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
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

This presentation represents the speaker’s own beliefs, which may differ from Philips’ and/or AIPES’ formal positions.
Molecular Imaging – Evolution

**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

<table>
<thead>
<tr>
<th>INSTALLED BASE</th>
<th>AGE VS ‘GOLDEN RULES’</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2008</td>
</tr>
<tr>
<td>PET I ≤ 5 years - units</td>
<td>430</td>
</tr>
<tr>
<td>PET I 6-10 years - units</td>
<td>118</td>
</tr>
<tr>
<td>PET I ≤ 10 years - units</td>
<td>40</td>
</tr>
<tr>
<td>PET Total</td>
<td>588</td>
</tr>
</tbody>
</table>

(COCIR 2014)
### Nuclear Medicine – General Trends*

<table>
<thead>
<tr>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume and sales have decreased since 2007, and projections for growth in the US through 2017 are flat to minimal.</td>
</tr>
<tr>
<td>The majority (85-87%) of procedures will continue to be based on Tc-99m and other single photon agents (SPECT and planar).</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>More outreach is needed to patients, referring physicians, payers and regulatory agencies. Continued emphasis on advocacy is important – CMS, FDA (and partnerships).</td>
</tr>
<tr>
<td>Health care reform (USA) is driving medicine that is evidence based and patient centered.</td>
</tr>
<tr>
<td>New tracers and new technologies will drive growth.</td>
</tr>
<tr>
<td>Quality is important to drive growth:</td>
</tr>
<tr>
<td>a. Training of professionals</td>
</tr>
<tr>
<td>b. <strong>Quantification</strong></td>
</tr>
<tr>
<td>c. <strong>Standardization</strong></td>
</tr>
<tr>
<td>Concerns about radiation safety should be addressed by dose optimization and education about the benefits of nuclear medicine/molecular imaging.</td>
</tr>
</tbody>
</table>

*April 2013, SNM Board of Directors Meeting*
Radiopharmaceuticals
PET Radioisotopes & Production

Cyclotrons

Companies

- General Electric
- Siemens
- IBA
- ASCI
- D.V. Efremov Institute
- Sumitomo Heavy Industries
- KIRAMS
- Best Cyclotron Systems
- ABT
PET Radioisotopes & Production

Cyclotrons

<table>
<thead>
<tr>
<th>BIOMARKER GENERATOR</th>
<th>CONVENTIONAL CYCLOTRON</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET LAB FOOTPRINT</td>
<td>300 FT²</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>24 TONS</td>
</tr>
<tr>
<td>PERSONNEL</td>
<td>1 FTE</td>
</tr>
<tr>
<td>OPERATING EXPENSES</td>
<td>$150K/YR</td>
</tr>
<tr>
<td>REPETITIVE PRODUCTION CYCLE</td>
<td>30 MIN.</td>
</tr>
</tbody>
</table>

(ABT Cyclotrons)
PET Radioisotopes & Production

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

New PET Tracers - USA

**PET Oncology**

- Threshold Pharma (Hypoxia HX-4)
- GE Integrin (Melanoma/Renal)
- Siemens Integrin (Angiogenesis)
- Blue Earth Diag. (Prostate)
- CLR-1404 (Colon)
- NuView FMAU (Breast)
- NuView VPAC (Breast & Prostate)
- FDG

**PET Neurology**

- Avid RP-133 Parkinson's
- Lilly Anti-Tau
- Navidea 4694
- Neuraceq
- Vizamyl
- Amyvid
- FDG

**PET Cardiology**

- Lantechus Neuronal
- FluoroPharma VasoPET
- FluoroPharma CardioPET
- FluoroPharma BFPET
- Flurpiridaz
- Rb-82
- PET FDG Viability

Conditional on successful of anti-amyloid (other AD?) therapies
## Existing Novel PET Tracers - EU

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Care Cycle</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{18}$F-FLT</td>
<td>Oncology</td>
<td>Cell proliferation</td>
</tr>
<tr>
<td>$^{18}$F-DOPA</td>
<td>Oncology</td>
<td>Neuroendocrine</td>
</tr>
<tr>
<td>$^{18}$F-MISO</td>
<td>Oncology</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>Aposense $^{18}$F-ML-10</td>
<td>Oncology</td>
<td>Apoptosis</td>
</tr>
<tr>
<td>$^{68}$Ga-DOTATATE</td>
<td>Oncology</td>
<td>Neuroendocrine Tumours</td>
</tr>
<tr>
<td>$^{68}$Ga-DOTATOC</td>
<td>Oncology</td>
<td>Bone Metastases</td>
</tr>
<tr>
<td>$^{18}$F-FET</td>
<td>Oncology</td>
<td>Brain Tumours</td>
</tr>
<tr>
<td>$^{18}$F-FES</td>
<td>Oncology</td>
<td>Response to therapy Breast Cancer</td>
</tr>
<tr>
<td>Sirtex/BTG $^{90}$Y-spheres</td>
<td>Oncology</td>
<td>Liver Radioablation</td>
</tr>
<tr>
<td>$^{124}$I / $^{90}$Y / $^{89}$Zr / $^{64}$Cu – DOTA &amp; MABs</td>
<td>Oncology</td>
<td>Theranostics</td>
</tr>
</tbody>
</table>

### Other Interesting tracers (just three examples)...

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Care Cycle</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{68}$Ga-PSMA</td>
<td>Oncology</td>
<td>Prostate (Afshar-Oromieh, EJNMMI 2014)</td>
</tr>
<tr>
<td>$^{18}$F-PBR111</td>
<td>Neurology/ Inflammation</td>
<td>Multiple Sclerosis (Colasanti, JNM 2014)</td>
</tr>
<tr>
<td>$^{18}$F-Mannose</td>
<td>Oncology + Metabolism (Furumoto, JNM 2013)</td>
<td></td>
</tr>
</tbody>
</table>
Positron Emission Tomographs
Innovation in PET

1953
Brownell and Sweet. First PET images with 18F (Nucleonics 1953, 11:40-45)

1969
The MGH Positron Camera PC-I

1973
Early TOF PET scanner, SuperPET I

1978
PET/CT Prototype: CTI/Siemens Somatom AR.SP + ECAT ART

1982
Commercial Coincidence Imaging

Mid-80s
Commercial PET/CT

1995
1998
2001
2006
2008
2010
2011
2012
2014
2015

Clinical TOF-PET/CT Philips GEMINI TF

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

Digital Prototype
Philips TOF-PET/PET/CT

Digital TOF-PET/CT
Philips Vereos

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

Innovations:
- 1953: Brownell and Sweet's first PET images with 18F.
- 1969: The MGH Positron Camera PC-I.
- 1973: Early TOF PET scanner, SuperPET I.
- Mid-80s: Commercial PET/CT.
- 1995-2015: Various commercial PET scanners and TOF-PET/CT systems.

Timeline highlights:
- 1998: GE Discovery LS.
- 2001: Commercial PET/CT.
- 2005: Siemens Biograph mMR.
- 2006: Philips Ingenuity TF.
- 2012: Digital TOF-PET/CT Philips Vereos.
- 2014: Integrated (SIPM) TOF-PET/MR GE Signa PET/MR.

Key developments:
- 1953: Brownell and Sweet's PET images with 18F.
- 1969: The MGH Positron Camera PC-I.
- 1973: Early TOF PET scanner, SuperPET I.
- 1978: PET/CT Prototype: CTI/Siemens Somatom AR.SP + ECAT ART.
- Mid-80s: Commercial PET/CT.
- 1998: GE Discovery LS.
- 2001: Commercial PET/CT.
- 2005: Siemens Biograph mMR.
- 2006: Philips Ingenuity TF.
- 2012: Digital TOF-PET/CT Philips Vereos.
- 2014: Integrated (SIPM) TOF-PET/MR GE Signa PET/MR.
New PET Detectors
Towards the digitisation of photon detection - #1 from PMT to APD

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

Advantages:
High gain
Fast Response → good TOF
Can operate within Magnetic Field

<table>
<thead>
<tr>
<th>Photodetector</th>
<th>APD</th>
<th>SiPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active area (mm²)</td>
<td>1–100 mm²</td>
<td>1–10 mm²</td>
</tr>
<tr>
<td>Gain</td>
<td>$10^2$</td>
<td>$10^3$–$10^6$</td>
</tr>
<tr>
<td>Dynamic range</td>
<td>$10^4$</td>
<td>$10^3$</td>
</tr>
<tr>
<td>Excess noise factor</td>
<td>$&gt;2$</td>
<td>1.1–1.2</td>
</tr>
<tr>
<td>Rise time (ns)</td>
<td>2–3</td>
<td>~1</td>
</tr>
<tr>
<td>Time jitter (ns FWHM)</td>
<td>&gt;1</td>
<td>0.1</td>
</tr>
<tr>
<td>Dark current/count rate</td>
<td>1–10 nA/mm²</td>
<td>0.1–1 MHz/mm²</td>
</tr>
<tr>
<td>Capacitance (pF/mm²)</td>
<td>2–10</td>
<td>&gt;30</td>
</tr>
<tr>
<td>QE @ 420 nm (%)</td>
<td>60–80%</td>
<td>&lt;40%*</td>
</tr>
<tr>
<td>After-pulsing</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bias voltage (V)</td>
<td>~100–1,500</td>
<td>~50</td>
</tr>
<tr>
<td>Power consumption (µW/mm²)</td>
<td>10</td>
<td>&lt;50 µW/mm²</td>
</tr>
<tr>
<td>Temperature coefficient</td>
<td>2–3%°C</td>
<td>3–5%°C</td>
</tr>
<tr>
<td>Bias coefficient</td>
<td>10%/V</td>
<td>100%/°C</td>
</tr>
<tr>
<td>Magnetic susceptibility</td>
<td>No (up to 9.4 T)</td>
<td>No (up to 15 T)</td>
</tr>
</tbody>
</table>


New PET Detectors
Towards the digitisation of photon detection - #3 from SiPM to Digital SiPM & from Anger-logic to 1:1 coupling

- **Advantages:**
  - High gain
  - Faster Response → good TOF
  - Can operate within Magnetic Field
  - Better spatial resolution
  - Significantly lower dead-time
  - Further TOF Improvement

Images: Hammamatsu Photonics
Images: Philips
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

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

Signa PET/MR
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)

Better system linearity (reduced dead-time)

Data Courtesy of Philips
Technical Benefits of Digital PET

Better lesion detection (Spatial Resolution)

Better contrast/ noise control (TOF timing resolution)

Better system linearity (reduced dead-time)
Oncology: Lesion Detection

Injected activity: 370MBq (FDG)
Injected once, scanned twice
Acquisition time: 1.5 min/bed
Same for both systems

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 2mm
SUV max 6.9

ΔSUVmax = 91.8%

Digital 1mm
SUV max 8.2

ΔSUVmax = 121.6%

Results from case studies are not predictive of results in other cases. Results in other cases may vary.
Y-90 Microspheres Preliminary Results

Analogue PET

Digital PET

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.*
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

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

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

<table>
<thead>
<tr>
<th>Retractors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Market Access for new Radiotracers</strong></td>
</tr>
<tr>
<td>• Slow development</td>
</tr>
<tr>
<td>• Slower approval</td>
</tr>
<tr>
<td><strong>Reimbursement</strong></td>
</tr>
<tr>
<td>• Clinical efficacy based on patient outcomes</td>
</tr>
<tr>
<td>• Inhomogeneous reimbursement model in EU</td>
</tr>
<tr>
<td><strong>Lag in patient referrals</strong></td>
</tr>
<tr>
<td><strong>Current Economic Climate</strong></td>
</tr>
</tbody>
</table>
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