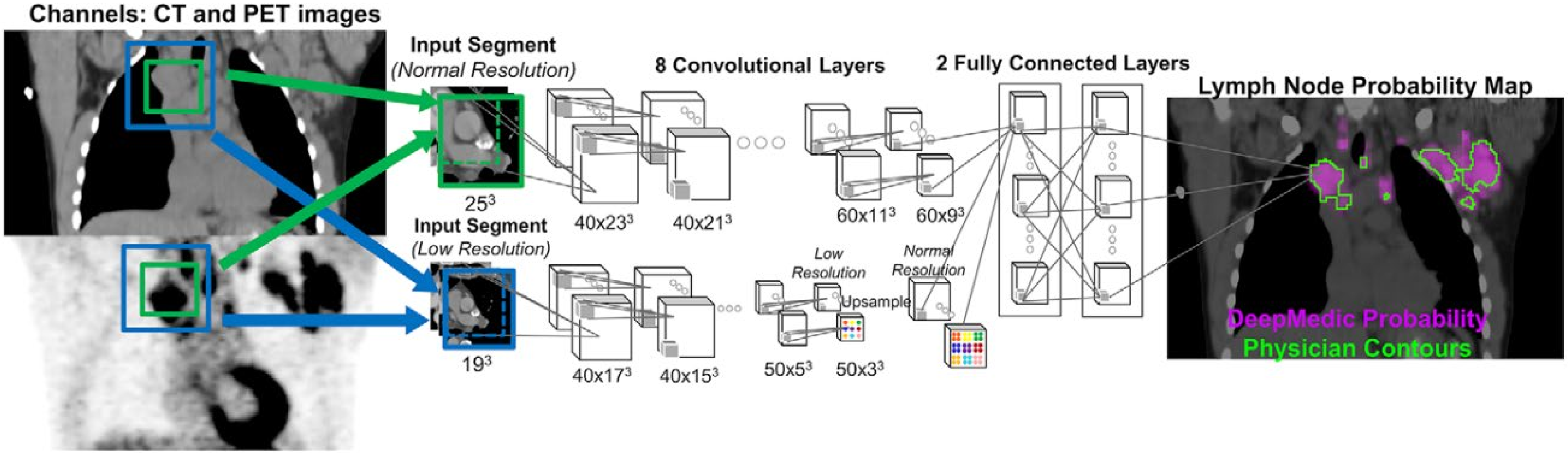
Treatment response assessment – AI-based workflow

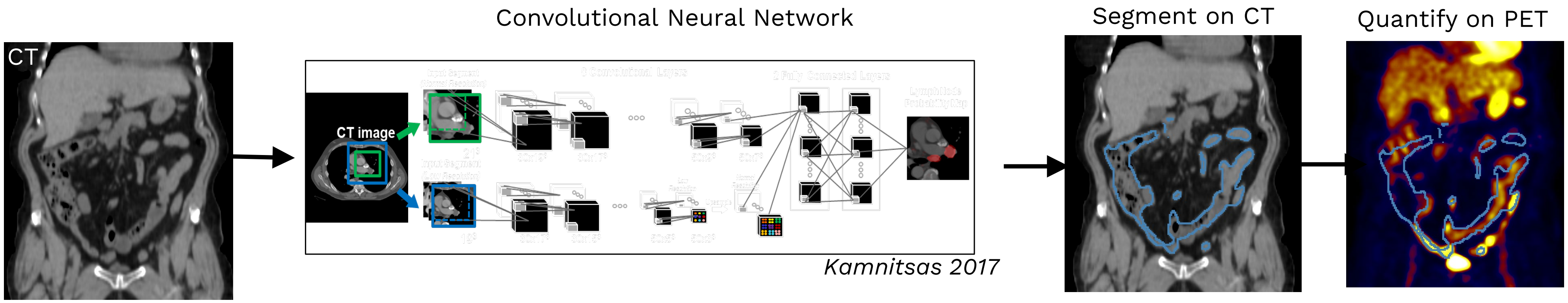




Yip et al. *Phys Med Biol*. 2014
Santoro-Fernandes et al. *Phys Med Biol*. 2021
US Patent 9,603,567

AI-driven lesion & organ segmentation



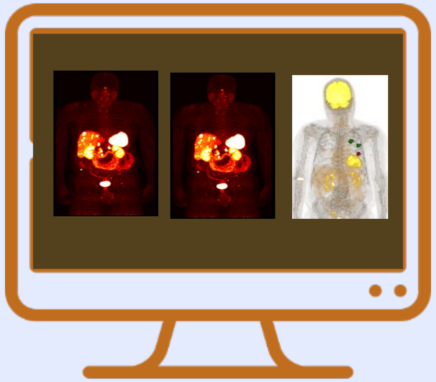


Kamnitsas 2017

Blue: CNN bowel contour

Treatment response assessment –
AI-based approach

Automatic and Quantitative Assessment



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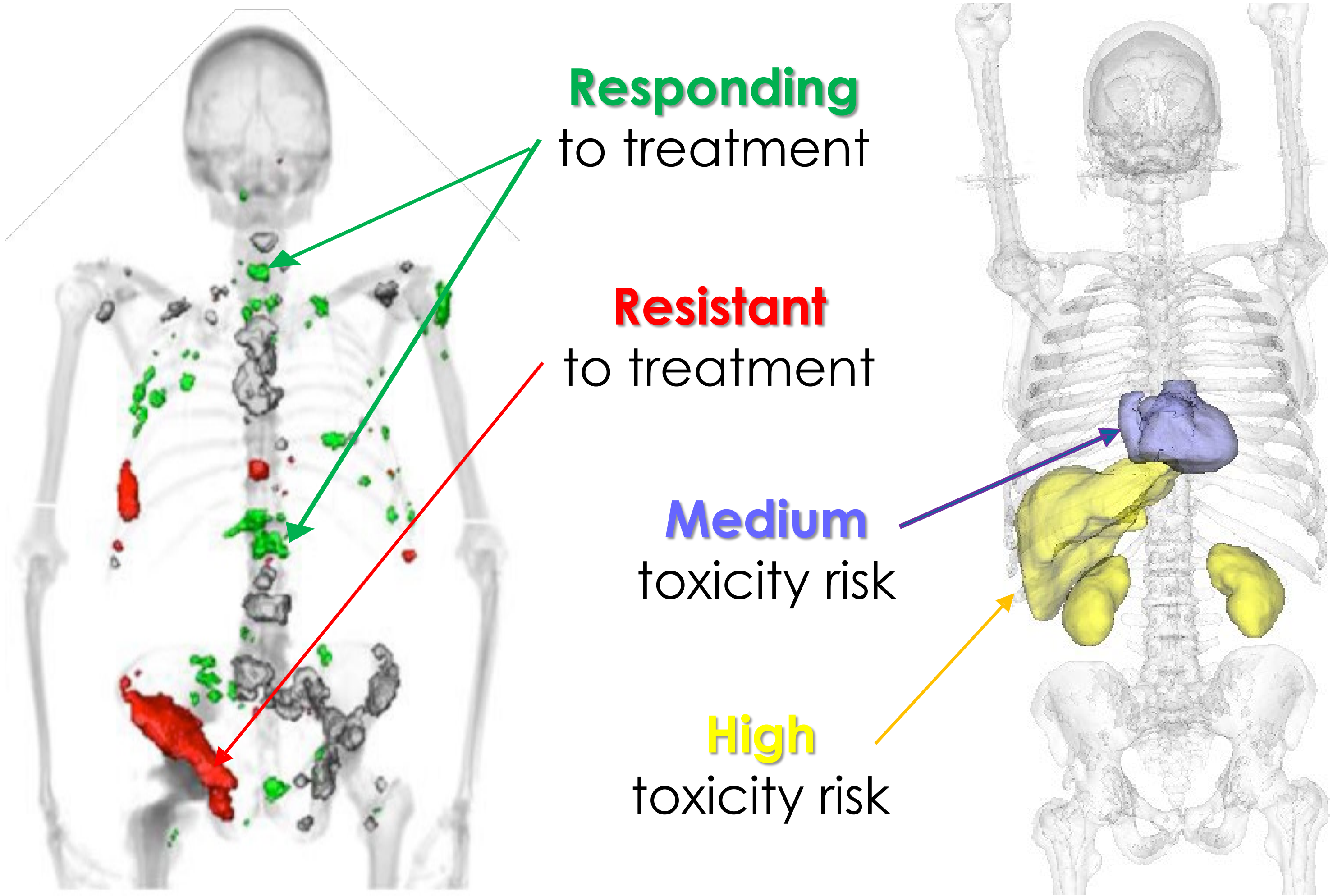
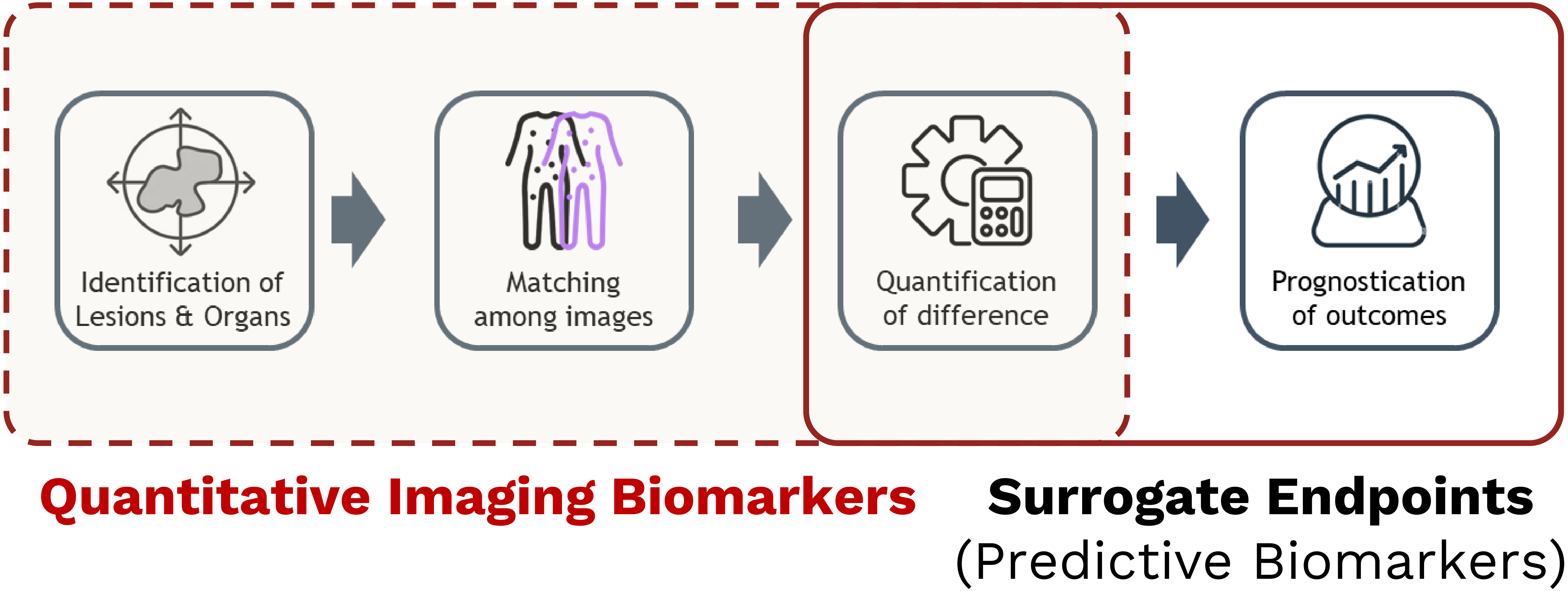


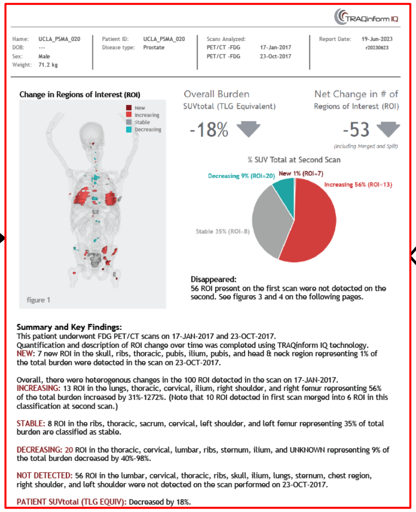
Associating data with clinical outcomes



What to do with this intelligence?

Treatment response

Serial imaging and other data →



TRAQinform IQ

Name:	UCLA_PSMA_020	Patient ID:	UCLA_PSMA_020	Scans Analyzed:		Report Date:	19-Jun-2023
DOB:	---	Disease type:	Prostate	PET/CT -FDG	17-Jan-2017		r20230623
Sex:	Male			PET/CT -FDG	23-Oct-2017		
Weight:	71.2 kg						

Change in Regions of Interest (ROI)

Overall Burden
SUVtotal (TLG Equivalent)
-18%

Net Change in # of
Regions of Interest (ROI)
-53
(including Merged and Split)

% SUV Total at Second Scan

Disappeared:
56 ROI present on the first scan were not detected on the second. See figures 3 and 4 on the following pages.

Summary and Key Findings:
This patient underwent FDG PET/CT scans on 17-JAN-2017 and 23-OCT-2017.
Quantification and description of ROI change over time was completed using TRAQinform IQ technology.
NEW: 7 new ROI in the skull, ribs, thoracic, pubis, ilium, pubis, and head & neck region representing 1% of the total burden were detected in the scan on 23-OCT-2017.

Overall, there were heterogenous changes in the 100 ROI detected in the scan on 17-JAN-2017.
INCREASING: 13 ROI in the lungs, thoracic, cervical, ilium, right shoulder, and right femur representing 56% of the total burden increased by 31%-1272%. (Note that 10 ROI detected in first scan merged into 6 ROI in this classification at second scan.)

STABLE: 8 ROI in the ribs, thoracic, sacrum, cervical, left shoulder, and left femur representing 35% of total burden are classified as stable.

DECREASING: 20 ROI in the thoracic, cervical, lumbar, ribs, sternum, ilium, and UNKNOWN representing 9% of the total burden decreased by 40%-98%.

NOT DETECTED: 56 ROI in the lumbar, cervical, thoracic, ribs, skull, ilium, lungs, sternum, chest region, right shoulder, and left shoulder were not detected on the scan performed on 23-OCT-2017.

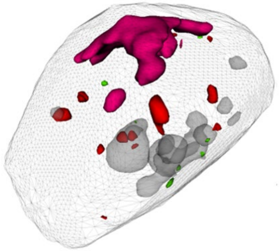
PATIENT SUVtotal (TLG EQUIV): Decreased by 18%.

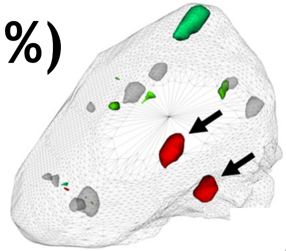
Suboptimal (72%)

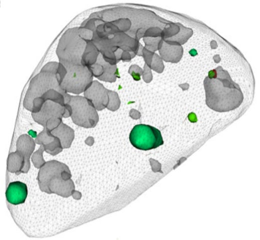
- widespread resistance → **Change approach (29%)** (different drug, palliative care, etc.)
- limited resistance → **Treat resistance (43%)** (localized ablation, etc.)

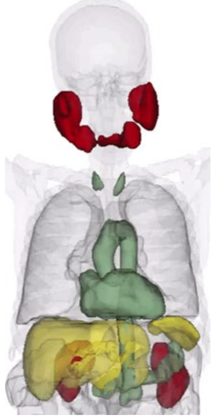
Optimal (28%)

- disease controlled → **Continue therapy**
- toxicity risk → **De-escalate therapy, monitor response**









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RISK-BENEFIT

- Population-based risk and benefit
- Patient-specific risk and benefit

Risk-benefit
Population-based

- Clinical trial-based data on probability of benefit and toxicity for each immunotherapy treatment
  - Risk-benefit ratio metric $M = \frac{probability\ of\ risk}{probability\ of\ benefit} = \frac{p_R}{p_B}$
  - Multiple possible definitions of benefit, based on clinical evaluation criteria (e.g., OS, PFS, RECIST evaluation)

Definition of Benefit	Expression for p_B	Classification
Clinical Benefit	$p_{CR} + p_{PR} + p_{SD}$	RECIST-based
Objective Response	$p_{CR} + p_{PR}$	RECIST-based
PFS > time T	$1 - p_{PFS,T}$	Outcome-based
OS > time T	$1 - p_{OS,T}$	Outcome-based

CR – complete response
PR – partial response
SD – stable disease
OS – overall survival
PFS – progression free survival

Risk-benefit
Population-based

	Ipilimumab + nivolumab	Nivolumab	Ipilimumab
N	**314**	**316**	**315**
Best overall response – N (%)			
Complete Response (CR)	61 (19)	52 (16)	16 (5)
Partial Response (PR)	122 (39)	88 (28)	43 (14)
Stable Disease (SD)	38 (12)	31 (10)	69 (22)
Progressive Disease (PD)	74 (24)	121 (38)	159 (50)
Unknown	19 (6)	24 (8)	28 (9)
Toxicity – N (%)			
High-grade, any-toxicity	184 (59)	67 (21)	86 (28)

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Wolchok *et al*, 2017, N Engl J Med; 377: 1345
Wolchok *et al*, 2022, J Clin Oncol 40(2):127

Risk-benefit
Population-based

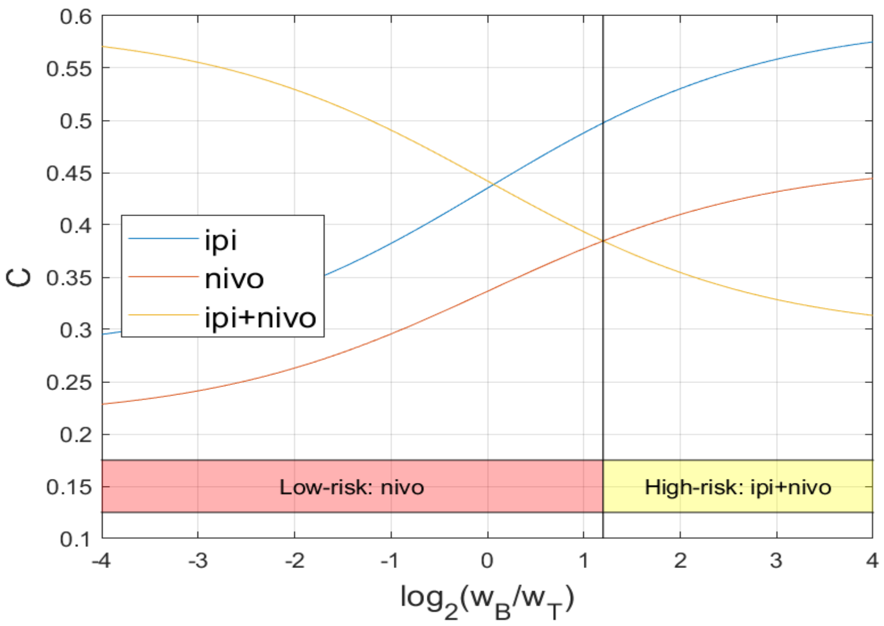
- Likelihood of risk and benefit of three ICI treatments:

	Ipilimumab + nivolumab	Nivolumab	Ipilimumab
$p_B = p_{CR}+p_{PR}+p_{SD}$	0.70	0.54	0.41
$p_R = p_{AE,\text{high-grade, any-toxicity}}$	0.59	0.21	0.28
M	0.84	0.40	0.68

- The cost function C is a function of patient risk tolerance:

$$C = w_B(1 - p_B) + w_T p_T$$

- In spite of a higher *M* a combination ipi+nivo is currently used as the first treatment option



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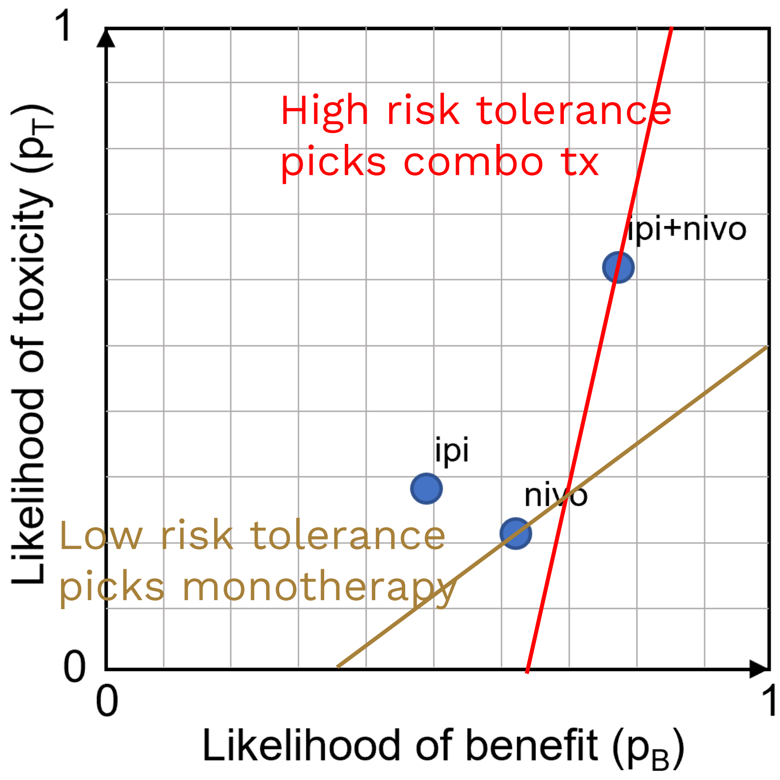
Risk-benefit space

Population-based risk-benefit



$p_B = 1 - p_{PD}$ $\quad\quad$ $p_T = p_{g3-4, any\ organ}$

Risk-benefit
Individual patient imaging data (FDG PET)

TREATMENT RESPONSE

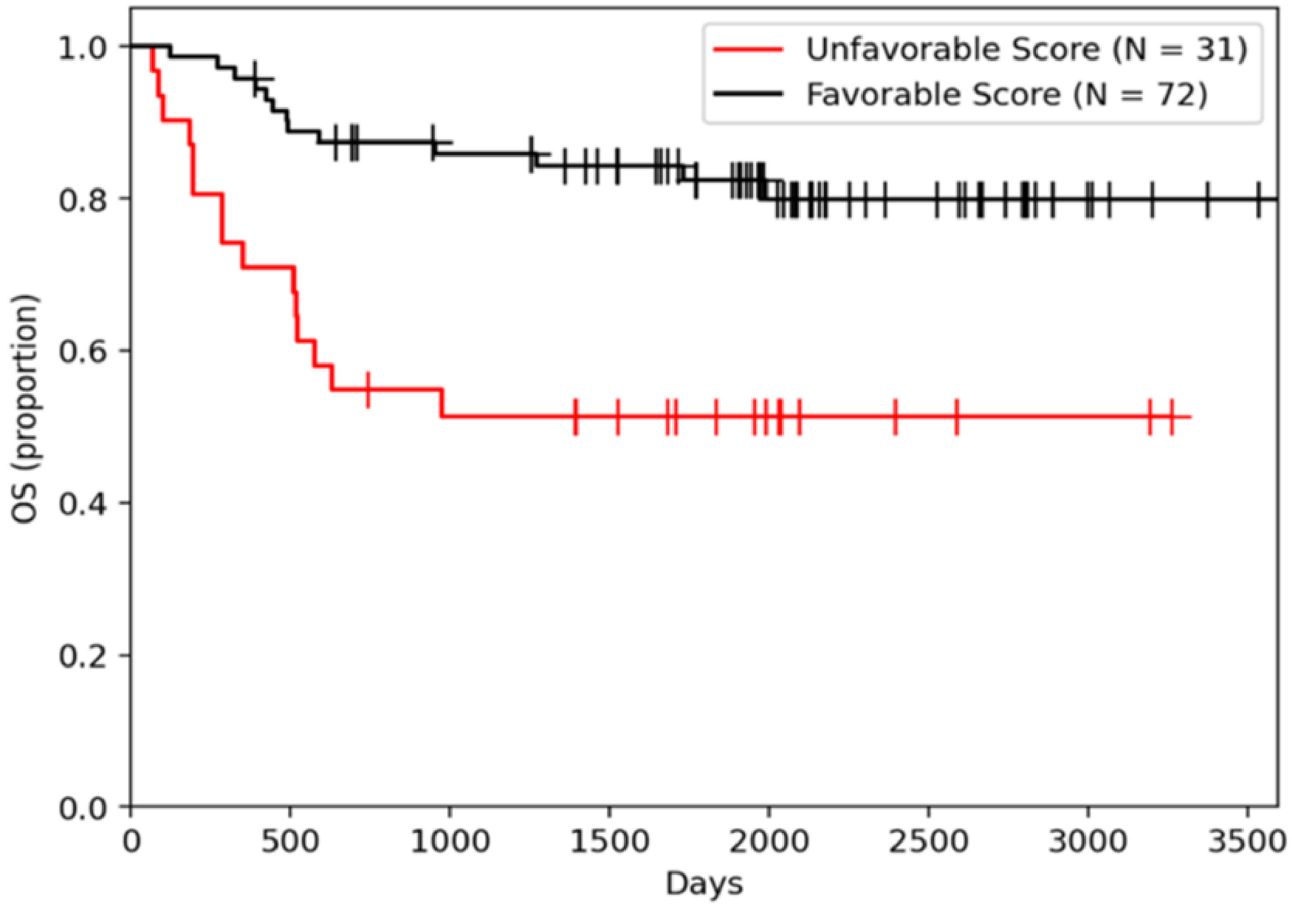
Number of new lesions (Anwar et al, 2018)
Tumor burden (Cho et al, 2017, Seban et al, 2019, Ito et al, 2019, Nobashi et al, 2019, Iravani et al, 2023)
Tumor shape (Breki et al, 2016, Sana et al, 2019)
Lymphoid cell-rich organs (Nobashi et al, 2019, Prigent et al, 2021)

TOXICITY

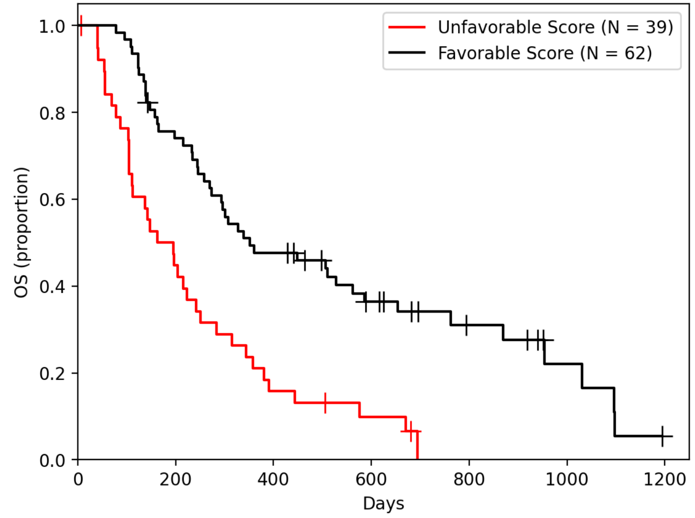
Pneumonitis (Gandy et al, 2020)
Colitis (Lang et al, 2019, Vani et al, 2020, Lang et al, 2020, Sachpekidis et al, 2023)
Thyroiditis (Eshgi et al, 2018)
Pancreatitis (Alabed et al, 2015, Das et al, 2019)
Endocrinopathies (Shalit et al, 2023)
Sarcoid reaction (Cheshire et al, 2018)
Hepatitis (Prigent et al, 2020)
Hypophysitis (Caranci et al, 2020)
Skeletal (Moseley et al, 2018)

Predicting BENEFIT
Individual patient imaging data (FDG PET)

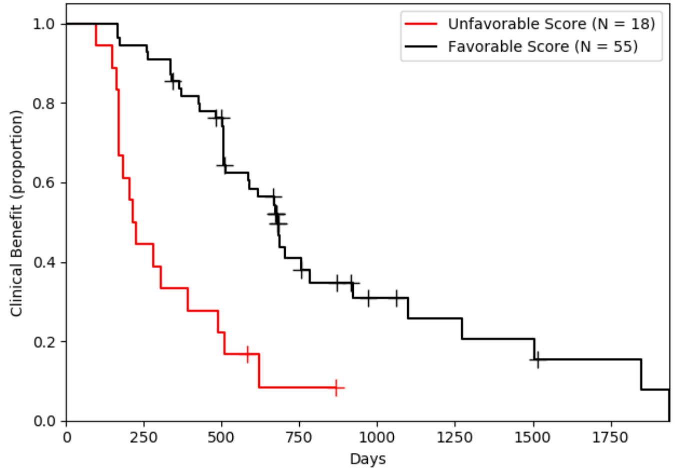
Melanoma/ICI (n=117)



GU/Cabo+Nivo+/-Ipi (n=101)



Prostate/Vaccine+/-ICI (n=32)



Courtesy of AIQ Solutions

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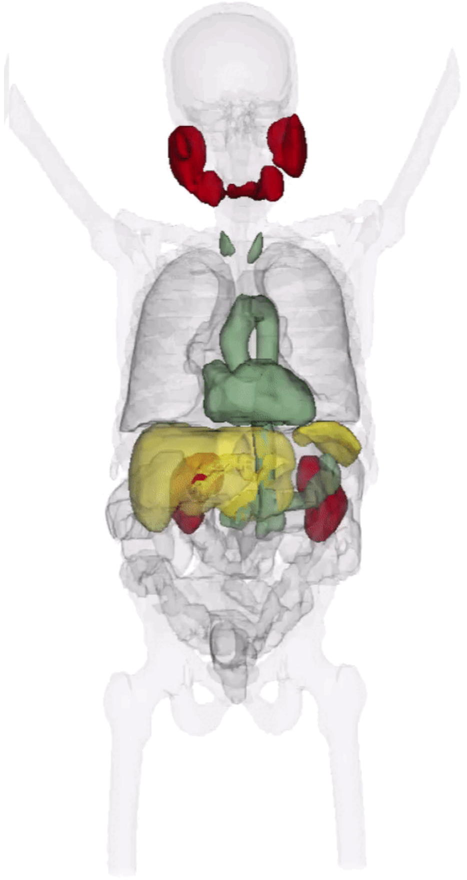
Predicting RISKS
Individual patient imaging data (FDG PET)



Treatment	Effected Organ	AUC	Sense	Spec
Immunotherapy	Kidneys	0.98	0.98	1.00
Immunotherapy	Pancreas	0.96	1.00	0.91
Immunotherapy	Bowel	0.95	1.00	0.80
Immunotherapy	Liver	0.93	0.90	1.00
Immunotherapy	Lungs	0.92	0.78	0.89
Immunotherapy	Adrenals	0.85	0.72	1.00
Immunotherapy	Thyroid	0.84	0.83	0.82

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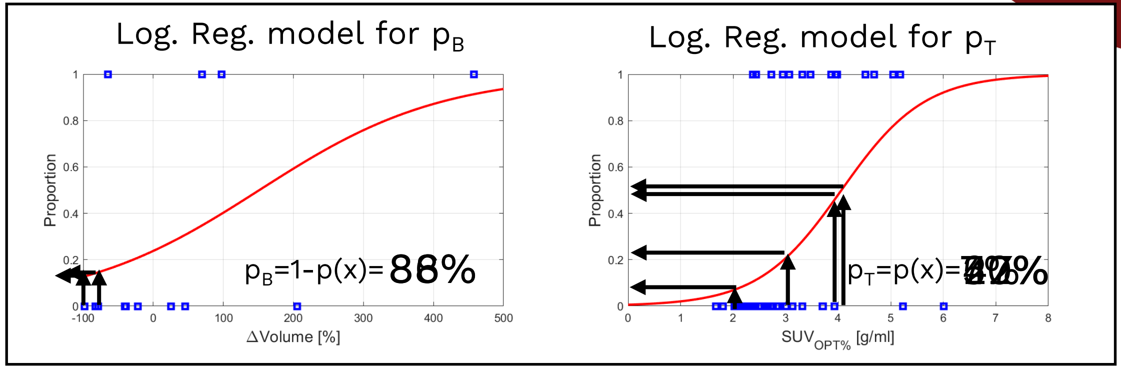
Courtesy of AIQ Solutions

Example patient

MM patient starting on ipi+nivo

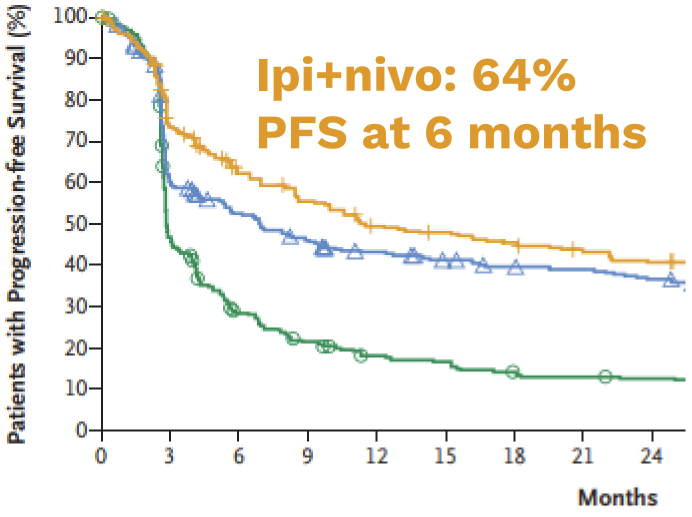
Benefit: PFS>6 mo.   Toxicity: colitis g3/4



Day -11

Disease:

Toxicity (bowel):



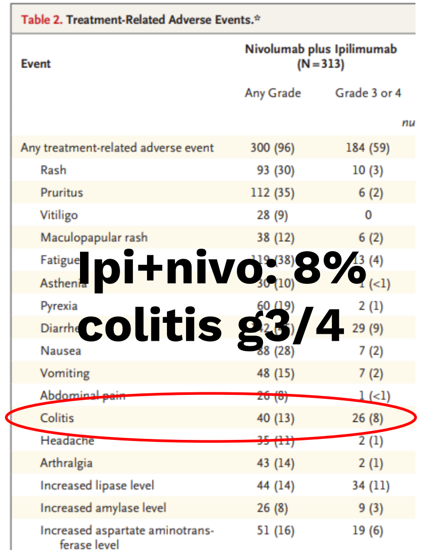
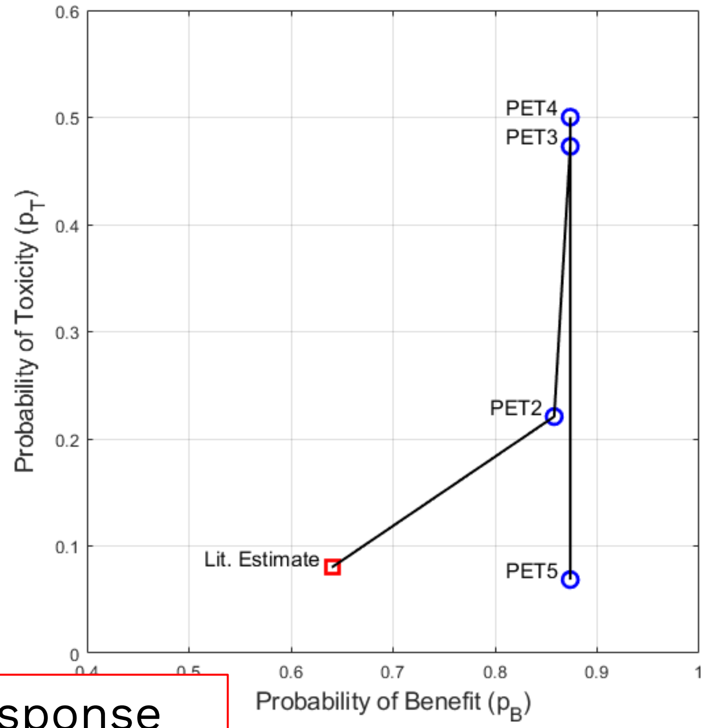


Table 2. Treatment-Related Adverse Events.*

Event	Nivolumab plus Ipilimumab (N=313) Any Grade	Grade 3 or 4
	number of patients (percent)	
Any treatment-related adverse event	300 (96)	184 (59)
Rash	93 (30)	10 (3)
Pruritus	112 (35)	6 (2)
Vitiligo	28 (9)	0
Maculopapular rash	38 (12)	6 (2)
Fatigue	119 (38)	3 (4)
Asthenia	30 (10)	1 (<1)
Pyrexia	60 (19)	2 (1)
Diarrhea	[illegible]	29 (9)
Nausea	88 (28)	7 (2)
Vomiting	48 (15)	7 (2)
Abdominal pain	26 (8)	1 (<1)
Colitis	40 (13)	26 (8)
Headache	35 (11)	2 (1)
Arthralgia	43 (14)	2 (1)
Increased lipase level	44 (14)	34 (11)
Increased amylase level	26 (8)	9 (3)
Increased aspartate aminotransferase level	51 (16)	19 (6)

Ipi+nivo: 8% colitis g3/4



Baseline response and toxicity from CHECKMATE-067 (Wolchok *et. al.* 2017)

Risk-benefit space can be used to track disease response and toxicity risk at each imaging timepoint during treatment.

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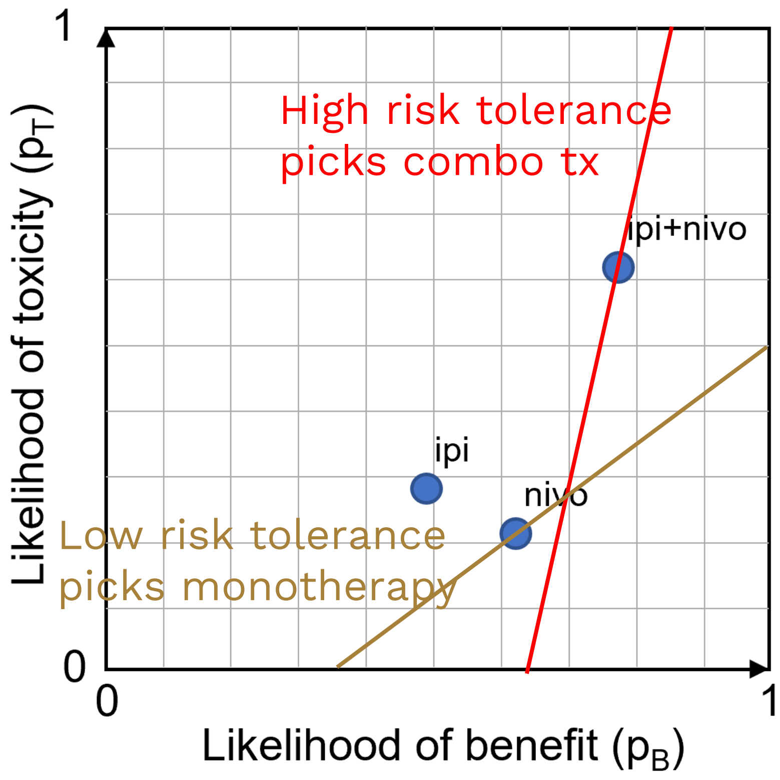
Risk-benefit space

Population-based risk-benefit



$p_B = 1 - p_{PD}$ $\qquad$ $p_R = p_{g3-4, any\ organ}$

Patient-specific risk-benefit

Summary

- Optimizing cancer treatments (schedule, dose) is complex:
  - Balancing risks and benefits of individual patients
  - Accounting for spatial and temporal (response) heterogeneity
- Computationally complex AI-supported analytics is needed:
  - Assessment of each individual lesion response (metastatic disease)
  - Modeling complex relationship to predict risks and benefits
- Data-driven risk-benefit models are needed:
  - Population-based risk-benefit models (large clinical trials)
  - Individual patient risk-benefit models (patient-specific data)

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Thank you for your attention

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