Digital Photon Counting PET:
technology powering precision molecular imaging

Piotr Maniawski
Director, Clinical Science,
Advanced Molecular Imaging & CT Oncology

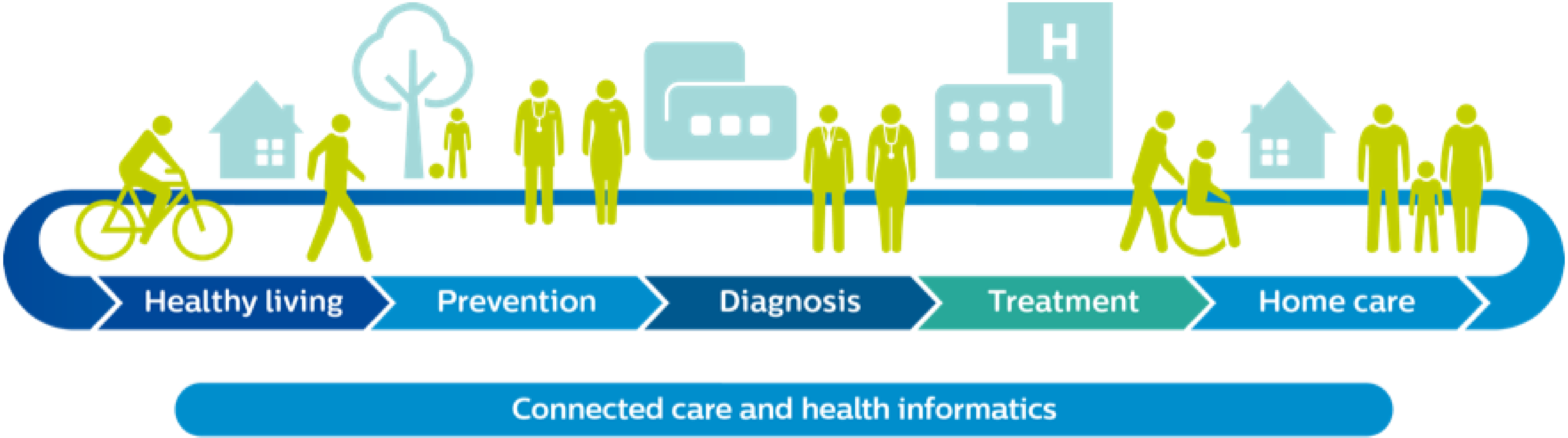
PHILIPS

The success of personalized medicine depends on having accurate diagnostic tests that identify patients who can benefit from targeted therapies.

Margaret A. Hamburg, M.D., and Francis S. Collins, M.D., Ph.D.
N Engl J Med 2010; 363:301-304, “The Path to Personalized Medicine”

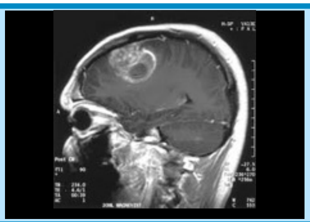
Our corporate strategy revolves around the continuum of care

Precision Health along the Care Continuum

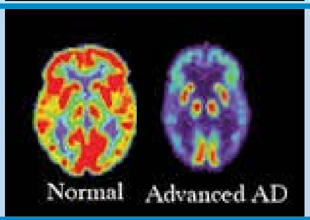


Imaging is central to precision medicine

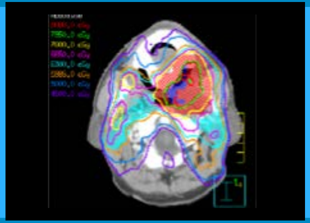
Localization and staging of disease



Diagnose a variety of conditions



Enables precise therapies



Early interventions through screening

Pervasive accessibility

Our development efforts emphasize the *Five I's* of Imaging

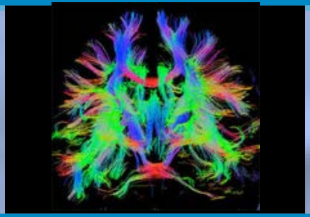
Drive patient care

Improve quality and patient experience

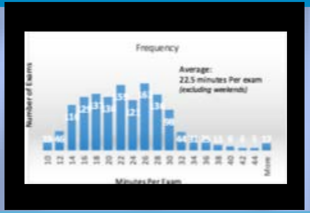
Reduce waste, inefficiency, and cost

Intuitive

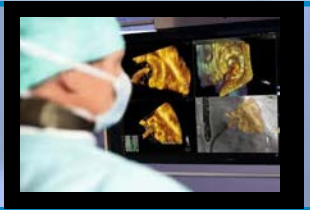
Intelligent



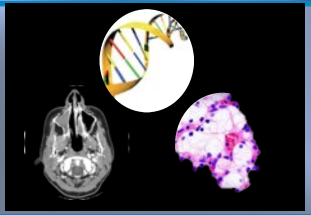
Industrialized

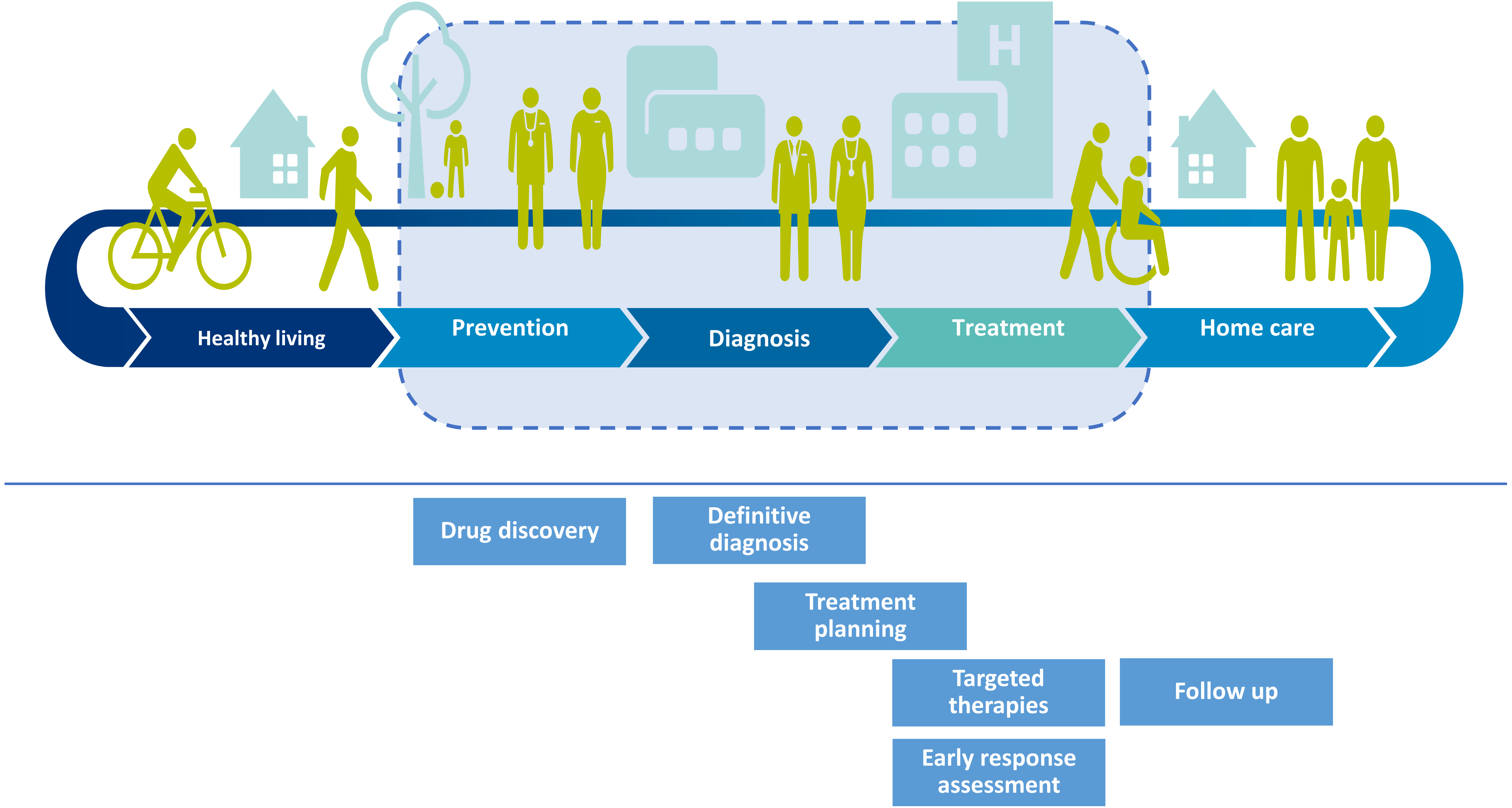


Integrative

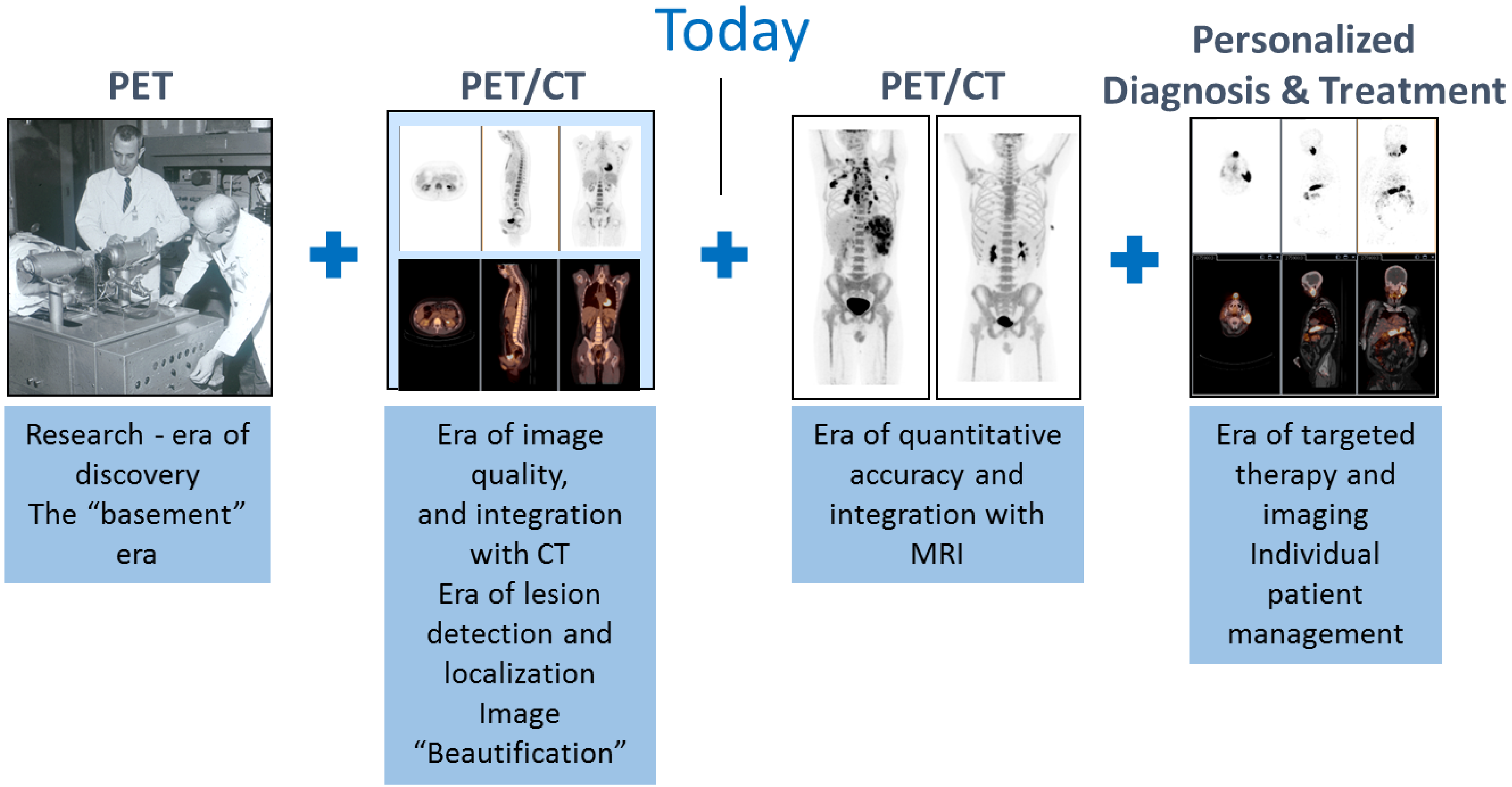


Individualized

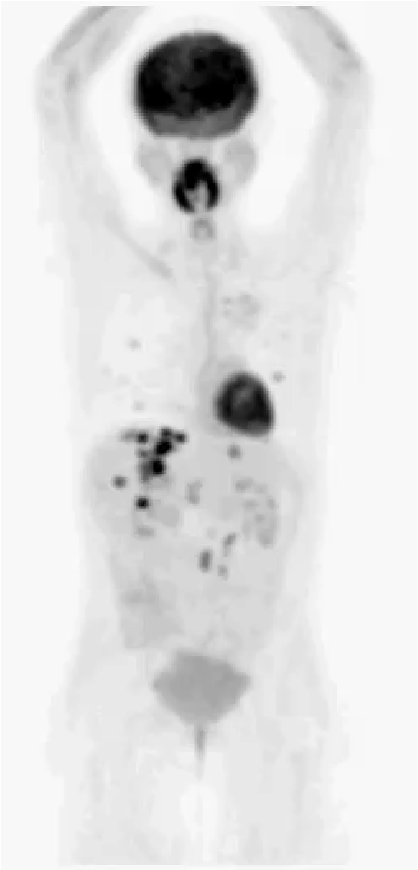




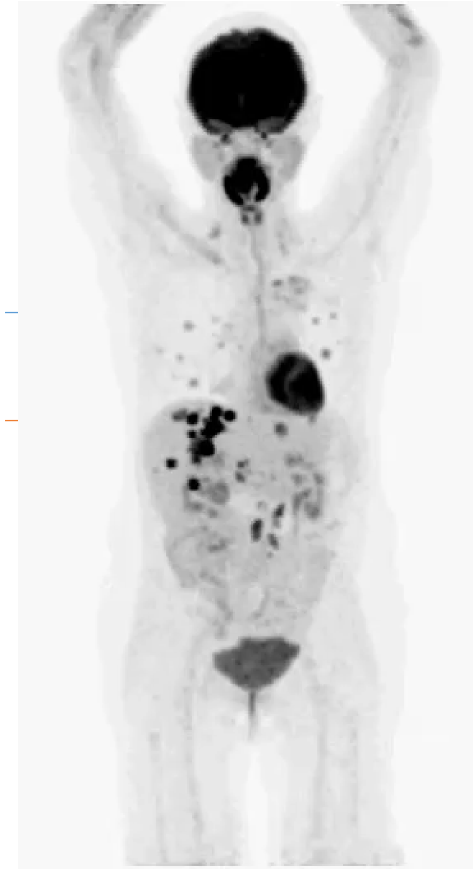
Healthy living
Prevention
Diagnosis
Treatment
Home care
Drug discovery
Definitive diagnosis
Treatment planning
Targeted therapies
Follow up
Early response assessment

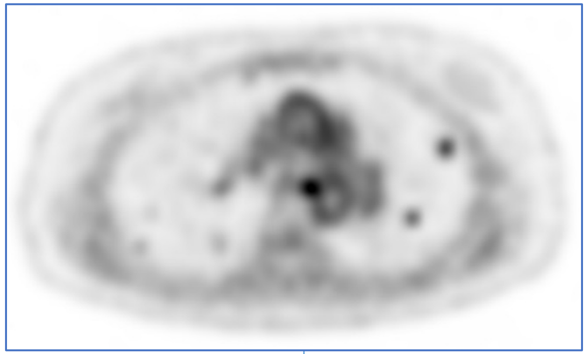

Today
PET
PET/CT
PET/CT
Personalized
Diagnosis & Treatment
Research - era of
discovery
The "basement"
era
Era of image
quality,
and integration
with CT
Era of lesion
detection and
localization
Image
"Beautification"
Era of quantitative
accuracy and
integration with
MRI
Era of targeted
therapy and
imaging
Individual
patient
management

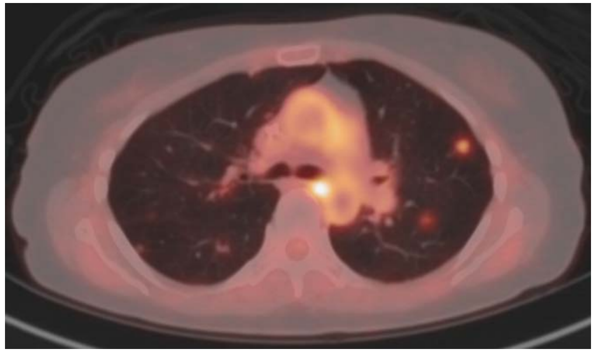
PET Technology 2007

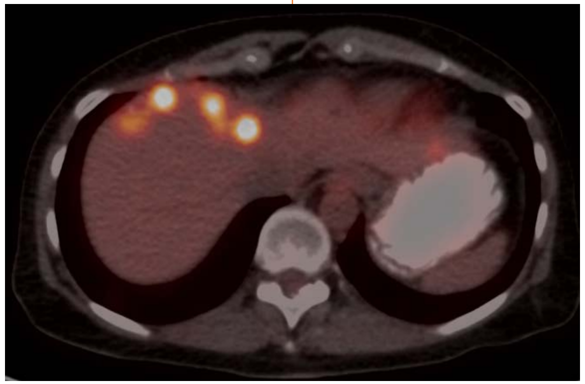


PET Technology 2017









Cancer Type	PET/CT Staging Accuracy
Non–small cell lung*	84% to 93%
Colorectal**	89% to 97%
Lymphoma***	99%

Patient data courtesy of Dr. M. Knopp
"Results from case studies are not predictive of results in other cases. Results in other cases may vary."

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Wright Center of Innovation in Biomedical Imaging

*Lardinois D et al. N Engl J Med. 2003;348:2500–2507

**Cohade C et al J Nucl Med. 2003;44:1797–1803

***Freudenberg LS et al Eur J Nucl Med Mol Imaging. 2004;31:325–329

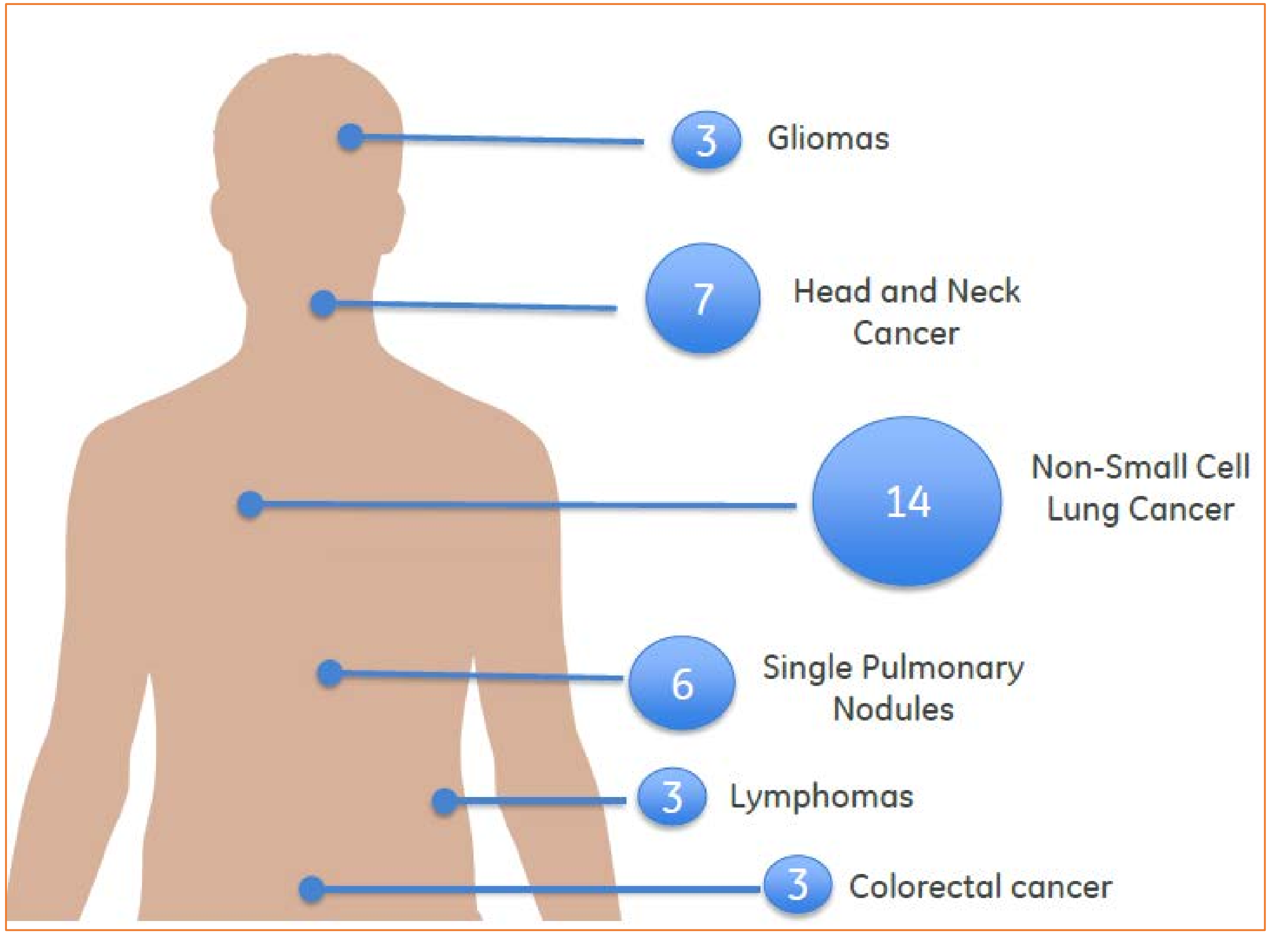
Definitive diagnosis

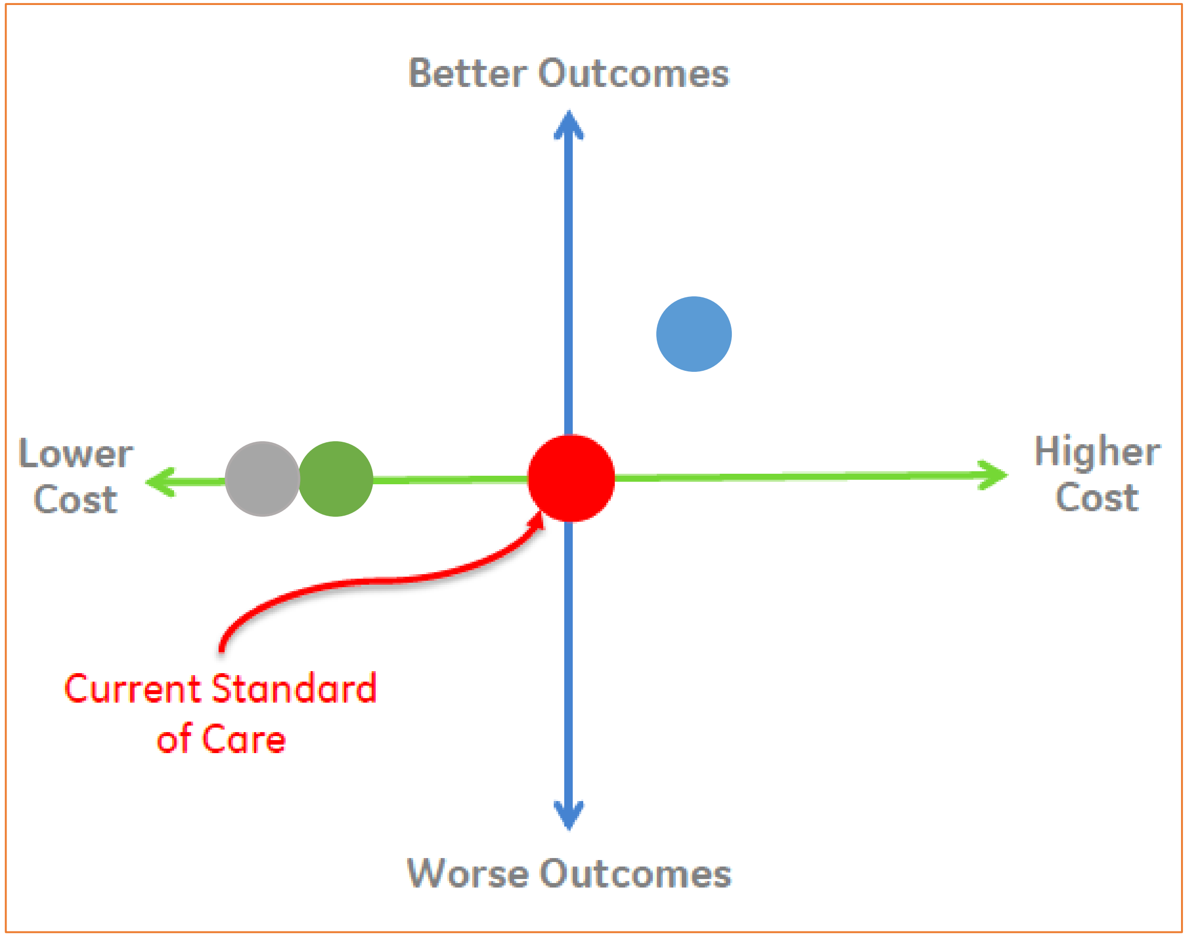
Cancer Type	PET/CT Staging Accuracy	Impact on Patient Management
Non–small cell lung	84% to 93%	Stage was discordant on PET/CT and conventional imaging in 50.6% of patients (41.1% upstaged, 9.5% down staged), with high management impact (change in treatment modality or curative intent) in 42.3% of patients.*
Colorectal	89% to 97%	Structural lesion suggestive of recurrence - Additional disease in 48.4%; change in management in 65.6% Resectable pulmonary or hepatic metastases - Additional disease in 43.9%; change in management in 49%
Lymphoma	99%	Researchers found that PET-CT upstaged 159 (14%) and down staged 74 (6%) patients.***

*Gregory DL et al, J Nucl Med. 2012 Jul;53(7):1007-15
**Scott el al, J Nucl Med. 2008 Sep;49(9):1451-7.
***Barrington SF, Blood. doi: 10.1182/blood-2015-11-679407

Definitive diagnosis

PET/CT Cost Effectiveness Studies





Data courtesy of David Lee, PhD, GE Healthcare

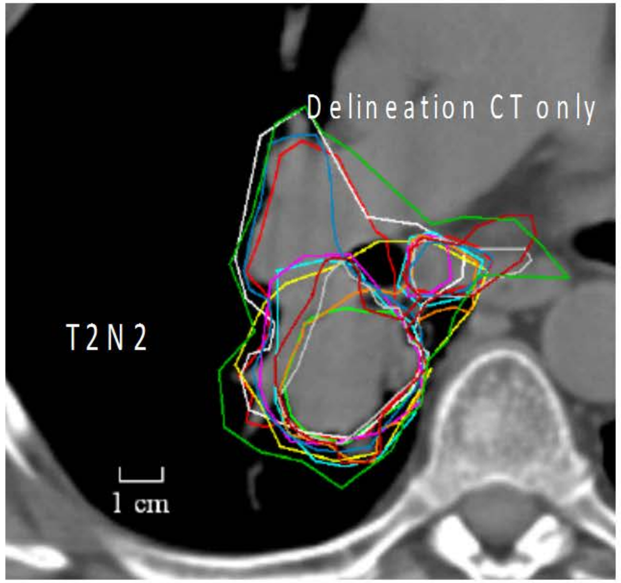
- FDG PET/CT for staging of liver metastasis (surgery benefit)
- Preoperative FDG PET/CT for staging of lung cancer (avoid thoracotomy)
- FDG PET/CT for H&N cancer treatment response (neck dissection)

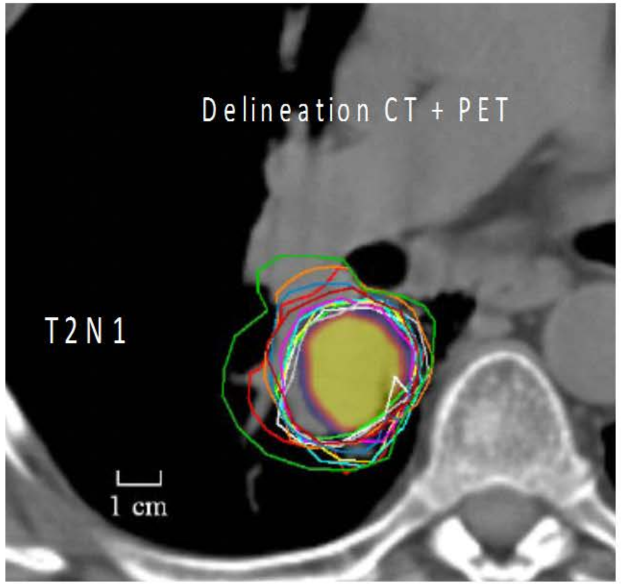
Definitive diagnosis

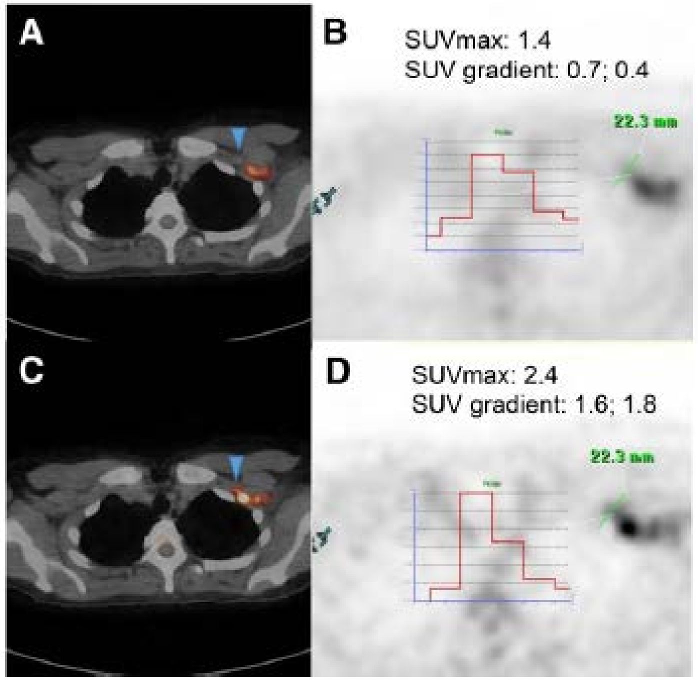
Steenbakkers et al, IJROBP 2005

Lung case: T2N2

11 observers from 5 institutions, 22 patients







"Implementing FDG-PET in radiation therapy treatment planning has a **major impact on accurate target definition and the prediction of treatment outcome**. For high precision radiotherapy, target definition based on CT alone results in too great a variability between radiation oncologists.

With the addition of FDG-PET, radiotherapy can be delivered more accurately allowing safe dose escalation"

Steenbakkers et al, NKI-AVL Amsterdam, Medica Mundi vol 51/2+3, November 2007

Image Quality and Diagnostic Performance of a Digital PET Prototype in Patients with Oncologic Diseases: Initial Experience and Comparison with Analog PET

Nghi C. Nguyen[1], Jose L. Vercher-Conejero[1], Abdus Sattar[2], Michael A. Miller[3], Piotr J. Maniawski[3], David W. Jordan[1], Raymond F. Muzic, Jr.,[1] Kuan-Hao Su[1], James K. O'Donnell[1], and Peter F. Faulhaber[1]

[1]Department of Radiology, Case Western Reserve University/University Hospitals Case Medical Center, Cleveland, Ohio; [2]Epidemiology and Biostatistics, School of Medicine, Case Western Reserve University, Cleveland, Ohio; and [3]Philips Healthcare, Advanced Molecular Imaging, Cleveland, Ohio

We report our initial clinical experience for image quality and diagnostic performance of a digital PET prototype scanner with time-of-flight (DigitalTF), compared with an analog PET scanner with time-of-flight (GeminiTF PET/CT). **Methods:** Twenty-one oncologic

Key Words: digital PET; direct photon counting; ^{18}F-FDG PET; oncology

J Nucl Med 2015; 56:1378–1385
DOI: 10.2967/jnumed.114.148338

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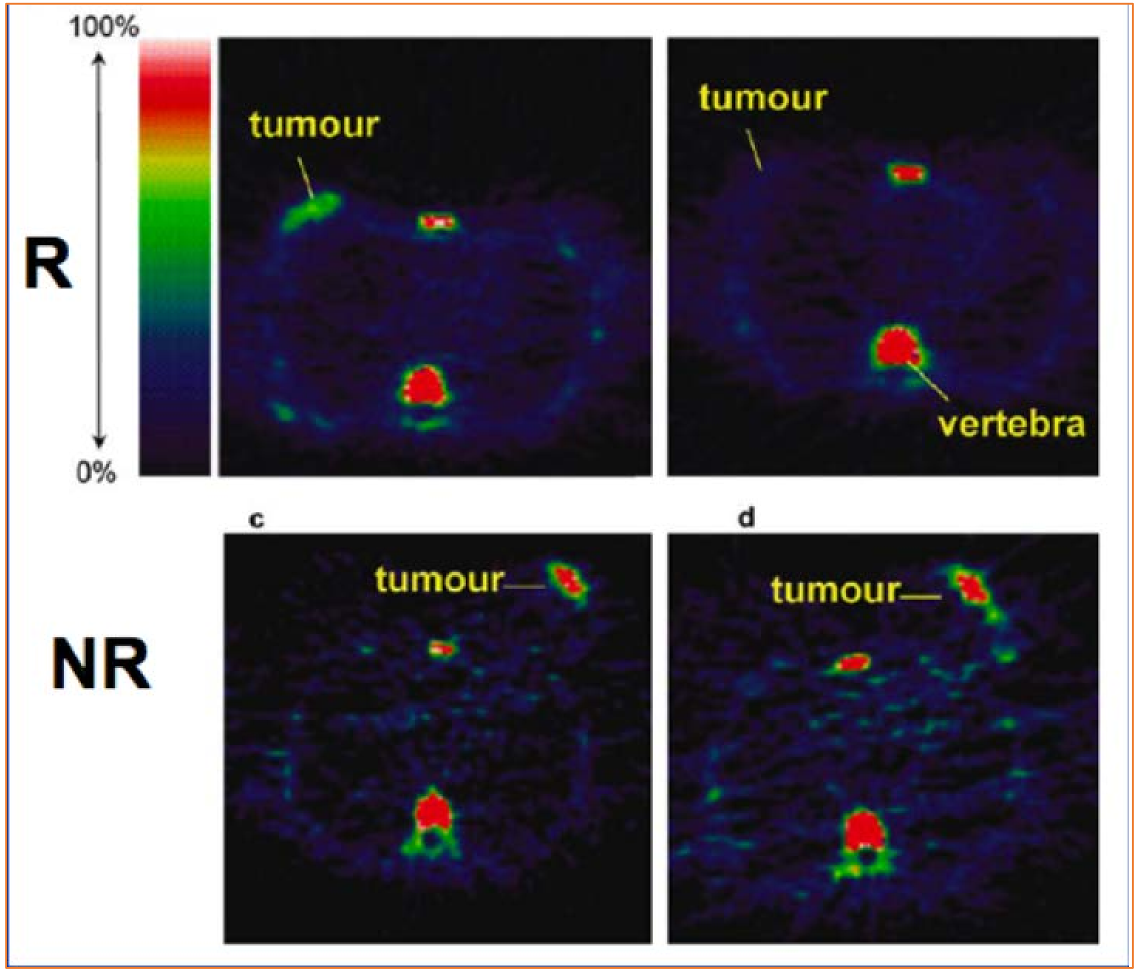
University Hospitals Case Medical Center

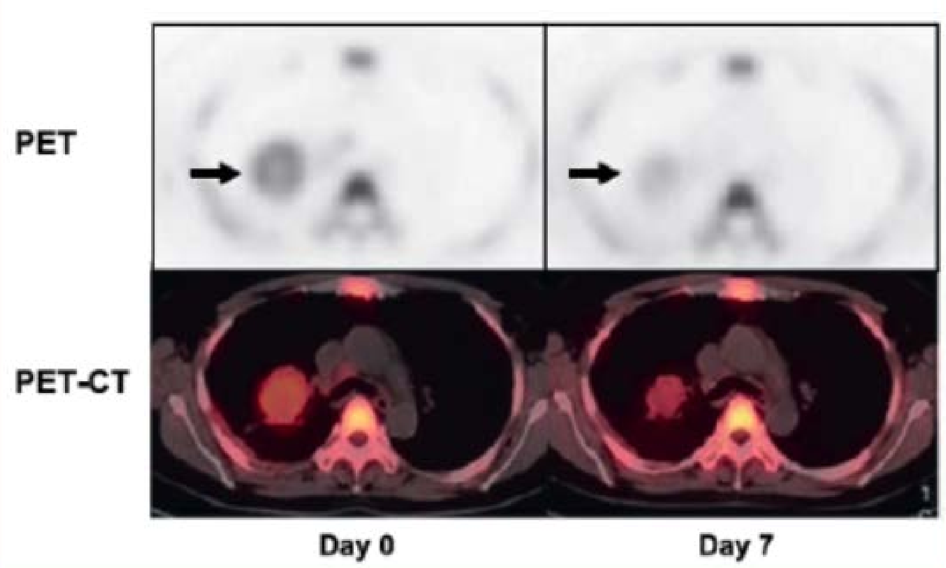
Treatment planning

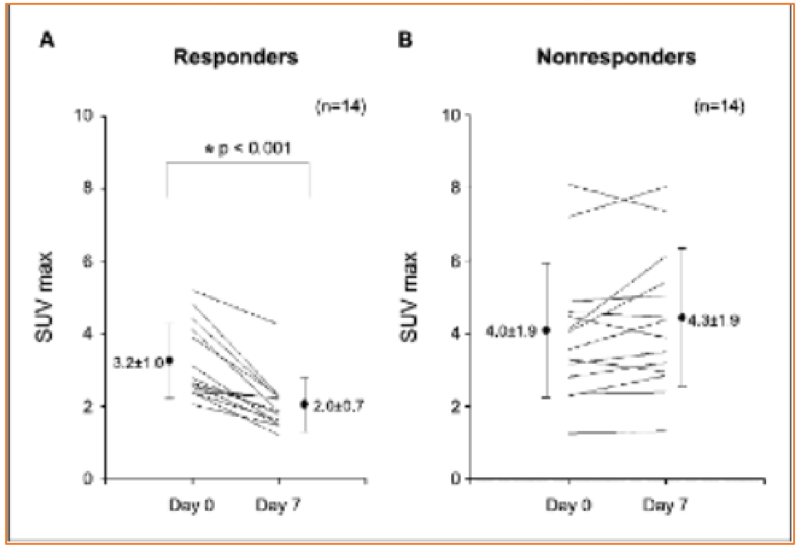
Pre Therapy 1 Week Post Therapy



Kenny et al, Eur J Nucl Med Mol Imaging. 2007 Sep;34(9):1339-47.

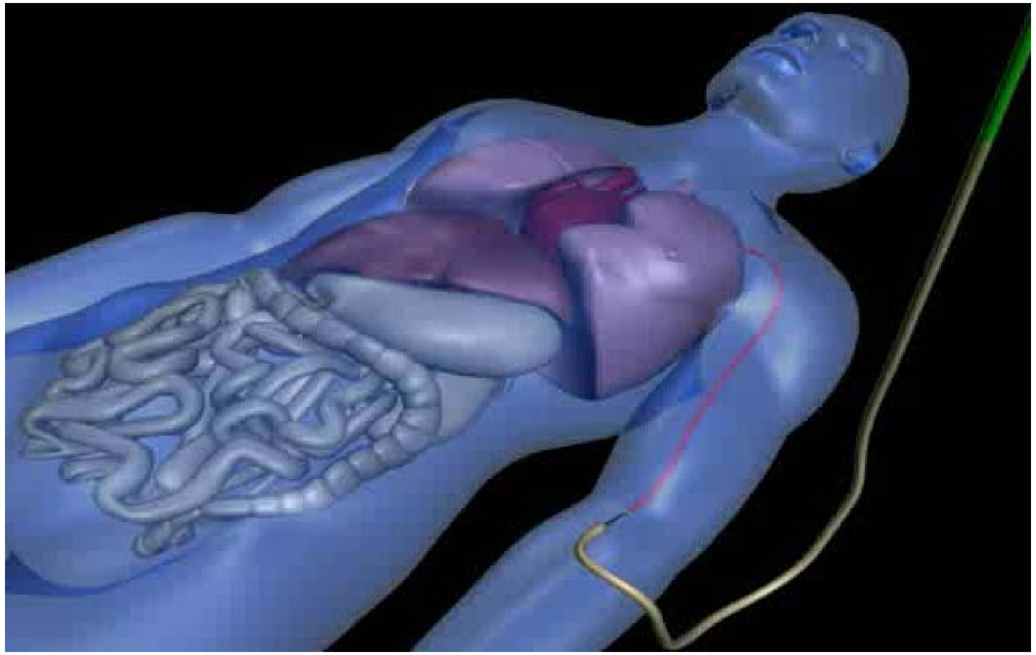
Pre Therapy 1 Week Post Therapy

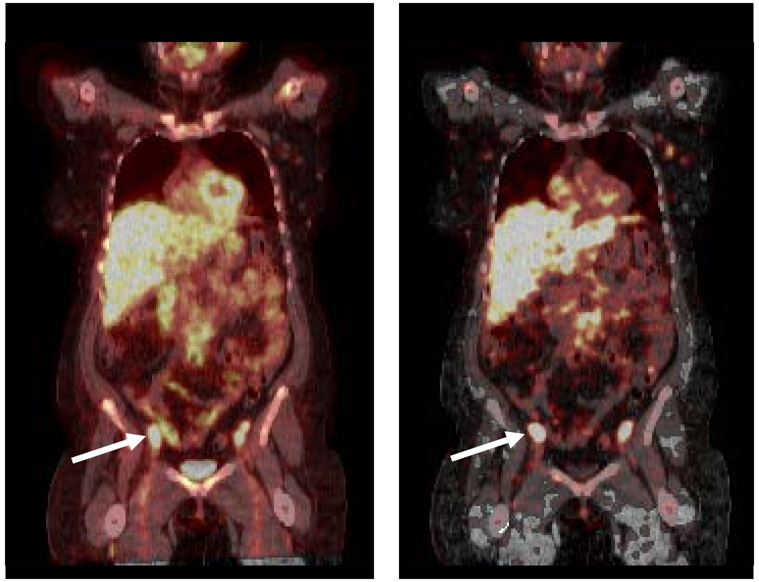




Sohn et al, Clin Cancer Res 14:7423, 2008

Early response assessment





"… Imaging of targeted drugs can be a valuable tool for selection of those patients that most likely will benefit from expensive treatments by measuring drug kinetics in the individual patient, for early selection of promising drugs in drug development, and for radiation dosimetry of therapy with radiolabelled targeted drugs."

M. Lubberink, N. Rizvi O. Hoekstra, G. van Dongen, VUmc Amsterdam

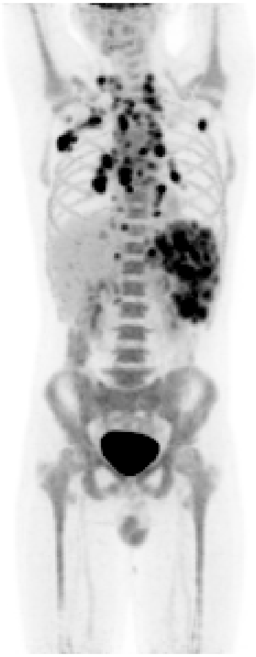
- [18F]FDG (left) and 6 days p.i. [89Zr]ibritumomab tiuxetan ([89Zr]Zevalin) PET image of a patient with Non-Hodgkin lymphoma showing high Zevalin uptake in parailiac lymph nodes.

- FDG uptake in the lymph nodes is only moderate (SUV=2). Images were acquired on a GEMINI TF-64 PET-CT scanner (Philips Healthcare, Cleveland).

Targeted therapies

Molecular imaging for visualization and quantification of individualized targeted cancer therapy. M. Lubberink, N. Rizvi O. Hoekstra, G. van Dongen, VUmc Amsterdam, Medicamundi 54.2 , Follow up

Cancer Staging



Therapy Response

Patient data courtesy of University Hospitals, Cleveland
"Results from case studies are not predictive of results in other cases. Results in other cases may vary."

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University Hospitals Case Medical Center

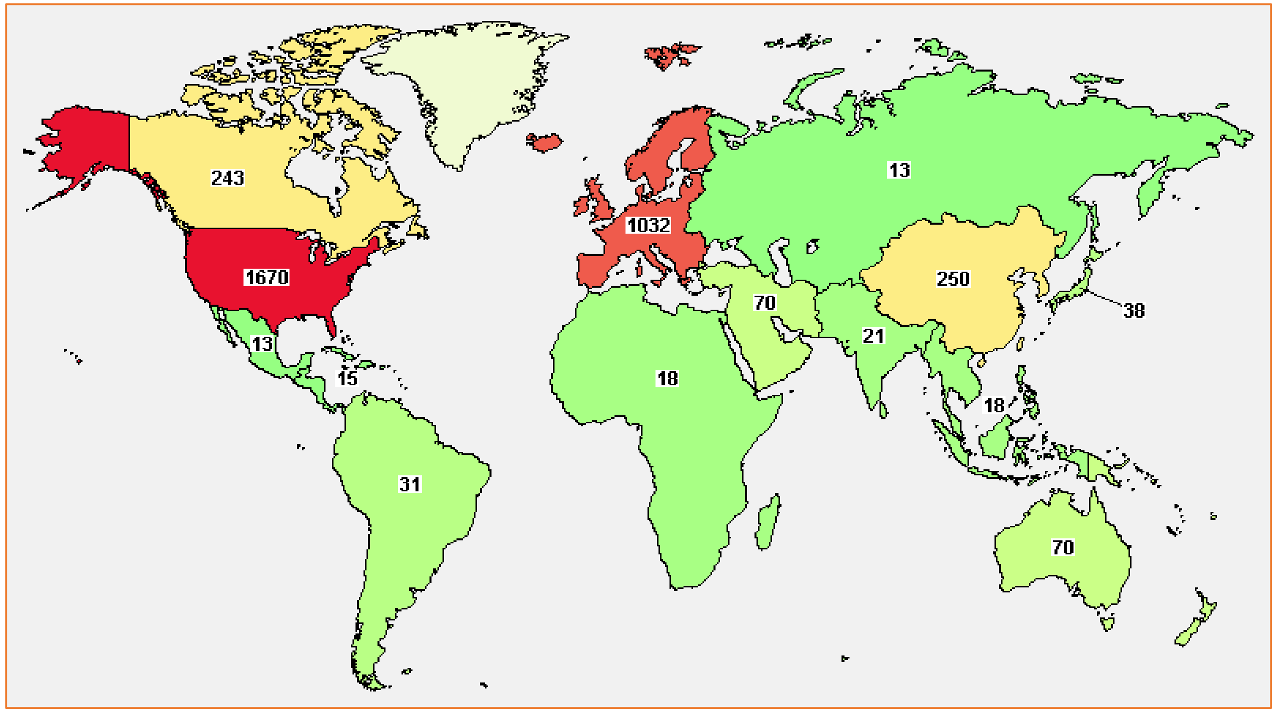
Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group

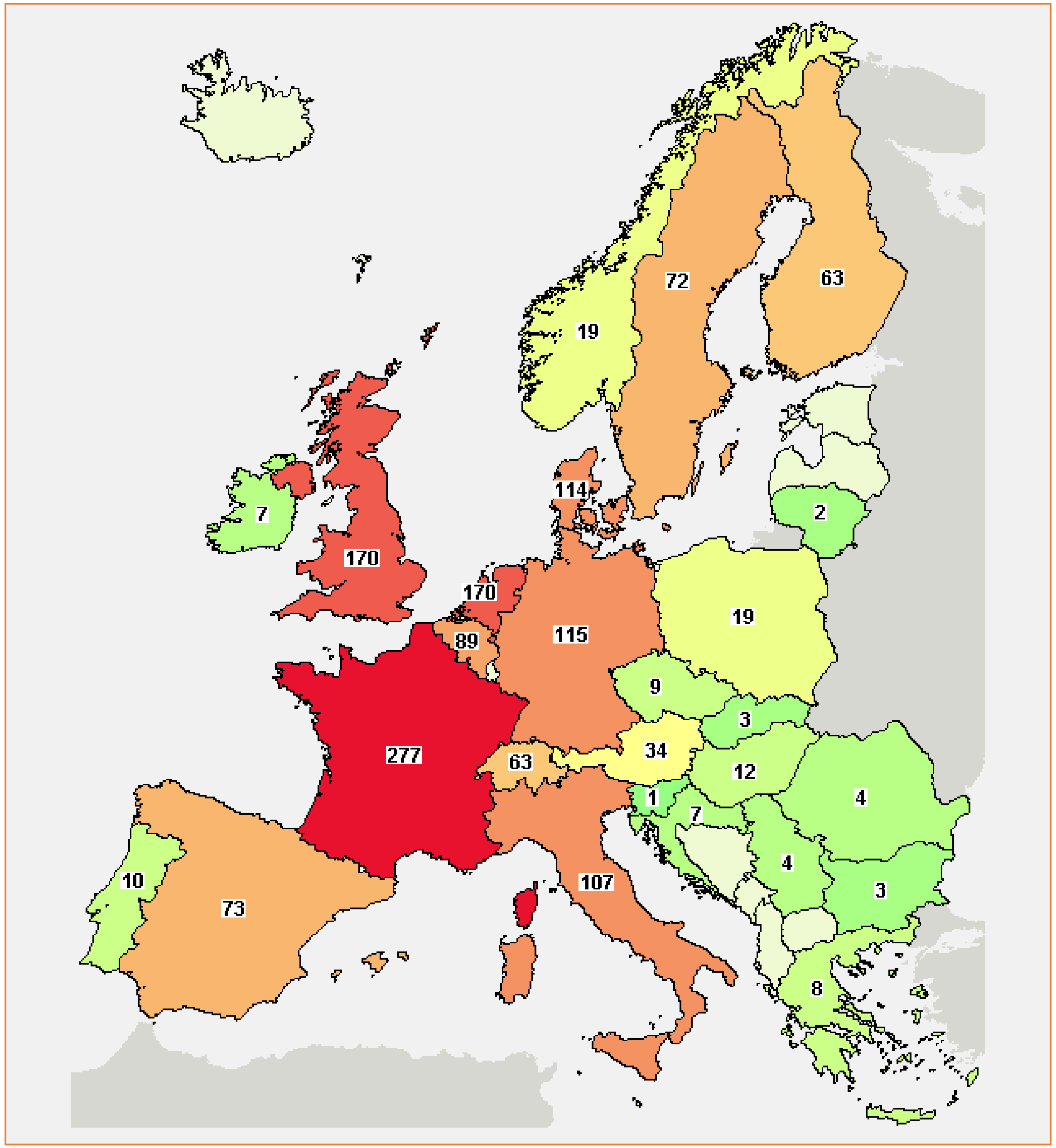
Studies, Including ≥ 50 Patient Populations With HL or Aggressive NHL or FL, Reporting Outcomes According to Visual Assessment With End-of-Treatment PET

Study	Year	No. of Patients	Disease and Stage	NPV	PPV
Spaepen K et al: Br J Haematol 115:272-278, 2001	2001	60	IIA-IVB HL	100	91
Cerci et al	2010	50	I-IV HL (patients in CRu/PR on CT)	100	92
Engert et al	2012	739	IIB-IV HL	95	NA
Barnes et al	2011	96	I-II nonbulky HL	94	46
Spaepen et al	2001	93	Aggressive NHL	100	70
Micallef et al	2011	69	DLBCL	90	50
Pregno et al	2012	88	DLBCL	100	82

PET-CT is the standard of care for remission assessment in FDG-avid lymphoma.

Sally F. Barrington et al, J Clin Oncol 32:3048-58, 2014

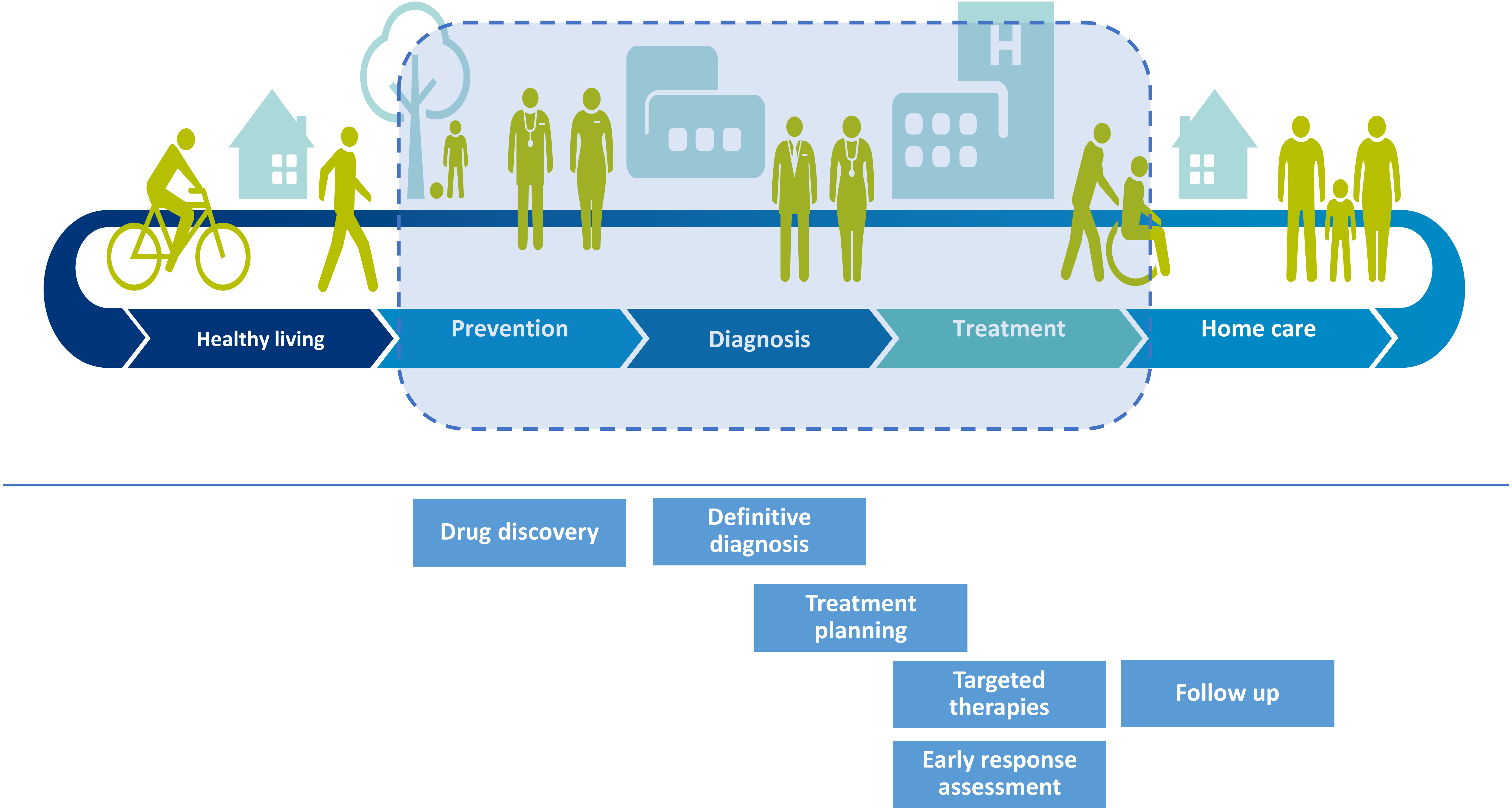




- ✓ First in man distribution studies
- ✓ Hit the target?
- ✓ Dosimetry for radiotherapy studies
- ✓ Speed up studies
- ✓ New endpoints for clinical trials
- ✓ More efficient go/ no-go decisions earlier in the process
- ✓ Patient selection
- ✓ Monitoring treatment

Drug discovery

ClinicalTrials.gov



Healthy living
Prevention
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Drug discovery
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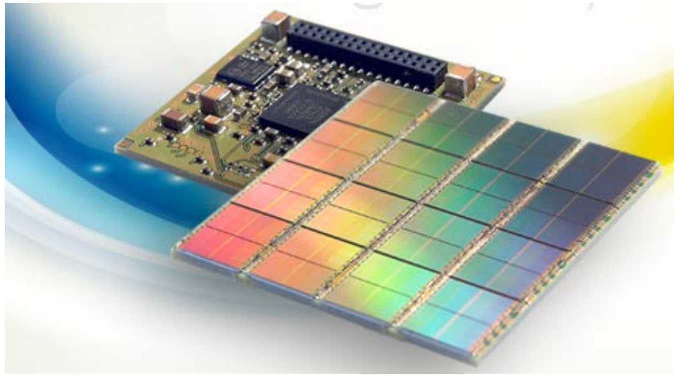
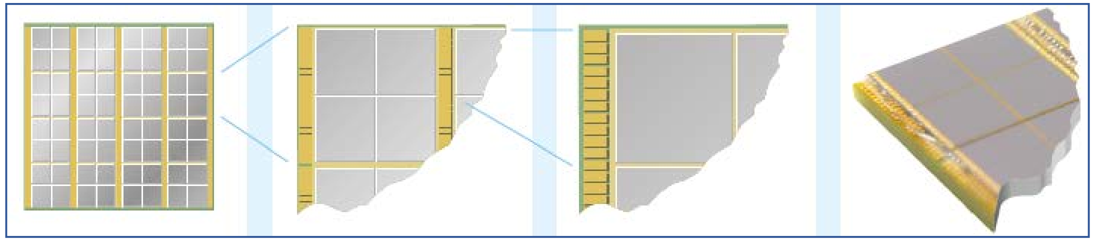
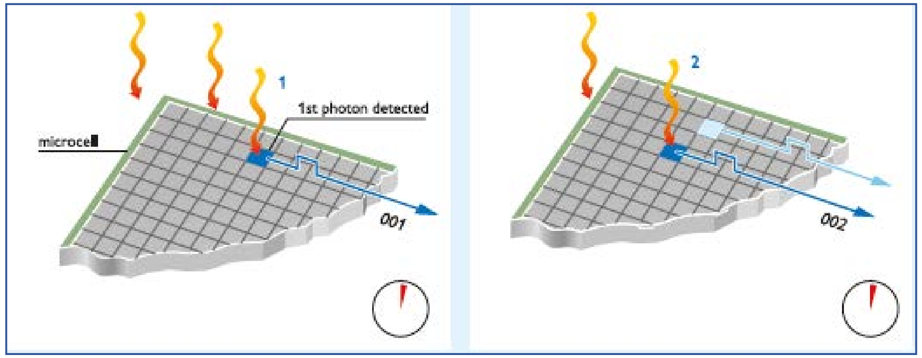
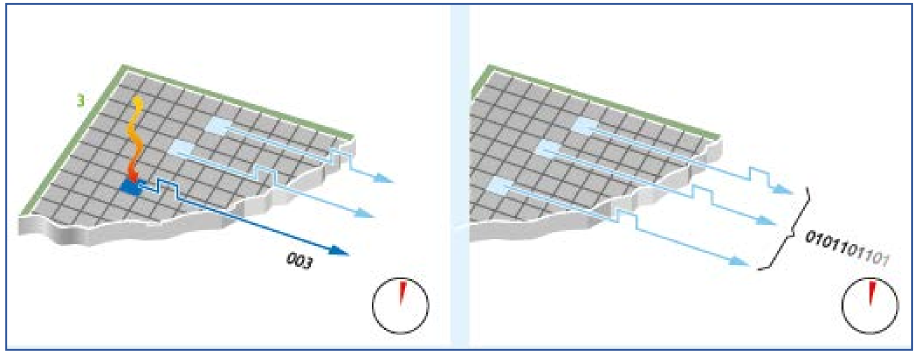
Digital photon counting PET

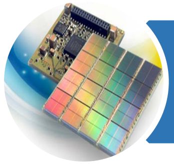
Digital Photon Counting



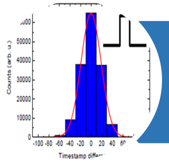








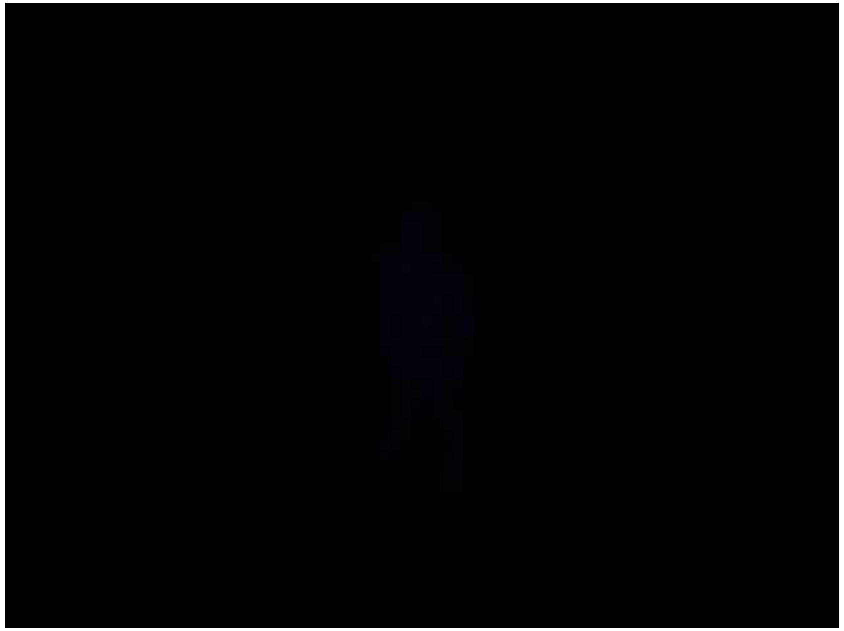
Digital Photon Counting

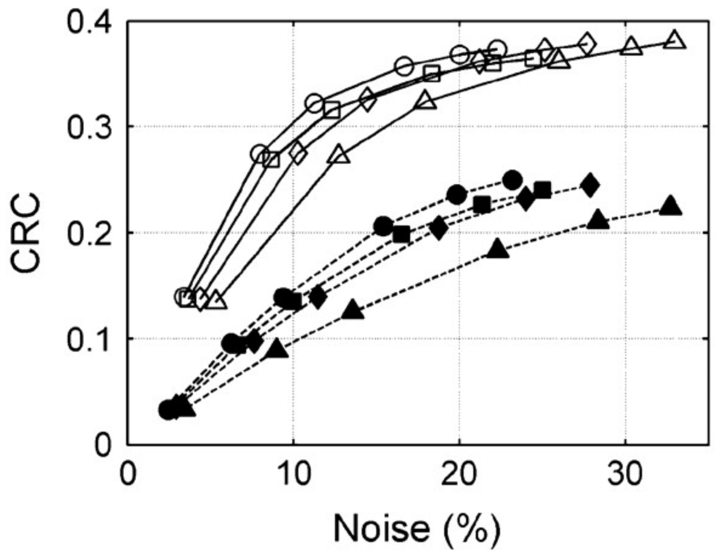


Digital Time of Flight

1:1 Coupling

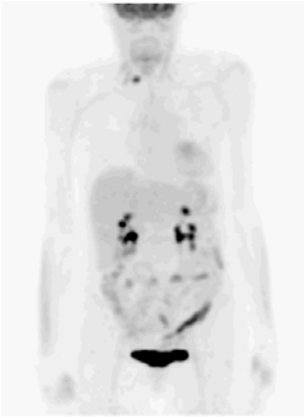
Digital Time of Flight – Sensitivity Gain



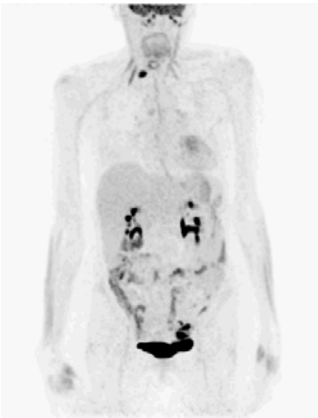


Benefit of Time-of-Flight in PET: Experimental and Clinical Results, Joel S. Karp, et al *J Nucl Med March 2008 vol. 49 no. 3 462-470*

Analog *
Time of Flight



Digital
Time of Flight



Patient data courtesy of University Hospitals, Cleveland
"Results from case studies are not predictive of results in other cases. Results in other cases may vary."

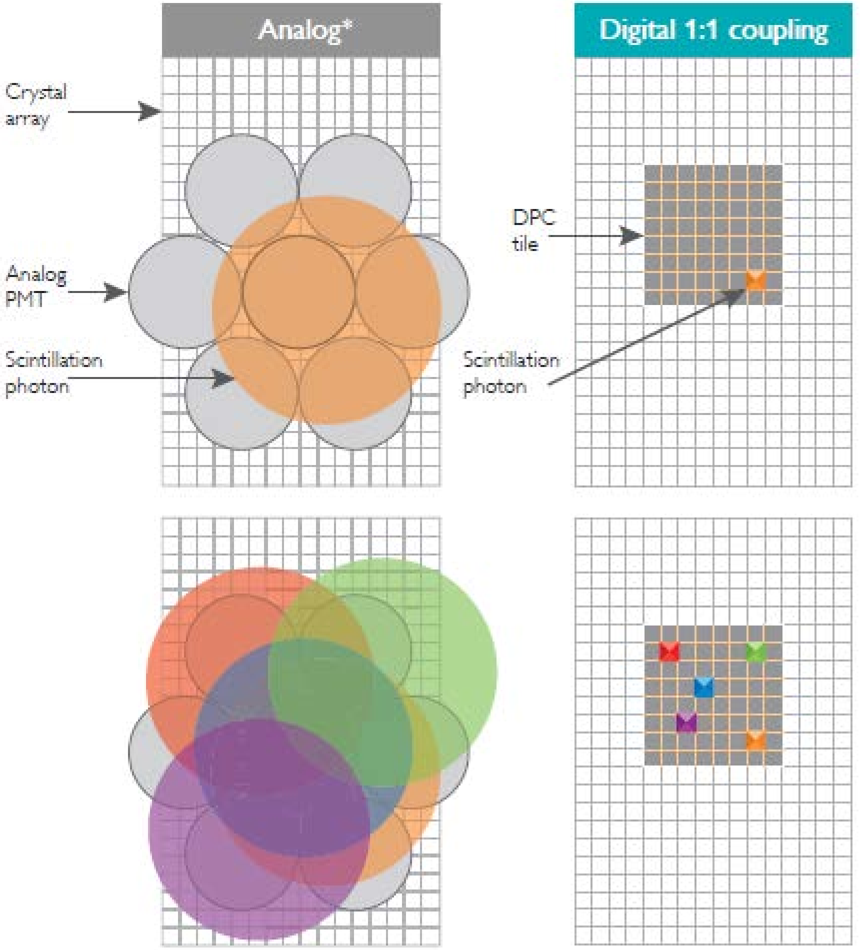
* Analog (*GEMINI TF)* to digital comparison

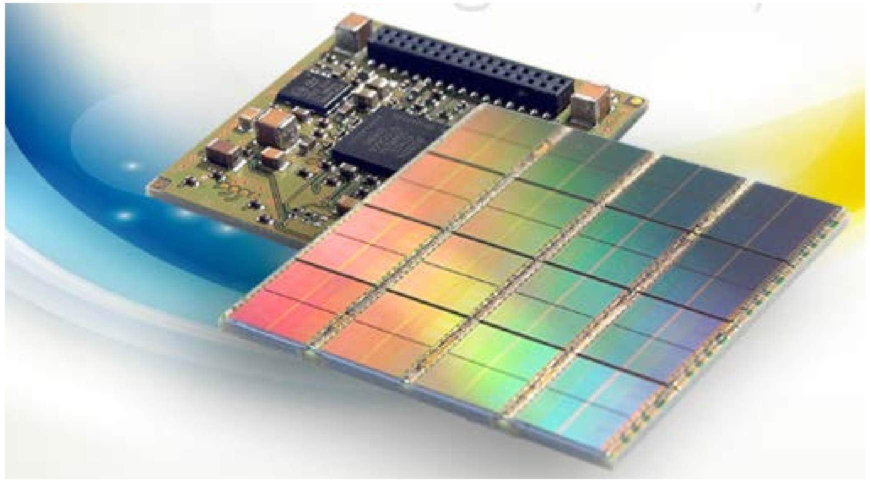
School of Medicine Case Western Reserve University
University Hospitals Case Medical Center

Digital Photon Counting - Geometry

Many-to-many coupling

One-to-one coupling





- 1:1 coupling eliminates need for position decoding
- Timing and energy calibrations per crystal
- Improved timing resolution
- Reduced dead time
- Increased count rate performance
- Early digitization eliminates as much as possible analog noise and distortion.

Description of the Digital PET/CT System

Presentation includes performance results from:

- Investigational device installed at The Wright Center of Innovation in Biomedical Imaging at The Ohio State University
- Multiple systems installed at Philips

Detector design	Digital Photon Counting
Number of detectors	23,040
Number of crystals	23,040
Crystal size	4 x 4 x 19 mm
Crystal material	LYSO
Ring diameter	76.4 cm
Transaxial FOV	Up to 676 mm
Axial FOV	164 mm
Coincidence window size[1]	4.0 ns
Lower level discriminator	450 keV

Characterization of the Vereos Digital Photon Counting PET System
Michael A. Miller, Jun Zhang, Katherine Binzel, Jerome Griesmer, Thomas Laurence, Manoj Narayanan, Deepa Natarajamani, Sharon Wang, Michael V. Knopp
SNMMI 2015

THE OHIO STATE UNIVERSITY
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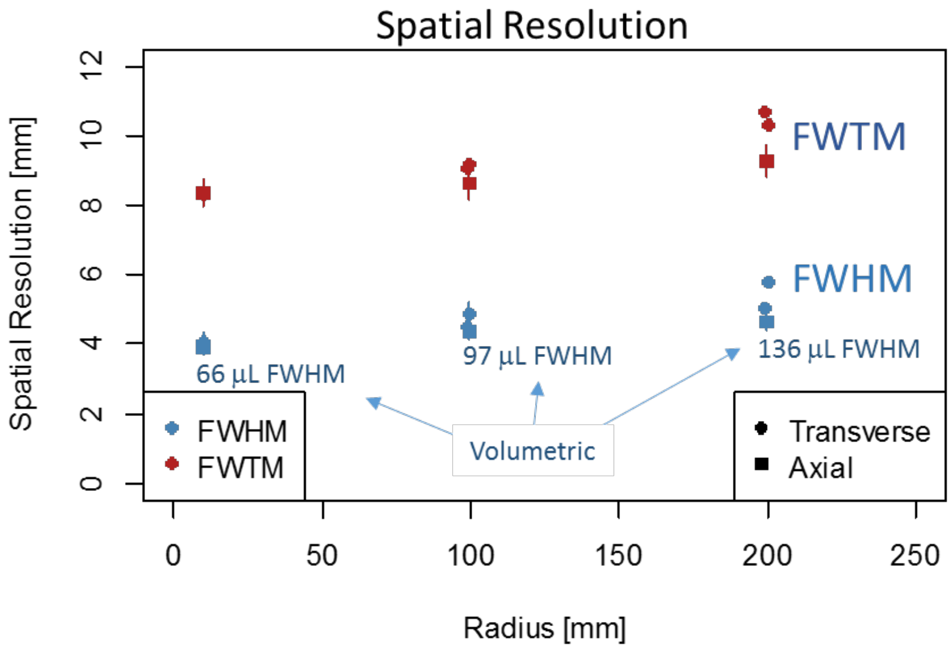
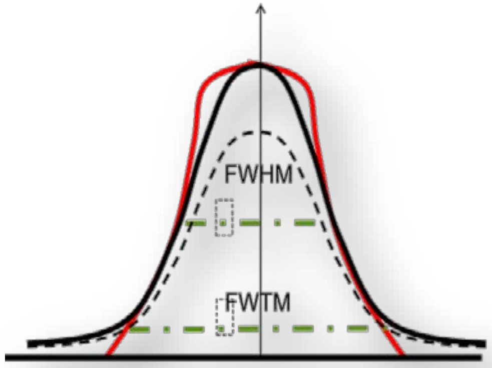
Spatial Resolution and Sensitivity

FWHM = 4.1 mm at center, Volumetric = 66 μL
5.1 mm at 20 cm, Volumetric = 136 μL

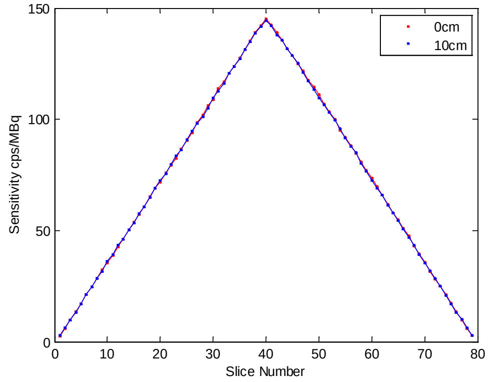


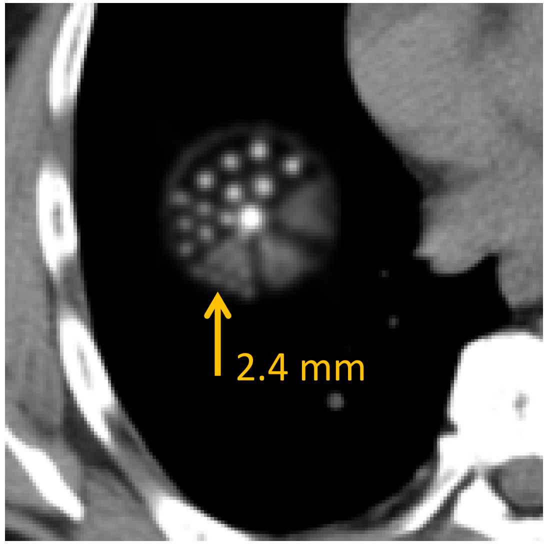
- Measured at NEMA NU 2-2012 locations: 1, 10, 20 cm
- Reconstructed with analytic 3D FRP

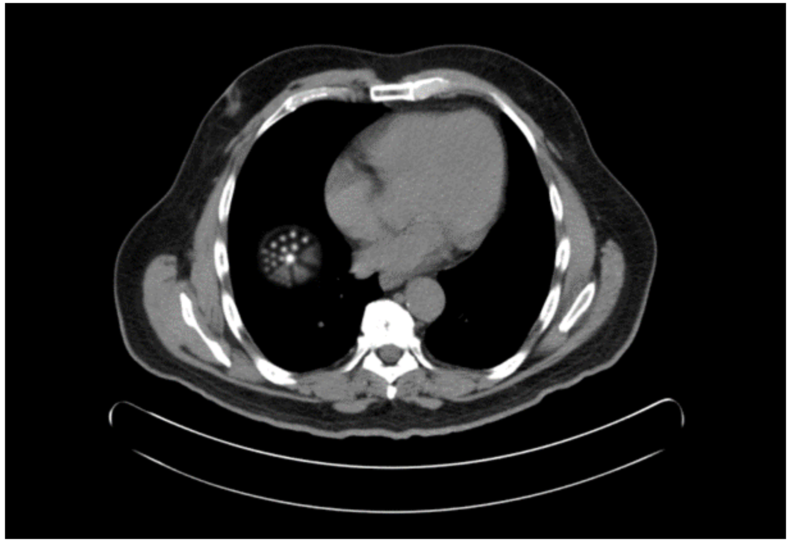
$$FWHM = a\sqrt{\left(d/2\right)^2 + b^2 + (0.0022D)^2 + r^2}$$



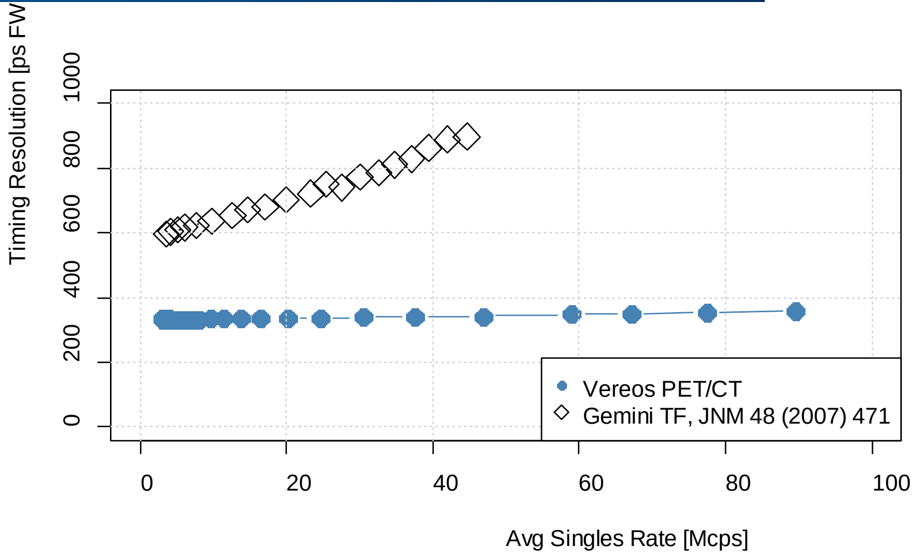
NEMA NU 2 Sensitivity Profile
5.5-5.7 kcps/MBq







Time-of-Flight Stability with Count Rate

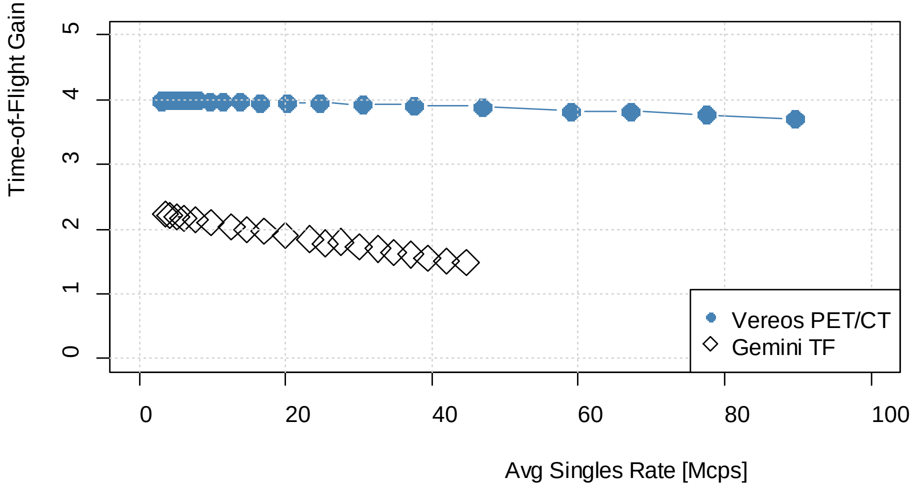


Timing resolution stable within 5% up to singles rates observed at peak NECR

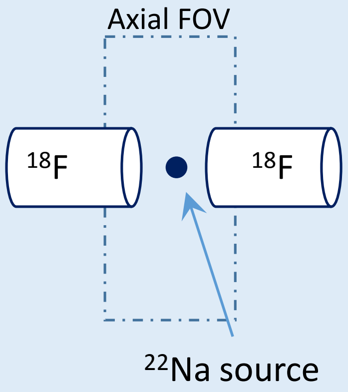
$$G_{\mathrm{tof}} = \frac{2D}{c\Delta t} = \text{time-of-flight gain}^{\dagger}$$

$$D = 20\ \mathrm{cm}$$

† JNM **24**(1): 73-78

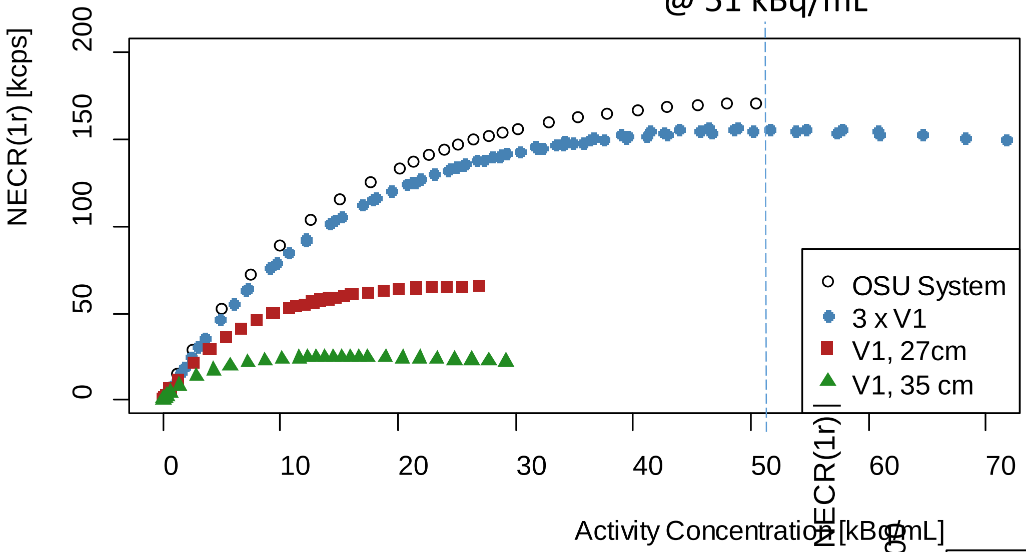


Measured with the method of Surti et al, JNM **48** (2007) 471.



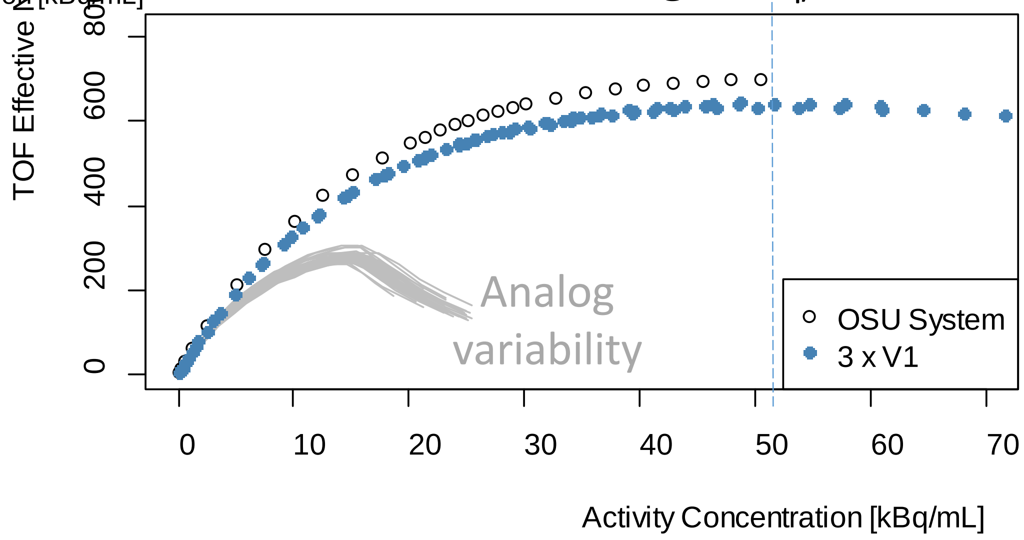
Noise Equivalent Count Rate

Peak NECR = 156 kcps
@ 51 kBq/mL



High peak NECR
very reproducible

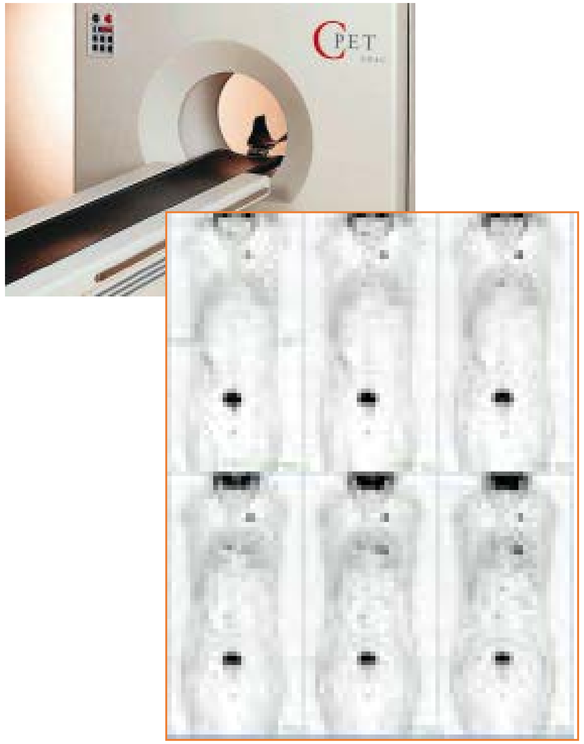
Peak TOF NECR = 641 kcps
@ 51 kBq/mL



Measured TOF res:
OSU = 325 ps→ G = 4.1
V1 = 316 ps → G = 4.2
Analog ~ 500 ps → 2.7

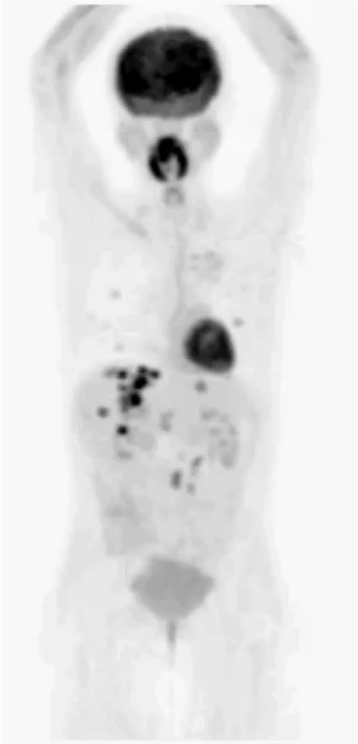
$G_{\text{tof}} = \frac{2D}{c\Delta t}$ = time-of-flight gain†
D = 20 cm

† JNM **24**(1): 73-78



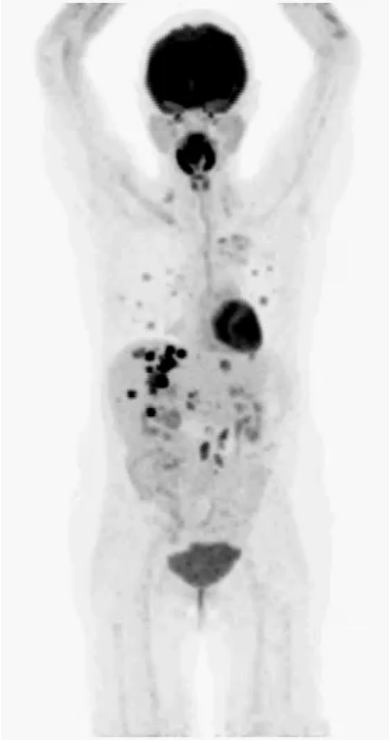
Positron Emission Tomography (PET)
F.D. Rollo and H. Hines, Medicamundi 2001

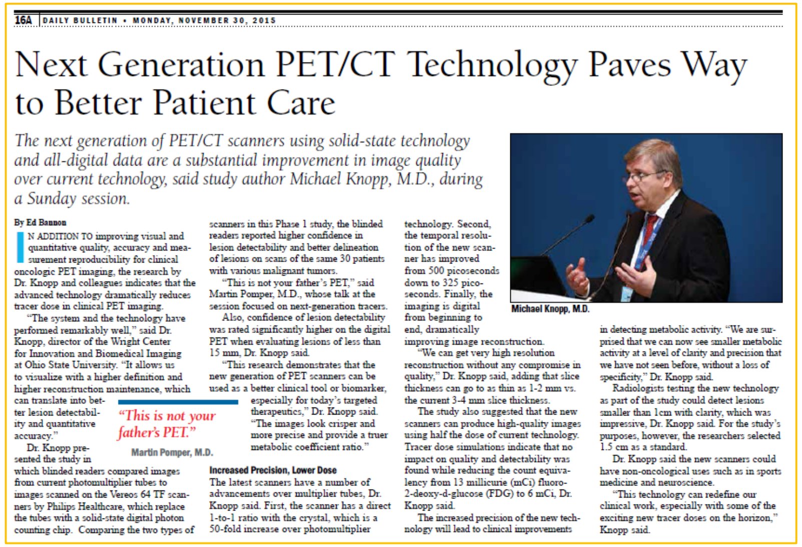
Analog *
Time of Flight



* Analog (*GEMINI TF*)
to digital comparison

Digital
Time of Flight





16A DAILY BULLETIN • MONDAY, NOVEMBER 30, 2015

Next Generation PET/CT Technology Paves Way to Better Patient Care

The next generation of PET/CT scanners using solid-state technology and all-digital data are a substantial improvement in image quality over current technology, said study author Michael Knopp, M.D., during a Sunday session.

By Ed Bannon

IN ADDITION TO improving visual and quantitative quality, accuracy and measurement reproducibility for clinical oncologic PET imaging, the research by Dr. Knopp and colleagues indicates that the advanced technology dramatically reduces tracer dose in clinical PET imaging.

"The system and the technology have performed remarkably well," said Dr. Knopp, director of the Wright Center for Innovation and Biomedical Imaging at Ohio State University. "It allows us to visualize with a higher definition and higher reconstruction maintenance, which can translate into better lesion detectability and quantitative accuracy."

Dr. Knopp presented the study in which blinded readers compared images from current photomultiplier tubes to images scanned on the Vereos 64 TF scanners by Philips Healthcare, which replace the tubes with a solid-state digital photon counting chip. Comparing the two types of scanners in this Phase 1 study, the blinded readers reported higher confidence in lesion detectability and better delineation of lesions on scans of the same 30 patients with various malignant tumors.

"This is not your father's PET," said Martin Pomper, M.D., whose talk at the session focused on next-generation tracers.

Also, confidence of lesion detectability was rated significantly higher on the digital PET when evaluating lesions of less than 15 mm, Dr. Knopp said.

"This research demonstrates that the new generation of PET scanners can be used as a better clinical tool or biomarker, especially for today's targeted therapeutics," Dr. Knopp said. "The images look crisper and more precise and provide a truer metabolic coefficient ratio."

"This is not your father's PET."
Martin Pomper, M.D.

Increased Precision, Lower Dose

The latest scanners have a number of advancements over multiplier tubes, Dr. Knopp said. First, the scanner has a direct 1-to-1 ratio with the crystal, which is a 50-fold increase over photomultiplier technology. Second, the temporal resolution of the new scanner has improved from 500 picoseconds down to 325 picoseconds. Finally, the imaging is digital from beginning to end, dramatically improving image reconstruction.

"We can get very high resolution reconstruction without any compromise in quality," Dr. Knopp said, adding that slice thickness can go to as thin as 1-2 mm vs. the current 3-4 mm slice thickness.

The study also suggested that the new scanners can produce high-quality images using half the dose of current technology. Tracer dose simulations indicate that no impact on quality and detectability was found while reducing the count equivalency from 13 millicurie (mCi) fluoro-2-deoxy-d-glucose (FDG) to 6 mCi, Dr. Knopp said.

The increased precision of the new technology will lead to clinical improvements in detecting metabolic activity. "We are surprised that we can now see smaller metabolic activity at a level of clarity and precision that we have not seen before, without a loss of specificity," Dr. Knopp said.

Radiologists testing the new technology as part of the study could detect lesions smaller than 1cm with clarity, which was impressive, Dr. Knopp said. For the study's purposes, however, the researchers selected 1.5 cm as a standard.

Dr. Knopp said the new scanners could have non-oncological uses such as in sports medicine and neuroscience.

"This technology can redefine our clinical work, especially with some of the exciting new tracer doses on the horizon," Knopp said.

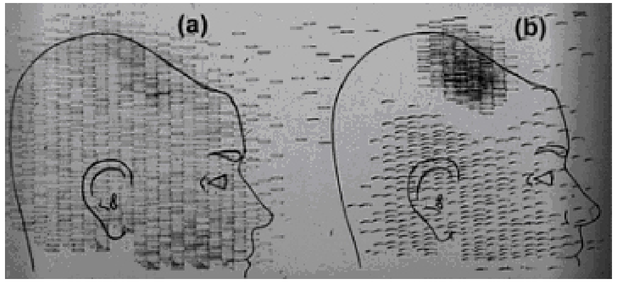
Michael Knopp, M.D.

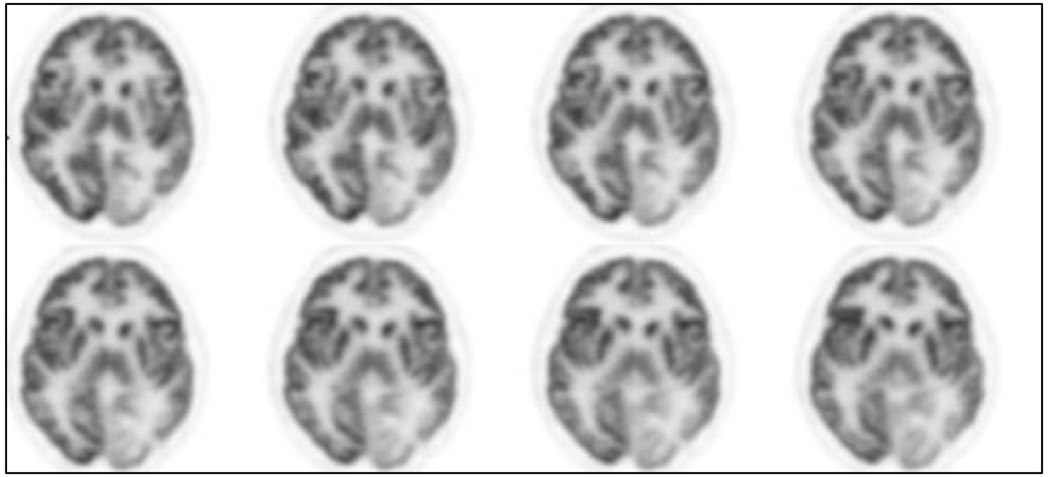
"This is not your father's PET."

Martin Pomper, M.D.

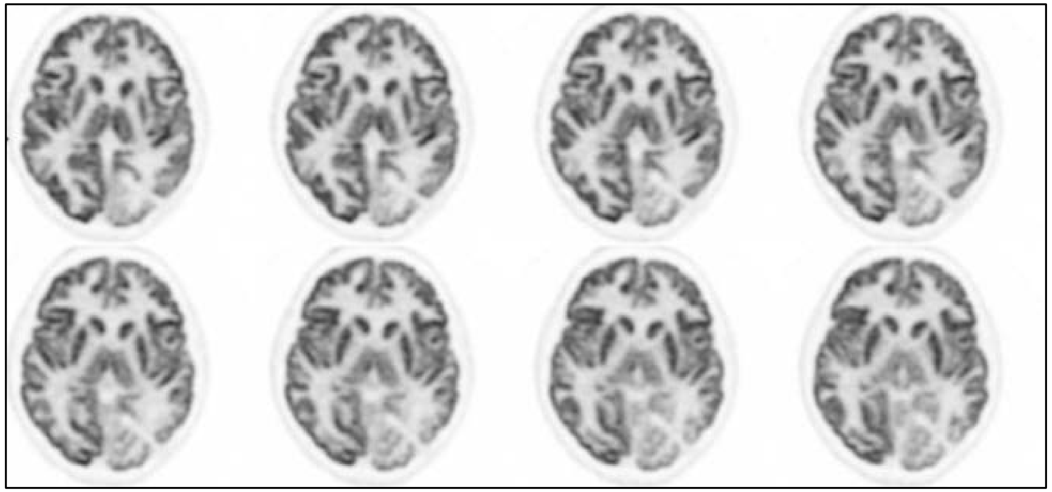
THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER
Wright Center of Innovation in Biomedical Imaging

G. Brownell, W. Sweet, PET Scanning, *Nucleonics* 11:40-45, 1953





Analog *
Time of Flight



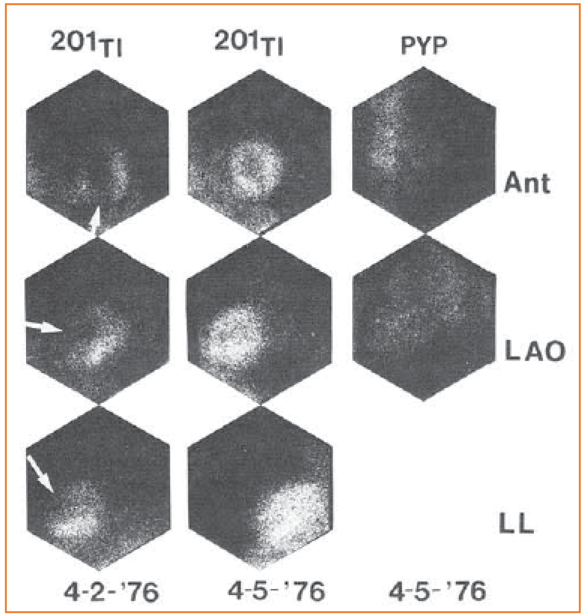
Digital
Time of Flight

* Analog (*GEMINI TF)* to digital comparison

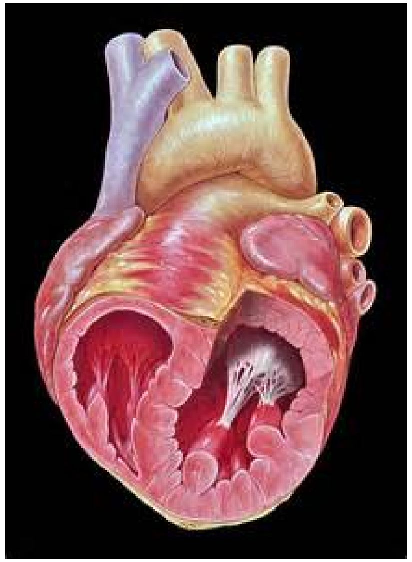
Patient data courtesy of University Hospitals, Cleveland
"Results from case studies are not predictive of results in other cases. Results in other cases may vary."

SCHOOL OF MEDICINE CASE WESTERN RESERVE UNIVERSITY
University Hospitals Case Medical Center

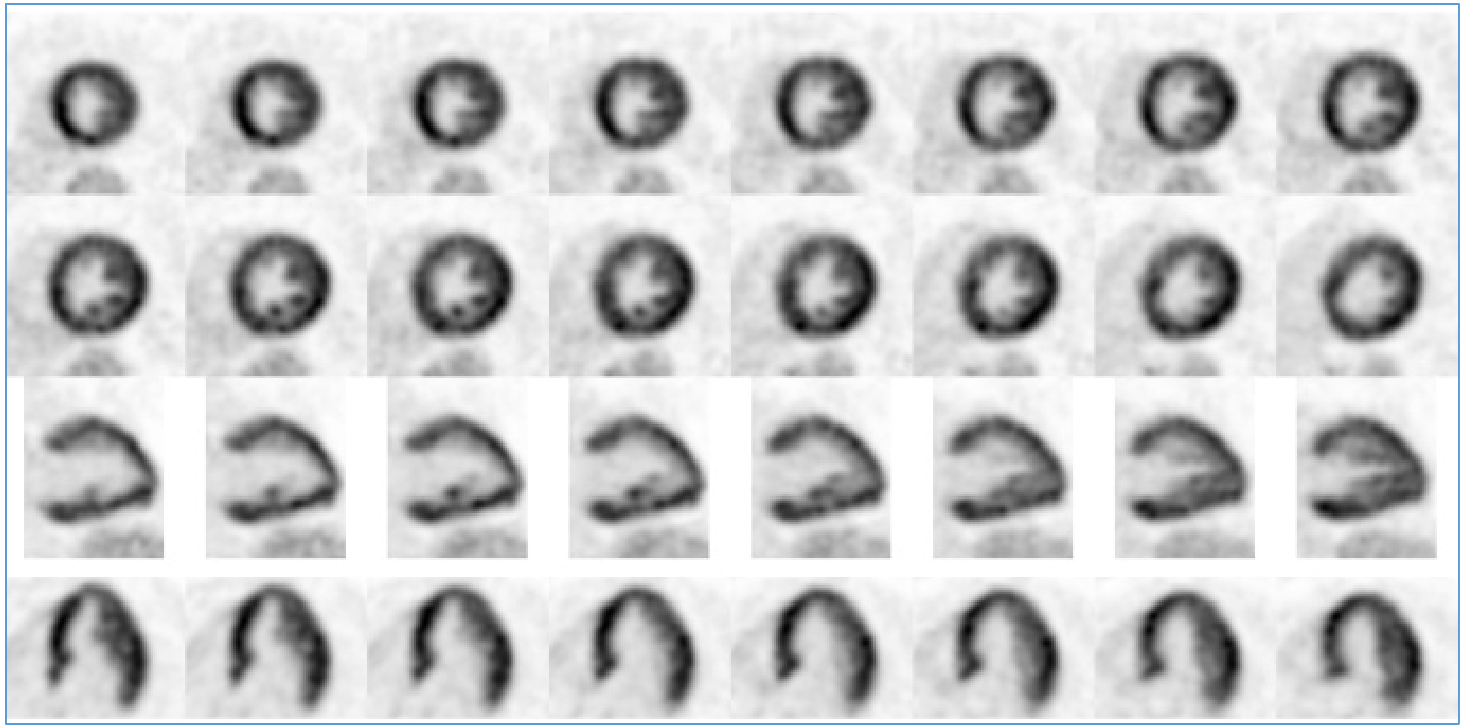
Nghi Nguyen et al, Brain imaging of neurological disorders using a digital PET prototype: Initial clinical experience and comparison with analog PET, J. NUCL. Med. MEETING ABSTRACTS, May 2014; 55: 206.



Tl-201 scintigraphy in unstable angina pectoris.
Frans J. Th. Wackers et al, Circulation, vol 57, No 4, 1978



Digital Time of Flight



Patient data courtesy of University Hospitals, Cleveland
"Results from case studies are not predictive of results in other cases. Results in other cases may vary."

School of Medicine Case Western Reserve University

University Hospitals Case Medical Center

The success of personalized medicine depends on having accurate diagnostic tests that identify patients who can benefit from targeted therapies.

Margaret A. Hamburg, M.D., and Francis S. Collins, M.D., Ph.D.
N Engl J Med 2010; 363:301-304, “The Path to Personalized Medicine”

PHILIPS