A change in usage of cyclotrons for medical isotope production?

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Global Sales Director

Imagination at work.

GE & Cyclotron history – things you did not know

Inventor of Cyclotron and Nobel Prize Winner got parts of his knowledge from GE during summer sabbaticals

Lawrence arrived in Berkeley in the summer of 1928 and adapted easily to his new surroundings. Within a few months, his friend Beams judged him "a 'Native Son' of California." Continuing his research on the action of light on electrons, Lawrence spent the summers of 1929 and 1930 in Schenectady, New York, where the General Electric Company had a major industrial research lab staffed with physical scientists and engineers. At G.E. he found his host, physicist A.W. Hull, an expert on X-rays, diverted by work on high electric voltages. At that time, many academic physicists were also starting to work on high voltages, although for different reasons than G.E. scientists. High-voltage accelerators promised breakthroughs in the study of radioactive particles and atomic nuclei. An attempt in 1930 by Northwestern University to lure Lawrence away led Berkeley to promote him to full professor at the age of 29.

Seeing the difficulties, Lawrence hesitated to build a device and instead set out for his summer sojourn at General Electric. Otto Stern, visiting Berkeley from Germany toward the end of the year, encouraged him to pursue his idea, and Tuve's successes in Washington with the Tesla coil further spurred Lawrence, lest he lose out in the race to high energies.

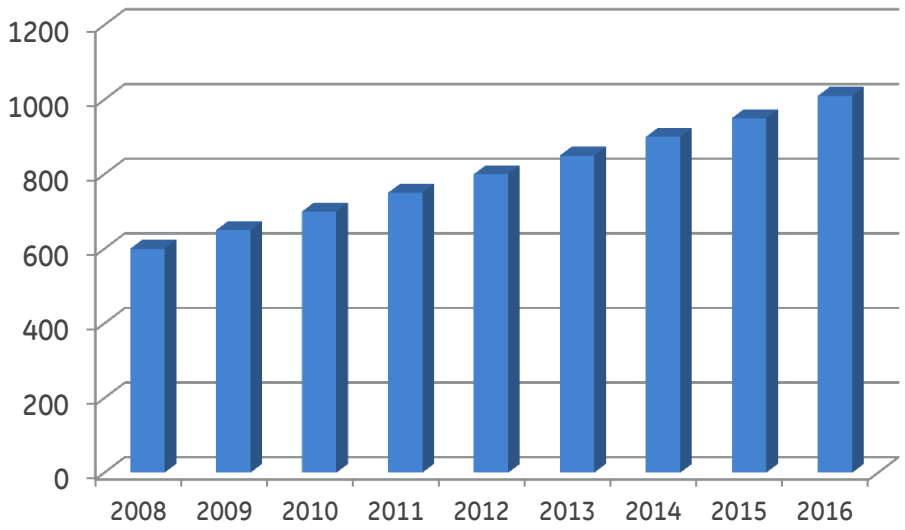
Lawrence and Livingston around 1933.

http://www.aip.org/history/lawrence/index.htm

The 11-inch cyclotron installed in Room 329 Le Conte Hall (University of California at Berkeley), was the first cyclotron to exceed 1 MeV. Livingston and David Sloan, whom Lawrence had found at the **General Electric Research Laboratory** and persuaded to come to Berkeley as a graduate student, improved cyclotron technique. About the time the great magnet was moving into the new laboratory, the 11-inch cyclotron in LeConte gave out one billionth of an ampere of 1.22 MeV protons. "Lawrence literally danced around the room with glee," Livingston recalled." (The preceding information was excerpted from the text of the Fall 1981 issue of LBL Newsmagazine.)

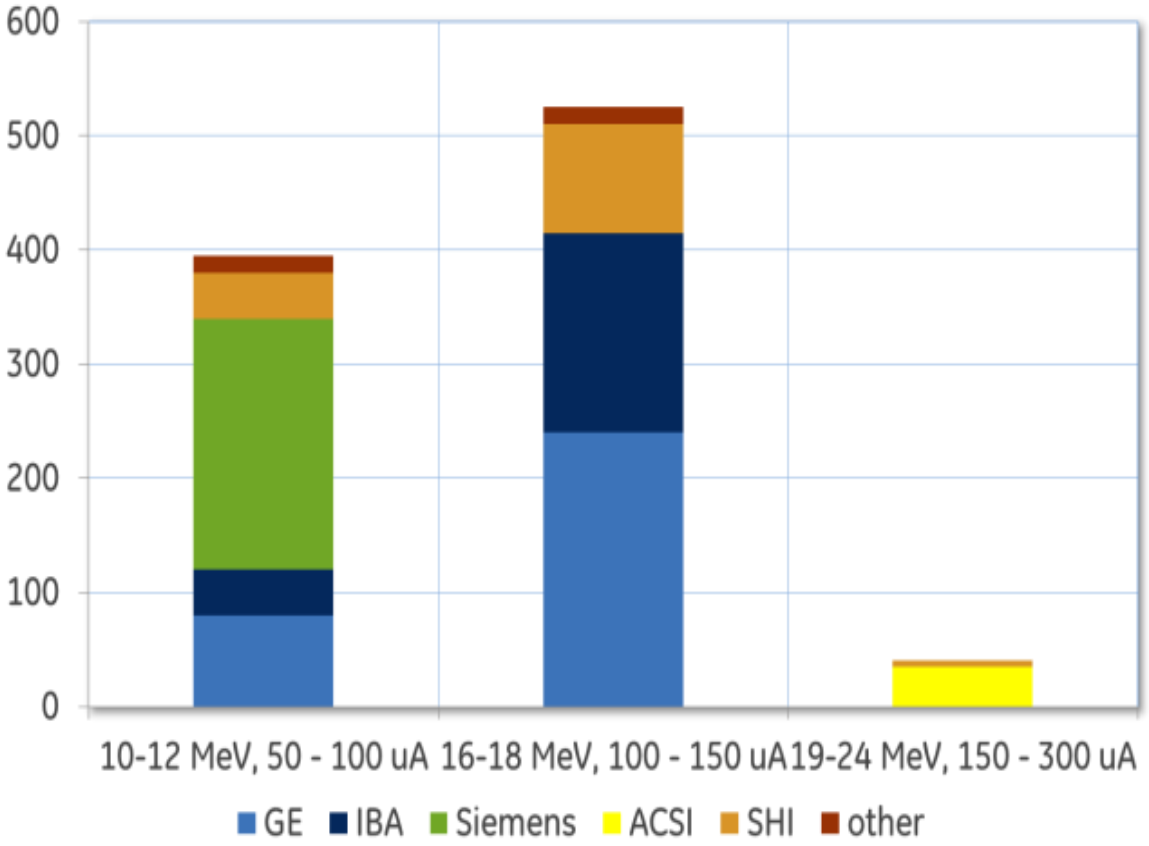
Courtesy: M K Craddock, UBC/TRIUMF, APS 2011

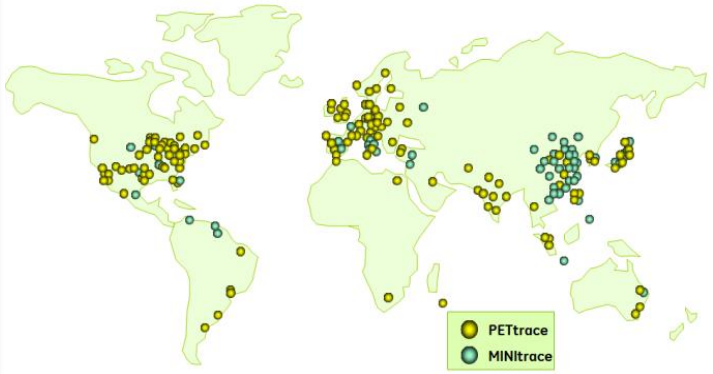
PET Market growth 2010 - 2015



In line with GE estimate!

Cyclotron IB



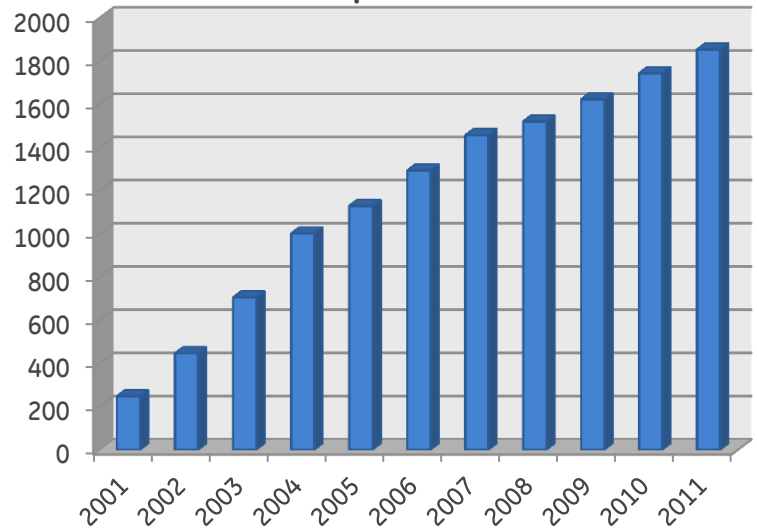


PET scanner & procedure growth

Projected Global PET/CT scanner IB

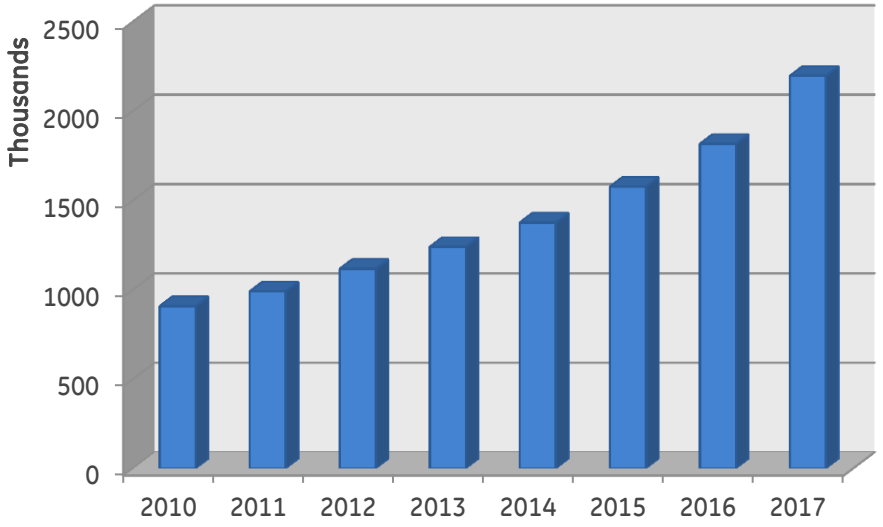
To consider:
- Regional dynamics
- Scanner: cyclotron ratio
- Tracer profile

US - procedures



Source: IMV 2012 PET Imaging report

Europe - procedures



Source: Medical Options 2013

The list of tracers in man is long.....

(R)-[^{11C}]MDL-00907
[^{11C}]5-HTP
[^{11}C]Acetate
[^{11}C]Acetone
[^{11}C]acylchloride
[^{11}C]Bisoprolol
[^{11}C]Carazolol
[^{11}C]Carfentanil
[^{11}C]CH23390
[^{11}C]Choline
[^{11}C]DAA1106
[^{11}C]DASB
[^{11}C]Deprenyl
[^{11}C]DTBZ
[^{11}C]EGF(ML04)
[^{11}C]FLB 457
[^{11}C]Flumazenil
[^{11}C]Fluvoxamine
[^{11}C]FMZ),
[^{11}C]GR103545
[^{11}C]HED
[^{11}C]ICI-^{118}551
[^{11}C]McN5252
[^{11}C]MeI
[^{11}C]MET
[^{11}C]Methionine
[^{11}C]Methylspiperone
[^{11}C]Nicotine
[^{11}C]NNC^{11}2
[^{11}C]Palmitate
[^{11}C]PBR28
[^{11}C]PD153035
[^{11}C]PIB
[^{11}C]PK11195
[^{11}C]PMP
[^{11}C]Raclopride
[^{11}C]Ritalin
[^{11}C]SB235753
[^{11}C]ST1159
[^{11}C]Toluenes
[^{11}C]Verapamil
[^{11}C]WAY-100635
[^{11}C]Zofenoprilat
[^{11}C]-β-CFT
[^{18}F]Acetate
[^{18}F]ADAM
[^{18}F]Altanserin
[^{18}F]Annexin
[^{18}F]DPA-714
[^{18}F]F-A-85380
[^{18}F]FAC
[^{18}F]Fallypride
[^{18}F]FAMV
[^{18}F]Fatty Acids
[^{18}F]FAZA
[^{18}F]FAZDR
[^{18}F]FBBA
[^{18}F]FCWAY
[^{18}F]FDDNP
[^{18}F]FDM
[^{18}F]FDOPA
[^{18}F]FEAU
[^{18}F]FEC
[^{18}F]FECH
[^{18}F]FEDAA^{11}06
[^{18}F]FEOBV
[^{18}F]FES
[^{18}F]FET
[^{18}F]FECH
[^{18}F]FETO
[^{18}F]FHAR
[^{18}F]FHBG
[^{18}F]FLT
[^{18}F]FMC
[^{18}F]FMAU
[^{18}F]FMCH, FCH
[^{18}F]FMISO
[^{18}F]FMT
[^{18}F]FMTEB
[^{18}F]FP-CIT
[^{18}F]FPHCys
[^{18}F]FP-TZTP
[^{18}F]FTHA
[^{18}F]FVOZ
[^{18}F]ML-10
[^{18}F]MPPF
[^{18}F]NaF
[^{18}F]N-b-fluoroethyl-amines, ethers and esters
[^{18}F]PAC
[^{18}F]PBR102
[^{18}F]PBR^{11}1
[^{18}F]Peptides
[^{18}F]SFB
[^{18}F]SPA-RQ
[^{18}F]Tyrosine
[^{18}F]Uracil
[^{18}F]VL115
[2-^{11}C]Acetone
[^{68}Ga]Ga-AMBA
1-(4-[^{11}C]Methoxyphenyl)-2-(4-methylsulfonyl)-1-cyclopenten
^{18}F-Methylfluoride

And the winner is……..

Proven: ^{18}F ^{11}C ^{68}Ga

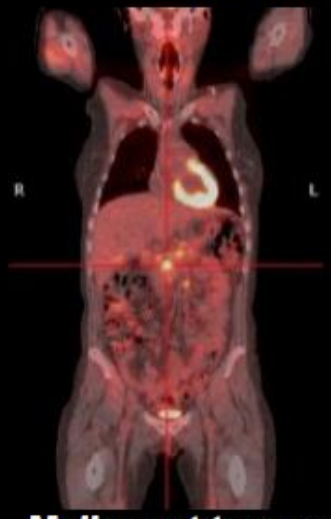
Candidates: ^{89}Zr ^{64}Cu ^{86}Y

(R,R-[11C]MDL-00907
[11C]Acetate
[11C]Acetone
[11C]acylchloride
[11C]Bisoprolol
[11C]Carazolol
[11C]Carfentanil
[11C]CH23390
[11C]Choline
[11C]DAA1106
[11C]DASB
[11C]Deprenyl
[11C]FLB 457
[11C]Flumazenil
[11C]Fluvoxamine
[11C]FMZ),
[11C]GR103545
[11C]HED
[11C]ICI-118551
[11C]McN5252
[11C]MeI
[11C]MET
[11C]Methionine
[11C]Methylspiperone
[11C]Nicotine
[11C]NNC112
[11C]Palmitate
[11C]PBR28
[11C]PD153035
[11C]PIB
[11C]PK11195
[11C]PMP
[11C]Raclopride
[11C]Ritalin
[11C]SB235753
[11C]WAY-100635
[11C]Zofenoprilat
[11C]-β-CFT
[18F]Acetate
[18F]ADAM
[18F]Altanserin
[18F]Annexin
[18F]DPA-714
[18F]F-A-85380
[18F]FAC
[18F]Fallypride
[18F]FAMV
[18F]FAZA
[18F]FAZDR
[18F]FBBA
[18F]FCWAY
[18F]FDDNP
[18F]FDM
[18F]FDOPA
[18F]FEAU
[18F]FEC
[18F]FECH
[18F]FECH
[18F]FETO
[18F]FHAR
[18F]FHBG
[18F]FLT
[18F]FMC
[18F]FMAU
[18F]FMCH, FCH
[18F]FMISO
[18F]FMT
[18F]FPHCys
[18F]FP-TZTP
[18F]FTHA
[18F]FVOZ
[18F]ML-10
[18F]MPPF
[18F]NaF
[18F]N-b-fluoroethyl-amines, ethers and esters
[18F]PAC
[18F]Peptides
[18F]SPA-RQ
[18F]Tyrosine
[18F]Uracil
[18F]VL115
[2-11C]Acetone
[68Ga]Ga-AMBA
1-(4-[11C]Methoxyphenyl)-2-(4-methylsulfonyl)-1-cyclopenten
18F-Methylfluoride

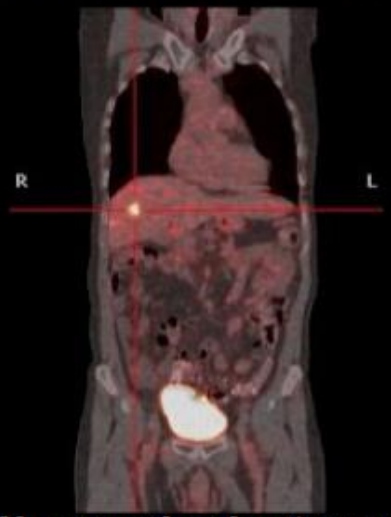
Non-FDG applications

Isotope	Tracer	Application
^{18}F	F-DOPA	Neurology (Parkinson's disease, schizophrenia, etc…)
^{18}F	F-Choline	Oncology (prostate, brain, breast, lung, esophagus)
^{18}F	FLT	Oncology (tumor growth rate (DNA), no inflammatory)
^{18}F	FMISO	Oncology (hypoxia (lung, brain, head & neck))
^{18}F	FET	Oncology (brain)
^{11}C	Methionine	Oncology (brain, head & neck, lung, breast). Monitoring of treatment
^{11}C	Raclopride	Neurology (dopamine receptors)
^{11}C	Choline	Oncology (same as ^{18}F, plus liver, kidney and spleen)
^{11}C	PIB	Neurology (Alzheimer's disease)
^{68}Ga	DOTATOC	Oncology (neuroblastoma, brain, gastrointestinal)
^{68}Ga	DOTANOC	Oncology (neuroendocrine tumors)
^{68}Ga	DOTATATE	Oncology (neuroendocrine tumors)
^{68}Ga	PSMA	Oncology (prostate)

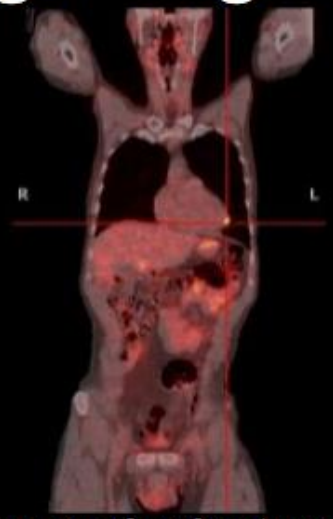
Clinical Research – Diagnosing cancer



Malignant tumors
^{18}F Fluorodeoxyglucose

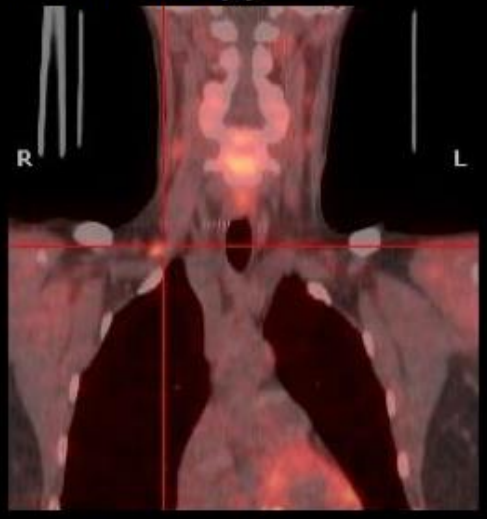


Neuroendocrine tumors
^{68}Ga DOTA-TOC

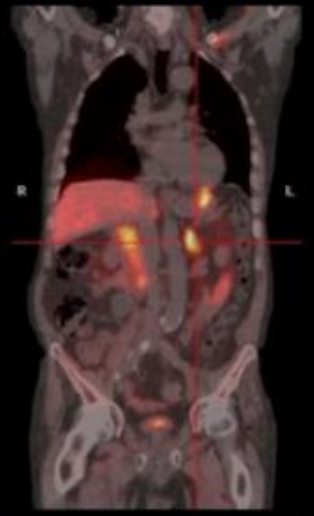


Neuroendocrine tumors
^{11}C 5-Hydroxytryptophan

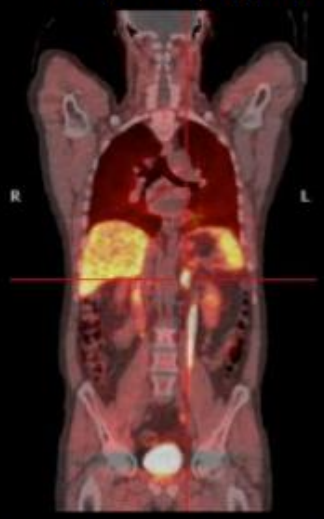
Bone metastases
^{18}F-Fluoride



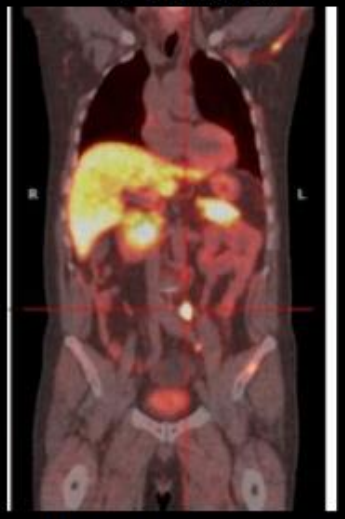
Parathyroid cancer
^{11}C Methionin



Adrenocortical tumors
^{11}C Metomidate



Pheochromocytomas
^{11}C Hydroxyephedrine



Prostate cancer
^{11}C Acetate

Courtesy from Jens Sörensen, Uppsala University

Tracer Production Workflow

Raw Materials

PET Isotope Produced

PET Tracer Synthesis

Dispensing / Quality Control

Clinical Patients

Pumped

$^{18}F^-$

Bulk FDG

OR

transport

Target Material
^{18}O-enriched H_2O

Cyclotron
PETtrace 800,
MINItrace Qilin

Synthesizer
FASTlab, 2
TRACERlab FX2

QC sample

QC Equipment
HPLC, TLC, pH meter, etc.

Inject patient

PET/CT scan

PET/CT Scanner

cGMP processes followed

Key challenges & goals for medical isotope production

Reducing costs

Decreasing the barrier to entry and total cost of ownership

Reducing the current footprint and traditional infrastructure needs

Optimizing workflow and minimizing staffing requirement for production of PET radiopharmaceuticals

Increasing access

Investing in novel technology advancements to streamline a single sourced, integrated production solution

Standardizing validated methods to remove the requirement of a large team of experts

Maintaining quality and regulatory standards to produce clinical doses compliantly

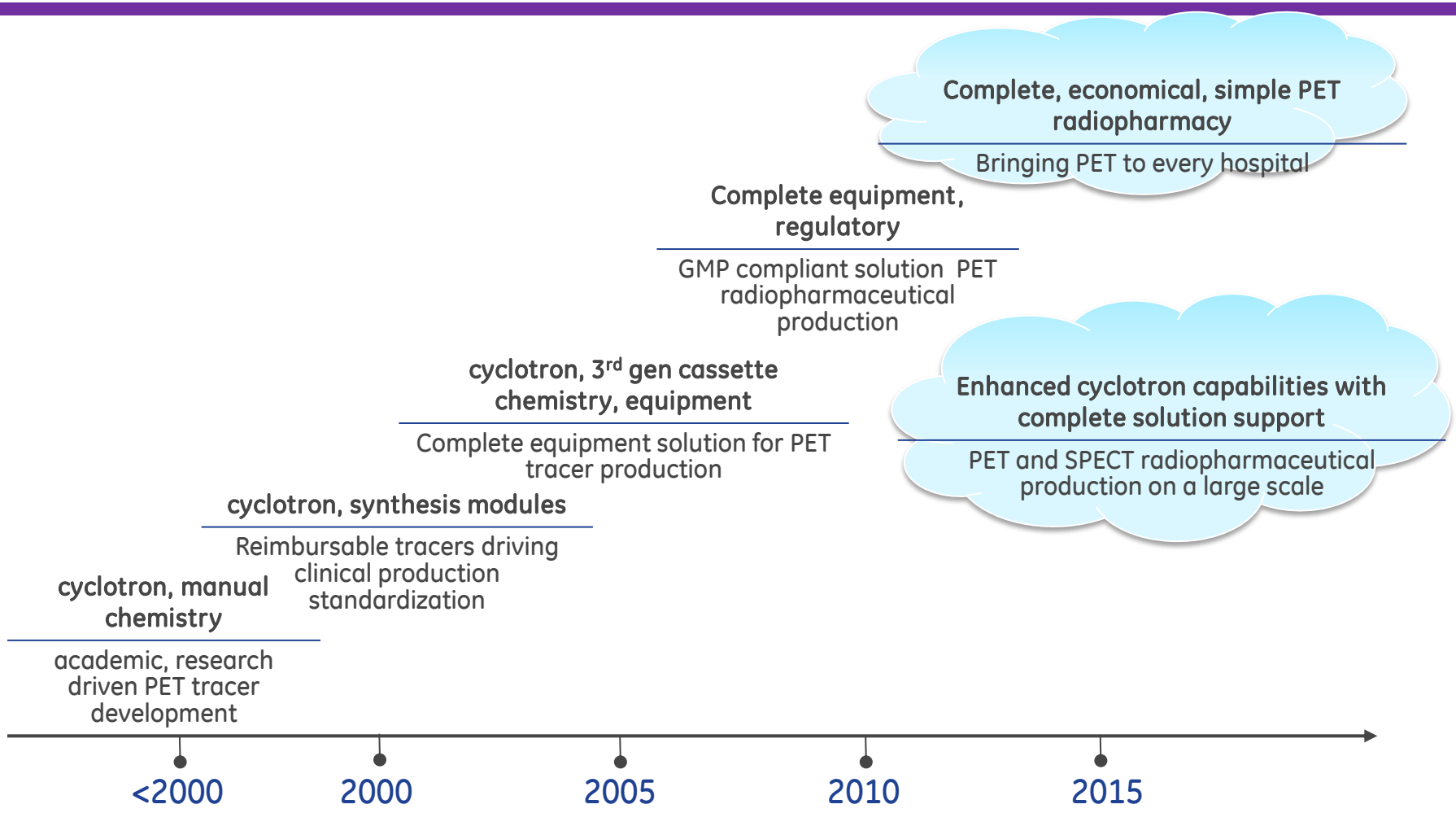
Improving quality

Enabling personalized diagnosis through access of Molecular Imaging tracers

Simplifying the complexity of tracer production

Enhancing production capabilities to expand the ability to produce a wider spectrum of PET and SPECT tracers

Past, present & future of radiopharmacy



GEHC PET Cyclotrons

7,8 MeV protons
Beam capacity: 35 µA

"PT600"

S

9,6 MeV protons
Beam capacity: 70 µA

MINItrace

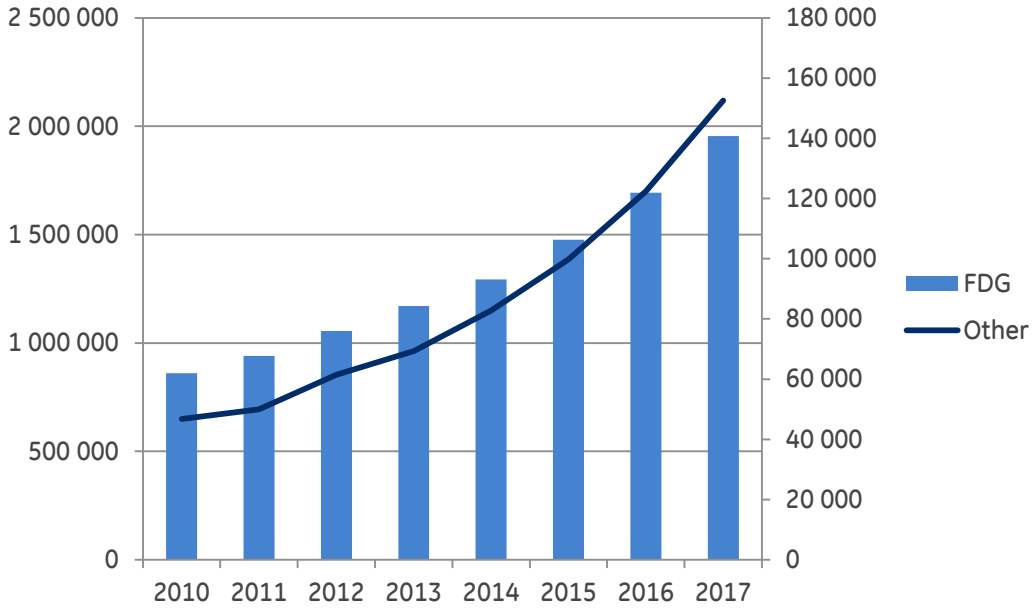
M

16,5 MeV protons
8,4 MeV deuterons
Beam capacity: 150 µA

PETtrace 800

L

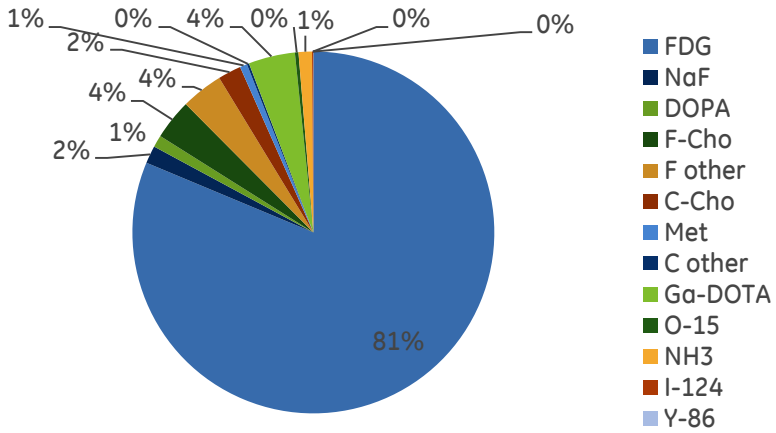
Cyclotron usage - future

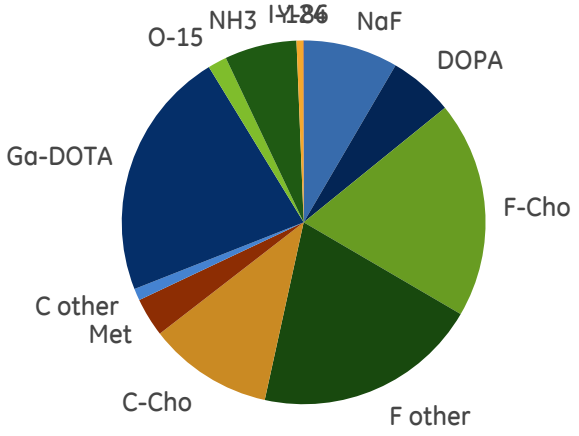


Western Europe
FDG vs non-FDG

- Trend is there
- Main drivers C-11/Ga-68

Source: Medical Options 2013

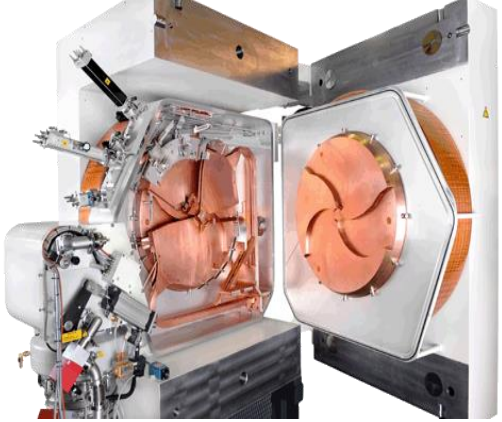




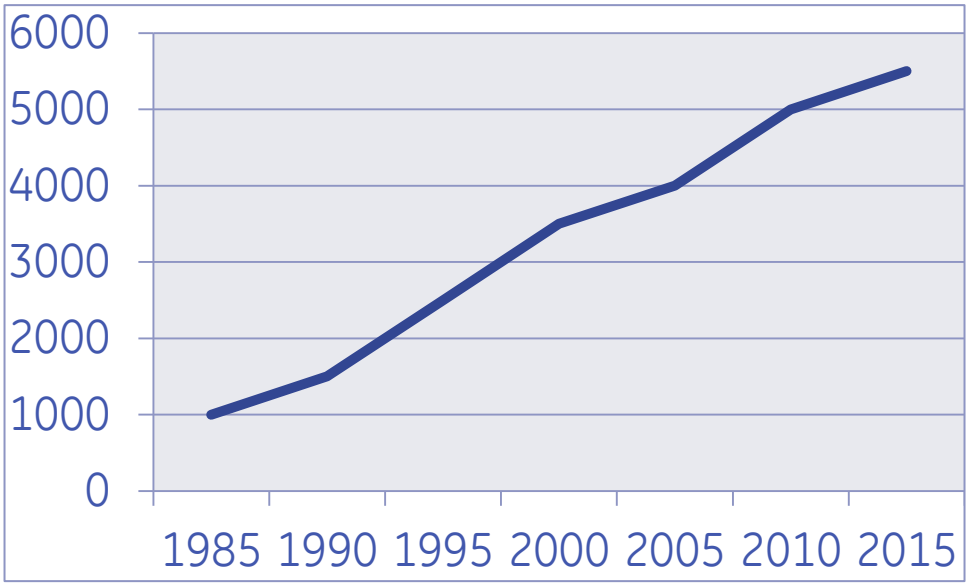
Germany 2008; data from Kotzerke et al (DGN 2010)

Large scale production – Tc99m & F-18 FDG

Cyclotron capacity

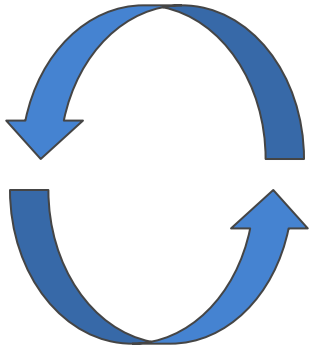


60 min F-18 target production capacity



Source: GE

Beam current

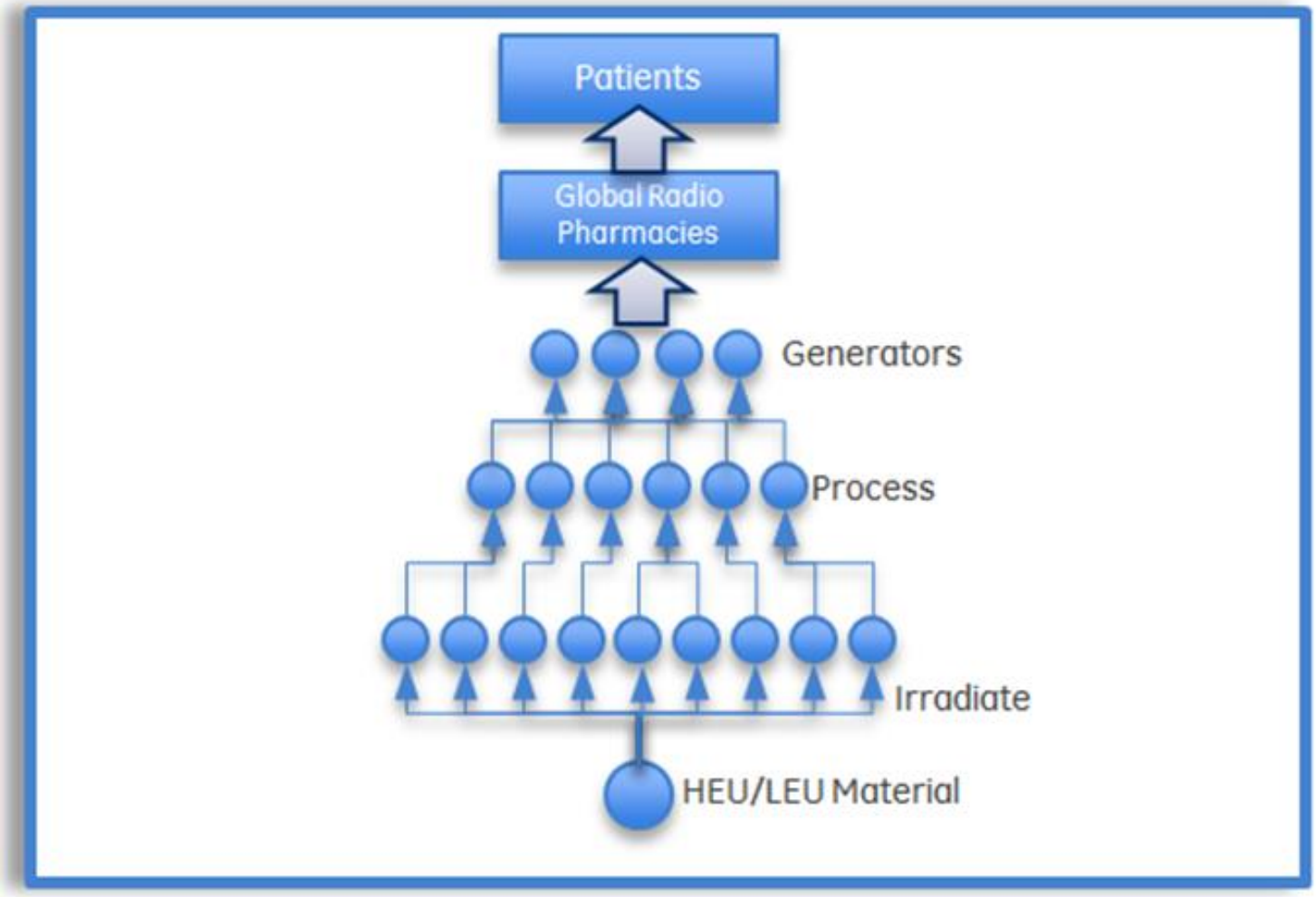


Target capacity

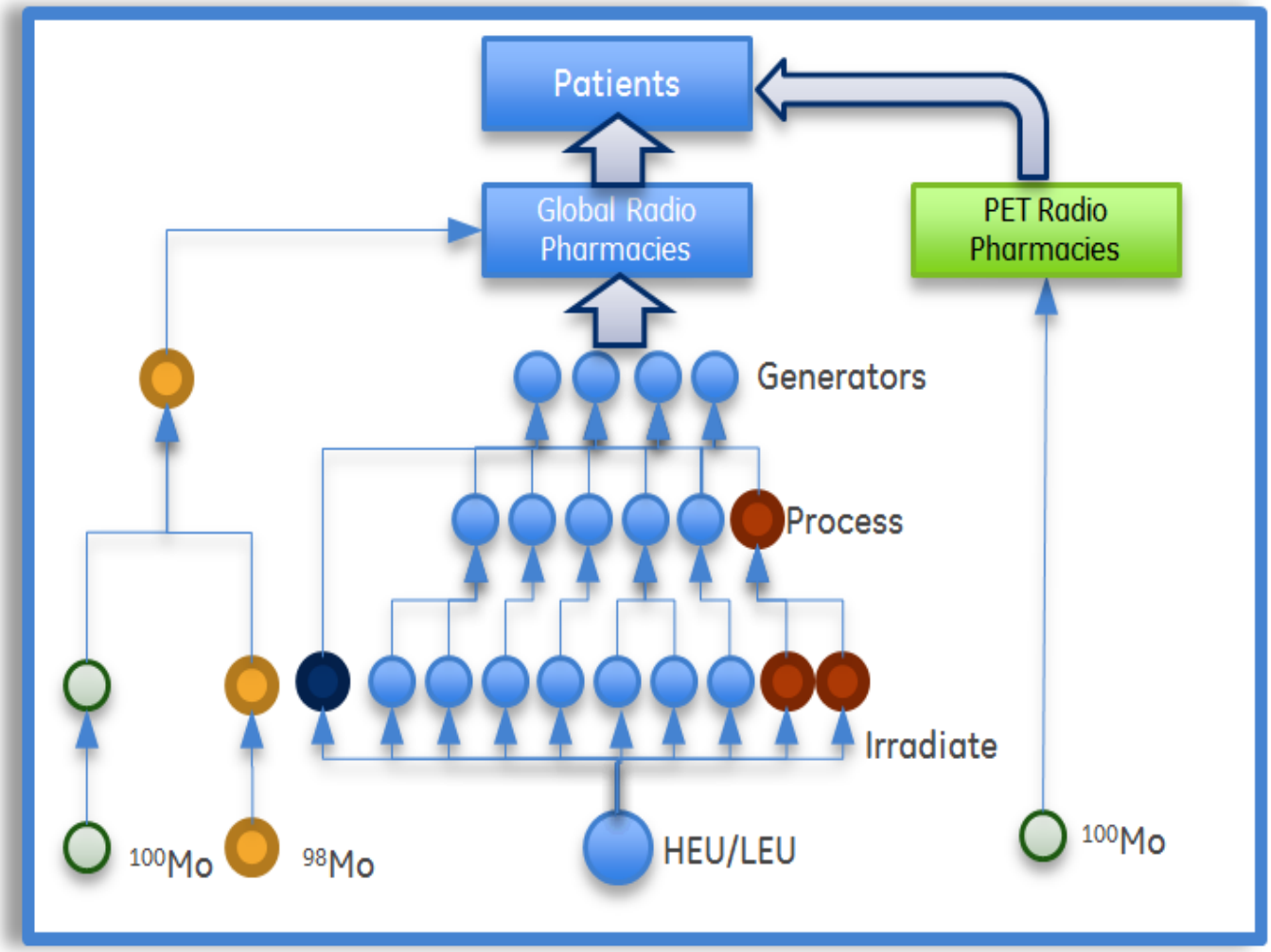
Where is the limit? Is there a limit?

Radiation to staff is already a challenge.....
The last patient needs a lot of activity.....

Today's Supply



Tomorrow's Supply



Small scale production – FDG and non-FDG PET tracers

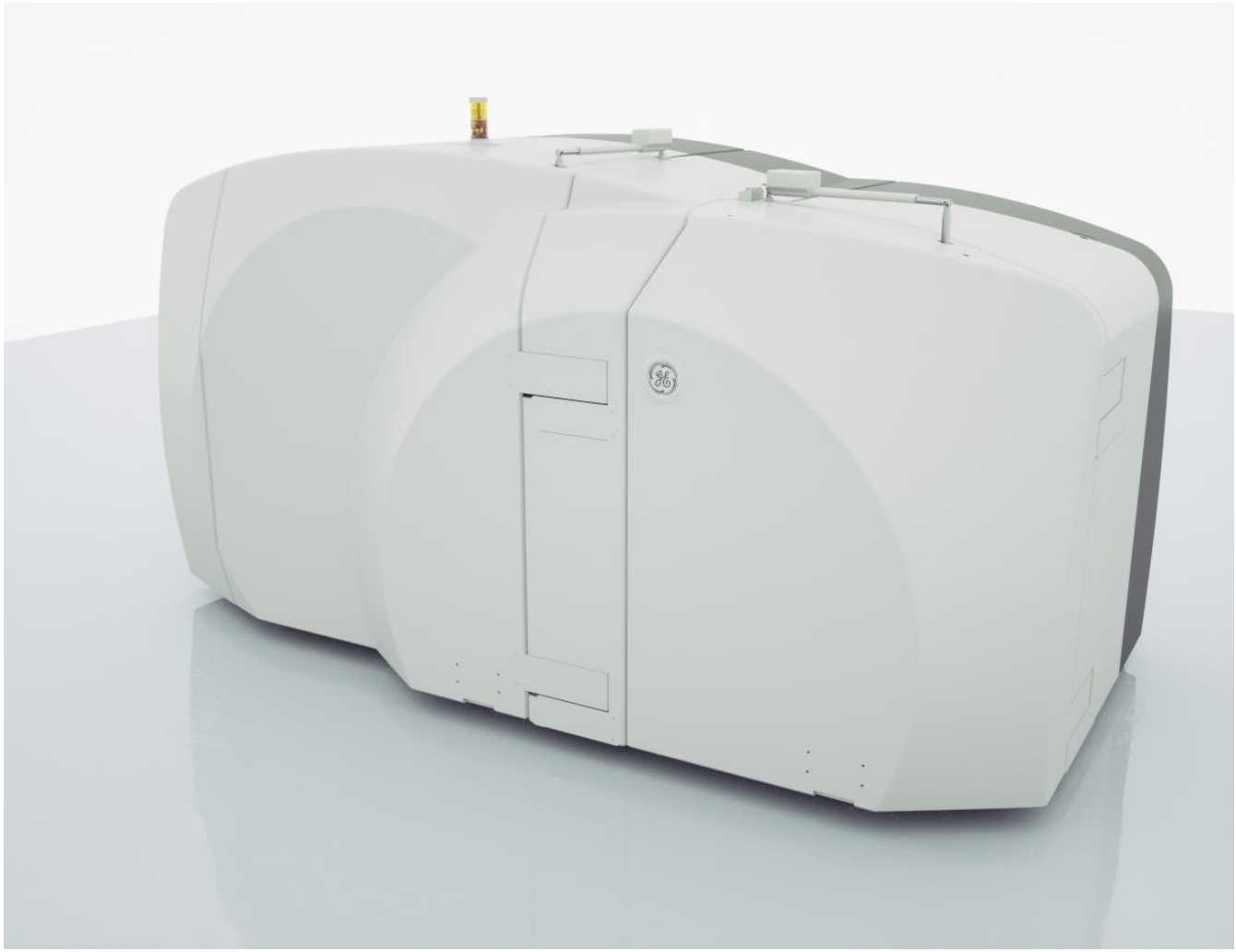
”PT 600” – basic info

- 7.8 MeV H^-, 30µA
- ^{18}F target yield 28 GBq (750 mCi) @ 120 min.
- $^{11}CO_2$ target yield 18 GBq (500 mCi) @ 50 min.
- Self shielded system, concrete based shield
- Room requirement ~6 x 6 x 2.5 meters
- Estimated/calculated <10 µSv/h on shield surface

More important:

- Completely automated operation
- Comes with a compelte solution (chemistry, dispensing, hot cell, QC etc)
- **And all the rest is about reliability!**

Cyclotron; self-shielded to enable easy siting



PET dose solution

TRACERcenter Today

Room 1

Room 2 (GMP)

- Chemistry Unit
- Chemistry Unit
- Dispensing Unit

Room 3

- QC HPLC
- QC GC
- QC MCA
- QC LAL
- QC Dose C
- QC TLC

Room 4

Market Research Findings

- Small footprint automated solution will enable access to PET/CT imaging
- Total cost of ownership reduction
- Sustaining GMP compliance for quality patient care

TRACERcenter NEW

Room 1

GMP

- Chemistry Unit
- Dispensing Unit

One QC Unit

Room 2

Workflow simplification

Million $ question: where does clinical PET go?

Headwinds:

There is no "new" FDG!
There are limitations in healthcare spend!
Complex workflow

Tailwinds:

Just scratched surface of molecular imaging
Demographics (age, improved welfare)
Dementia - therapeutics

Targeted tracers vs mass imaging w/ FDG?

Thank you for your attention!