AI in the Era of Precision Medicine: Role of Medical Imaging

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Disclosure

- Founder and CSO of AIQ Solutions

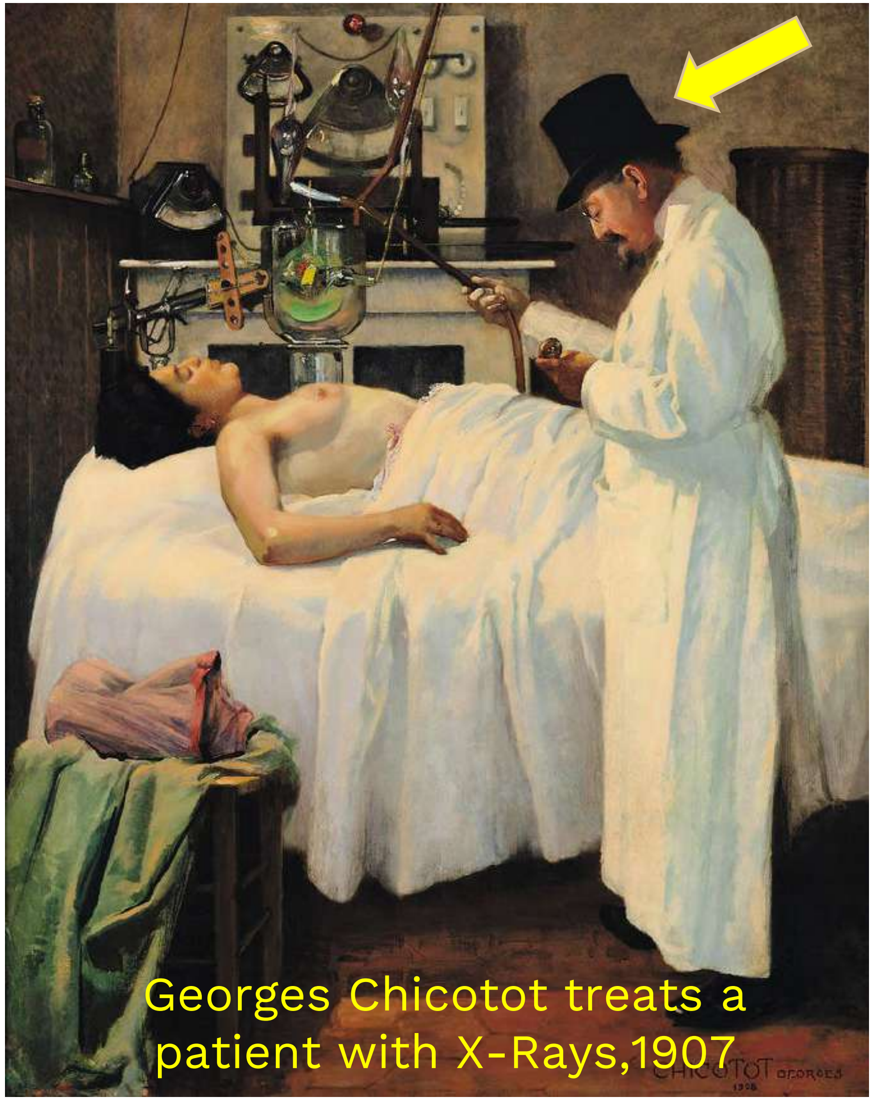
WHAT IS MEDICAL PHYSICS?

- Rich history of critical inventions
- Imaging, therapy, modeling in medicine

How was Medicine in Marie Currie's times?

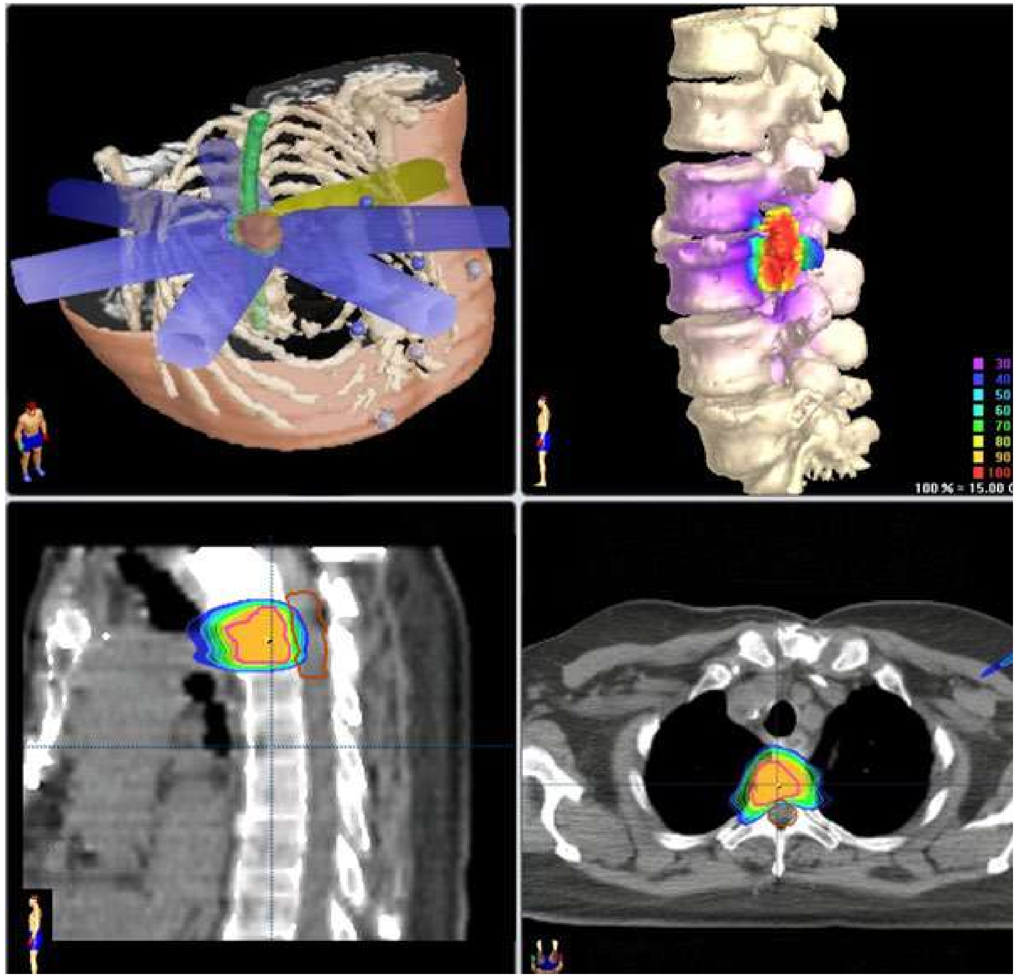
Imaging and therapy

Wilhelm Röntgen examines a patient with X-rays, 1896

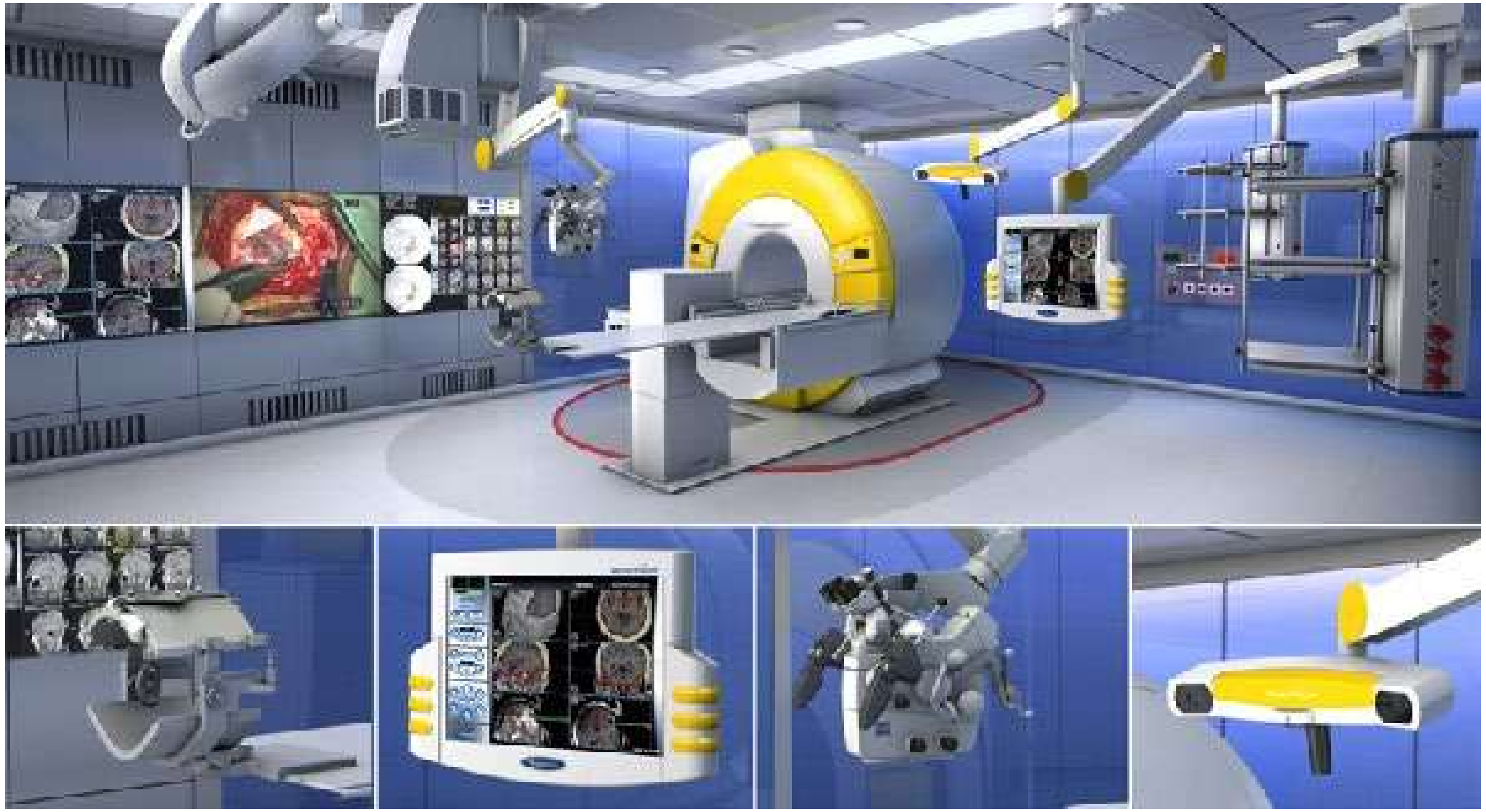


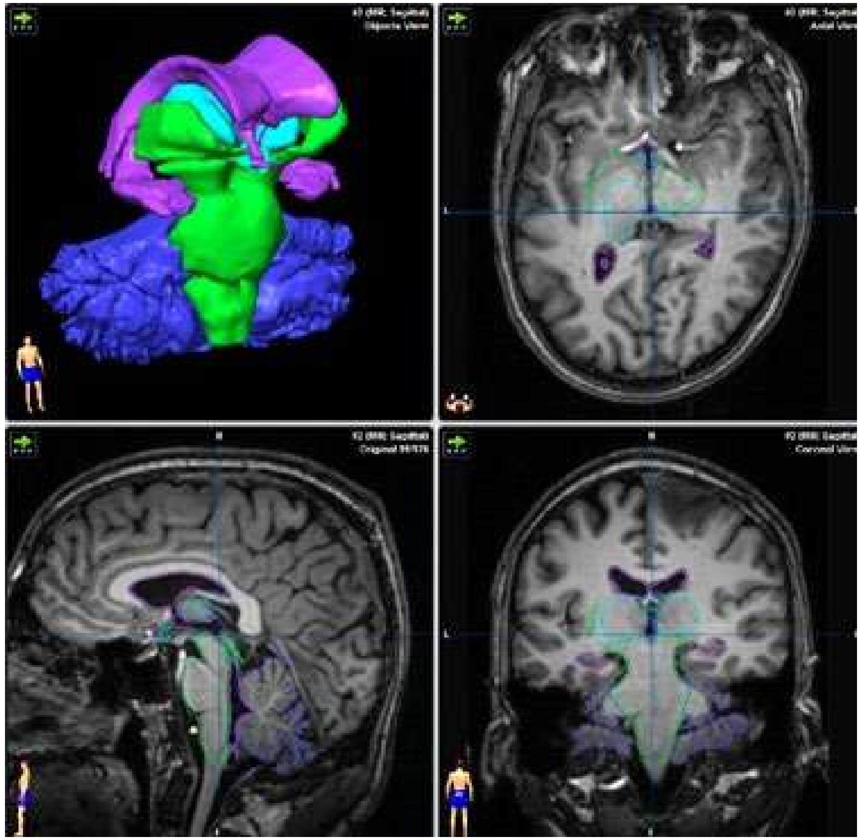
Georges Chicotot treats a patient with X-Rays,1907

120 years later…
Image Guided Radiation Therapy



120 years later...
Image Guided Surgery





AI AND PRECISION MEDICINE

- Just buzz words, or real thing?

What does MEDICAL COMMUNITY think?

”4 P’s of medicine”: Individuals respond differently to environmental conditions, according to their genetic endowment and their own behavior. In the future, research will allow us to **predict** how, when, and in whom a disease will develop. We can envision a time when we will be able to precisely target treatment on a **personalized** basis to those who need it, avoiding treatment to those who do not. Ultimately, this individualized approach will allow us to **preempt** disease before it occurs, utilizing the **participation** of individuals, communities, and healthcare providers in a proactive fashion, as early as possible, and throughout the natural cycle of a disease process.

Elias A. Zerhouni, M.D.

Director, National Institutes of Health (NIH), 2008

It is all about PM these days…

What does IMAGING COMMUNITY think?

- Imaging research laboratories are rapidly creating **machine learning systems that achieve expert human performance**

- **Roadmap for future research initiatives**:
  - New image reconstruction methods
  - Automated image labeling and annotation methods
  - New machine learning methods for clinical imaging data
  - Machine learning methods that can explain the advice they provide to human users
  - Validated methods for image de-identification and data sharing

2018 NIH/RSNA/ACR/The Academy Workshop
Radiology 2019; 291:781–791

It is all about AI these days…

"I'm sorry, the doctor no longer makes diagnoses."

What does BUSINESS COMMUNITY think?

- Medical imaging and machine learning are on a **collision course** that promises significant advancements in diagnostics and precision medicine

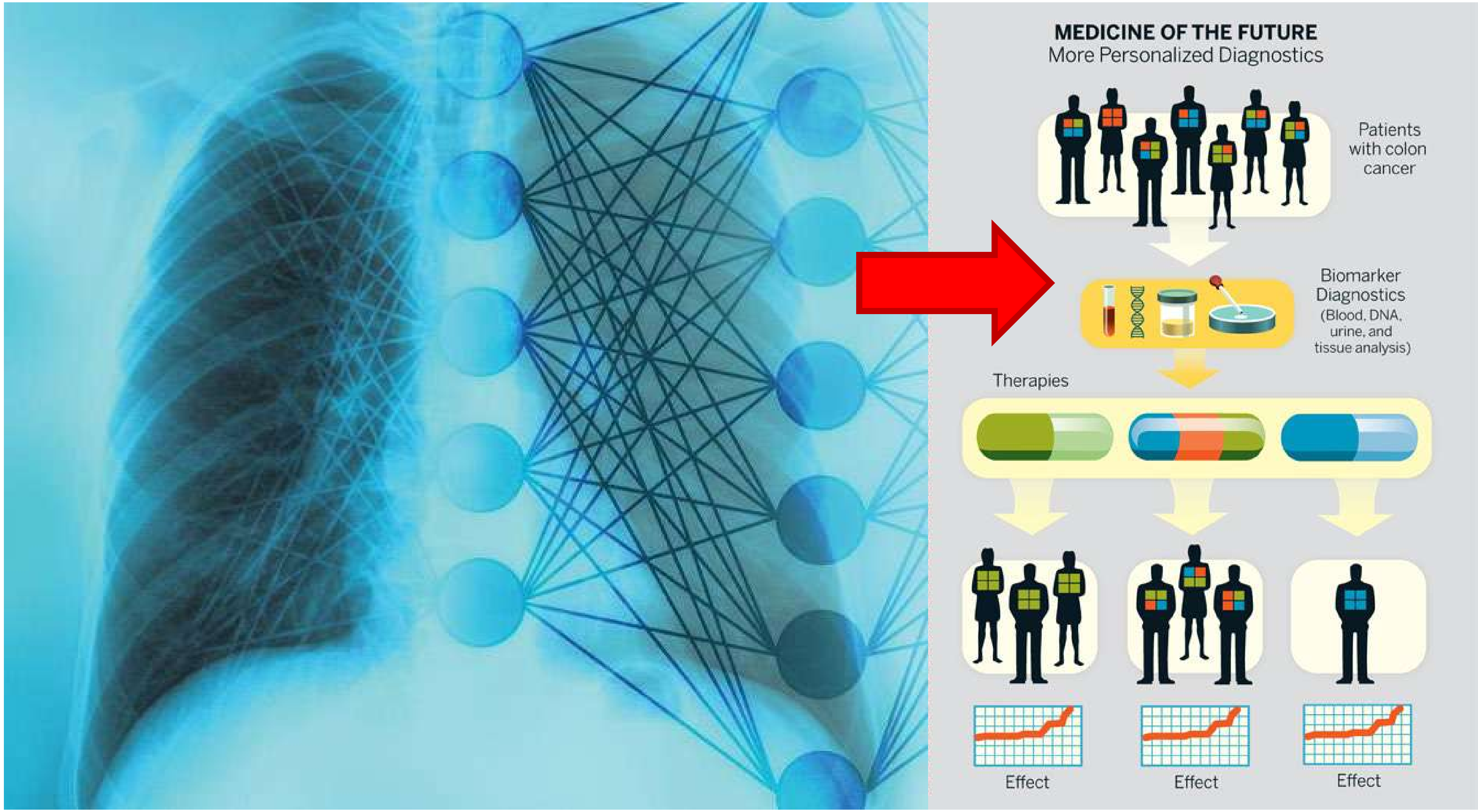
- **Precision medical imaging** market, worth **$120 million in 2017**, will explode into an **$8 billion opportunity by 2027** (Frost and Sullivan).

- Precision medical imaging has tremendous potential to improve all aspects of the care continuum, thus supporting emerging care approaches that are more **targeted, predictive, translational, personalized and effective**.

- **AI-enriched imaging equipment** will help adapt and personalize the imaging protocols and procedures while precise radiomic and phenomic datasets from the given clinical context will enable deep learning, thereby reinforcing medical imaging's contribution to precision medicine

Health IT analytics, 2018

It is all about AI+PM these days…



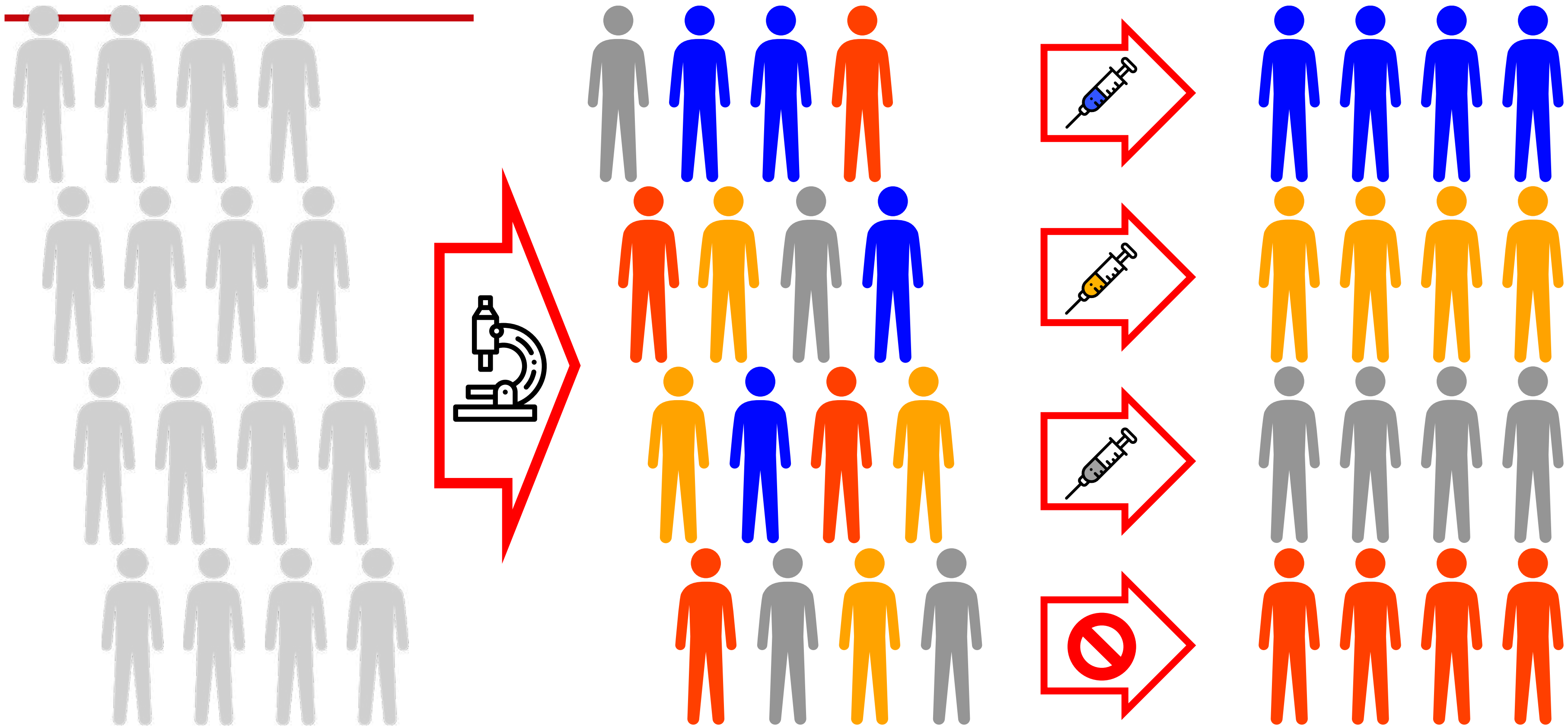
Kravka | Dreamstime

Peter Hoey; Source: Bayer Healthcare pharmaceuticals

PRECISION MEDICINE

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

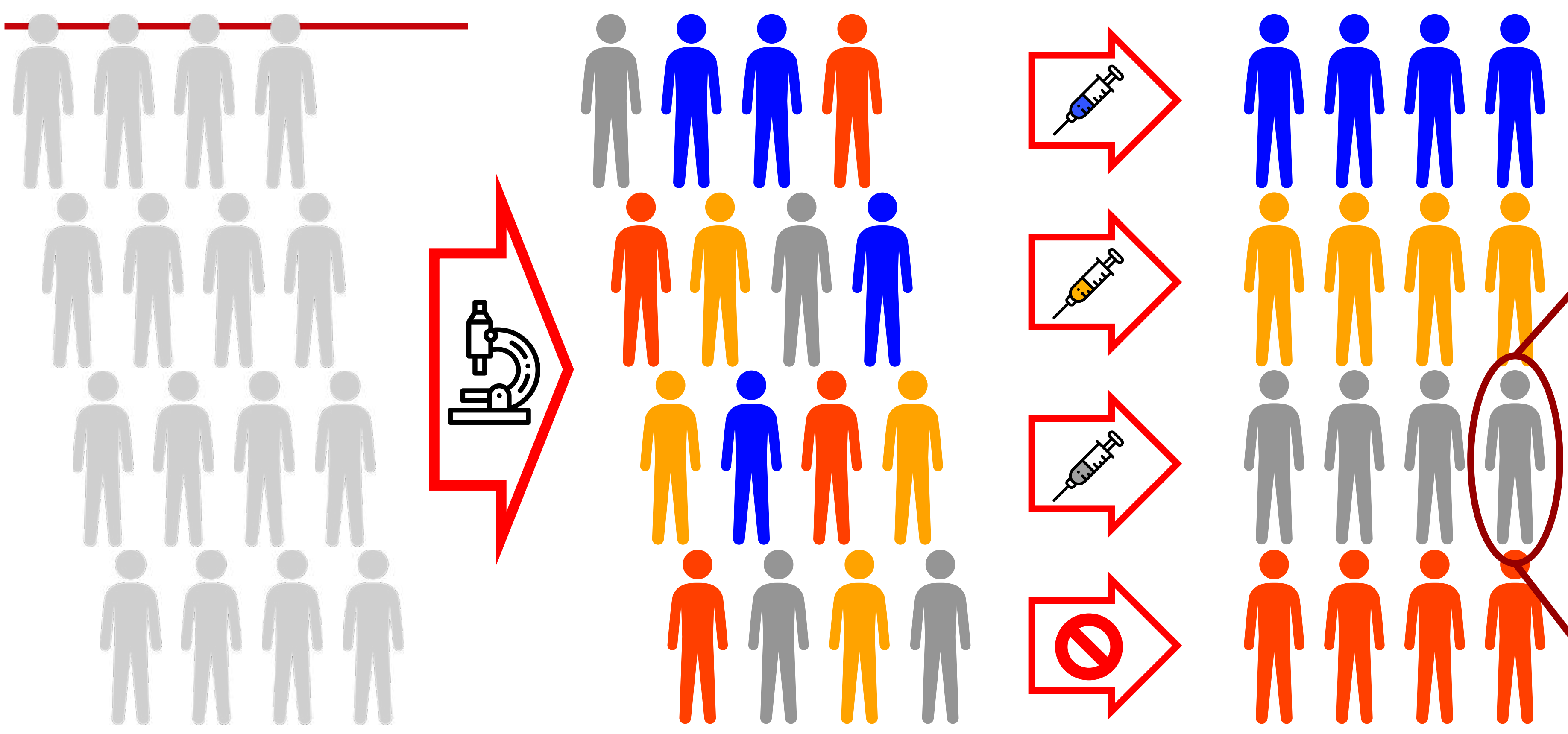
Precision medicine aims for this…

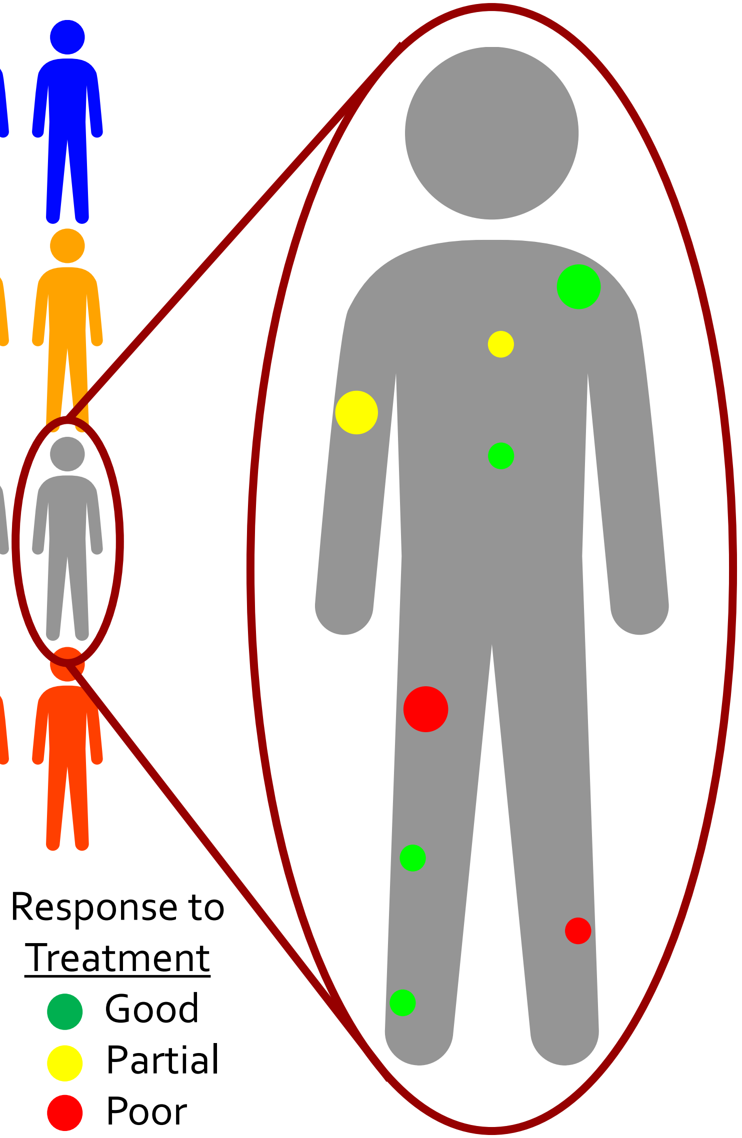


Not all patients respond the same to any given therapy, therefore different treatments need to be chosen

Icons made by Freepik from www.flaticon.com

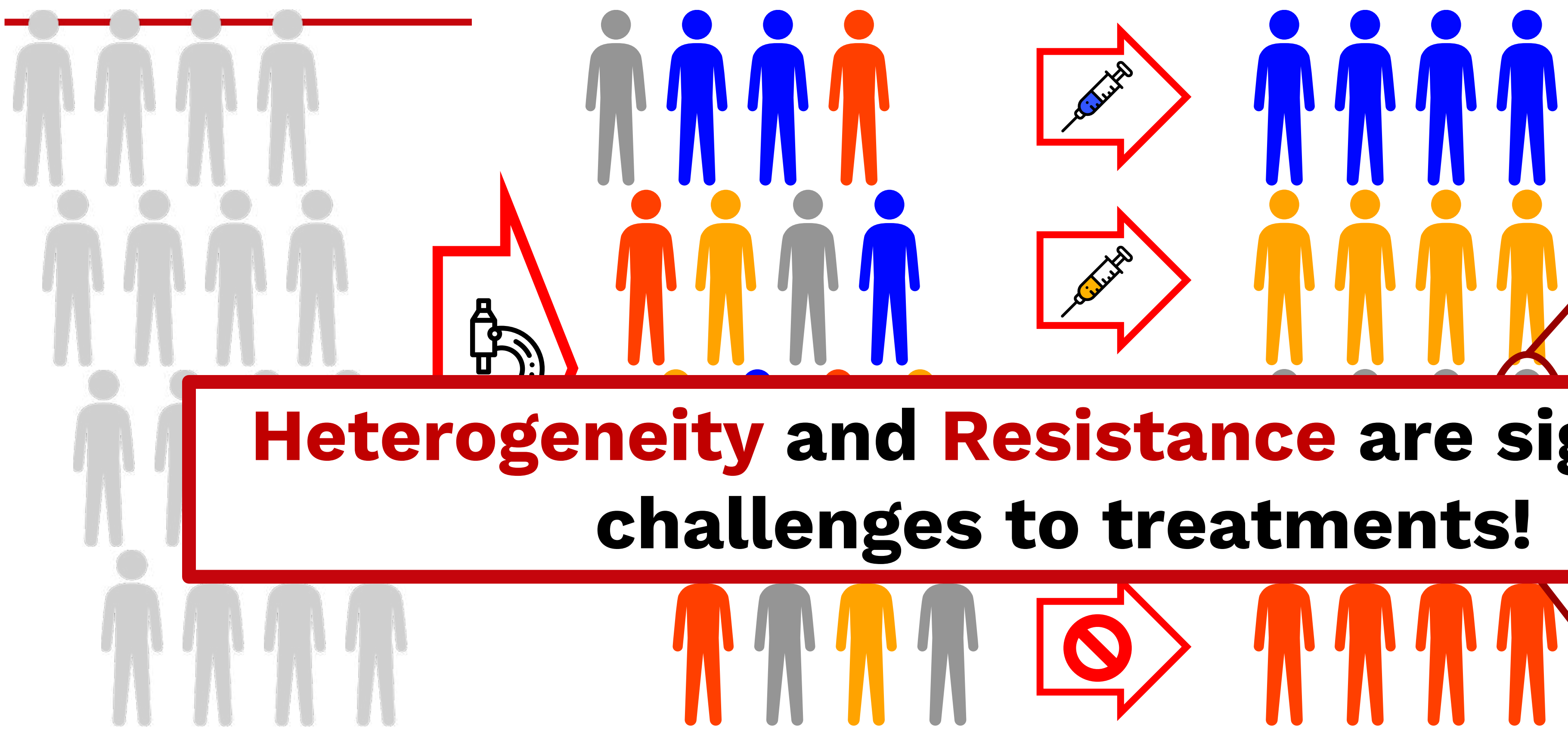
...but there is a big problem!



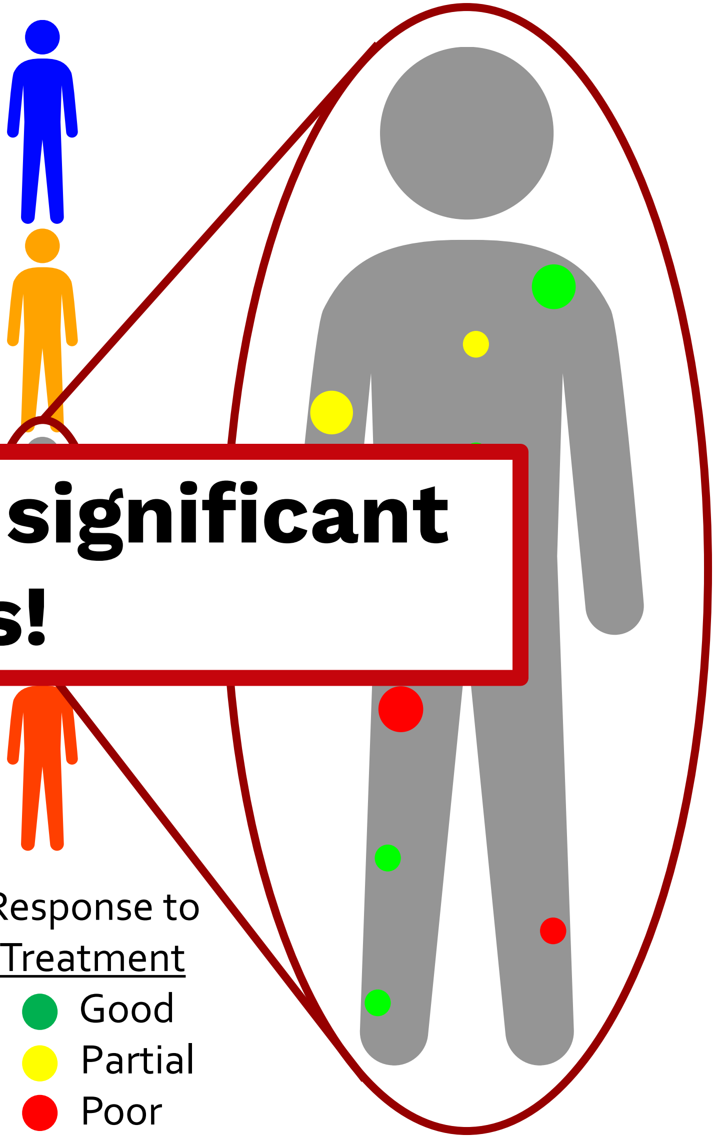


Just as not all patients respond the same to any given therapy, not all disease sites within a given patient respond the same.

...but there is a big problem!

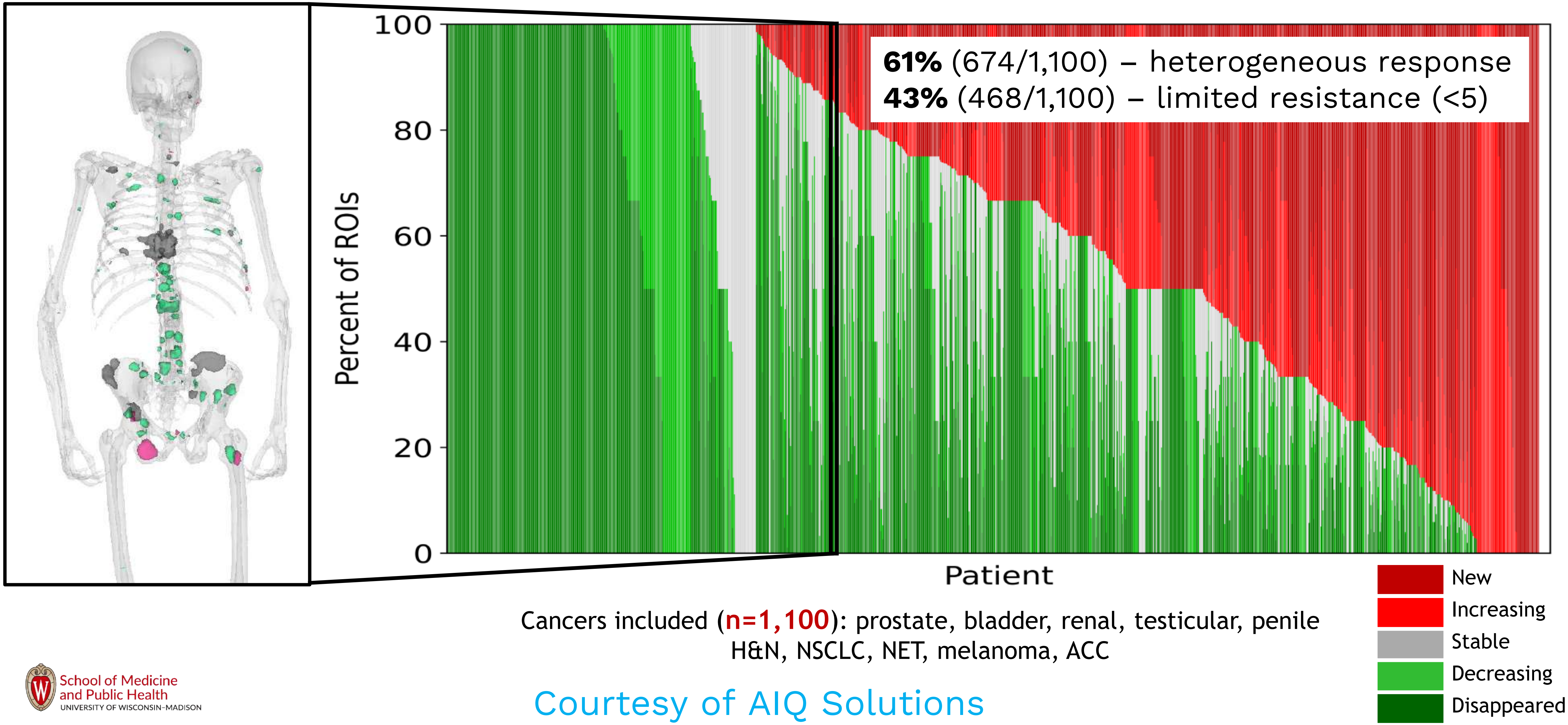


Heterogeneity and Resistance are significant challenges to treatments!



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

The problem of response heterogeneity



Cancers included (**n=1,100**): prostate, bladder, renal, testicular, penile H&N, NSCLC, NET, melanoma, ACC

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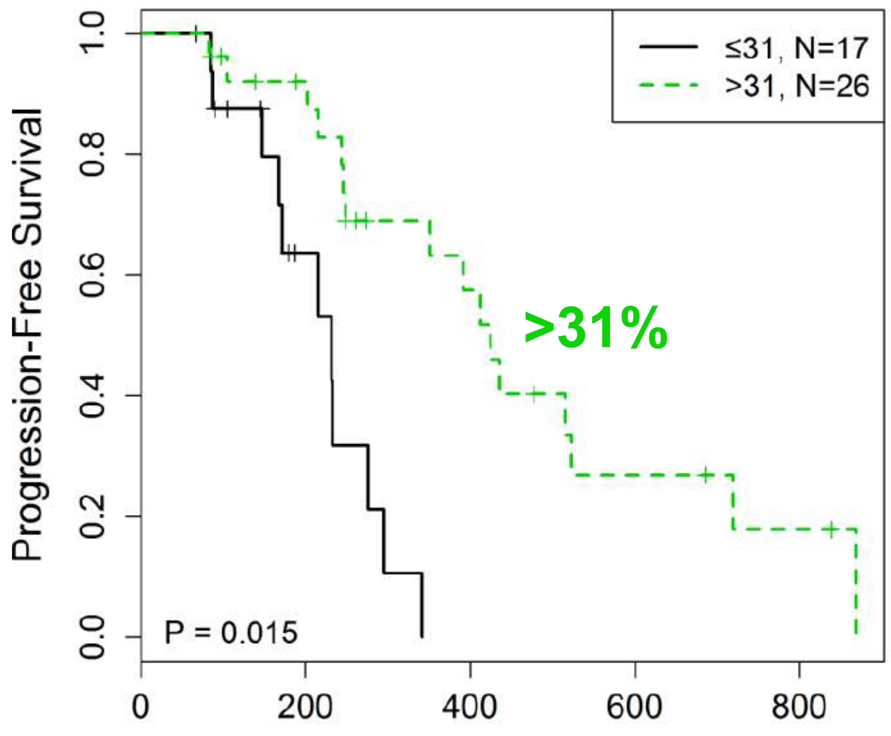
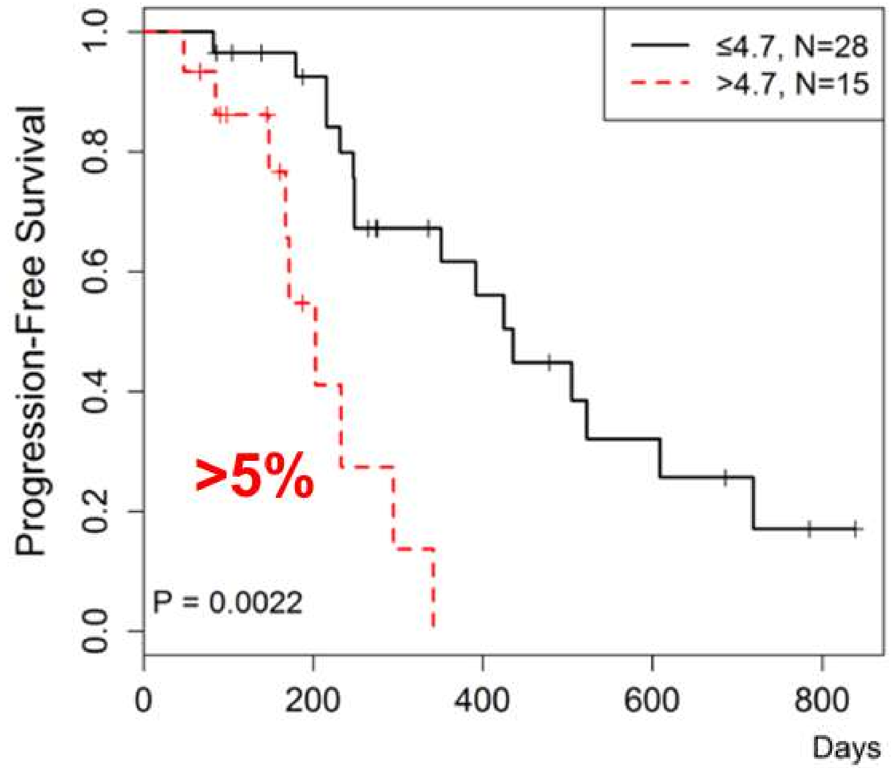
Courtesy of AIQ Solutions

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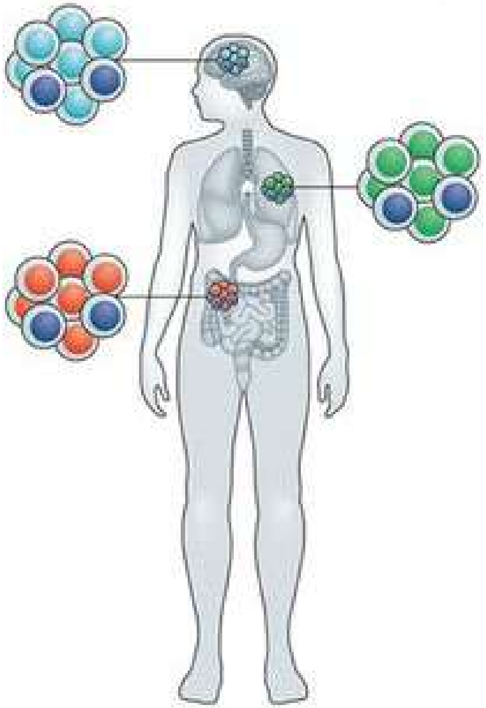
Harmon et al 2017, J Clin Oncol, 35(24): 2829

Why heterogeneity?

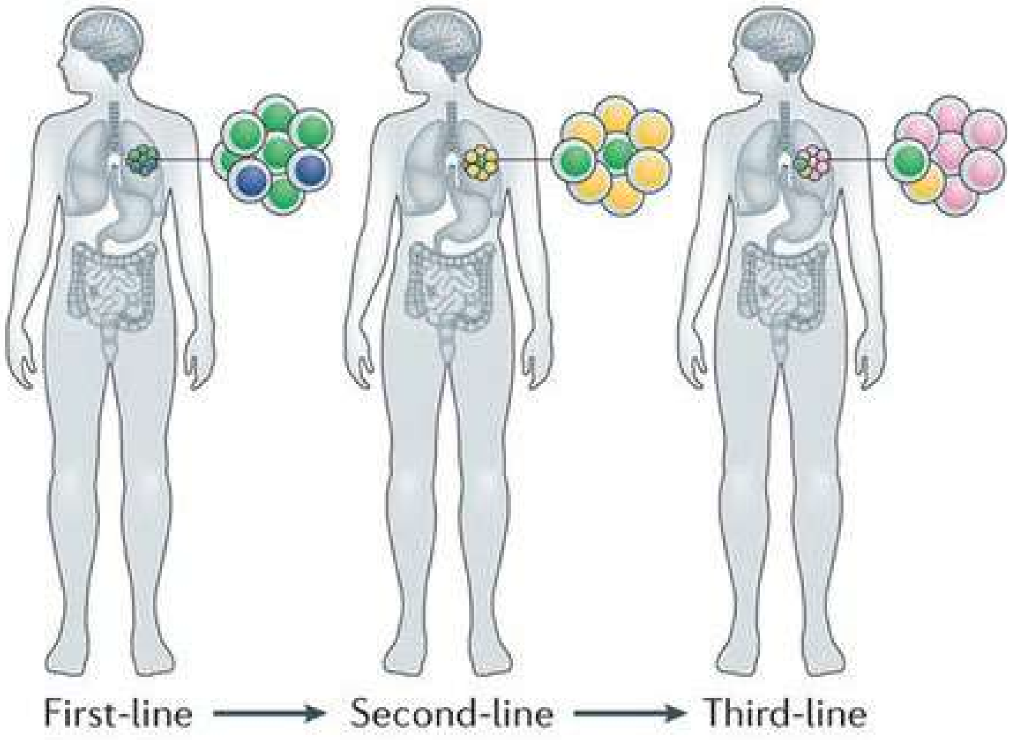
Spatial Heterogeneity

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

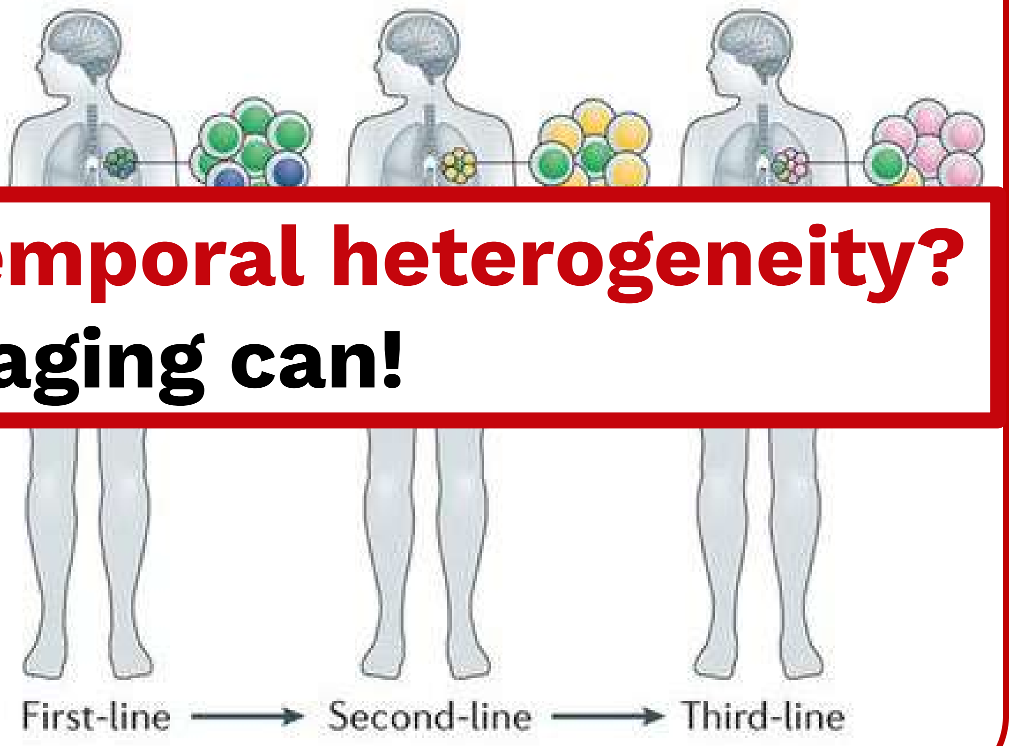
Why heterogeneity?

Spatial Heterogeneity

Different
disease
…
therapy at a
given point in
time

Temporal Heterogeneity

The same
…
different
points in time



How can we assess spatial-temporal heterogeneity?

Only Medical Imaging can!

Nature Reviews | Clinical Oncology

HOW CAN WE GET SUCH DATA?

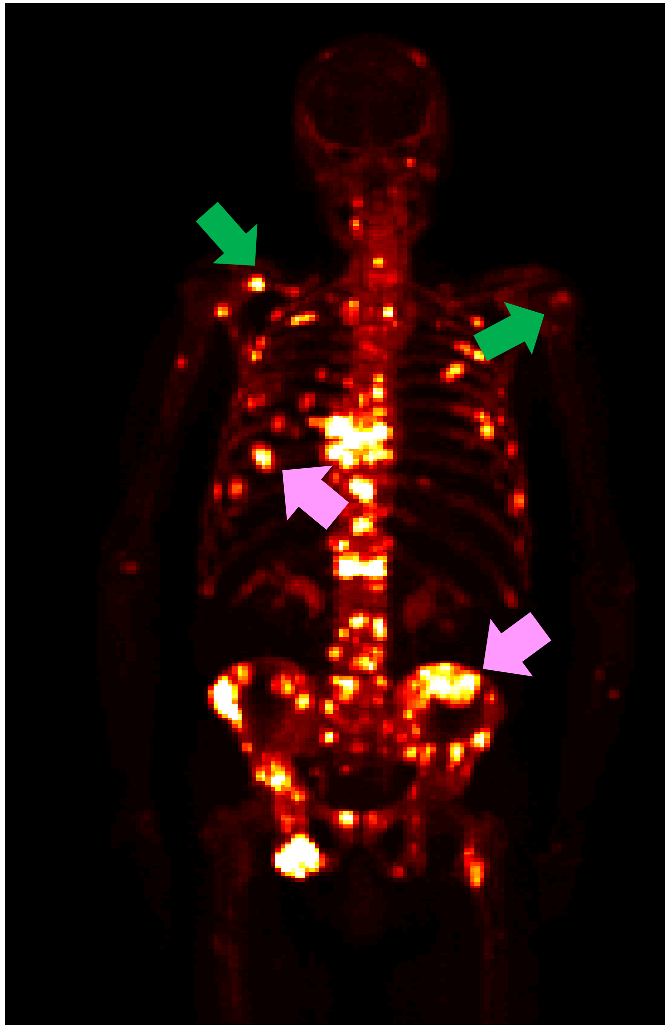
- AI-based Treatment Response Assessment

Treatment response assessment – Current practice

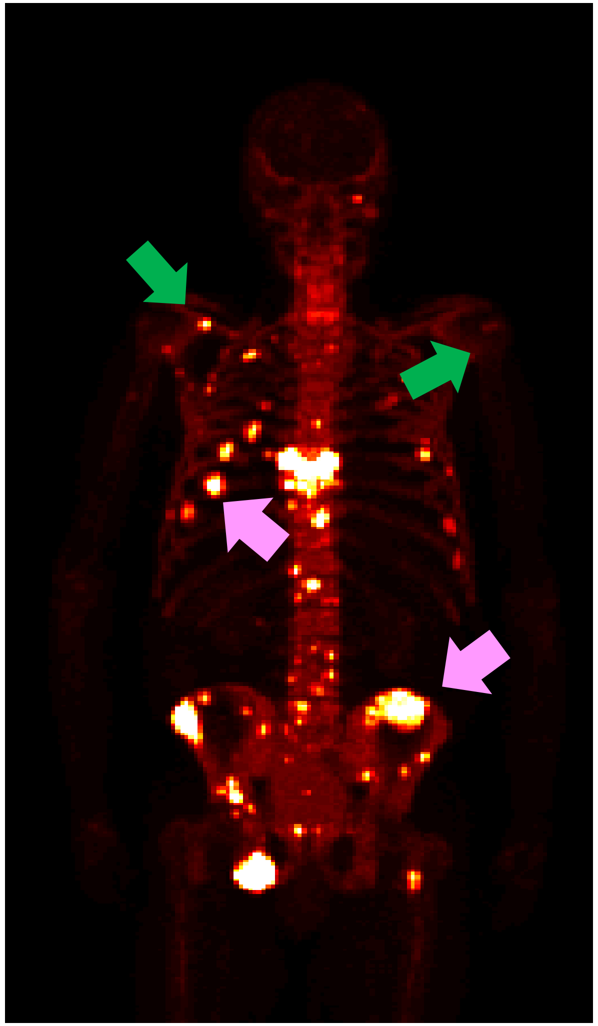
Manual and Qualitative Assessment

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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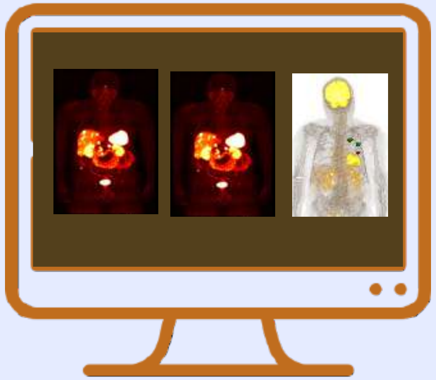
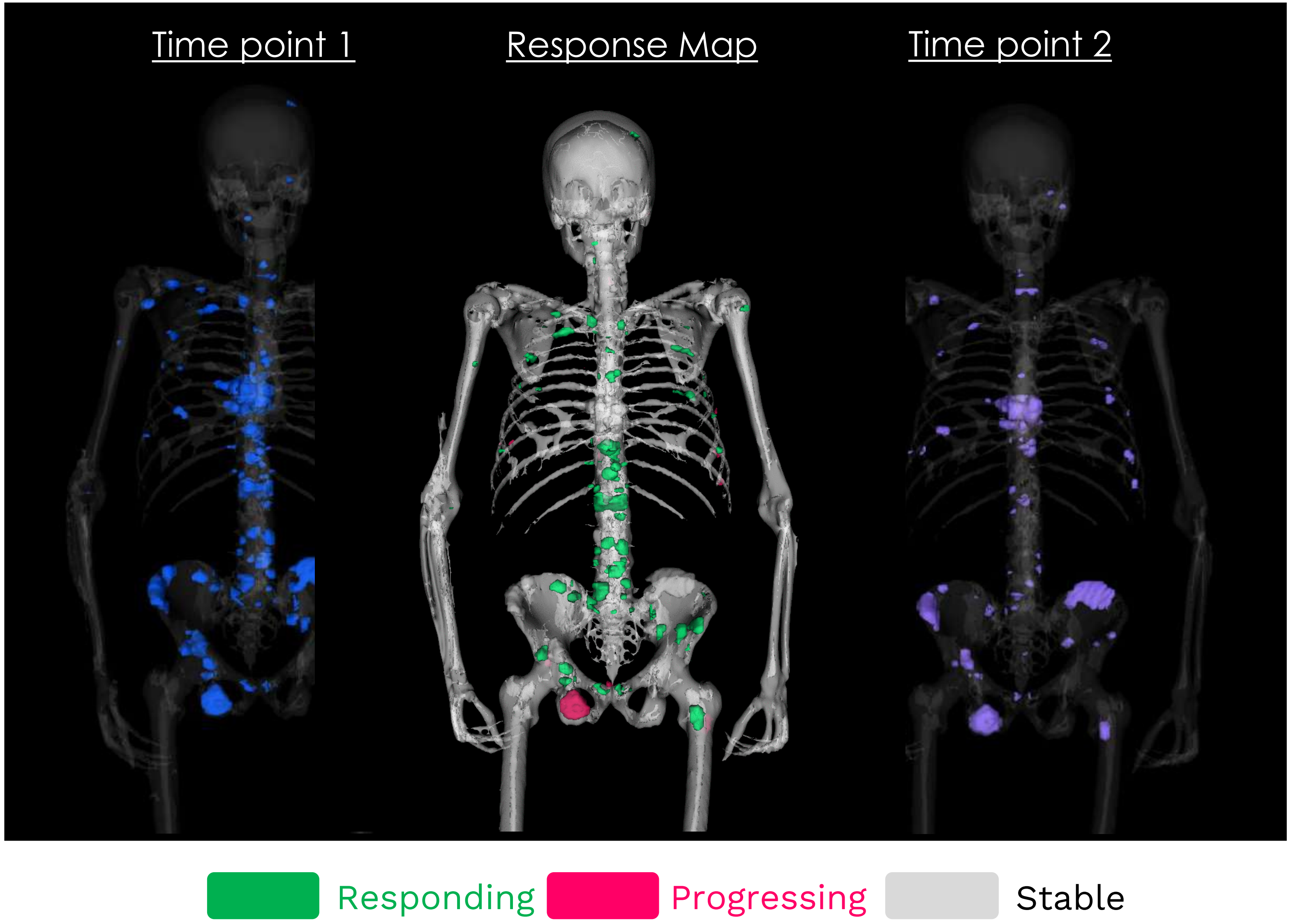
Treatment response assessment –
AI-based approach

Automatic and Quantitative Assessment

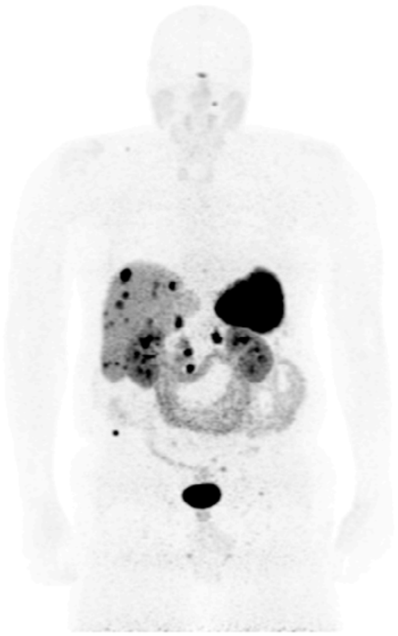


Our software automatically detects and classifies all lesions

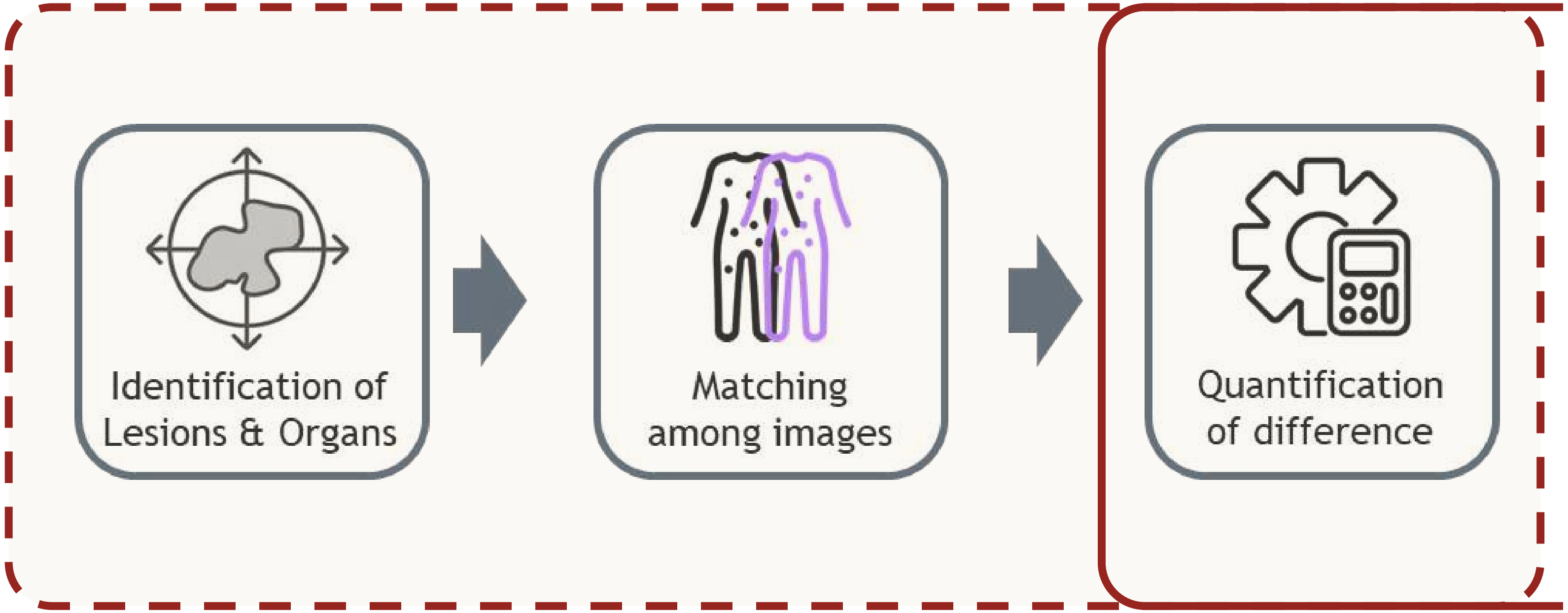
US Patents 9603567, 10445878
Licensed to our spin-off:
AIQ Solutions



Treatment response assessment – AI-based workflow



AI-driven association with outcomes



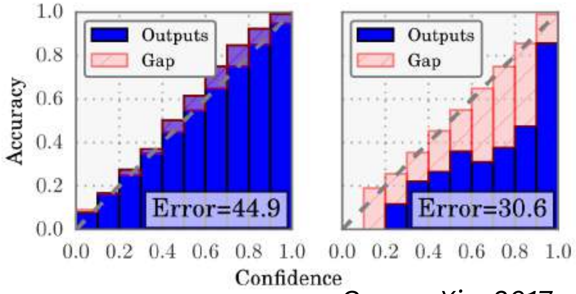
Quantitative Imaging Biomarkers

Surrogate Endpoints
(Predictive Biomarkers)

AI challenges – ignore or solve?

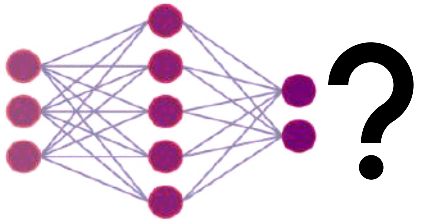
Challenges

Poorly Calibrated Probabilities Values

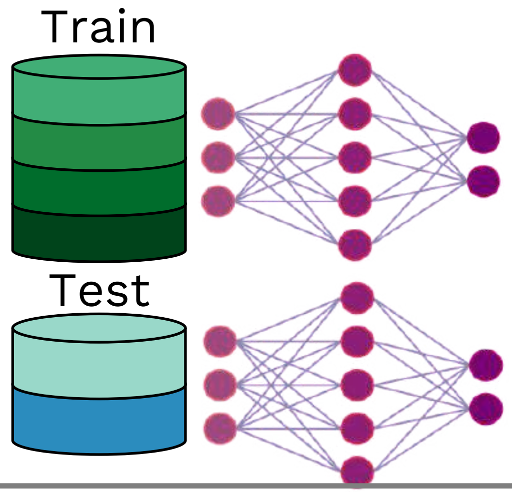


Guo. arXiv. 2017.

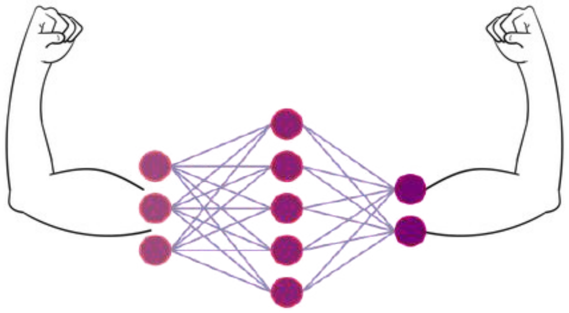
Model Uncertainty



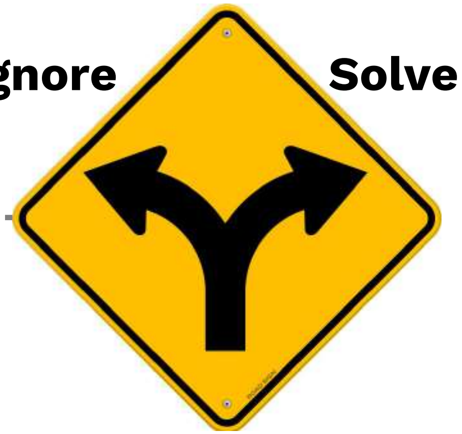
Small Datasets and Unknown Generalizability



Unknown Model Robustness

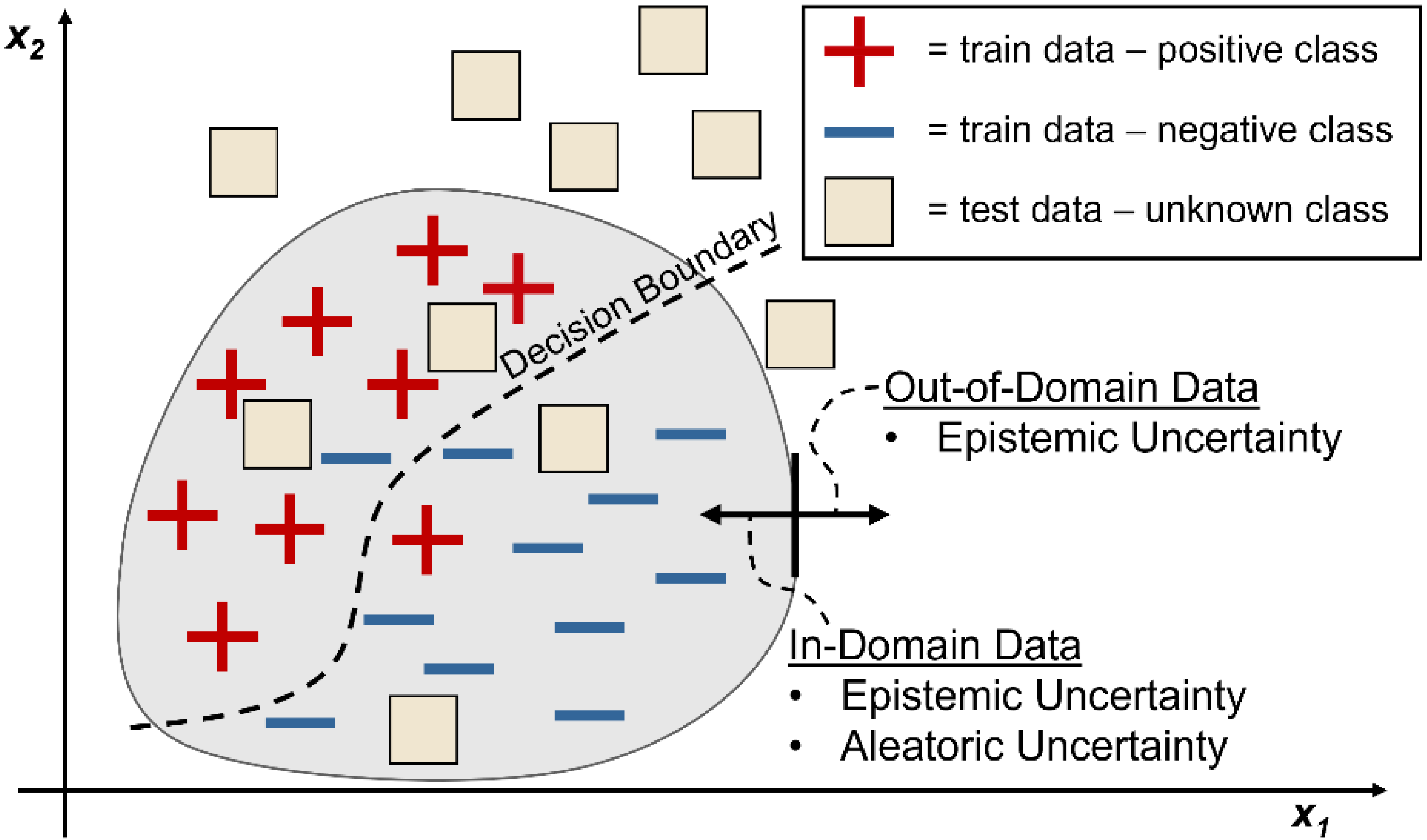


Ignore



Solve

AI comes with uncertainty!

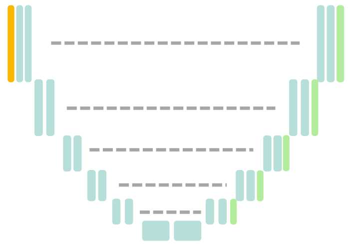


Understanding AI uncertainty

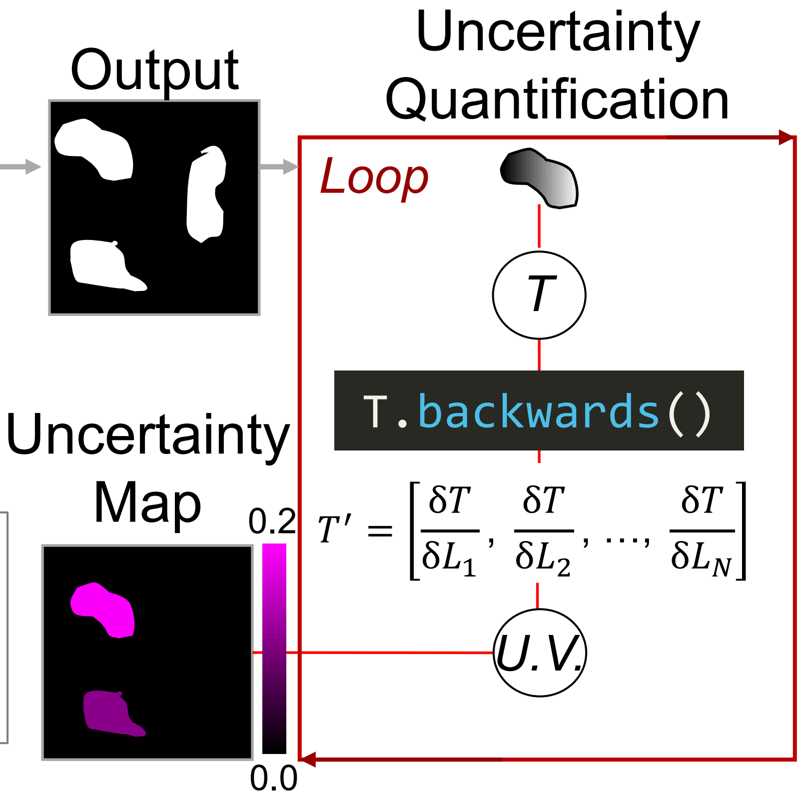
<u>Assessment of uncertainty</u>

(Novel *local gradients* method)

U-Net



nnUNet, F. Isensee, 2020.



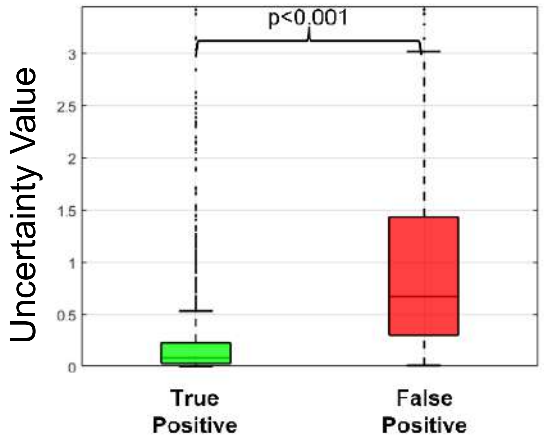
$T = Target = D_{KL}(p||q)$

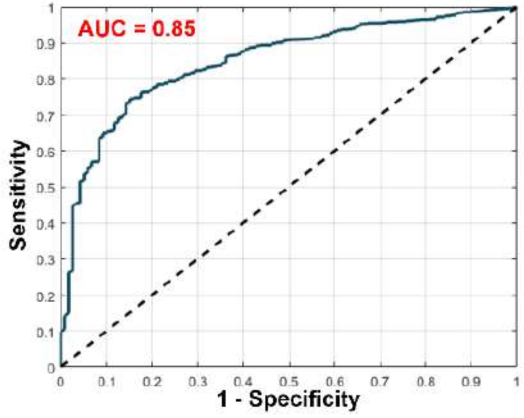
$p = Predicted\ Prob.Distr.$

$q = \left[\frac{1}{C}, \frac{1}{C}, \ldots, \frac{1}{C}\right] \in \mathbb{R}^C$

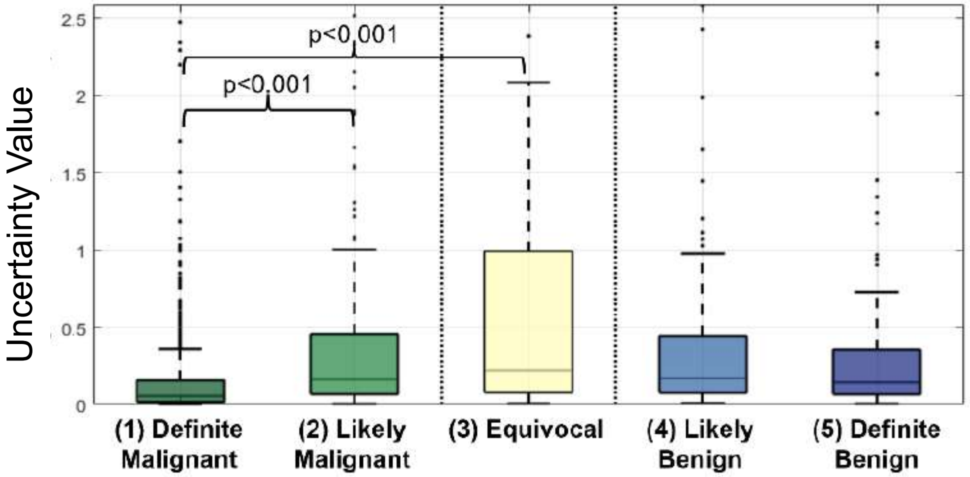
$U.V. = Unc.Val. = \|T'\|_1$

Identifies False Positives





Aligns With Physician Uncertainty



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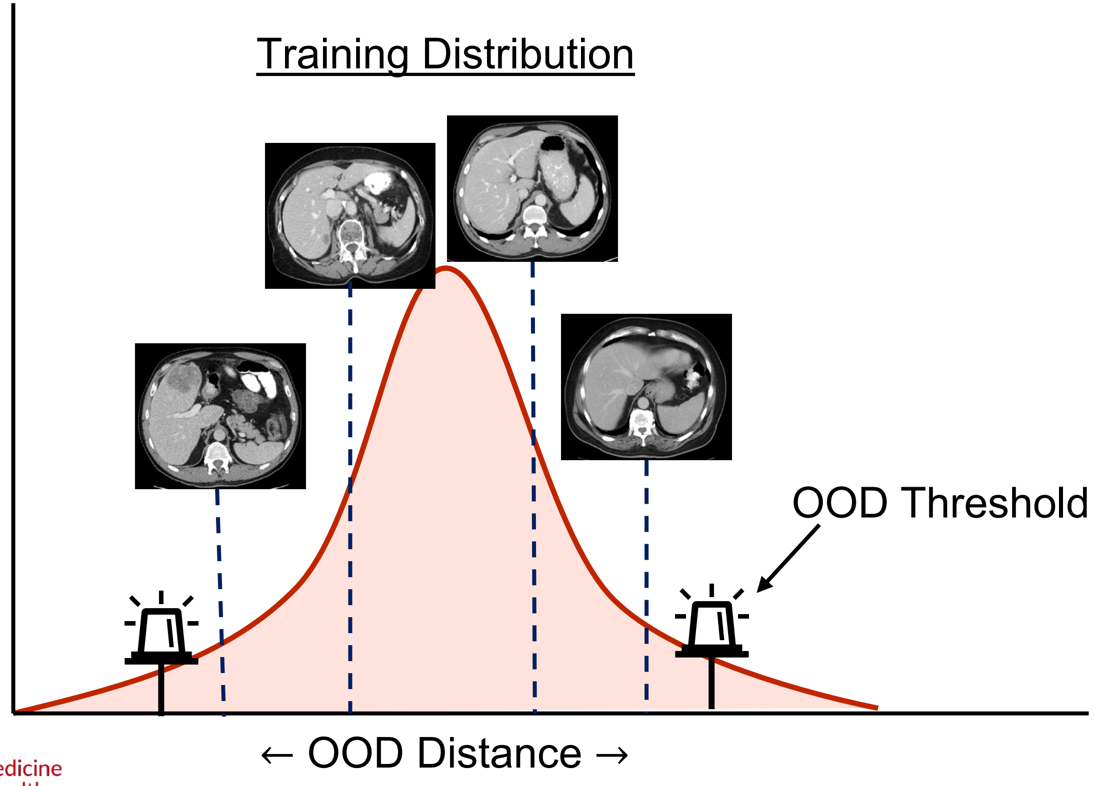
Out-of-distribution detection

OOD: Test data that differs substantially from the train dataset

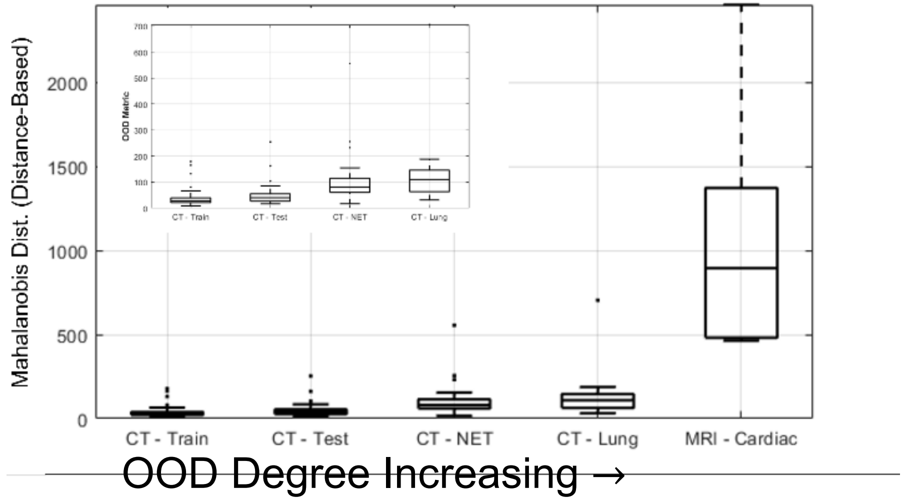
Generates untrustworthy model outputs

Goal: Detect OOD test inputs

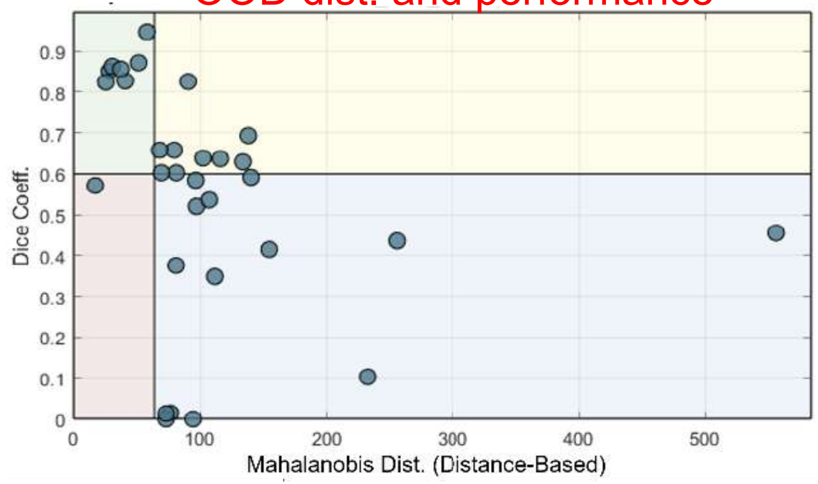


Metastatic tumor segmentation on CT

Distinguish ID from OOD data



Investigate correlations between OOD dist. and performance



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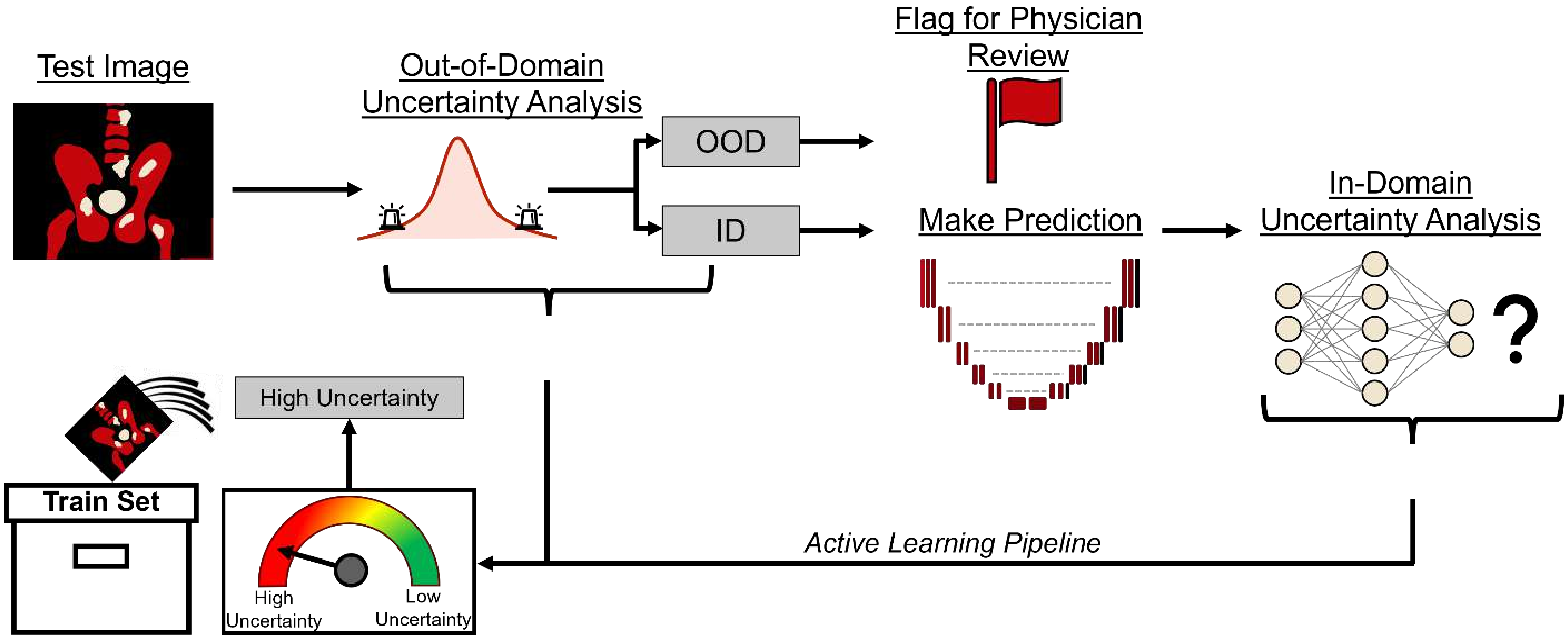
Ideal AI-based workflow



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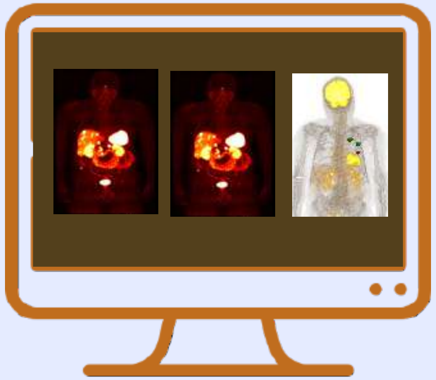
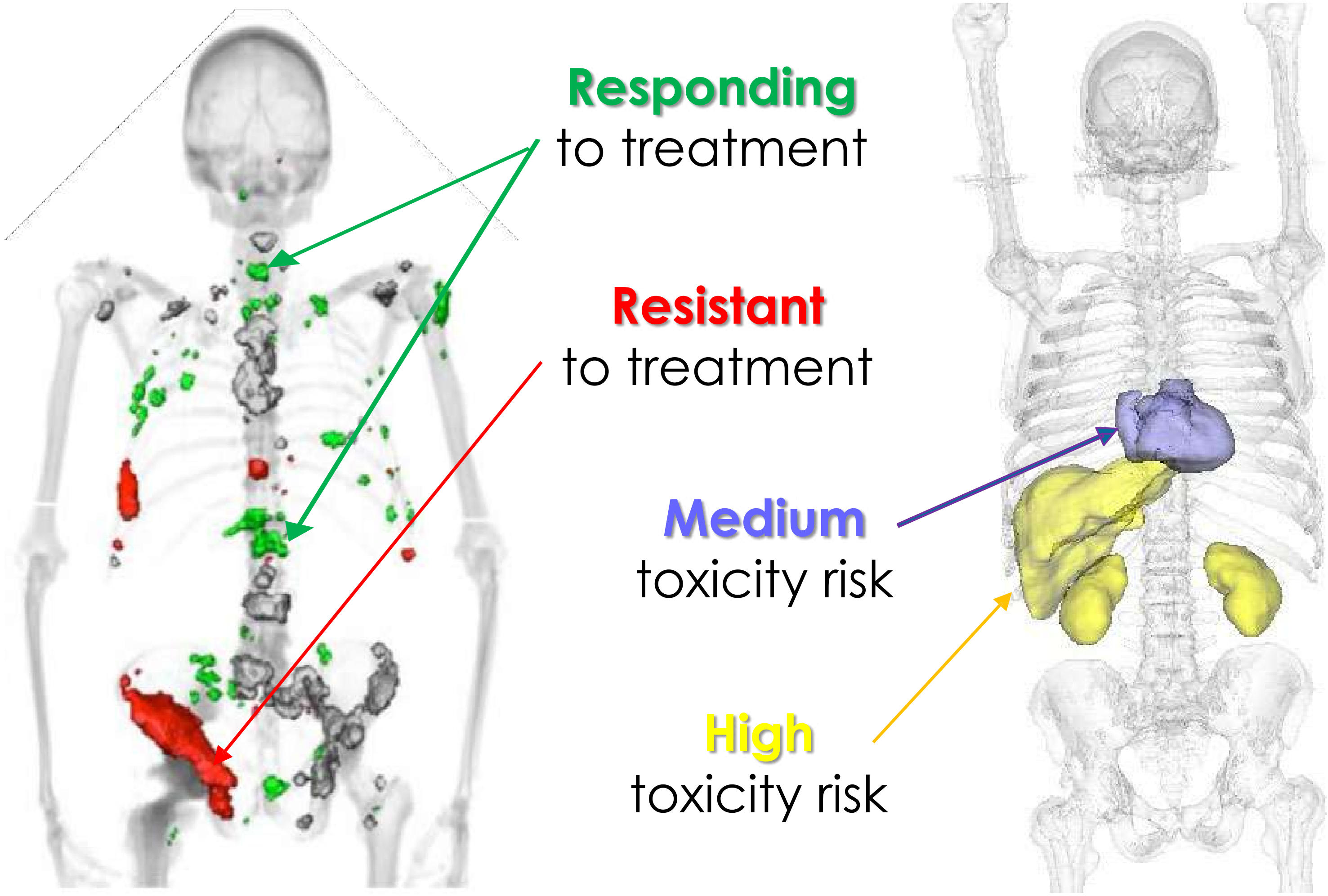
AI-based precision medicine

Automatic and Quantitative Assessment



Our software automatically detects and classifies all lesions



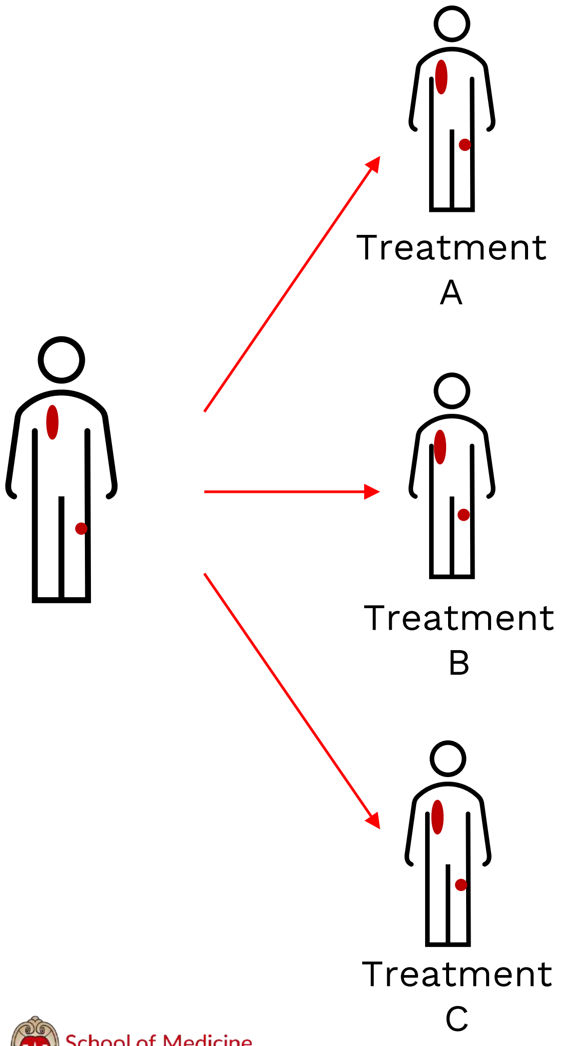
US Patents 9603567, 10445878
Licensed to our spin-off:
AIQ Solutions

WHERE DO WE GO FROM HERE?

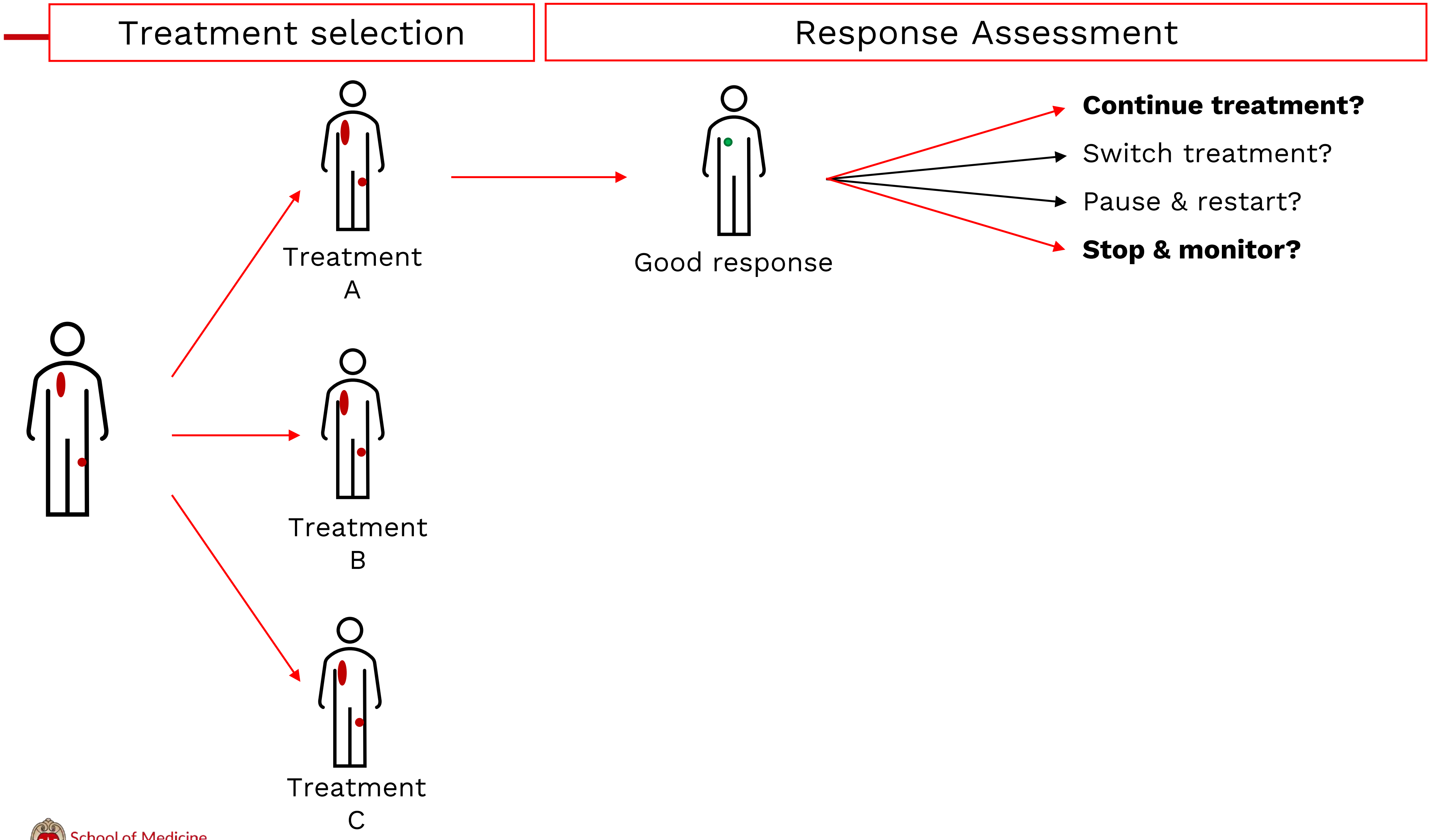
- Optimizing risk-benefit

Optimizing treatment decisions

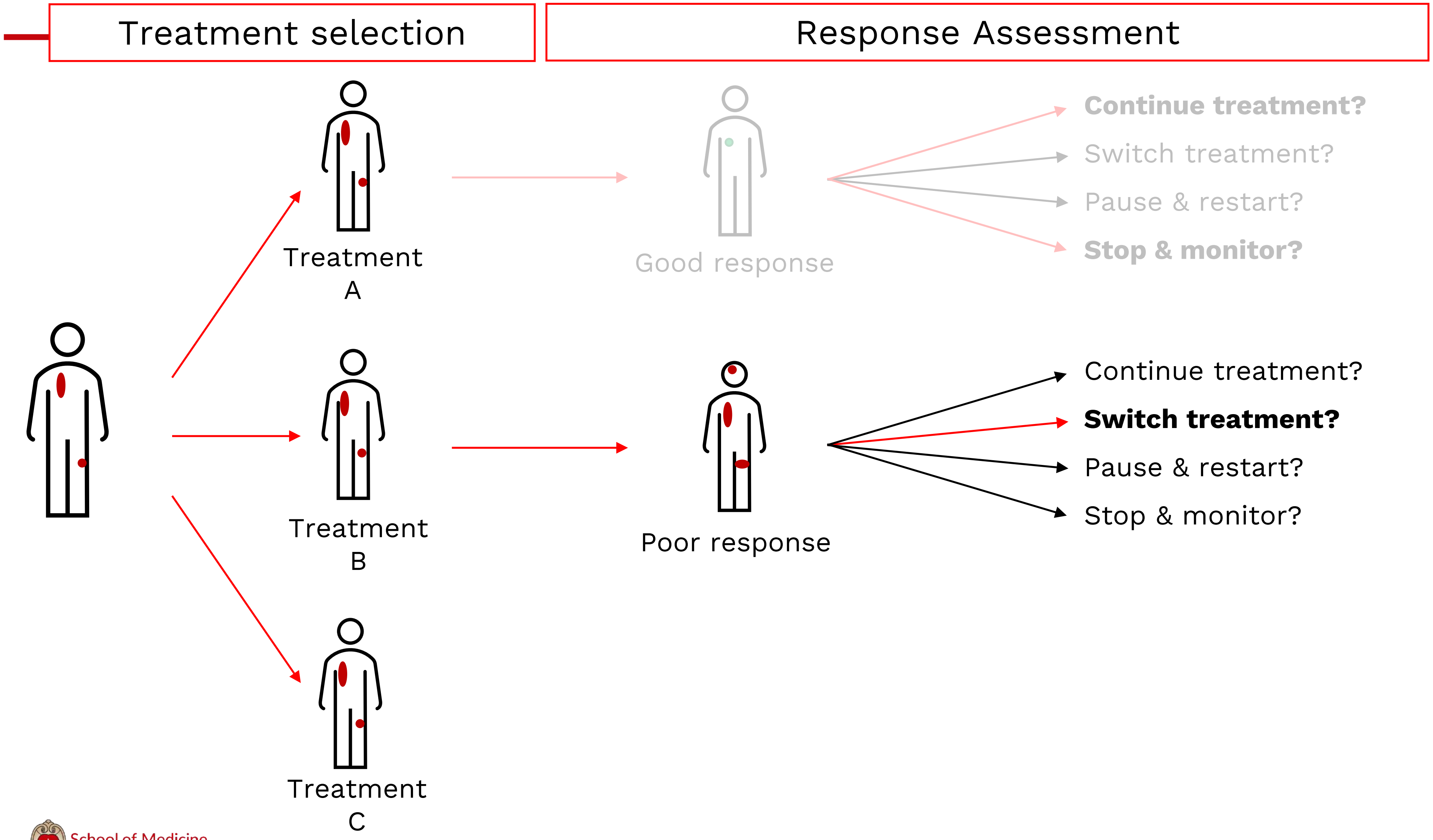
Treatment selection	Response Assessment



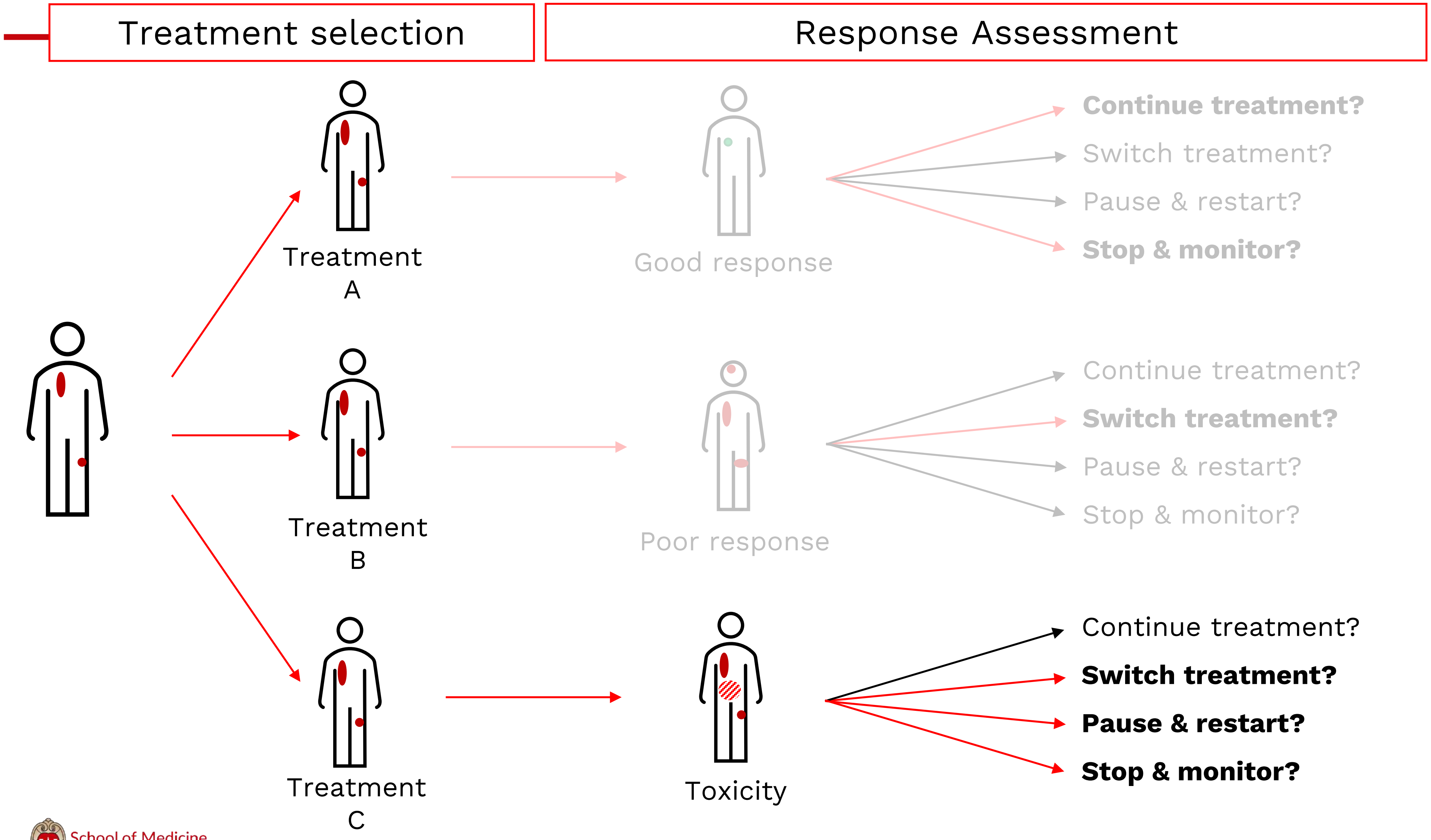
Optimizing treatment decisions



Optimizing treatment decisions



Optimizing treatment decisions



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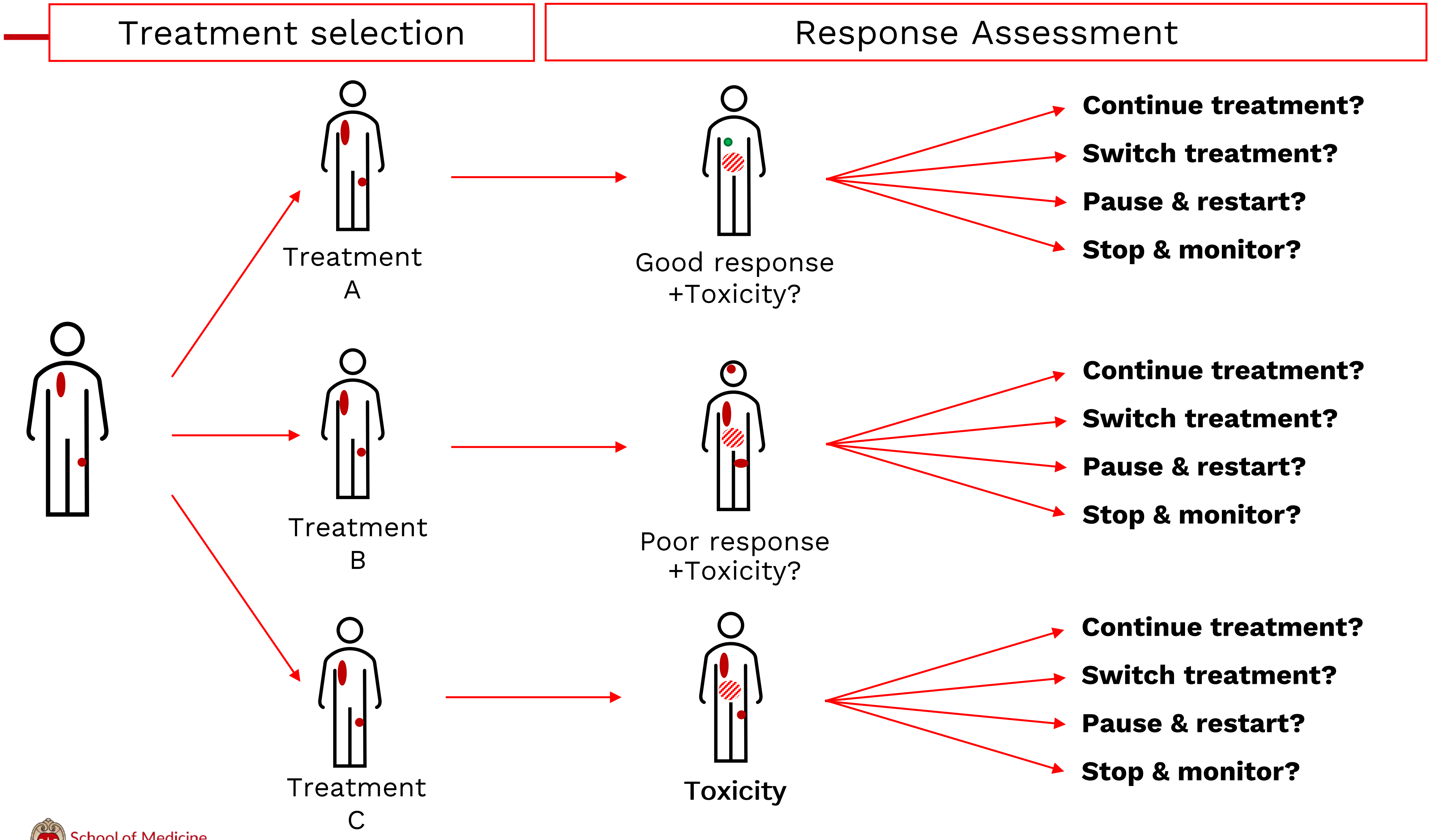
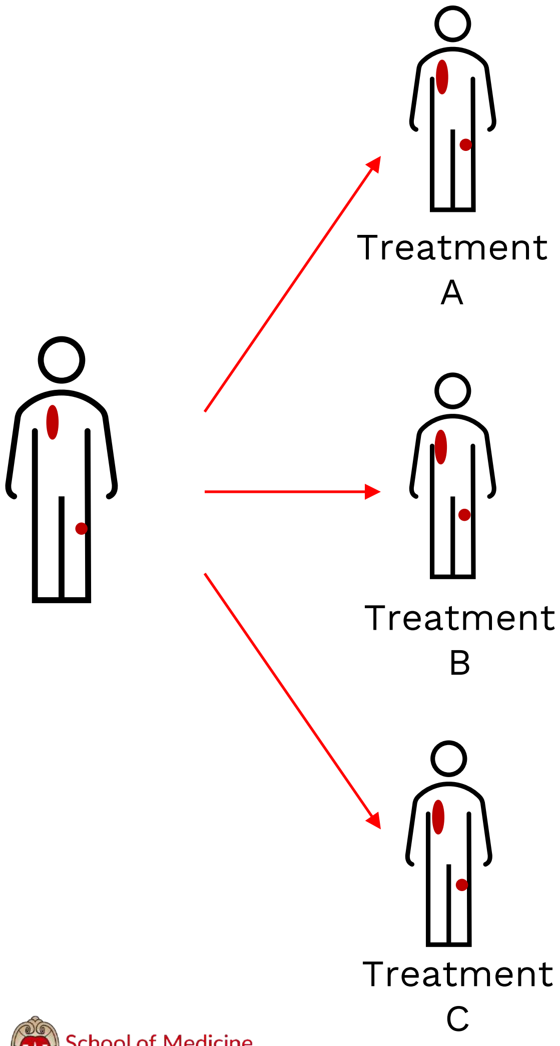
Optimizing treatment decisions



Balancing risks and benefit

Treatment selection	Response Assessment

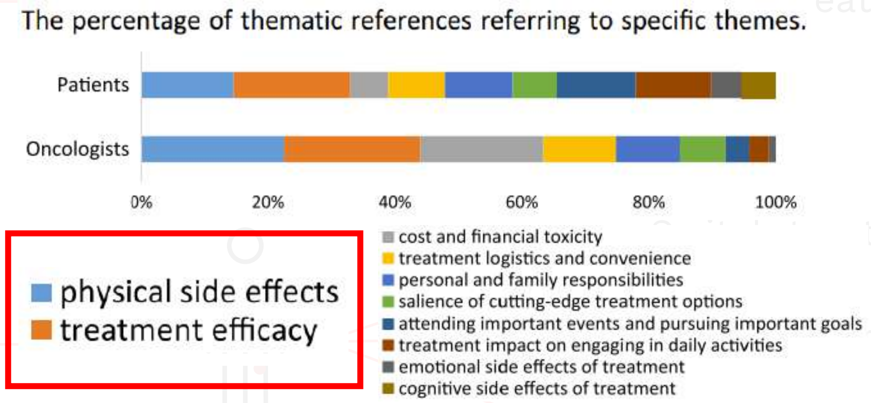


The Oncologist

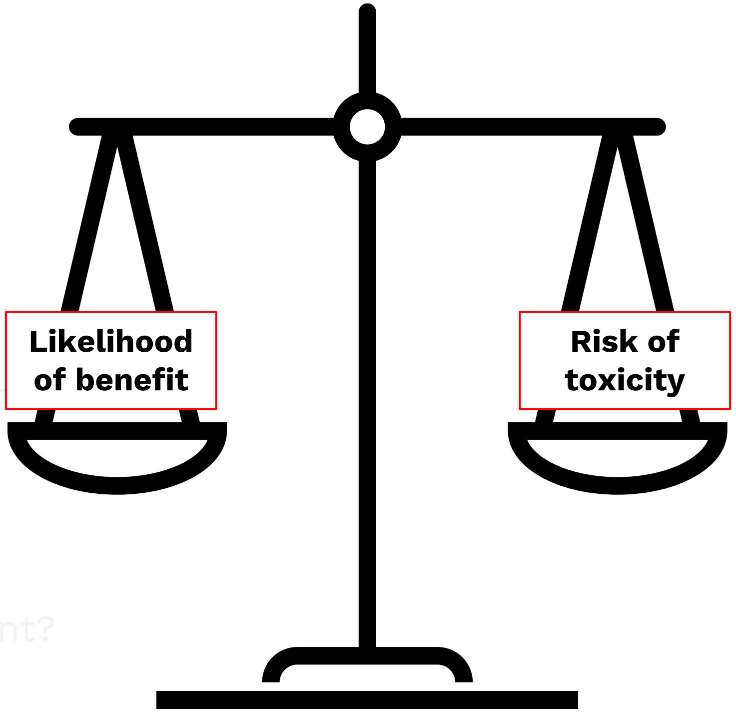
Breast Cancer

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. Niranian,[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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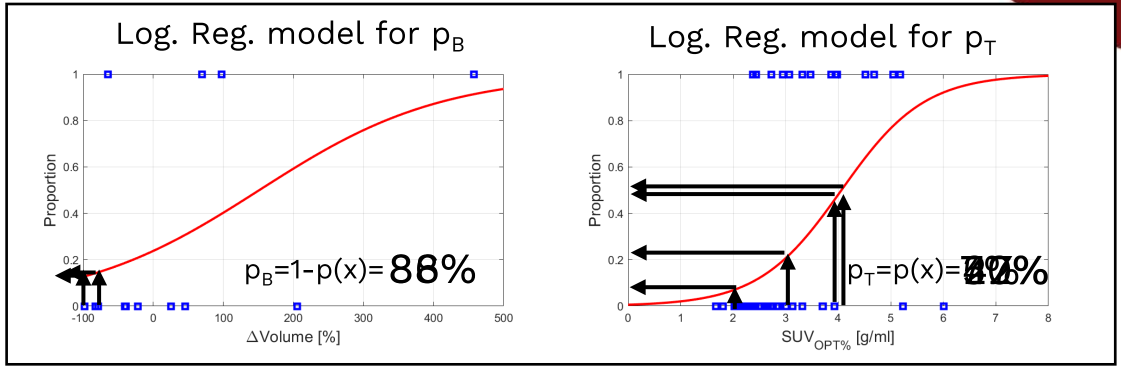
Risk-Benefit "game"

Example patient

MM patient starting on ipi+nivo

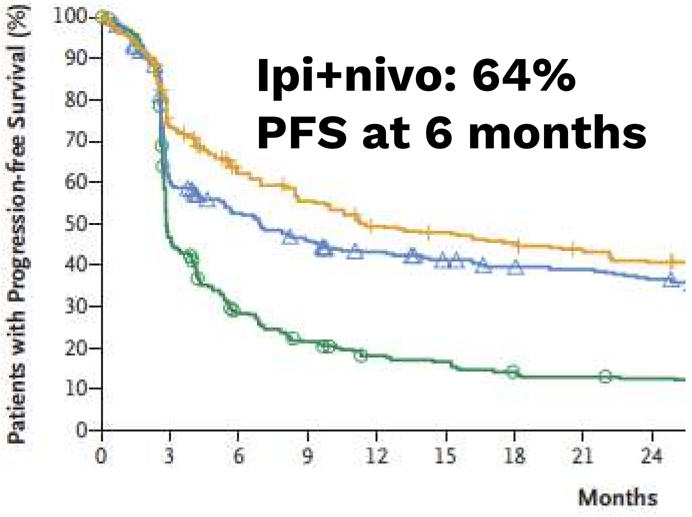
Benefit: PFS>6 mo. **Toxicity:** colitis g3/4



Day -11

Disease:

Toxicity (bowel):



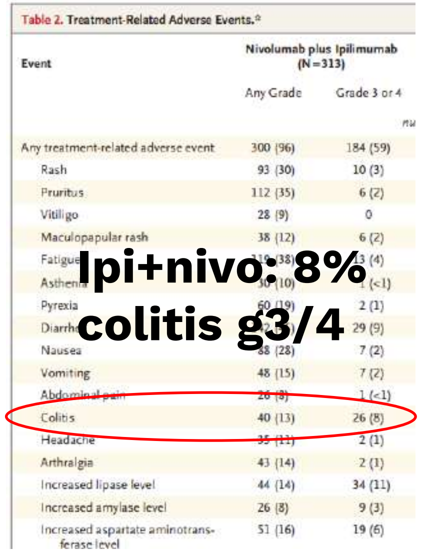
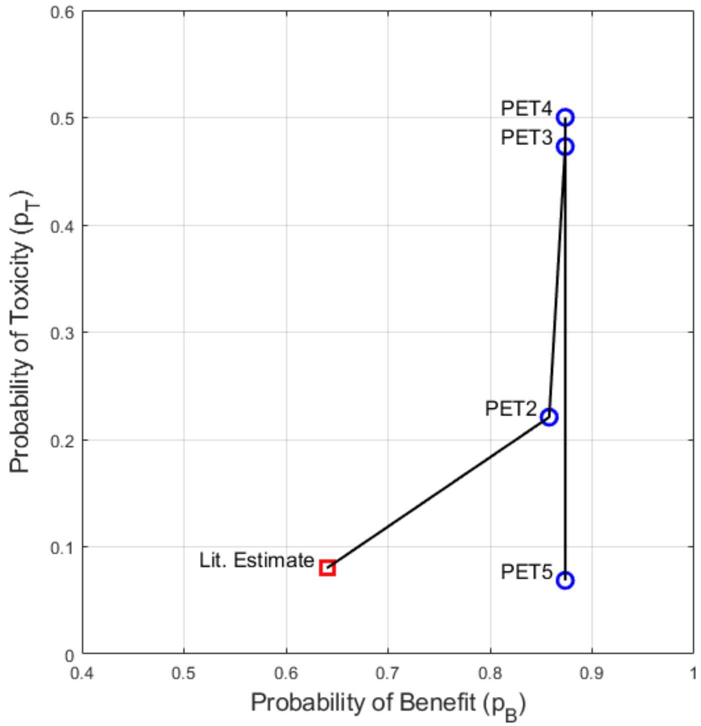


Table 2. Treatment-Related Adverse Events.*

Event	Nivolumab plus Ipilimumab (N=313)	
	Any Grade	Grade 3 or 4
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)	13 (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)

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



Risk-benefit space can be used to **track and predict disease response** and **toxicity risk** at each assessment timepoint during treatment

Risk-Benefit "game" – IQ Decide

Brazilians will be playing the key role!

Medical physics names first entrepreneurial fellowship recipient

Victor Santoro-Fernandes Named Inaugural Recipient

The Department of Medical Physics has selected Victor Santoro-Fernandes as its inaugural Entrepreneurial Fellowship Program recipient. This program was created to fast-track selected senior Ph.D. students and postdocs towards startup incubation. It focuses on customized training and mentorship for those who want to make real products out of innovative academic ideas.

Santoro-Fernandes, who will be defending his Ph.D. thesis over the summer, received both a bachelor's and master's degree in physics from the University of São Paulo in Brazil. He also earned a master's degree in medical physics from the University of Wisconsin-Madison.

Santoro-Fernandes serves as the Wisconsin Alumni Research Foundation (WARF) ambassador and technology writer, and has two patent disclosures with WARF.

IQDecide

Summary

- Precision medicine is a great concept, but also very complex:
  - The problem of response heterogeneity
  - The problem of treatment resistance
- AI-supported analytics is critically needed:
  - Assessment of each individual lesion response (metastatic disease)
  - Modeling complex relationship to predict risks and benefits
  - Beware of critical steps in safe application of AI-based technologies
- AI-supported Precision Medicine enables:
  - Population-based and individual risk-benefit models
  - Optimized treatment decisions to improve patient care

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Thank you
for your attention

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