Total-Body Positron Emission Tomography
From Concept to Reality: A 15-Year Journey

Simon R. Cherry, Ph.D.
Ramsey D. Badawi, Ph.D.
Lorenzo Nardo, M.D., Ph.D.

Disclosures

UC Davis has a revenue sharing agreement
and a research agreement with
United Imaging Healthcare

ImaginAb Inc. provided material support for one of the studies

About us

- Ramsey
  - PhD in Medical Physics, U
  - Postdoc at UW, Seattle (1

ana Farbe

iology and

PLORER Ce

L

it

E

r

ta'

ini

) 2

2018

clear Medicine, UC Davis

don (1989)

adiology,

), UC Davis

Content

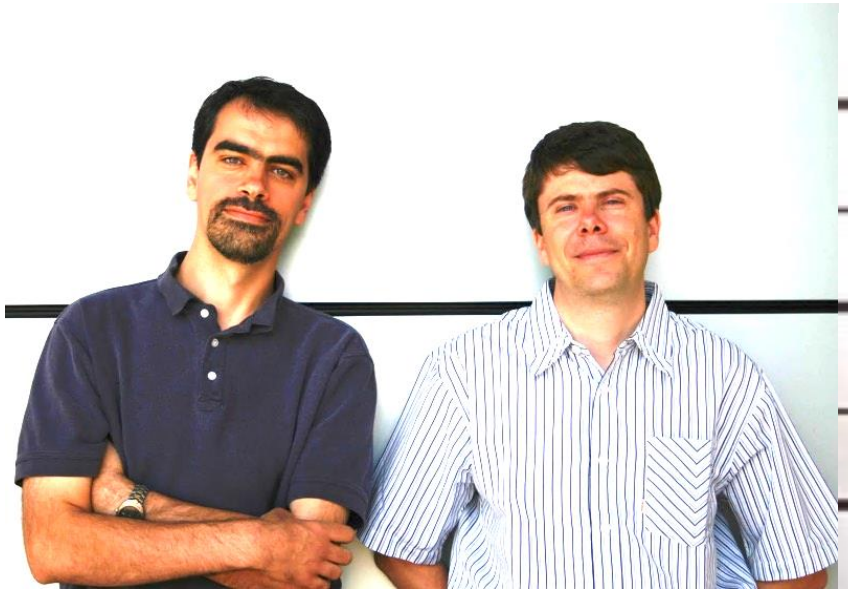
- The history of the EXPLORER total-body PET project
  - Ramsey D. Badawi, Ph.D.
- Clinical implementation of total-body PET
  - Lorenzo Nardo, M.D., Ph.D.
- Total-body PET in research
  - Simon R. Cherry, Ph.D.

Along the way we…

- Have traveled across the world
- Found support (and resistance!) from unanticipated quarters
- Have been caught up in trade wars
- Made new friends and tried not to lose old ones
- Experienced disappointment, frustration, surprise and elation
- Learned a lot about ourselves and stayed good friends

We are VERY grateful for the MANY people who did so much to help us

This is our story…



2005: The journey begins…

Timeline

(Not) Getting Funding

1. ~~Feb 2008: NIH– Badawi~~
2. ~~Nov 2008: NIH– Badawi~~
3. ~~Feb 2009: Keck – Badawi~~
4. ~~Feb 2011: NSF MRI – Cherry~~
5. Nov 2011: NIH– Badawi

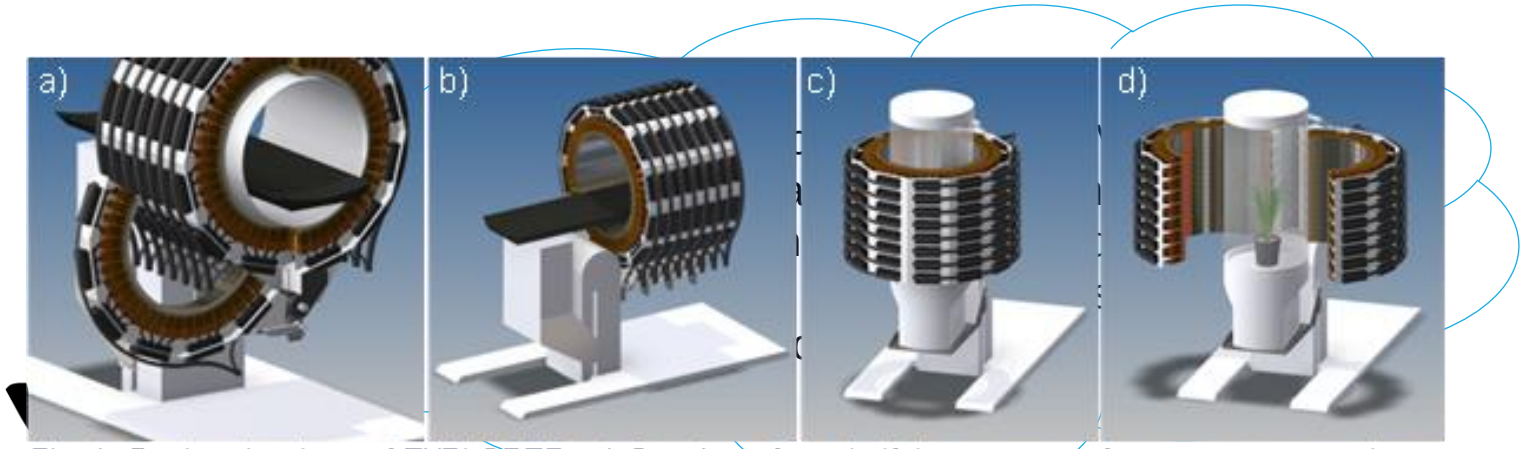


Fig. 1: Design drawings of EXPLORER: a) Opening of one half-ring segment for easy access to detectors; b) Horizontal orientation; c) Vertical orientation; d) Clam-shell opening for insertion of samples.

EXPLORER Consortium founder members:


Tom Budinger


Terry Jones


Joel Karp


Bill Moses


Simon Cherry

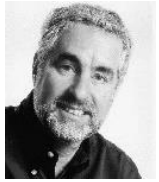

Jinyi Qi


Suleman Surti


Richard Wahl


Mike Graham


Dave Mankoff

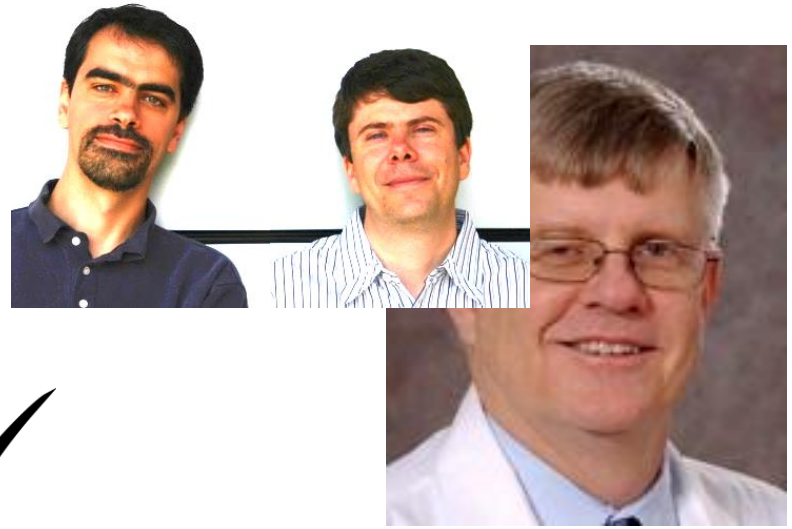

Bill Jagust

Industry Advisory Panel:
Michael Casey (Siemens)
Matthias Schmand (Siemens)
Chi-Hua Tung (Philips)
Chuck Stearns (GE)

(Not) Getting Funding

1. ~~Feb 2008: NIH– Badawi~~
2. ~~Nov 2008: NIH– Badawi~~
3. ~~Feb 2009: Keck – Badawi~~
4. ~~Feb 2011: NSF MRI – Cherry~~
5. Nov 2011: NIH– Badawi ✓
6. Apr 2012: UC Davis RISE – Cherry ✓
7. Sep 2013: Siemens – Cherry ✓
8. ~~Jun 2014: NIH – Cherry, Badawi~~
9. ~~Jul 2014: Keck – Cherry~~
10. ~~Oct 2014: MRC – Jones; UK consortium~~
11. Oct 2014: NIH – Badawi, Cherry ✓

(awarded Sep 2015)



Raymond Dougherty

The Expendables

Success!

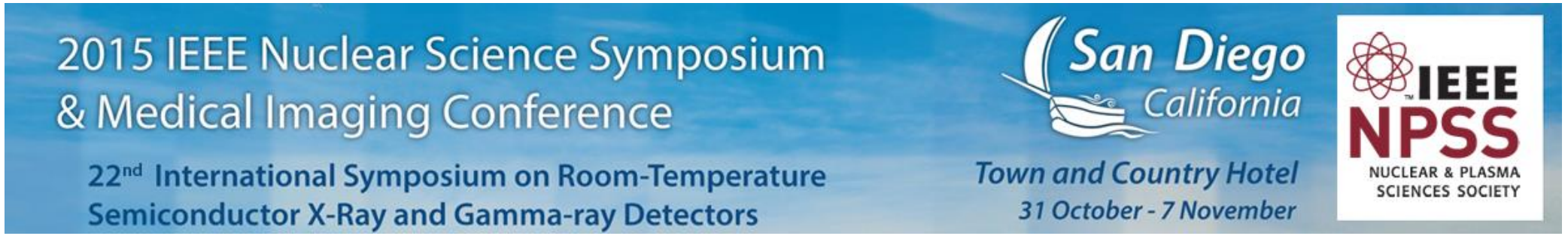
$15m Transformative R01 awarded

Sep

2015 201

2022

First contact with United Imaging



Hongdi Li

January 2016: UIH Factory Visit

$15m Transformative R01 awarded

Sep

2015 2016 2017 23 2024

Jan

Visit to United Imaging in Shanghai

The Mockup

$15m Transformative R01 awarded

Sep

Scanner Mock-Up

Nov

2015 2016 2017 201 21 2022 2023 2024

Jan

Visit to United Imaging in Shanghai

Clinical Expertise

$15m Transformative R01 awarded

Sep

Scanner Mock-Up

Nov

2015 2016 2017 2018 2019 023 2024

Jan

Visit to United Imaging in Shanghai

Lorenzo joins the team

Lorenzo Nardo, MD, PhD
Diagnostic Radiology, MRI physics, Nuclear Medicine, Musculoskeletal Imaging, Oncologic Imaging, …

Back to Shanghai

$15m Transformative R01 awarded

Sep

Scanner Mock-Up

Nov

Scanner completed

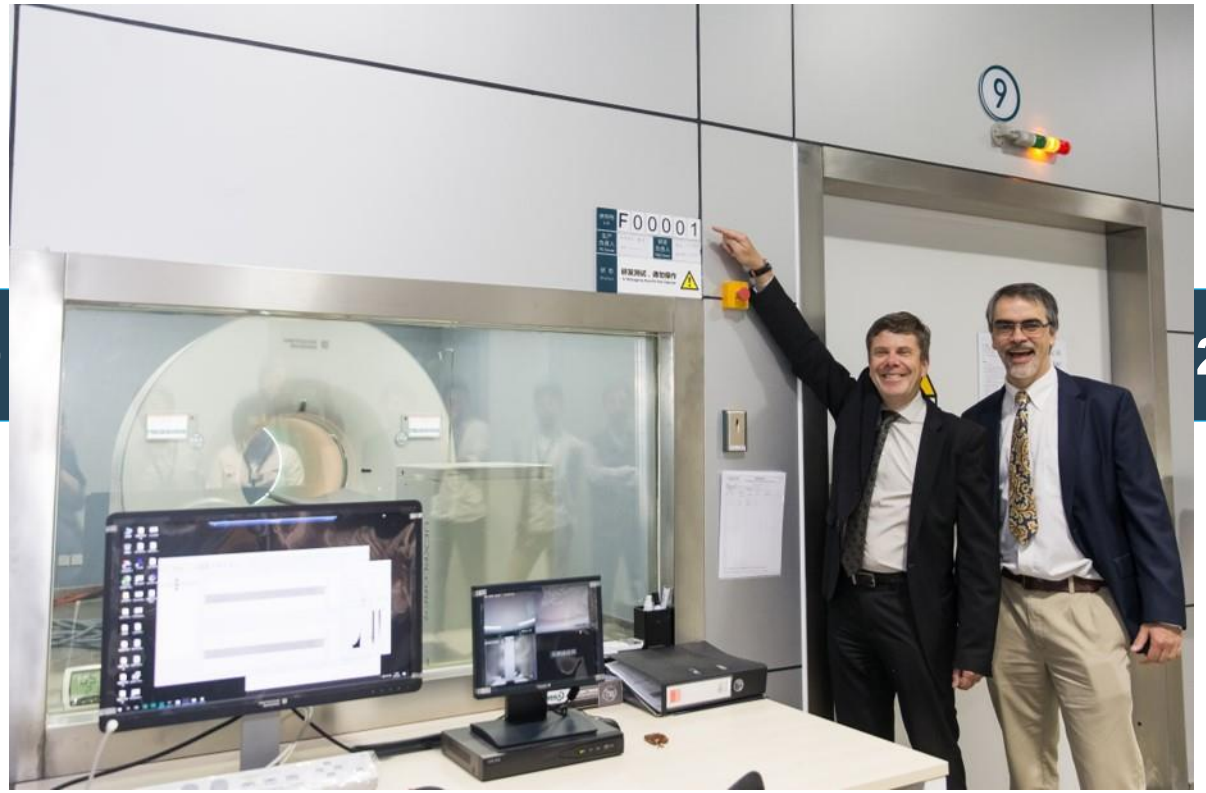
May

2015 2016 2017 2018 2019 24

Jan

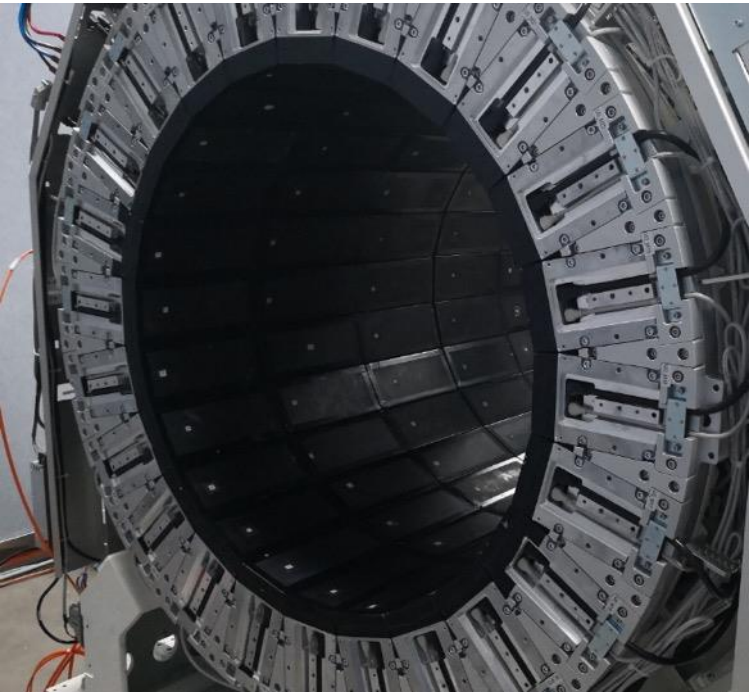
Visit to United Imaging in Shanghai

Lorenzo joins the team



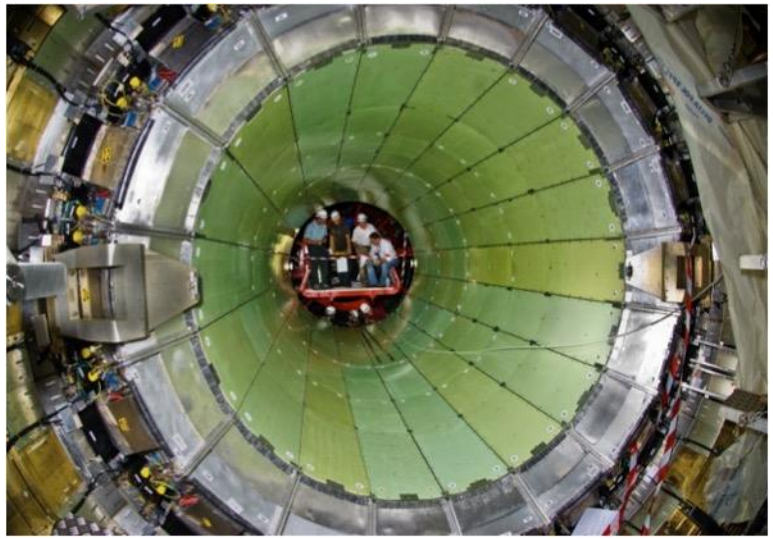
EXPLORER: facts and figures

EXPLORER



# of crystals: 564,480
# of photodetectors: 53,760
# of electronic channels: 53,760
Mass: ~11,000 kg

CMS EM Calorimeter

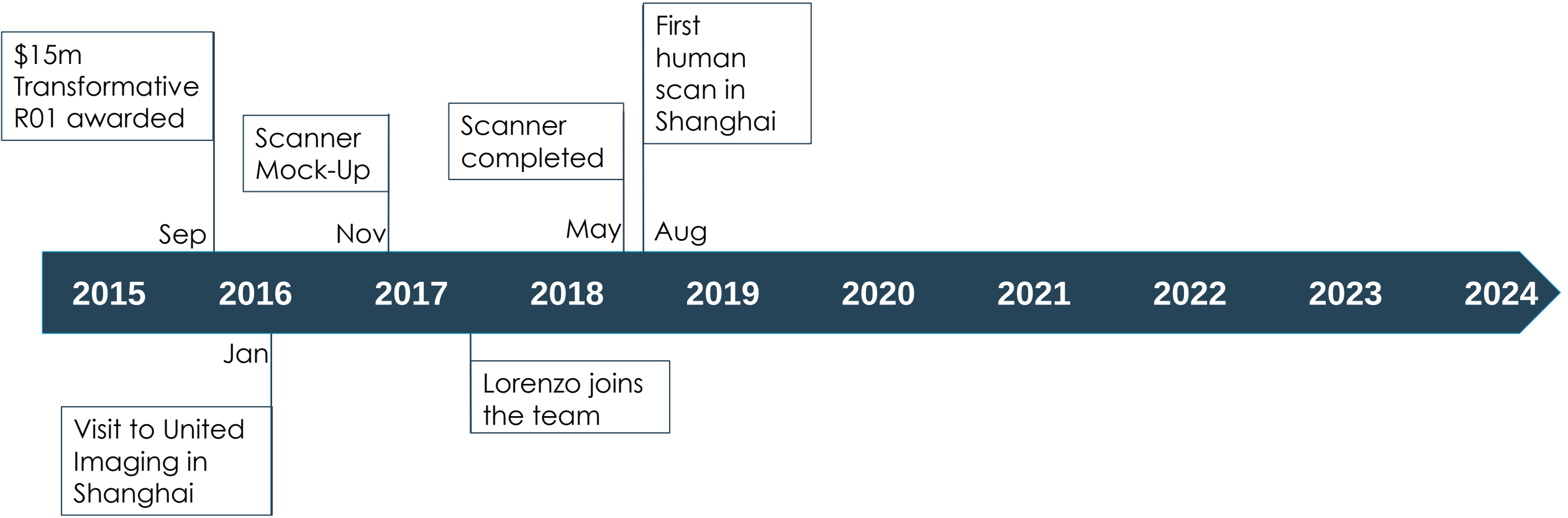


# of crystals: 75,848
# of photodetectors: 137,048
# of electronic channels: 75,848
Mass: ~100,000 kg

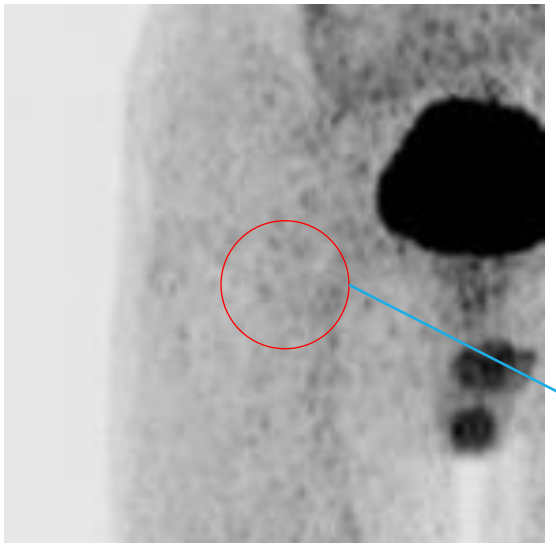
EXPLORER: test objects

EXPLORER: test objects

First human study



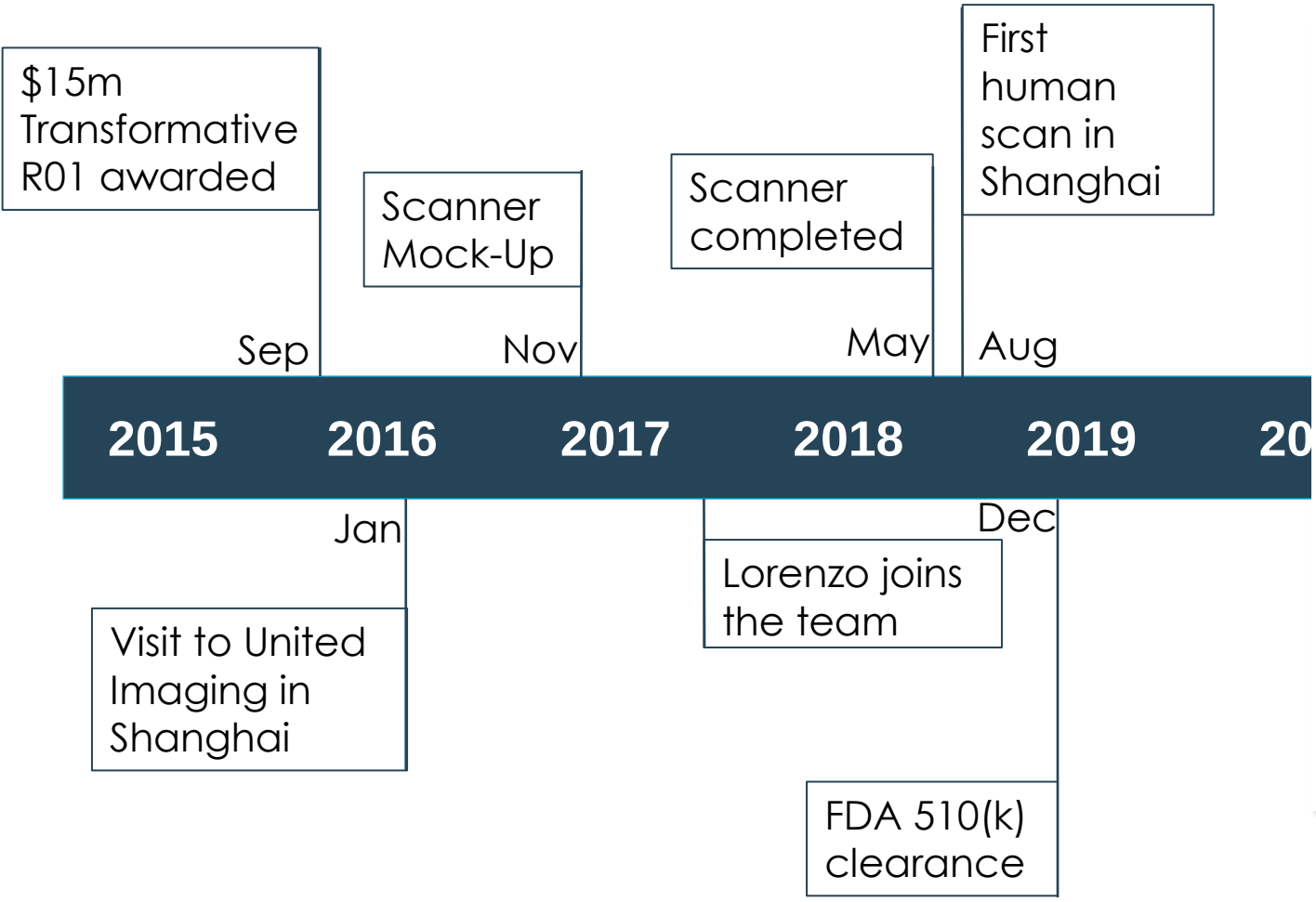
First human study

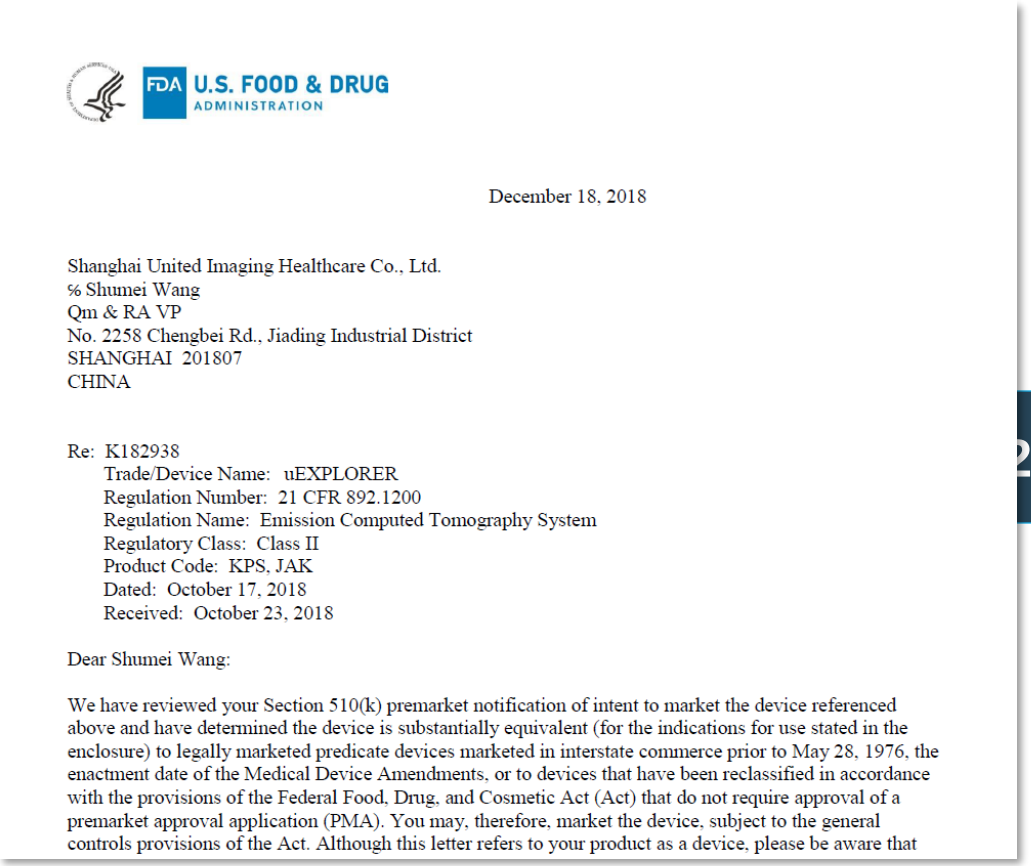


Conventional PET (uMI 780)
8 beds, 2 mins/bed,
50 min p.i.

EXPLORER
20 min scan, 1 bed
82 min p.i

FDA 510(k) clearance





FDA U.S. FOOD & DRUG ADMINISTRATION

December 18, 2018

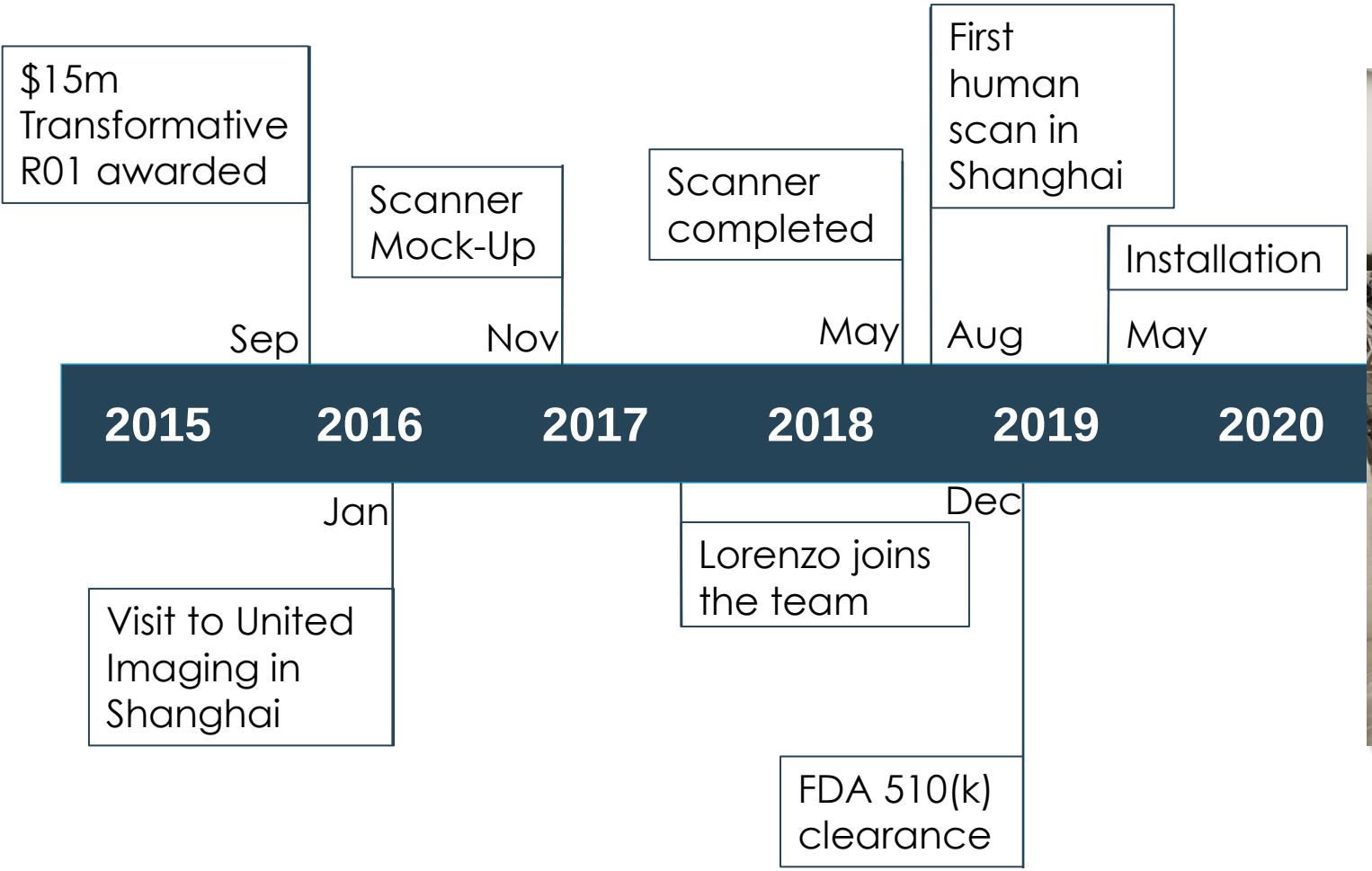
Shanghai United Imaging Healthcare Co., Ltd.
% Shumei Wang
Qm & RA VP
No. 2258 Chengbei Rd., Jiading Industrial District
SHANGHAI 201807
CHINA

Re: K182938
Trade/Device Name: uEXPLORER
Regulation Number: 21 CFR 892.1200
Regulation Name: Emission Computed Tomography System
Regulatory Class: Class II
Product Code: KPS, JAK
Dated: October 17, 2018
Received: October 23, 2018

Dear Shumei Wang:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that

Installation at UC Davis



First research scan

$15m Transformative R01 awarded — Sep 2015

Visit to United Imaging in Shanghai — Jan 2016

Scanner Mock-Up — Nov 2016

Lorenzo joins the team — Dec 2017

Scanner completed — May 2018

FDA 510(k) clearance — Aug 2018

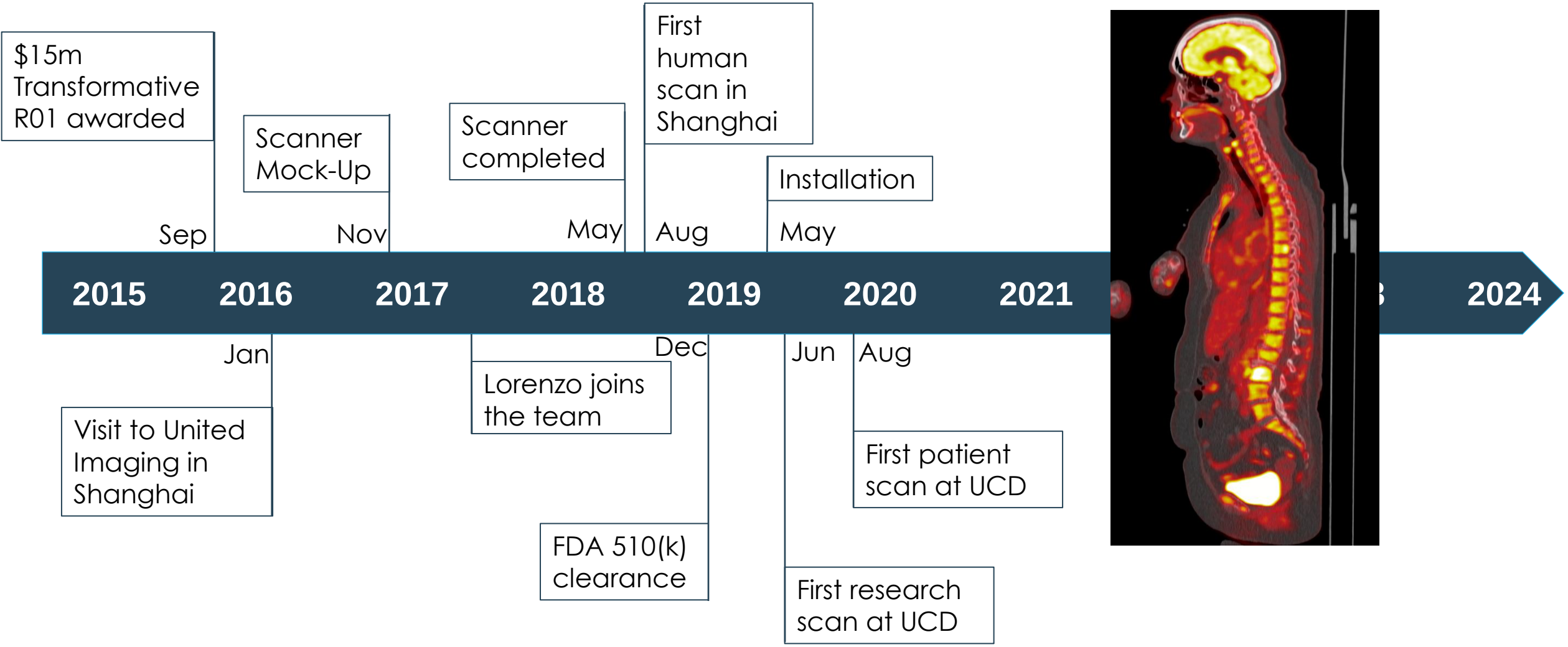
First human scan in Shanghai — Aug 2019

Installation — May 2020

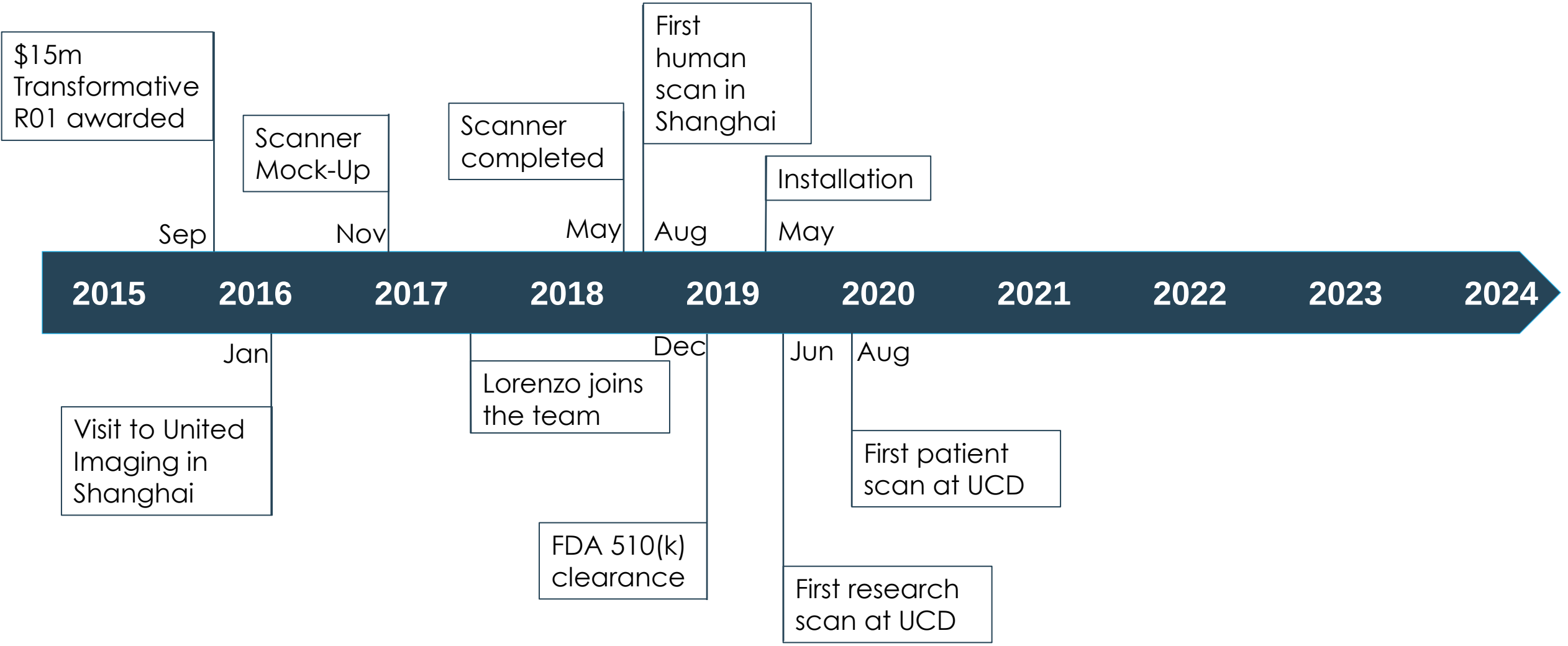
First research scan at UCD — Jun 2020

2015 2016 2017 2018 2019 2020 2021 2023 2024

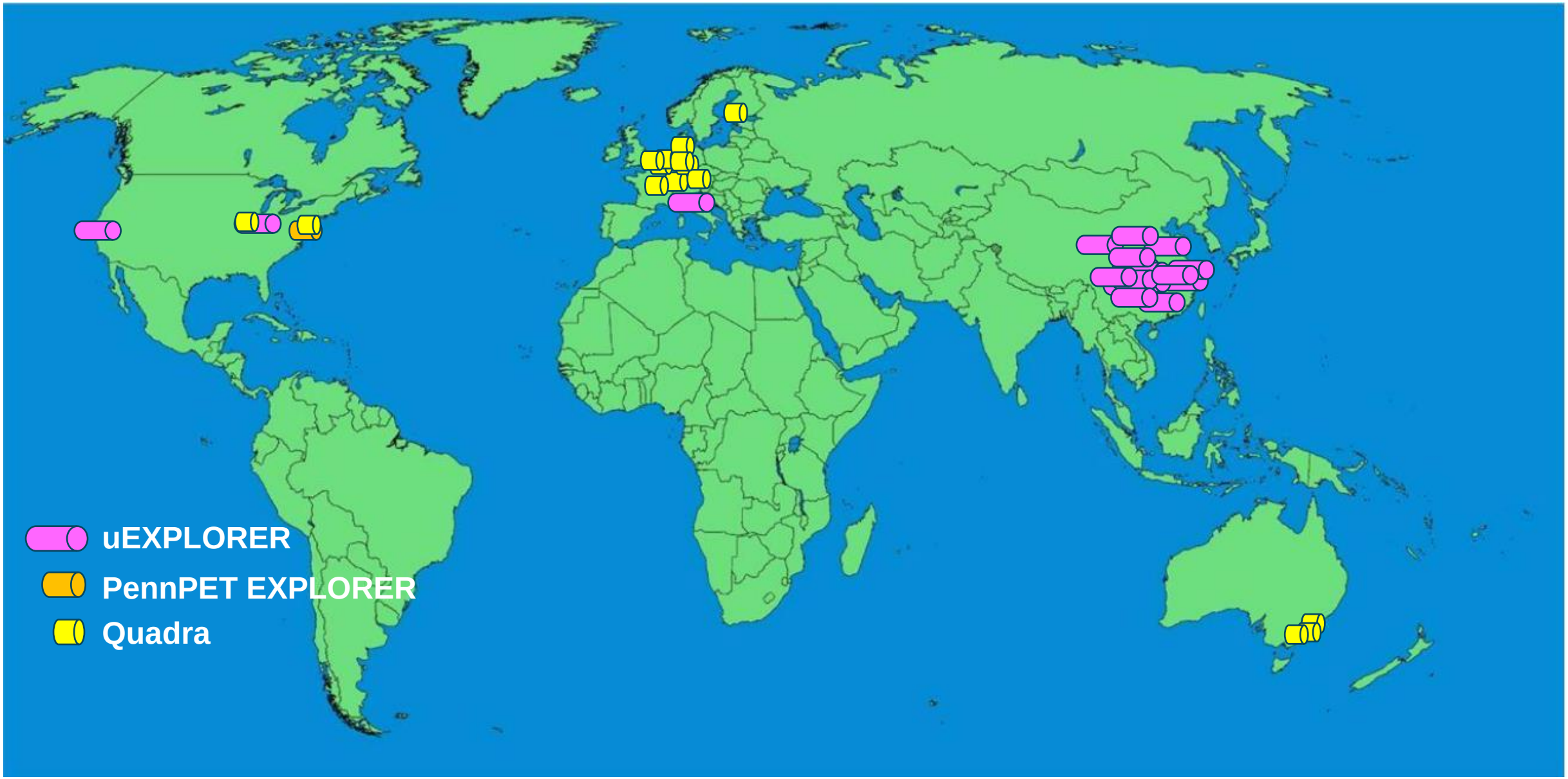
First patient study



EXPLORER concept goes world-wide

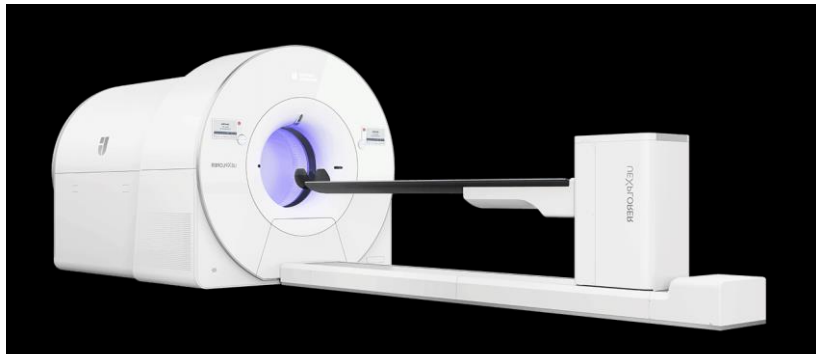


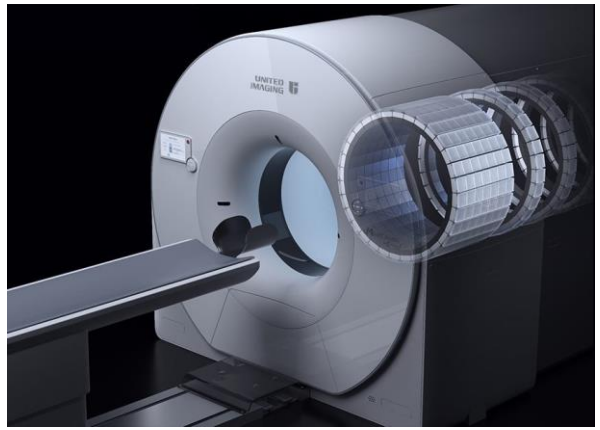
Installations: Nov 2023

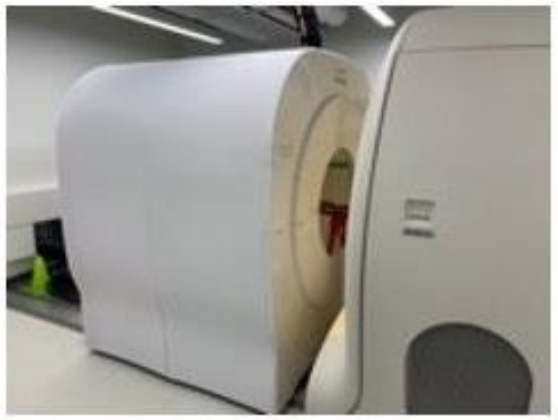


Ecosystem of Scanners

	UIH uEXPLORER	UIH Panorama GS	PennPET EXPLORER	GE OMNI Legend LAFOV	Siemens Quadra
Axial FOV	194 cm	148 cm	140 cm*	Up to 128 cm **	106 cm







* Not FDA 510(k) cleared

** 128 cm version not FDA 510(k) cleared

Long Axial FOV PET/CT

Improved signal collection efficiency[1,2] and spatial resolution[1,2] allow for:

- Improved image quality
- Delayed imaging
- Decreased acquisition time
- Decreased injected dose
- Simultaneous total body scan

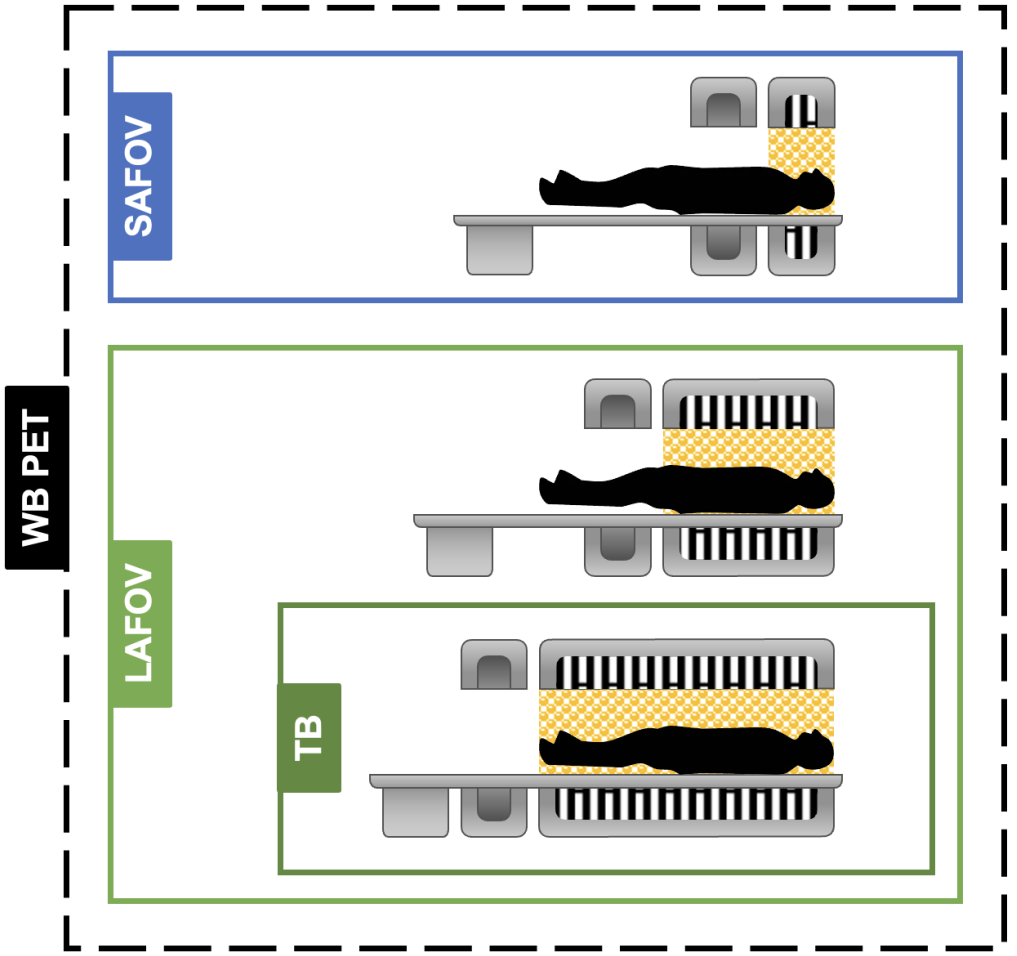


Image from "Mingels et al. Total-body PET/CT or LAFOV PET/CT? Axial field-of-view clinical classification. Accepted. EJNMMI 11.22.2023"

[1]Cherry et al. Sci Transl Med. 2017
[2]Spencer et al. JNM 2020

Protocol Variables

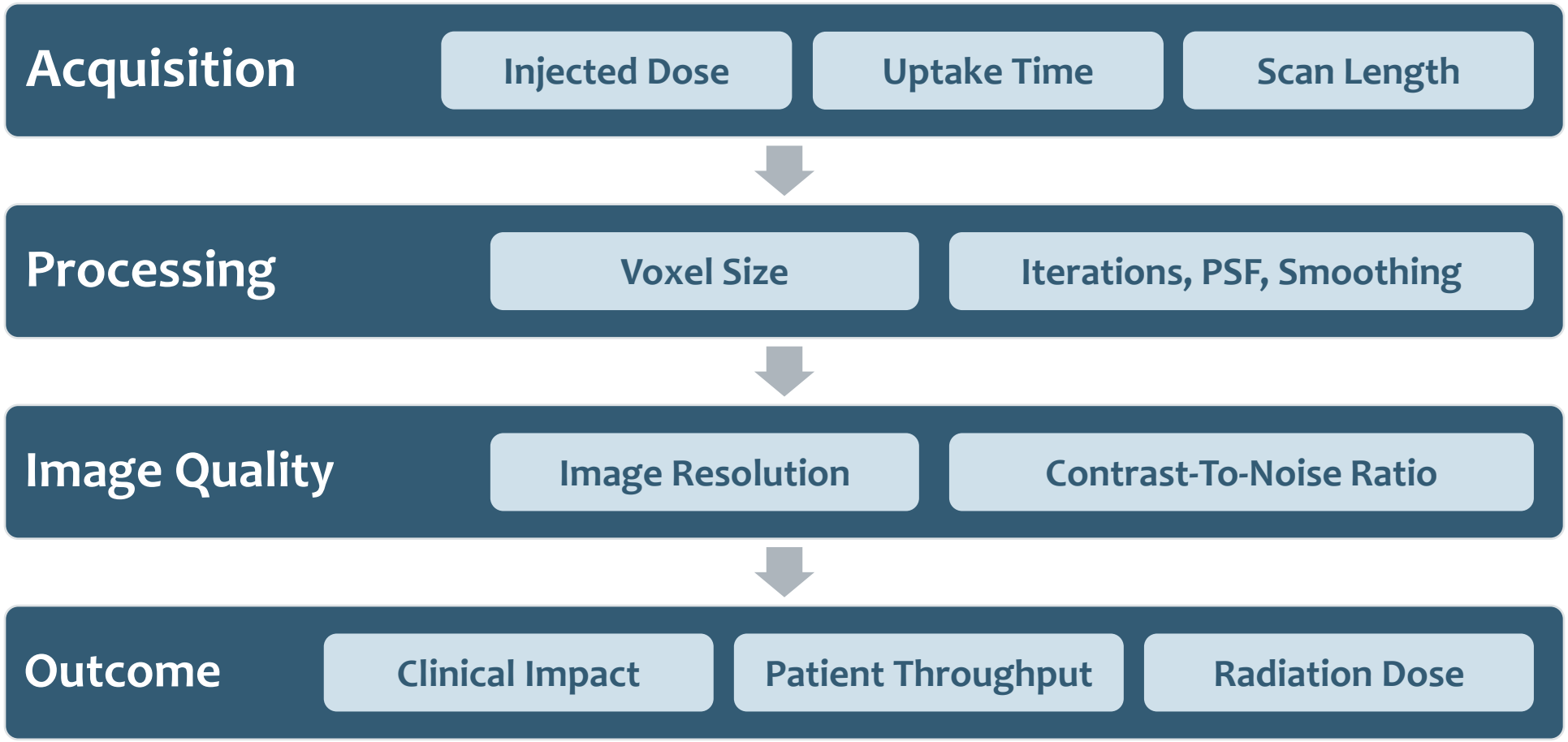
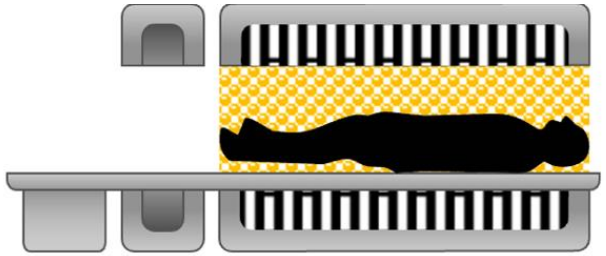


Image Wisely

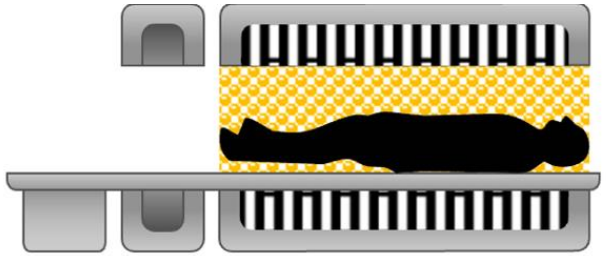


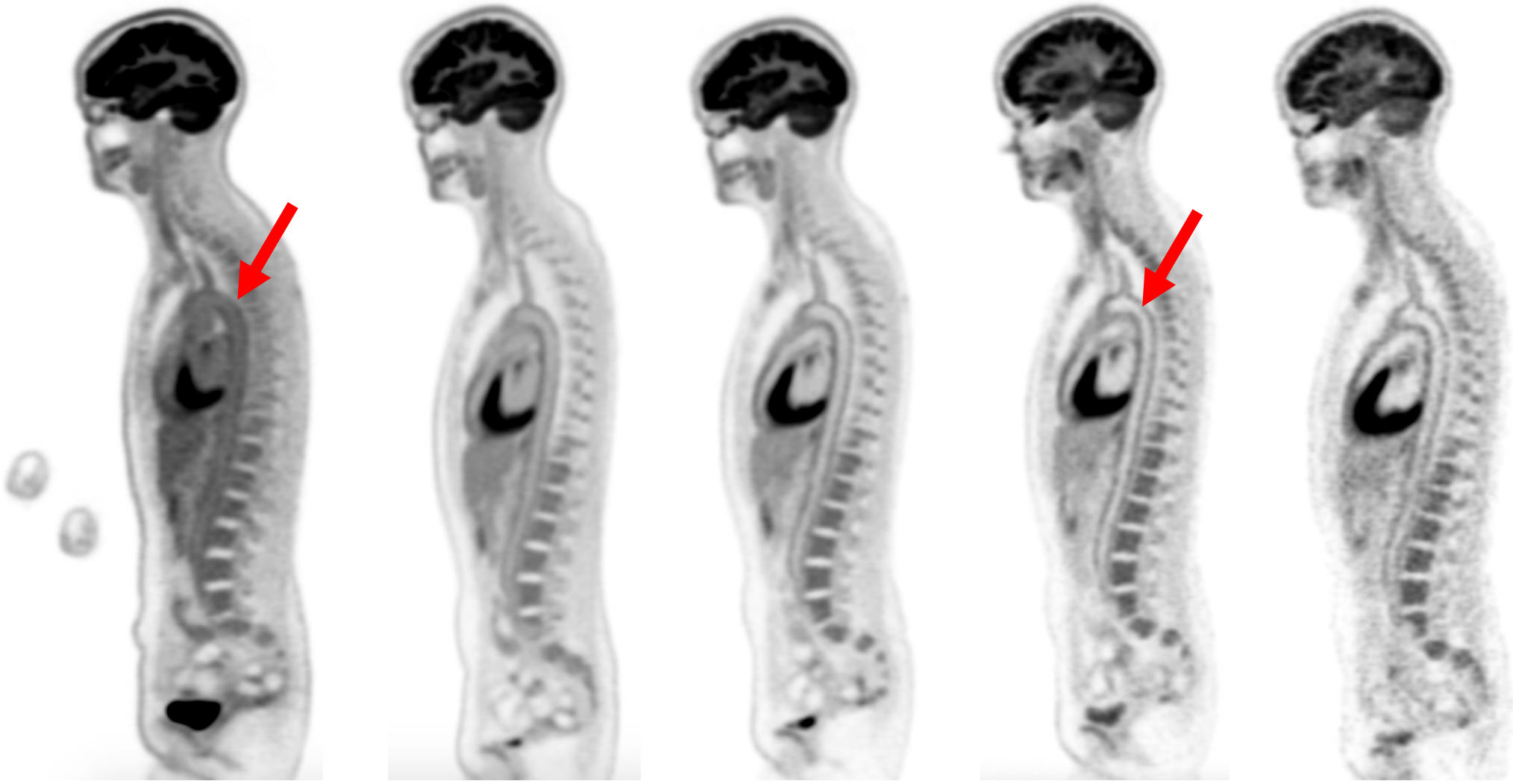
0.4 mCi

2 mCi

Abhijit Chaudhari

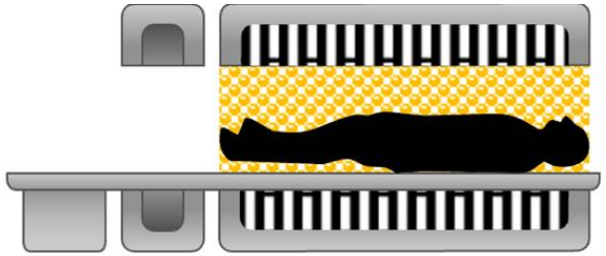
Increasing Uptake Time





40 min 90 min 3 hrs 6 hrs 9 hrs

Decreasing Scan Length



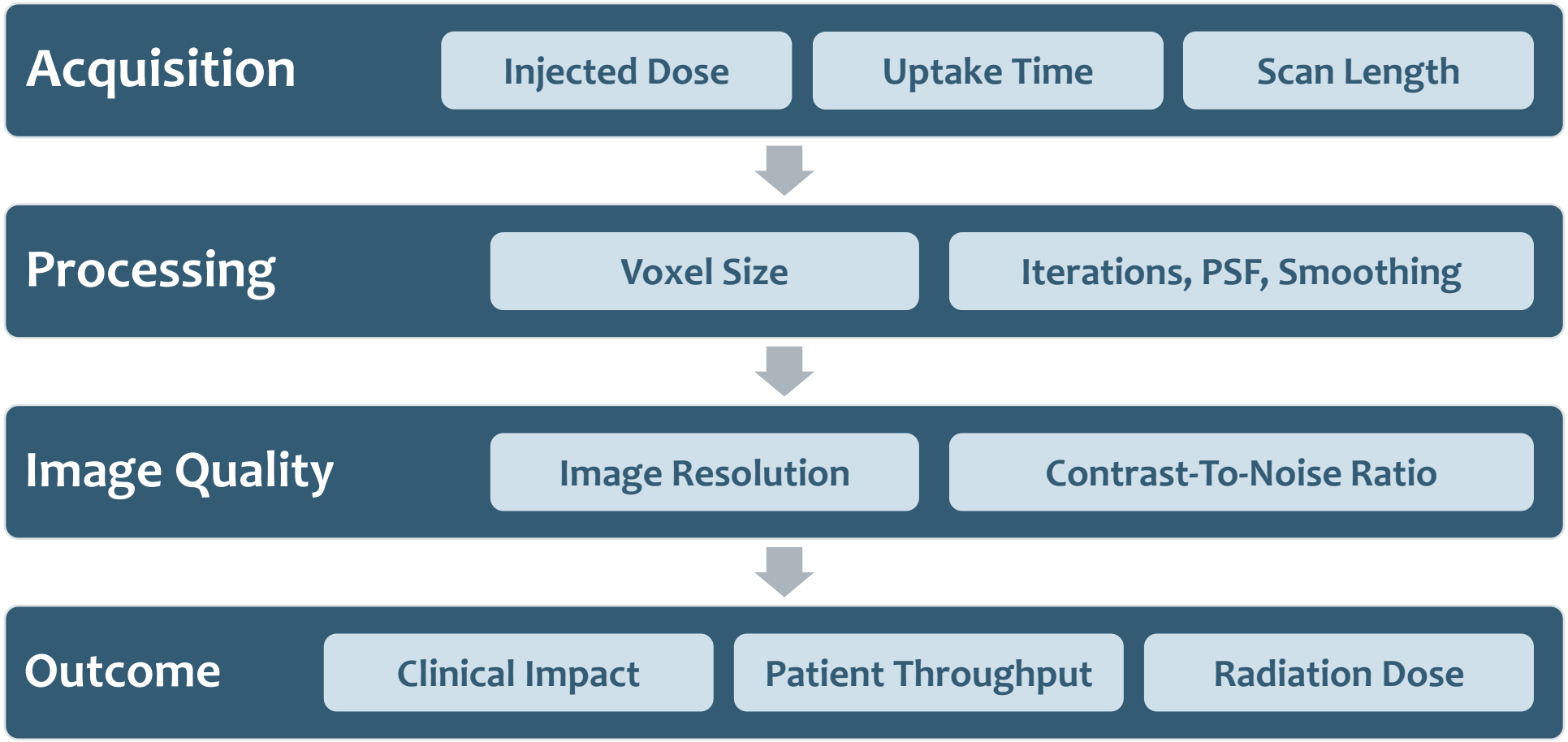
20 min

5 min

75 s

18.75 s

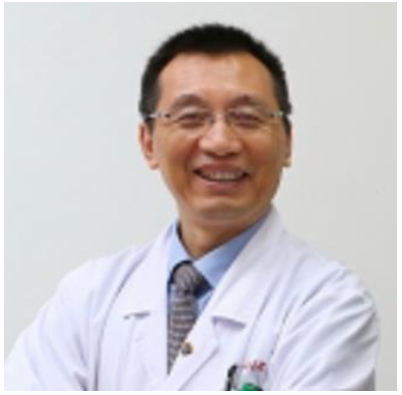
Protocol Variables



Protocol Examples

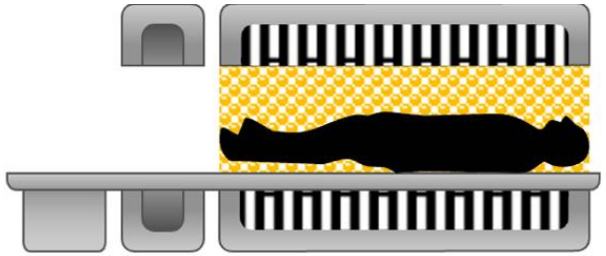
Location	Injected Activity	Uptake Time (min)	Acquisition Time (min)	Reconstruction Parameters
Davis	~300 MBq	120±10	20	256x256 matrix; 2.3mm voxels 4 iterations & 20 subsets PSF off and on
Zhongshan	3.7 MBq/kg	65±10	5	192x192 matrix; 3.1mm voxels 3 iterations & 20 subsets PSF off and on
Bern	3.0 MBq/kg	60±10	6	440x440 matrix; 1.65mm voxels 4 iterations & 5 subsets Gaussian filter: 2mm FWHM

Axel Rominger

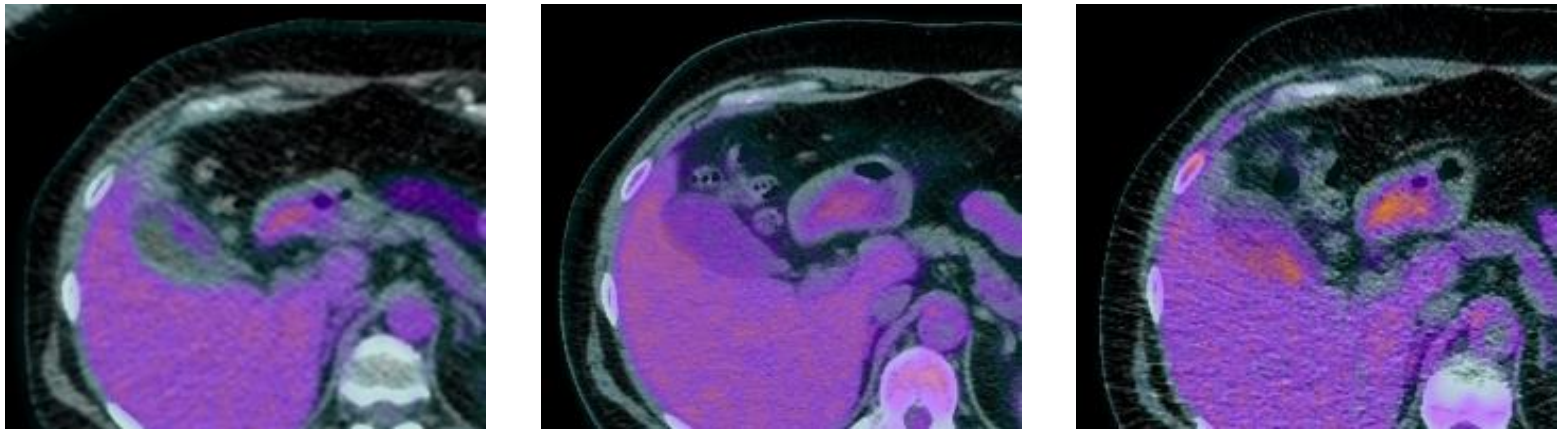


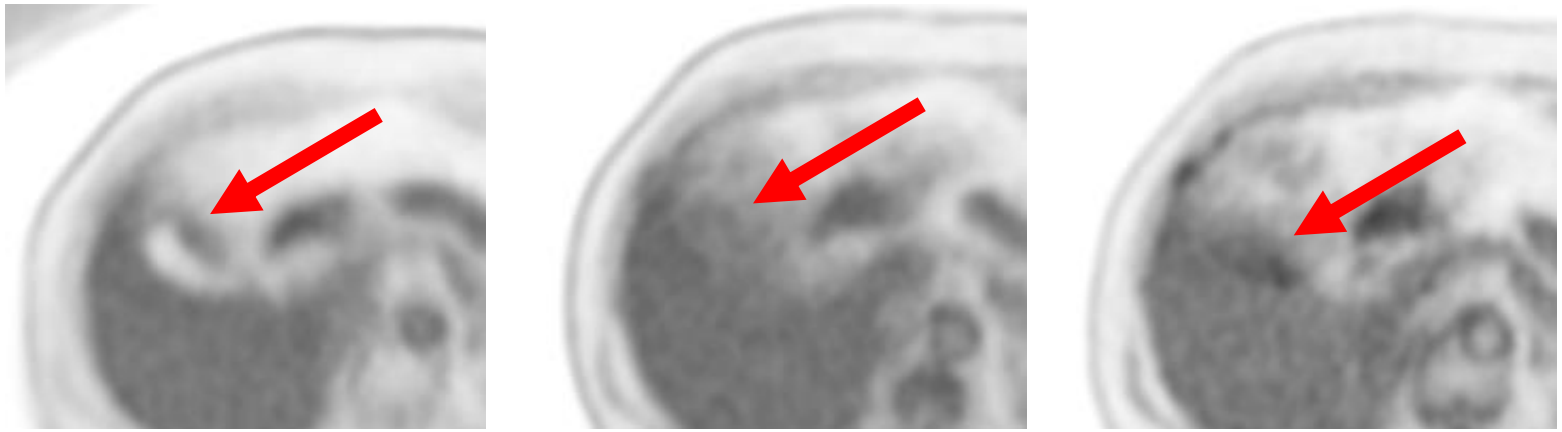
Hongcheng Shi

Physiologic Processes



40 min | 90 min | 3 hrs

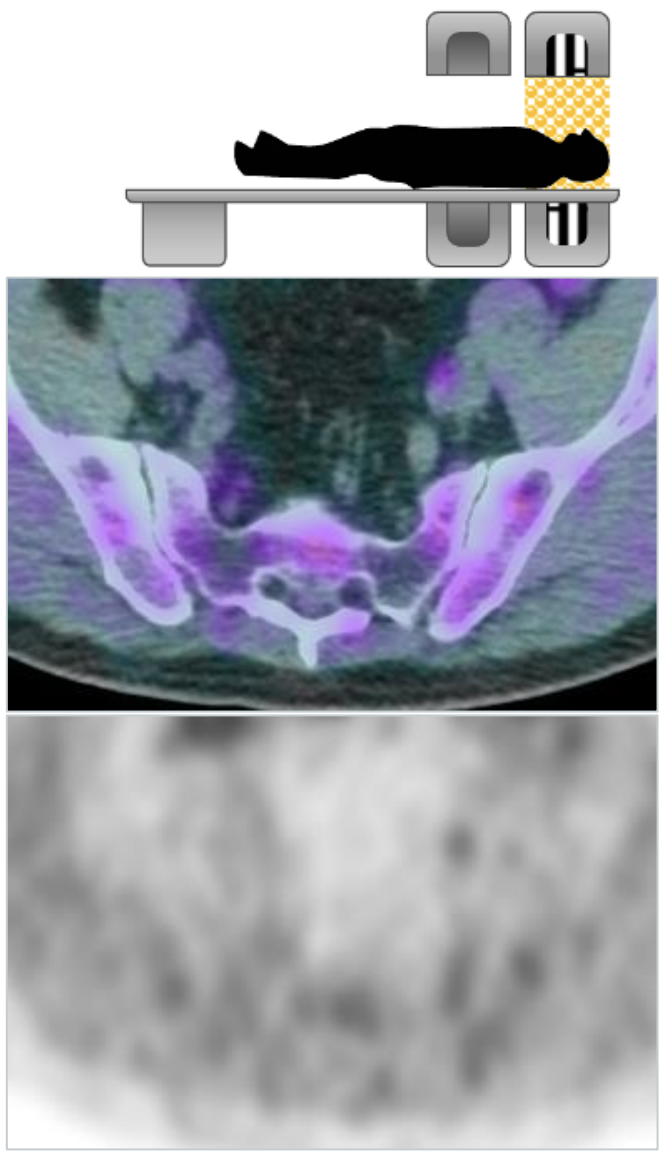


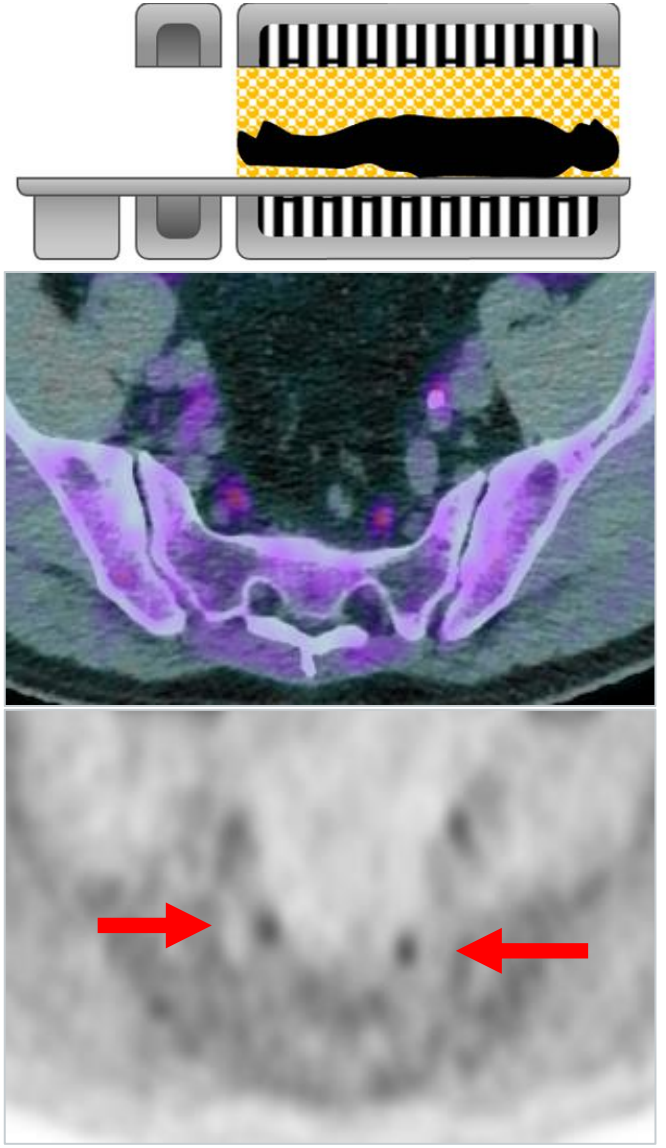


Anna Calabro'

Calabro' et al. BMC Med. Imaging 2023

Small Anatomic Structures

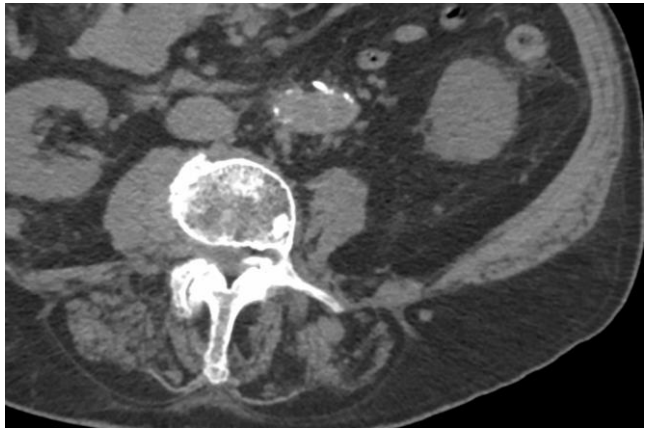


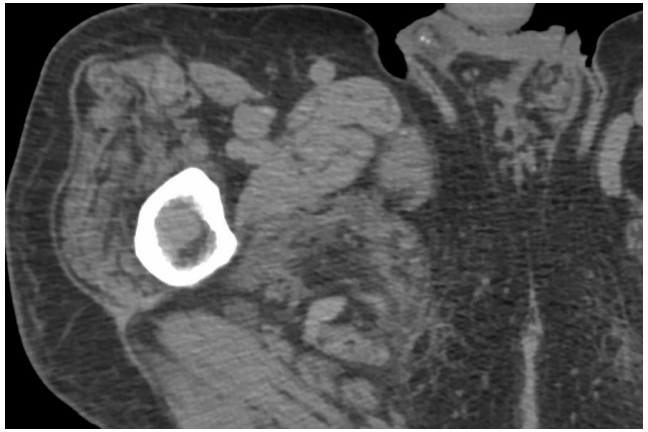


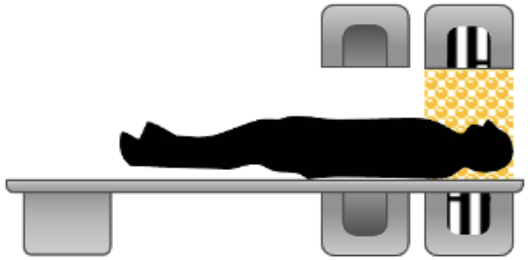
Elizabeth
Triumbari

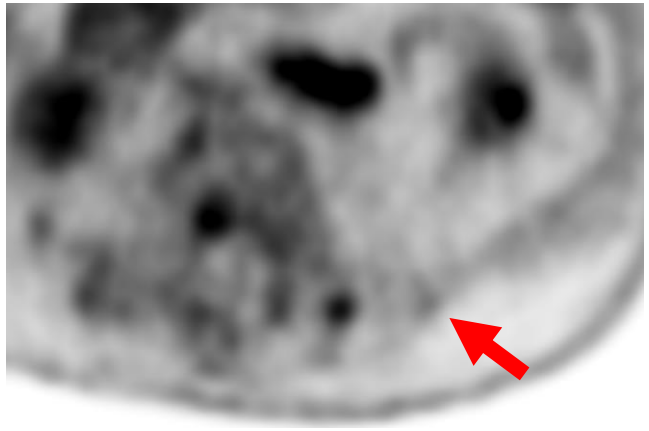
Lesion Detection

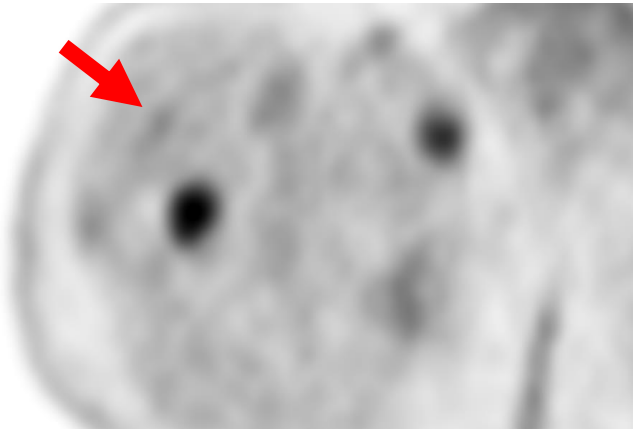
CT

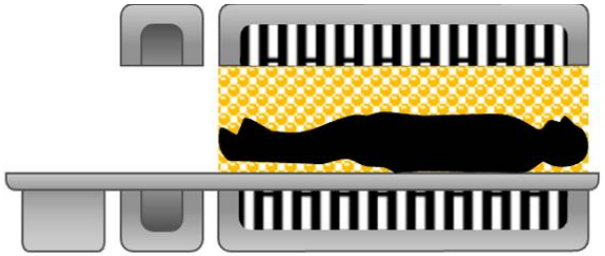


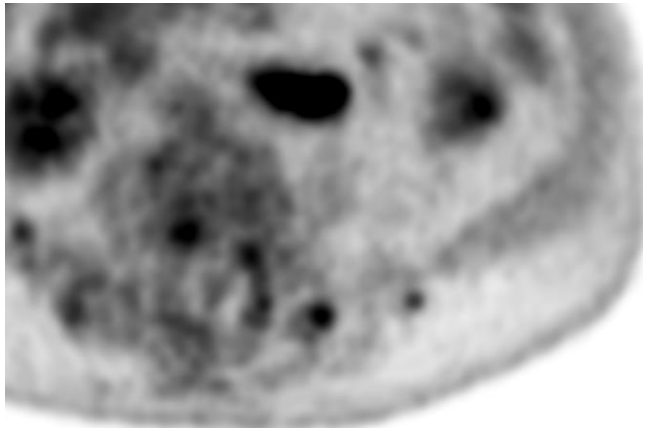


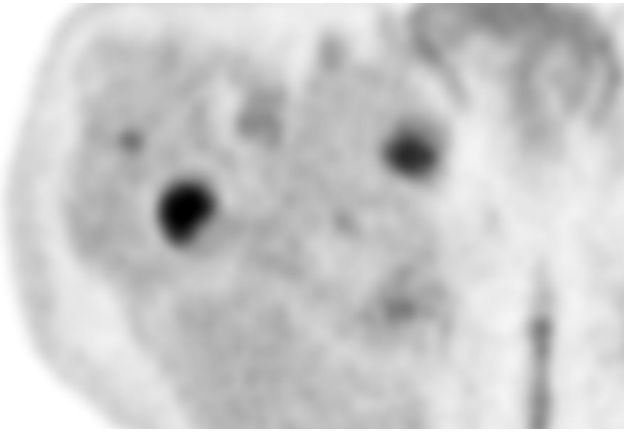








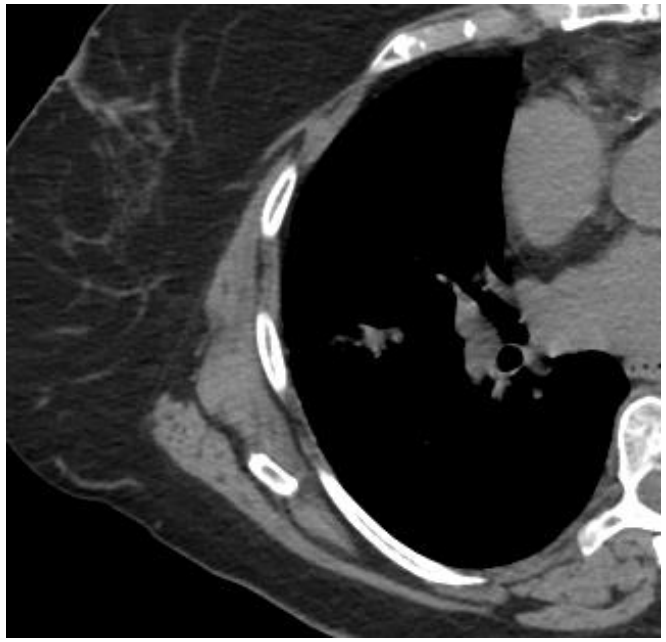


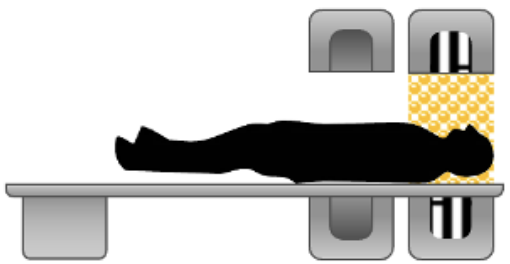


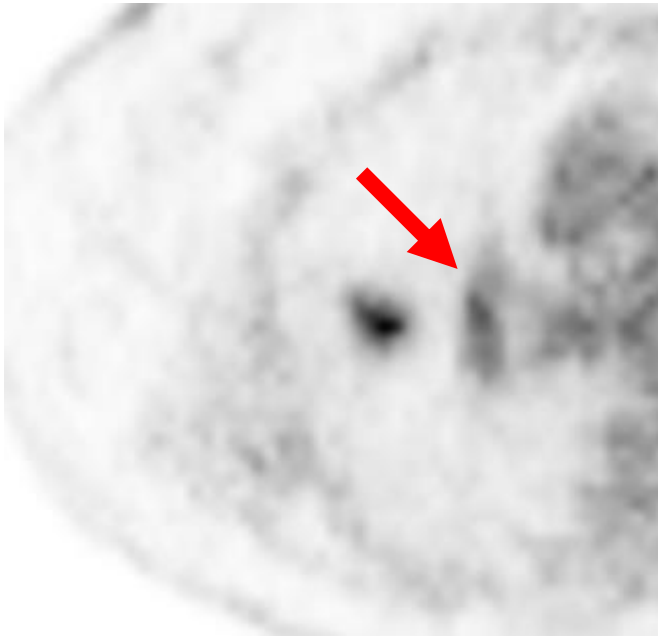
Ng et al. Semin Nucl Med. 2022 May; 52(3): 330–339

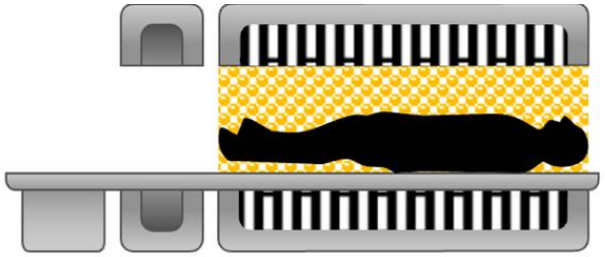
Lesion Detection

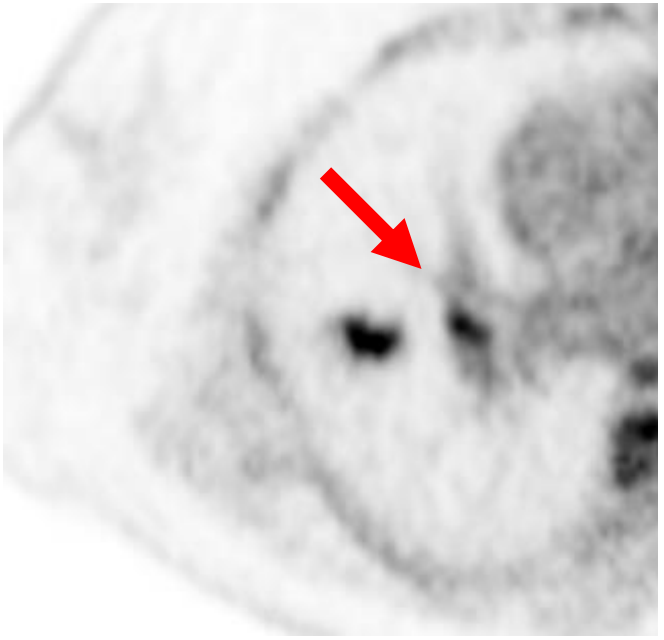
CT







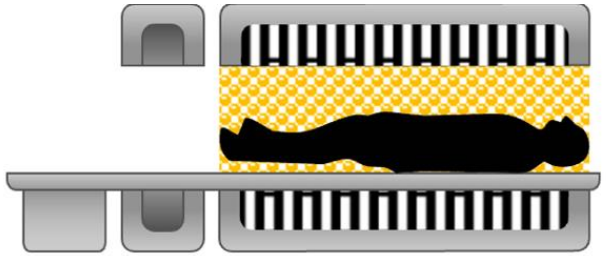




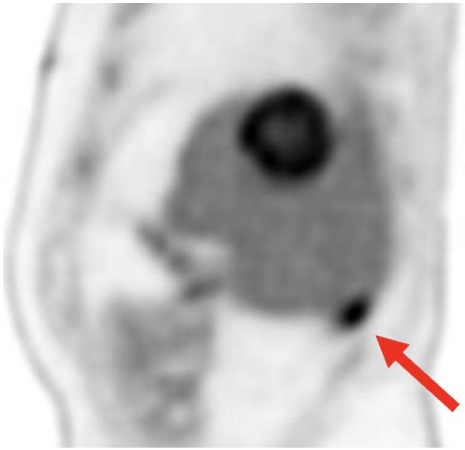
Fatma Sen

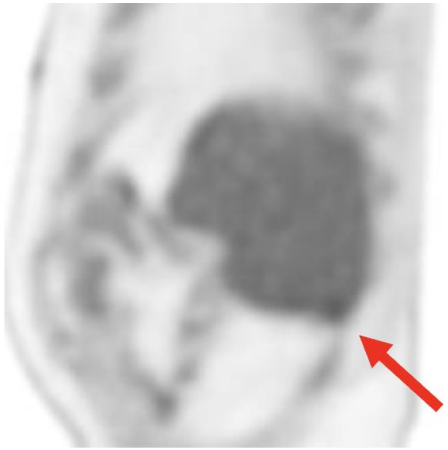
Clemens Mingels

Lesion Detection

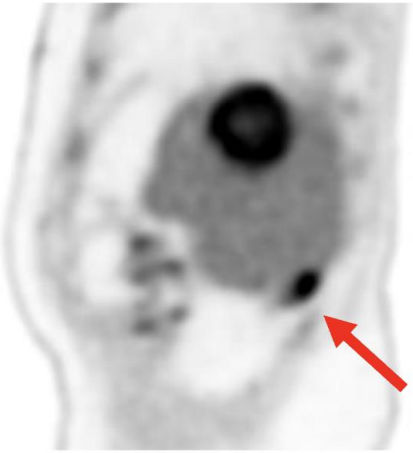


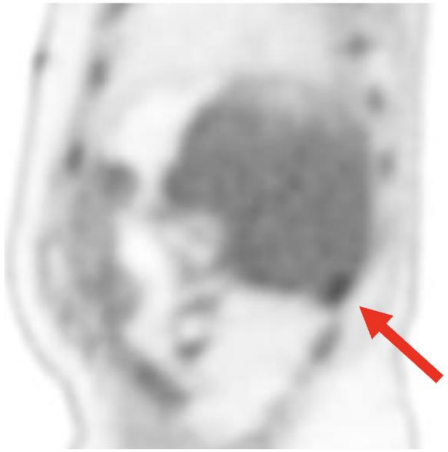
60 minutes





120 minutes





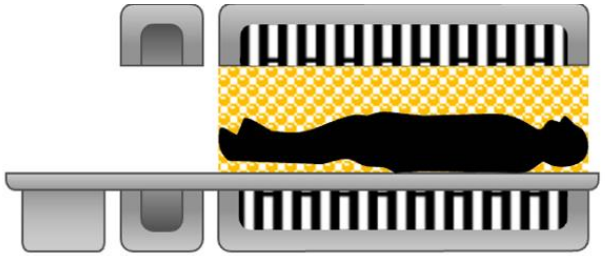
Mehrad Rokni

Yasser Abdelhafez

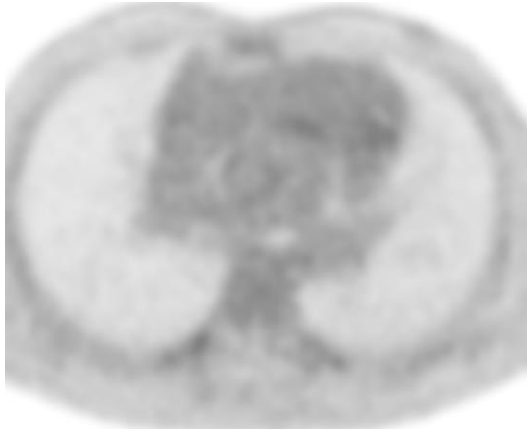
Staging

Follow Up

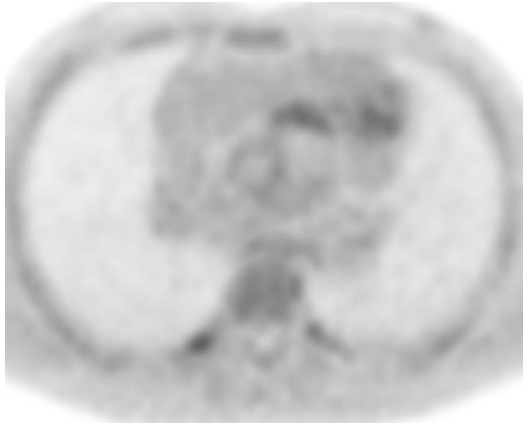
New Protocol Challenges



60 min



120 min



Hande Nalbant

Challenges and Opportunities

Challenges

Clinical:

- Sensitivity/false positives
- New experiences vs old Classifications
- New artifacts/QC

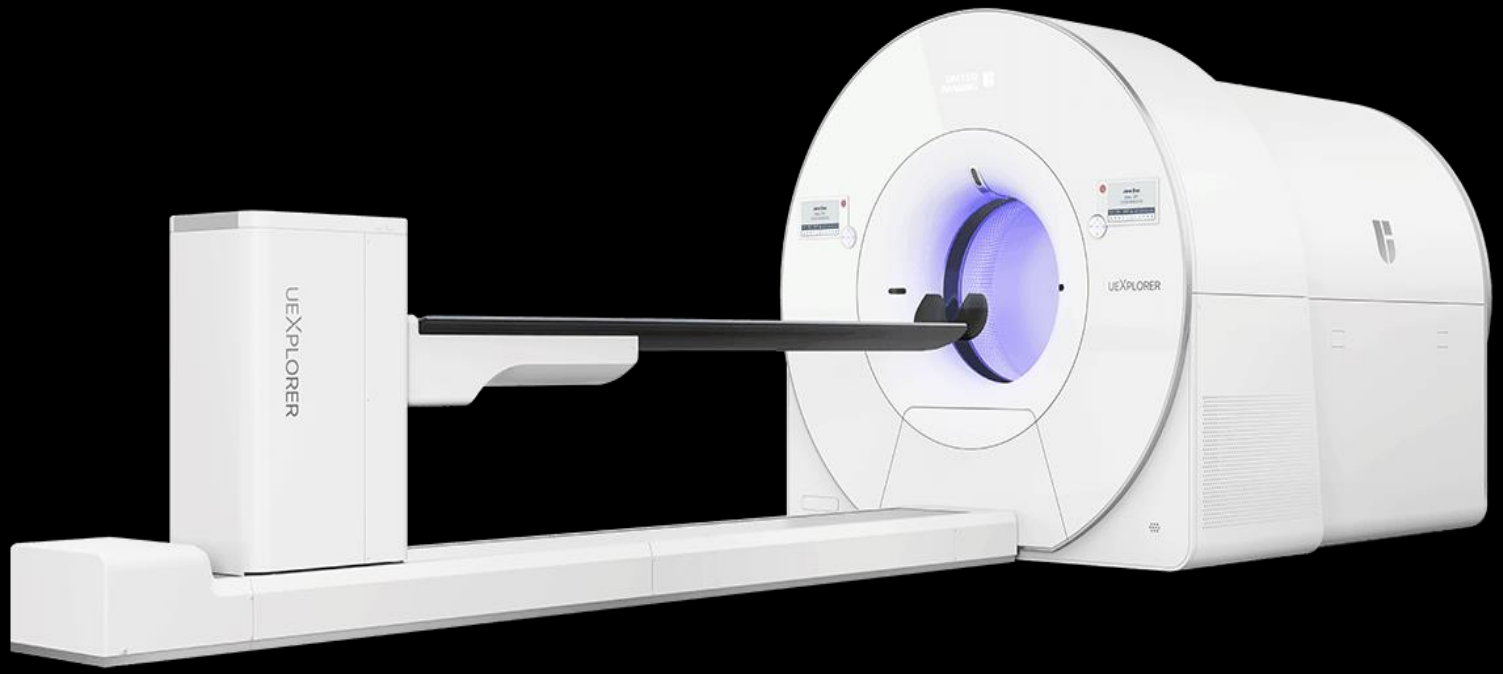
Logistics:

- Being the first US center
- PACS too slow to scroll large datasets
- Storage space

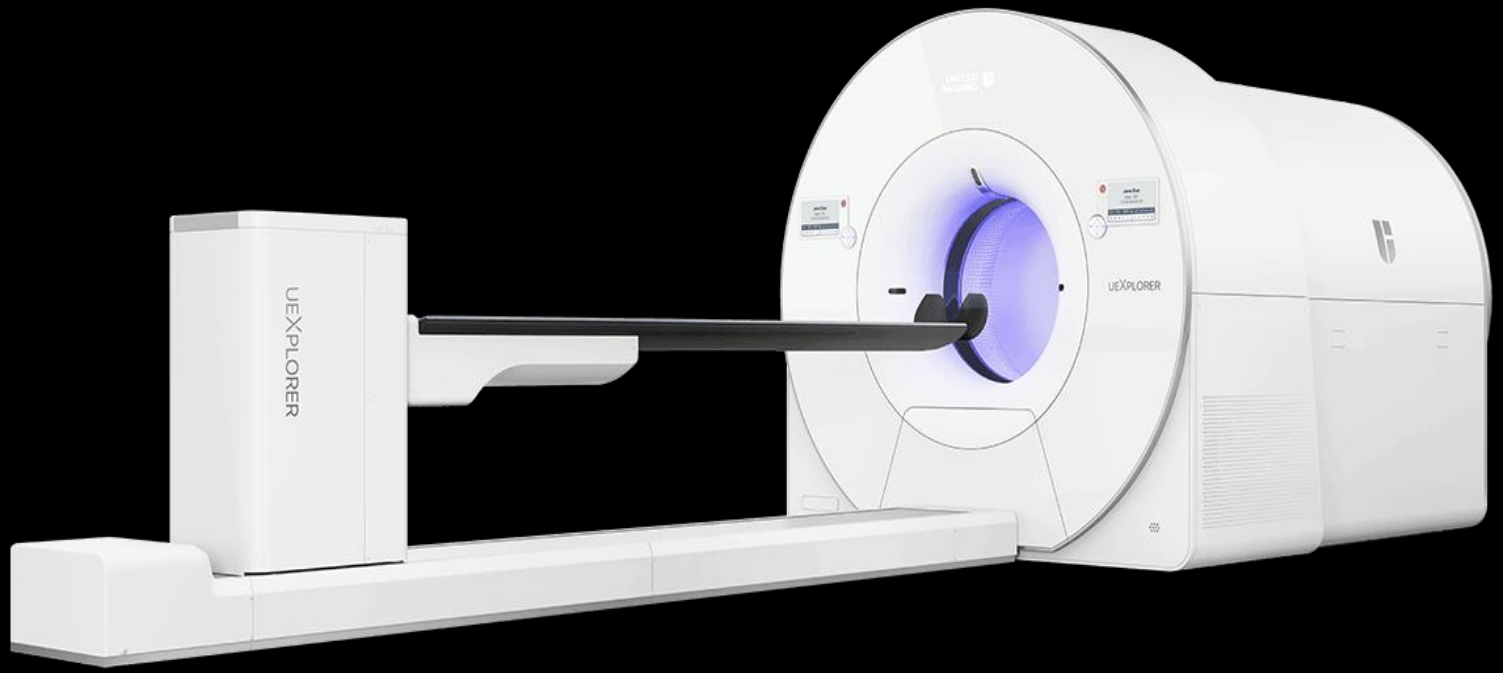
Opportunities

- Improving image quality
- Delayed and dynamic imaging
- Decreasing acquisition time
- Decreasing injected dose

Research with Total-Body PET



Research with Total-Body PET

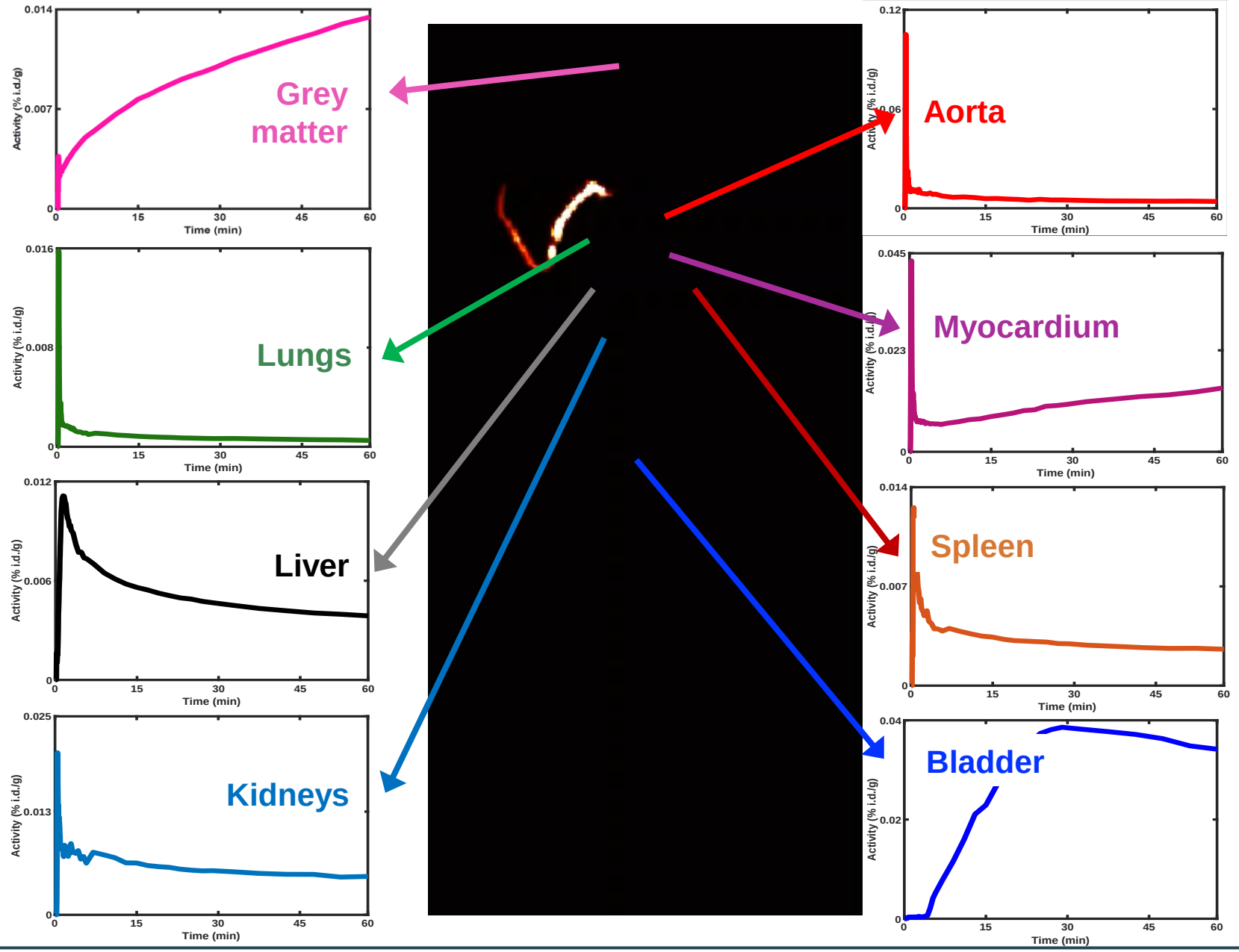


Yiran Wang, UC Davis

Total-Body Dynamic Imaging

Measuring pharmacokinetics in every tissue and organ of the body

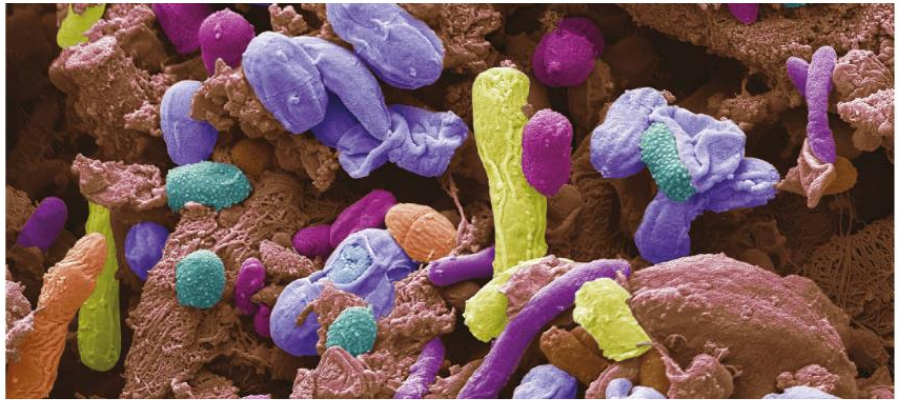
~1,000,0000 measured time-activity curves



Total-Body PET/CT:
A New Tool for Systems Medicine?

The international journal of science / 9 November 2023

nature



STEVE GSCHMEISSNER/SPL

Changes in the make-up of microorganisms in the gut have been linked to disorders such as Parkinson's disease.

Brain and body are more intertwined than we knew

A host of disorders once thought to be nothing to do with the brain are, in fact, tightly coupled to nervous-system activity.

"If some brain

The effect is two-way. There is a lengthening list of symptoms not typically viewed as disorders of the nervous system in which the brain and the neural processes that connect it to the body play a large part. For example, the development of a fever is influenced by a population of neurons that control body temperature and appetite. The effect of brain on body is underlined by the finding that stimulating a particular brain region in mice can 'remind' the body of previous bouts of inflammation — and reproduce them[1].

The list goes on. Evidence is mounting that cancers use nerves to grow and spread. In this week's *Nature*, Michelle Monje and her colleagues[2] show how some brain cancers

nature communications

Article

https://doi.org/10.1038/s41467-022-35321-2

Multi-organ imaging demonstrates the heart-brain-liver axis in UK Biobank participants

Received: 13 December 2021

Accepted: 28 November 2022

Published online: 21 December 2022

Check for updates

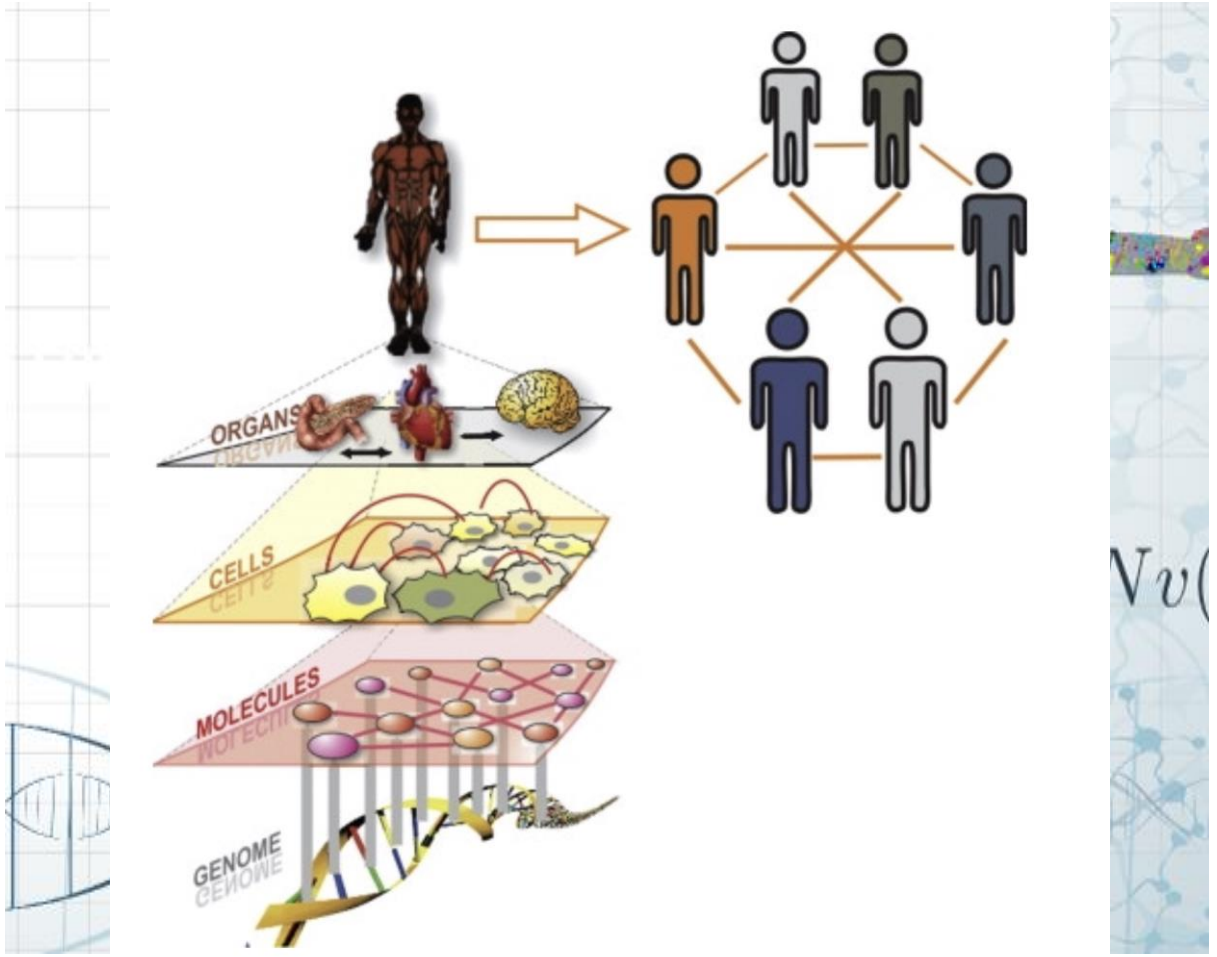
Celeste McCracken[1,11], Zahra Raisi-Estabragh[2,3,11] ✉, Michele Veldsman[4,5], Betty Raman[1], Andrea Dennis[6], Masud Husain[4,5,7], Thomas E. Nichols[4,8,12], Steffen E. Petersen[2,3,9,10,12] & Stefan Neubauer[1,12]

Medical imaging provides numerous insights into the subclinical changes that precede serious diseases such as heart disease and dementia. However, most imaging research either describes a single organ system or draws on clinical cohorts with small sample sizes. In this study, we use state-of-the-art multi-organ magnetic resonance imaging phenotypes to investigate cross-sectional relationships across the heart-brain-liver axis in 30,444 UK Biobank participants. Despite controlling for an extensive range of demographic and clinical covariates, we find significant associations between imaging-derived phenotypes of the heart (left ventricular structure, function and aortic distensibility), brain (brain volumes, white matter hyperintensities and white matter microstructure), and liver (liver fat, liver iron and fibroinflammation). Simultaneous three-organ modelling identifies differentially important pathways across the heart-brain-liver axis with evidence of both direct and indirect associations. This study describes a potentially cumulative burden of multiple-organ dysfunction and provides essential insight into multi-organ disease prevention.

Total-Body PET/CT:
A New Tool for Systems Medicine?

Omics-technologies
- deep phenotyping/genotyping
- large cohorts
- constrained spatial sampling
  (blood, urine, CSF, biopsy)

Total-body PET/CT imaging:
- >10^6 spatial measurements per scan
- function and anatomy
- small cohorts
- small parameter space

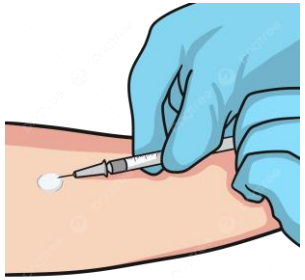


L. Hood and M. Flores, New Biotechnology (2012). 6:613-24 https://www.systemsmedicine.net

UCDAVIS
EXPLORER MOLECULAR IMAGING CENTER

From SUV to biology…

Static imaging



inject

wait

scan

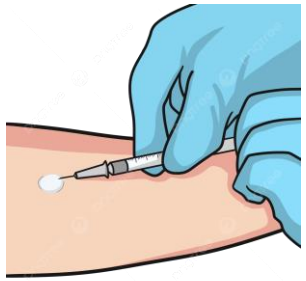
SUV image

Simple

Short time in scanner

Dynamic imaging

+



position subject in scanner, imaging starts just before injection

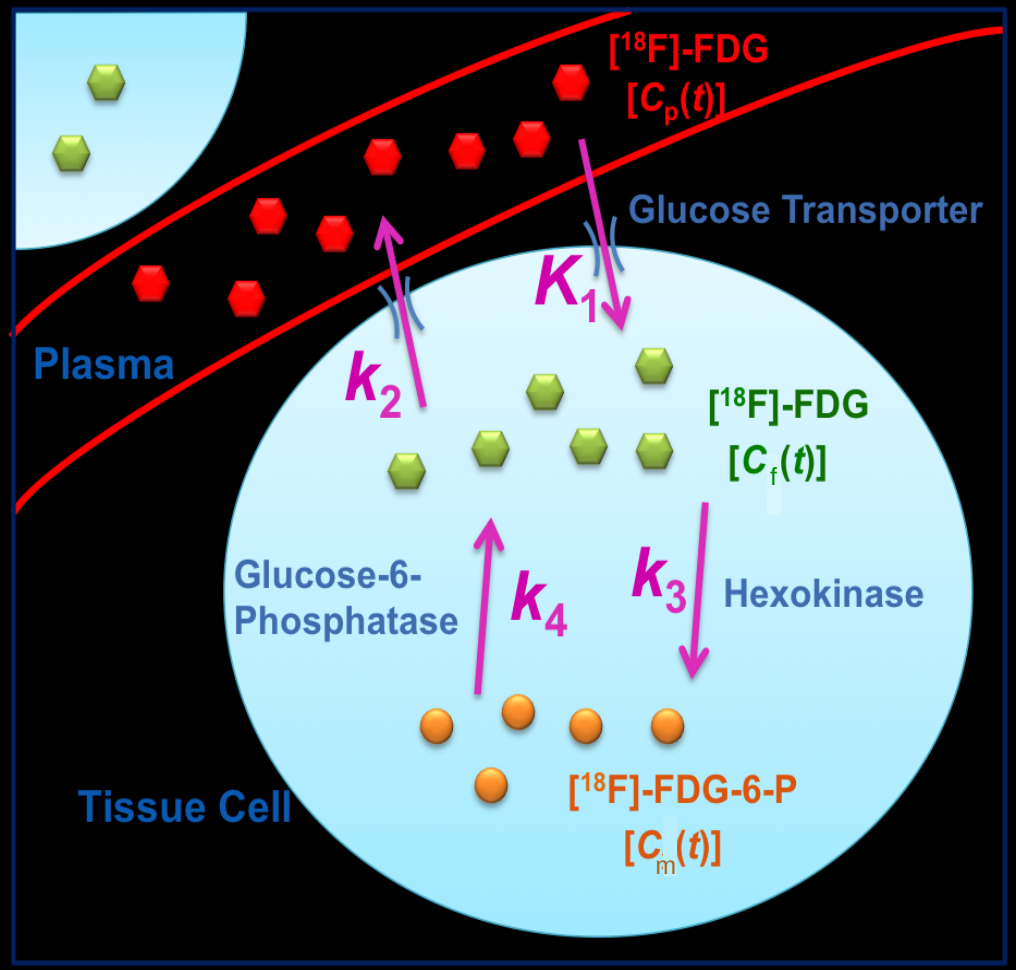
time series of images

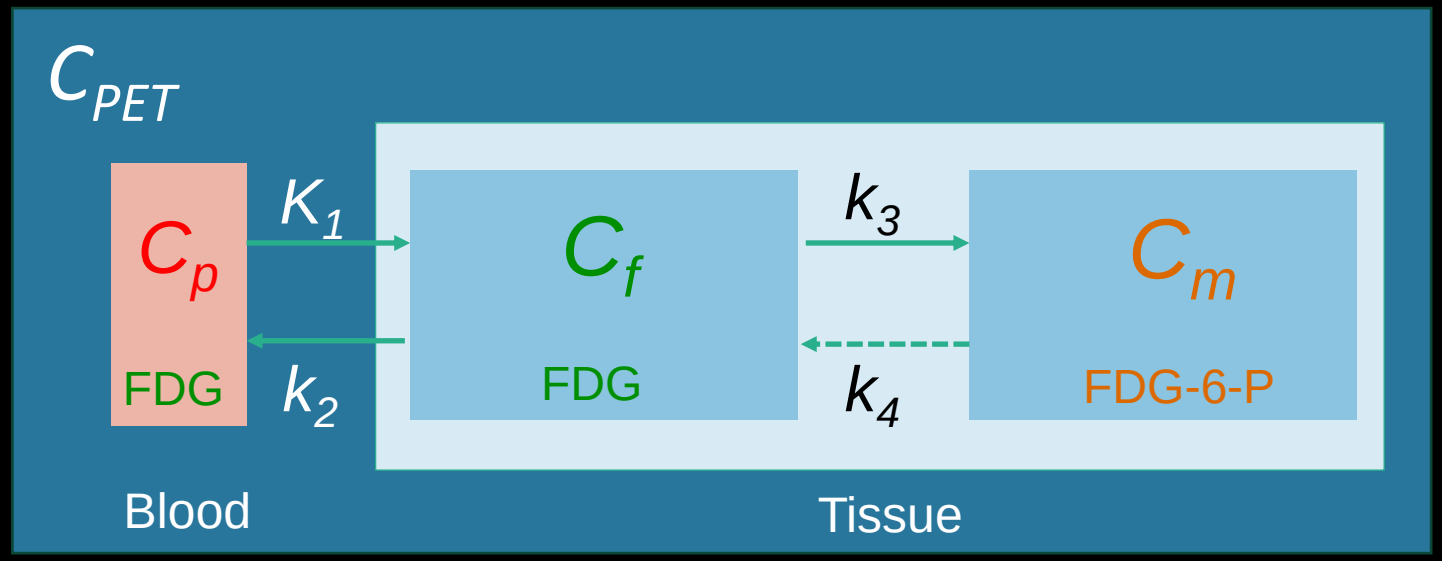
Tracer kinetic modeling

More time in scanner

More information

Kinetic Modeling





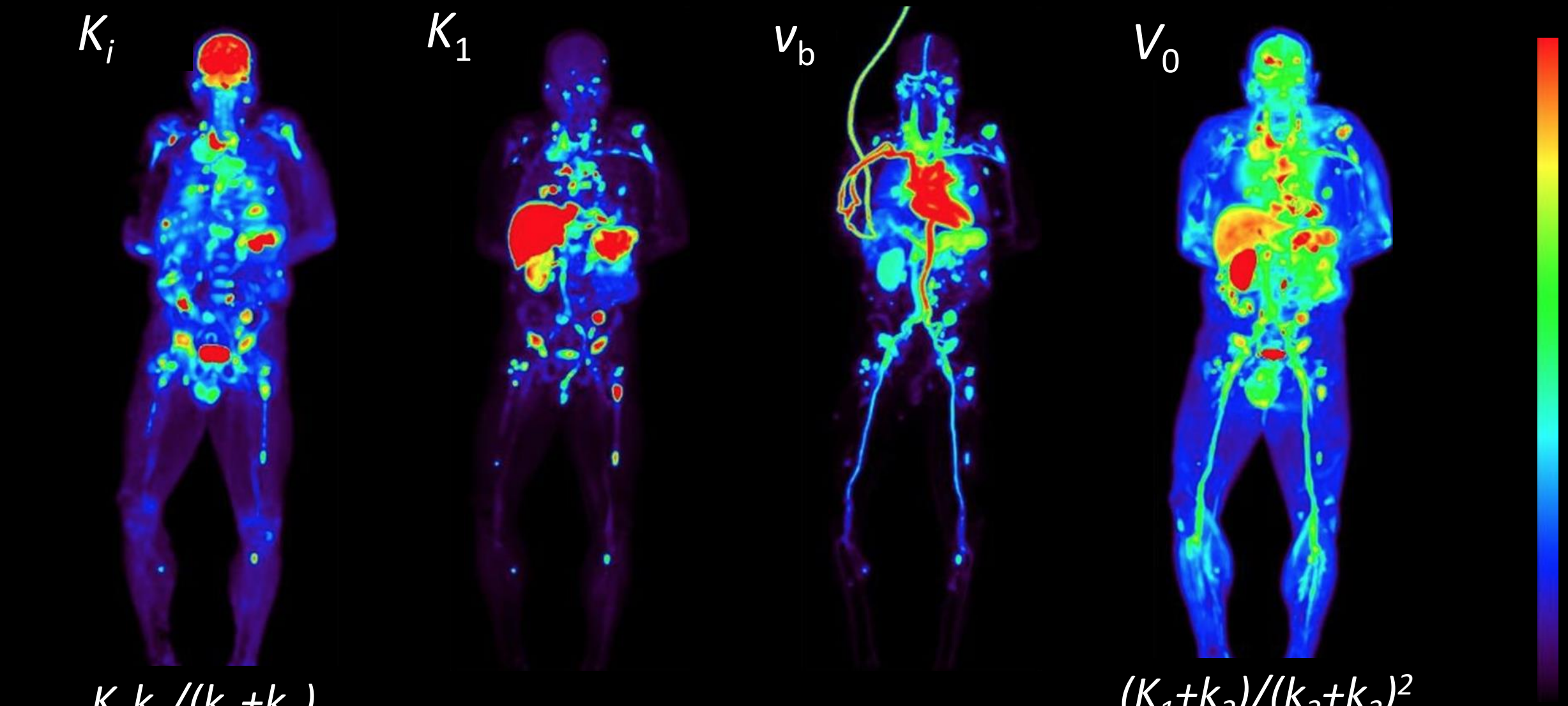
$$\frac{dC_f}{dt} = K_1 C_p - (k_2 + k_3) C_f + k_4 C_m$$

$$\frac{dC_m}{dt} = k_3 C_f - k_4 C_m$$

$$C_{PET}(t) = (1 - v_b)(C_f(t) + C_m(t)) + v_b C_p(t)$$

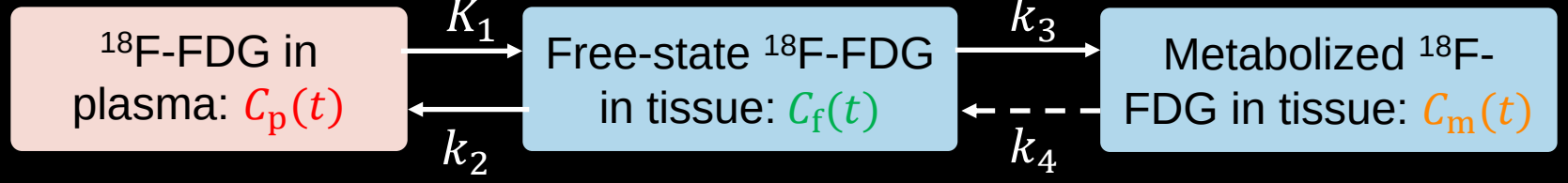
Guobao Wang, UC Davis

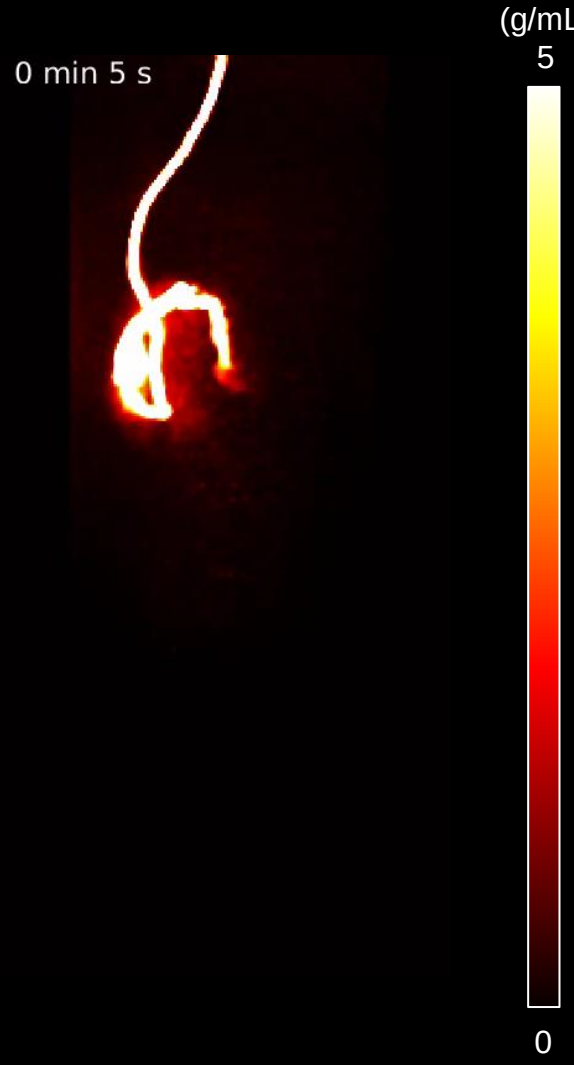
Total-Body Parametric Imaging with ^{18}F-FDG



Wang et al, J Nucl Med 63; 1274-81 (2022)

Measured dynamic ^{18}F-FDG data

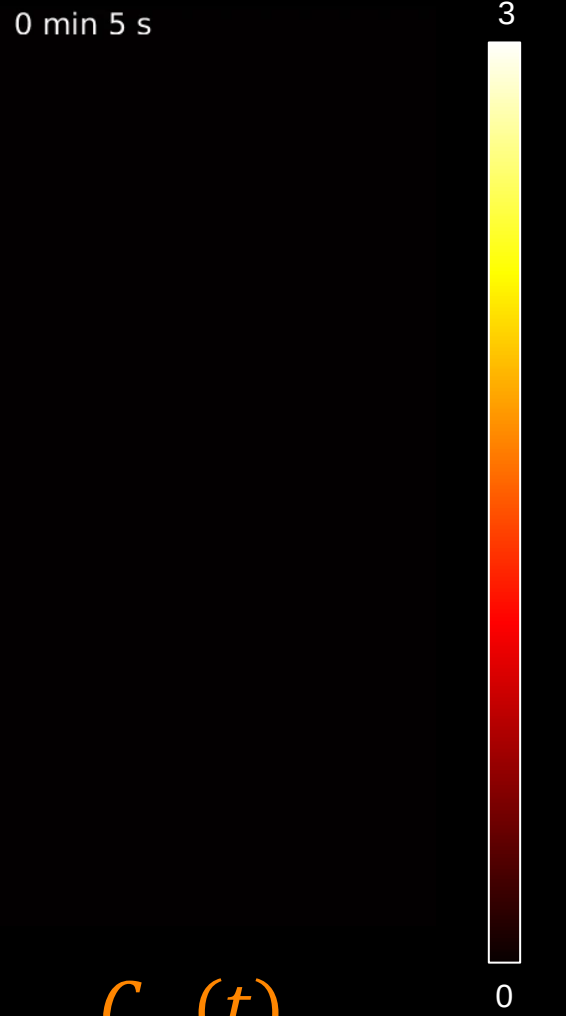




$v_b C_p(t)$

$C_f(t)$

$C_m(t)$

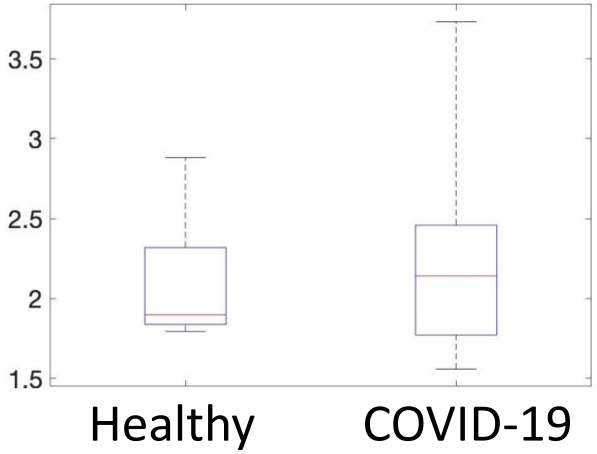


Guobao Wang and Yiran Wang, UC Davis

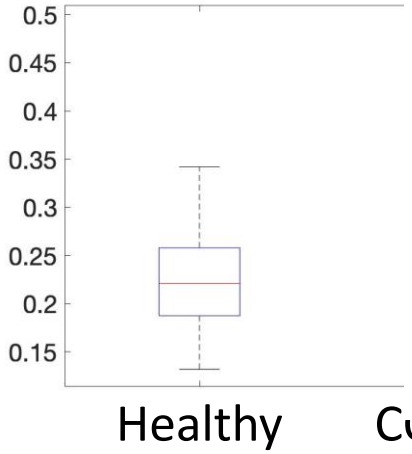
Parametric FDG Imaging in COVID-19 Recovery

- 8 subjects recovering from COVID-1
  13 control subjects
- 60 minute total-body dynamic imaging on uEXPLORER

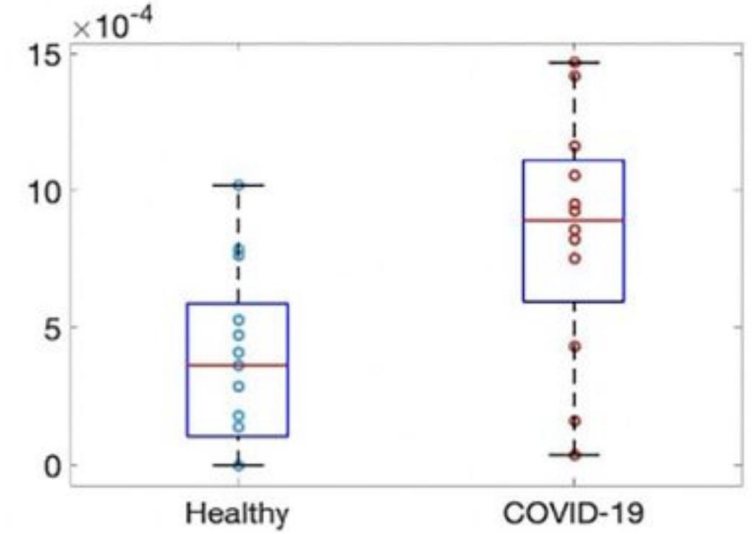
Spine SUV, p=0.60



Spine K_1, p=



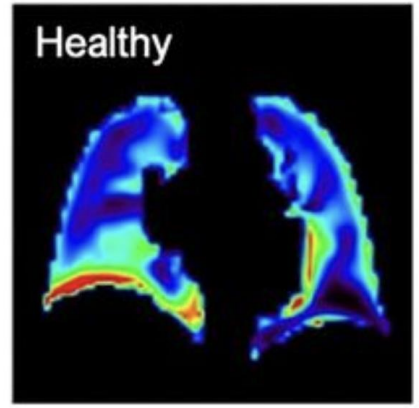
Lung ^{18}F-FDG net influx rate K_i

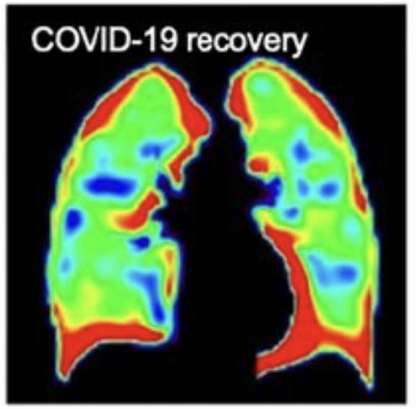


SUV

K_1

Lung K_i



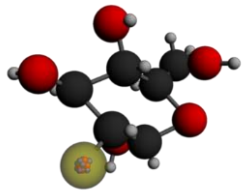


UCDAVIS
EXPLORER MOLECULAR IMAGING CENTER

Wang et al, J Nucl Med 64; 1824-30 (2023)

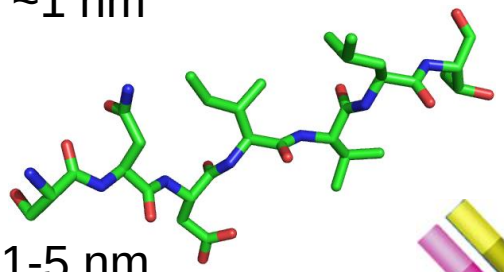
Radiolabeled Agents for PET Imaging

- **Small molecules**
  - Substrates for enzymes, receptor ligands, drugs…



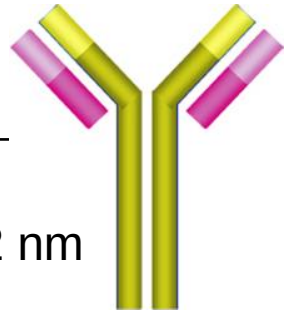
~1 nm

- **Peptides**
  - Receptor targeted, enzyme substrates…



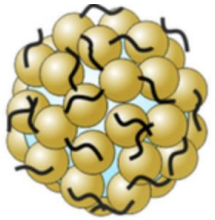
~1-5 nm

- **Antibodies**
  - Full length, minibodies, diabodies



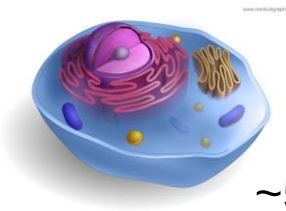
~10 x 2 nm

- **Particles**
  - Liposomes, lipospheres, nanoparticles…



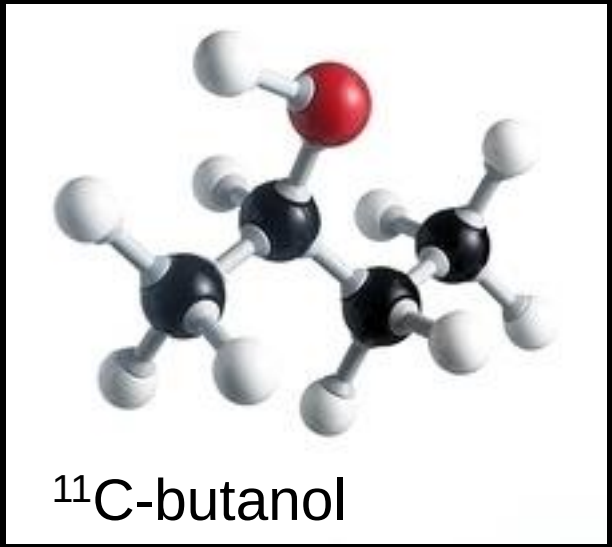
20-100 nm

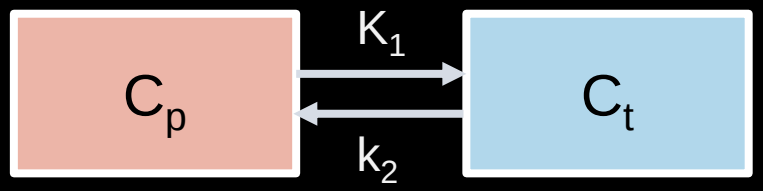
- **Cells**
  - T-cells, stem cells…

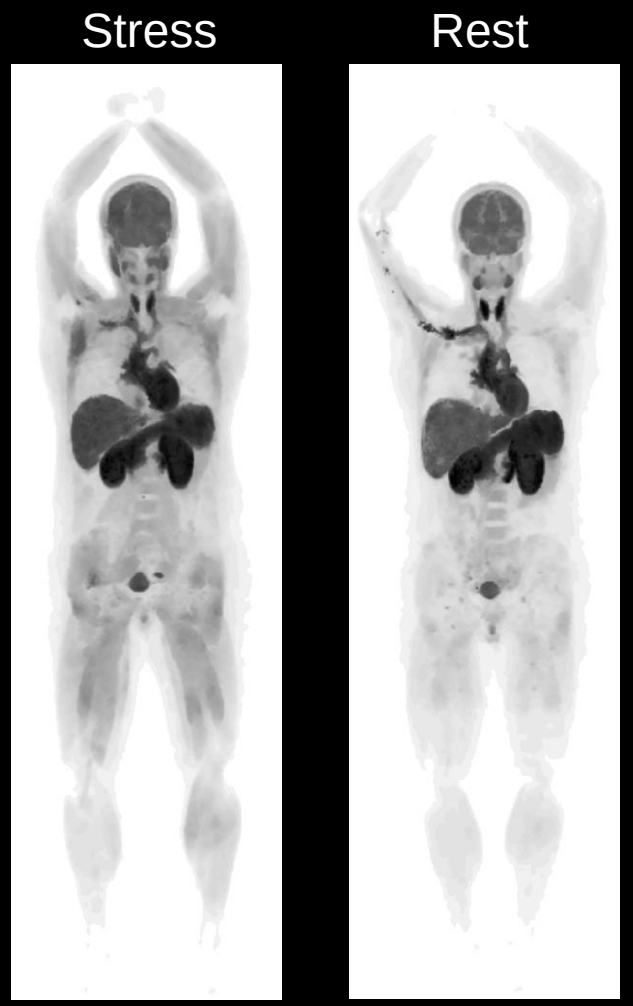


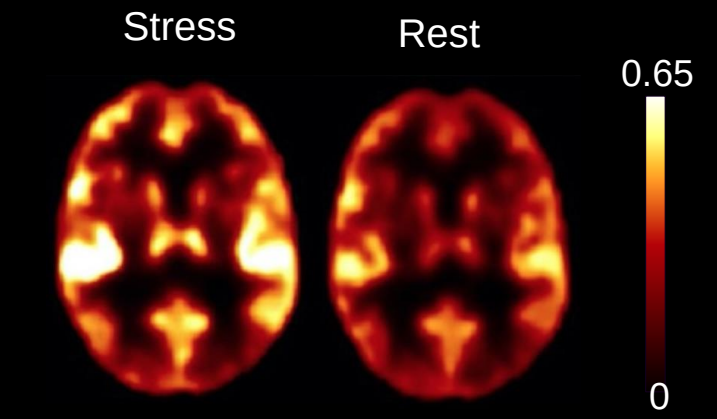
~5-100 µm

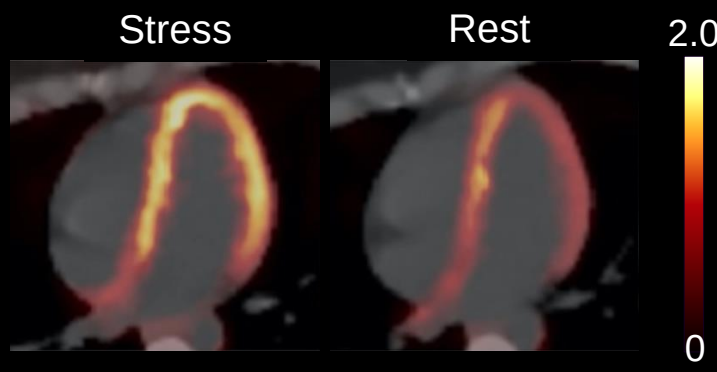
Total-Body Perfusion Imaging

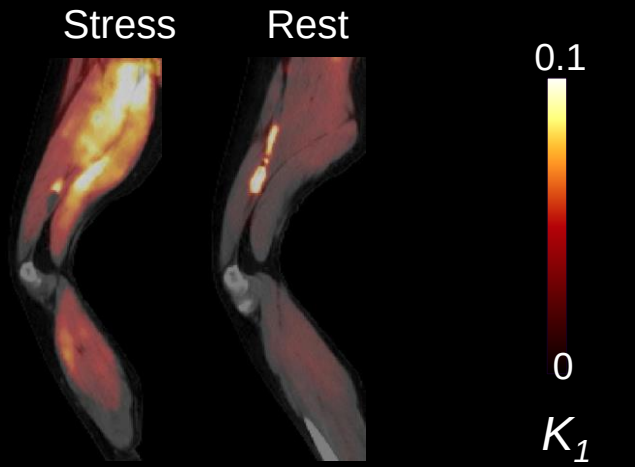






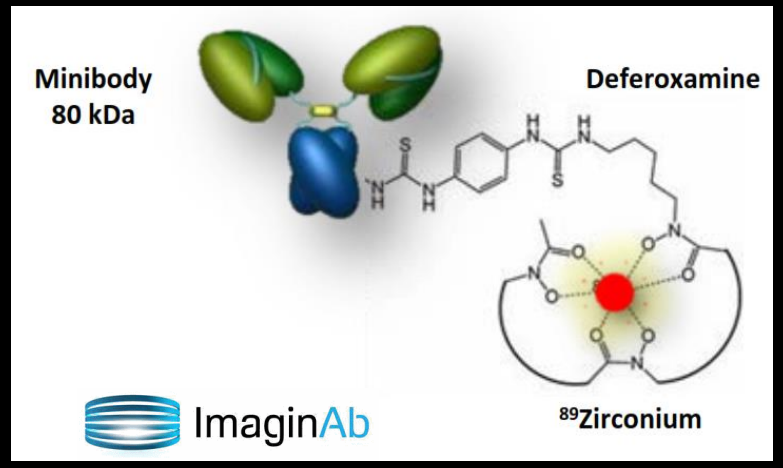






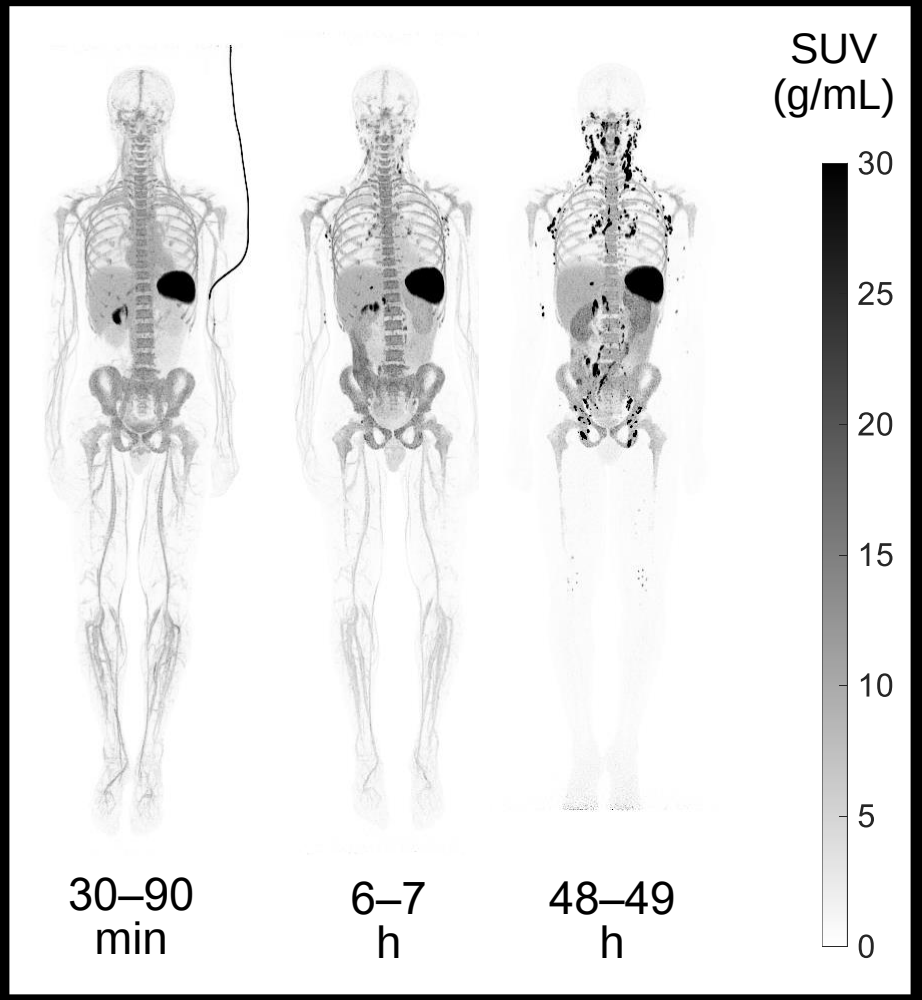
Li et al, J Nucl Med 64; 1831-8 (2023)

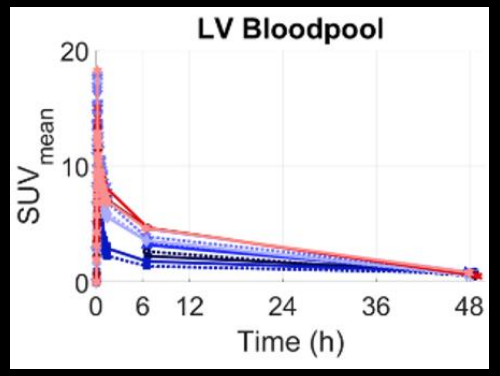
Targeted imaging of CD8+ T cells during COVID-19 recovery

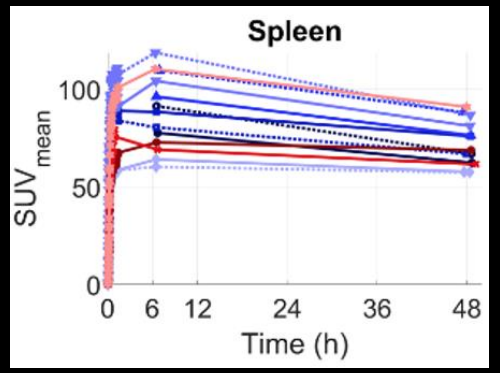


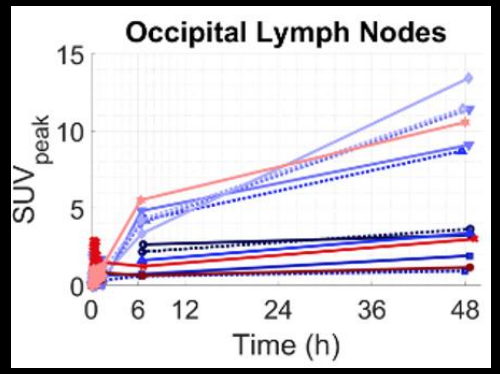
Crefmirlimab is a minibody with high affinity to **human CD8**

0.5 mCi (18 MBq) of ^{89}Zr-Df-Crefmirlimab-Berdoxam







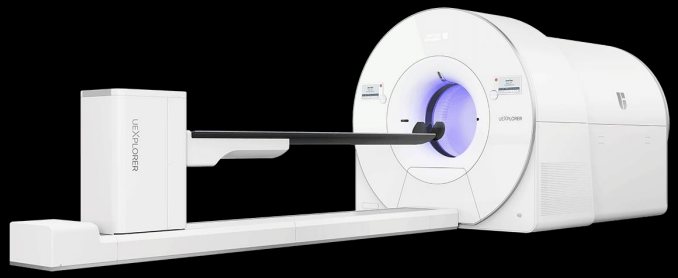


New models needed!

Omidvari et al, Science Advances 9, eadh7968(2023)

Systems Medicine with Total-Body PET/CT

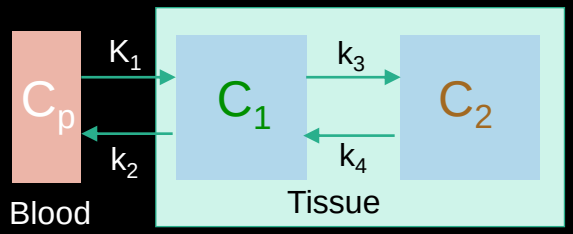
Thomas Beyer and Lalith Kumar Shiyam Sundar
Medical University of Vienna



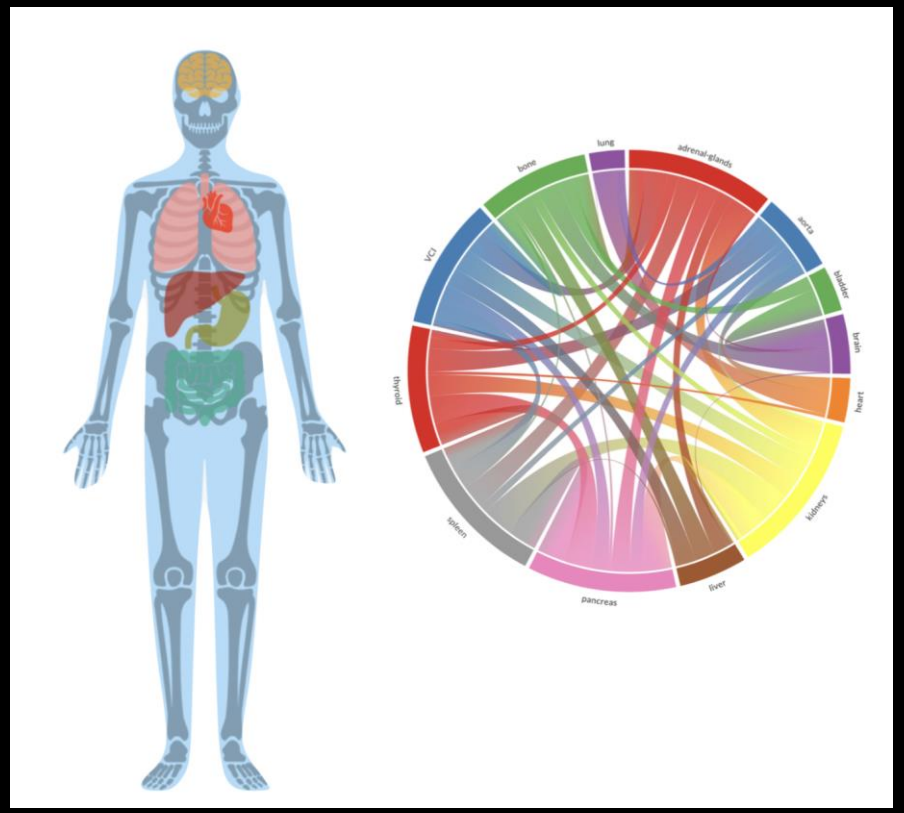
Total-Body PET

PET radiotracers

Dynamic imaging



Tracer kinetic modeling



A powerful new quantitative tool

Acknowledgements

EXPLORER Molecular Imaging Center

Benjamin Spencer
Yiran Wang
Jinyi Qi
Eric Berg
Phu Huynh
Lynda Painting
Kevin Chung

Terry Jones
Elizabeth Li
Abhijit Chaudhari
Xuezhu Zhang
Ofilio Vigil
Aaron Selfridge
Jonathan Poon

Guobao Wang
Negar Omidvari
Fatma Sen
Reimund Beyerlein
Yasser Abdelhafez
Dana Little
and many more…

UNITED IMAGING

Min Xue
Weiping Liu
Chao Wang
Yang Lv
Yu Ding
Ping Zhou
Songsong Tang

Jun Bao
Tianyi Xu
Yun Dong
Xinyu Lv
Debin Hu
Edwin Leung
James Xia

Hongdi Li
Al Zhang
Yong Zhao
Shaohui An
Shaoping Chu
Tao Feng
and many others…

EXPLORER

EXPLORER consortium
Joel Karp (U Penn)
William Moses (retired)

NATIONAL INSTITUTES OF HEALTH

Funding: R35 CA197608, R01 CA206187

Concluding Remarks

- Total-body PET/CT is now a reality
  - ~40 scanners with an axial coverage of > 1 meter installed worldwide
- Total-body PET/CT has impacted clinical care by demonstrating a step change in image quality
  - >250,000 patients have benefited from total-body PET scans since its introduction in 2019
- Total-body PET/CT can quantitatively measure physiology, metabolism and molecular targets across the entire human body
  - A new research tool for systems medicine

It has been a pleasure and privilege to share our story with you

Thank you