From CERN to PET/MR

David W. Townsend, PhD

A*STAR-NUS
CLINICAL IMAGING RESEARCH CENTRE
SINGAPORE
Joint venture between Agency for Science, Technology And Research (A*STAR) And National University of Singapore (NUS)

Biomedical Sciences Institutes
A*STAR

NUS National University of Singapore

February 10-14, 2014

ICTR-PHE 2014

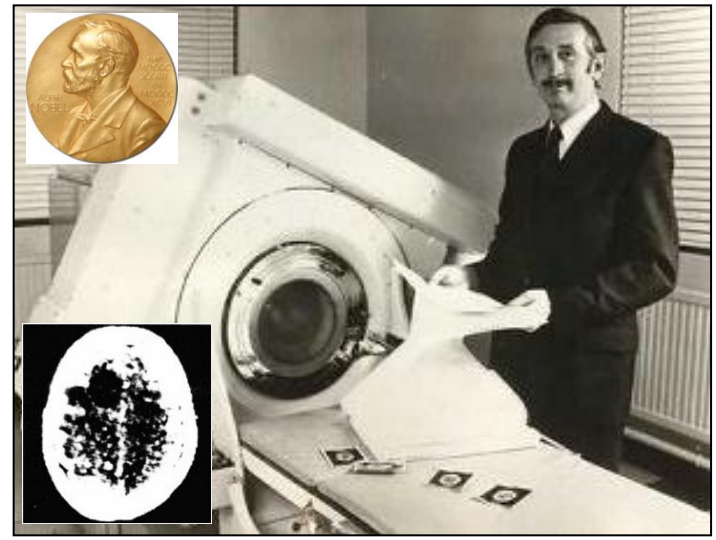
CERN

Uniting physics, biology and medicine for better healthcare

A conference that brings together the International Conference on Translational Research in Radio-Oncology and Physics for Health in Europe

Milestones of Non-invasive Imaging in Medicine

Invasive…….



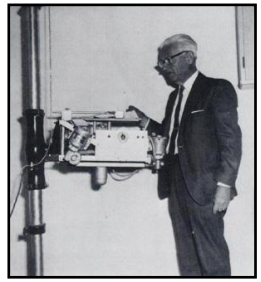
Tracer technique

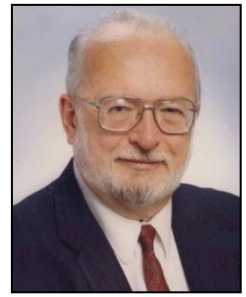
Nuclear Medicine

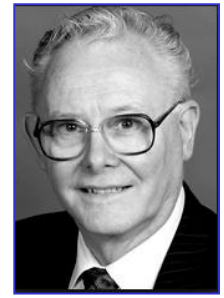
X-rays

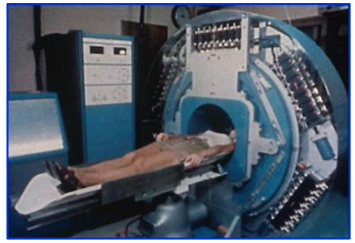
Radiology

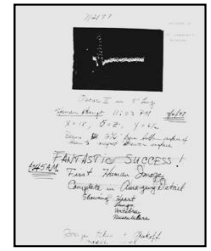
CT scanner











SPECT, PET

MRI and MRS

Imaging modalities today

Imaging Modality	Spatial Resolution (mm)	Acquisition time per frame(s)	Molecular probe mass required (ng)	Molecular sensitivity (mol/L)	Tissue penetration depth (mm)	Signal quantification capabilities
PET	1-2 (animal) 6-10 (clinical)	1-300	1-100	10^{-11}-10^{-12}	>300	High
SPECT	0.5-2 (animal) 7-15 (clinical)	60-2000	1-100	10^{-10}-10^{-11}	>300	Medium-High
Optical	2-5 (visible to IR)	10-2000	10^{3}-10^{6}	10^{-9}-10^{-11}	1-20	Low
MRI	0.025-0.1 (animal) 0.2 (clinical)	0.1-100	10^{3}-10^{6}	10^{-3}-10^{-5}	>300	High
US	0.05-0.5 (animal) 0.1-1 (clinical)	0.1-100	10^{3}-10^{6}	Not well characterized	1-300	Low
CT	0.03-0.4 (animal) 0.5-1 (clinical)	1-300	NA	Not well characterized	>300	Medium-High

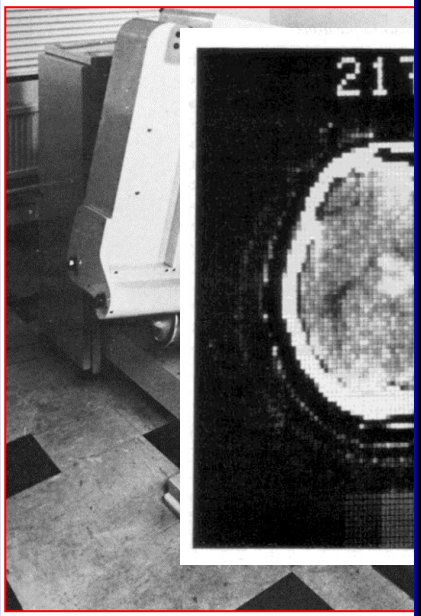
From Craig S Levin. Eur J Nucl Med & Mol Imag. 2005, 32(14), S-325-45

Evolution in CT

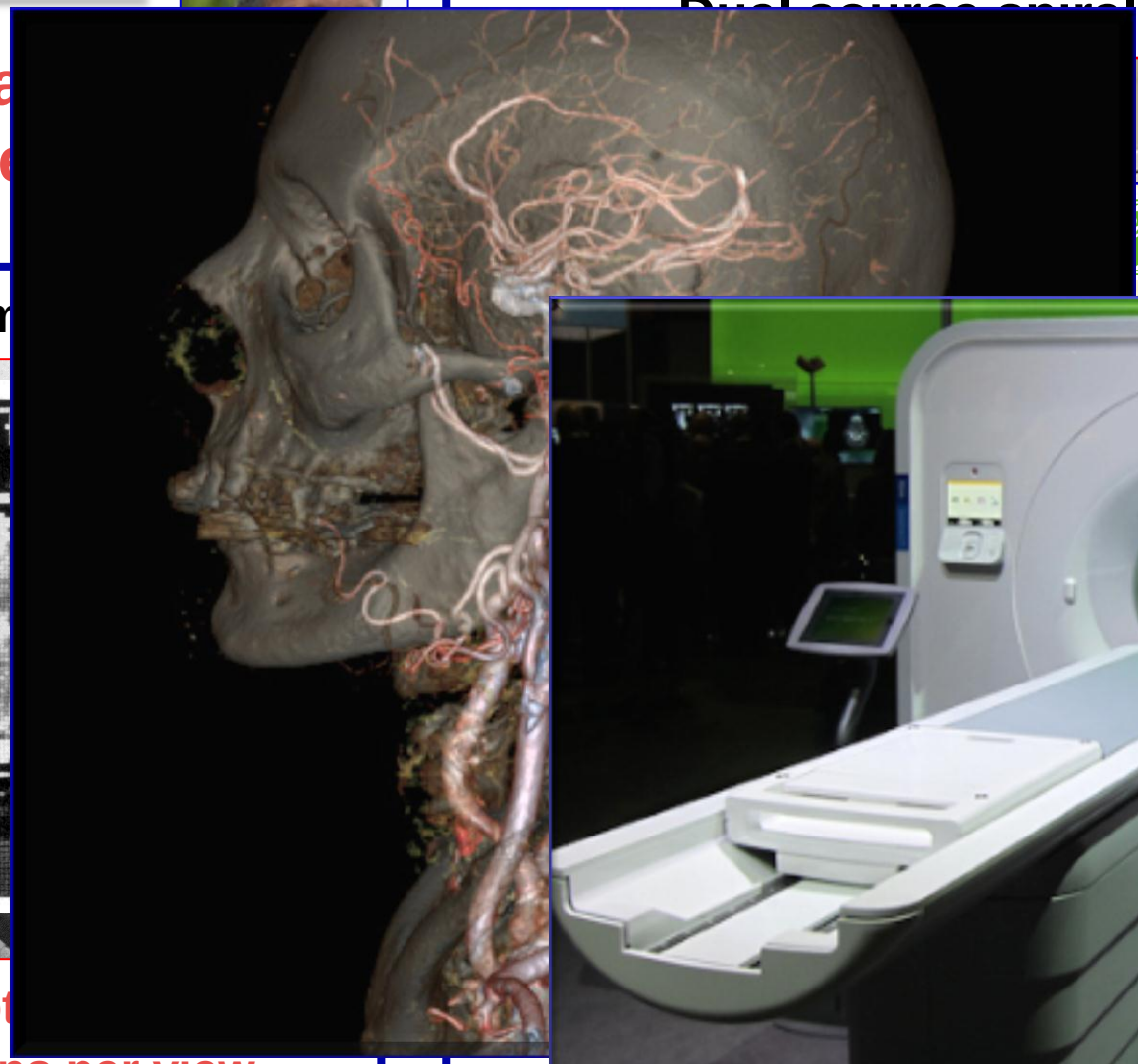
Siemens 128-slice
Dual source spiral CT (2005)

Over 40+ yea
of developme

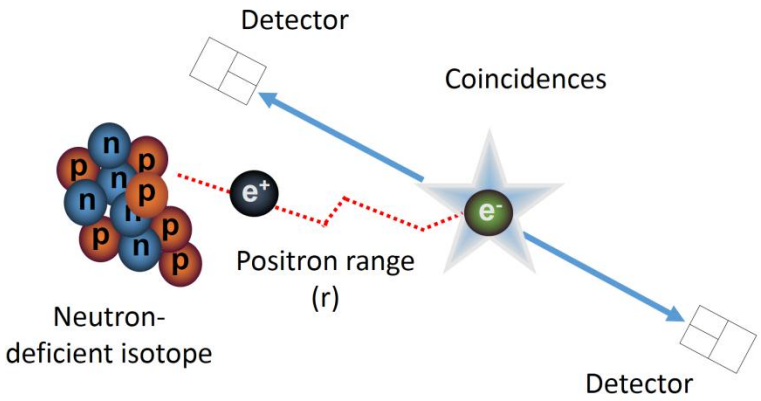
EMI parallel beam

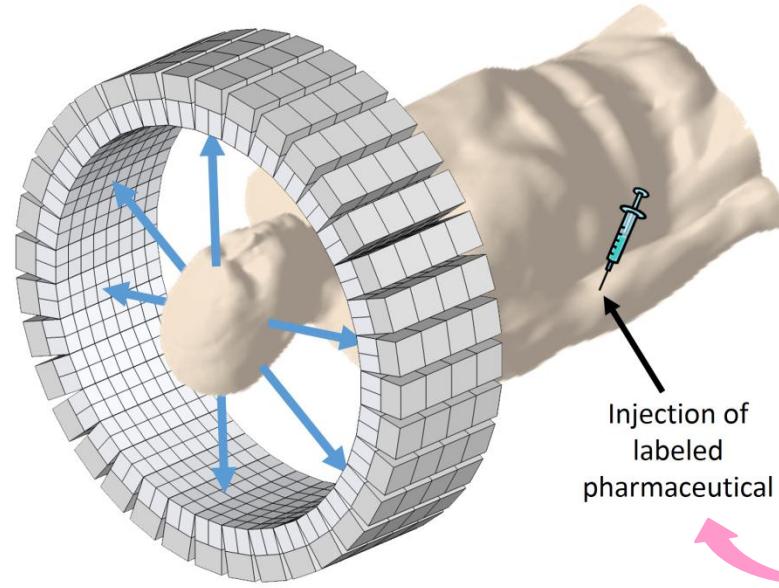


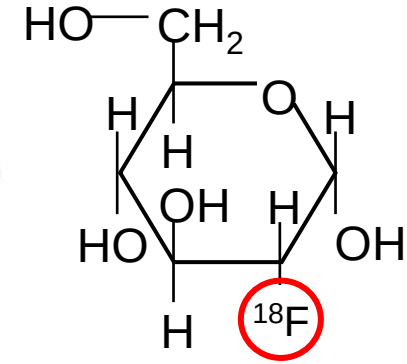
180 views per rot
2×160 positions per view
113 kB data



Positron Emission Tomography: how it works

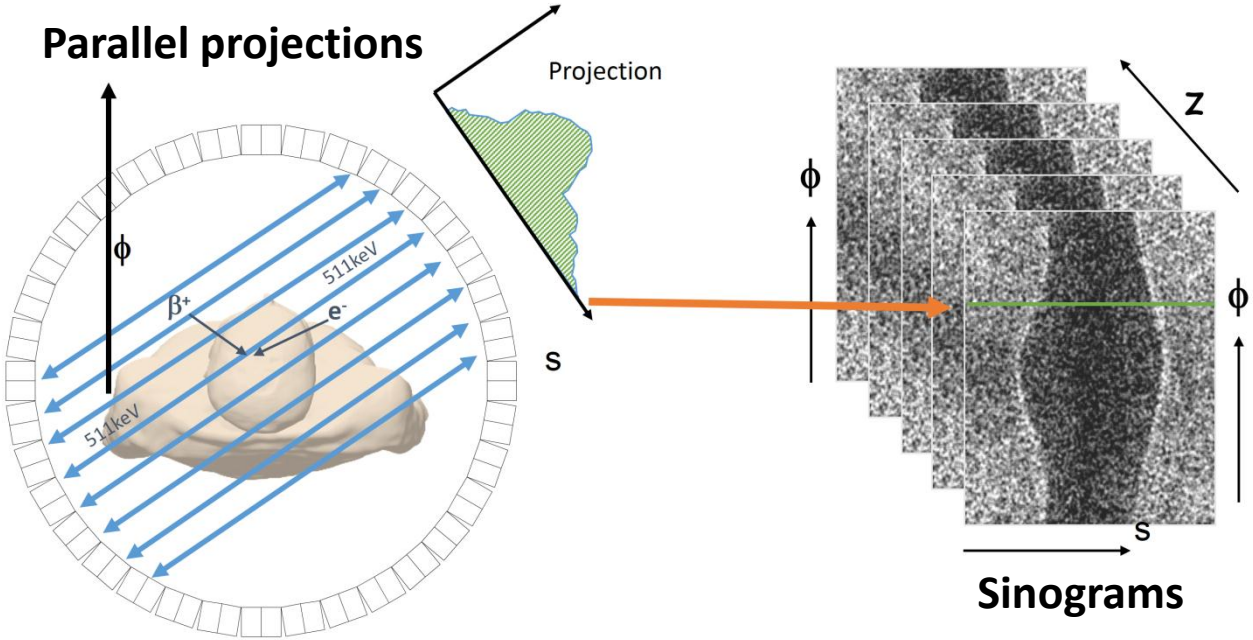




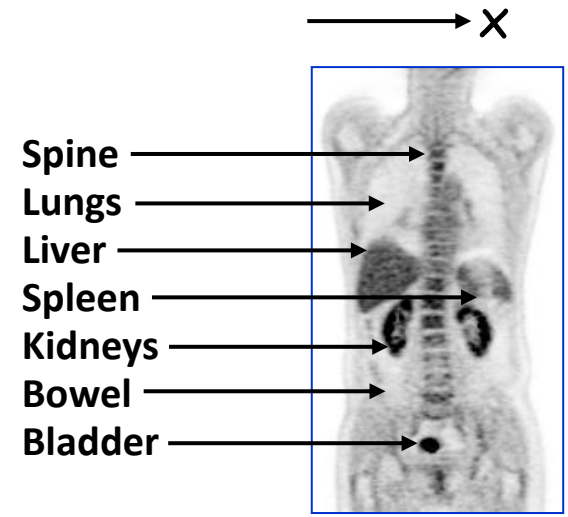


^{18}FDG

Parallel projections



Sinograms

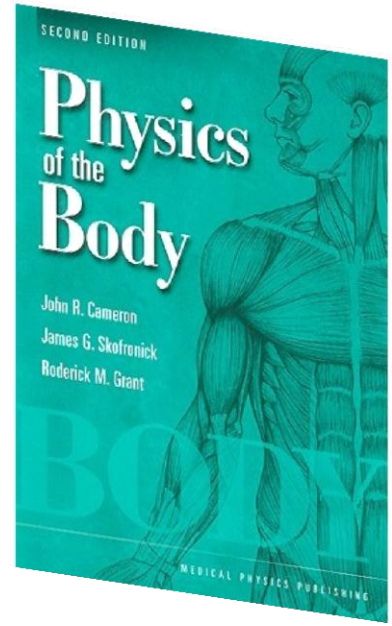


PET images

John Roderick Cameron

1922 - 2005

John Cameron (left) c.1958

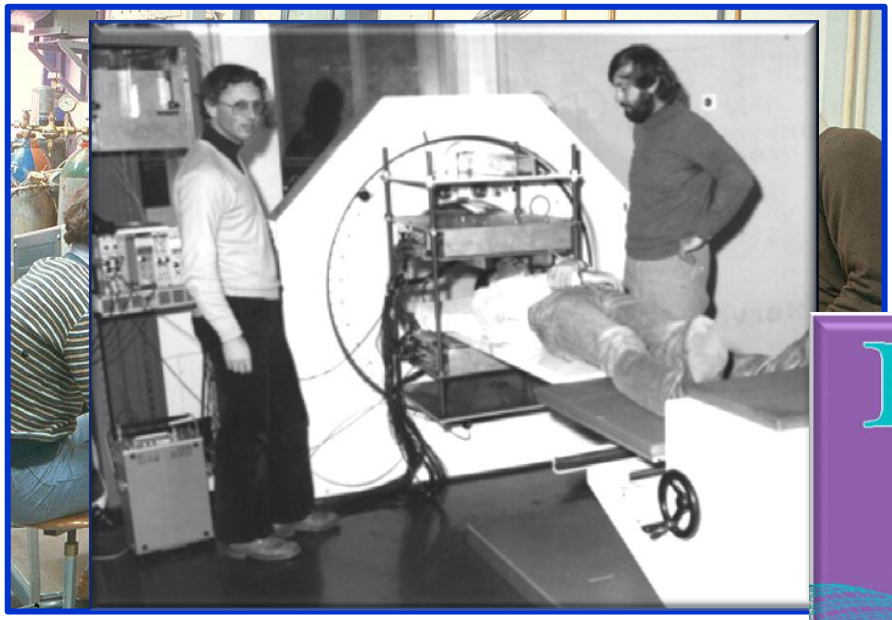


His Mission - *Making a Difference to Society*

"I found collaborating with congenial doctors about problems that physicists could help solve was very satisfying"

John Cameron

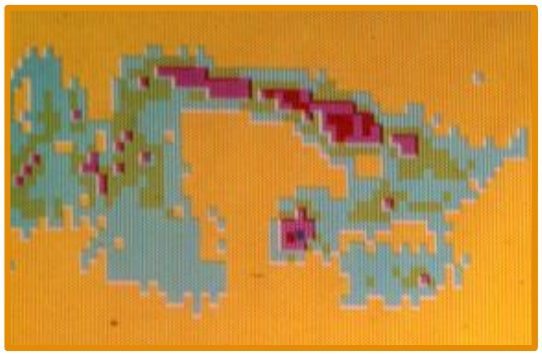
The HIDAC Camera Project, 1977-1988 CERN, Geneva



1978 CERN

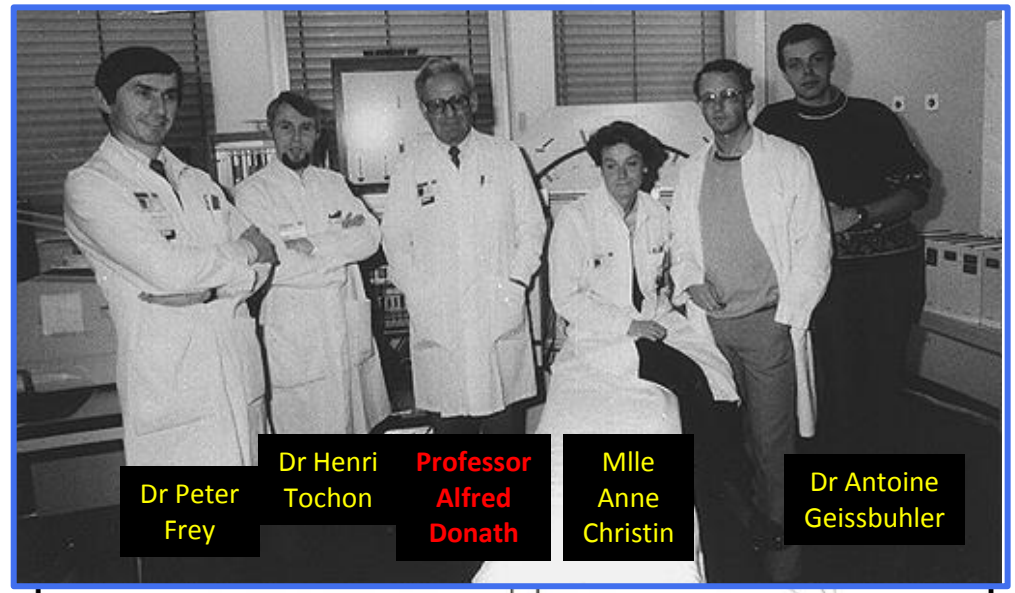
HIDAC PET Camera

Hopital Cantonal de Genève



First mouse imaged at CERN with Na-^{18}F in 1978

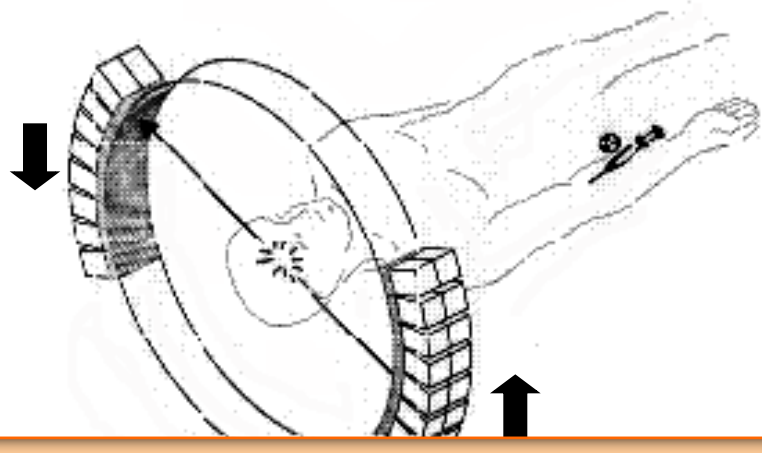
Thyroid imaging with ^{124}I

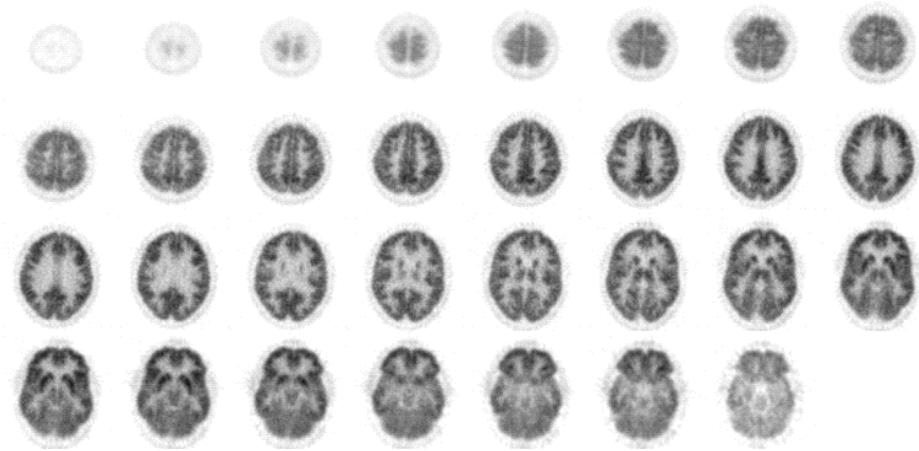


Tribune de Genève, January 1988

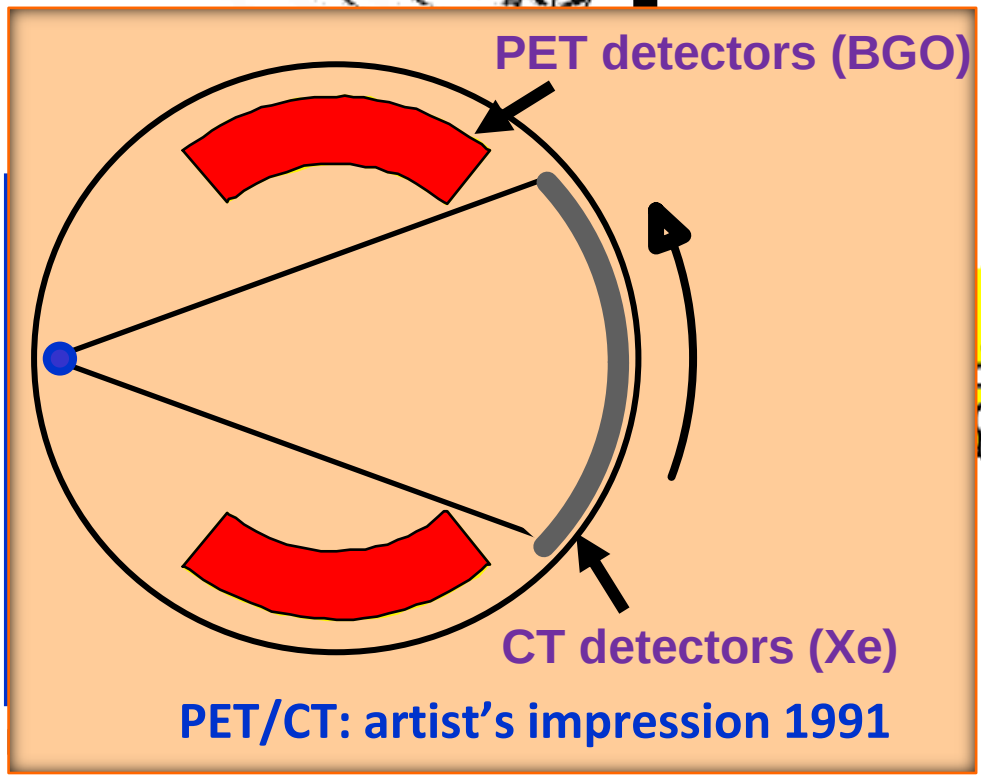
The PRT Camera Project 1990 - 1992

Financially supported by the CERS

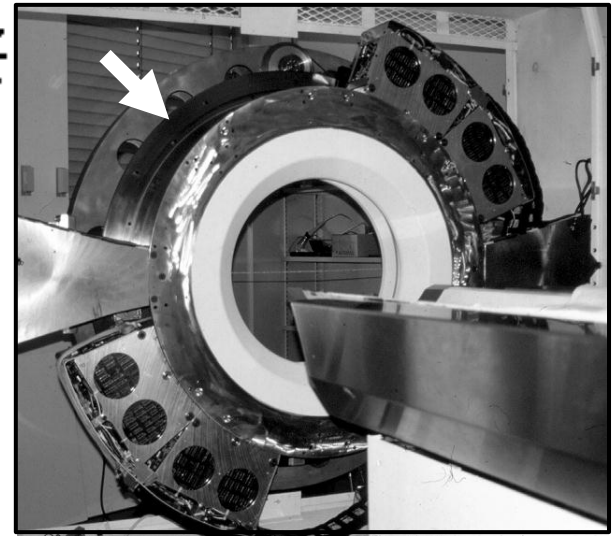




First FDG brain study on PRT-1, May 1991



PET/CT: artist's impression 1991



PRT-1

The device

First PET/CT device: 1995 - 1998

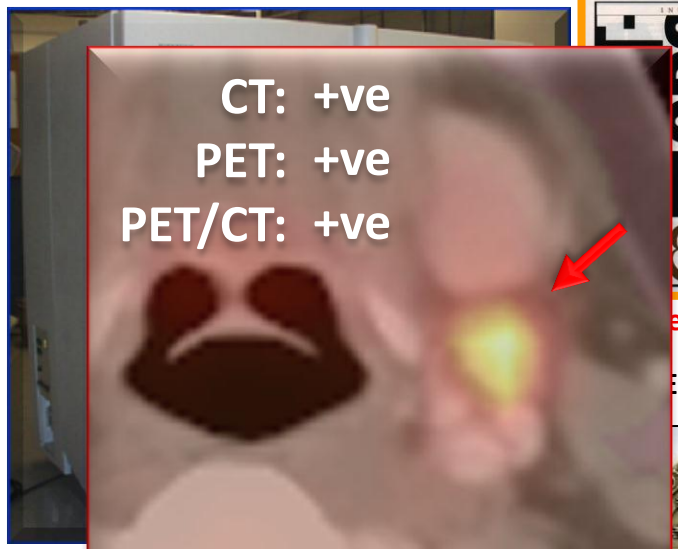
ECAT ART

PET

+

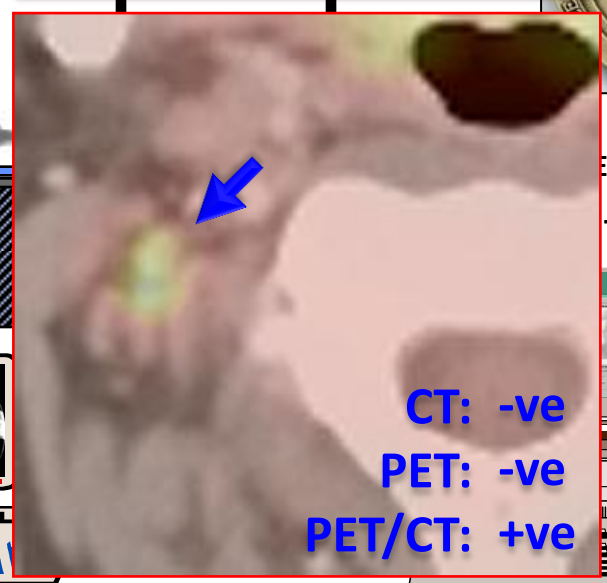
Somatom

AR.SP CT



edical Invention
of the Year
, December 2000

2010
Innovations in
Healthcare
Technology



CT console

PET console

Dr Ron Nutt

Dr Thomas Beyer

Dr Paul Kinahan

Dr Carolyn Meltzer

Ms Marsha Martinelli

nature International weekly journal of science

TECHNOLOGY

Multiple exposure

Combining imaging techniques can provide a wealth of inf

BY NEIL SAVAGE

In 1991, David Townsend, a physicist then at the University of Geneva in Switzerland, built a low-cost positron emission tomography (PET) scanner. The design left some spaces in the instrument's structure, and Townsend wondered whether he could fill them, and improve the machine, by squeezing a second scanning technology into the gaps. A doctor friend told him that surgeons were more familiar with the anatomical information provided by computed tomography (CT), so he added that, and the PET–CT scanner was born.

At first, many in the medical establishment were sceptical about the instrument's potential. "They all thought David Townsend was kind of loony," says Michael Vannier, a radiologist at the University of Chicago. "There was a lot of foot dragging associated with PET–CT."

But what was unfamiliar 15 years ago has since become the norm. These days, "any sensible person would not use PET a

adding that the PET–CT s
improved doctors' ability to
a lymphoma, allowing more
decisions." Simon Cherry, a
at the University of Californi
almost impossible to buy a P
a CT scanner attached to it

That succe
combine ima
many ways of
is perfect, bu
or more tech
to see details
improve the
ment of ailme
disease or Par

Imaging te
structural information — the physical shape of an organ or a tumour — or functional information, such as which molecules are present or what metabolic activity is occurring.

explains. "The end result is higher accuracy."

Wang is trying to improve endoscopy by combining conventional ultrasound with a technology called photoacoustics. Ultrasound

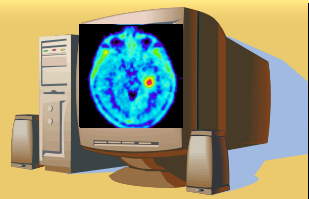
At first, many in the medical establishment were sceptical about the instrument's potential. "They all thought David Townsend was kind of loony," says Michael Vannier, a radiologist at the University of Chicago. "There was a lot of foot dragging associated with PET–CT."

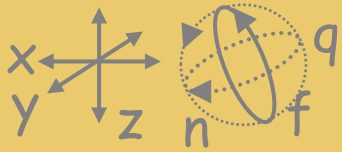
loon·y or **loon·ey** also **lun·y** (lo͞o'nē) *Informal*
adj. **loon·i·er** also **lun·i·er**, **loon·i·est** also **lun·i·est**
1. Extremely foolish or silly.
2. Crazy; insane.

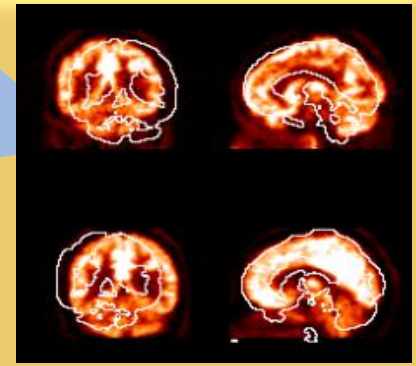
"I hate to say it, but radiologist and nuclear medicine docs don't work as a team now most of the time, and getting the two types of images from one device won't change this characteristic."

Fusion imaging: from software to hardware

1990

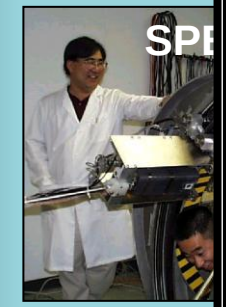




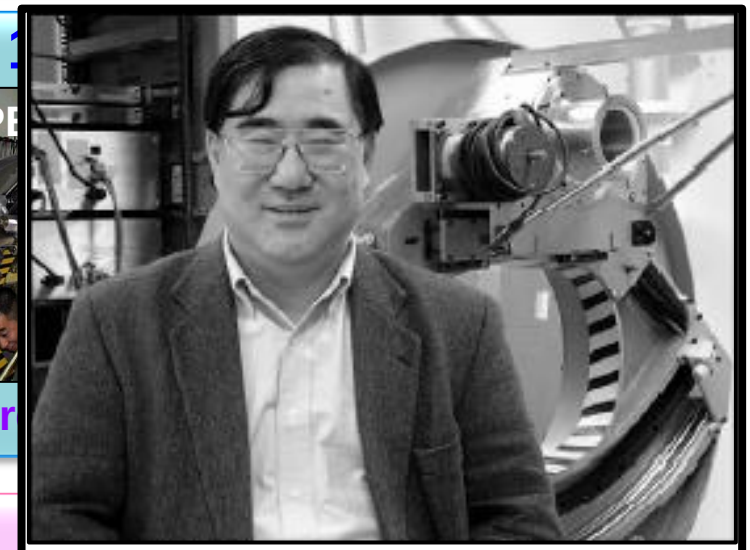


Software-based fusion (semi-automated)

1993 - 1



Hardwar

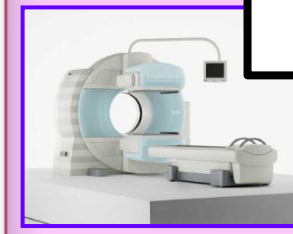


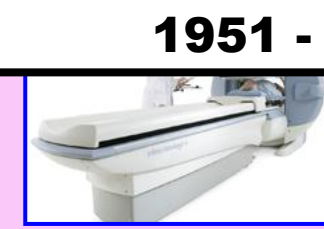
Bruce H Hasegawa, PhD
1951 - 2008

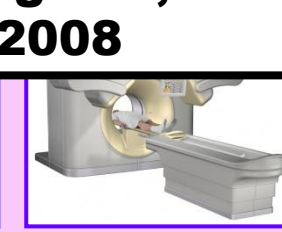
2001

Hardware-based fusion: Commercial PET/CT

2004

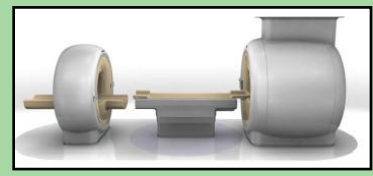


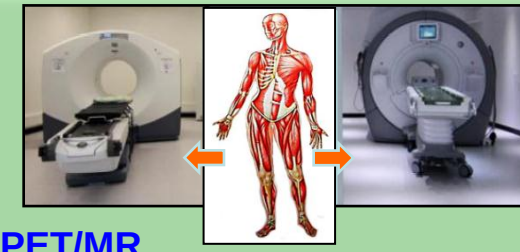




Hardware-based fusion: Commercial SPECT/CT

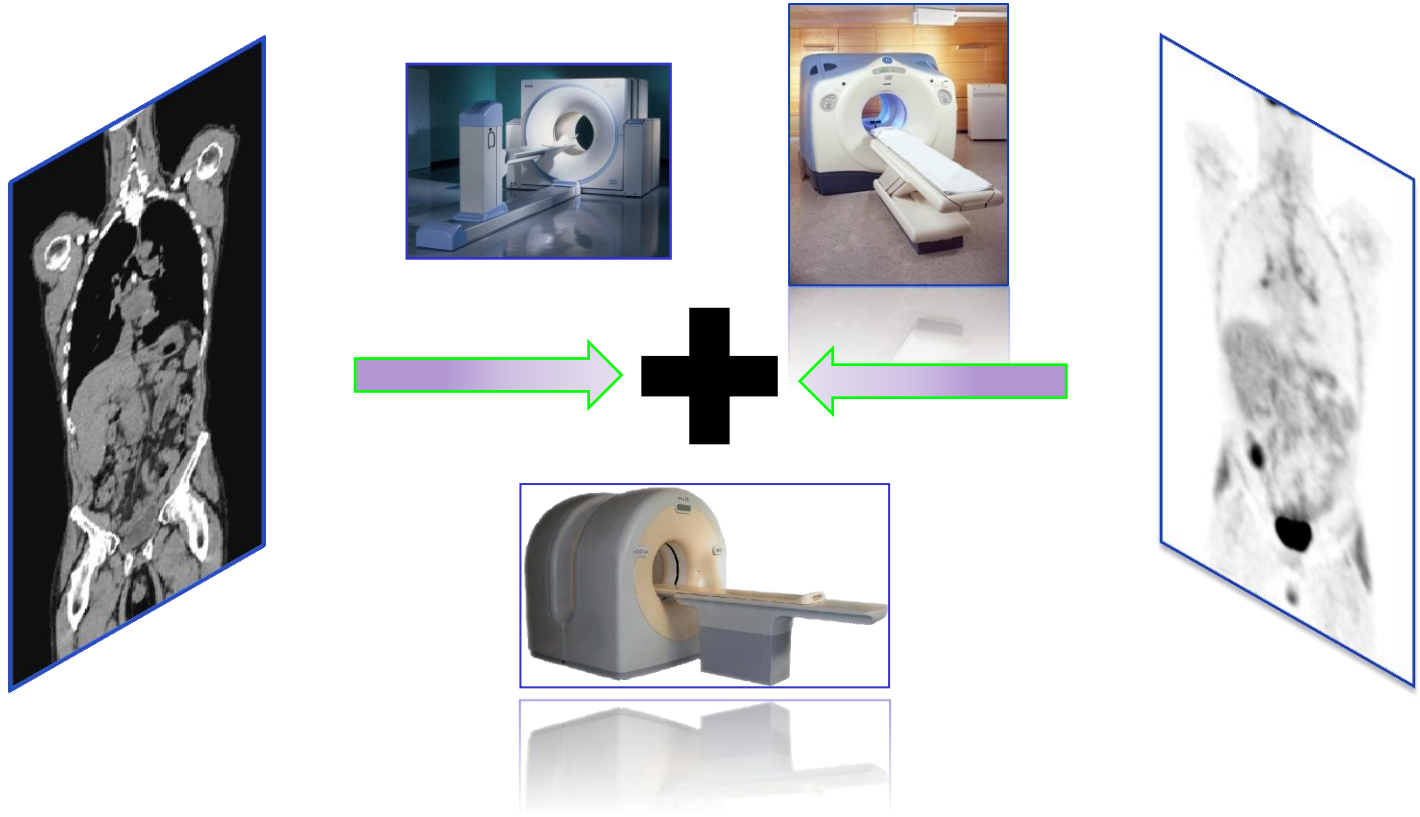
2010





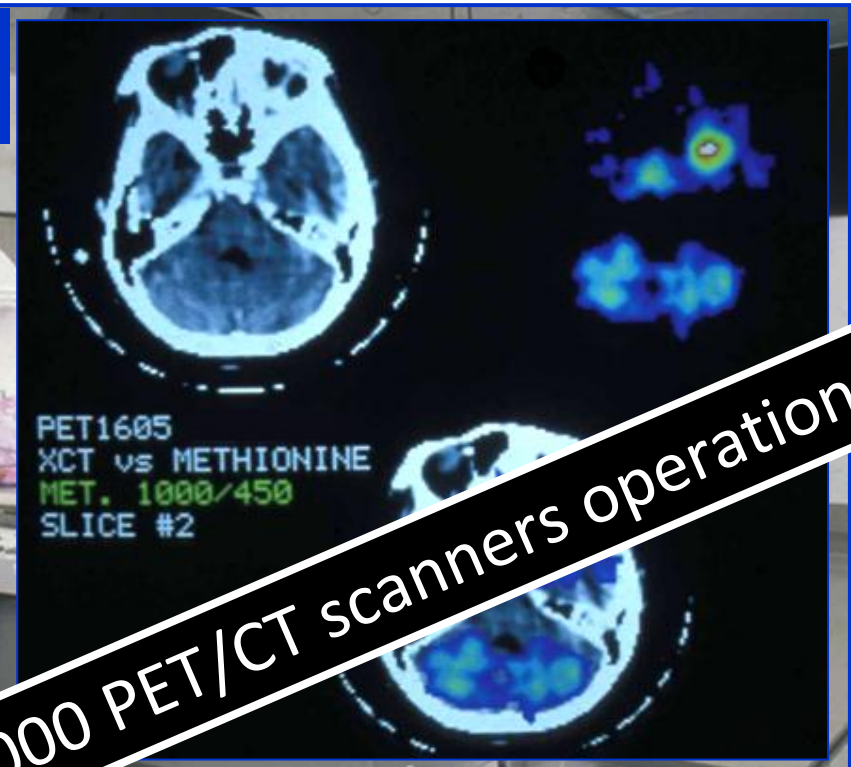
Hardware-based fusion: Commercial PET/MR

2001: PET/CT in the clinic



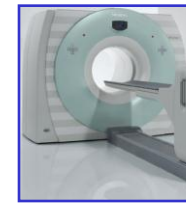
The evolution of PET/CT 1984 - 2013

Gunma University, Japan 1984
Prof. Teruo Negai

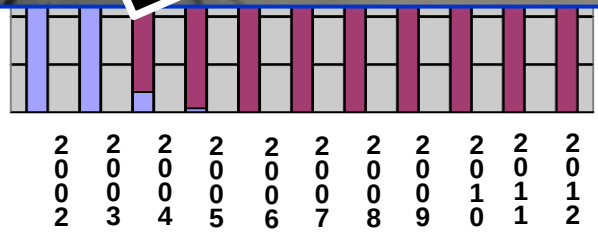


Now around 4000 PET/CT scanners operational worldwide

009 **2010** **2011** **2012** **2013**



Chuck Melcher



NEMA - US Shipments ($M)

Has PET/CT made a real difference?

PET/CT vs PET and CT: average over all cancers: **10-15% accuracy improvement**

- **Head and neck**

  Accuracy: 95% vs 83% PET; 73% CT

- **Thyroid**

  Accuracy: 93% vs 78% CT

- **S**

  Accuracy: 96% vs 81% CT

- **Lung cancer**

  Accuracy: 98% vs 80% PET (T stage)

- **Breast cancer**

  Accuracy: 90% vs 79%

- **Esophageal cancer**

  Accuracy: 92% vs 86% PET

- **Colorectal cancer**

  Accuracy: 89% vs 78% PET

PubMed on PET/CT: 6500+ publications

Accuracy: 93% vs 78% CT

- **Melanoma**

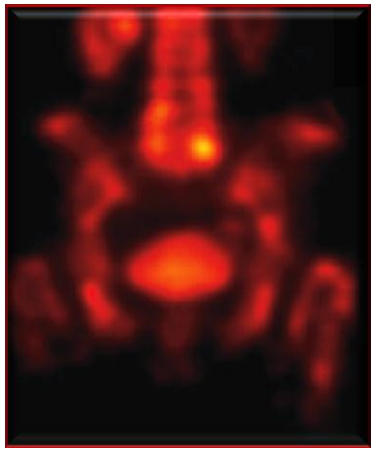
  Accuracy: 97% vs 93% PET

- **Unknown primary**

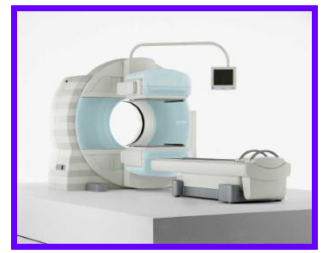
  No difference; 20-40% detected

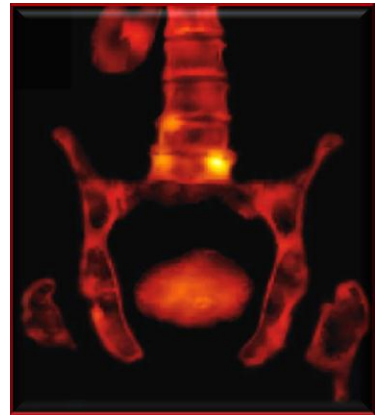
Czernin, Allen-Auerbach, Schelbert. J Nucl Med 48 (1, Supplement) 2007: 78S – 88S

2004: SPECT/CT in the clinic



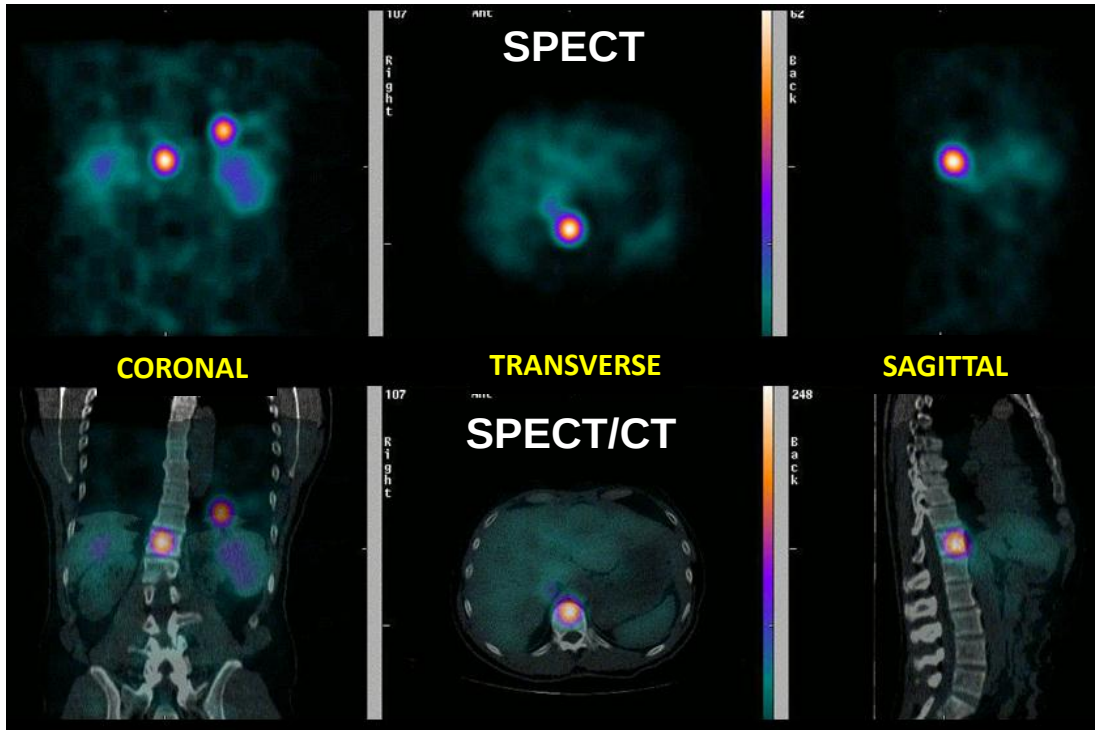
Conventional SPECT





SIEMENS xSPECT

Symbia TX

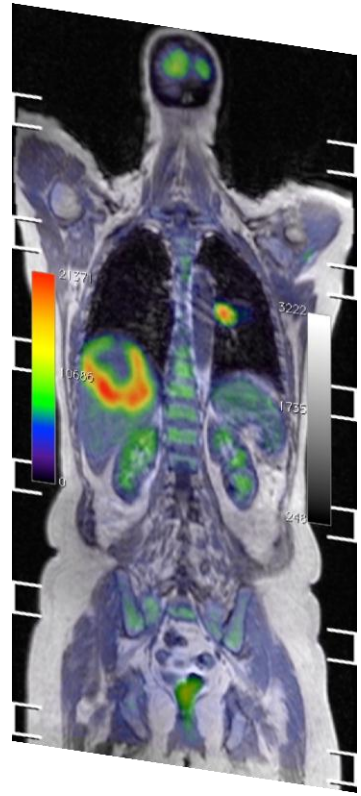


Discovery NM/CT 670

"CT is potentially more valuable for SPECT than for PET"

Bailey DL. Eur J Nuc Med & Mol Imag 2003; 30(7):1045-1046

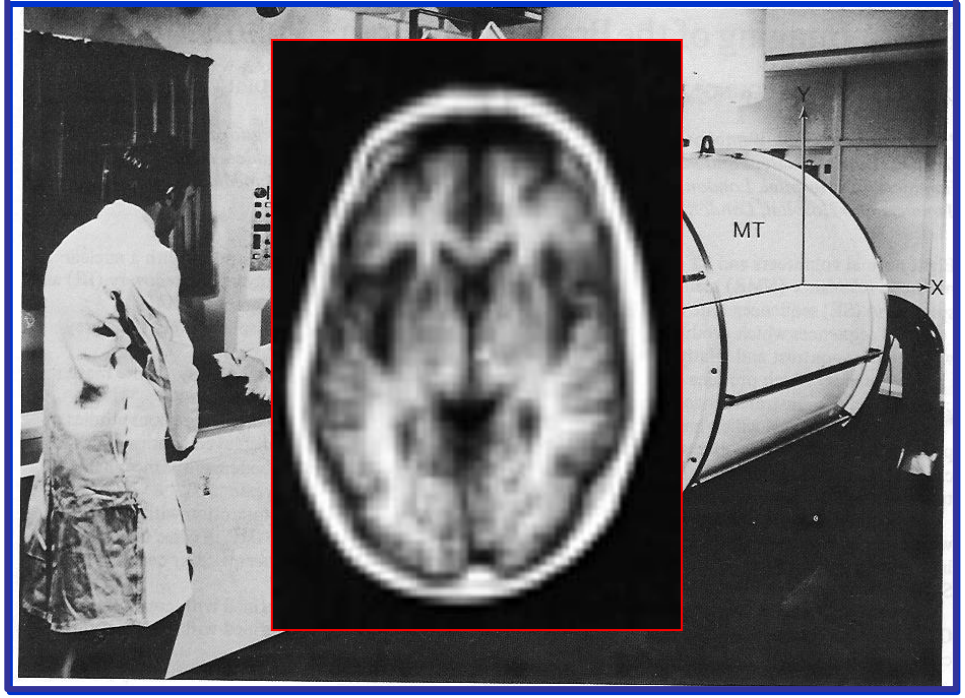
2010: PET/MR in the clinic



Advances in MR

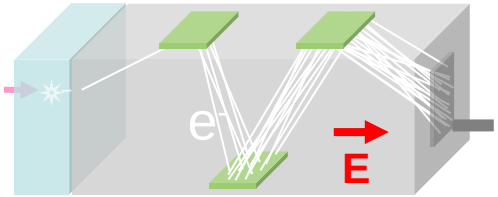
Over 30+ years of development

First patient on Aberdeen MRI (1980)

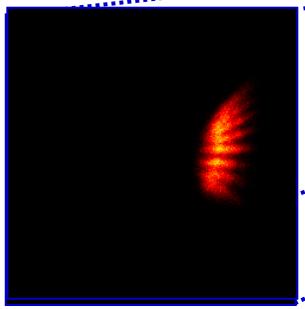


SIEMENS Skyra MRI scanner (2013)

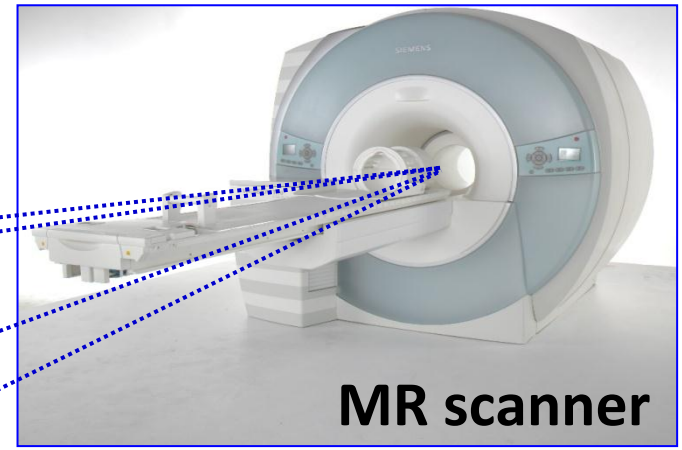
Solid state photodetectors for integrated PET/MR

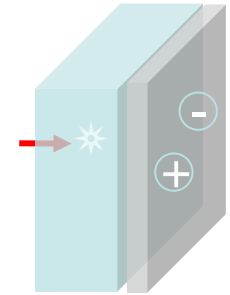


Block detector

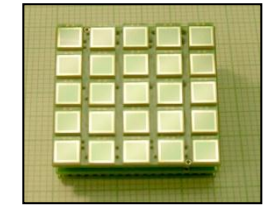


B = 1.5 T





APD-based
PET detector



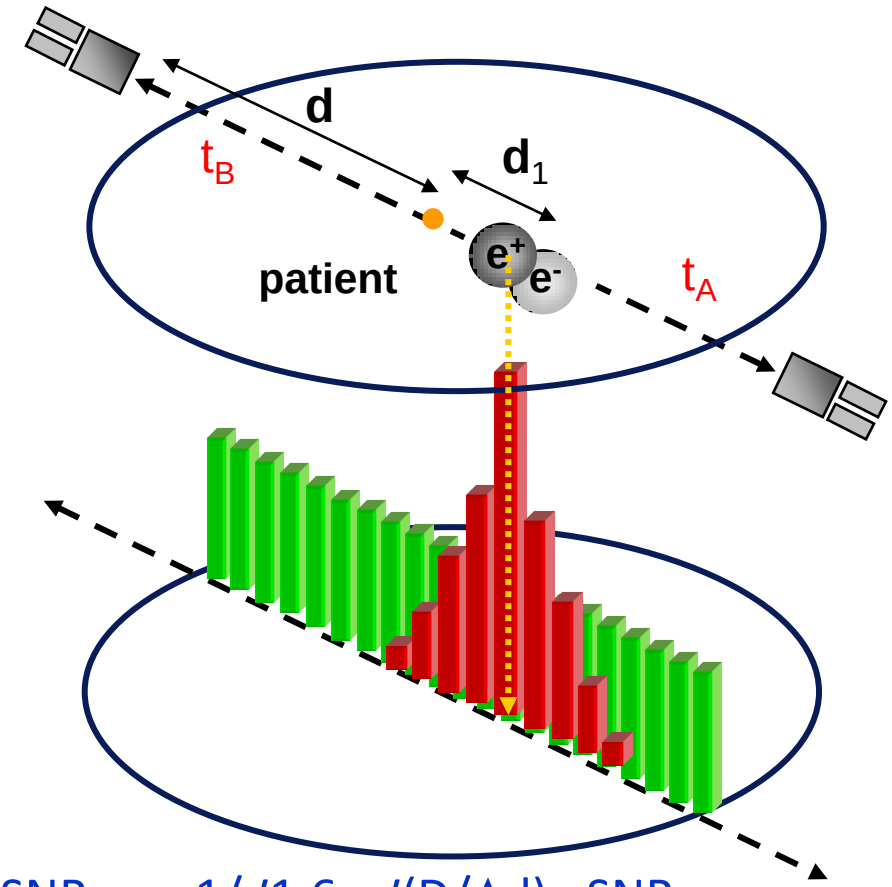
SiPM-based
PET detector

Photodetectors

	PMT	APD	SiPM	dSiPM
MR compatible	No	Yes	Yes	Yes
TOF capability	Yes	No	Yes	Yes
Stability	Good	Good	Unknown	Unknown
Amplification	High (10^6)	Low (10^3)	High (10^6)	N/A
Compactness	Bulky	Compact	Compact	Very compact
Power Readout	HV, ASIC Analog	HV, ASIC Analog	LV, ASIC Analog	LV, simple Digital

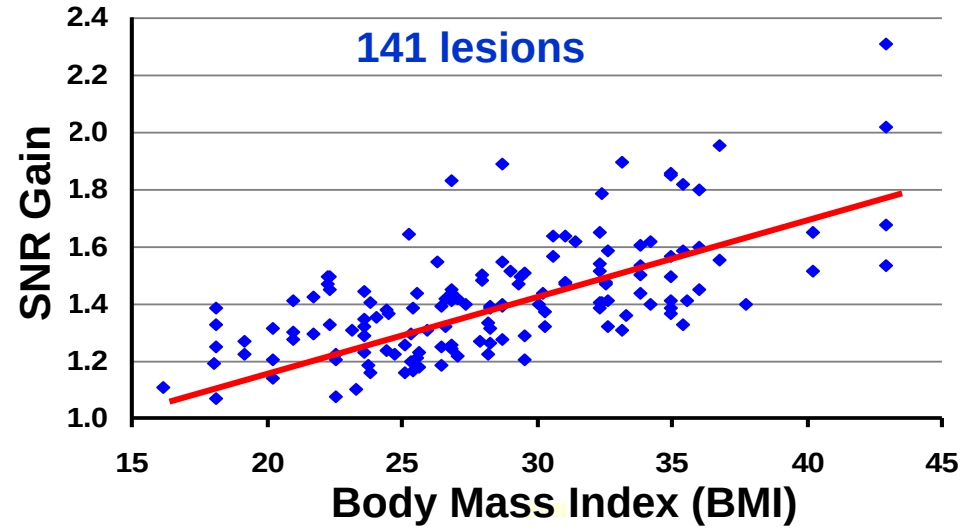
PHILIPS VEREOS PET/CT

Time-of-Flight (TOF)

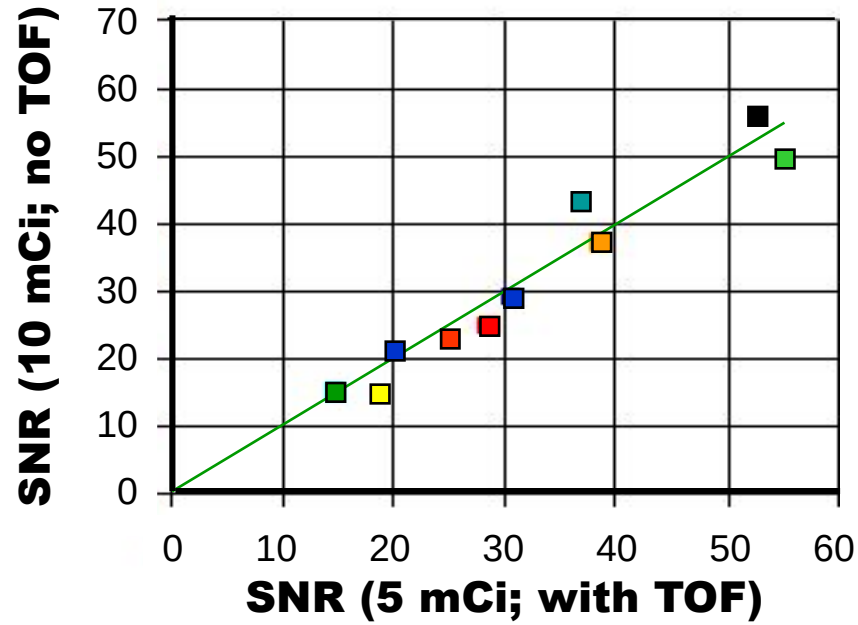


$SNR_{TOF} = 1/\sqrt{1.6} \cdot \sqrt{(D/\Delta d)} \cdot SNR_{conv}$

Δs (ps)	Δx (cm)	SNR gain
100	1.5	5.2
300	4.5	3.0
500	7.5	2.3
1200	18.0	1.5



✓ **Improved signal-to-noise**



✓ **Reduced radiation dose**

Current designs for MR/PET (/CT)

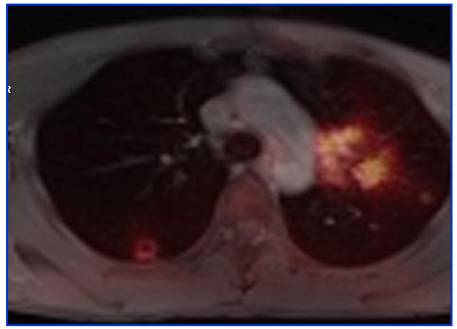
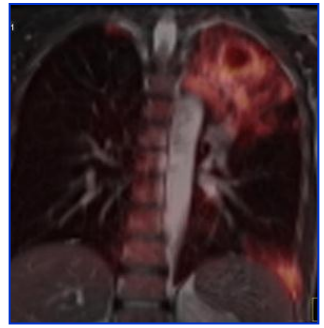
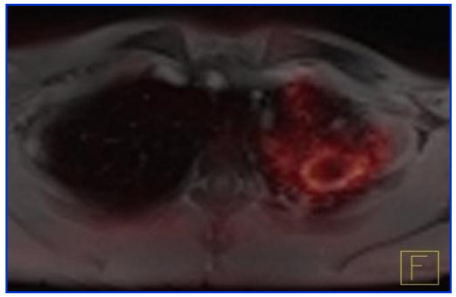
Discovery MR750w

Vendor	Installations
Siemens	39
Philips	12
GE	6
TOTAL:	**57**

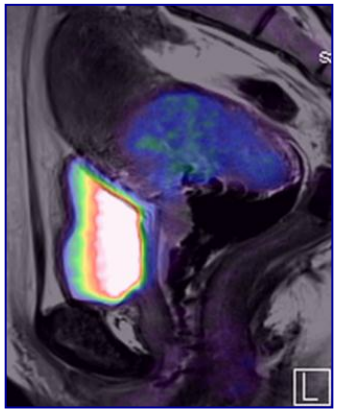
Achieva-X (3T MR)

SIEMENS mMR

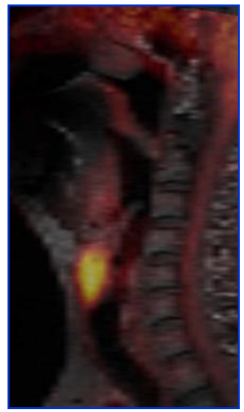
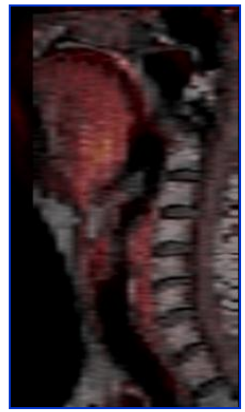
Malignant and non-malignant diseases


FDG-PET/MR in patients that are receiving treatment for tuberculosis

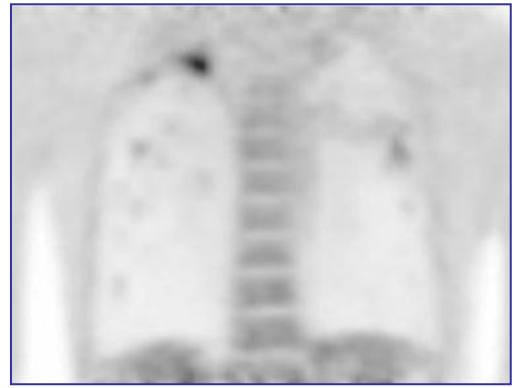
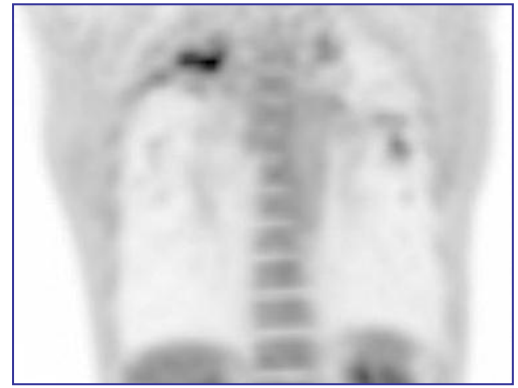
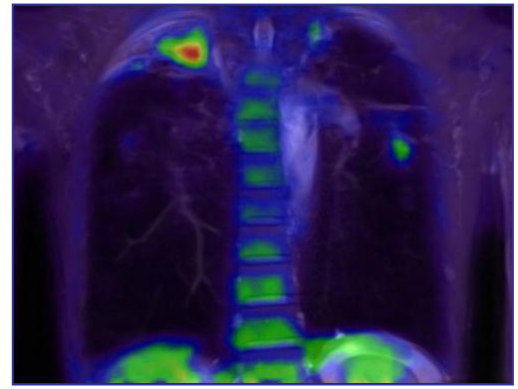
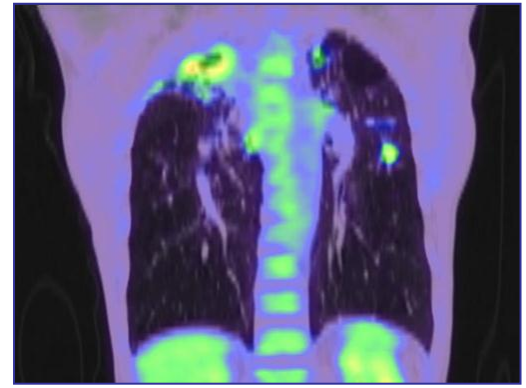


Ovarian cancer

Therapy response

Tuberculosis

PET/MR **PET/CT**

WB radiation dose for PET/MR: ~ 3mSv

Summary:

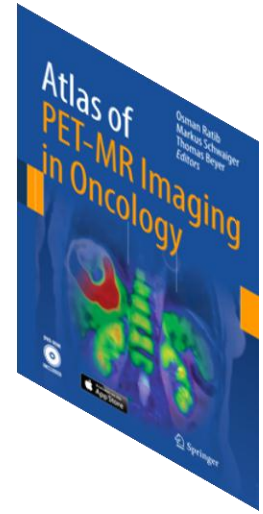
Johannes Czernin
UCLA

PET/CT: A technical *evolution* and an imaging *revolution*

- **2002 – 2004: *Units shipped in USA: 360***

PET/MR: A technical *revolution* and an imaging *evolution*

- **2010 – 2012: *Units shipped in USA: 14***



Is there evidence of real clinical benefit?

- ✓ **PET/CT over PET and CT separately** **1 + 1 = 3**
- ✓ **SPECT/CT over SPECT and CT separately** **1 + 1 = 4**
- ✓ **PET/MR over PET(/CT) and MR - TBD** **1 + 1 = ?**

Some challenges for medical imaging:

- to address the concern and “fear” of ionizing radiation
- for screening and early detection of disease (cancer, AD)
- for metabolic diseases such as diabetes (image β-cells)
- to develop molecular imaging as companion diagnostics
- ……and to do all that at a reasonable and affordable cost

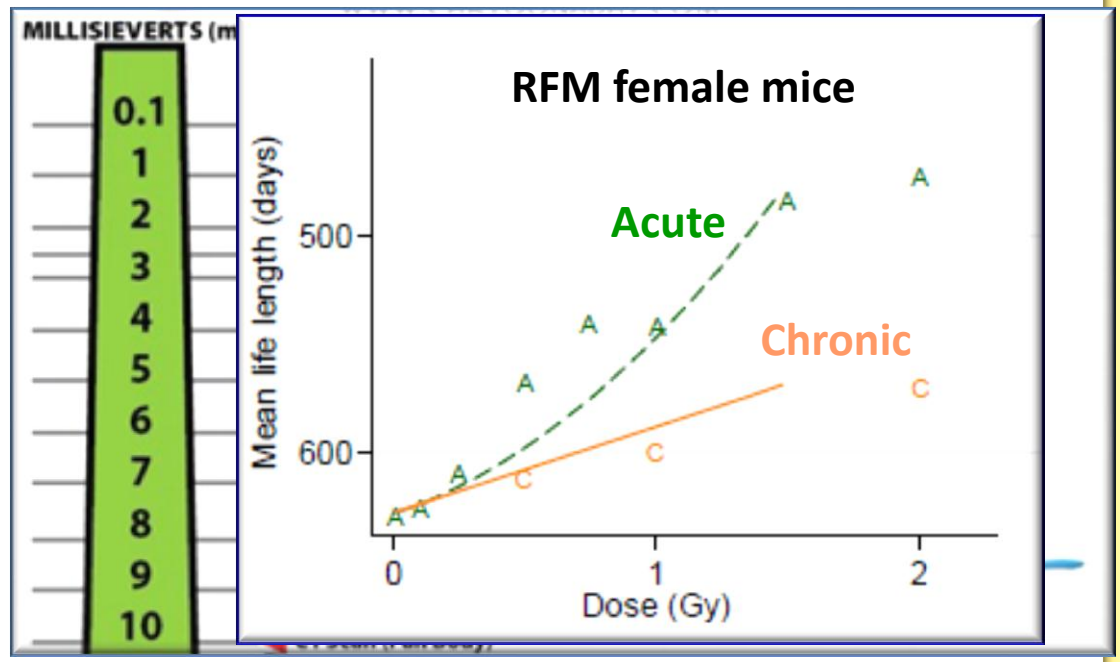
Radiation doses for clinical imaging procedures

Annual Background Radiation

Lower limit for known effects of radiation

No reliable data on effects of radiation

- CT Abdomen / Pelvis
- PET/CT (FDG)
- Myocardial Perfusion Scan
- Chest CT
- Virtual Colonscopy
- CT Screening Lung Cancer
- PET/MR (FDG)
- MBI (8 mCi)
- Mammogram + tomosynthesis
- Mammogram
- Chest X-ray
- Bone Densitometry

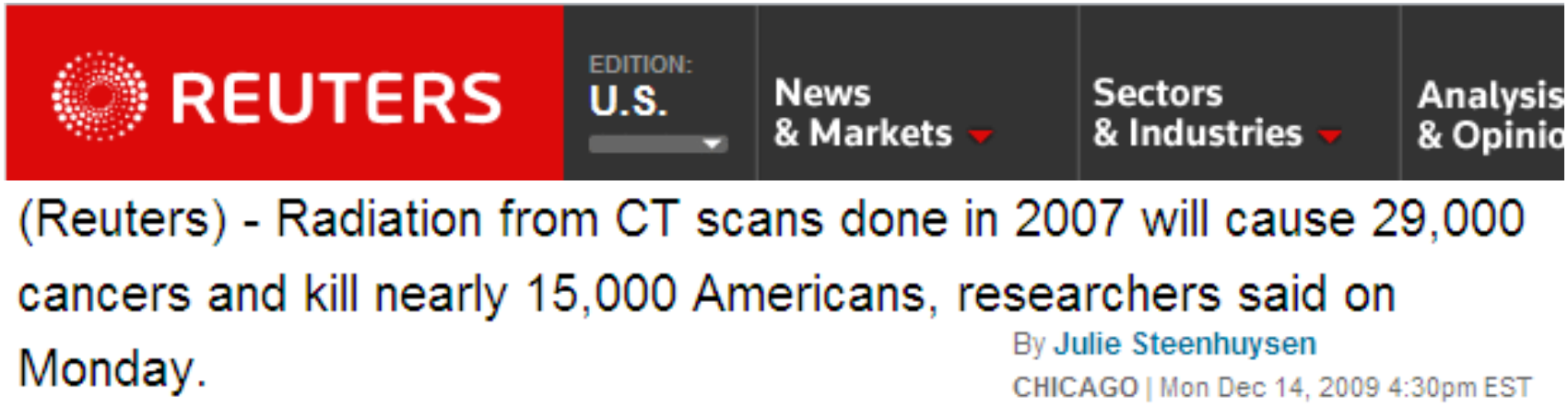


Very Low Dose | Low Dose

100

Radiation Dose (mSv)

Hype from the popular Press



"My main frustration is the fear of cancer from low dose radiation, even by radiologists"

"Too many radiologists still believe there is a risk from a chest x-ray. Few radiologists can explain radiation to the patient in words the patient can understand"

John Cameron

More hype from the popular Press

The New York Times

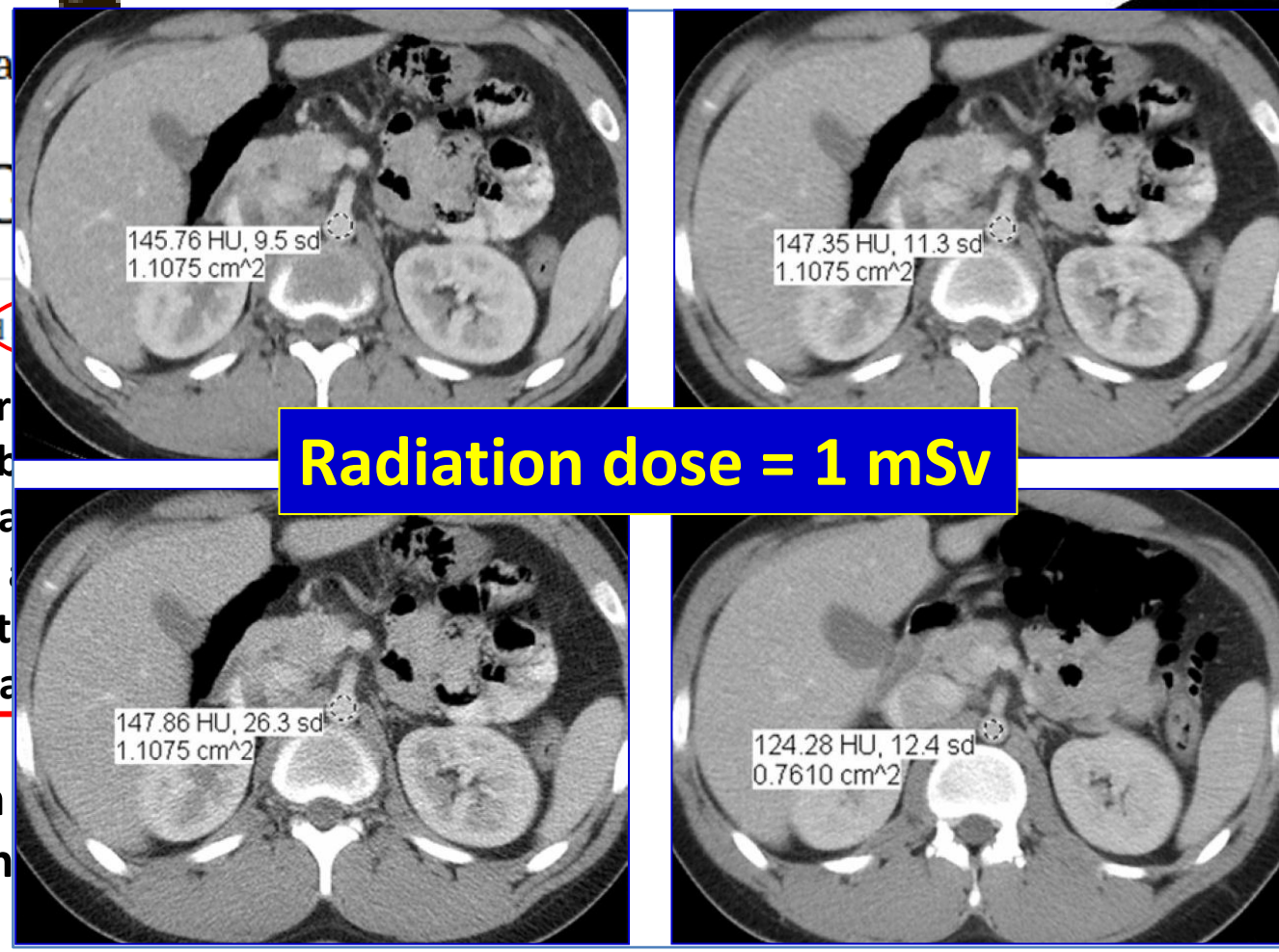
The Opinion Pa

We Are C

By RITA F. REDBERG and

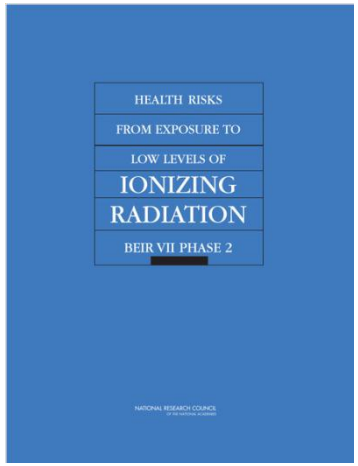
DESPITE great str
rates remain stub
disease as the lea
Increasingly, we
important culprit
are silently irradia

2012: 14 million
→ 1 in 5 men



Focus areas: ***stop smoking, reduce obesity, vaccination against HPV (cervical and liver)***

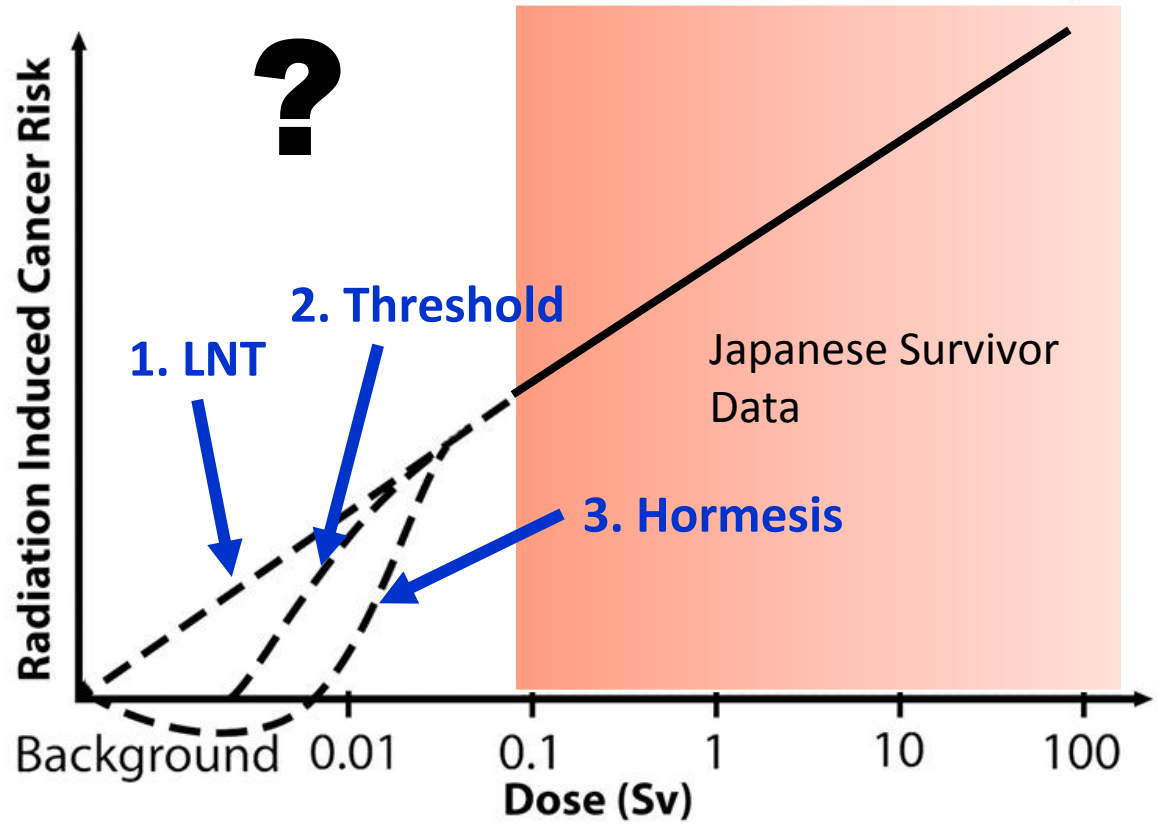
The BEIR Report: theoretical models



Biological Effects of Ionizing Radiation (BEIR) VII Phase 2 (2007)

The models:

1. Linear No Threshold
2. Threshold
3. Hormesis



Potential sources of data:

A. Environmental Radiation Studies
B. Occupational Radiation Studies
C. Medical Radiation Studies
D. Atomic Bomb Survivor Studies

No scientific data to distinguish between any of the models

The challenge:

Michael O'Connor, Mayo Clinic

We need to reduce radiation dose from imaging procedures:

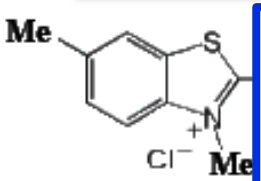
- Not necessarily because it causes cancer
- But because people *fear* it will cause cancer
- And where does this fear come from?

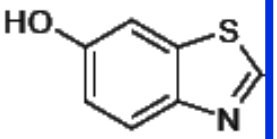
  - inappropriate use of the BEIR risk models

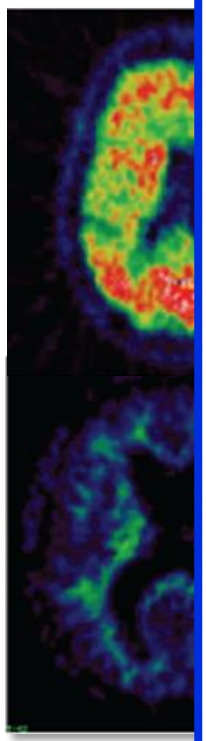
Consequences: Negative impact on patient care:

- Patients declining needed exams or procedures
- Physicians ordering alternate exams, which may be less accurate, more expensive, or require anesthesia

Amyloid and tau imaging agents for Alzheimer's Disease





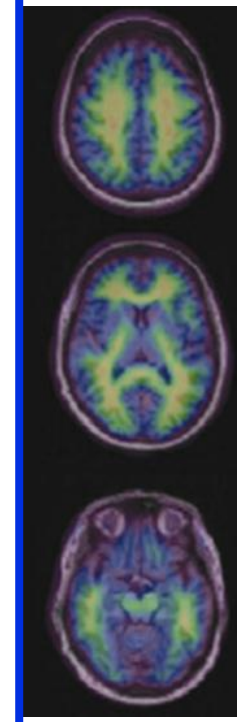


^{11}C-P

Imaging of amyloid plaques

nd 105 B€

to a greater
mbinant tau
rils.



AD (Aβ+)

^{18}F-THK523 imaging of τ-protein

Villemagne et al., JNM 2012

Mail Online

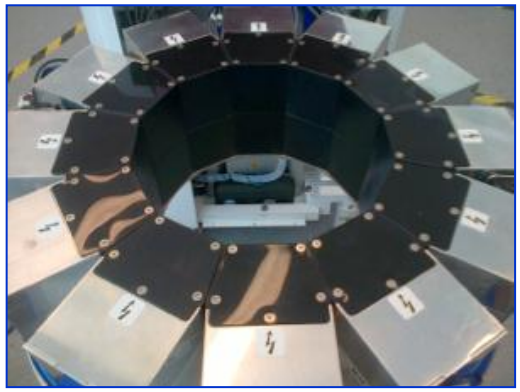
Thursday January 16th 2014

Can this 'science-inspired' soft drink REALLY help prevent Alzheimer's?

- 'Brainwave' contains ingredients which 'help reduce cognitive degradation'
- Scientifically developed drink 'could help to maintain a healthy mind'
- Available in one flavour, Mango, Pineapple and Jasmine, drink has 2.5 cals
- Comes in multipacks of 24 for £35, from brainwavedrinks.com

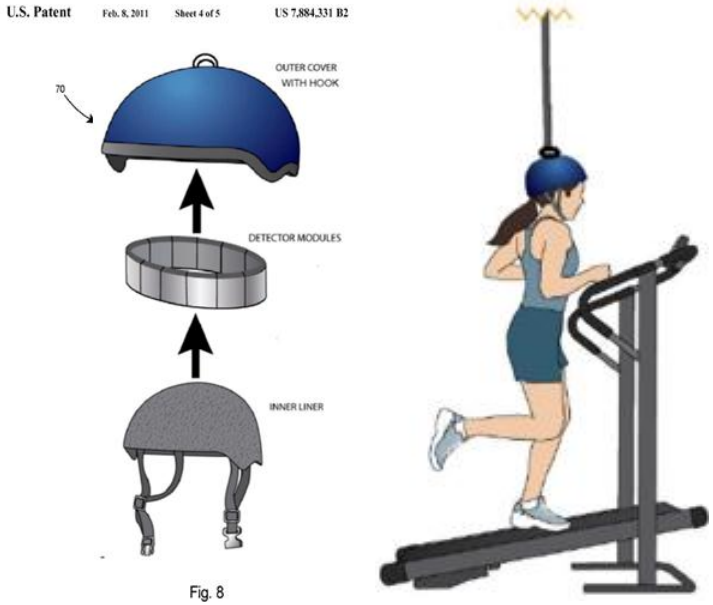
Studies show drinking green tea at a certain level combined with other natural ingredients at a specific dosage encourages positive cognitive health

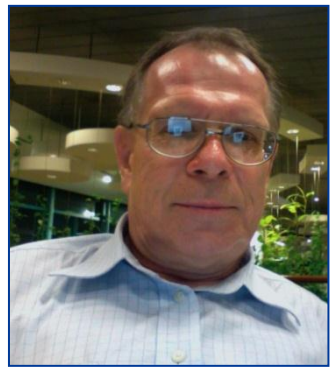
Dedicated imaging devices



Dual-ring MAMMI breast PET scanner

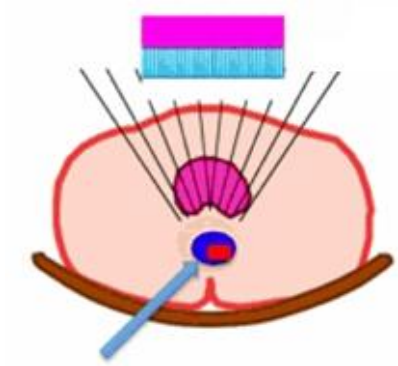
Field of view	Transaxial: Axial: Axial/frame:	170 mm 190 mm 94 mm
Spatial resolution	Radial: Tangential: Axial:	1.8 mm 1.7 mm 1.5 mm
Absolute sensitivity	3.6% (250 – 750 keV)	
Energy resolution	26%	

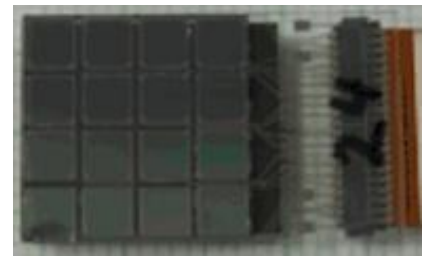




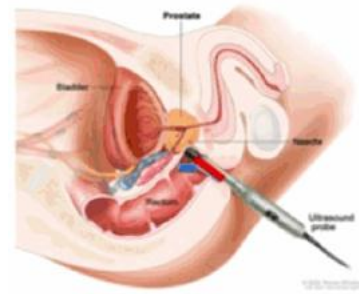
CENTER FOR ADVANCED IMAGING AT WEST VIRGINIA UNIVERSITY

Helmet PET
Brain imaging



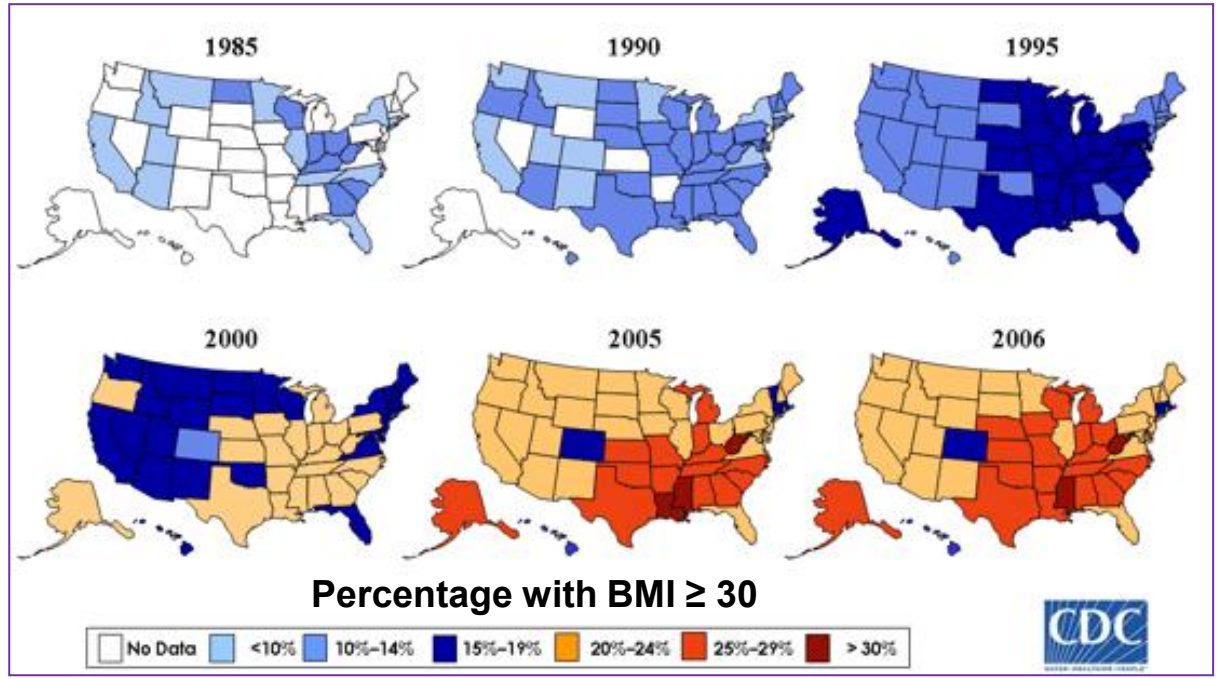


Prostate
PET Probe

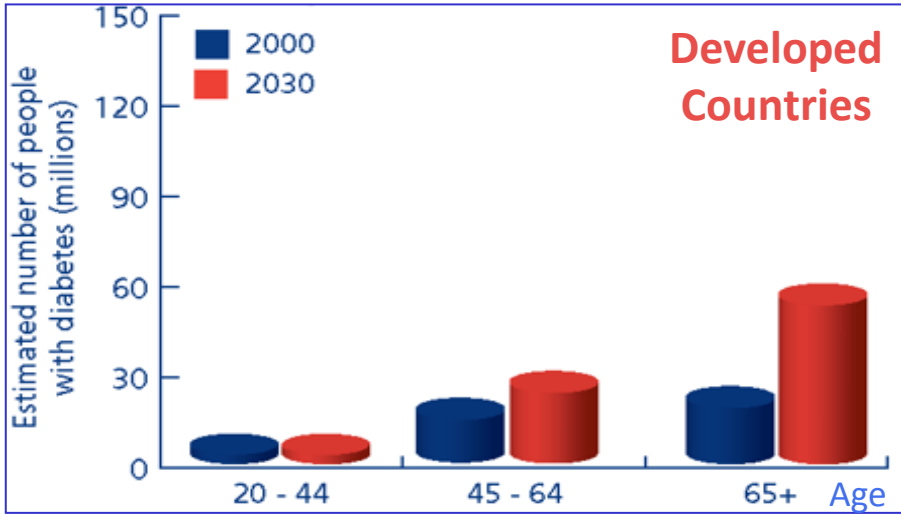


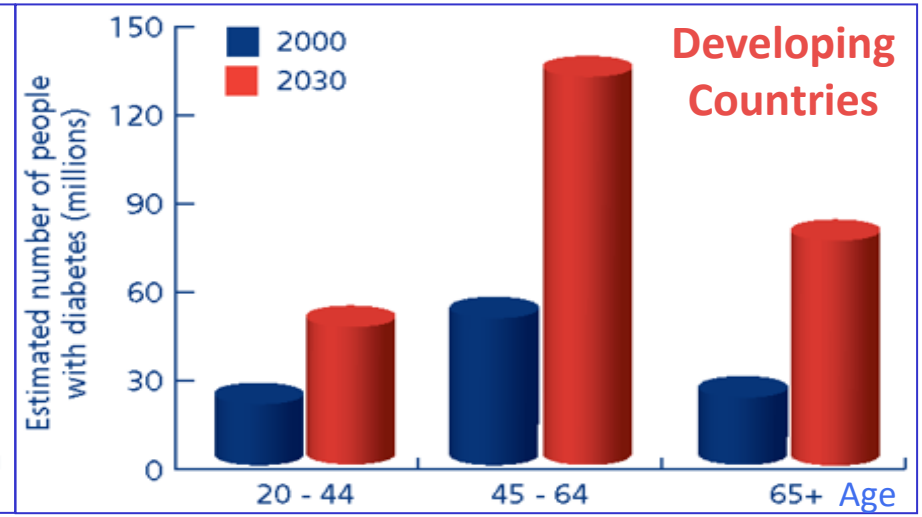
Obesity, diabetes and metabolic diseases

Cold Stone PB&C:
- **2010 calories**
- **131 g fat (68g)**
- **153 g sugar**



The Tuscan General Alessandro del Borro
Charles Mellin, 1645

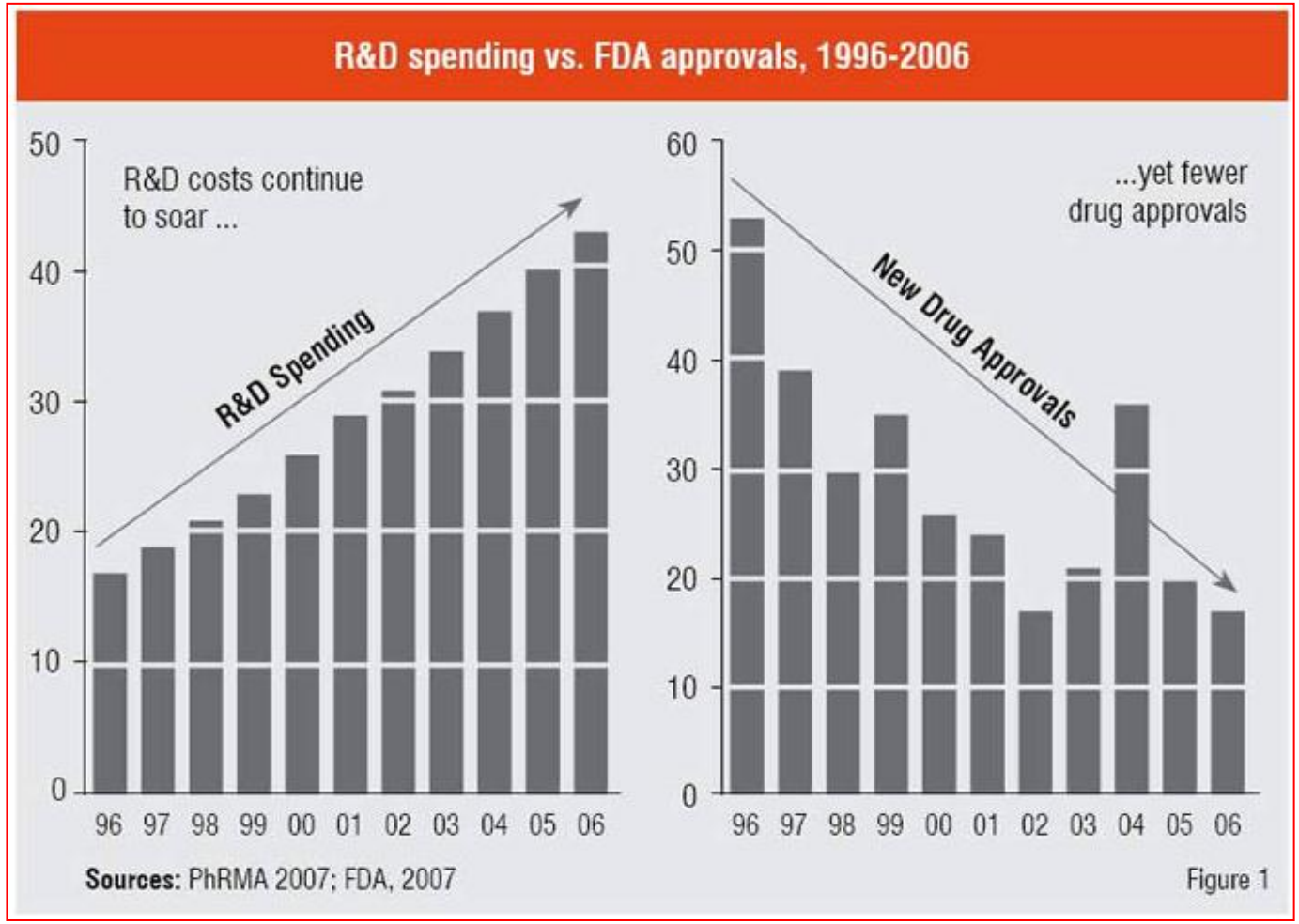




New drug applications and approvals

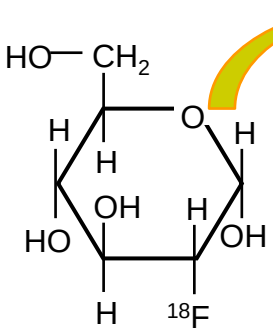
New drug applications, circa 1960

Company	New Drugs	10 year R&D ($B)	R&D per drug ($M)
Abbot	1	13.183	13.183
Sanofi	6	60.768	10.128
AZ	4	38.245	9.561
Roche	8	70.928	8.866
Pfizer	10	77.786	7.779

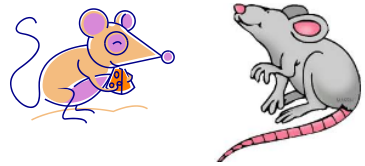


The Cost Of Creating A New Drug Now $5 Billion, Pushing Big Pharma To Change

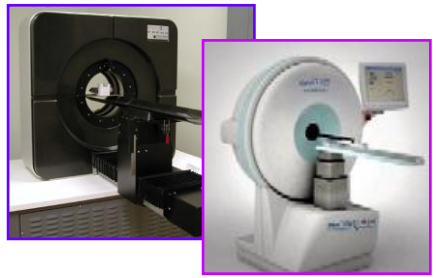
Translational Research – another challenge



Biomarkers



Animal models



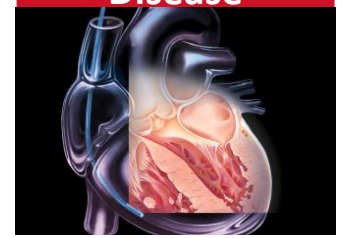
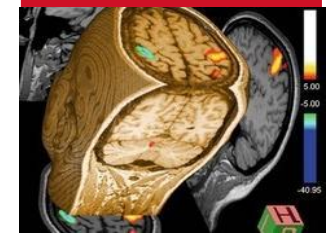
Man

TRANSLATION

"I'm going home today. They cured me using this new miracle drug. I am afraid it'll be years before it gets into humans"

Where should we focus our imaging resources?

Population Growth | **Ageing Population** | **Obesity**

Diabetes	Mental Illness	Cardiovascular Disease	Cancer	Joint Disorders
				
⬆ 520%	⬆ 342%	⬆ 142%	⬆ 190%	⬆ 223%

Predicted Growth in Healthcare Expenditure: 2003 - 2033

Source Goss, J., 2008


Thank you for your attention
A*STAR-NUS Clinical Imaging Research Centre, Singapore