Development of Radioactivity Standards for Quantitative Positron Emission Tomography

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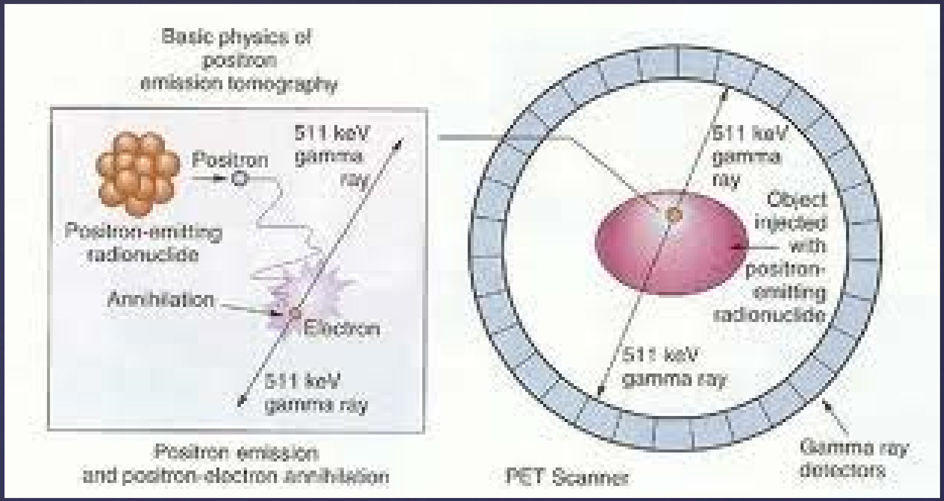
CIRMS Medical Subcommittee Meeting
10 April, 2016

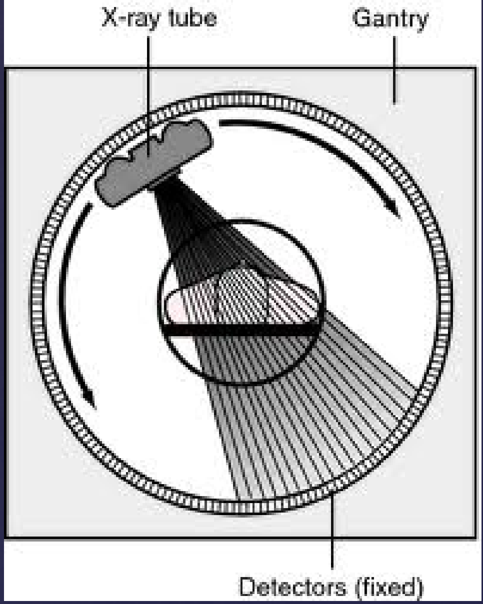
NM vs. x-ray Computed Tomography

NM (Positron Emission Tomography – PET)



- Radiation source located **inside** the body, emission rates measured
- Provides functional/metabolic information

X-ray Computed Tomography (CT)

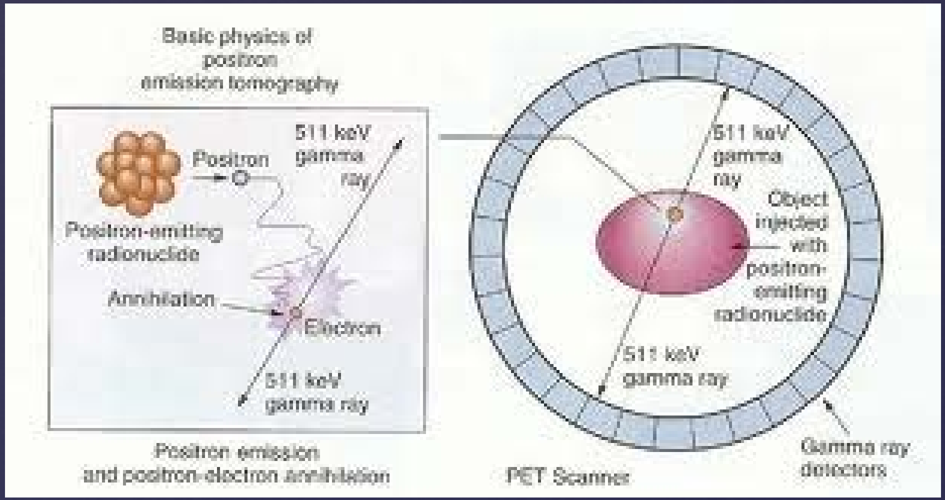


- Radiation source located **outside** the body, transmission measured
- Provides structural information

Images from:
medical-dictionary.thefreedictionary.com
cellsighttech.com

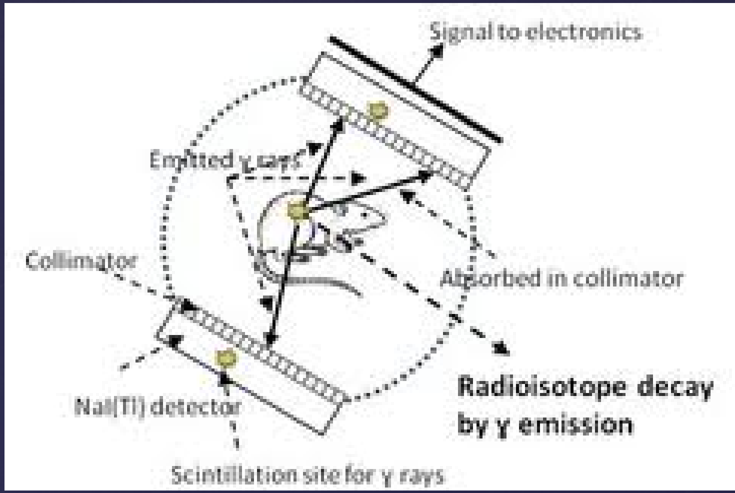
PET vs. SPECT

Positron **E**mission **T**omography



- Uses 180° coincidences to define line of response (LOR)
- Resolution about 2x better than SPECT
- Most used radionuclide is ^{18}F (110 min)
- Most nuclides are short-lived, cyclotron produced

Single **P**hoton **E**mission **C**omputed **T**omography



- Uses collimators to define line of response (LOR)
- Most used radionuclide is ^{99m}Tc (6 h)
- ^{99m}Tc is available from long-lived decay parent (generator), providing convenient availability

Images from:
med.lund.se
cellsighttech.com

PET as a biomarker

- Changes in ^{18}F[FDG] tumor accumulation as a function of time during therapy can often predict clinical outcome sooner than changes in standard anatomic measurements*
- Clinical trials – evaluate effectiveness of new radiopharmaceuticals
- Patient management – monitor disease state during treatment
- Lower variability
  - Smaller sample sizes needed for trials
  - Smaller effects discernable earlier
  - Decision about effectiveness of drug/treatment can be made earlier

*Weber WA. Assessing tumor response to therapy. J Nucl Med 50 Suppl 1:1S-10S, 2009. PMID: 19380403.

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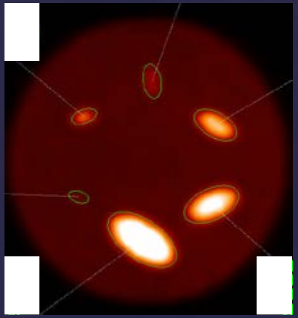
Image quantification from PET-CT or PET-MR is a complicated process involving many variables

- Activity calibration
  - Activity calibrator accuracy
  - Accuracy of transfer from calibrator to phantom
- Within-scanner variability
  - Activity calibrator accuracy
  - Accuracy/stability of scanner calibration
  - Correction methods (scatter, attenuation, randoms, decay, partial volume)
  - Reconstruction method
  - ROI/VOI definition
- Between-scanner variability
  - Equivalence of calibrations (scanner, activity calibrator)
  - Proprietary reconstruction, correction algorithms



Calibrated phantoms can help
- investigate and quantify components of uncertainty
- minimize uncertainty
- normalize data between scanners

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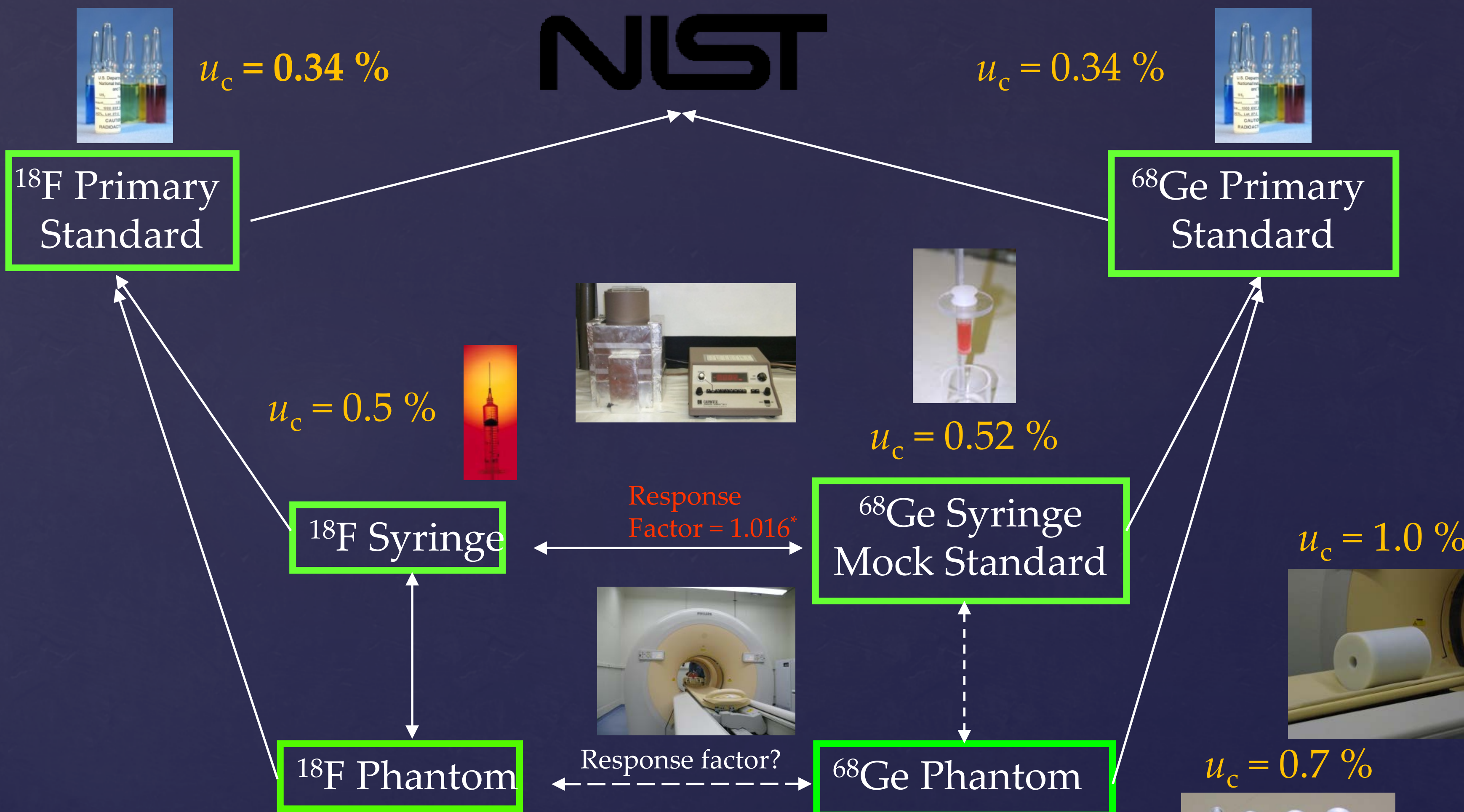
Why standards?

Traceability to common standard ensures

- all measurements are made to the same reference
- calibrations do not change over time
- existence of “ground truth” for evaluating accuracy

Linking phantoms, injected activity to common standard



*Dependent on activity calibrator manufacturer, model

Goal at beginning: uncertainty in phantom calibration ≤ 1%

Large solid ^{68}Ge phantoms – prototype 2013

- Collaboration between NIST, Univ. Iowa and commercial company
- 30 cm length, 20 cm diameter,
  - ≈9 L
  - ≈10 kg
- $^{68}GeCl_4$ in epoxy, inside polyethylene cylinder with 1.27 cm wall thickness
- "Universal" mounting for Philips, Siemens, GE scanners
- Two prototypes constructed, calibrated

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New phantom configurations 2015-present

Volume (L)	A_{tot} (MBq)	C_A (kBq/mL)
1.3 (annulus)	55	43
6	130	22
8.5	110	13

Modified calibration methodology

Mix $^{68}GeCl_4$ with epoxy for each phantom

Dispense epoxy into pre-weighed shell

Epoxy

Take 5 samples (6 mL) of epoxy into pre-weighed cylinders

Reweigh to obtain mass of epoxy

After curing, reweigh to obtain mass of epoxy mixture

Stock soln $^{68}GeCl_4$
4 MBq/g
(calibrated using NIST secondary standard IC)

Dilute to volume with carrier*

Dilution
70 kBq/g

Gravimetrically dispense 3 mL into “mock syringes”

Phanmast1

Phanmast2

Phanmast3

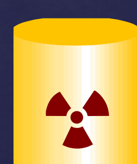
Liquid

Vinten 672 (“VIC”)

Determine calibration coefficients (K_{VIC}) for liquid-filled sources

Measure on VIC, determine A_{tot}

Apply attenuation correction factors (PENELOPE)



$$C_{A,\ phan} = C_{A,\ cyl}$$

*Carrier consisted of 45 mg each of non-radioactive $GeCl_4$ and $GaCl_3$ per gram of solution in 0.5 mol·L^{-1} HCl

Results – annular phantom

Typical standard uncertainties on the activity concentration, $C_{A,cyl}$, of ^{68}Ge in the annular epoxy phantoms as measured for the epoxy samples in the VIC.

Component, u_i	**u_i, % (typical)**
Measurement repeatability	0.16
Measurement reproducibility	0.24
Source reproducibility/epoxy inhomogeneity	0.10
Calibration factor	0.48
Decay correction	1.3×10^{-2}
Background	0.08
$u_c = (\sum u_i^2)^{1/2}$	**0.57**

Activity concentrations ($C_{A,ann}$), epoxy masses, and total activities (A_{ann}) for ^{68}Ge for annular phantoms. The percent differences given in the final column are the differences in $C_{A,ann}$ and $C_{A,ann,SMP}$ for aech annular phantom.

Phantom ID	**$C_{A,ann}$, kBq·g^{-1}**	**Mass, g***	**A_{ann}, MBq**	**$C_{A,ann,SMP}$, kBq·g^{-1}**	**Δ, %**
H340	**41.18(24)**	1368.7	56.36(33)	41.14(11)	0.10
H341	**38.59(26)**	1370.1	52.87(36)	38.30(8)	0.74
H342	**40.68(27)**	1364.5	55.51(37)	39.73(4)	2.34

Transferring standard to customer

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One epoxy phantom retained at NIST for on-going measurements

Half of calibrated epoxy cylinders retained at NIST for on-going measurements

Report of Test for cylinders and phantoms.

Half of calibrated epoxy cylinders returned to customer

Two calibrated epoxy phantoms returned to customer

Calibration factors for Vinten 671 ionization chamber

Customer

Installed copy of NIST Vinten 671 system

Measured calibration factor for epoxy cylinders

Verified their calibration factor with NIST-measured factor

Results – 6 L cylindrical phantom

Typical standard uncertainties on the activity concentration, $C_{A,cyl}$, of ^{68}Ge in the 6L epoxy phantoms as measured for the epoxy samples in the VIC.

Component, u_i	**u_i, % (typical)**
Measurement repeatability	0.54
Measurement reproducibility	0.31
Source reproducibility/epoxy inhomogeneity	0.28
Calibration factor	0.48
Decay correction	4.2×10^{-3}
Background	0.38
$u_c = (\sum u_i^2)^{1/2}$	**0.92**

Activity concentrations ($C_{A,ann}$), epoxy masses, and total activities (A_{ann}) for ^{68}Ge for 6 L phantoms. The percent differences given in the final column are the differences in $C_{A,phan}$ and $C_{A,phan,SMP}$ for each phantom.

Phantom ID	**$C_{A,phan}$, kBq·g^{-1}**	**Mass, g***	**A_{phan}, MBq**	**$C_{A,phan,SMP}$, kBq·g^{-1}**	**Δ, %**
J771/B1	22.38(18)	6439.50	144.1(12)	22.35(31)	0.13
J772/B2	22.74(19)	6443.33	146.5(12)	22.79(10)	-0.26
J773/B3	22.59(21)	6440.89	145.5(13)	22.63(27)	-0.20

In the meantime, QIBA recommends using calibrated, traceable phantoms for clinical trials when investigating ^{18}F[FDG] for different oncology applications

"The scanner calibration shall be tested using a NIST-traceable (or equivalent) simulated F-18 source object, e.g. a uniform cylinder, large enough to avoid partial volume effects or other resolution losses."

Quantitative Imaging Biomarker Alliance, "QIBA Profile. FDG-PET/CT as an Imaging Biomarker Measuring Response to Cancer Therapy", Radiological Society of North America/QIBA (Nov. 2013).

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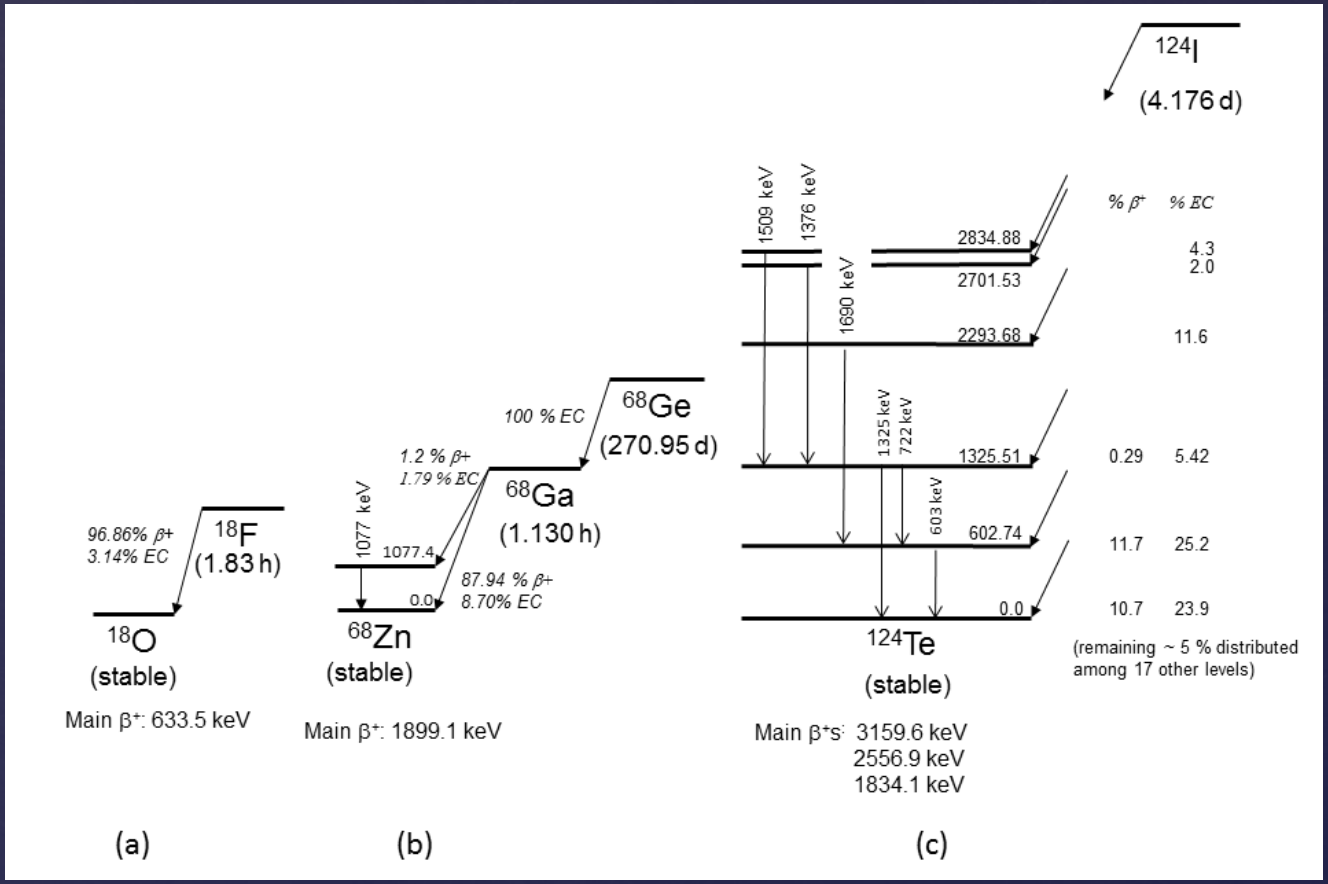
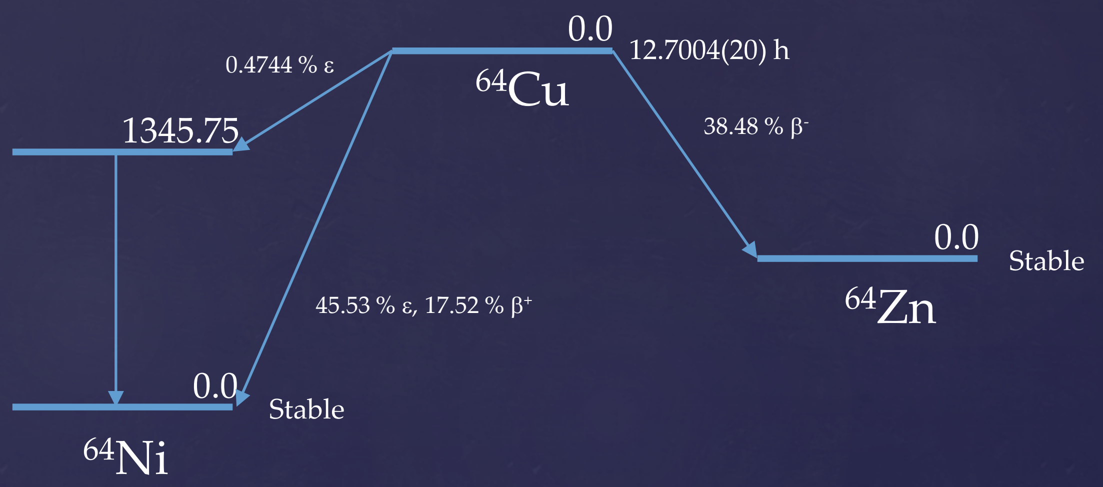
Other on-going activities

Quantitation and nuclides with complex decay schemes



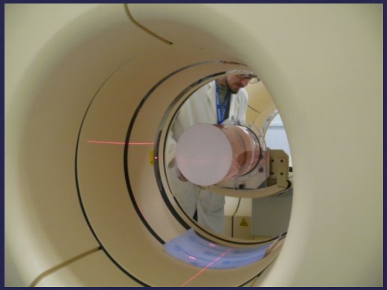
How will differences in decay schemes influence responses in activity calibrator and scanner?

Standardization of ^{64}Cu, in progress



Calibration of scanner and other clinical instrumentation against NIST ^{18}F standard

- Only scanner in the world directly calibrated against NIST primary standard for ^{18}F, uncertainty on phantom activity ~ 1 %.
- Several models of activity calibrators ("dose calibrators") and a gamma well counter calibrated against same standard
- On-going studies
  - Accuracy, uncertainty of PET imaging quantification
    - Current accuracy/recovery = ± 0.8 % to ± 5 % for uniform liquid phantoms
    - Partial volume effect corrections
    - Study sources of uncertainty/error, limits of accuracy for absolute quantification
  - Effect of ^{18}F calibration on accuracy of quantitation with other radionuclides



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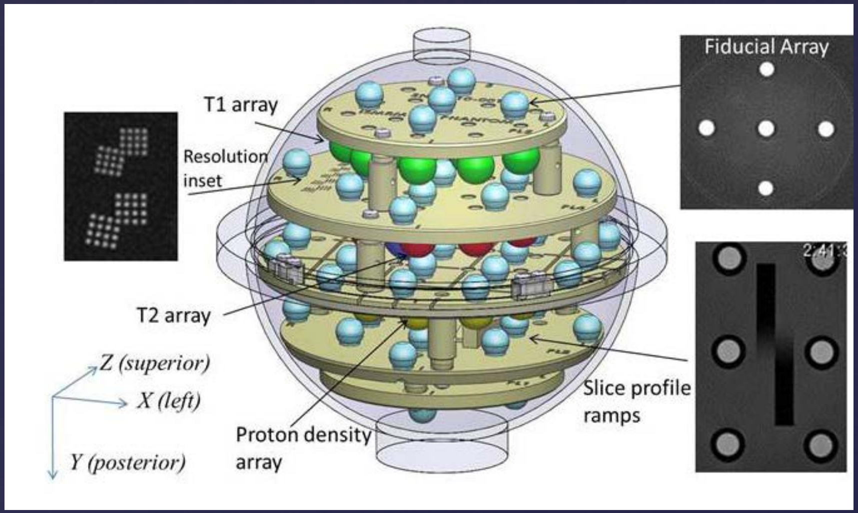
Underlying goal: calibrate and characterize scanner so that it can be used as a secondary standard (like an activity calibrator) for phantoms

Traceable Phantoms for PET-MR

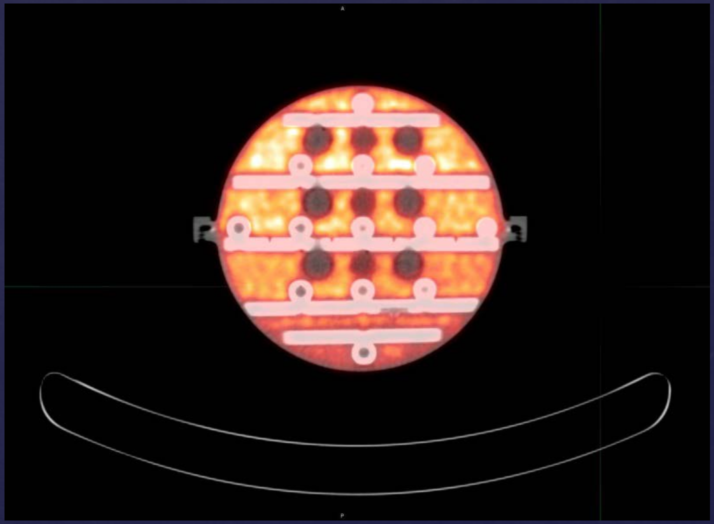
PHANNIE: NIST system phantom for MR

Traceable calibration sets for:

1. T1
2. T2
3. Proton density (varying [^{2}H])
4. Resolution



New design includes inserts for solid ^{68}Ge hemispheres or discs (currently without partial volume effects), easier background filling.



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Conclusions

- Radioactivity standards play important role in ensuring accuracy and precision of quantitative PET
- NIST develops a number of primary standards for PET radionuclides with typical uncertainties < 1 %
- Secondary standards are used to make NIST standard relevant to clinical application
- Calibration methodology developed for large solid PET phantoms, making traceable phantoms commercially available
- Developments in phantom development, including for PET-MR, are on-going

Thanks to

NIST:
Denis Bergeron
Jeffrey Cessna
Matt Mille (also RPI)
Ryan Fitzgerald
K. Stupic, K. Keenan, M. Boss, S. Russek (NIST Magnetics Group)

Keith Allberg, RadQual, LLC
John Sanders, Sanders Medical Products, Inc.
Dr. John Sunderland, Univ. Iowa
RSNA/QIBA