Quantitative molecular imaging biomarkers and impact on patient safety

Robert Jeraj

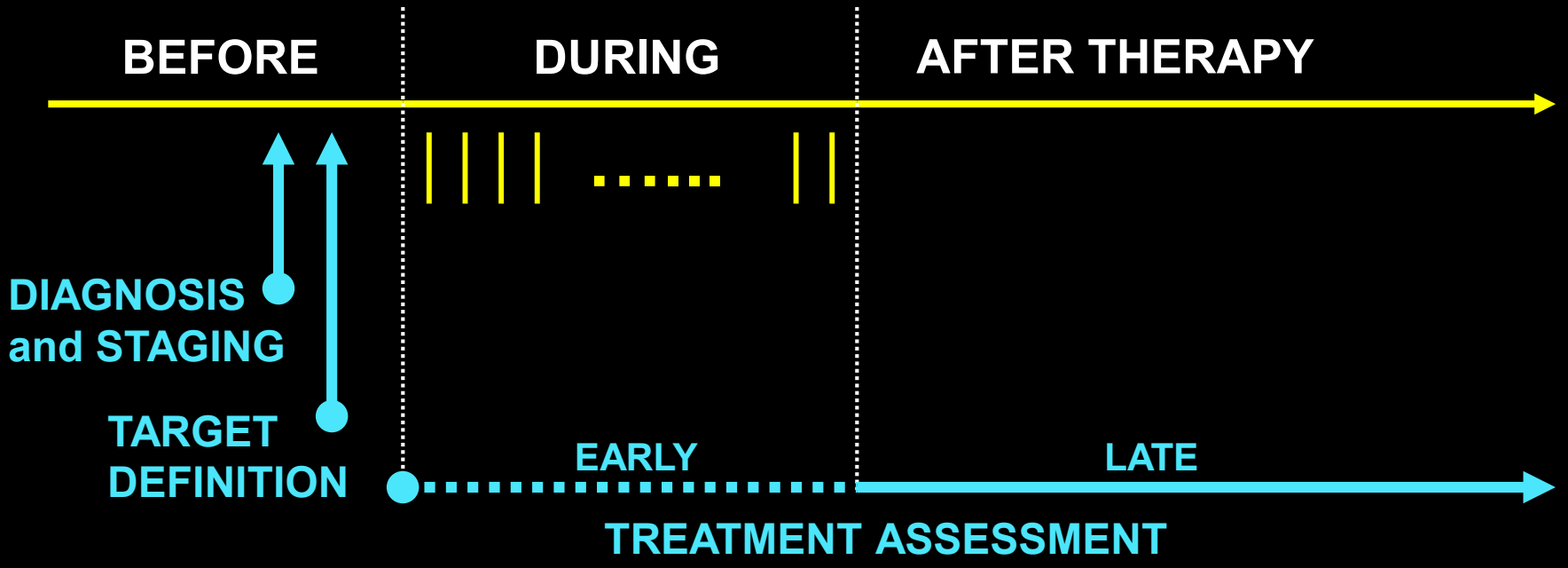
Professor of Medical Physics, Human Oncology,
Radiology and Biomedical Engineering
Fakulteta za matematiko in fiziko, Univerza v Ljubljani
University of Wisconsin Carbone Cancer Center, Madison, WI
robert.jeraj@fmf.uni-lj.si; rjeraj@wisc.edu

University of Wisconsin
SCHOOL OF MEDICINE
AND PUBLIC HEALTH

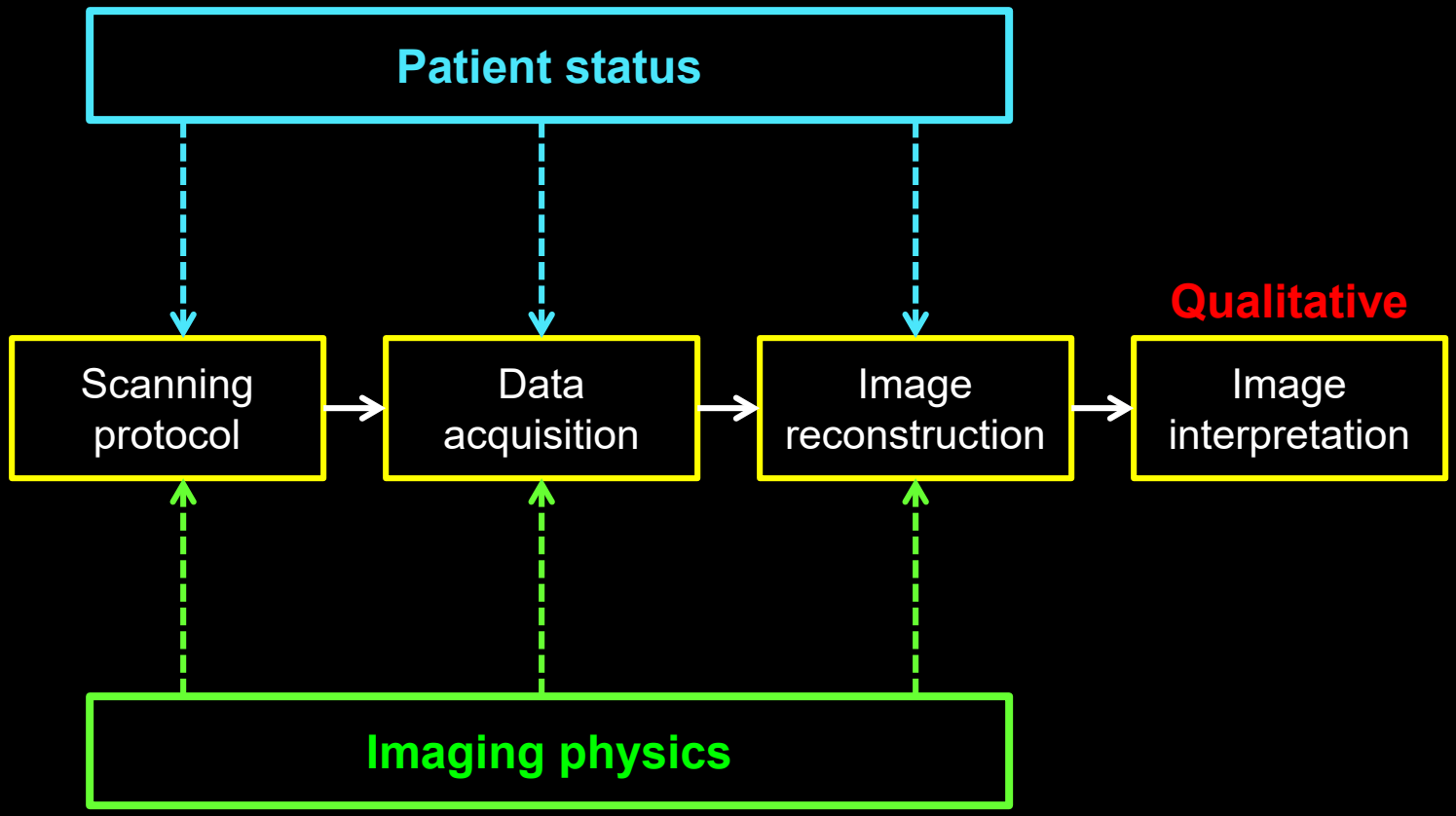
Type of imaging (biomarkers)

Qualitative imaging (Diagnostics)

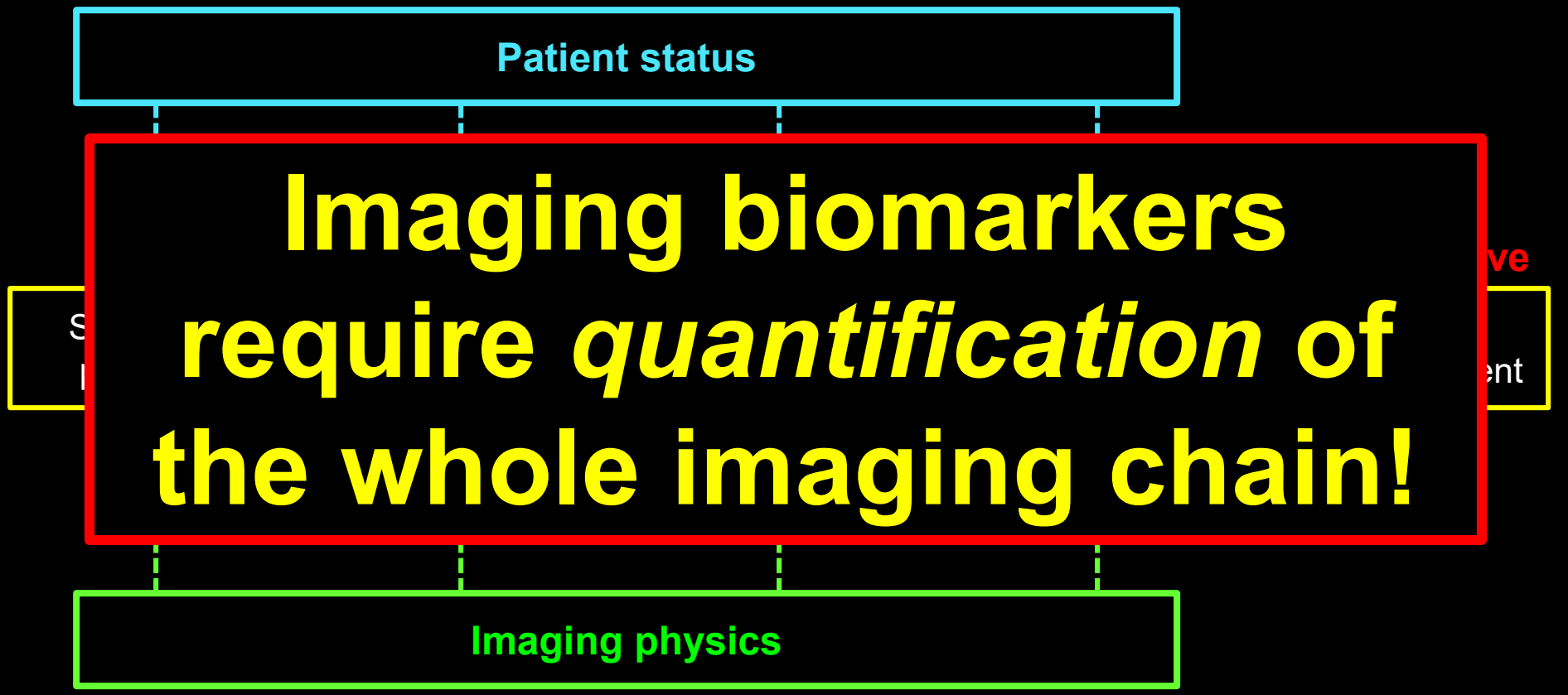
Quantitative imaging (Quantitative Imaging Biomarkers)



Qualitative imaging chain



Quantitative imaging chain



Main issues for Quantitative Imaging Biomarkers (QIB)

- **Imaging Equipment ≠ Measurement Device**

- **Measurement Device:**
  - Specific measurand(s) with known bias and variance (confidence intervals)
  - Specific requirements for reproducible quantitative results
  - Example: a pulse oximeter

- **Imaging Equipment:**
  - Historically: best image quality in shortest time (qualitative)
  - No specific requirements for reproducible quantitative results (with few exceptions)

QIB challenges

- **General QIB challenges:**
  - Lack of detailed assessment of sources of bias and variance
  - Lack of standards (acquisition and analysis)
  - Highly variable quality control procedures
  - QC programs / phantoms, if any, typically not specific for quantitative imaging
  - Little support (historically) from imaging equipment vendors
  - No documented competitive advantage of QIB (regulatory or payer)
- All lead to **varying measurement results** across vendors, centers, and/or time

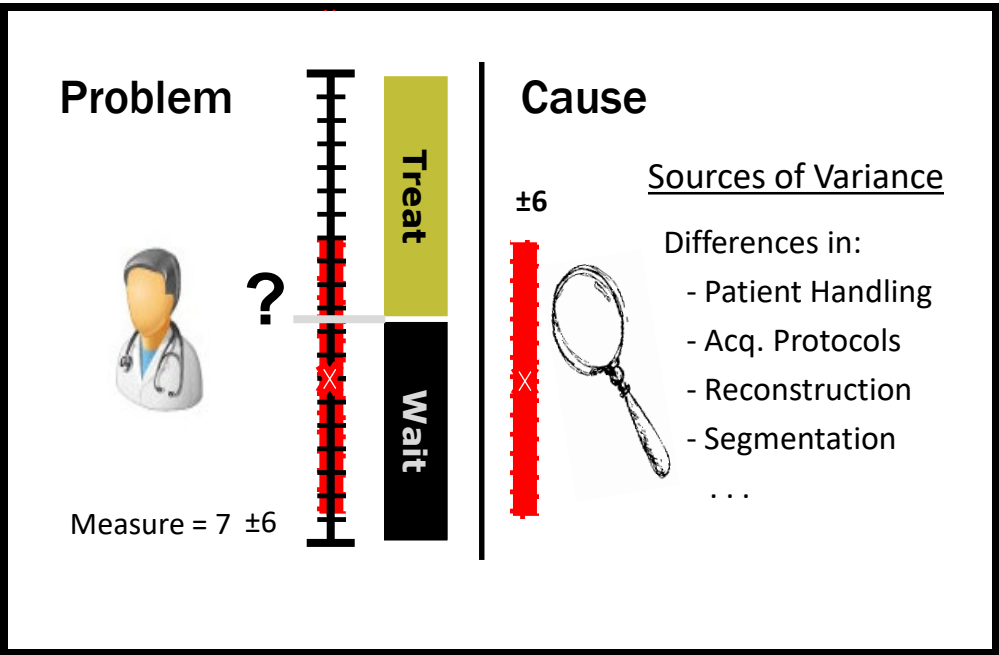
QIB challenges

- **Other QIB challenges:**
  - Cost of QIB studies (comparative effectiveness) / reimbursement
  - Radiologist acceptance
    - Limited number of use cases for QIBs vs. conventional practice
    - QIBs are not part of radiologist education & training
    - The software and workstations needed to calculate and interpret QIBs are often not integrated into the radiologist's workflow
    - Clinical demand on radiologists is high --- "time is money"

Consumer expectations of QIB

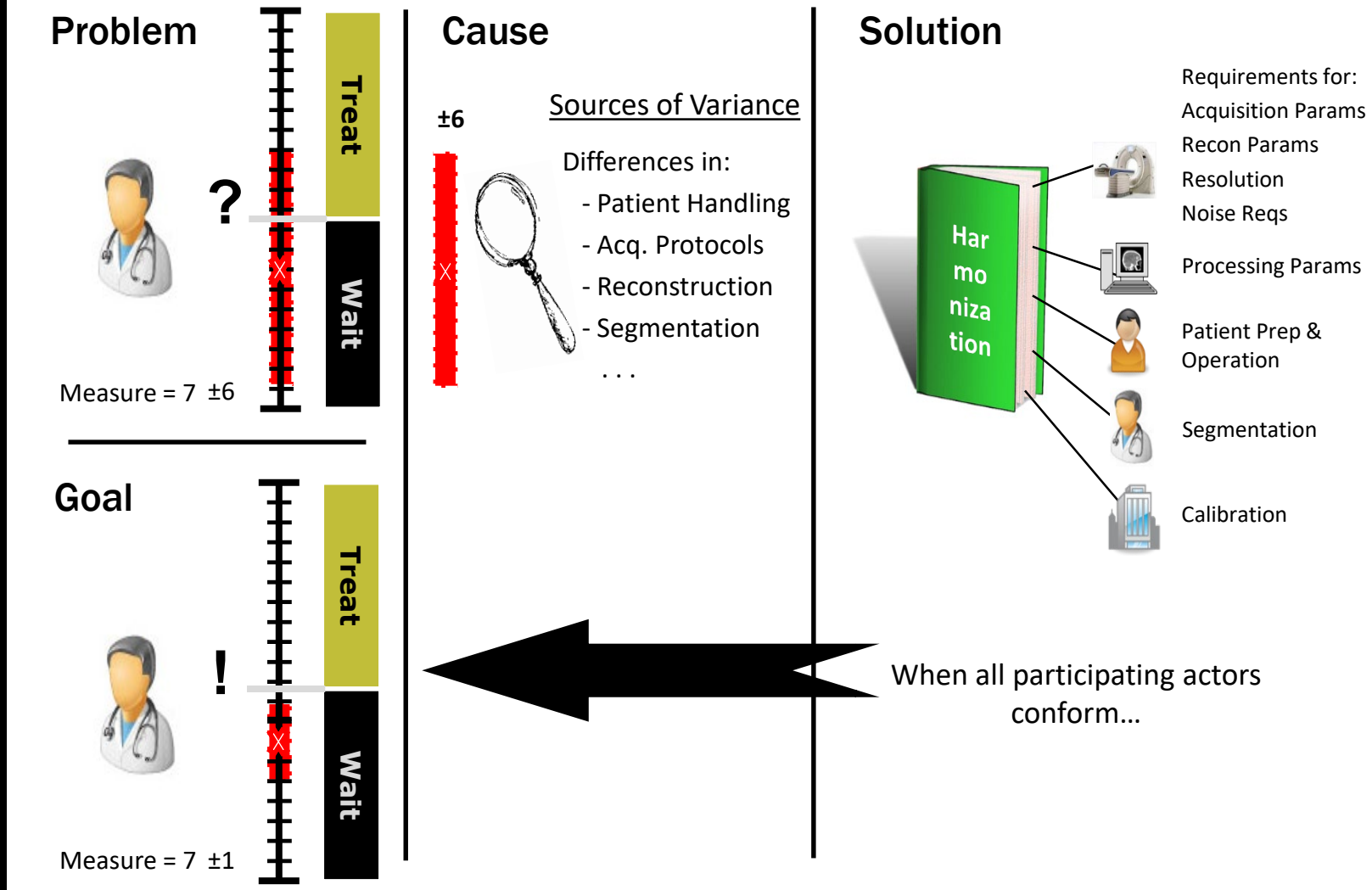
- **Oncologists** (94%) expect some or all tumors to be measured at the time of standard initial clinical imaging. (Jaffe T, *AJR* 2010)
- **Pulmonologists** desire CT-derived quantitative measures in COPD and asthma patients. (ATS/ERS Policy statement, *Am J Resp Crit Care Med* 2010)
- **Hepatologists** desire quantitative measures of liver fat infiltration (Fitzpatrick E, *World J Gastro* 2014)
- **Rheumatologists** desire quantitative measures of joint disease (Chu C, *JBJS:J Bone Joint Surg* 2014)
- **Neurologists and psychiatrists** desire quantitative measures of brain disorders (IOM Workshop, August 2013).
- **Regulatory agencies** desire more objectivity in interpretations.

Problem: QIB uncertainties



Courtesy of Kevin O'Donnell

Reducing QIB uncertainties



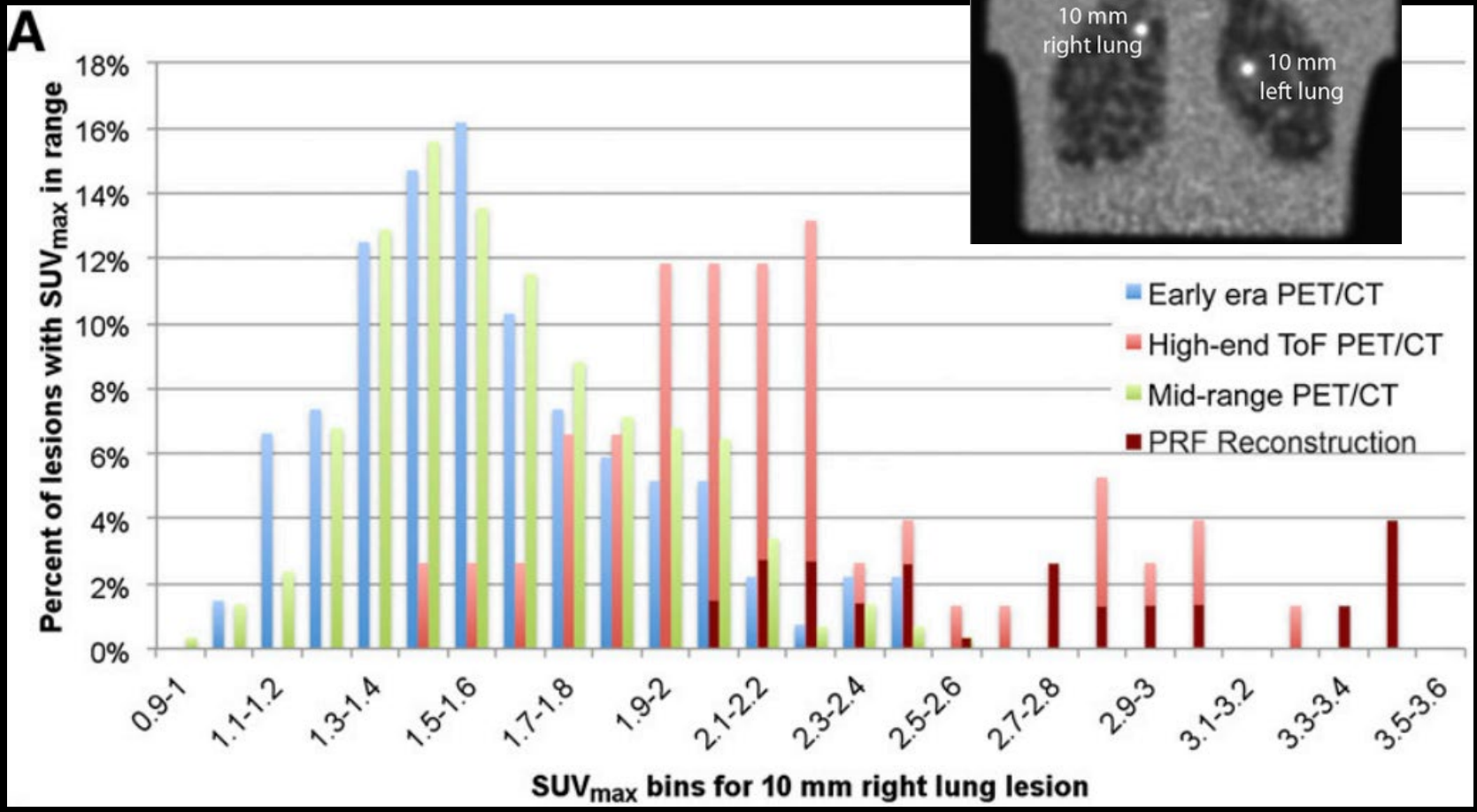
Courtesy of Kevin O'Donnell

Harmonization

- **Harmonization of acquisition**
  - Minimize limitations due to different scanner hardware and software
- **Harmonization of scanning protocols**
  - Creating harmonized imaging protocols, which need to be tuned to specific scanners
- **Harmonization of image analysis**
  - Unifying image analysis protocols, which often means *centralized analysis*
- **Harmonization of reporting**
  - Standardized reporting, otherwise not comparable data

How much variability is there?

SNMMI's Clinical Trials Network (CTN) sent the same phantom to 170 sites, and collected and analyzed the PET/CT images.



Sunderland and Christian 2015, J Nucl Med 56: 145-152.

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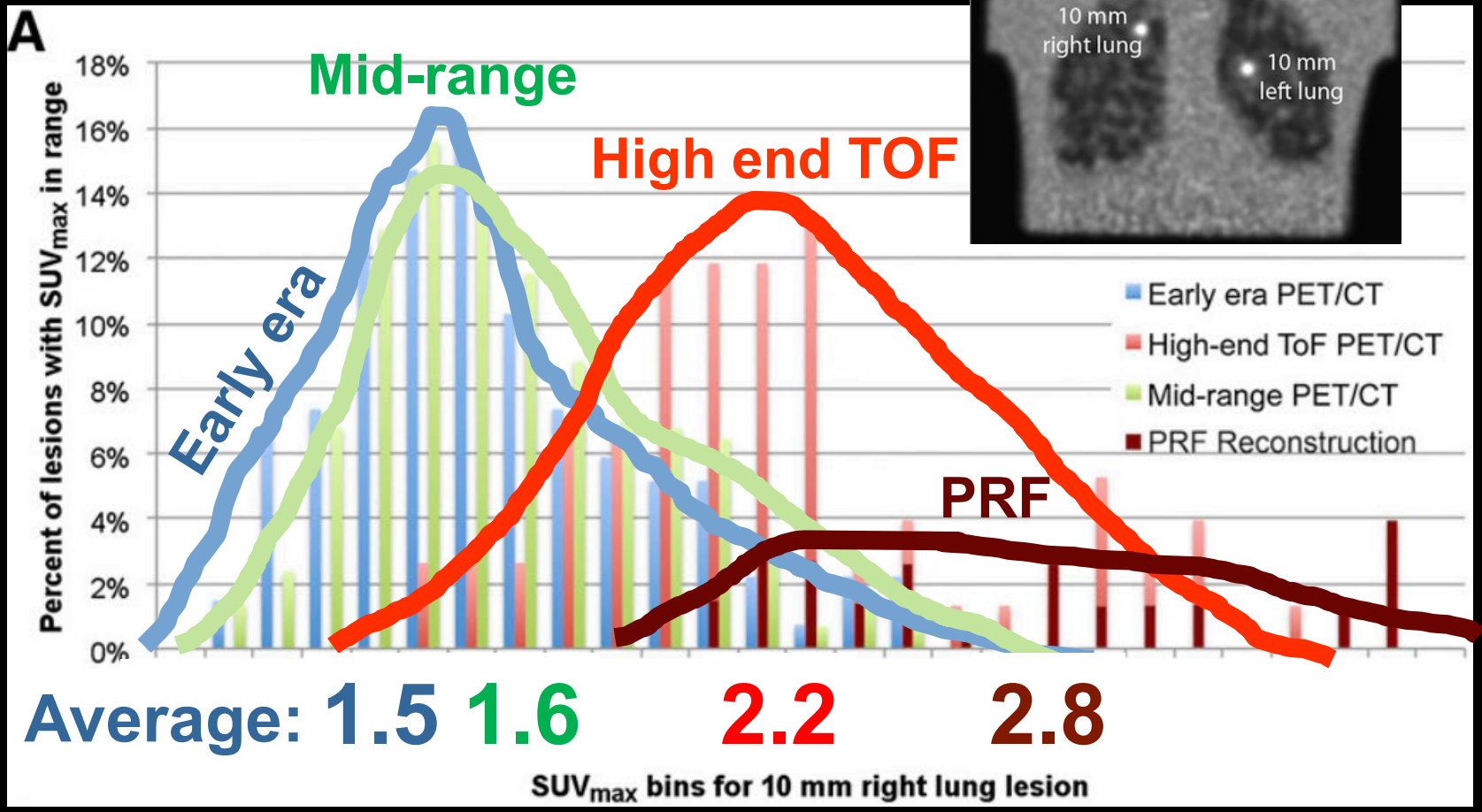

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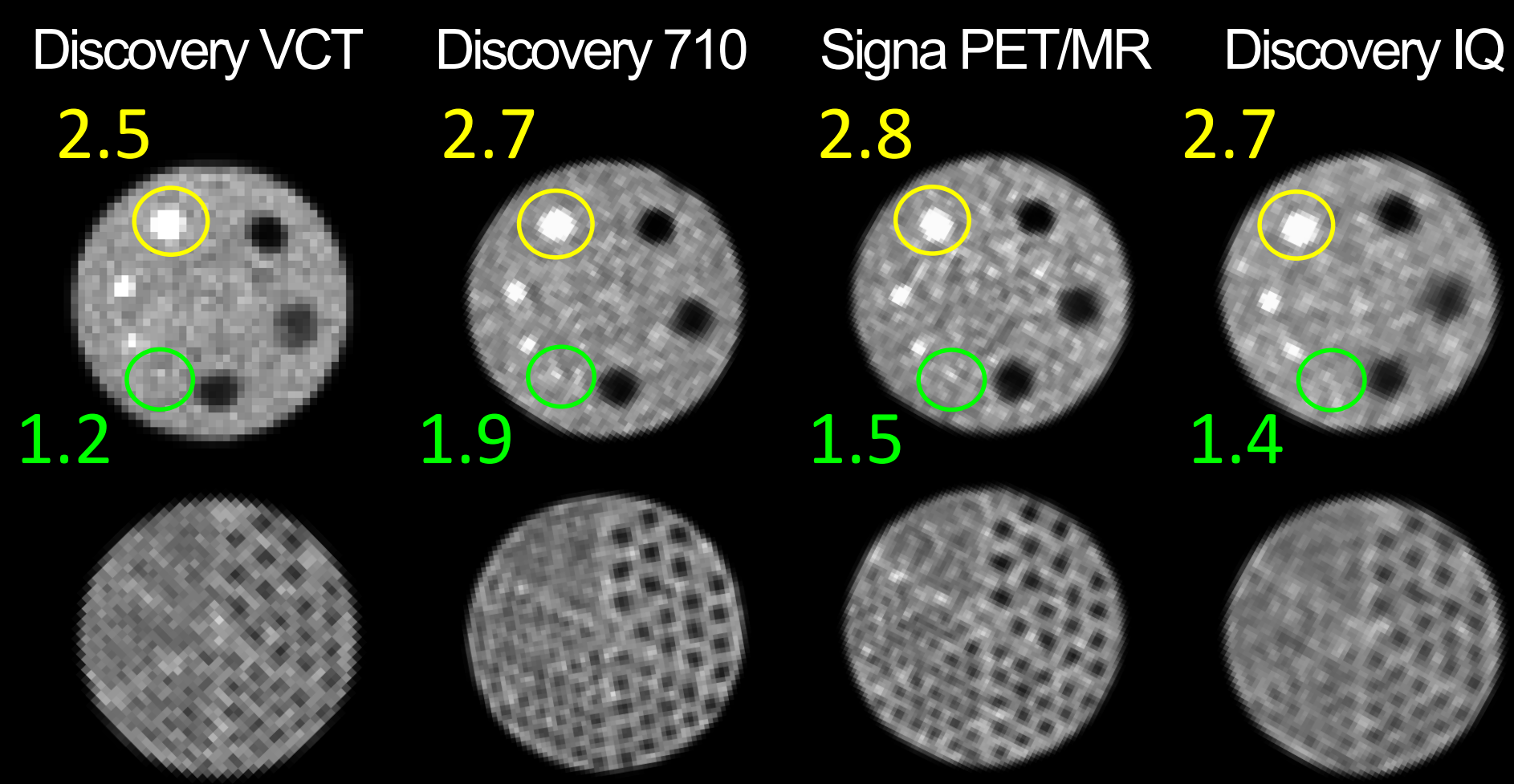
Typical academic site (UW example)

ACR Phantom

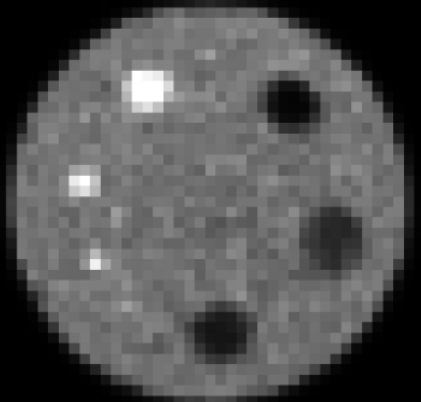


Note: scanners **have already been tuned** to fall within ACR's guidelines

Scanner harmonization (phantom)

ACR phantom scanned on DVCT and D710

DVCT



25 mm RC = 0.99

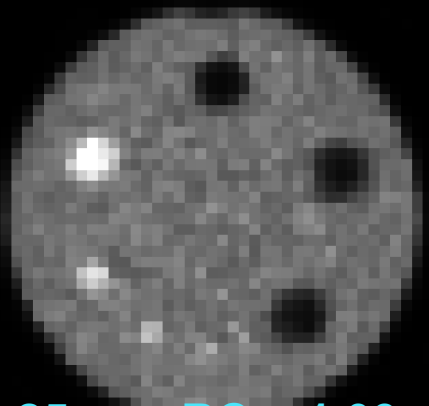
StDev = 3.53

Original D710

25 mm RC = 1.15

StDev = 4.32

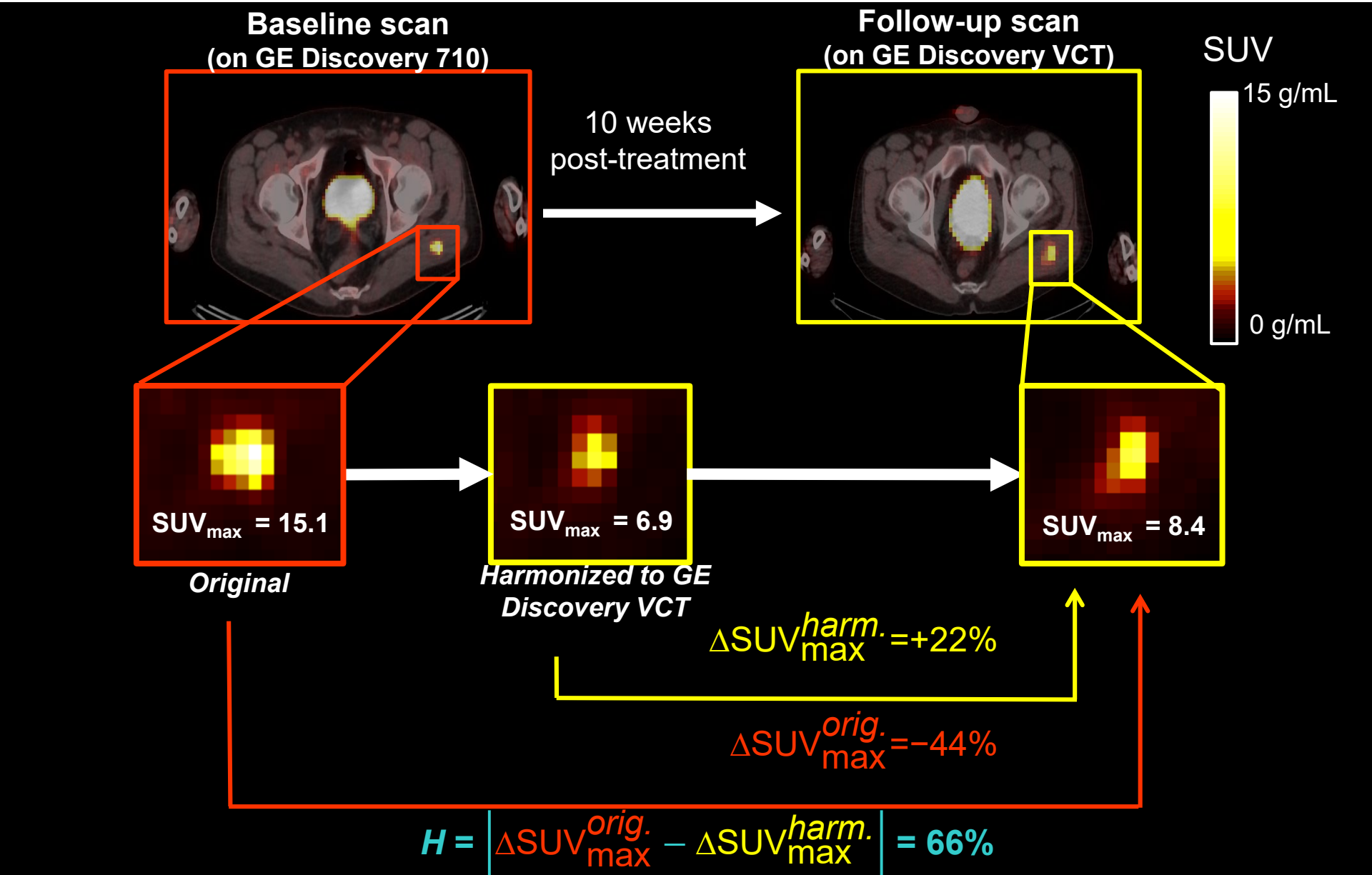
Harmonized D710



25 mm RC = 1.03

StDev = 3.71

Harmonization changes values!



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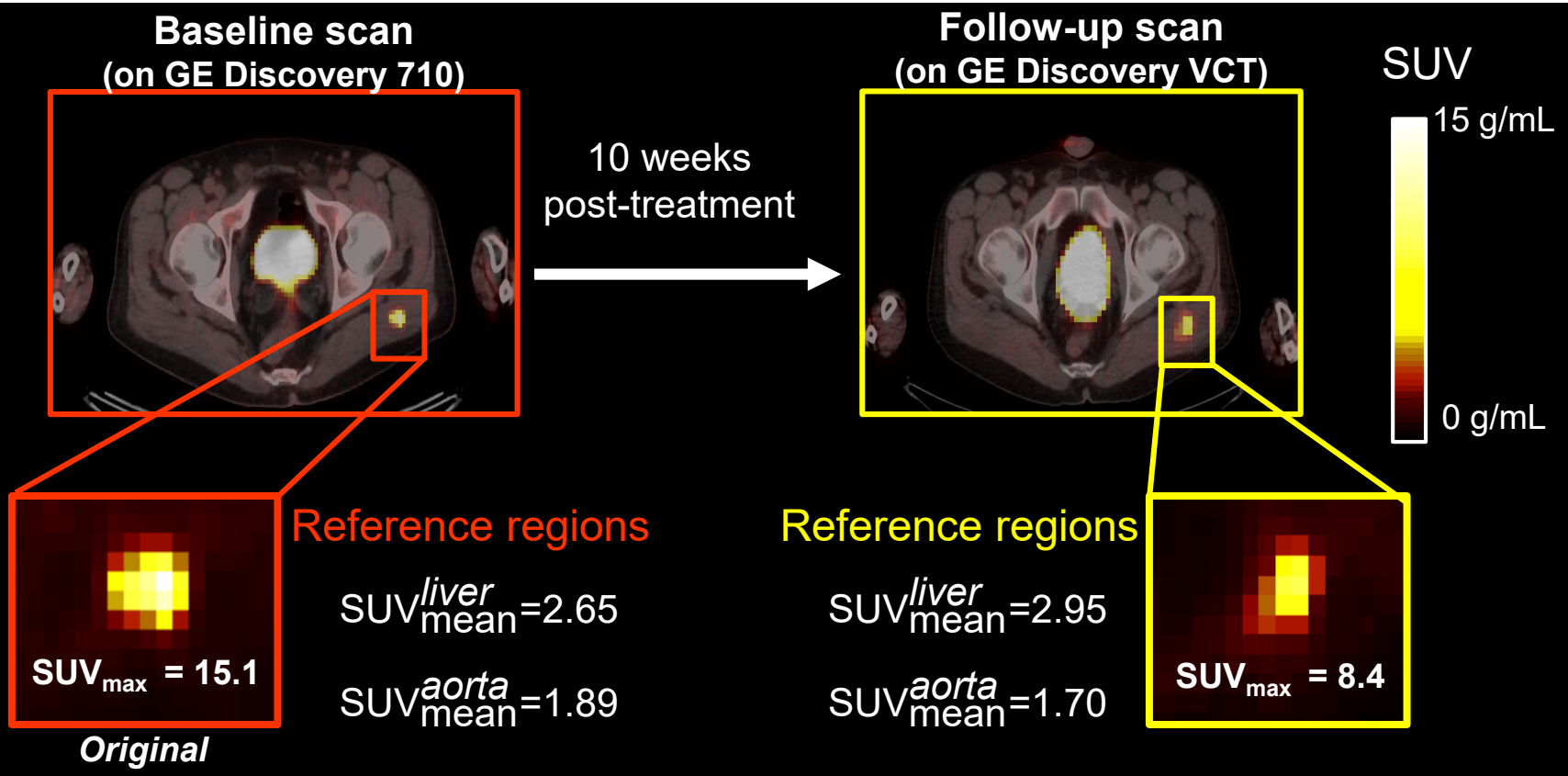
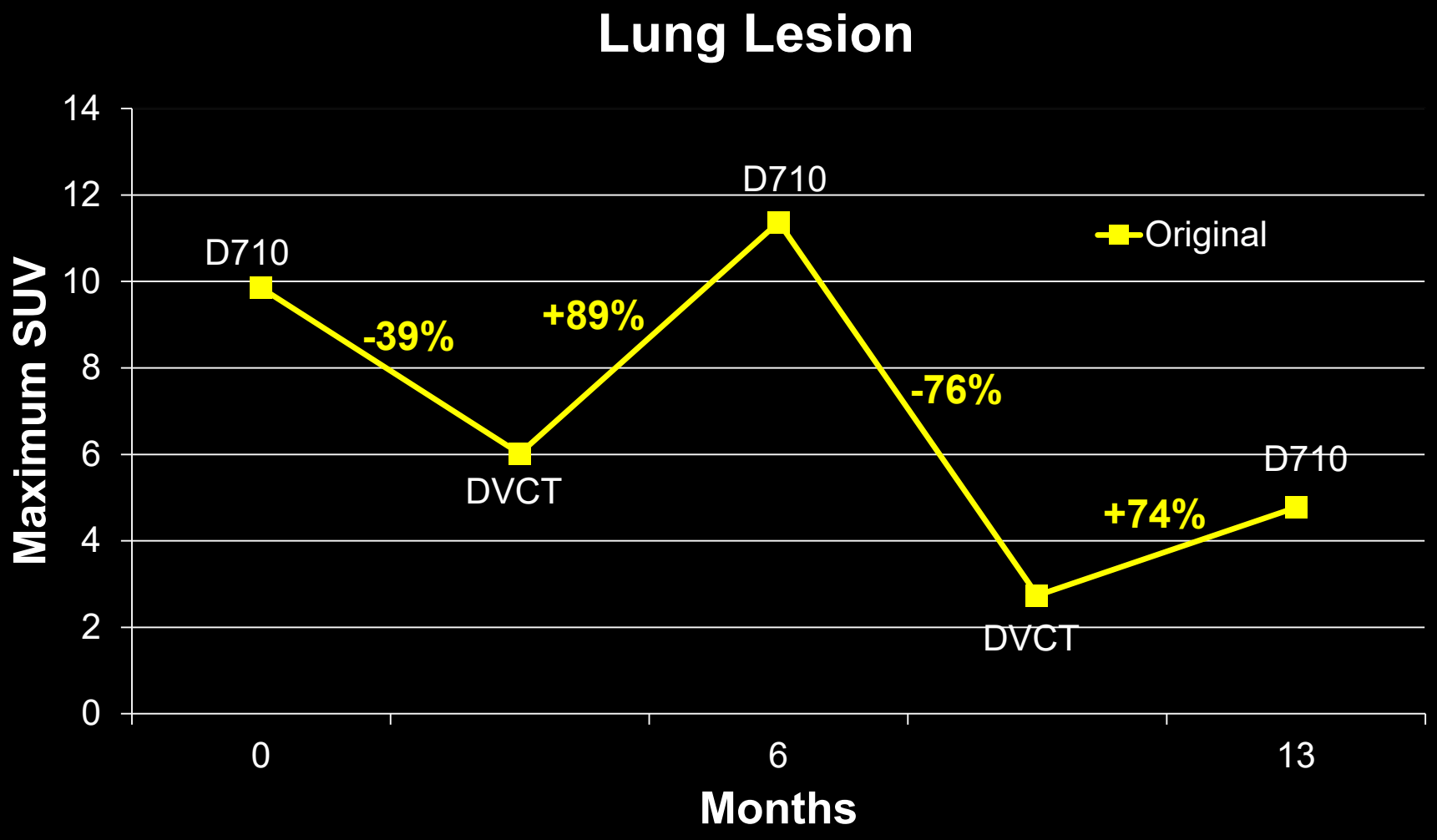


→ **Change in normalized values:** $\frac{SUV_{max}}{SUV_{mean}^{reference}}$

Example: lung cancer patient



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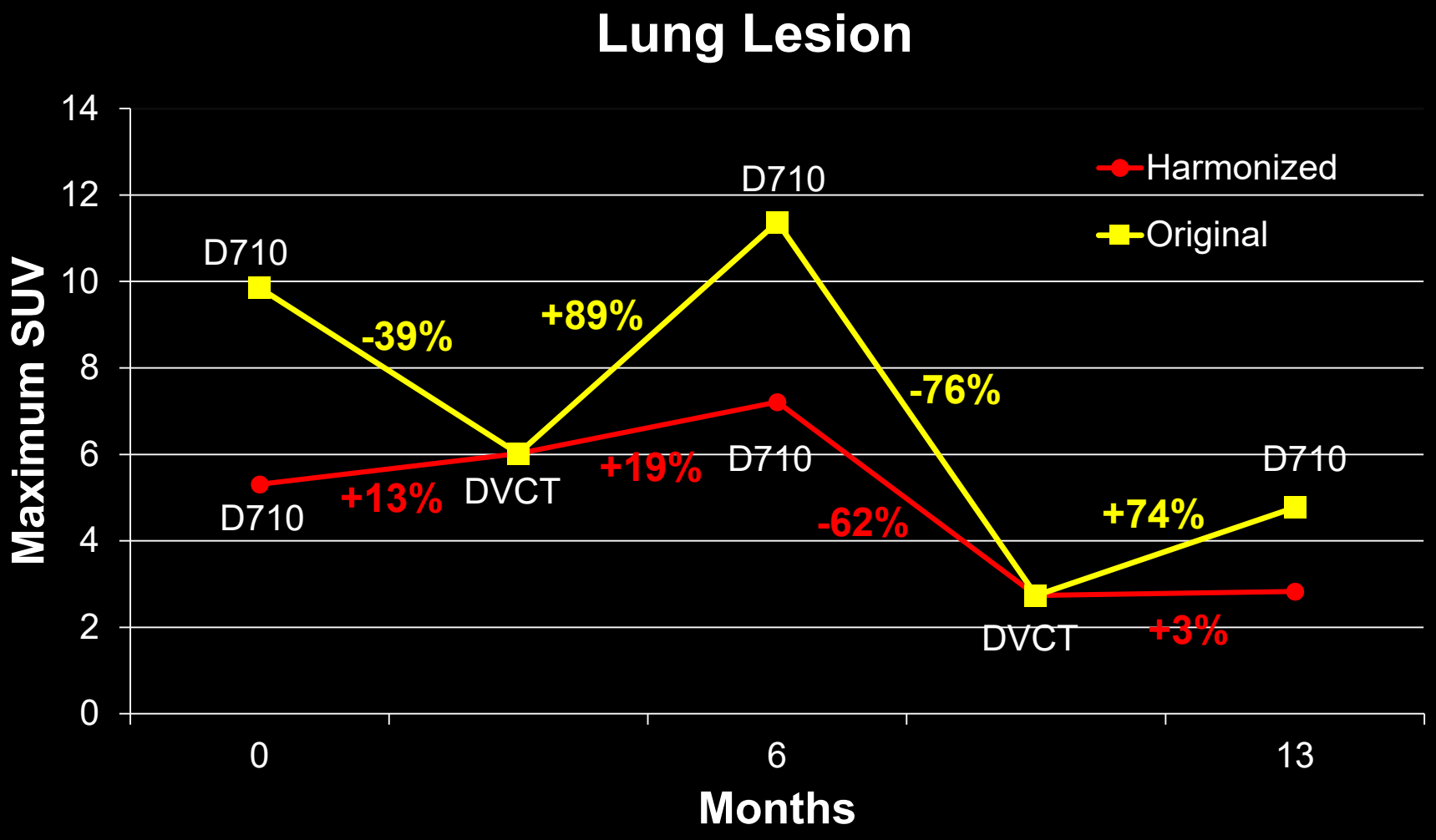
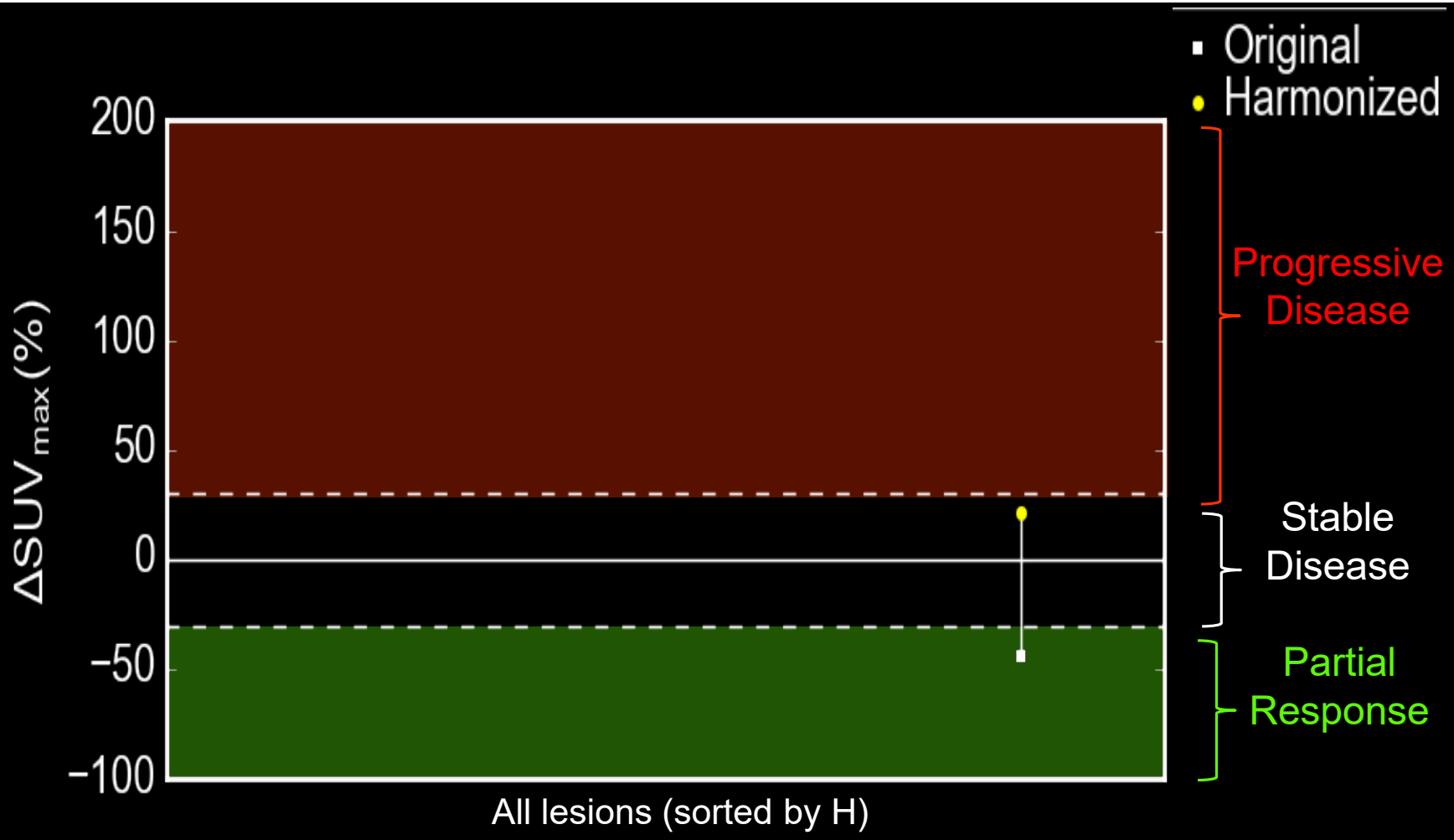
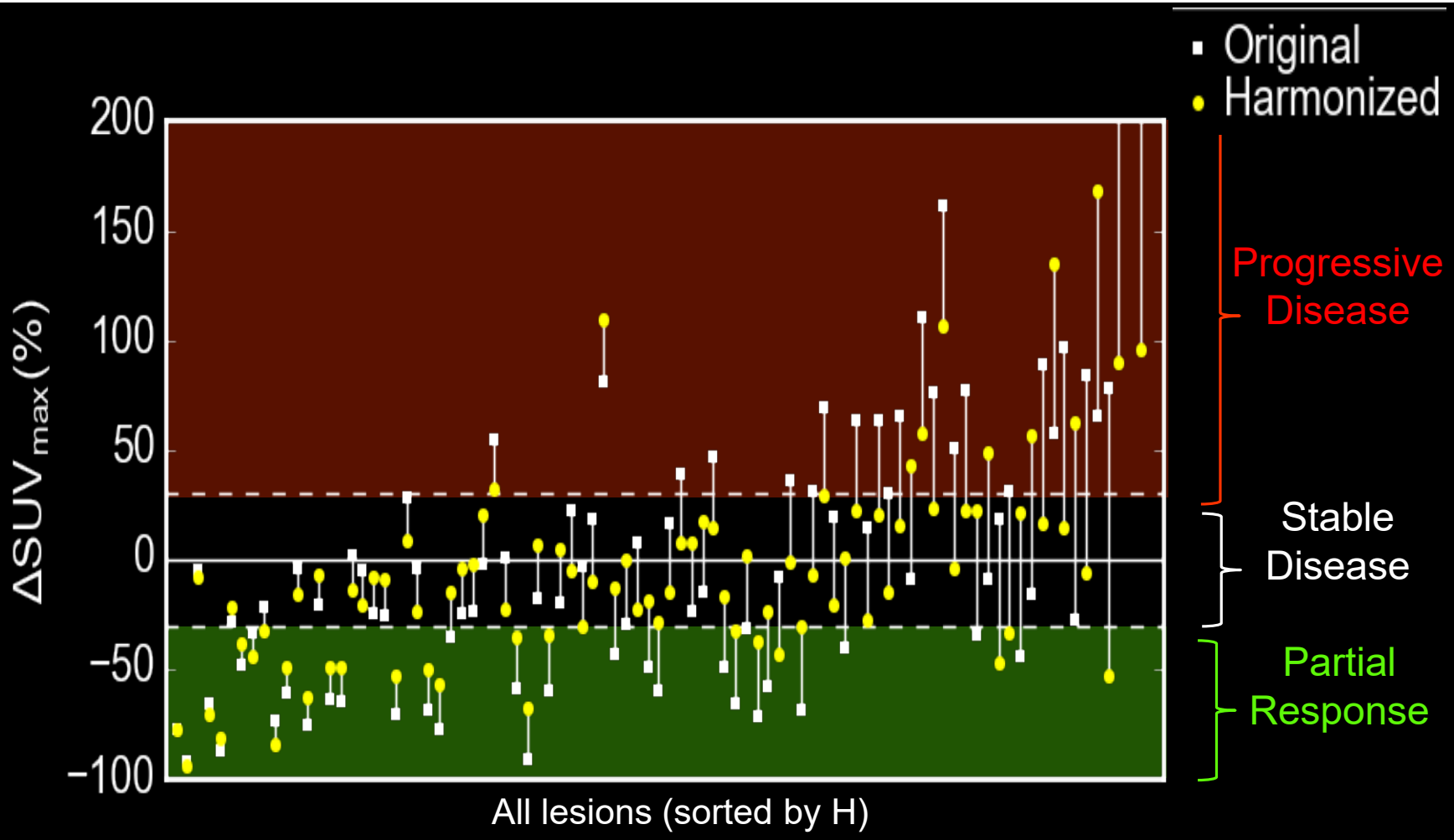


Response classification



±30% changes in SUV_{max} used for classification based on PERCIST (Wahl et al, JNM, 2009)

Response classification



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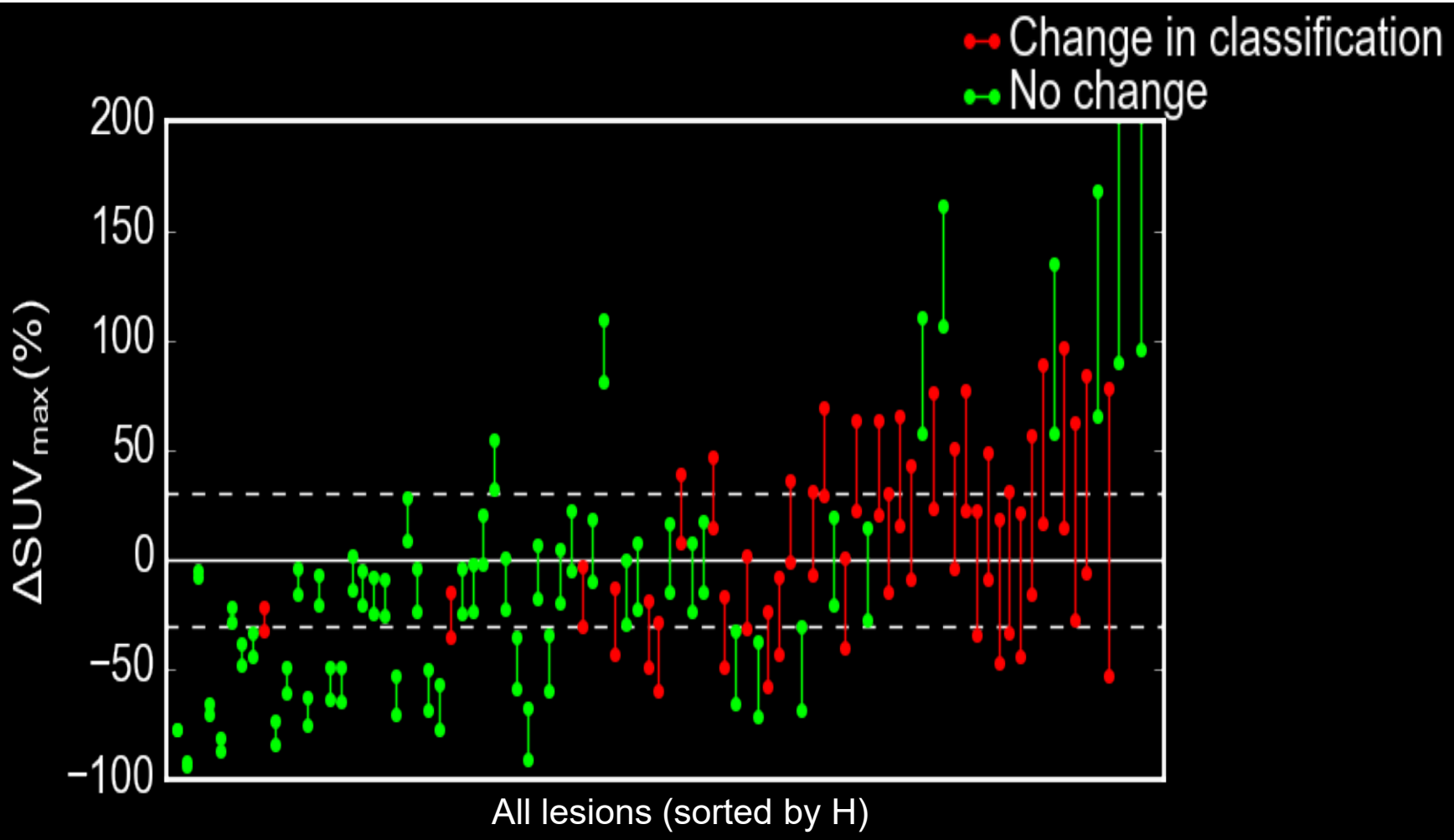
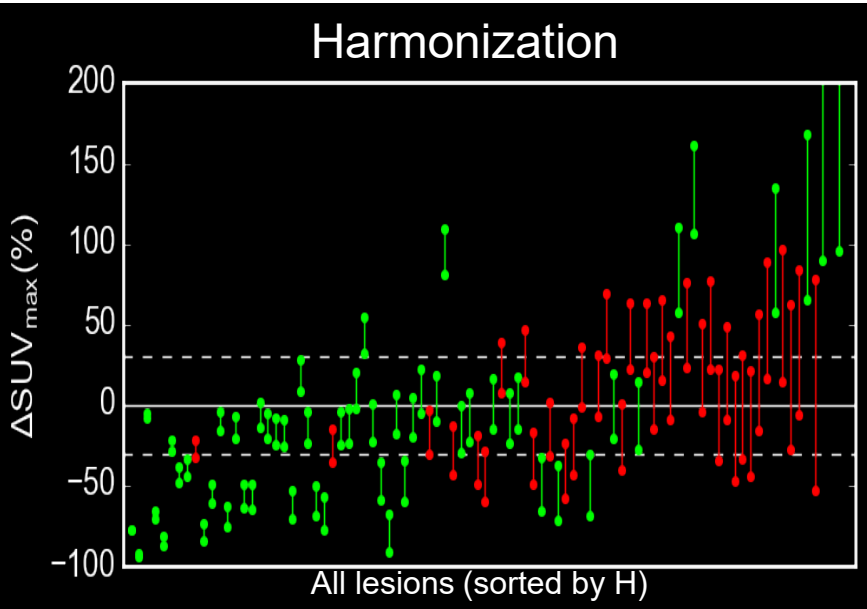
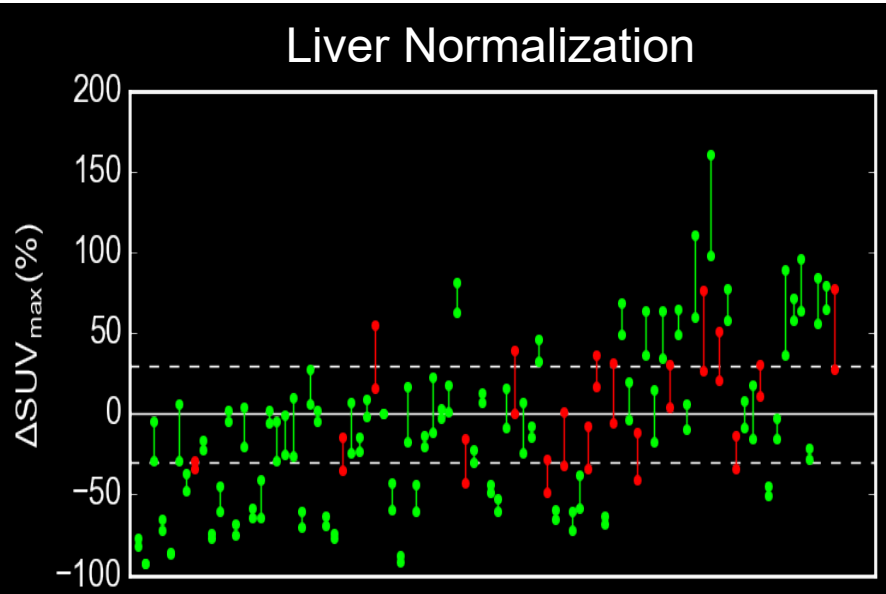
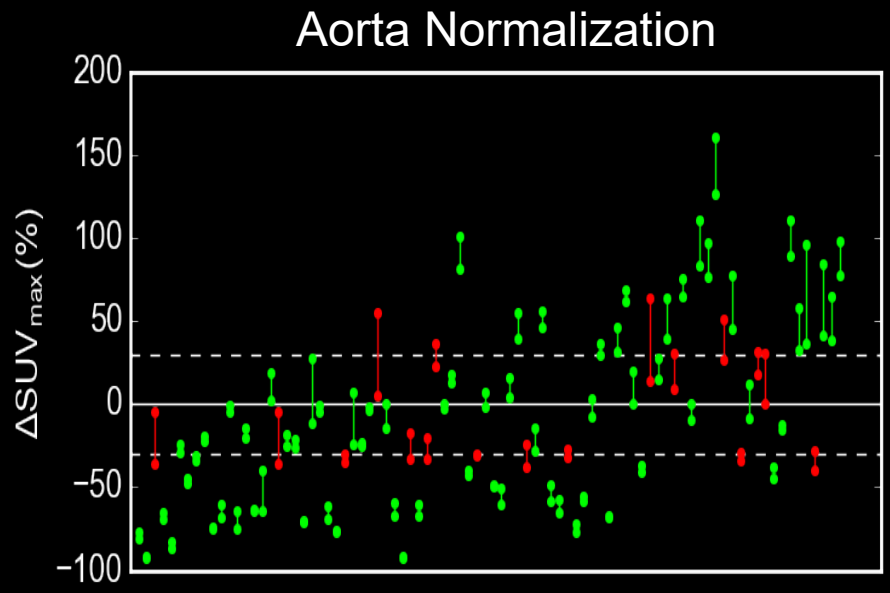


Is normalization able to capture the same changes that harmonization does?

Harmonization vs normalization







Method	Changed Classification
Harmonization	35
Liver Normalization	17
Aorta Normalization	17

Conclusions

- **Quantitative Image Biomarkers (QIB)** are needed for assessment of treatment response
- **Harmonization** is necessary for decreasing uncertainties of QIB (e.g., QIBA profiles)
- Harmonization directly **impacts clinical outcome evaluation**
- **QIBs directly impact patient safety!**