Technological leapfrogging at a hospital near you

What's going on and why it matters?

Antonis Kalemis, PhD MBA

Philips - Advanced Molecular Imaging
Snr Manager, Clinical Science

AIPES (European Association of Imaging Producers & Equipment Suppliers)
Chairman of New Technologies Working Group

PHILIPS

Topics (Focus on PET)

- Molecular Imaging (MI) in a changing Healthcare environment
- New technologies in MI already in the clinic (or almost there)
- Clinical Impact
- Growth Factors & Barriers for Adoption

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This presentation represents the speaker's own beliefs, which may differ from Philips' and/or AIPES' formal positions.

PHILIPS

Molecular Imaging – Evolution

Today

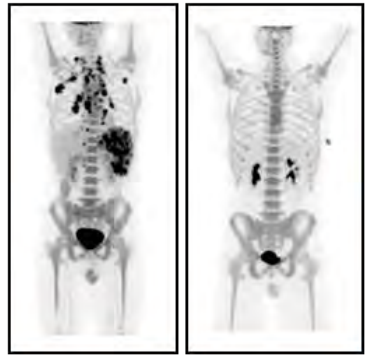
PET

Research - era of discovery
The "basement" era

PET/CT

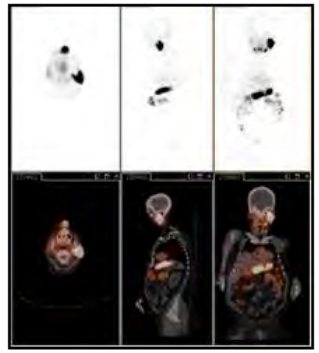
Era of image quality,
and integration with CT
Era of lesion detection and localization
Image "Beautification"

PET/CT

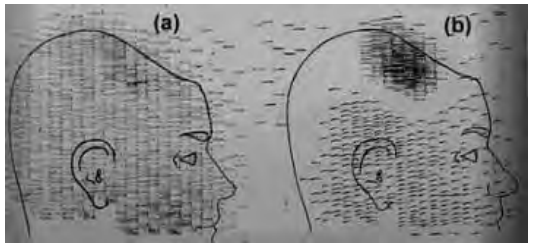


Era of quantitative accuracy and integration with MRI

Personalized Diagnosis & Treatment



Era of targeted therapy and imaging
Individual patient management



Slide courtesy of Piotr Maniawski, Philips

European Molecular Market – Facts & Figures

European Market Data

- Nuclear Medicine Department ≈ 2,250
  - University Hospital : 16%
  - Public : 56%
  - Private : 28%
- Nuclear Medicine Physicians ≈ 5,300
- Diagnostic Procedures ≈ 10M / year
- Therapy Treatments ≈ 220,000
- Cameras ≈ 4,900
- SPECT ≈ 4,000
- PET ≈ 900

Source :
- EANM 2012
- Medical Options UK
- AIPES

		INSTALLED BASE			AGE VS 'GOLDEN RULES'		
		2008	2011	2013	Mkt% by age 2008	Mkt% by age 2013	Golden rules
PET	IB 1-5 years - units	430	532	448	73.1%	51.8%	60%
PET	IB 6-10 years - units	118	294	325	20.1%	37.6%	30%
PET	IB >10years - units	40	110	91	6.8%	10.6%	10%
PET Total		588	936	864			

(COCIR 2014)

Nuclear Medicine – General Trends*

Volume and sales have decreased since 2007, and projections for growth in the US through 2017 are flat to minimal

The majority (85-87%) of procedures will continue to be based on Tc-99m and other single photon agents (SPECT and planar)

Emerging markets and the US market are at different time points in development.
Education regarding the value of nuclear medicine/molecular imaging that is evidence based is very important

More outreach is needed to patients, referring physicians, payers and regulatory agencies.
Continued emphasis on advocacy is important – CMS, FDA (and partnerships)

Health care reform (USA) is driving medicine that is evidence based and patient centered

New tracers and new technologies will drive growth

Quality is important to drive growth
a. Training of professionals
b. **Quantification**
c. **Standardization**

Concerns about radiation safety should be addressed by dose optimization and education about the benefits of nuclear medicine/molecular imaging

SNMMI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

*April 2013,
SNM Board of Directors Meeting

Radiopharmaceuticals

PET Radioisotopes & Production

Cyclotrons

KnoxvilleNews.com Jan 20, 2013

Companies
General Electric
Siemens
IBA
ASCI
D.V. Efremov Institute
Sumitomo Heavy Industries
KIRAMS
Best Cyclotron Systems
ABT

PET Radioisotopes & Production

Cyclotrons

Image: GE Healthcare

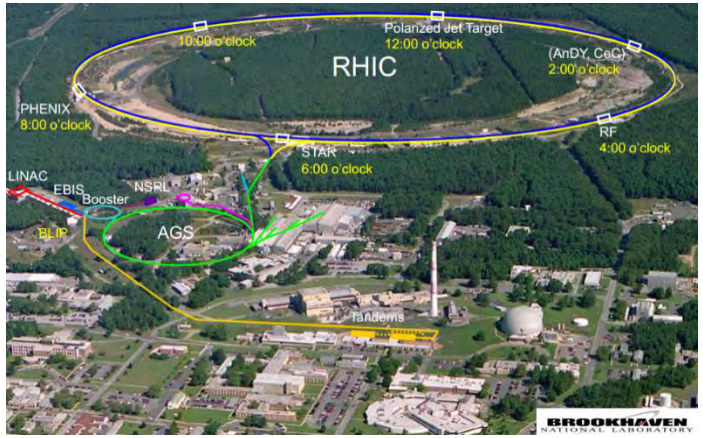
Image: ABT Molecular Imaging Inc.

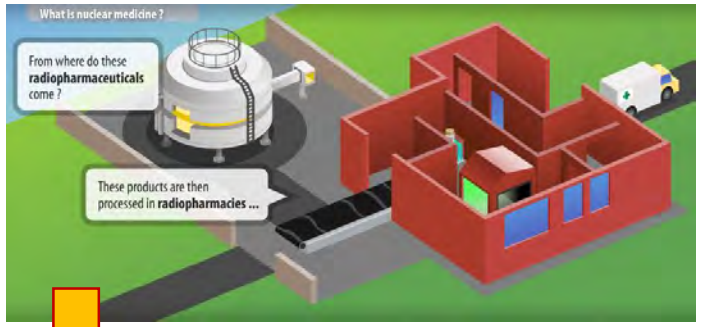
AMIT Cyclotron Project
8.5 MeV, 10 µA

	BIOMARKER GENERATOR	CONVENTIONAL CYCLOTRON
PET LAB FOOTPRINT	300 FT2	4,000 FT2
WEIGHT	24 TONS	50 TONS
PERSONNEL	1 FTE	4 FTE
OPERATING EXPENSES	$150K/YR.	$600K/YR.
REPETITIVE PRODUCTION CYCLE	30 MIN.	3 HOURS

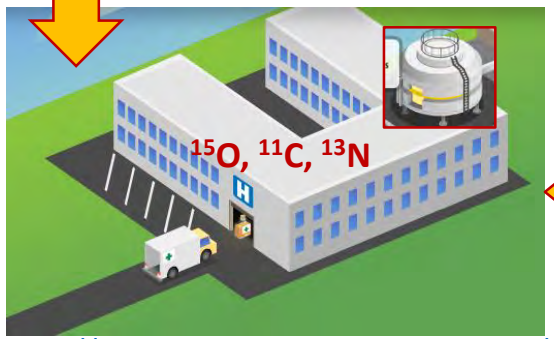
(ABT Cyclotrons)

PET Radioisotopes & Production





^{18}F-labelled radiopharmaceuticals



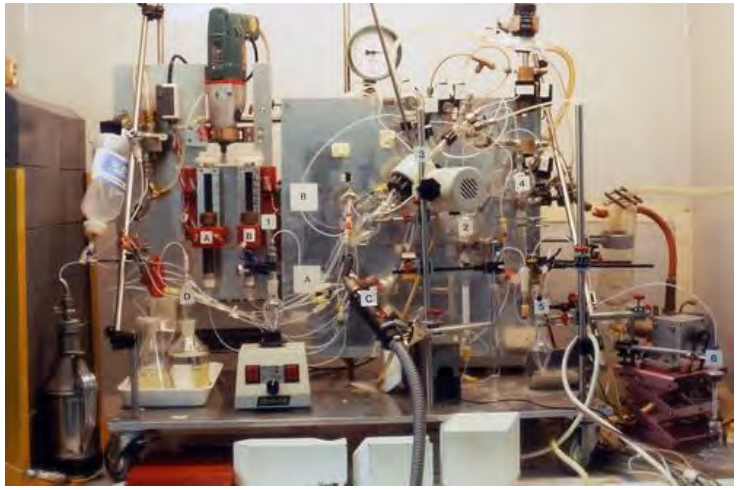
http://www.whatisnuclearmedicine.com/

1218 Cyclotrons producing medical radionuclides globally.
Expected 60 new cyclotrons/year – 2015-2030.

MEDraysintell – Cyclotrons Report 2015

PET Radioisotopes & Production

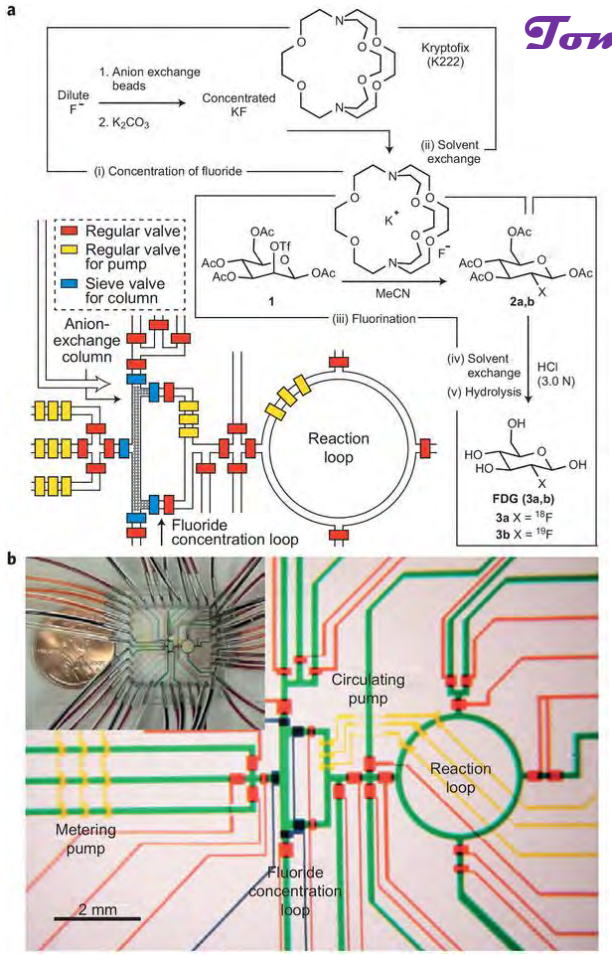
Simplification of Radiopharmaceutical Production



Once upon a time...

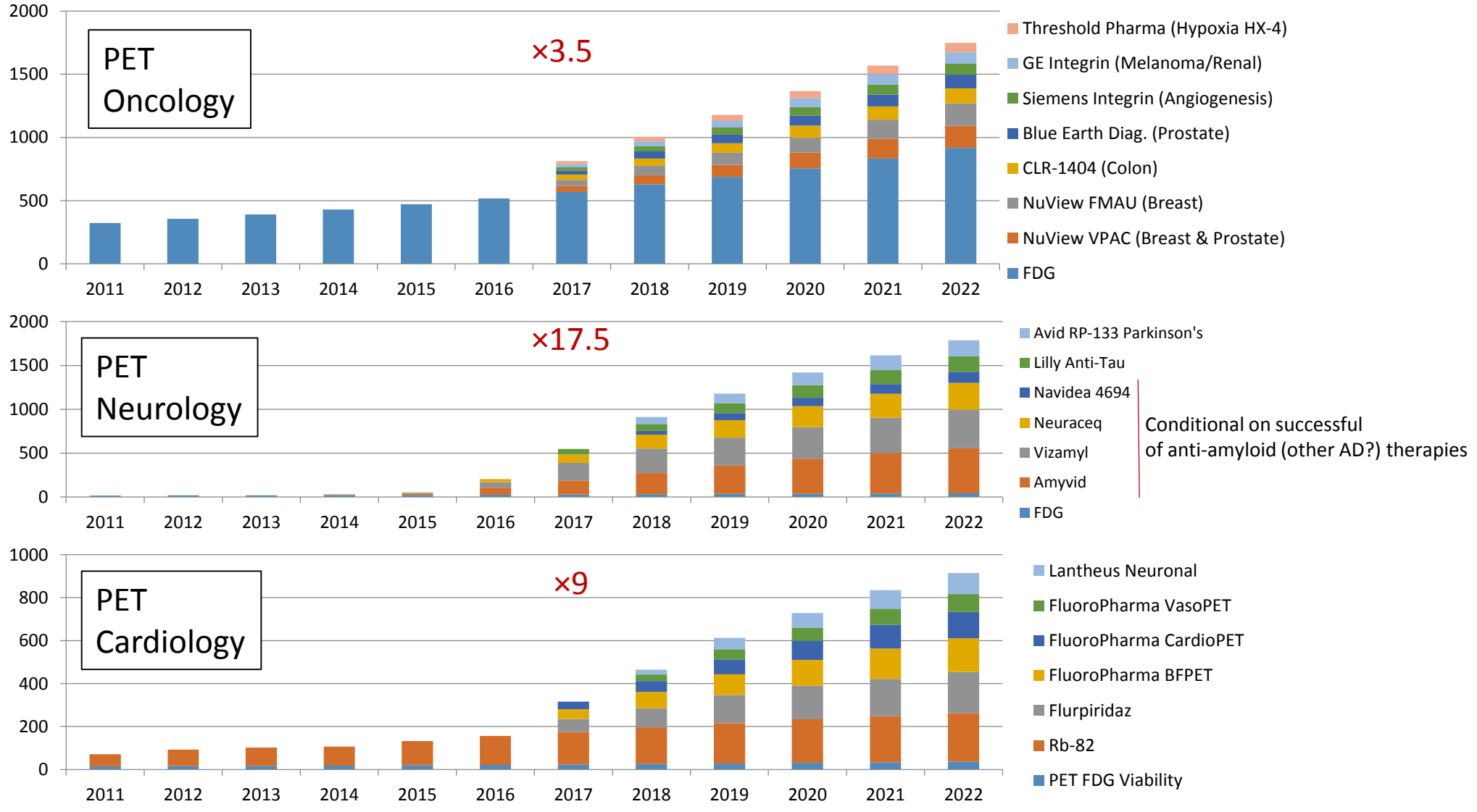
Today

Tomorrow?



Elvira, et al., (2013) Nature Chemistry

New PET Tracers - USA



BIO-TECH SYSTEMS, INC.

THE NORTH AMERICAN MARKET FOR SPECT AND PET RADIOPHARMACEUTICALS

Existing Novel PET Tracers - EU

Tracer	Care Cycle	Indication
^{18}F-FLT	Oncology	Cell proliferation
^{18}F-DOPA	Oncology	Neuroendocrine
^{18}F-MISO	Oncology	Hypoxia
Aposense ^{18}F-ML-10	Oncology	Apoptosis
^{68}Ga-DOTATATE ^{68}Ga-DOTATOC	Oncology	Neuroendocrine Tumours
^{18}F-NaF	Oncology	Bone Metastases
^{18}F-FET	Oncology	BrainTumours
^{18}F-FES	Oncology	Response to therapy Breast Cancer
Sirtex/BTG ^{90}Y-spheres	Oncology	Liver Radioablation
^{124}I / ^{90}Y / ^{89}Zr / ^{64}Cu – DOTAs & MABs	Oncology	Theranostics

Other Interesting tracers (just three examples)…

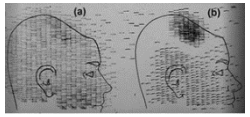
Tracer	Care Cycle	Indication
^{68}Ga-PSMA	Oncology	Prosate (Afshar-Oromieh, EJNMMI 2014)
^{18}F-PBR111	Neurology/ Inflammation	Multiple Sclerosis (Colasanti, JNM 2014)
^{18}F-Mannose	Oncology +	Metabolism (Furumoto, JNM 2013)

Positron Emission Tomographs

Innovation in PET

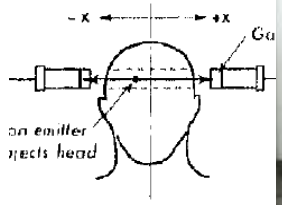
FDG

1953 1966 1969 1973 1978 1982 Mid-80s 1995 1998 2001 2006 2008 2010 2011 2012 2014 2015

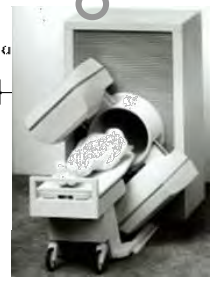


Brownell and Sweet. First PET images with ^{74}As.
(Nucleonics 1953, 11:40-45)

The MGH Positron Camera PC-I



H.O.Anger's Description of TOF



Cyclotron Corp. PC-4200 (PC-II)

NeuroECAT

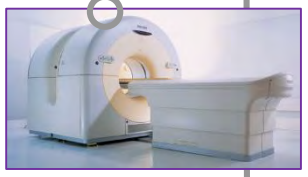
Early TOF PET scanner, SuperPETT I

Commercial PET Scanners
Scanditronix
Nucleonix
EG&G Ortec
Berkley Donner Lab
CTI
UGM

Commercial Coincidence Imaging

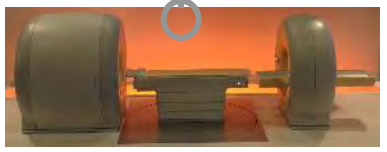
PET/CT Prototype: CTI/Siemens Somatom AR.SP + ECAT ART

Commercial PET/CT GE Discovery LS



Clinical TOF-PET/CT Philips GEMINI TF

Siemens APD brain-PET Insert in MRI



Clinical WB TOF-PET/MR Philips Ingenuity TF PET/MR

Integrated (APD) WB PET/MR Siemens Biograph mMR

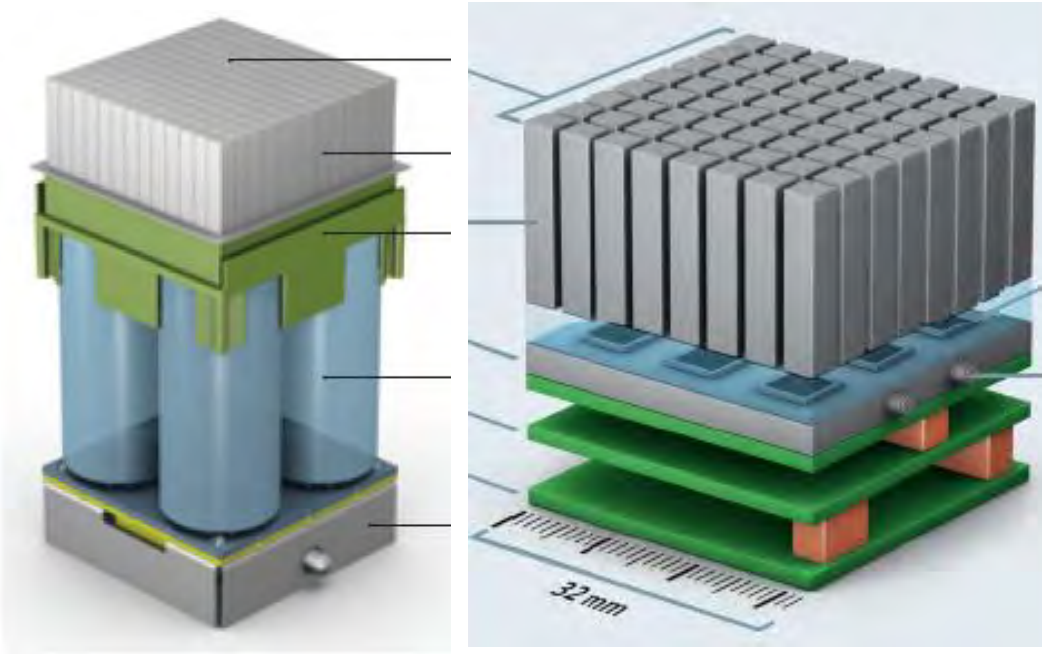
Digital Prototype Philips TOF-PET/PET/CT

Integrated (SiPM) TOF-PET/MR GE Signa PET/MR

Digital TOF-PET/CT Philips Vereos

New PET Detectors

Towards the digitisation of photon detection - #1 from PMT to APD



Images from Siemens Healthcare Product Brochures

Photodetector	PMT	APD
Active area (mm^2)	1–2,000 cm^2	1–100 mm^2
Gain	10^5–10^7	10^2
Dynamic range	10^6	10^4
Excess noise factor	0.1–0.2	>2
Rise time (ns)	<1	2–3
Time jitter (ns FWHM)	0.3	>1
Dark current/countrate	<0.1 nA/cm^2	1–10 nA/mm^2
Capacitance (pF/mm^2)	8.6±0.4	2–10
QE @ 420 nm (%)	25%	60–80%
After-pulsing	Yes	No
Bias voltage (V)	1,000–2,000	~100–1,500
Power consumption	100 mW/ch	10 µW/mm^2
Temperature coefficient	<1%/°C	2–3%/°C
Bias coefficient	<1%/V	10%/V
Magnetic susceptibility	Very high (mT)	No (up to 9.4 T)

Lecomte R (2009) Eur J Nucl Med Mol Im 36 Suppl 1:S69-85.

Advantages:

Compact design

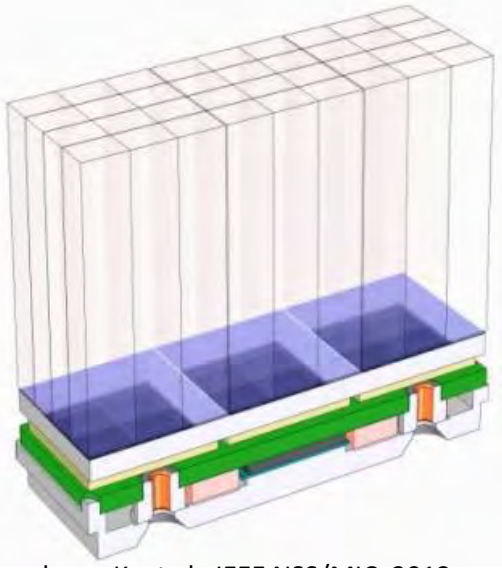
Much better Quantum Efficiency

Smaller size → potentially smaller detector blocks

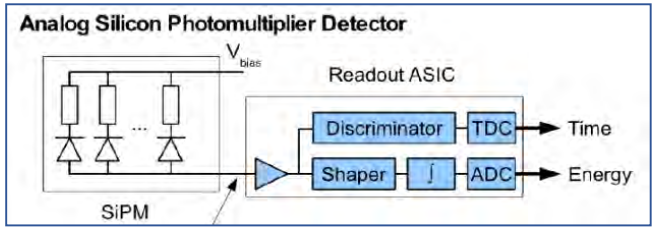
Can operate within Magnetic Field

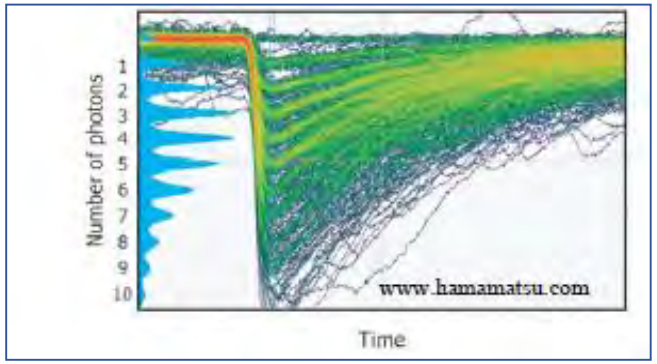
New PET Detectors

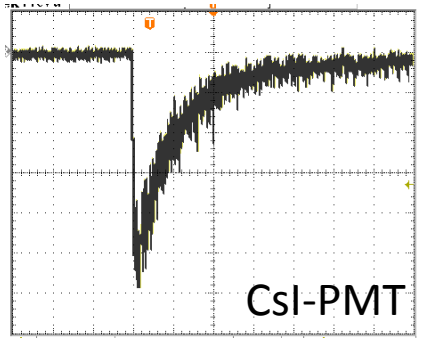
Towards the digitisation of photon detection - #2 from APD to SiPM



Changlyong K, et al., IEEE NSS/MIC, 2012, pp 3533-3536.







<u>Advantages:</u>

High gain

Fast Response → good TOF

Can operate within Magnetic Field

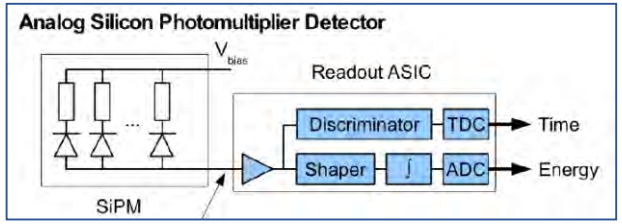
Photodetector	APD	SiPM
Active area (mm^2)	1–100 mm^2	1–10 mm^2
Gain	10^2	10^5–10^6
Dynamic range	10^4	10^3
Excess noise factor	>2	1.1–1.2
Rise time (ns)	2–3	~1
Time jitter (ns FWHM)	>1	0.1
Dark current/countrate	1–10 nA/mm^2	0.1–1 MHz/mm^2
Capacitance (pF/mm^2)	2–10	>30
QE @ 420 nm (%)	60–80%	<40%[a]
After-pulsing	No	Yes
Bias voltage (V)	~100–1,500	~50
Power consumption	10 μW/mm^2	<50 μW/mm^2
Temperature coefficient	2–3%/°C	3–5%/°C
Bias coefficient	10%/V	~100%/°C
Magnetic susceptibility	No (up to 9.4 T)	No (up to 15 T)

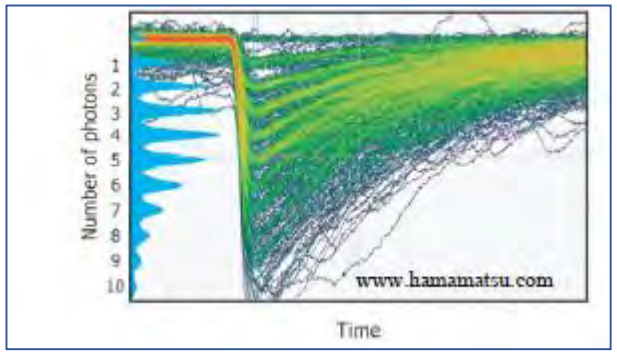
Lecomte R (2009) Eur J Nucl Med Mol Im 36 Suppl 1:S69-85.

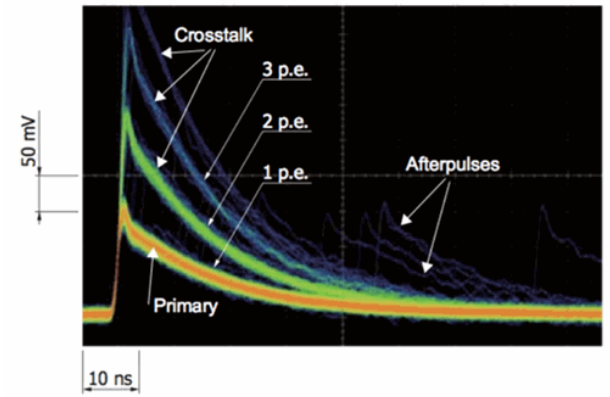
New PET Detectors

Towards the digitisation of photon detection - #3 from SiPM to Digital SiPM &

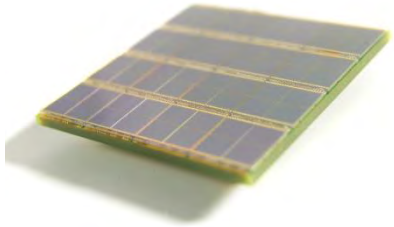
from Anger-logic to 1:1 coupling

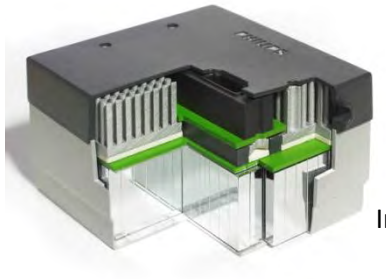




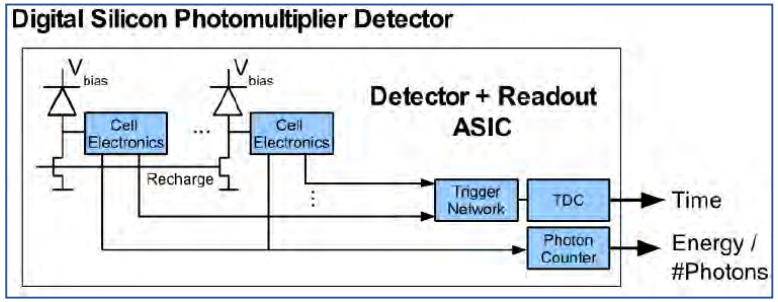


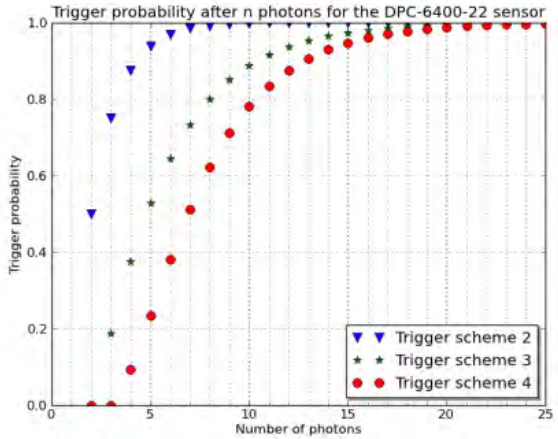
Images: Hammamatsu Photonics





Images: Philips





<u>Advantages:</u>

High gain

Faster Response → good TOF

Can operate within Magnetic Field

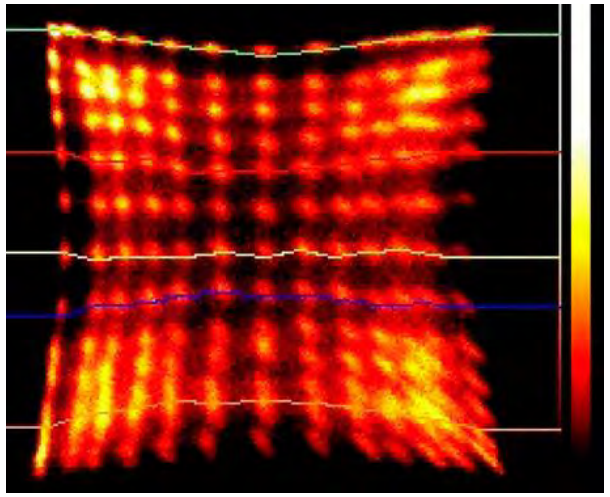
Better spatial resolution

Significantly lower dead-time

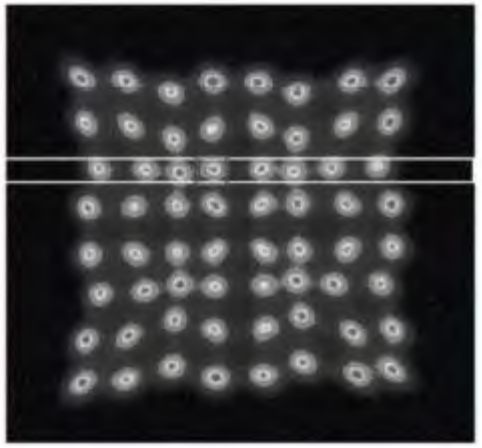
Further TOF Improvement

Technical Benefits of Digital PET

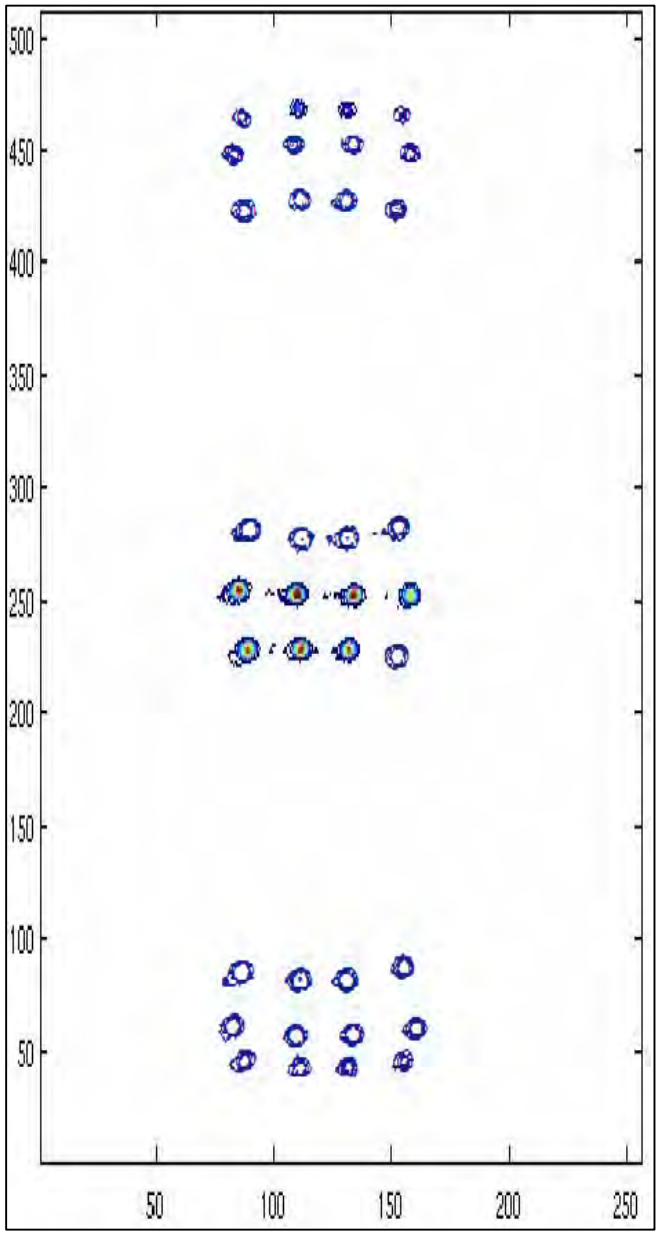
Spatial Resolution



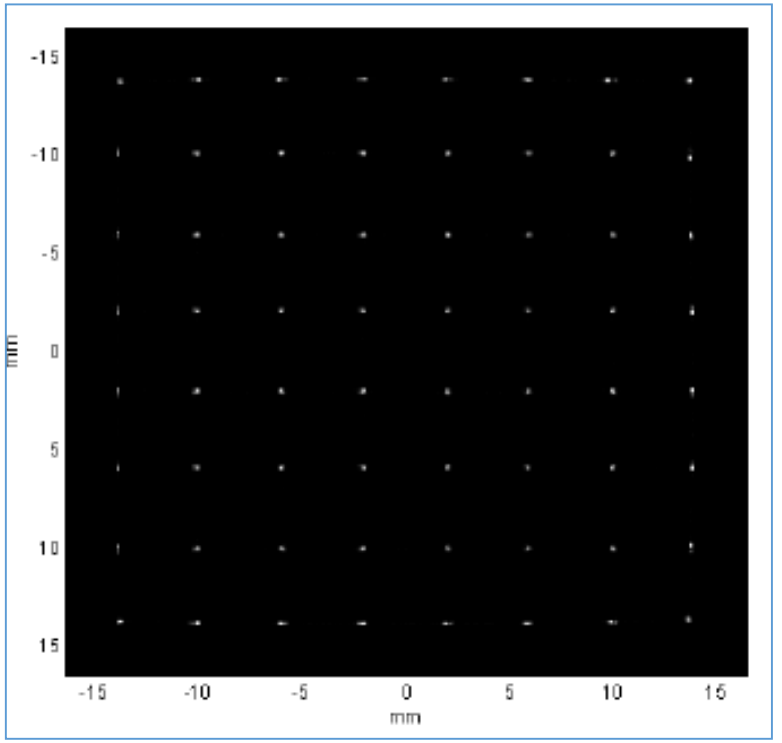
Biograph HiRez /169 LSO
Thompson et al., (2014)
Sensors 14 (8):14654-71



Biograph mMR
Schmidt H, et al.,(2014)
Invest Radiol 49 (6):373-381



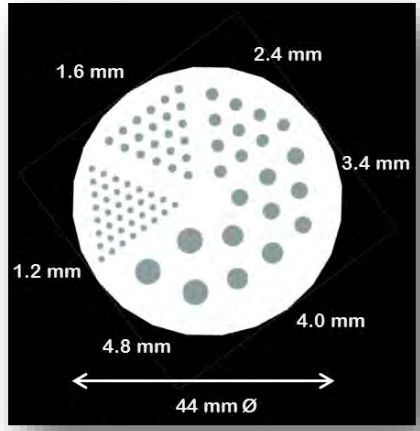
Signa PET/MR
Changlyong K, et al., IEEE NSS/MIC, 2012, pp 3533-3536.



Vereos
Miller M, et al., SNMMI, St Louis, MO, 2014

Technical Benefits of Digital PET

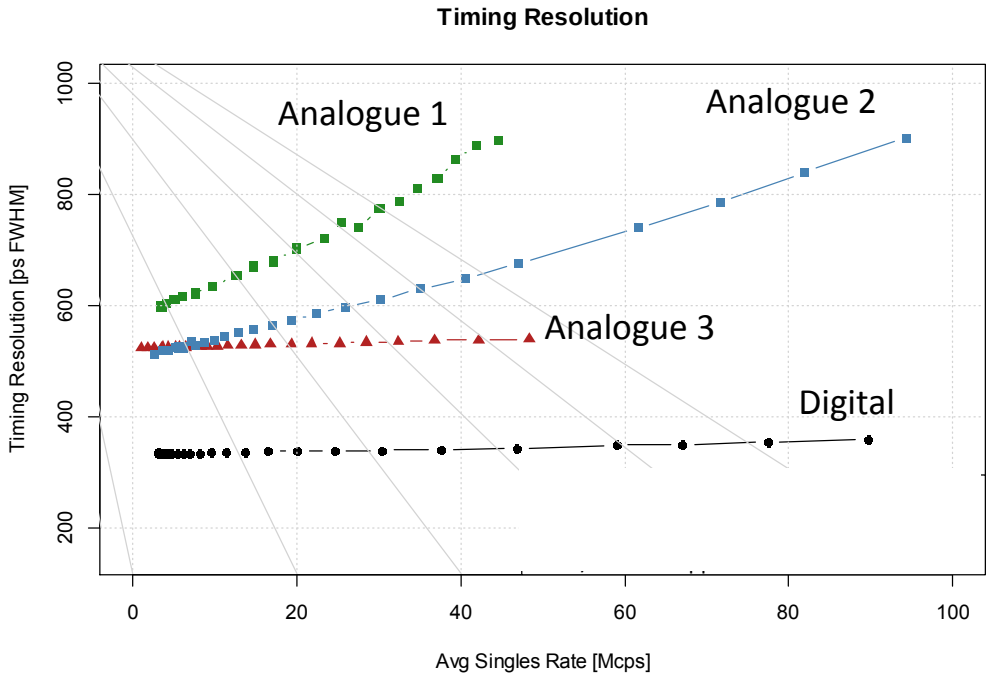
Better lesion detection (Spatial Resolution)



Data Courtesy of Philips

Technical Benefits of Digital PET

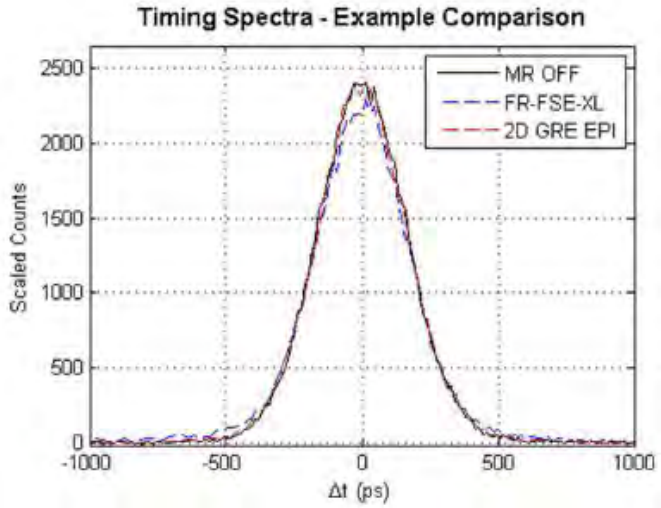
Better lesion detection (Spatial Resolution)



Better contrast/ noise control (TOF timing resolution)

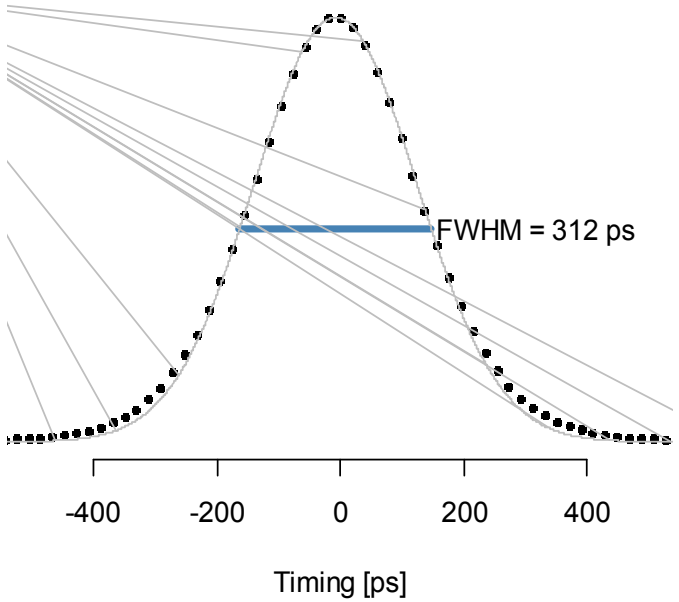
Data Courtesy of Philips

Better [illegible]uced dead-time)



Timing Resolution (ps)	
Outside MR (No MR coil in PET FOV)	386

Deller et al., ISMRM 2014 Talk M08-6

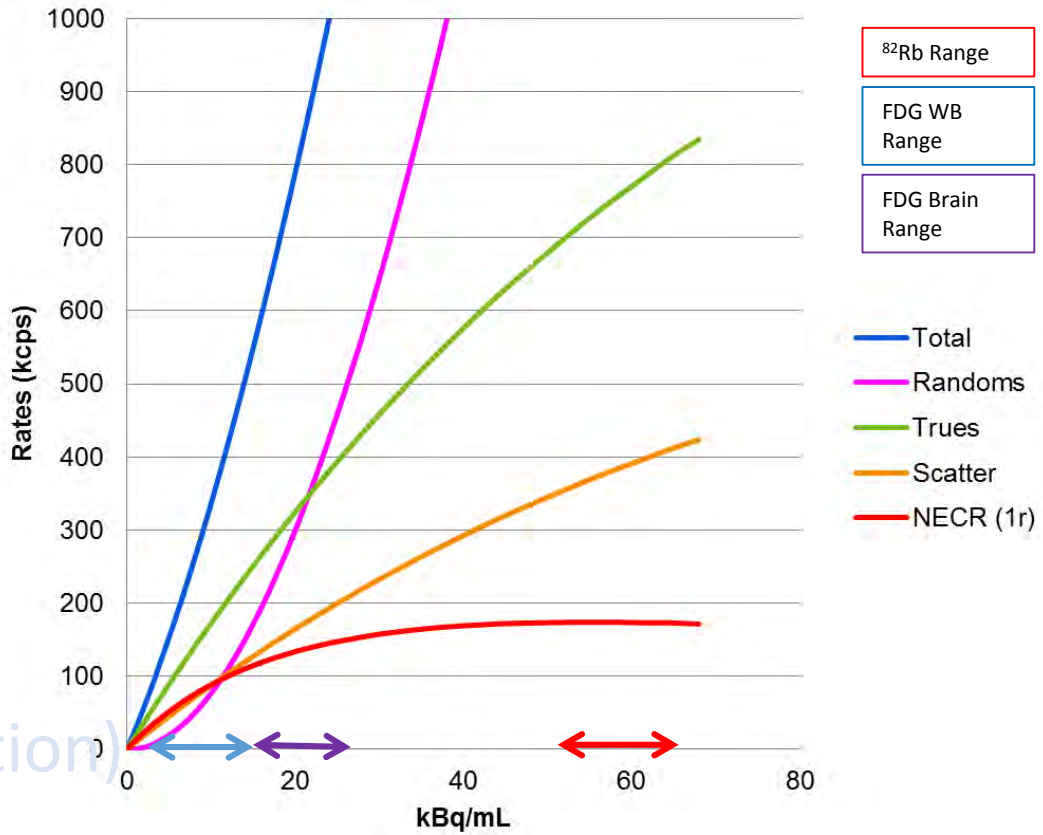


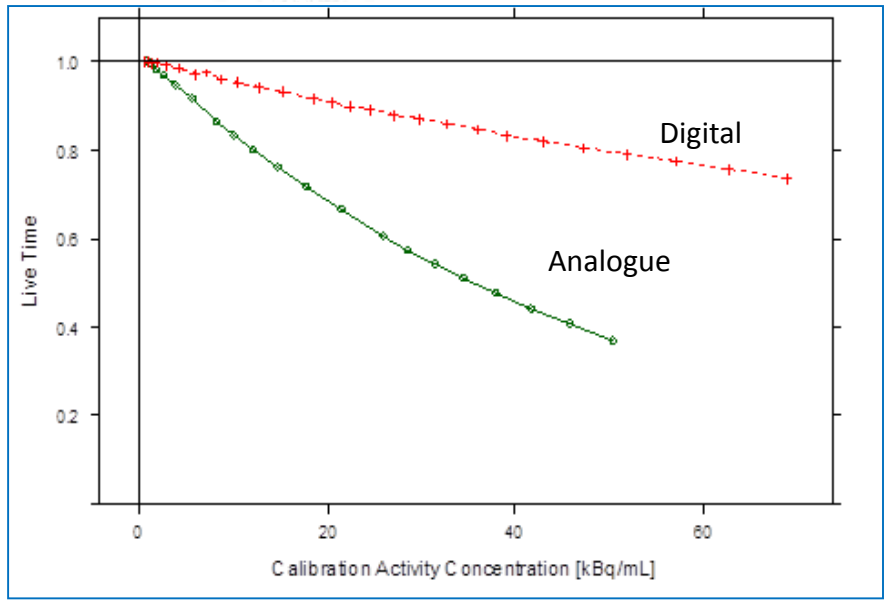
Technical Benefits of Digital PET

Better lesion detection (Spatial Resolution)

Better contrast/ noise control (TOF timing resolution)

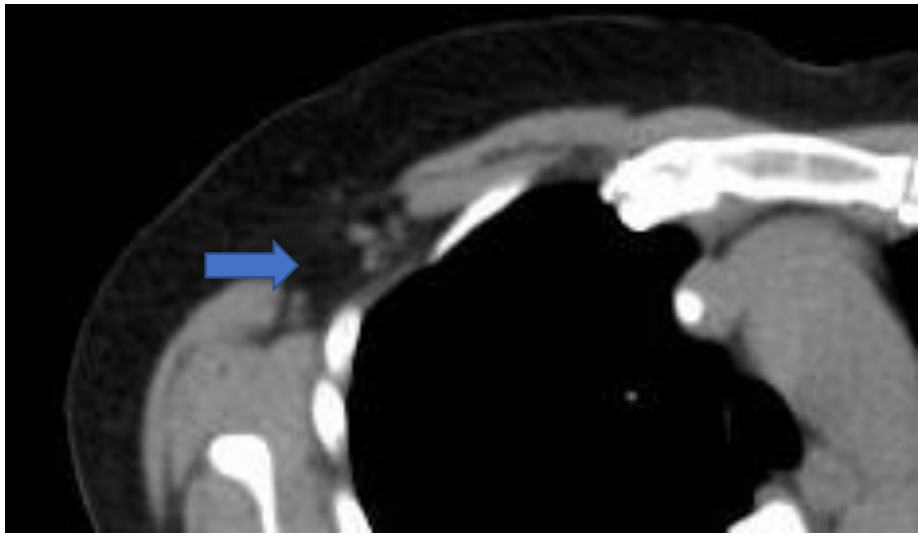
Better system linearity (reduced dead-time)





Data Courtesy of Philips

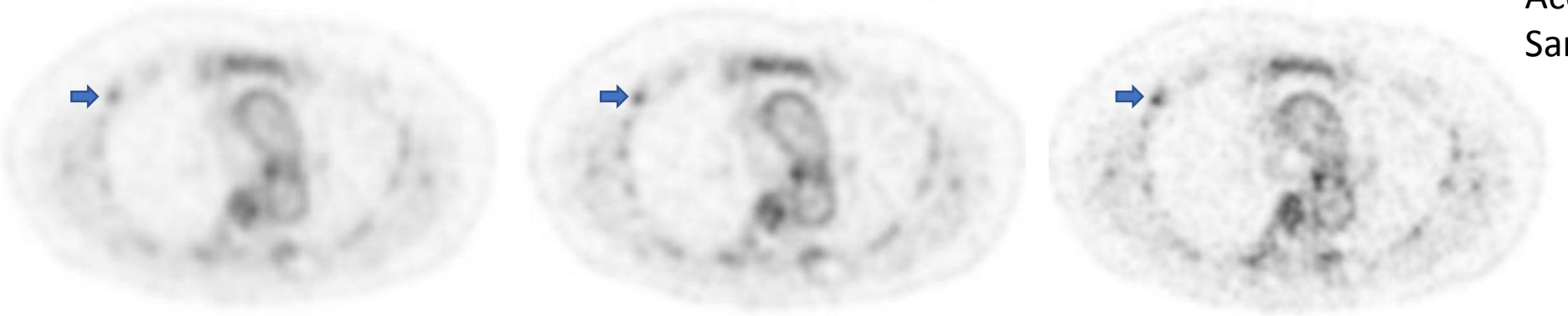
Oncology: Lesion Detection



Injected activity: 370MBq (FDG)
Injected once, scanned twice

Acquisition time: 1.5 min/bed
Same for both systems

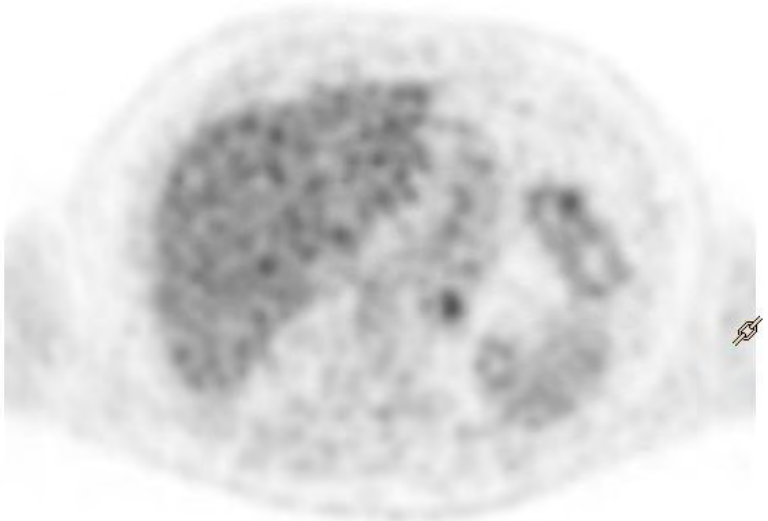
Analogue TOF 4mm



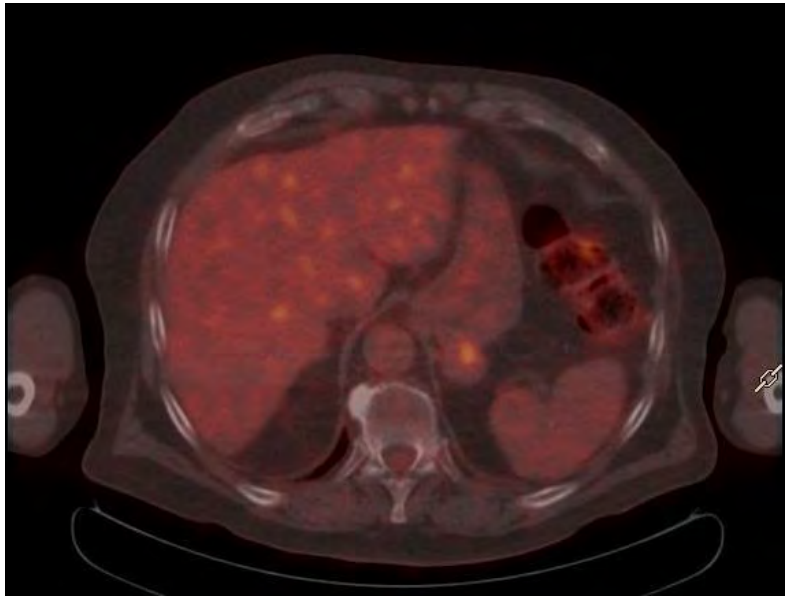
Digital TOF 4mm 2mm 1mm

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

Data courtesy of The Ohio State University – Wright Center of Innovation in Biomedical Imaging
"Results from case studies are not predictive of results in other cases. Results in other cases may vary."



Analogue SUV max 3.7

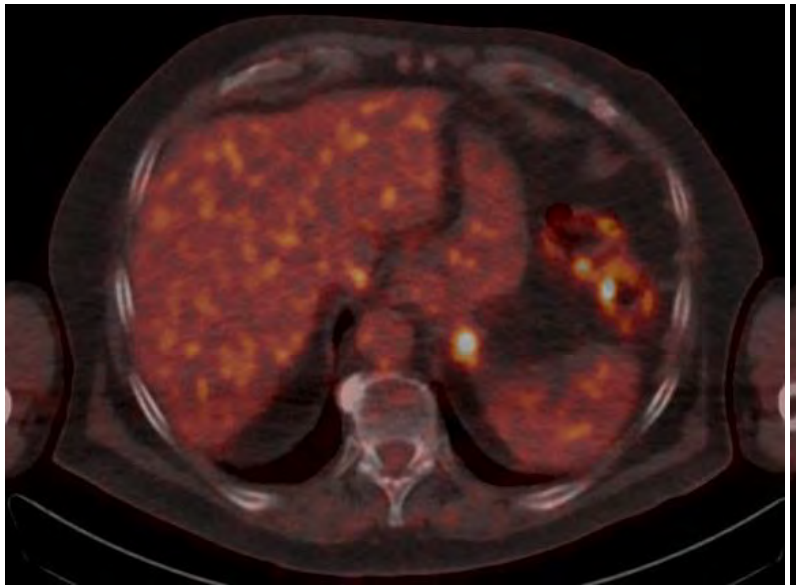


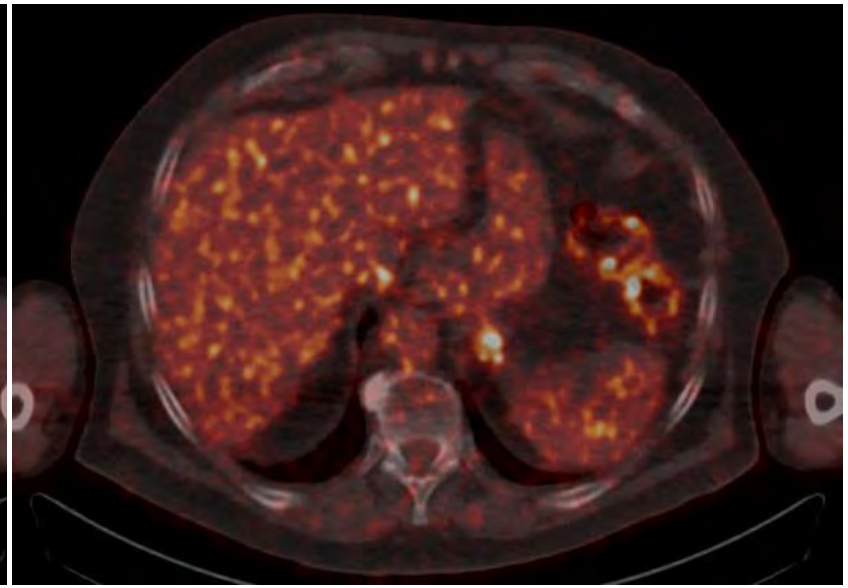
Digital 1mm
SUV max 8.2

ΔSUVmax = 121.6%

Digital 2mm
SUV max 6.9

ΔSUVmax = 91.8%





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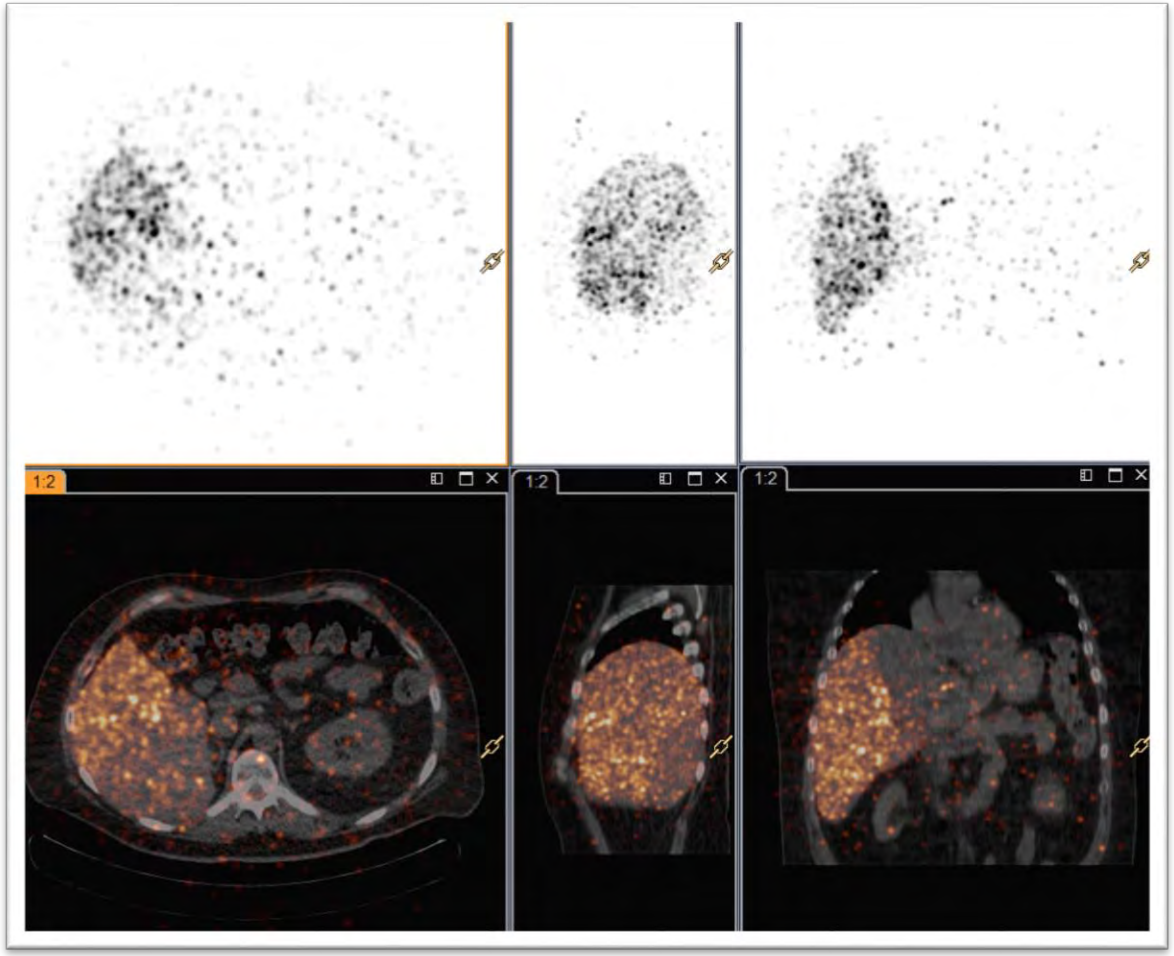
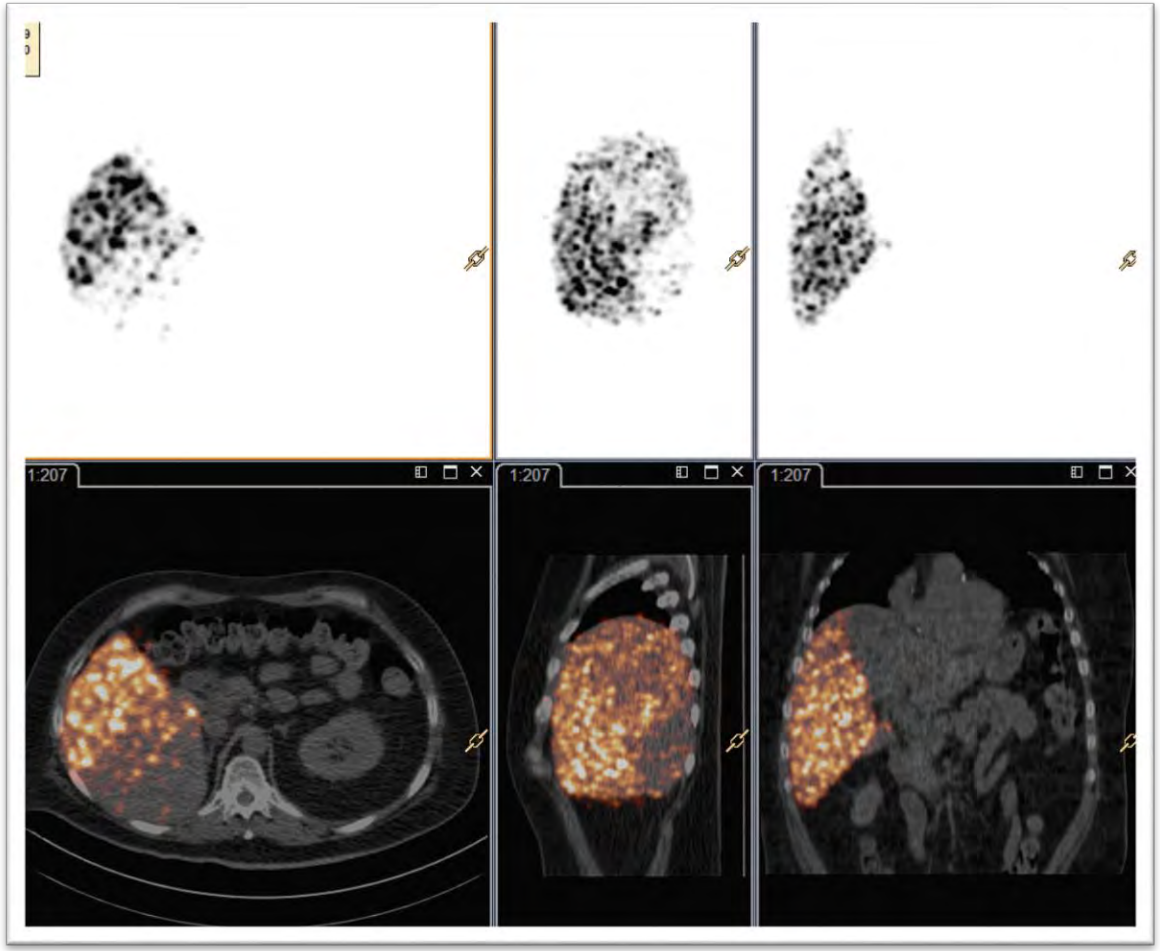
Y-90 Microspheres Preliminary Results

Analogue PET



Digital PET



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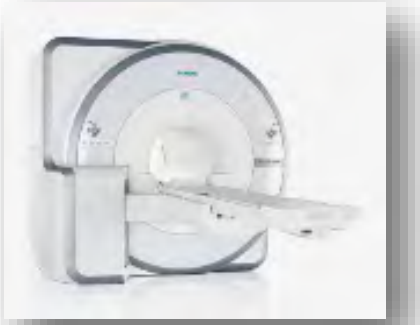
PET/MR

(Existing) Enabling Technologies



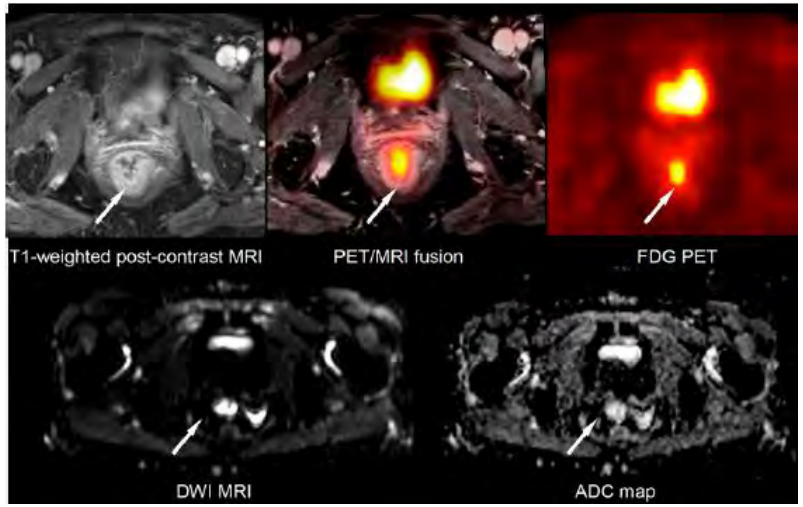
Solid-State Detectors

Multi-Transmit/Receive MRI

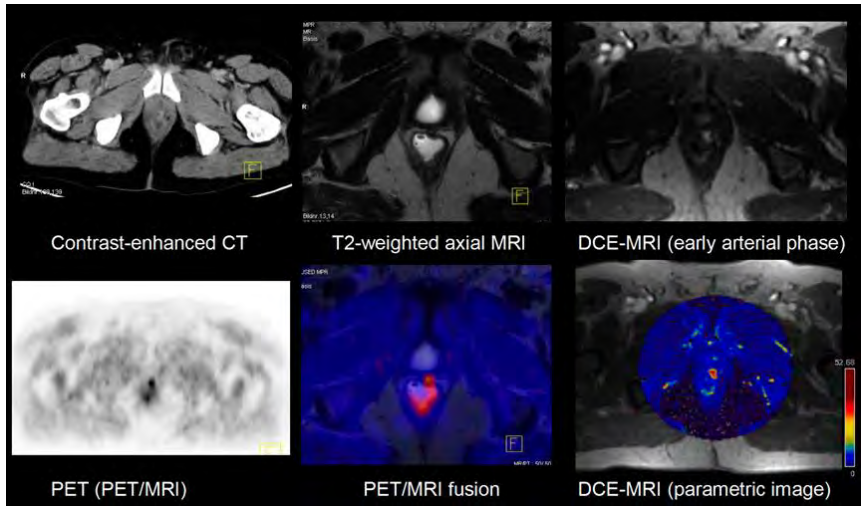
TOF

MRAC, Truncation, Scatter + Corrections

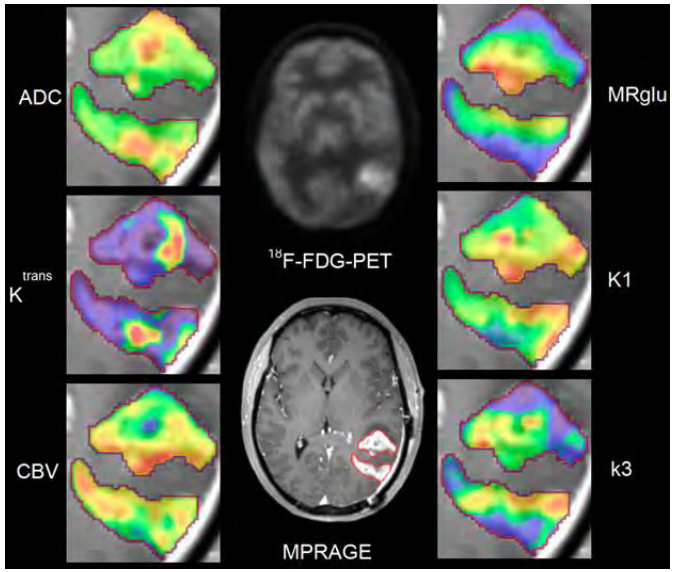
Novel MRI Sequences (e.g. Dixon & DWI)



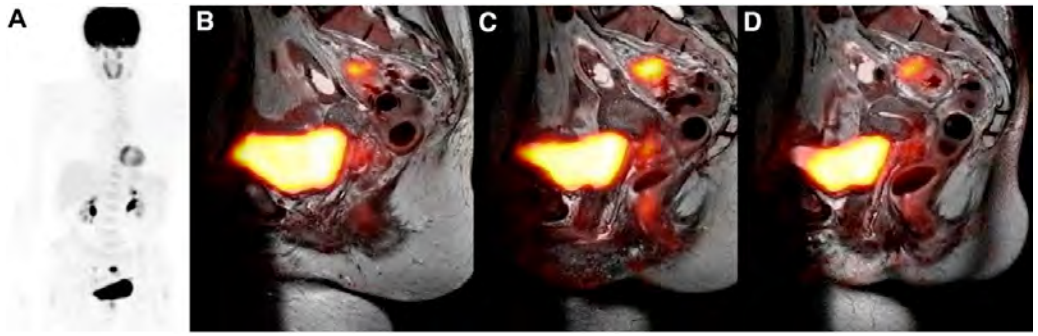
Colorectal cancer



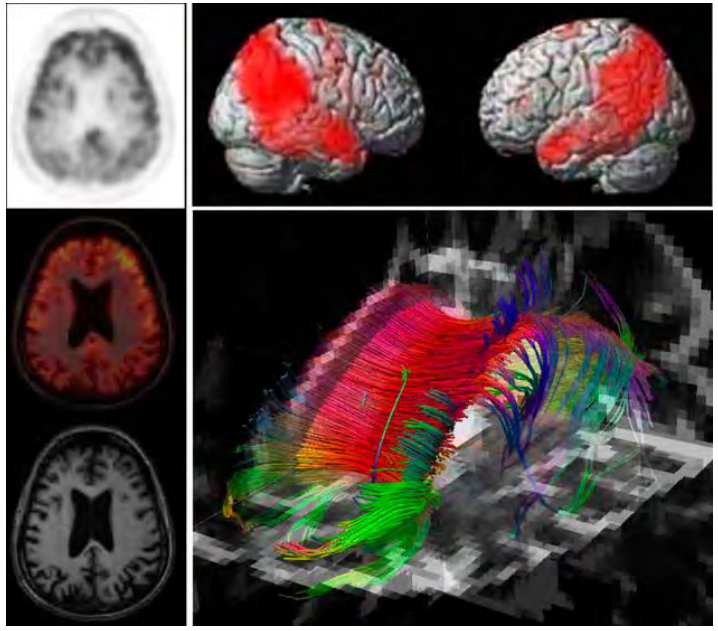
Prostate cancer



Glioblastoma



Cervical cancer



Alzheimer Disease

Catana, Guimaraes, Rosen (2013) J Nucl Med.

PET/MR: an MRI with PET inside/adjacent to it?

Evolution

PET

New detectors [APD, SiPM]

MRI

Redesigned Body Coils (with less photon attenuation, “MR visible”)

Redesigned RF/Gradient(?) Coils

Extra focus on WB MR sequences

MRI → PET

Attenuation correction based on MRI + segmentation + Truncation

Motion correction based on MRI

Scatter correction using information from MRI

PET → MRI

PET-guided MRI

Enhanced MR Quantification through PET

More investment is needed.

Solid Clinical Applications

Increased Clinical Efficacy
Evident Benefit on Positive Cost Impact

Growth Factors & Adoption Barriers

PET Utilisation – Growth Factors

Drivers
Proof for FDG in Oncology - e.g. Lung, H&N Cancer Staging
Combination of PET + CT - Reduced scan time dramatically - Gave 'anatomical' reference to function
Novel Indications - e.g. NET Therapy Monitoring
Better Access to tracers - $^{68}Ga/^{82}Rb$ Generators - Novel Business models for tracer distribution - baby-Cyclotrons
Reduction of Costs - Systems. Clear focus from most manufacturers to value segments. - Radiopharmaceuticals
New Manufacturers (re-/entered) the Molecular Imaging Space Toshiba (PET/CT SPECT) - United Imaging (PET/CT, PET/MR WIP) - Neusoft (PET/CT) - Positron Copr. (cardiac PET) Samsung (CT → PET/CT?)

PET Utilisation –Areas of Concern

Retractors
Market Access for new Radiotracers • Slow development • Slower approval
Reimbursement • Clinical efficacy based on patient outcomes • Inhomogeneous reimbursement model in EU
Lag in patient referrals
Current Economic Climate

Clinical Efficacy

more challenging now than it was in the 1980s and 1990s. Regulatory agencies often require not only demonstration of increased diagnostic accuracy but also evidence for changes in patient management and improvement in patient-relevant outcomes before granting reimbursement for new imaging tests (*33*). As a consequence, decisions about reimbursement for imaging tests are increasingly based on the principles established for therapeutic agents (*33*). This situation represents a significant challenge for the entire field of medical imaging because the result of a diagnostic test often is only indirectly linked to patient outcome.

EXAMPLE:

Increased diagnostic accuracy by 30%
→ Treatment changes in patients 50%
→ Improved outcomes in patients 30%

Improved outcome shown in cases 4.5%

CONSEQUENCE:

Randomised clinical trials of several hundreds of patients will be needed.

Each for a specific indication
(e.g. Preoperative staging of II breast cancer followed by surgery)

(Weber, JNM 2014)

Thank you

antonis.kalemis@philips.com