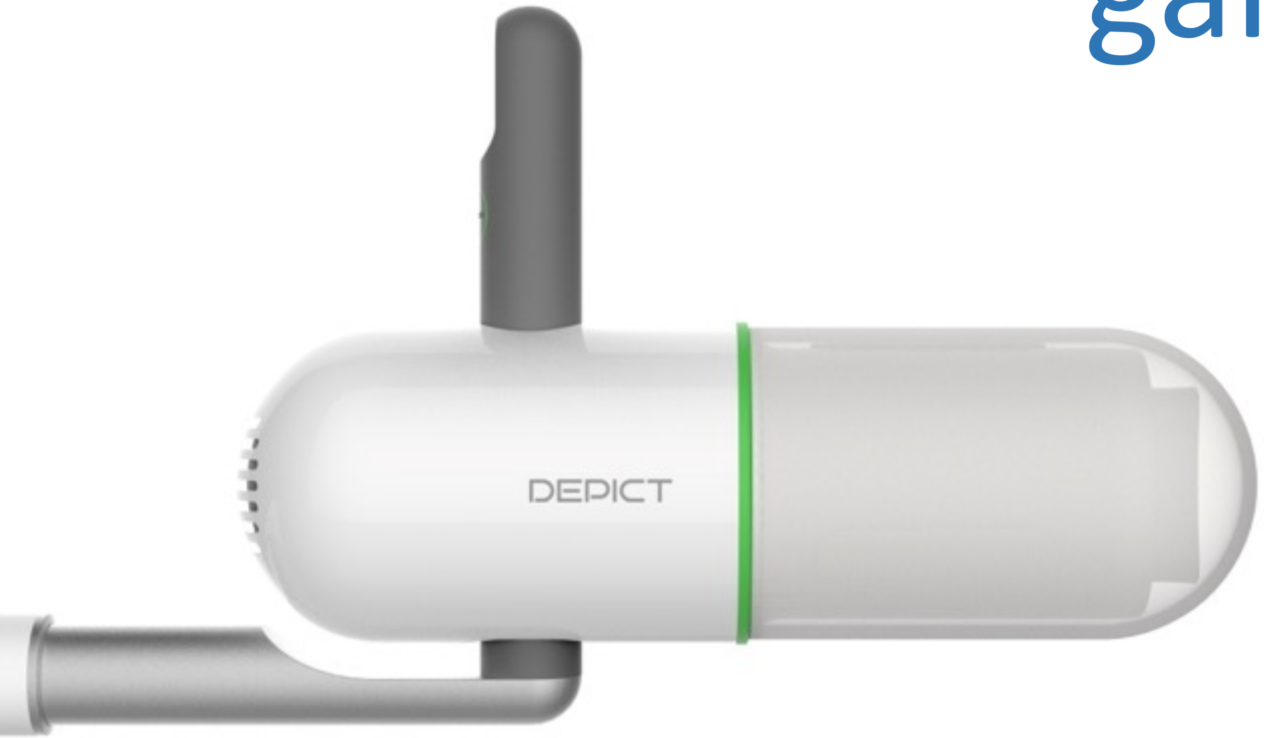
Addressing cancer challenges with gamma-ray detectors



Dr Laura Harkness-Brennan

The University of Liverpool

kromek

The Royal Liverpool and Broadgreen University Hospitals NHS Trust

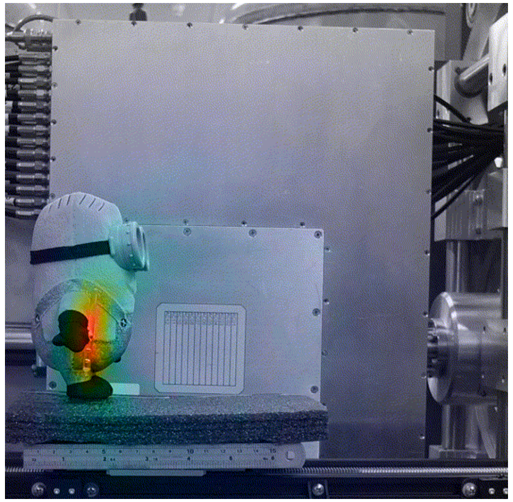
UKRI Science and Technology Facilities Council

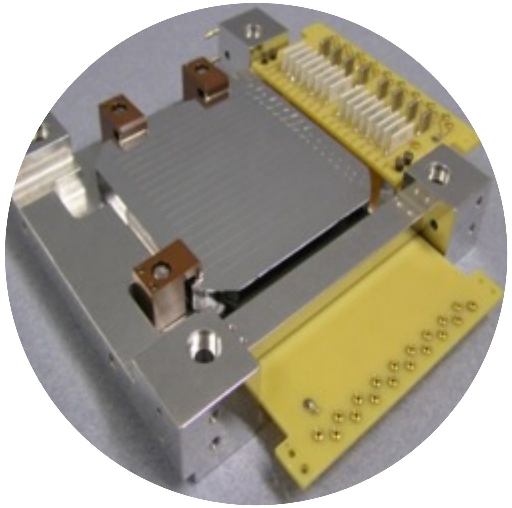
ICR The Institute of Cancer Research

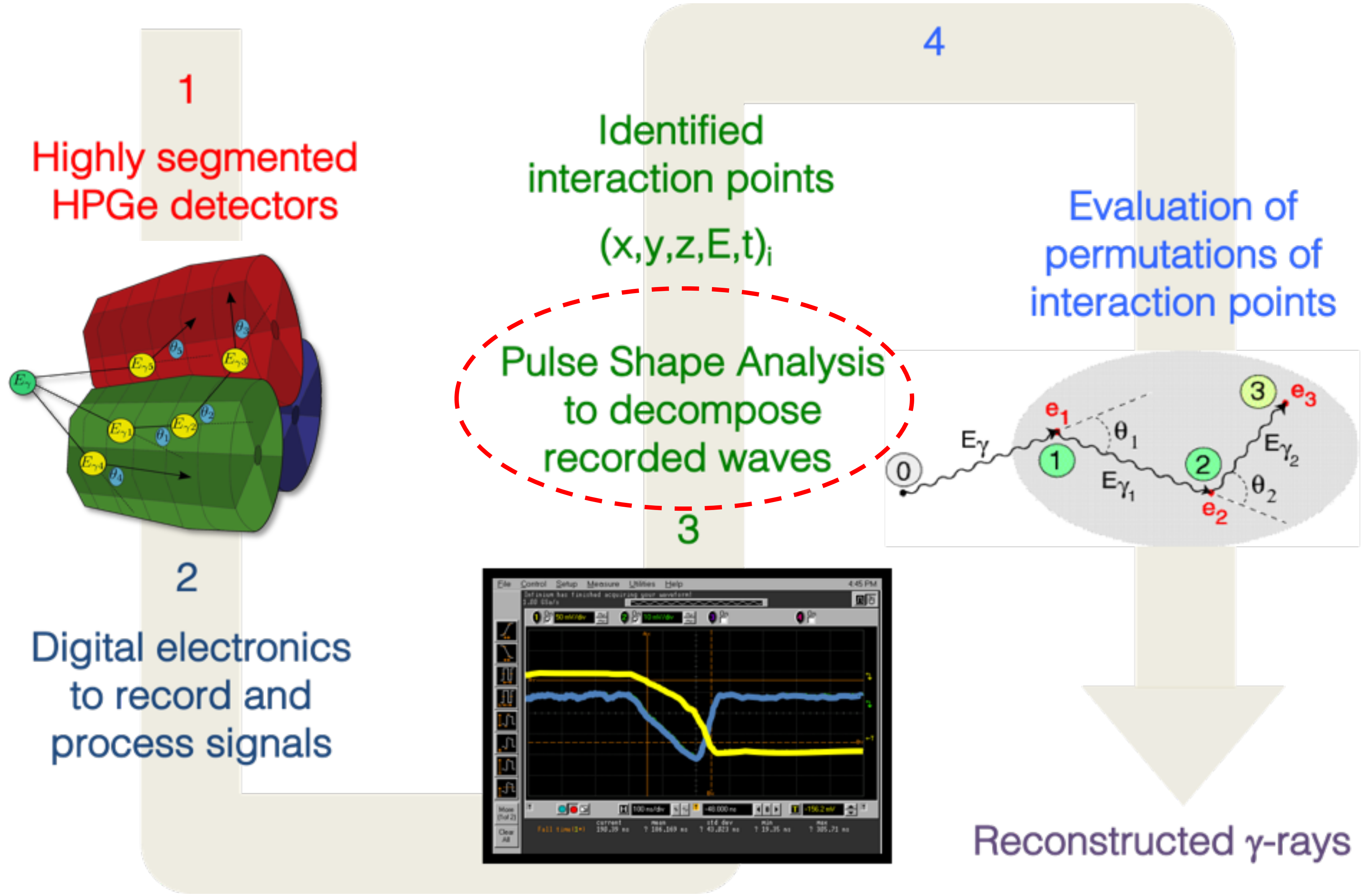
The ROYAL MARSDEN NHS Foundation Trust

My expertise

- Designing detector systems for gamma-ray spectroscopy and imaging in nuclear structure physics experiments and applications (Monte-Carlo)
- Characterisation of charge collection response in semiconductor detectors under irradiation (experimental gamma-ray beam scanning and theoretical modelling)
- Algorithms to determine gamma-ray interaction position within a detector, based on the determined charge collection response






1
Highly segmented HPGe detectors
2
Digital electronics to record and process signals
3
Pulse Shape Analysis to decompose recorded waves
Identified interaction points
(x,y,z,E,t)$_i$
4
Evaluation of permutations of interaction points
0
1
2
3
e_1
e_2
e_3
E_γ
E_{γ_1}
E_{γ_2}
θ_1
θ_2
Reconstructed γ-rays

2010

Completed PhD "**Prospectus** Design"

Innovations Club Healthcare event (NHS partners)

IEEE Conference (industry partners)

2014

John Matheson (STFC) organised workshop "Detector needs for isotope therapy"

Applied for STFC CLASP project "DEPICT for dosimetry in radionuclide therapy"

2015

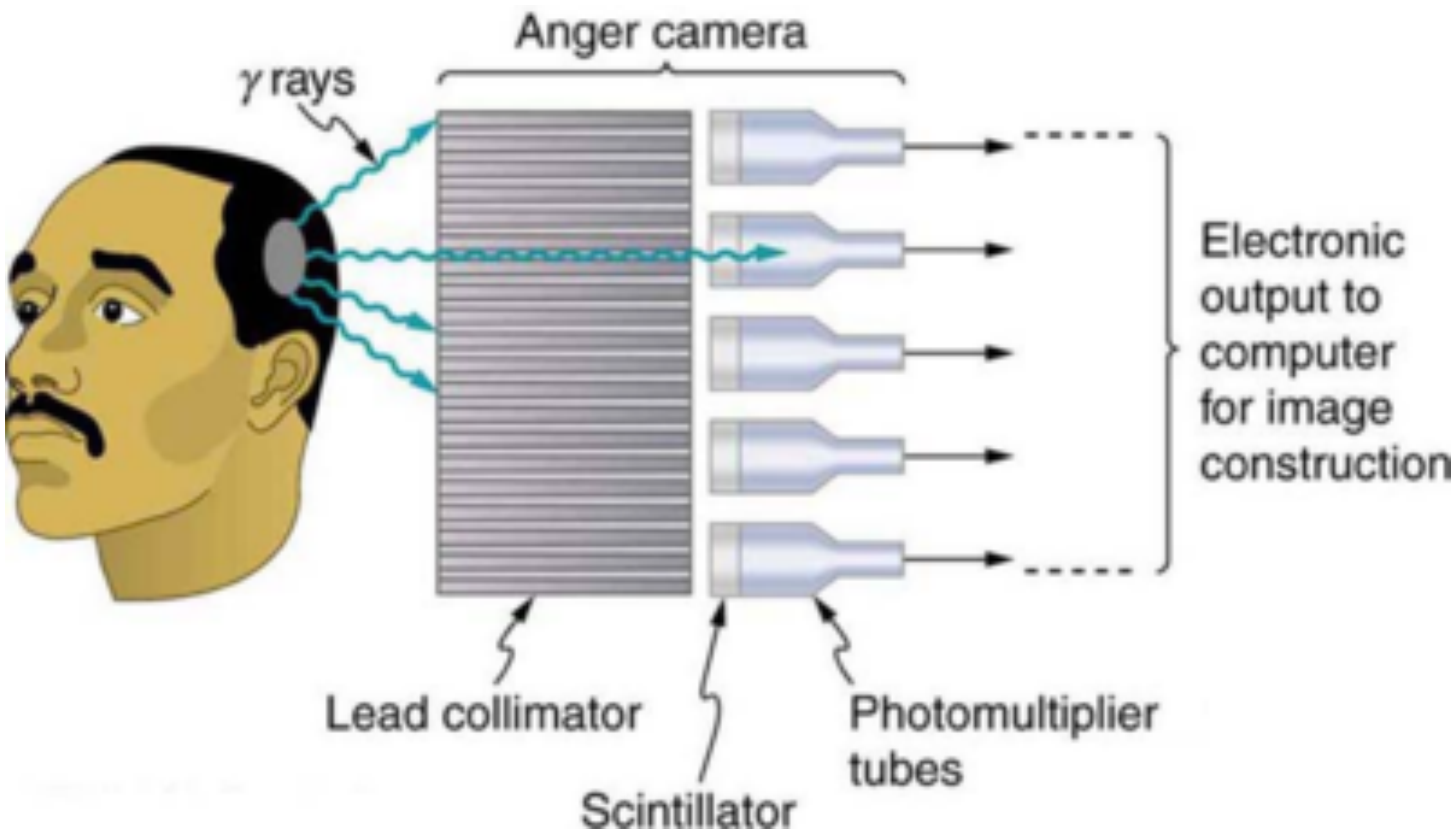
Started 2-year CLASP project "**DEPICT**" with Royal Marsden hospital and Kromek Ltd

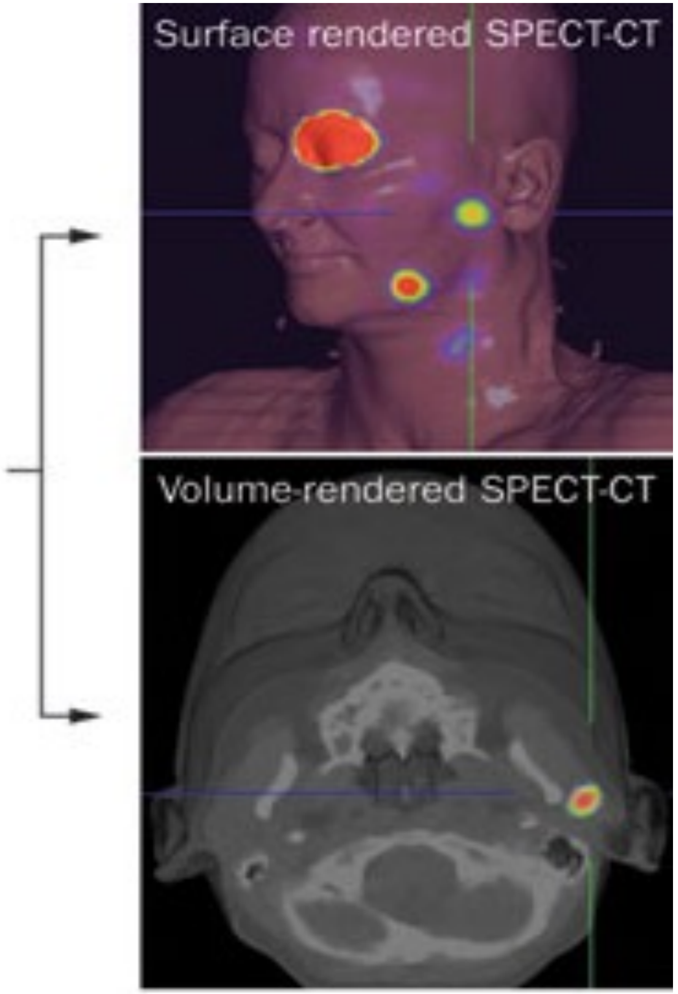
2019

Started 3-year STFC IPS project "**Algorithms for sub-voxel resolution in Low Dose MBI**"

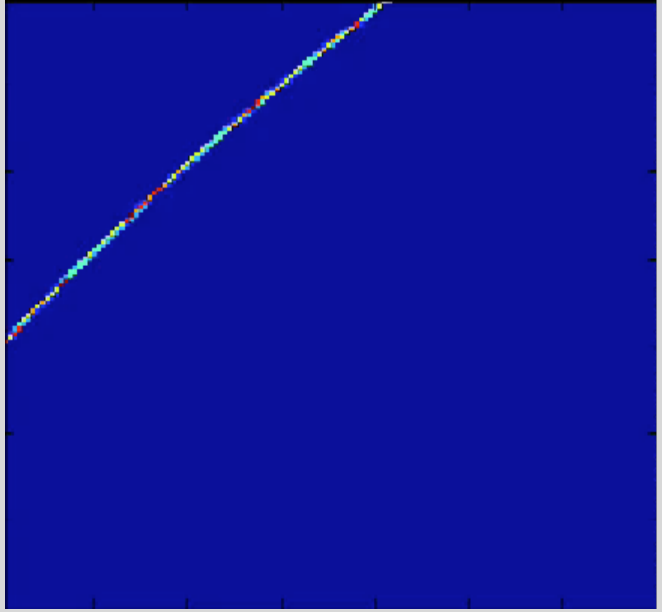
Lead STFC Cancer Diagnosis Network+

SPECT



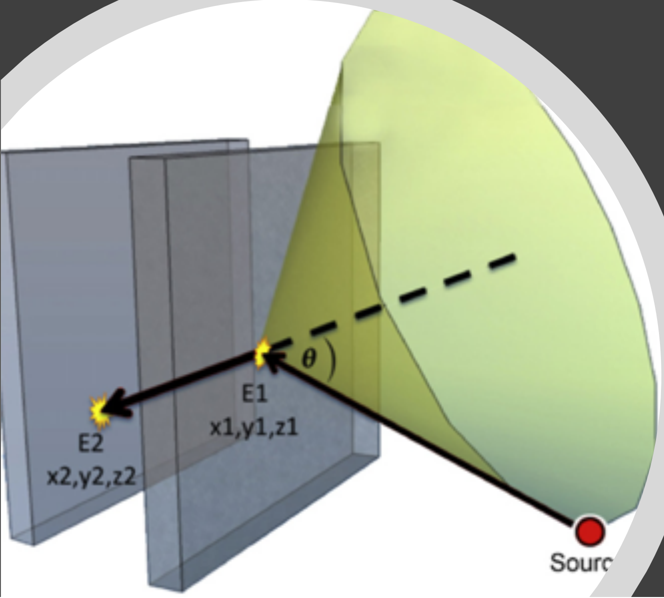


Elhendy, A, Bax JJ, Poldermans D (2002) Journal of Nuclear Medicine 43(12): 1634-1646



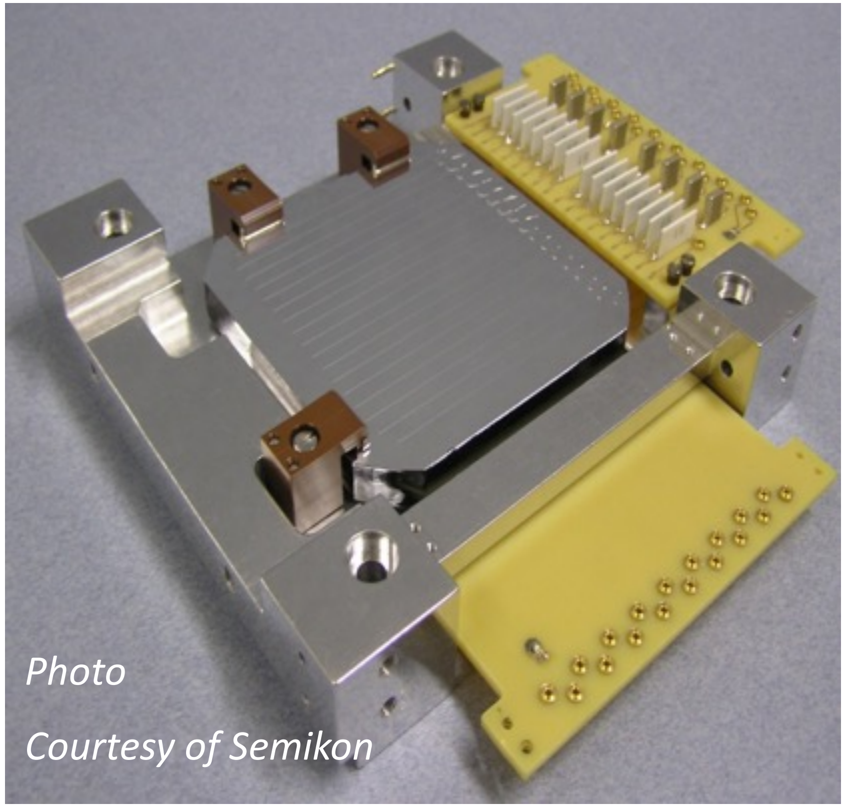
ProSPECTus

$$\cos\vartheta = 1 - m_e c^2 \left(\frac{1}{E_1} - \frac{1}{E_0} \right)$$

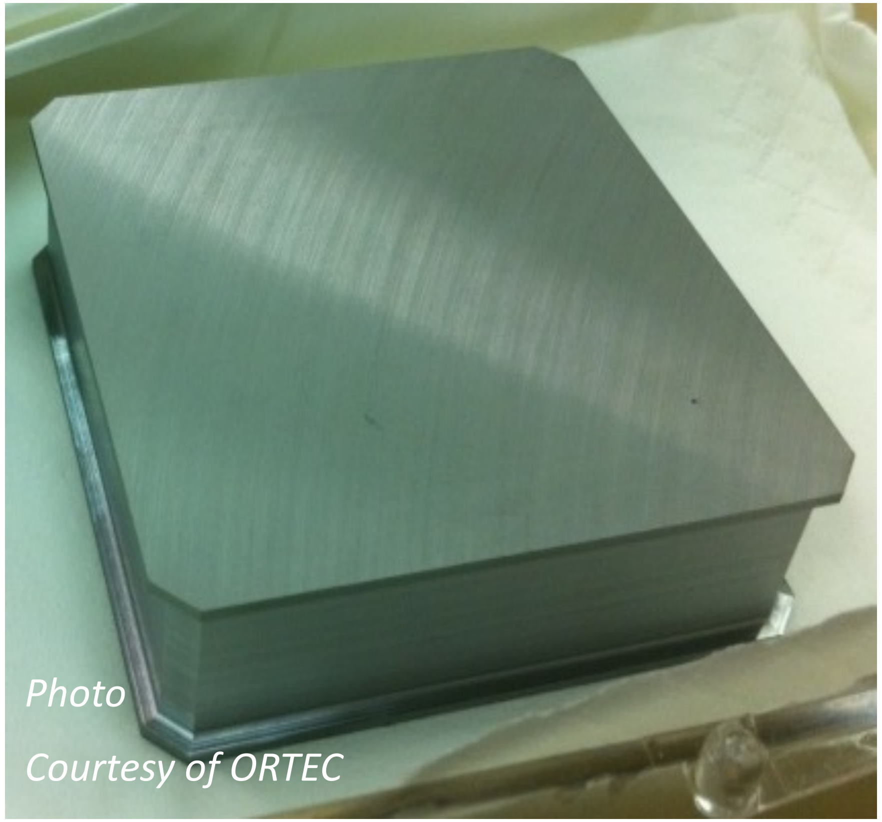


- **High sensitivity** (low dose) alternative to diagnostic SPECT
- Uses gamma-ray tracking (nuclear physics technique)
- No mechanical collimator required
- Design optimised for 141keV gamma-rays using GEANT4
- 100 times more sensitive than SPECT
- Multiple isotope imaging possible

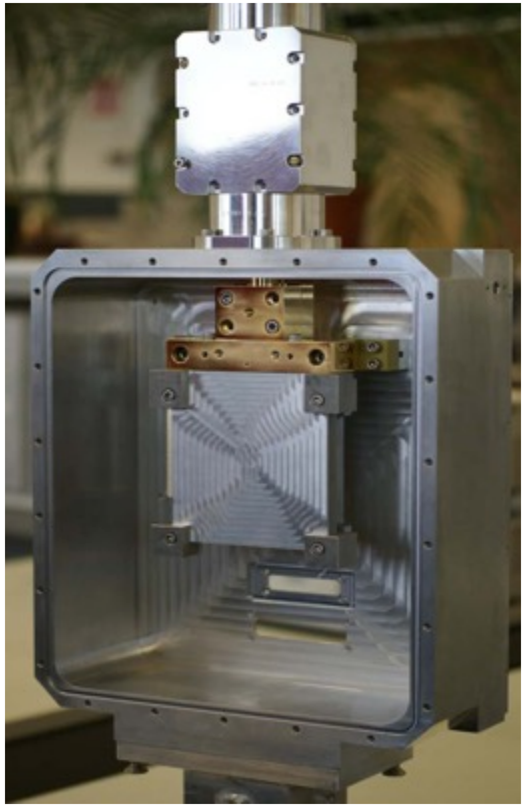
ProSPECTus system



- Planar Si(Li) (60 x 60 x 9) mm
- 16 strips on each face, 4mm pitch



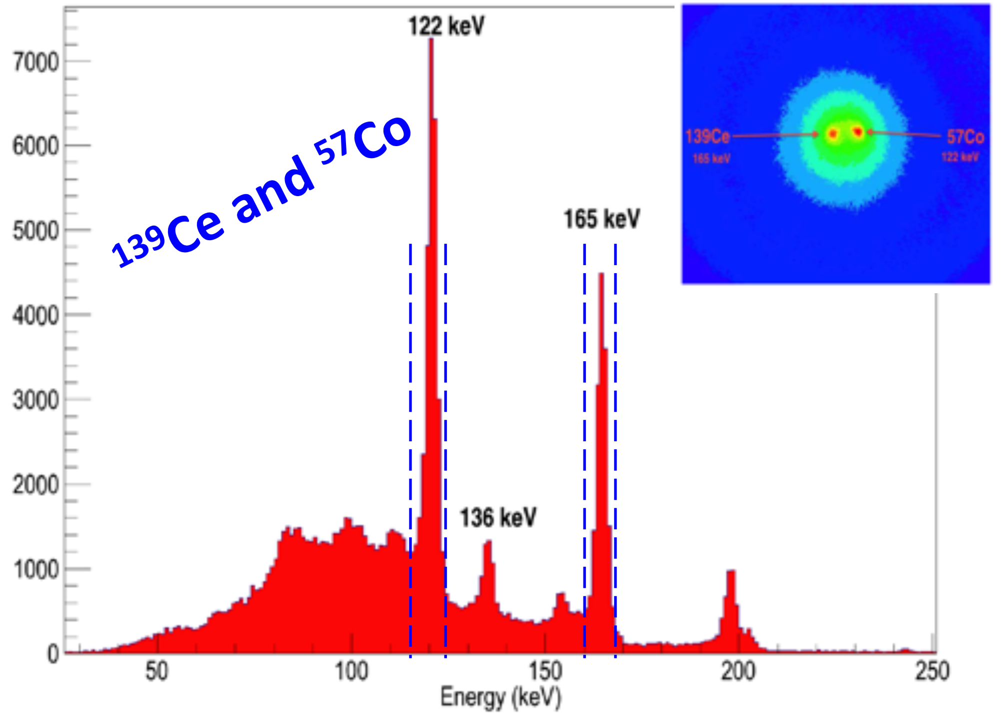
- Planar HPGe (60 x 60 x 20) mm
- 12 strips on each face, 5mm pitch



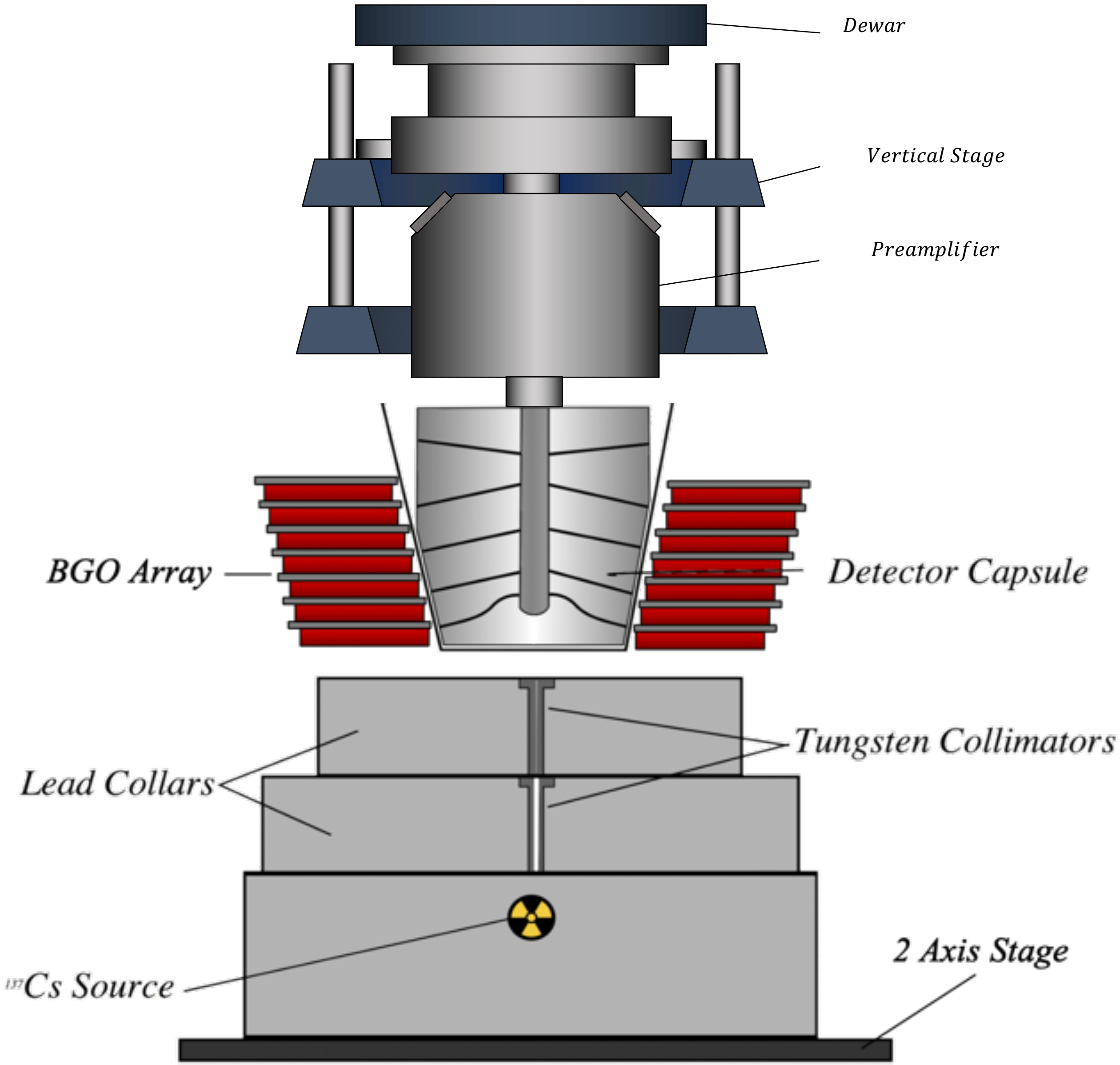
MRI compatible cryostat developed by STFC Daresbury

Image Quality

- Contributions to Compton camera image quality include:
  - Doppler Broadening
  - Energy Resolution
  - **Position Resolution**
  - Geometrical configuration
- Energy resolution is characteristic of the detectors (< 2keV)
- Doppler broadening is a property of the detector material
- Position resolution can be improved beyond electrode segmentation
- Optimisation of image reconstruction algorithms



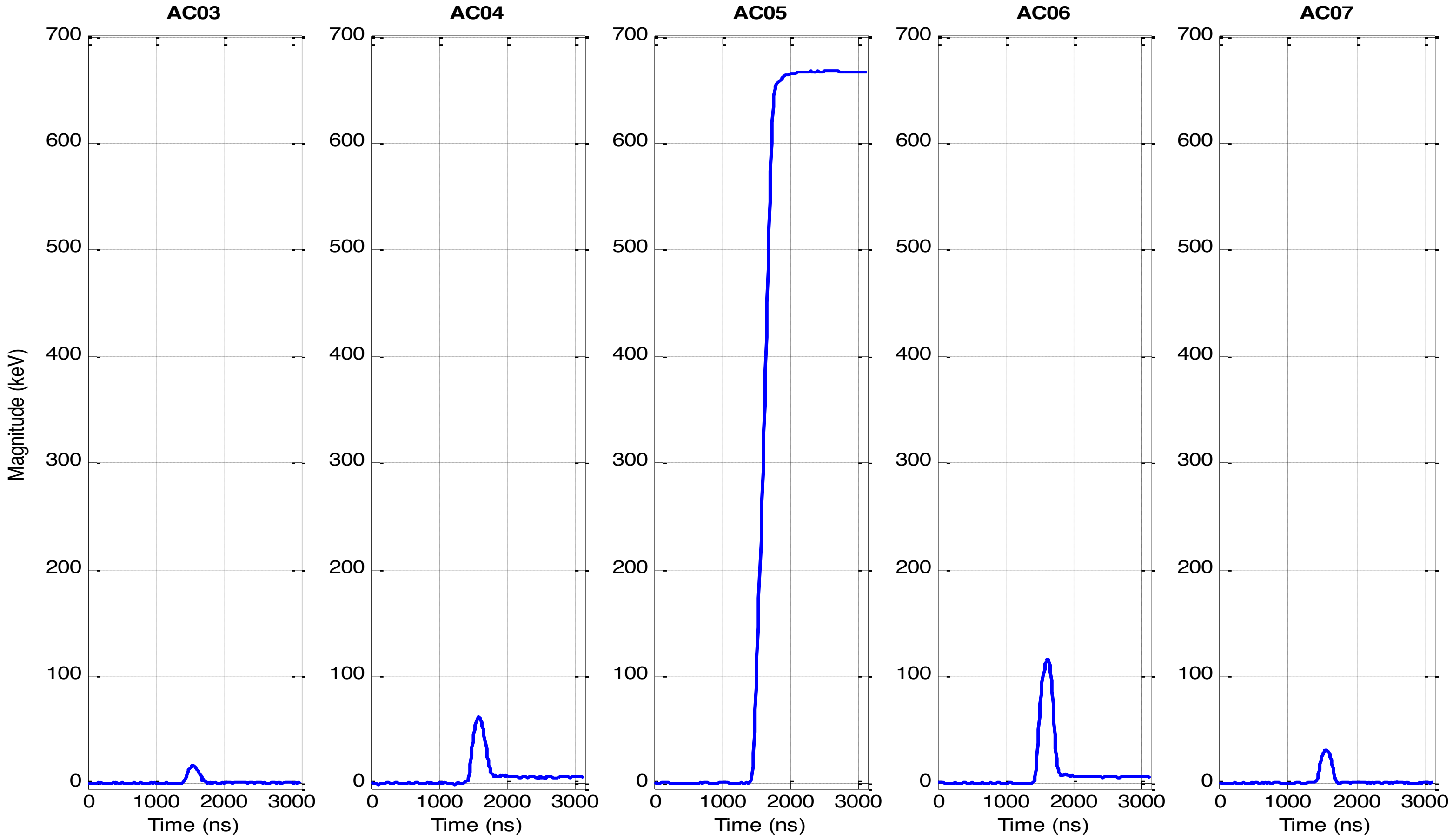
Liverpool Scanning system

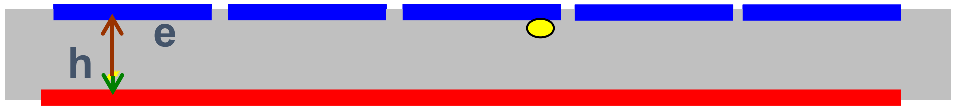


Coincidence scanning apparatus found at Liverpool

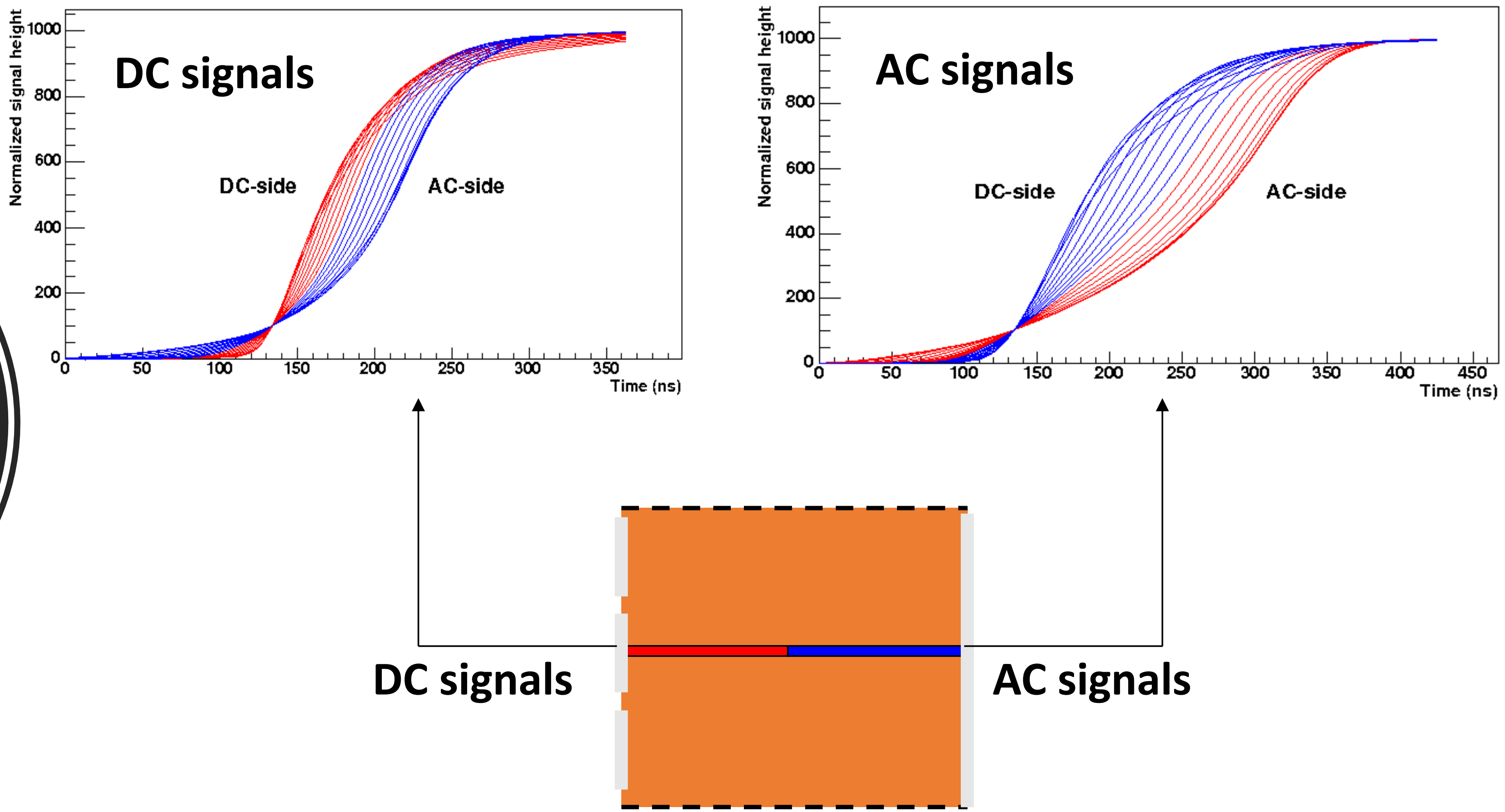
F Holloway

Liverpool Scanning system

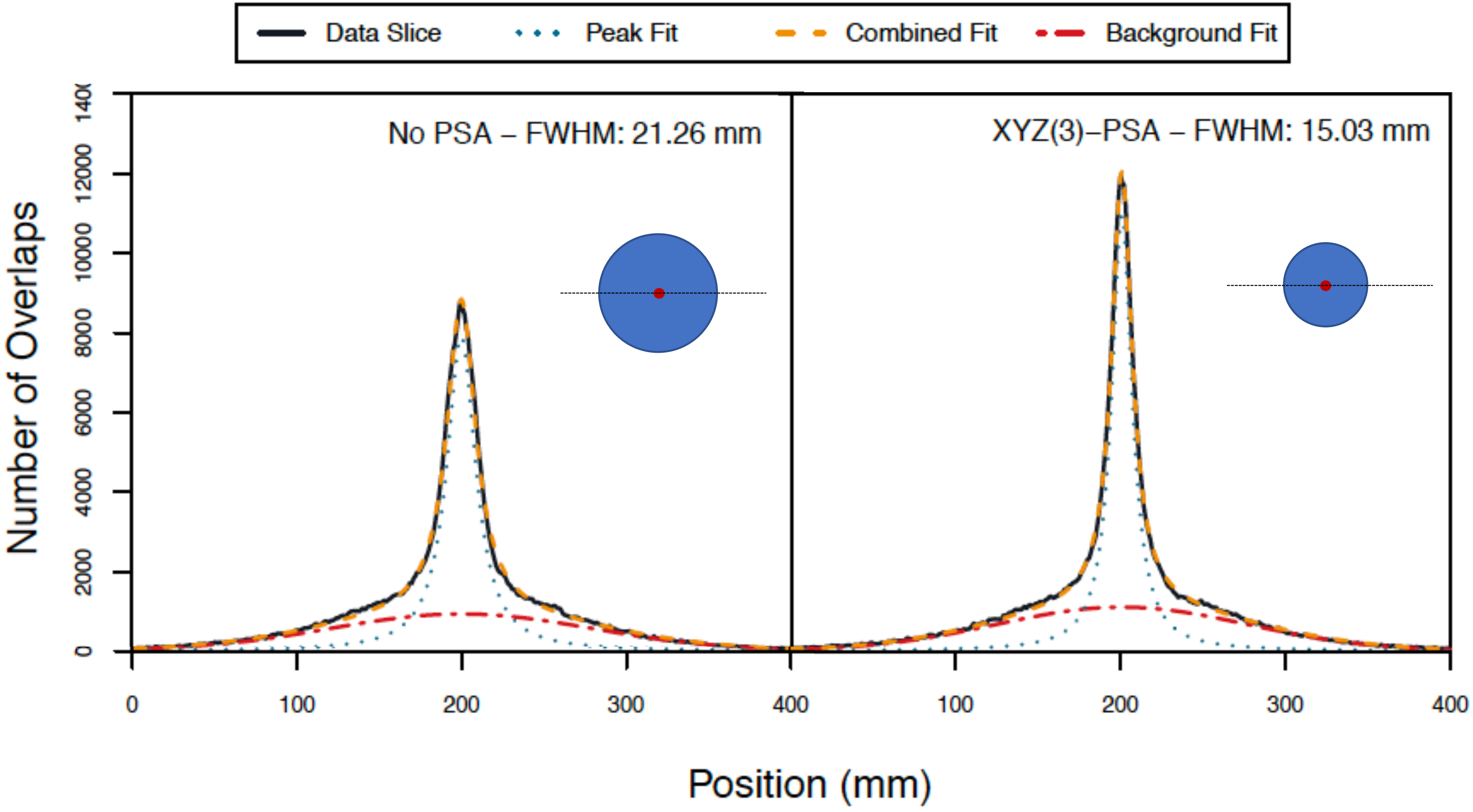




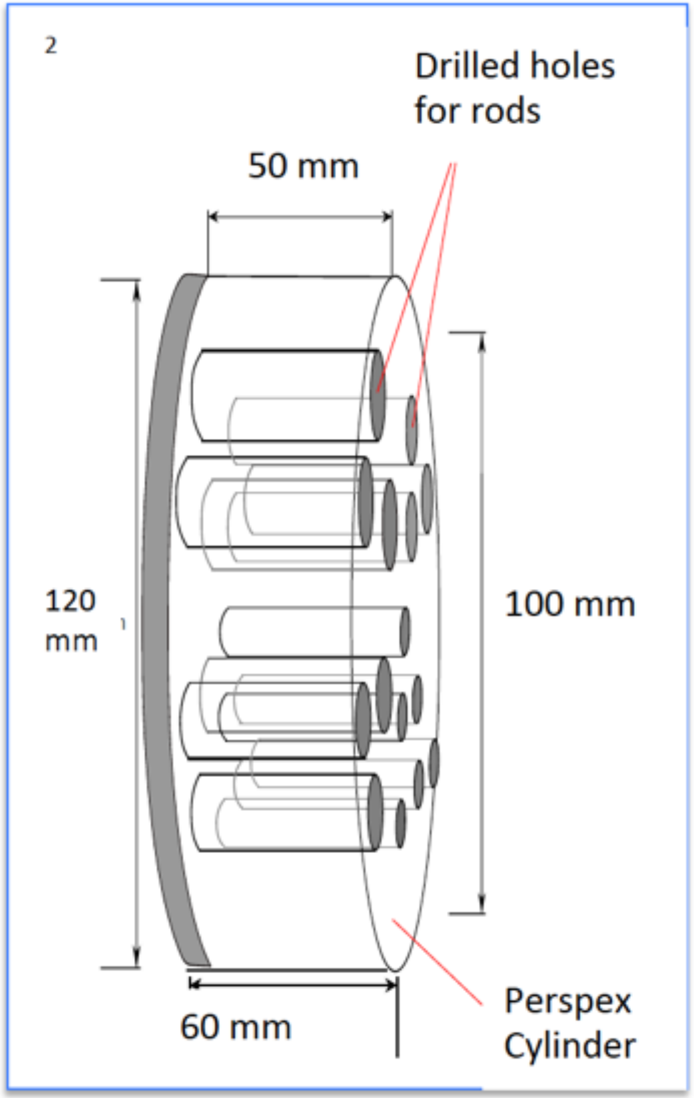
Liverpool Scanning system



Parametric PSA



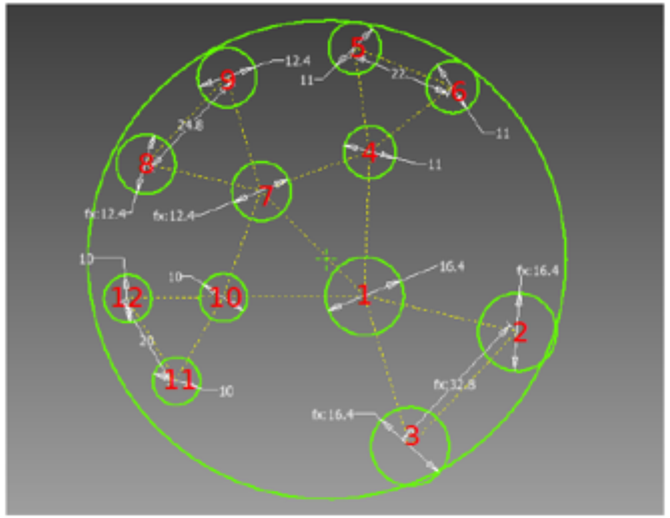
ProSPECTus Phantom



- Source: ^{139}Ce (165 keV)
- Rod diameter: 16, 12.4 , 11, 10 mm

Medical Imaging quantitative assessments:

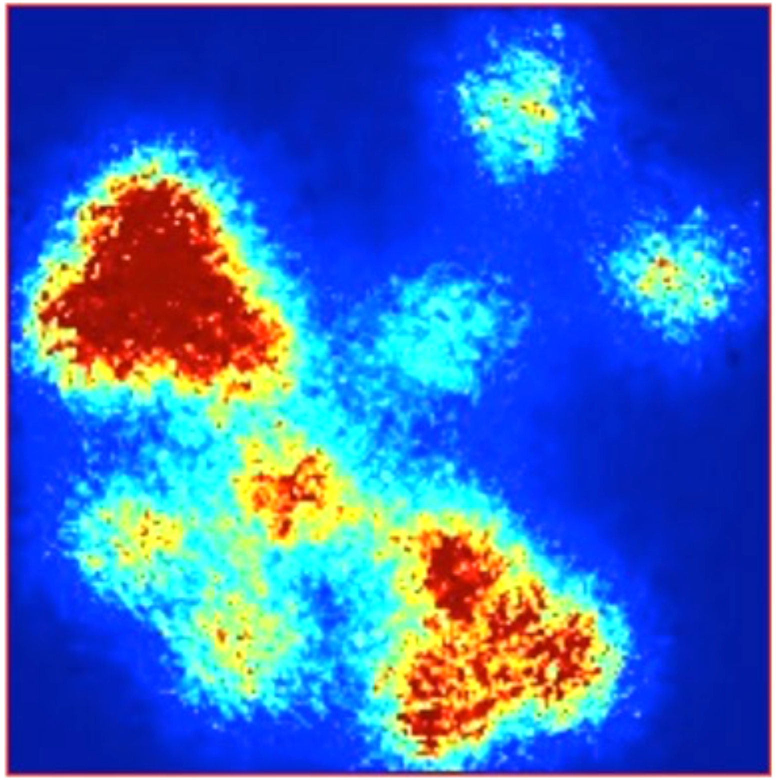
1. Resolution
2. Noise
3. Sensitivity
4. Contrast



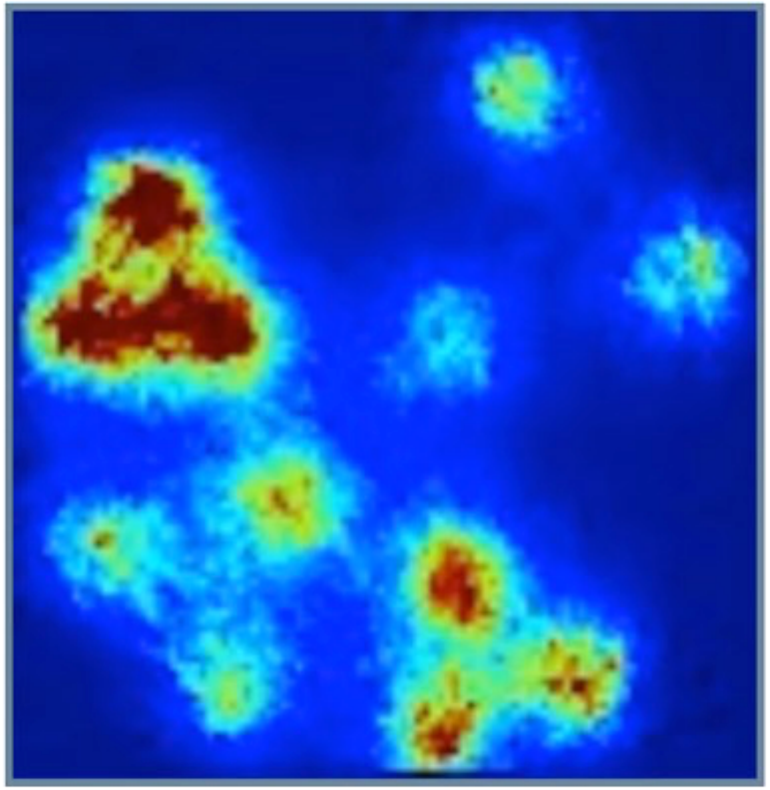
S Colosimo

[2] sjc@ns.ph.liv.ac.uk - SPECT data acquisition, phantom holder design

ProSPECTus Phantom



Characteristic Position resolution

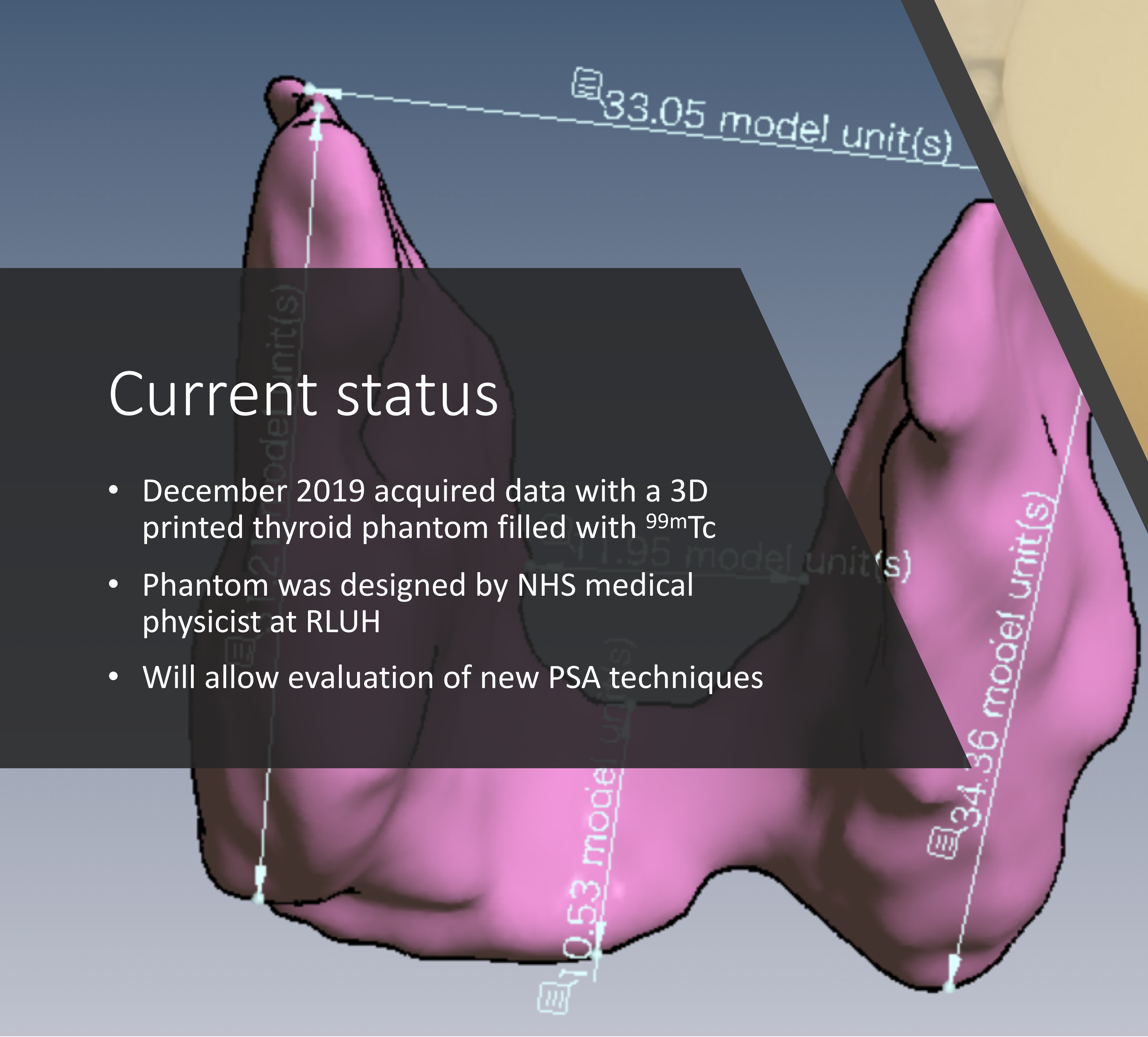


$1mm^3$ Position resolution in absorber

A Patel

Current status

- December 2019 acquired data with a 3D printed thyroid phantom filled with ^{99m}Tc
- Phantom was designed by NHS medical physicist at RLUH
- Will allow evaluation of new PSA techniques



STFC CLASP Healthcare

- **Remit:** Themed call to apply STFC funded research/technology to help address societal challenge areas
- **Project:** Quantitative SPECT for dosimetry of ^{131}I radionuclide therapy (July 2015 to June 2017)
- **Partners:** Royal Marsden NHS Trust, Institute of Cancer Research, Royal Liverpool & Broadgreen University Hospitals NHS Trust & Kromek Group plc. Project driven by challenges identified by the hospital partners.

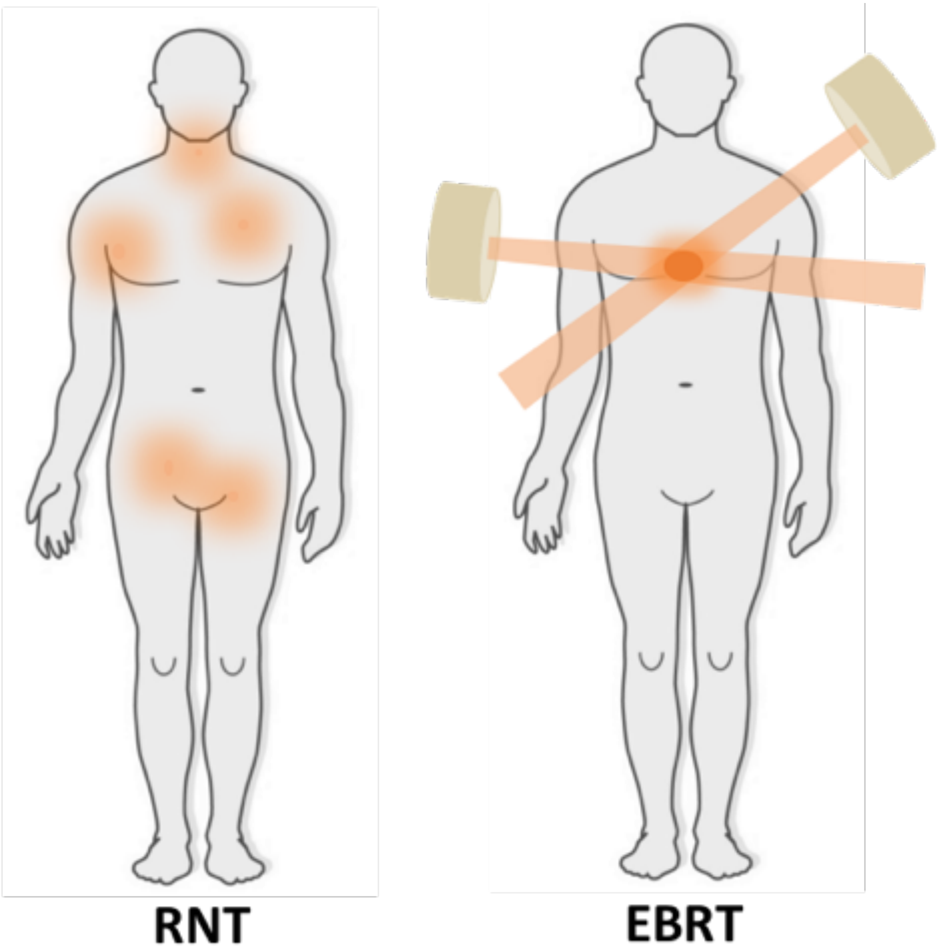
Radiotherapy

Approximately 50% of cancer patients undergo radiotherapy treatment.

Aim to deliver a lethal radiation dose to a target volume to stop/slow progression of disease

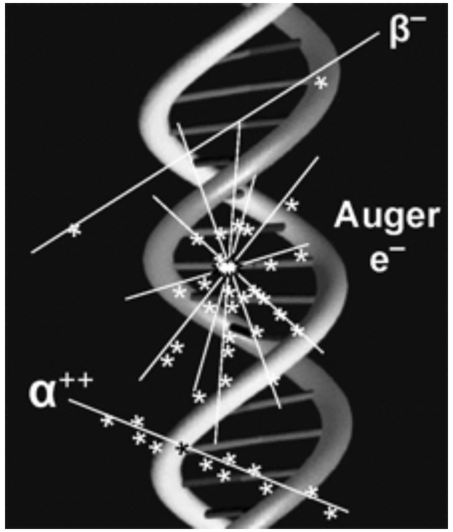
$$D = \frac{d\tilde{E}}{dm}$$

Radiobiological principles of EBRT and RNT are same. Differences in biophysical and radiobiological effects arise from sources of radiation.

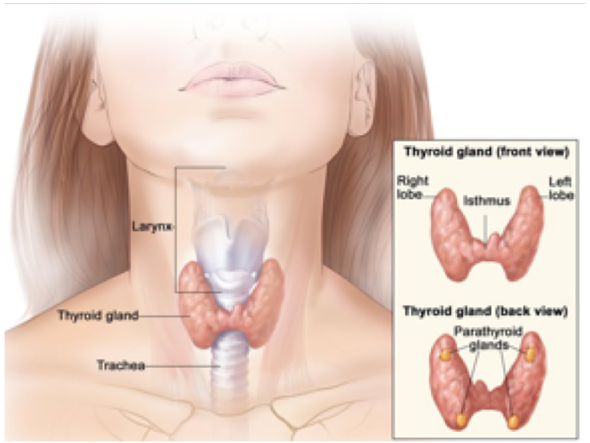


Radionuclide Therapy

1. Radioisotopes emit charged particles
2. Extended exposures and declining dose rates
3. Non-uniformities in the radioactivity distribution (and dose)
4. Particles of varying ionisation density



Radionuclide	Decay Mode	$T_{1/2}$ (d)	R_m (mm)	Medical Use
^{89}Sr	β^-	50.5	2.4	Bone metastases
^{90}Y	β^-	2.7	3.9	Non-Hodgkin lymphoma
^{131}I	β^-	8.0	0.4	Thyroid disease
^{153}Sm	β^-	2.0	0.6	Bone metastases
^{177}Lu	β^-	6.7	0.23	Neuroendocrine tumours
^{223}Ra	α	11.5	0.1	Bone metastases



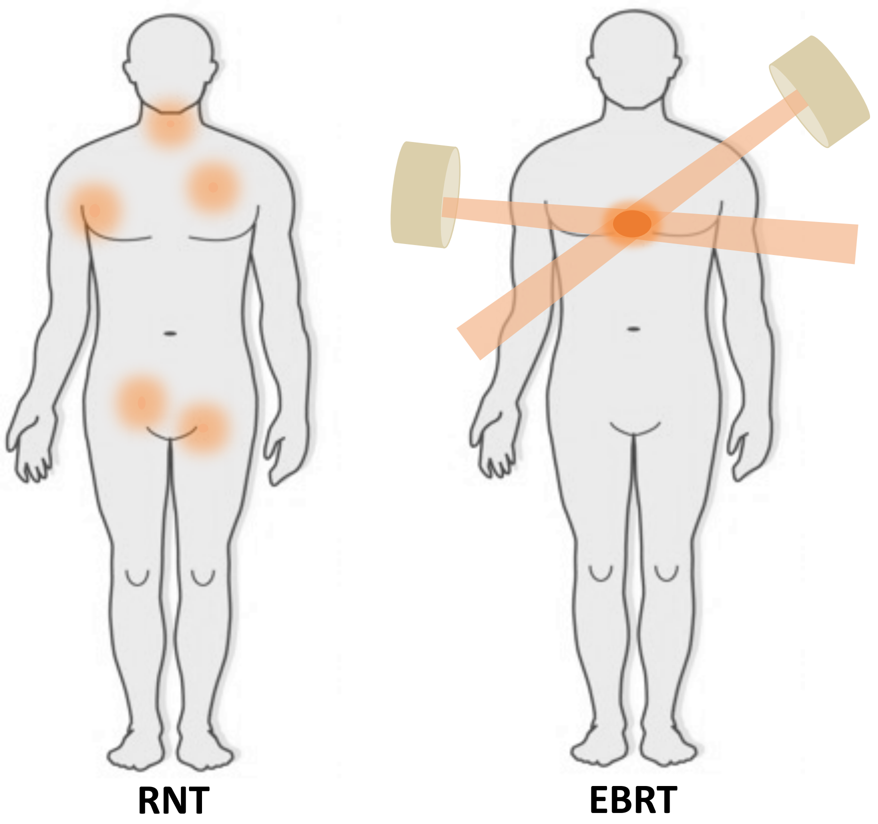
Radionuclide Therapy

- Biological uptake depends on patient and disease status
- ^{131}**I:** fixed activity level or weight scaled: doses vary up to a factor of 100 [1]

*[1] **G Flux** et al, Eur J Nucl Med Mol Imaging (2010) 37:370-275*

$$\overline{D}_T = \int_{t_1}^{t_2} A(r_S, t)\, dt \cdot \frac{1}{m_T} \sum_i n_i E_i \cdot \phi(r_T \leftarrow r_S, E_i)$$

TAC — **S factor**



Challenges

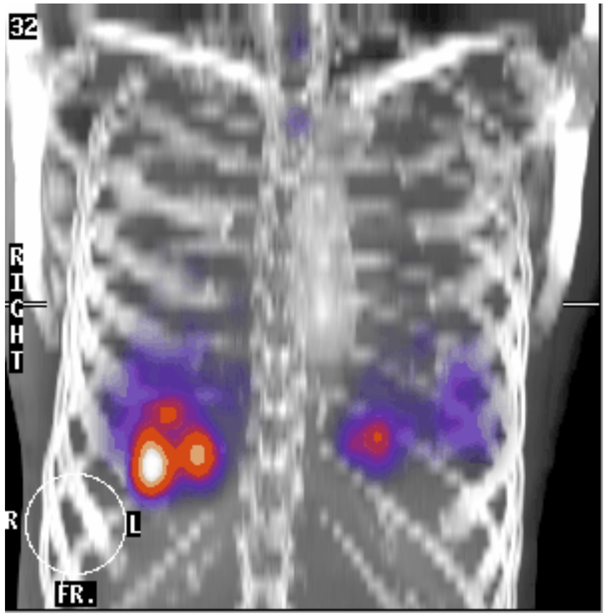
EU directive 2013/59/EURATOM Article 56: For radiotherapeutic purposes...exposures of target volumes shall be **individually planned and their delivery appropriately verified**

Solution

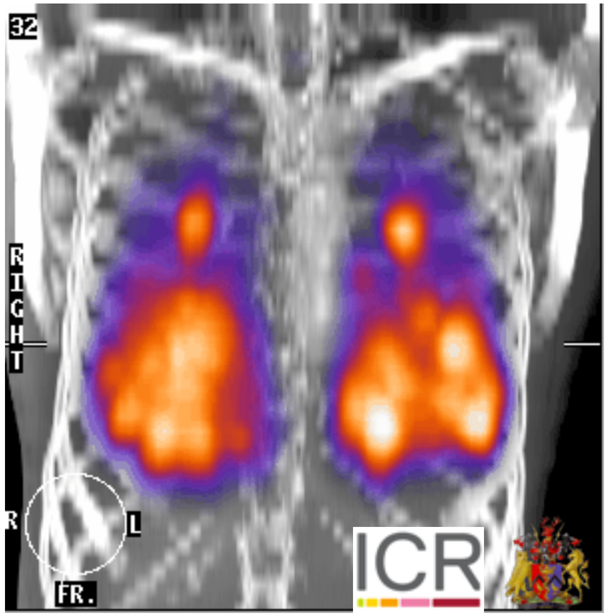
Quantitative SPECT images to produce activity distribution (dose map), if gamma-rays are emitted

Implementation

1. Pre-therapy tracer (same isotope), however can lead to “stunning” and uncertainties due to changes between scans



Pre therapy: 118 MBq ^{131}I-NaI



Therapy: 8193 MBq ^{131}I-NaI

Challenges

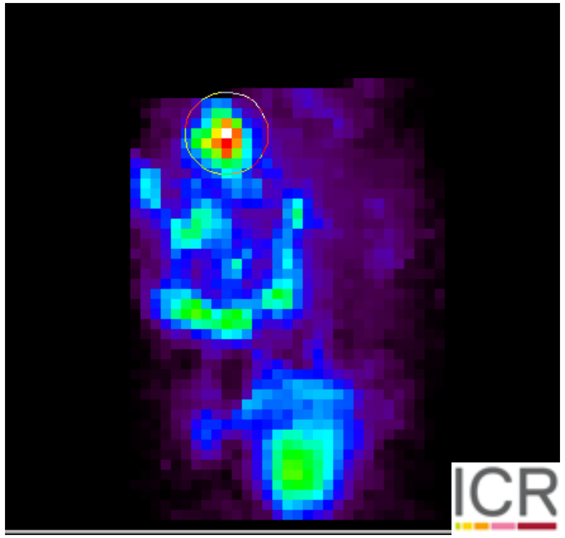
EU directive 2013/59/EURATOM Article 56: For radiotherapeutic purposes...exposures of target volumes shall be **individually planned and their delivery appropriately verified**

Solution

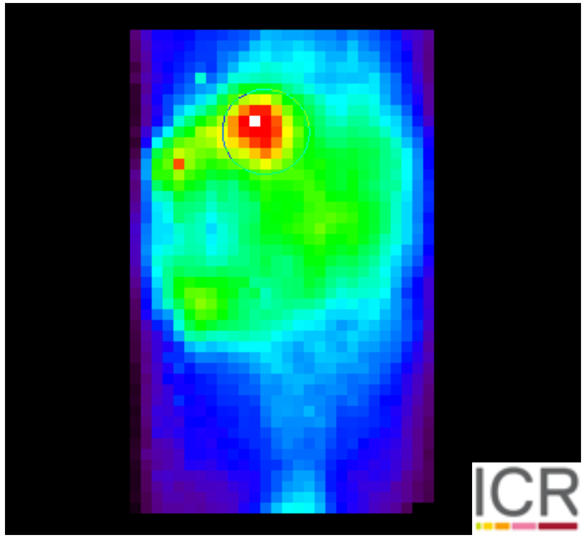
Quantitative SPECT images to produce activity distribution (dose map), if gamma-rays are emitted

Implementation

2. Pre-therapy tracer (different isotope, e.g. ^{123}I mIBG or ^{124}I mIBG before therapy with ^{131}I mIBG), however can influence the biodistribution



Predicted ^{131}I dose using ^{123}I



Delivered dose (^{131}I)

Challenges

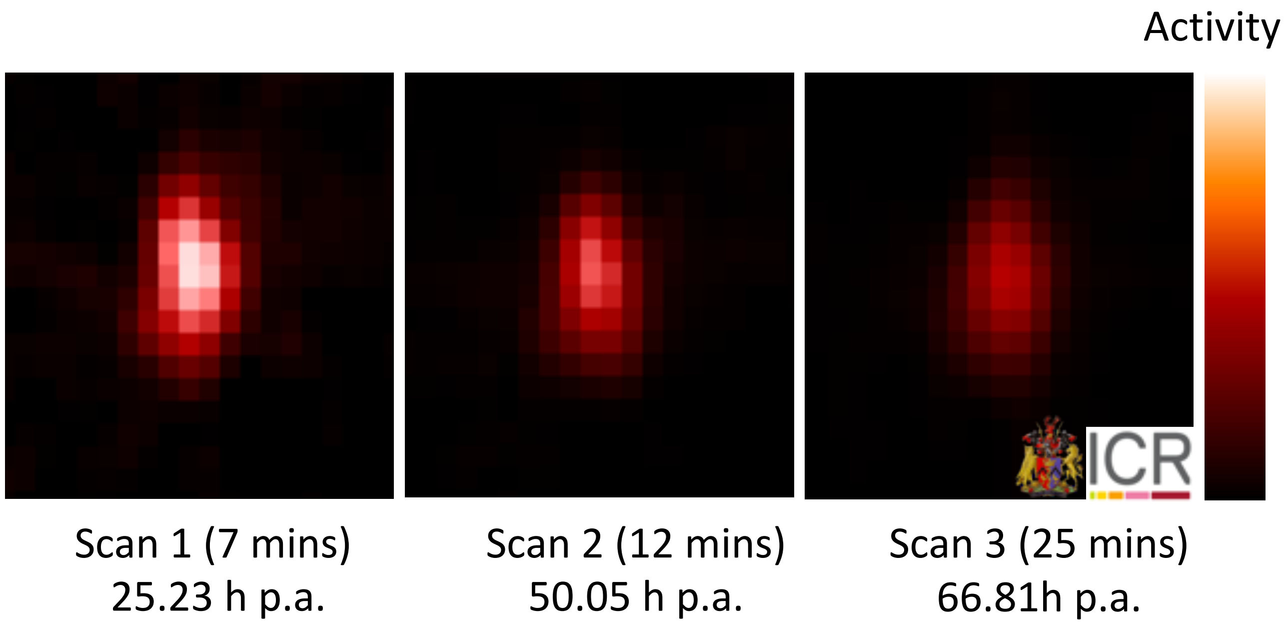
EU directive 2013/59/EURATOM Article 56: For radiotherapeutic purposes...exposures of target volumes shall be **individually planned and their delivery appropriately verified**

Solution

Quantitative SPECT images to produce activity distribution (dose map), if gamma-rays are emitted

Implementation

3. Multiple treatments: Secondary treatments informed by early dose response measured post therapy (need dosimetry improvements)



Challenges

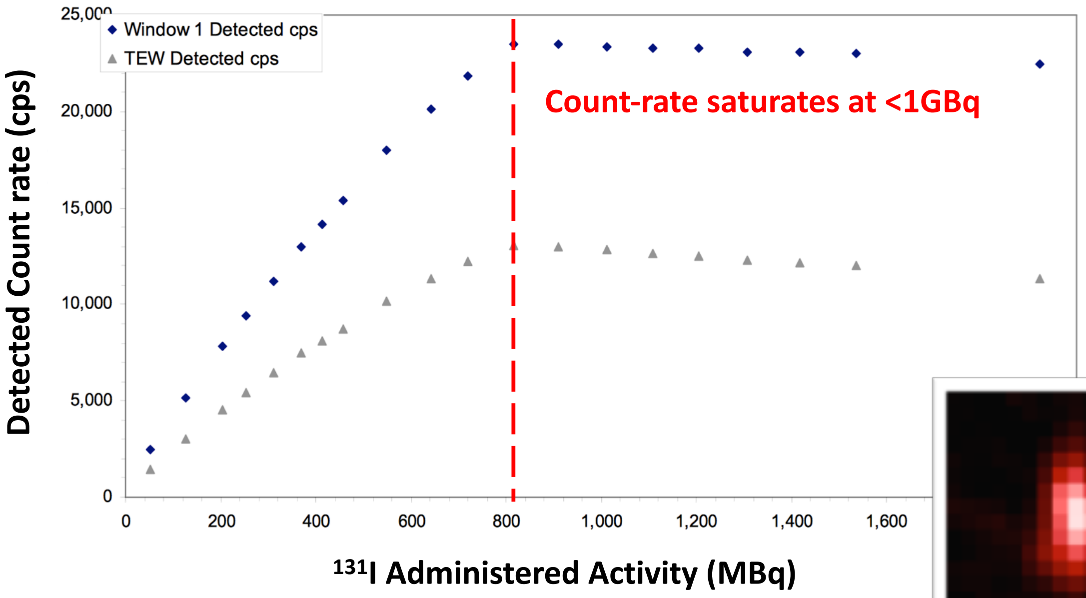
EU directive 2013/59/EURATOM Article 56: For radiotherapeutic purposes...exposures of target volumes shall be **individually planned and their delivery appropriately verified**

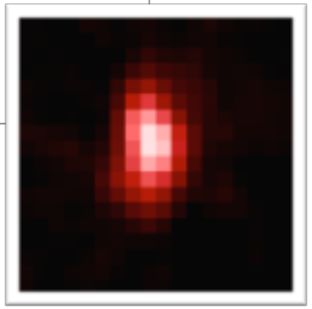
Solution

Quantitative SPECT images to produce activity distribution (dose map), if gamma-rays are emitted

Technical limitations in clinical systems

- System dead time, collimator scatter & resolution
- Inaccurate activity calculations & volume delineation



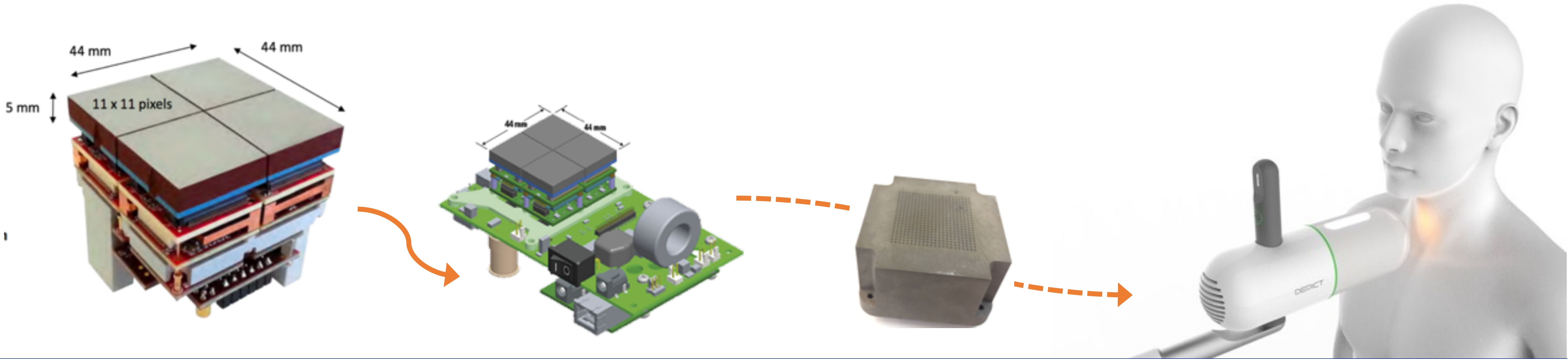


Images courtesy of G Flux, Royal Marsden NHS Trust

DEPICT System

- Room temperature pixelated CZT gamma-ray detector with ASIC readout (Kromek)
- Custom designed Tungsten parallel hole collimator, aligned to detector pixel map
- Improved position resolution, energy resolution and dead-time over conventional systems (up to 3GBq)

L McAreavey (2017) JINST, *Characterisation of a CZT detector for dosimetry in molecular radiotherapy*

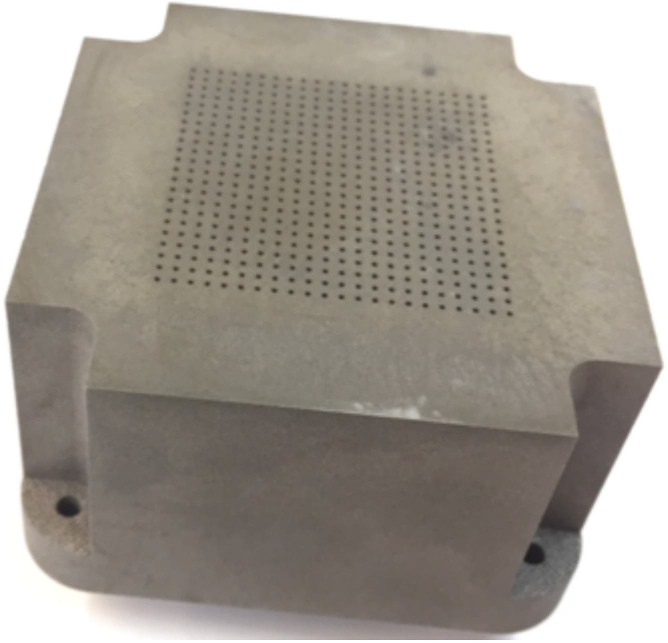


DEPICT Collimator

Aim: to reduce septal penetration & throughput, thus improving image resolution and dead-time

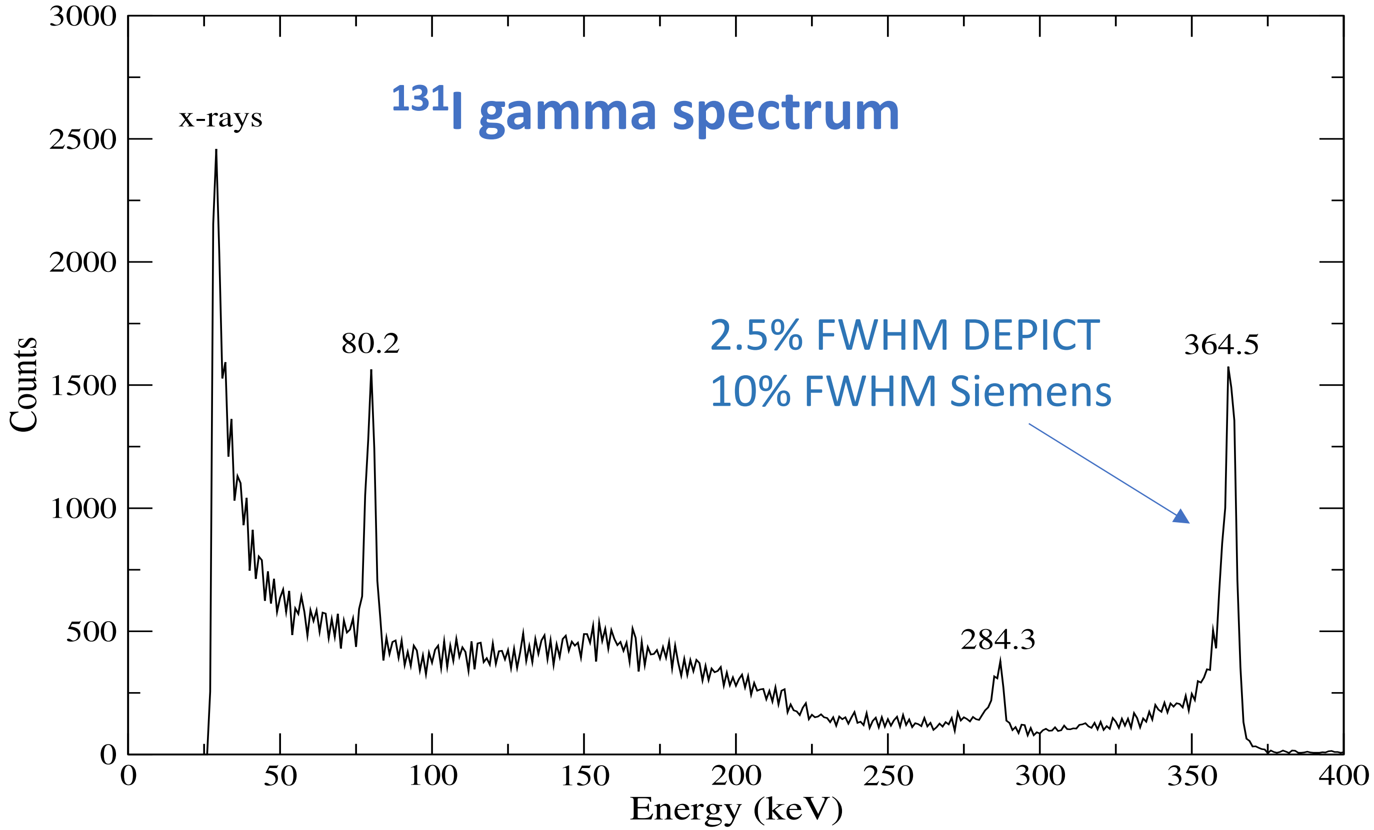
- Tungsten parallel hole collimator, aligned to detector pixel map
- Collimator length 55mm
- Septal thickness 1.4mm
- Aperture diameter 0.6mm

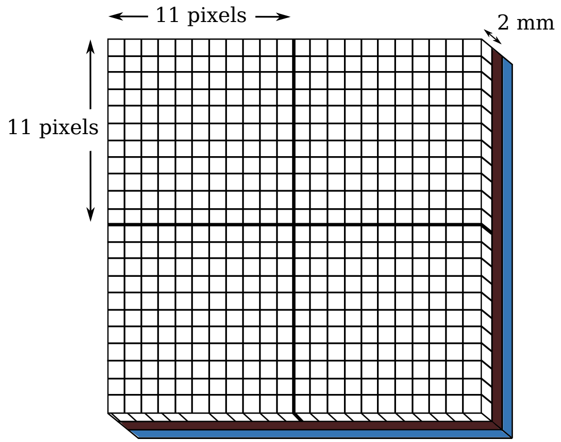
- Designed at Liverpool using Geant4 and input from partners
- Manufactured by M&I Materials
- Wolfmet 3D: high powered laser used to fuse successive layers of tungsten powder

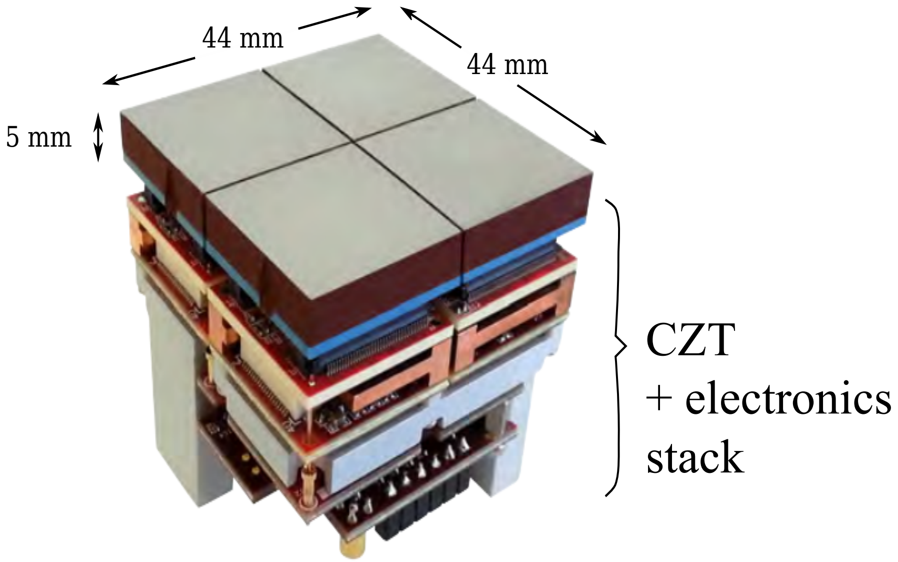


DEPICT CZT

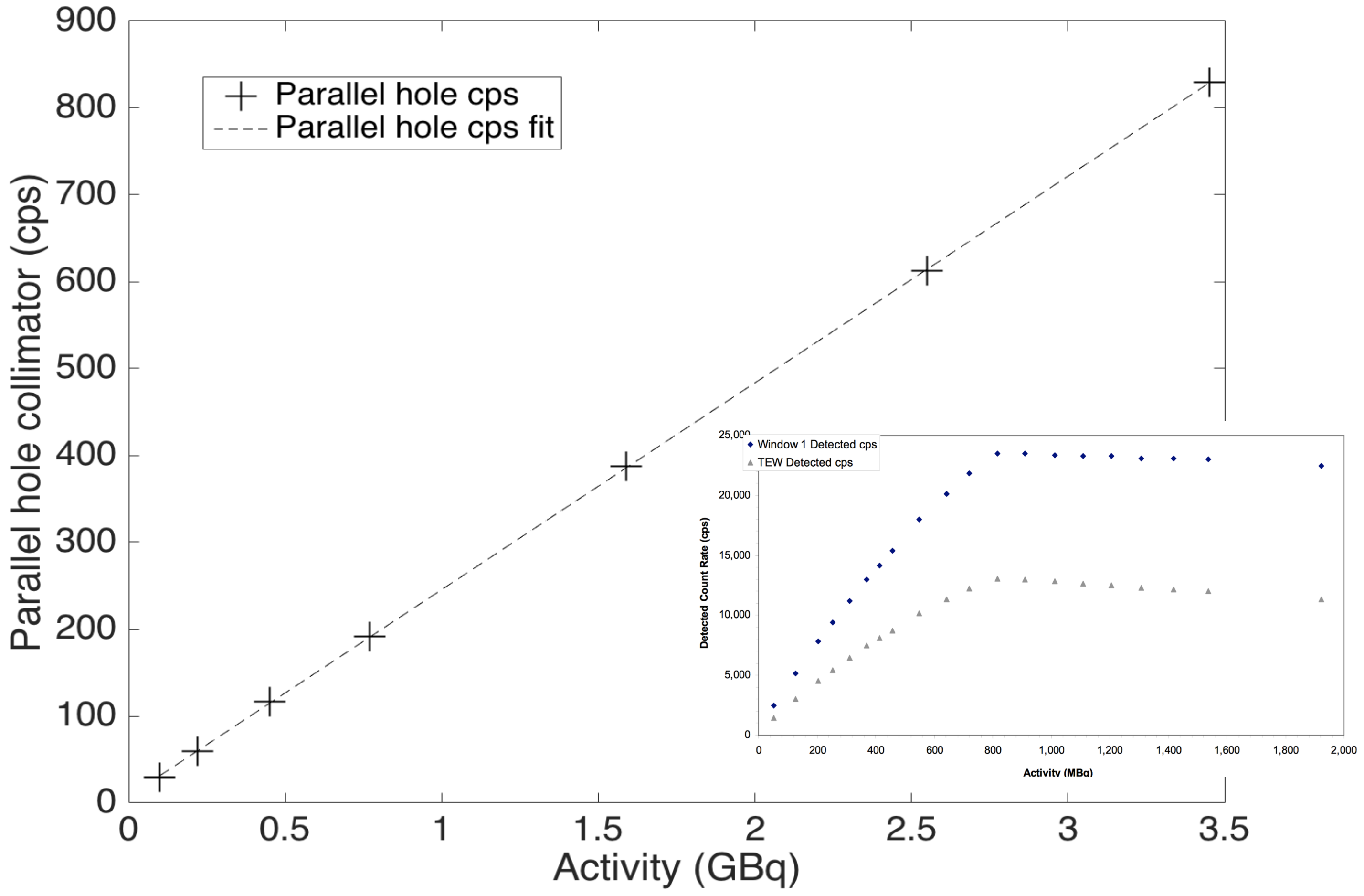
- Cadmium Zinc Telluride (CZT) with 484 anode pixels (each 2 x 2 mm)
- ASIC readout max 160kcps



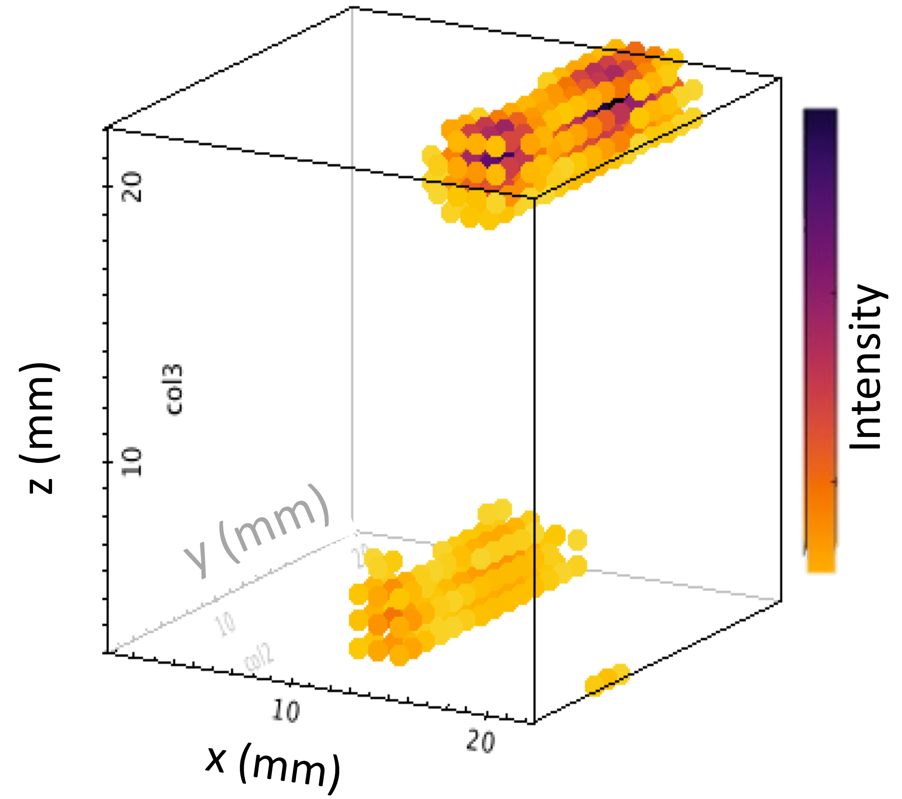




Prototype Results

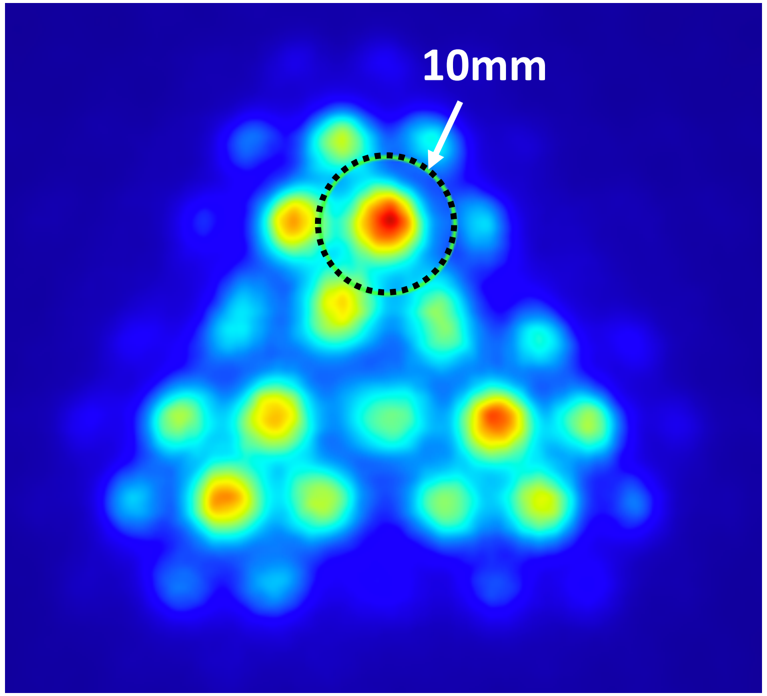


Tomographic reconstruction of rod phantom ^{131}I activity up to 3.6GBq

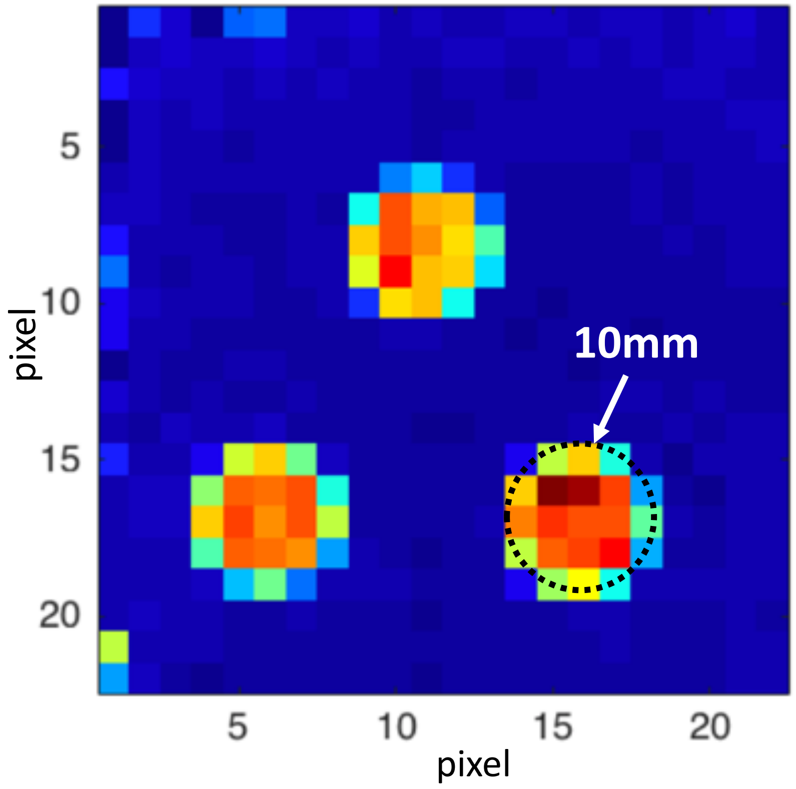


Prototype Results: Jaszczak Phantom

10mm diameter rods, each filled with 1.1GBq ^{131}I



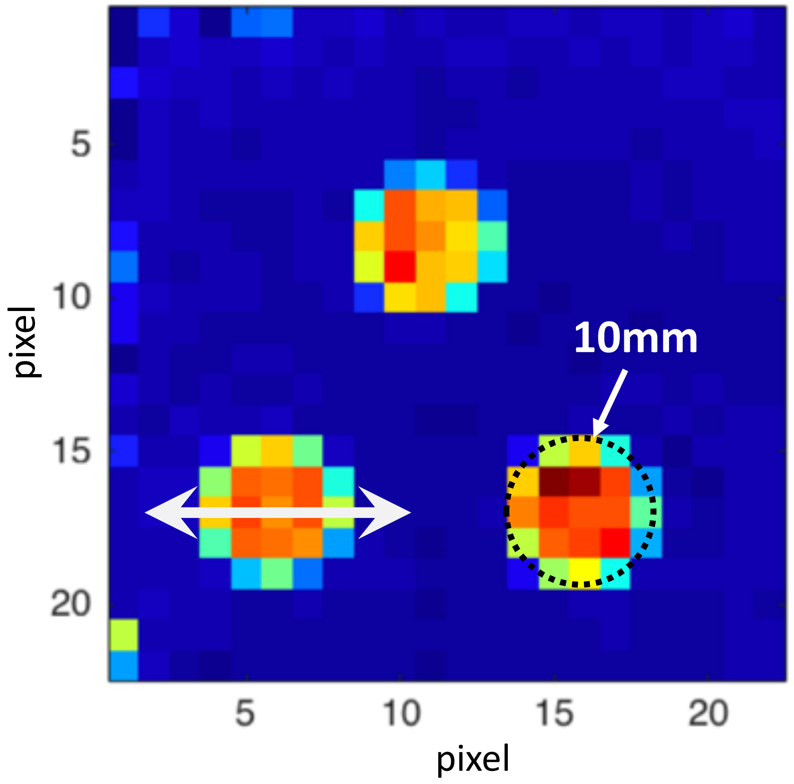
Siemens camera with HEGP



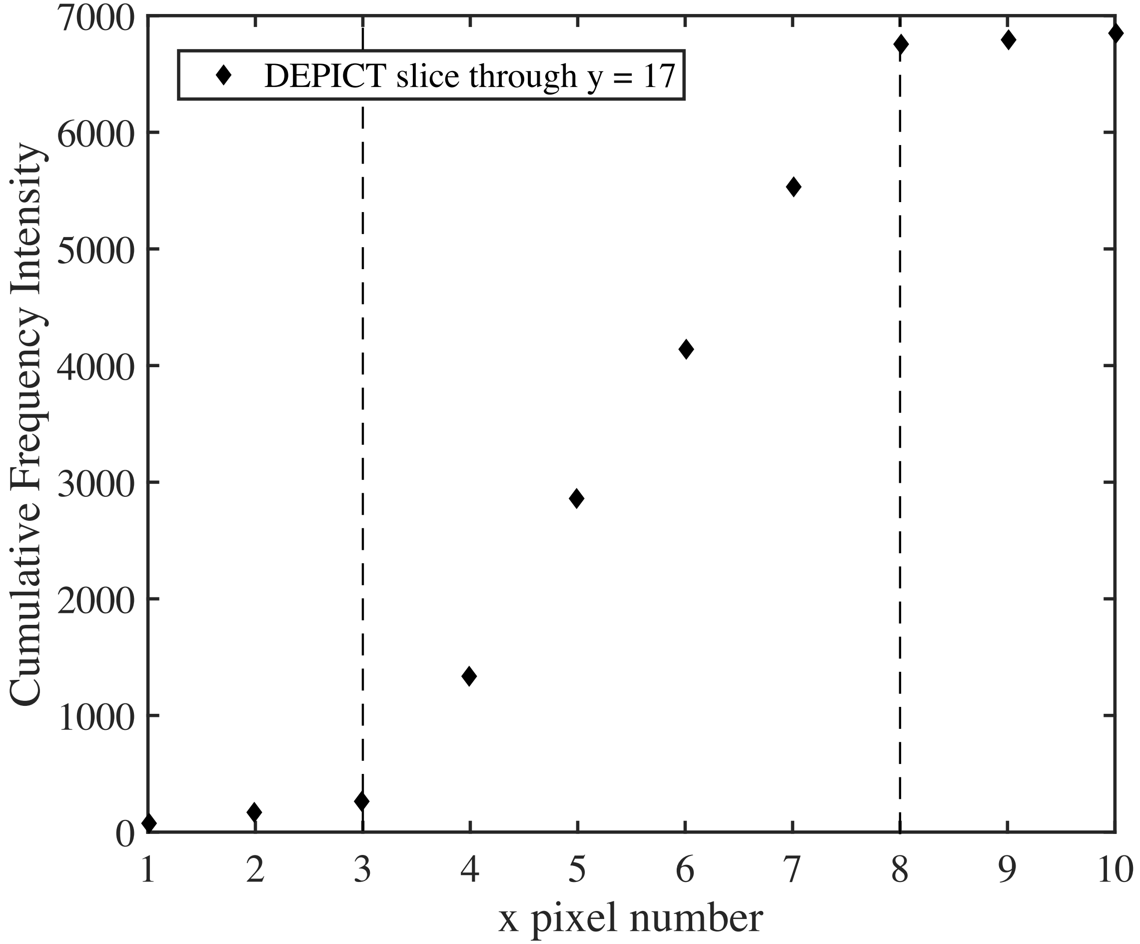
DEPICT

Prototype Results: Jaszczak Phantom

10mm diameter rods, each filled with 1.1GBq ^{131}I



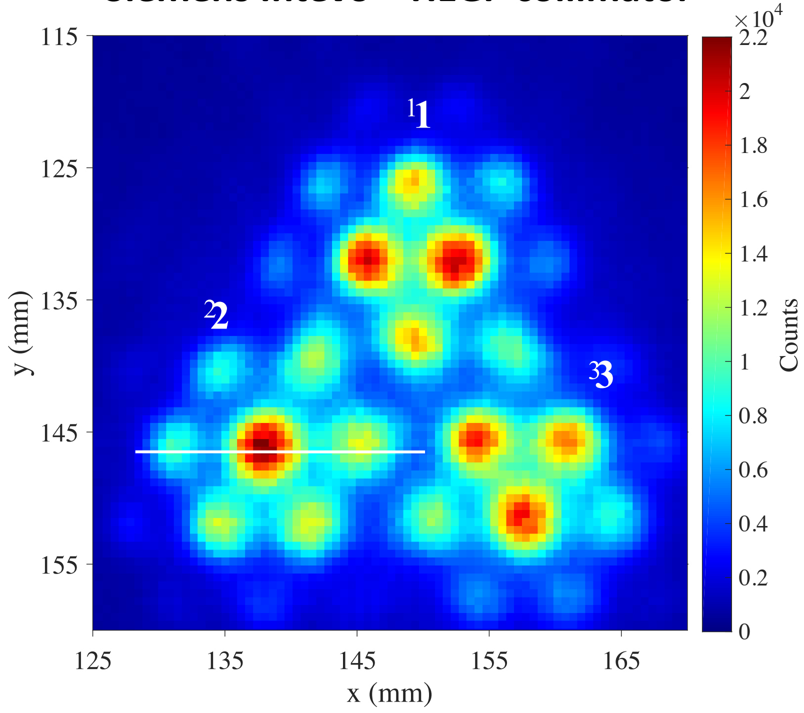
DEPICT

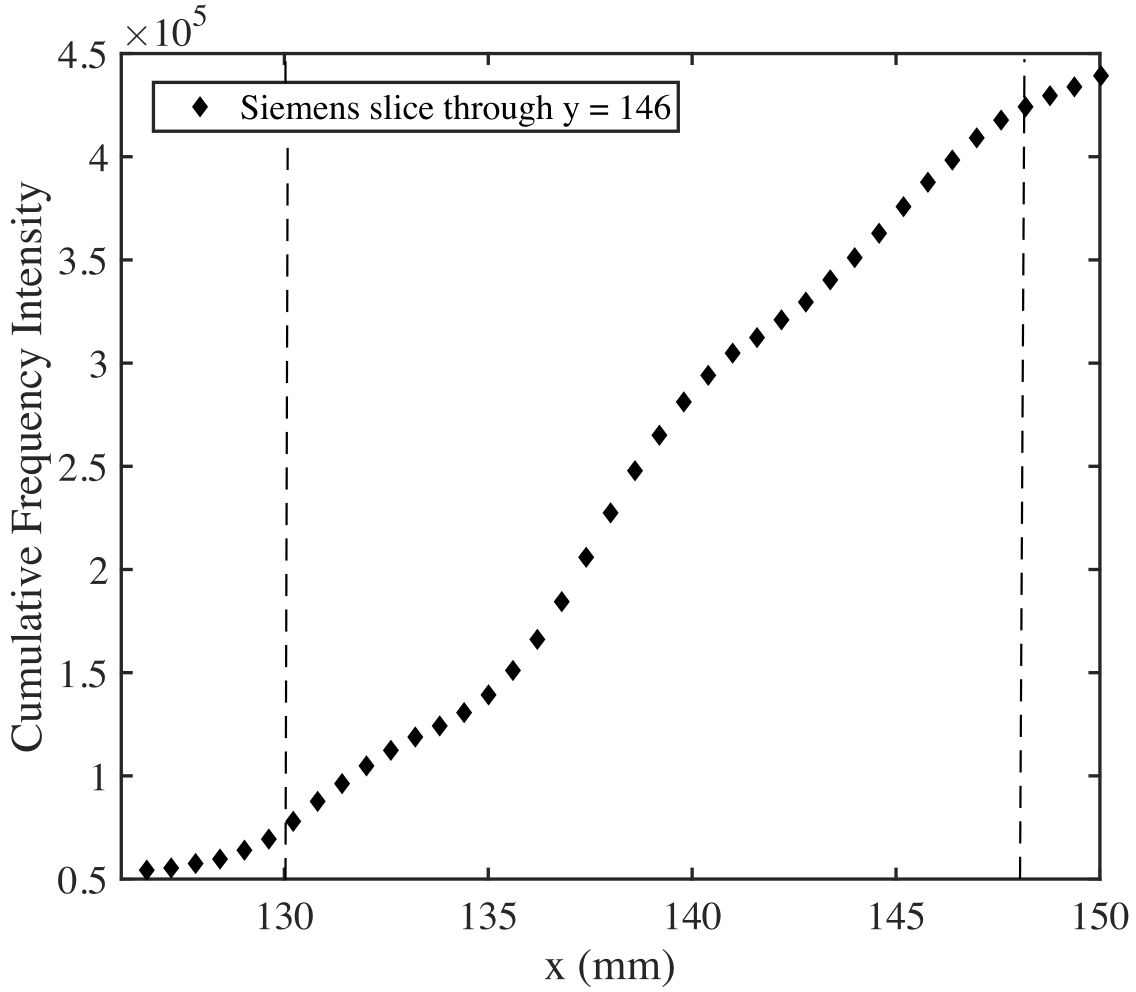


Prototype Results: Jaszczak Phantom

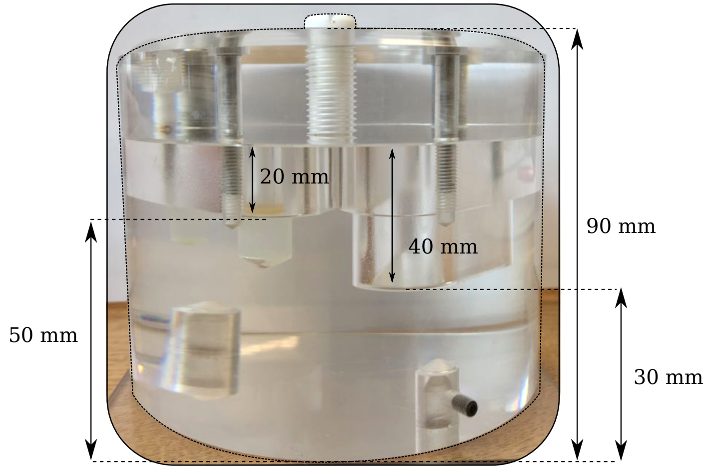
10mm diameter rods, each filled with 1.1GBq ^{131}I

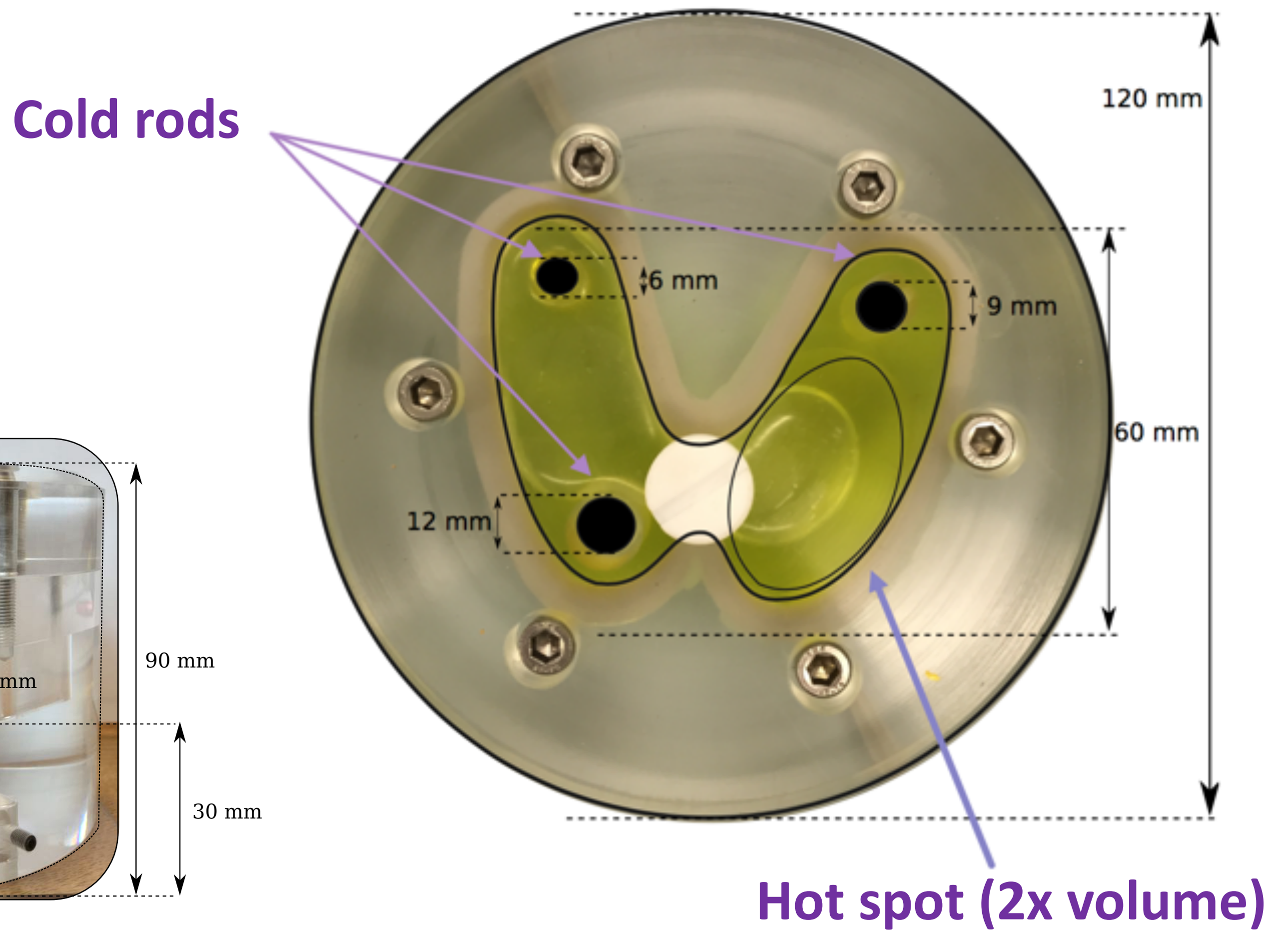
Siemens Intevo + HEGP collimator

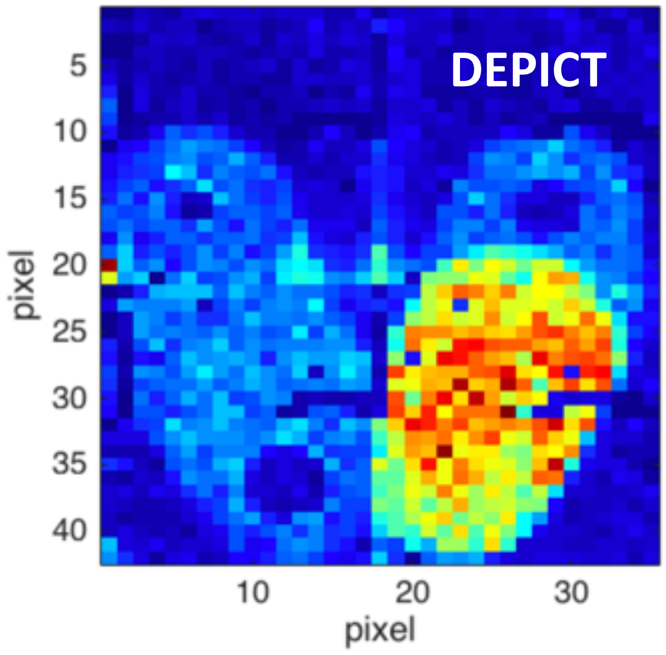


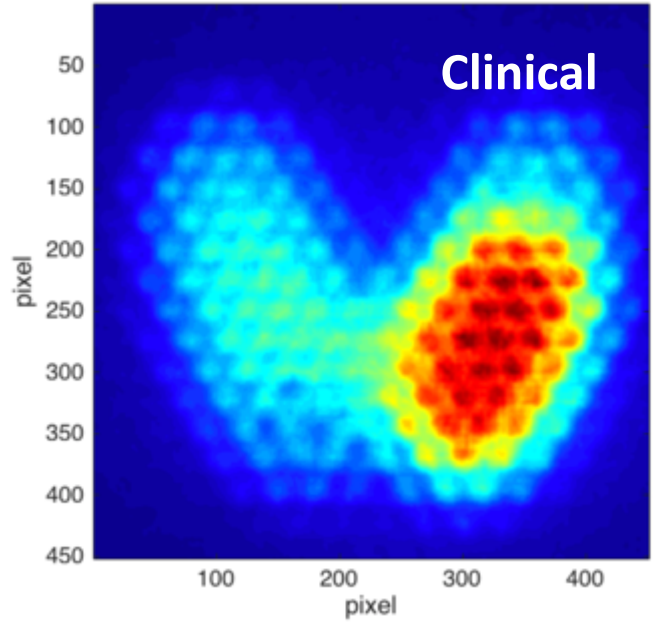


Prototype Results: Picker Phantom



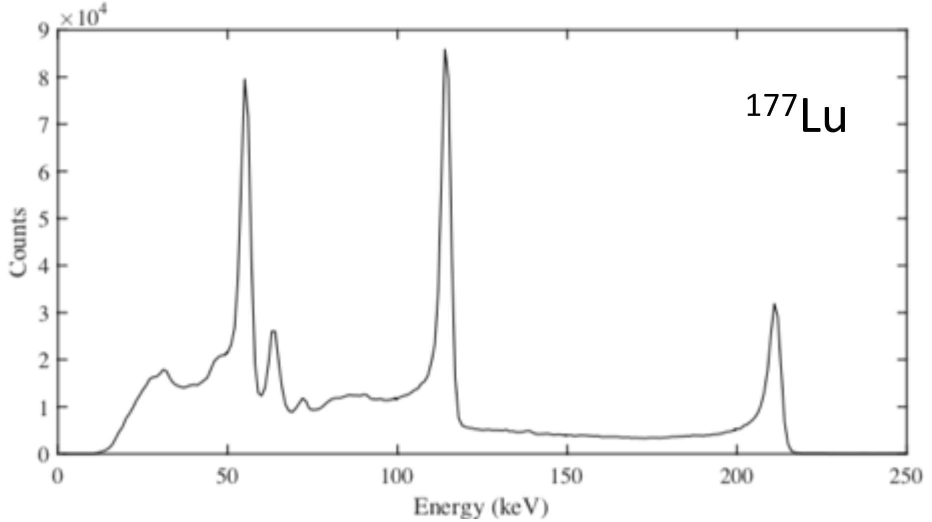


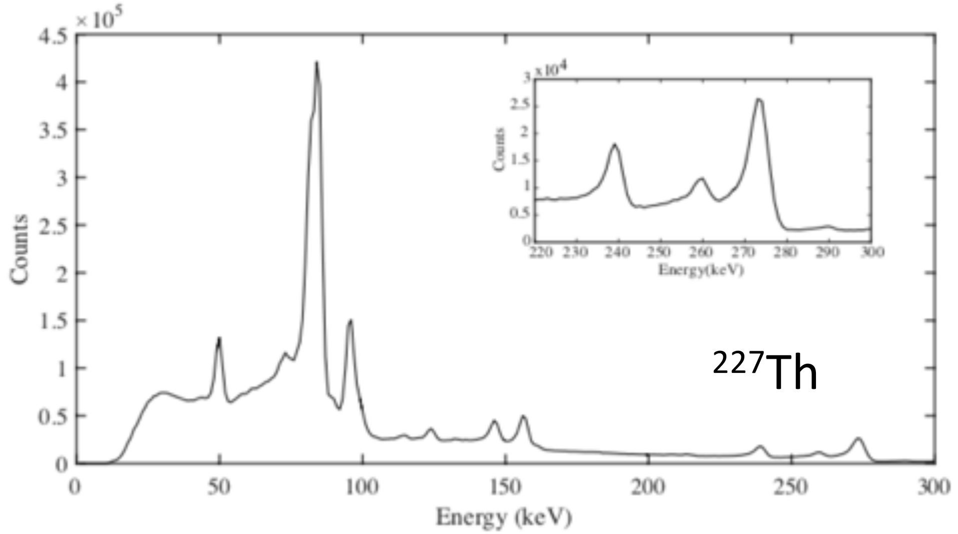


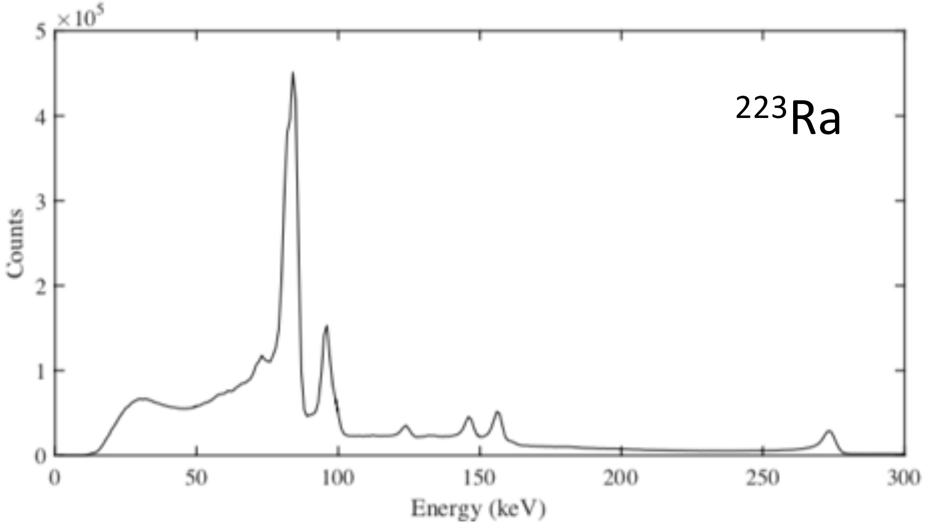


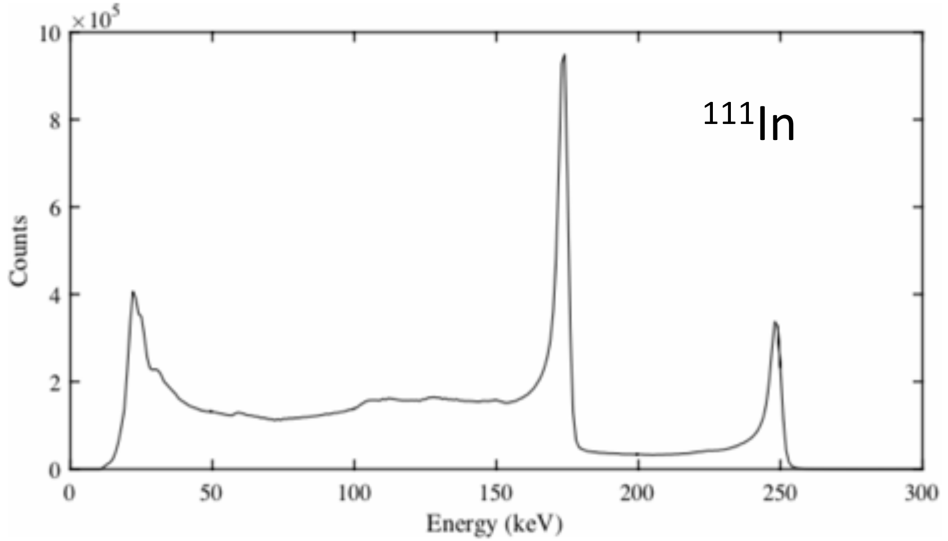
Thyroid phantom Total activity ~3.6Bq ^{131}I

Other radionuclides



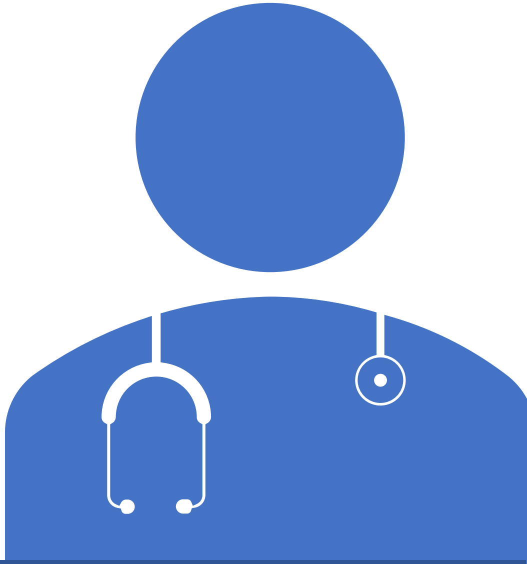






Outcomes

- Proof of concept system demonstrates improved imaging performance over clinical systems
- Data acquired at hospitals – developing relationships with the NHS
- 1 PhD student and 5 undergraduate project students who worked on the project are now working/training as medical physicists in NHS hospitals – developing skills & networks
- Since project started there has been a surge in interest with other radionuclides for therapy – business case being adapted
- Identified opportunities for product development collaboration with Kromek in other healthcare applications…. STFC IPS

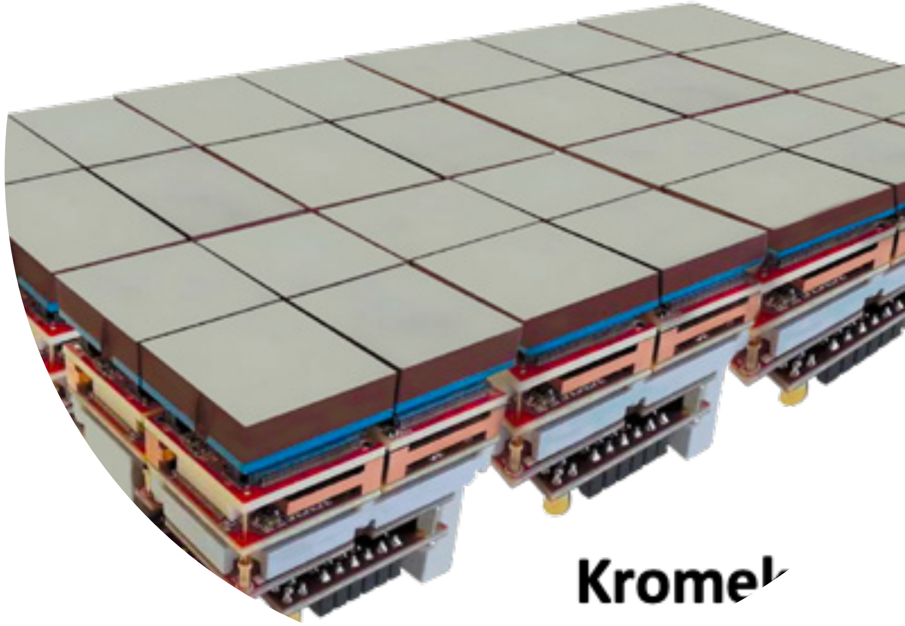


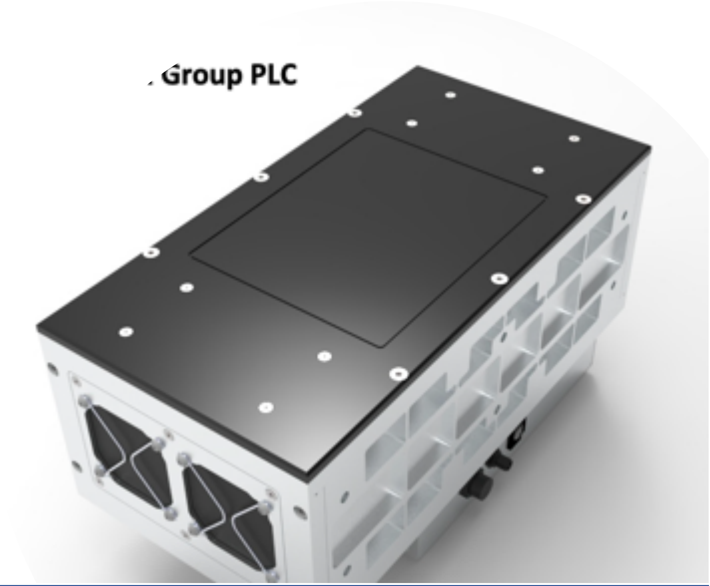
STFC IPS

- **Remit:** Use STFC funded research or technology to develop or enhance a new product or technique
- **Project:** Sub voxel position identification in Cadmium Zinc Telluride detectors for Low Dose Molecular Breast Imaging (July 2019 to June 2022)
- **Partner:** Kromek Group plc. Project driven by business case for product development.

Low Dose MBI

- A new method of detecting breast cancer through screening
- ^{99m}Tc-sestamibi selectively targets malignant breast tissue to provide high-resolution functional images
- Complements mammography but offers:
  - Better image resolution and contrast
  - Improved detection sensitivity especially for patients with dense breast tissue
  - Less compression of the breast
  - Fewer benign biopsies than MBI

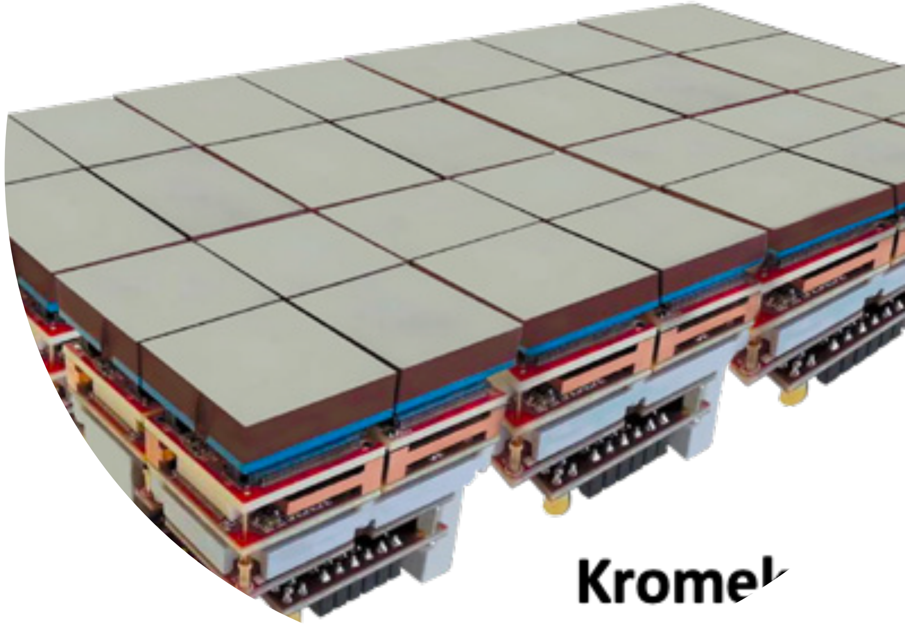


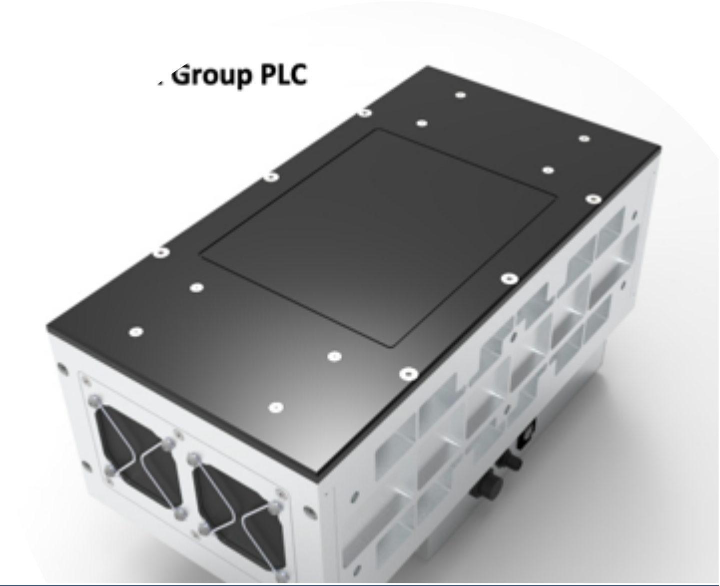


Low Dose MBI

- Producing high quality photon images relies on the accurate measurement of **photon interaction position** and energy deposited in the imaging device

- The IPS project will implement signal processing algorithms to offer sub-voxel resolution in CZT detectors, to enhance image quality for MBI and improve patient outcome.





- Characterise the position dependent signal response of CZT detectors with varying voxel geometries.
- Develop algorithms to provide sub-voxel position resolution that can be implemented in firmware.
- Design and manufacture photon imaging collimators that exploit the sub-voxel position resolution for low dose MBI.
- Evaluate performance using breast phantoms and ^{99m}Tc, to determine the minimum detectable breast lesion size for a given patient dose.
- Identify ways of reducing the data set required for sub-voxel resolution into a size, weight, power and cost envelope suitable a commercial system
- Apply for funding for pre-clinical tests, as required for commercialisation of the final system.

Lessons learned

- It takes time to build a working relationship – especially when it is with non academic partners and/or from other disciplines
- Take the time to learn what each other can offer (and what they can't)
- Be realistic with your partners about expectations of what can be achieved within the timescale about the project
- It is inevitable that further work will be required, consider the long term plan to achieving societal change or commercial impact
- Arranging collaboration agreements can take more time than you think

Collaborators

UNIVERSITY OF LIVERPOOL

University of Liverpool: A Boston, H Boston, H Brown, S Colosimo, D Judson, L McAreavey, P Nolan, E Rintoul

The Royal Marsden NHS Foundation Trust / ICR: G Flux, A Denis Baclear (now NPL), J Gear

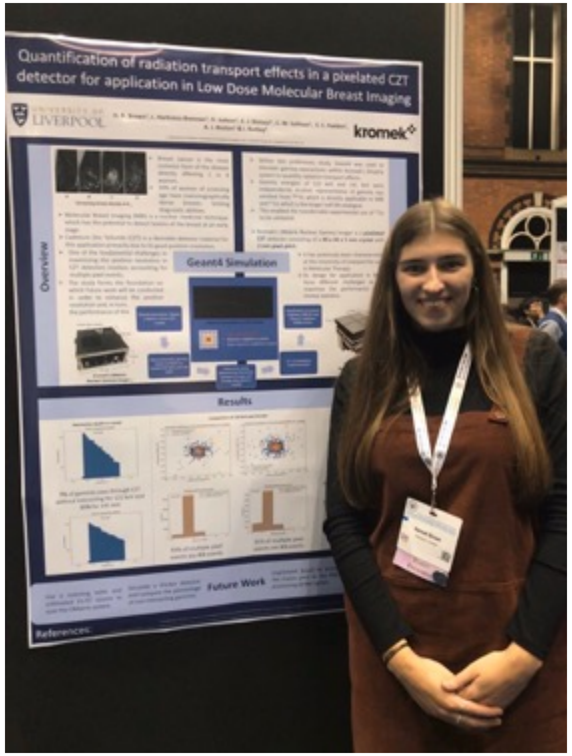
The Royal Liverpool and Broadgreen University Hospitals NHS Trust: M Carroll, I Hufton

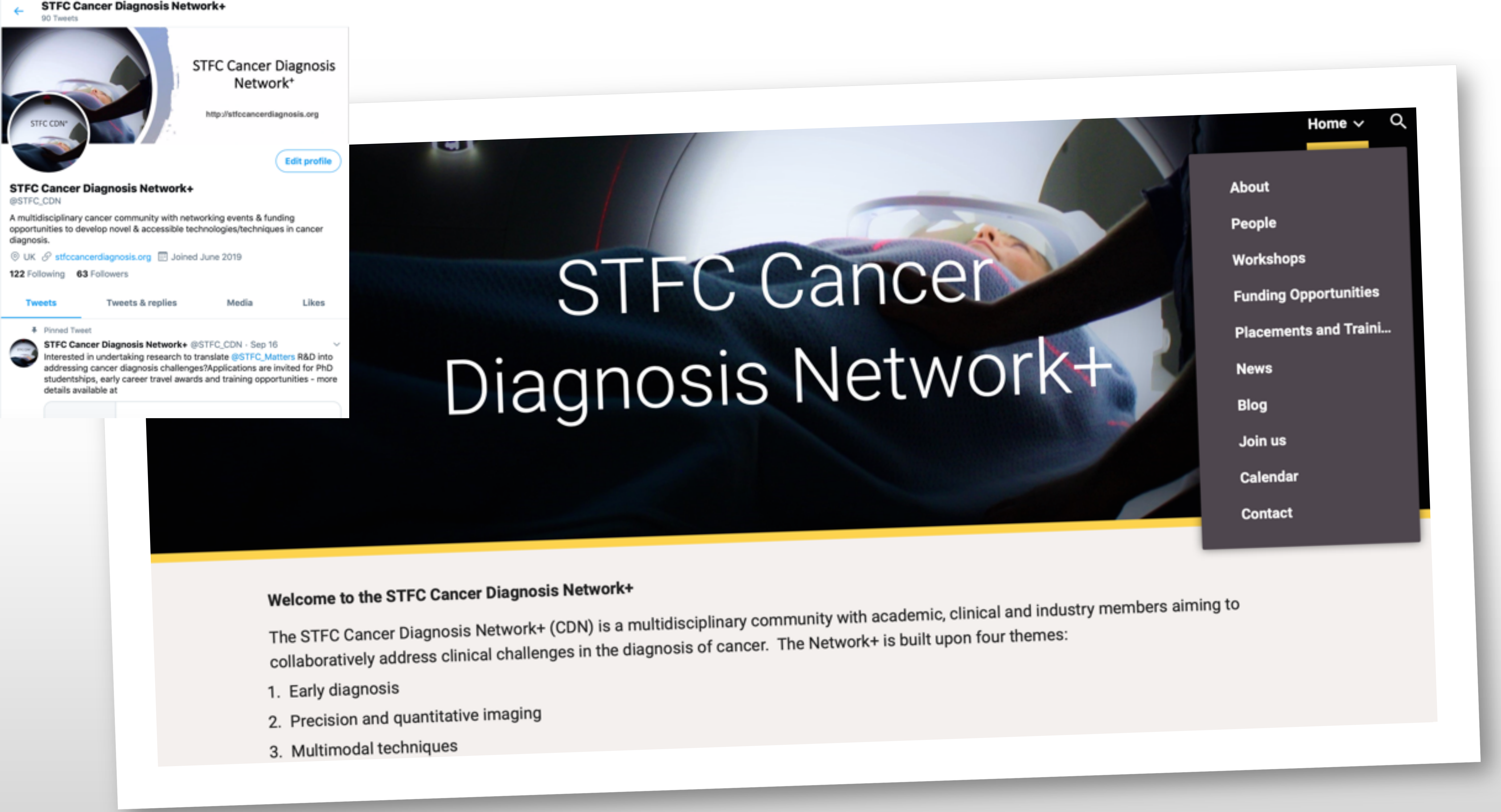
kromek: A Cherlin, B Harris, I Radley

UKRI Science and Technology Facilities Council: J Simpson, I Lazarus, M Labiche

Follow the group's latest news and updates:

@LauraHBPhysics





http://stfccancerdiagnosis.org

Funding Opportunities

3 PhD Studentships: funded at 50% cost of UK fees, stipend and research support fee

Proof of concept projects: up to £40k each

Scoping studies: up to £5k each

Travel awards: funded at 100% for PhD students, 50% for PDRAs, up to £2k max per application

MSc Clinical science modules: fee waiver and travel support

http://stfccancerdiagnosis.org