Imaging, quantifying and targeting hallmarks of cancer

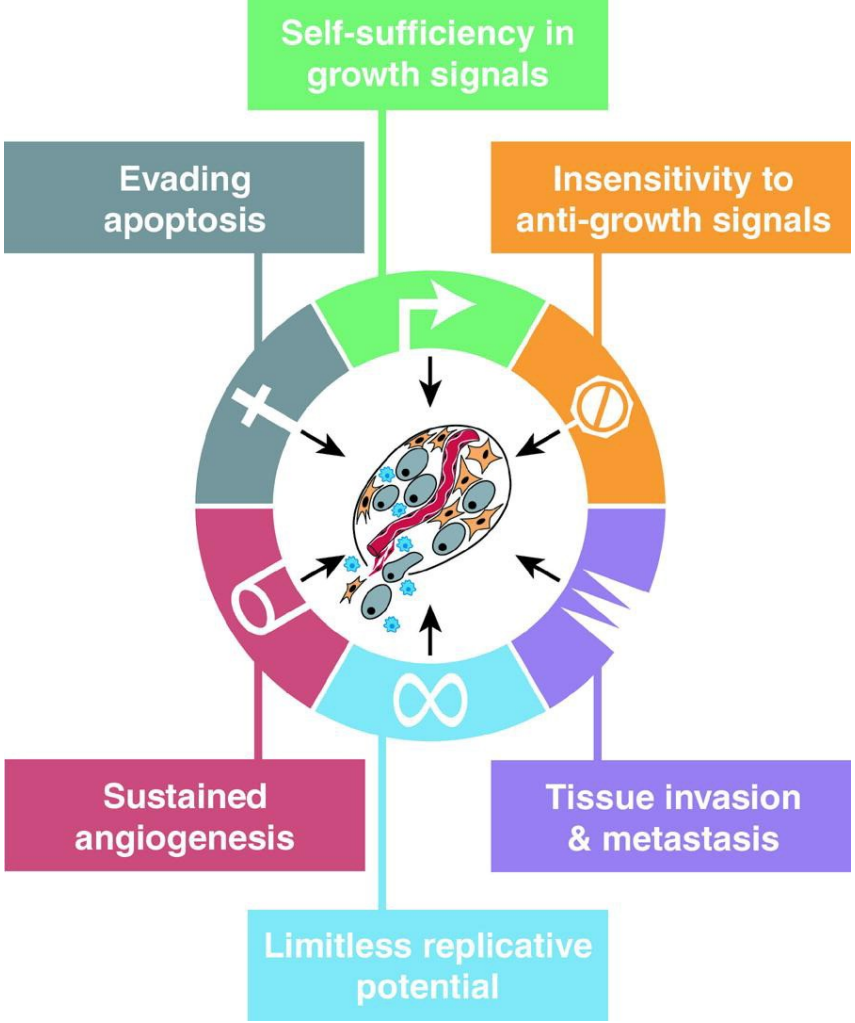
Ivan Ho Shon

UNSW SYDNEY

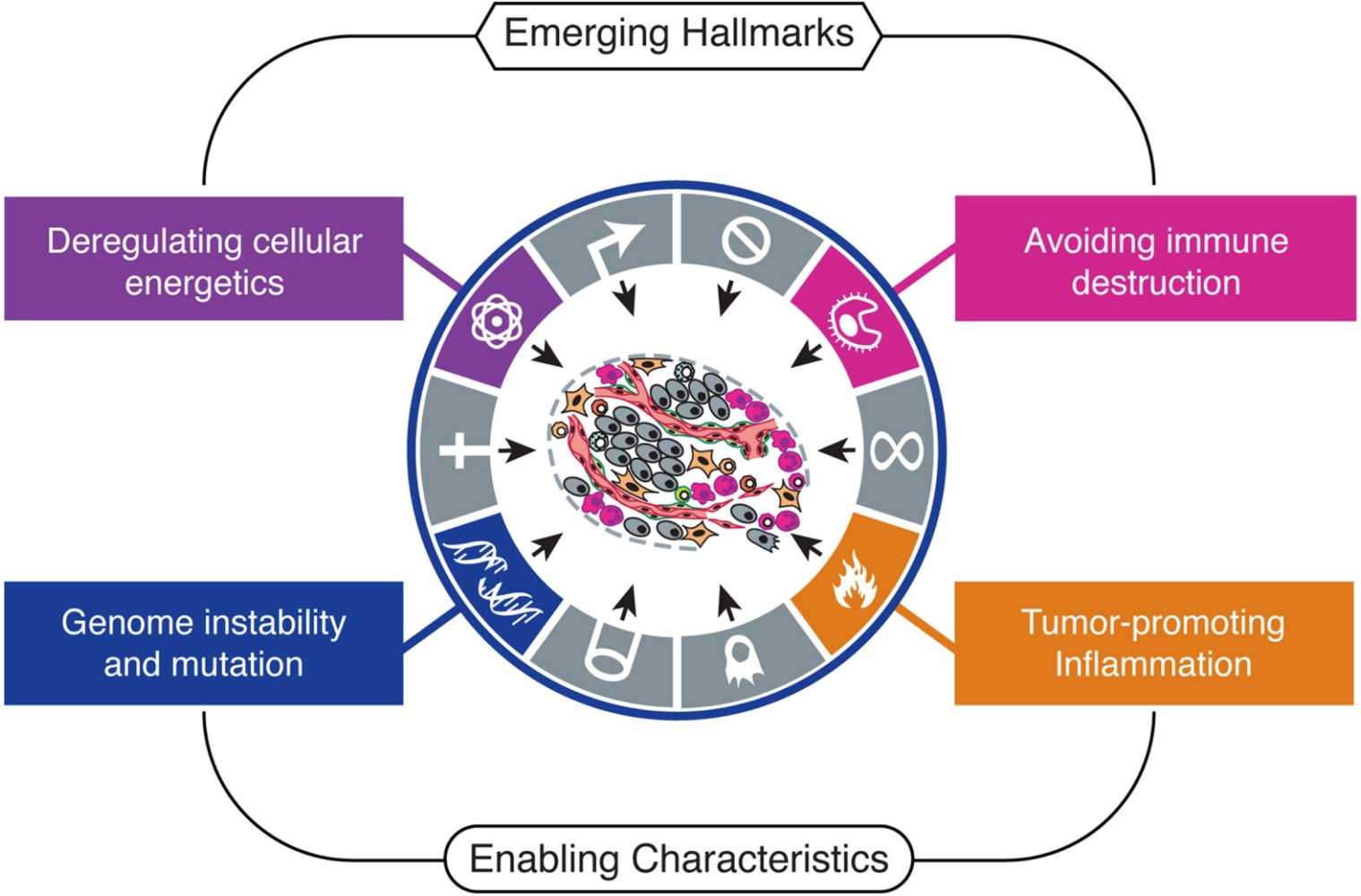
The Prince of Wales Hospital
& Community Health Service

Disclosures

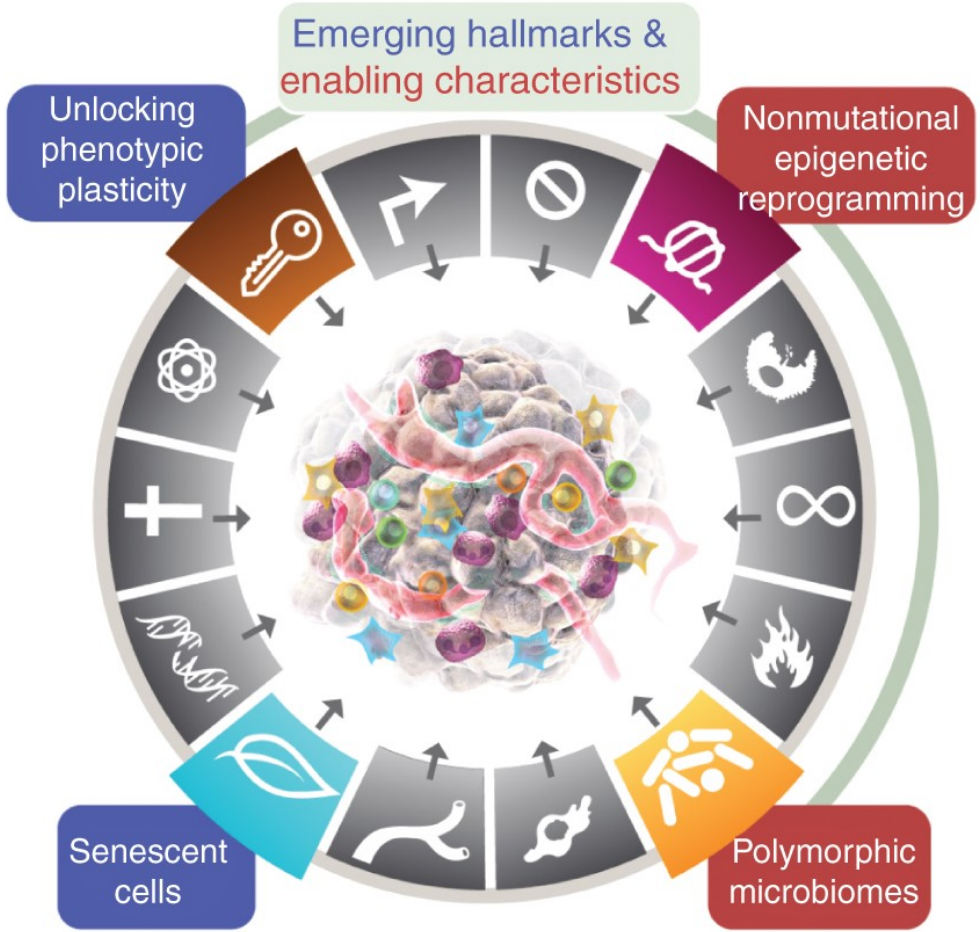
- Amplificare Pty Ltd



Hanahan D, Weinberg R; The Hallmarks of Cancer. Cell 2000 100(1,) 57 - 70



Hanahan D, Weinberg R, Hallmarks of Cancer: The Next Generation Cell, 2011, 144(5):646 - 674

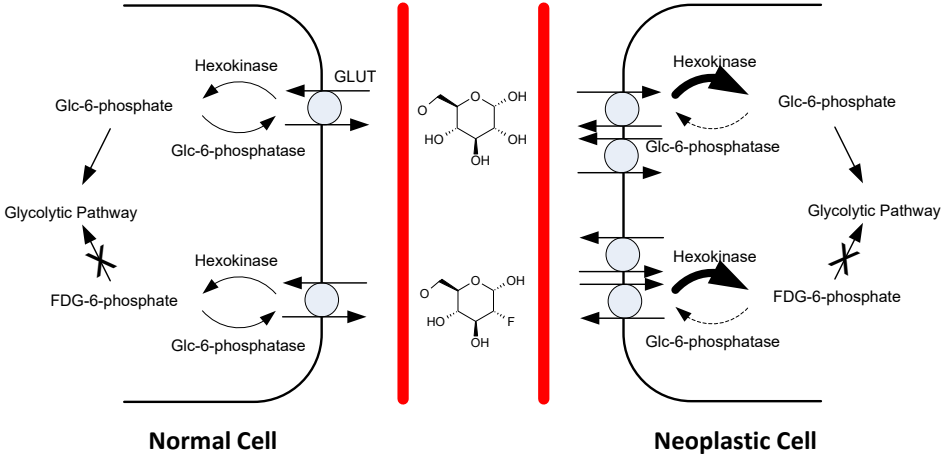


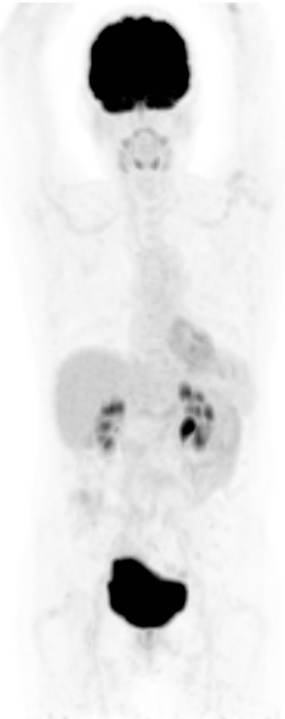
Hanahan D; Hallmarks of Cancer: New Dimensions. Cancer Discovery 2022; 12 (1): 31–46.

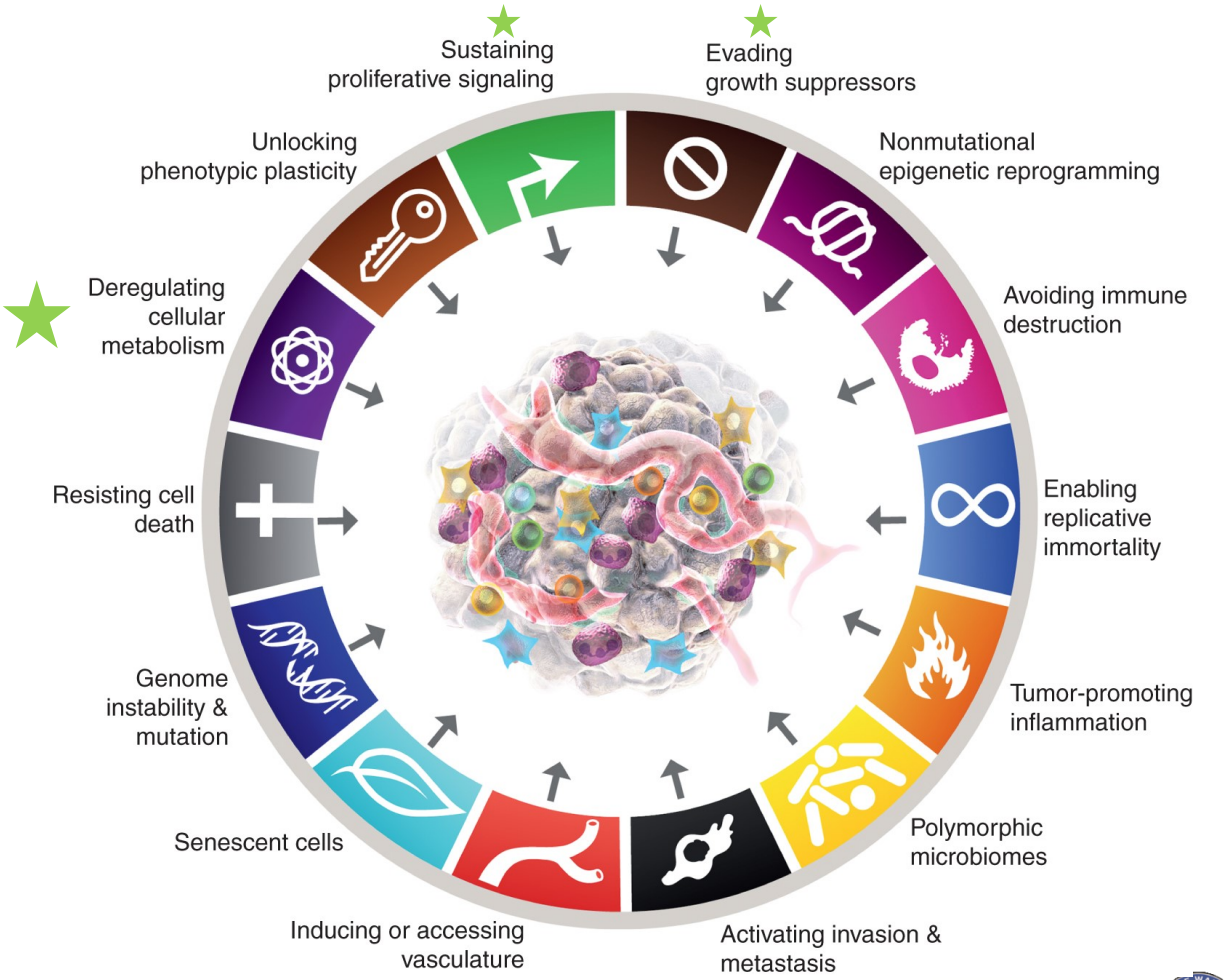
Imaging

FDG PET

https://www.nobelprize.org/prizes/medicine/1931/summary/

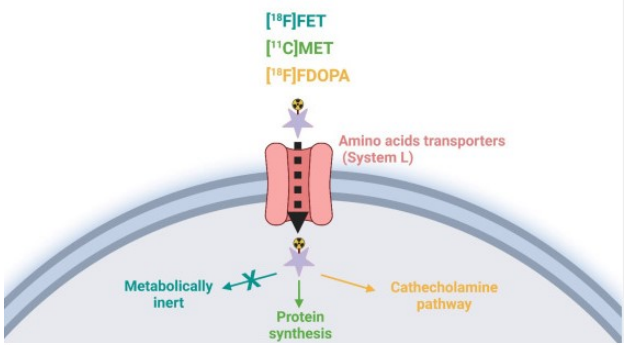


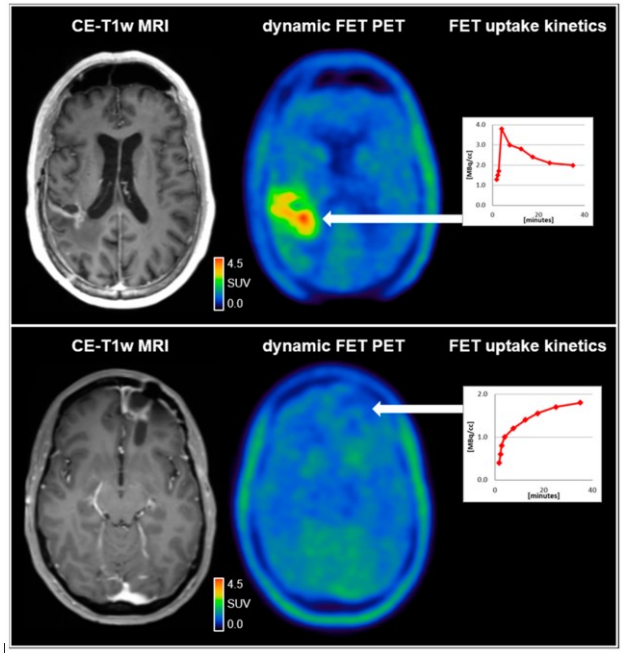


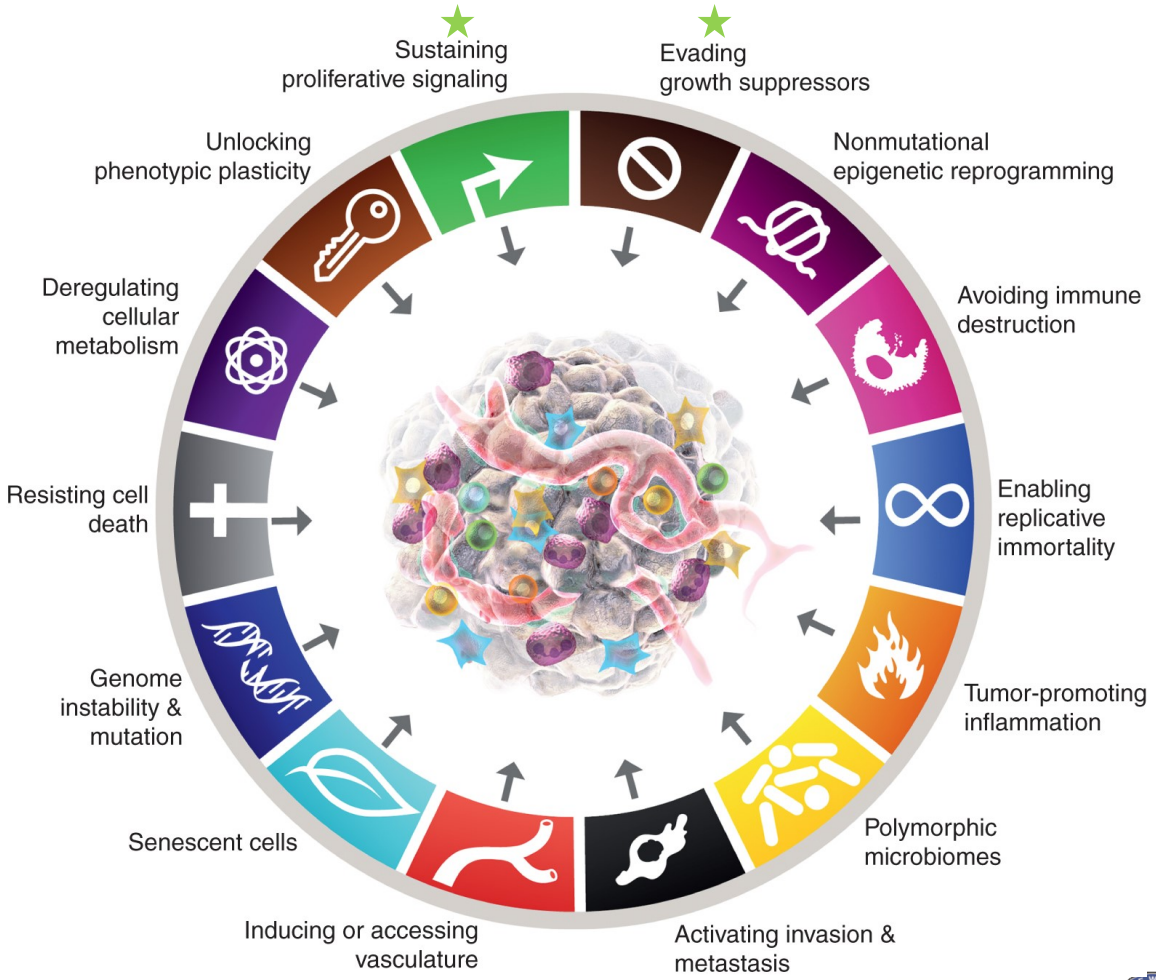


UNSW SYDNEY

The Prince of Wales Hospital & Community Health Service



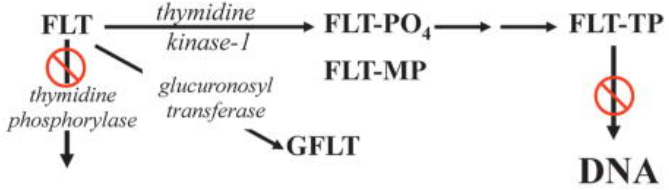


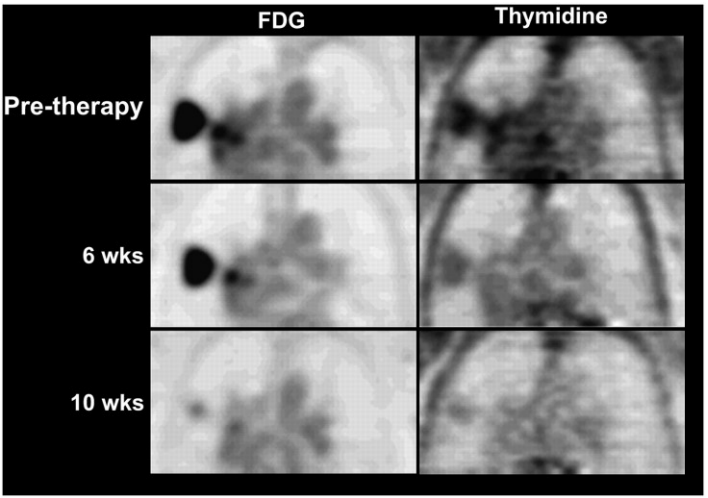


Robert JA, et. al. Pharmaceuticals (Basel). 2024 Sep 18;17(9):1228.
Holzgreve A, et. al. Cancers. 2021; 13(9):2093.

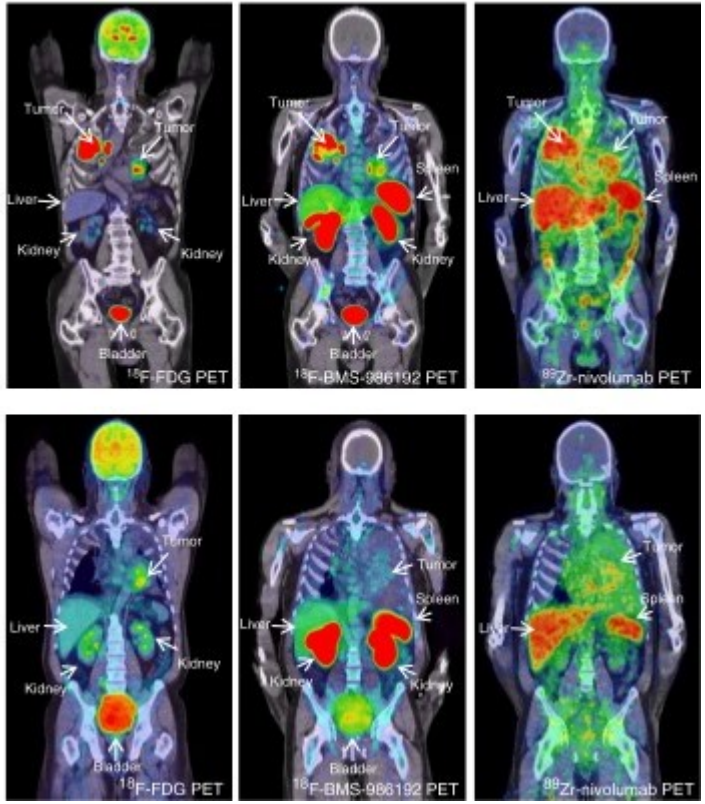
UNSW SYDNEY

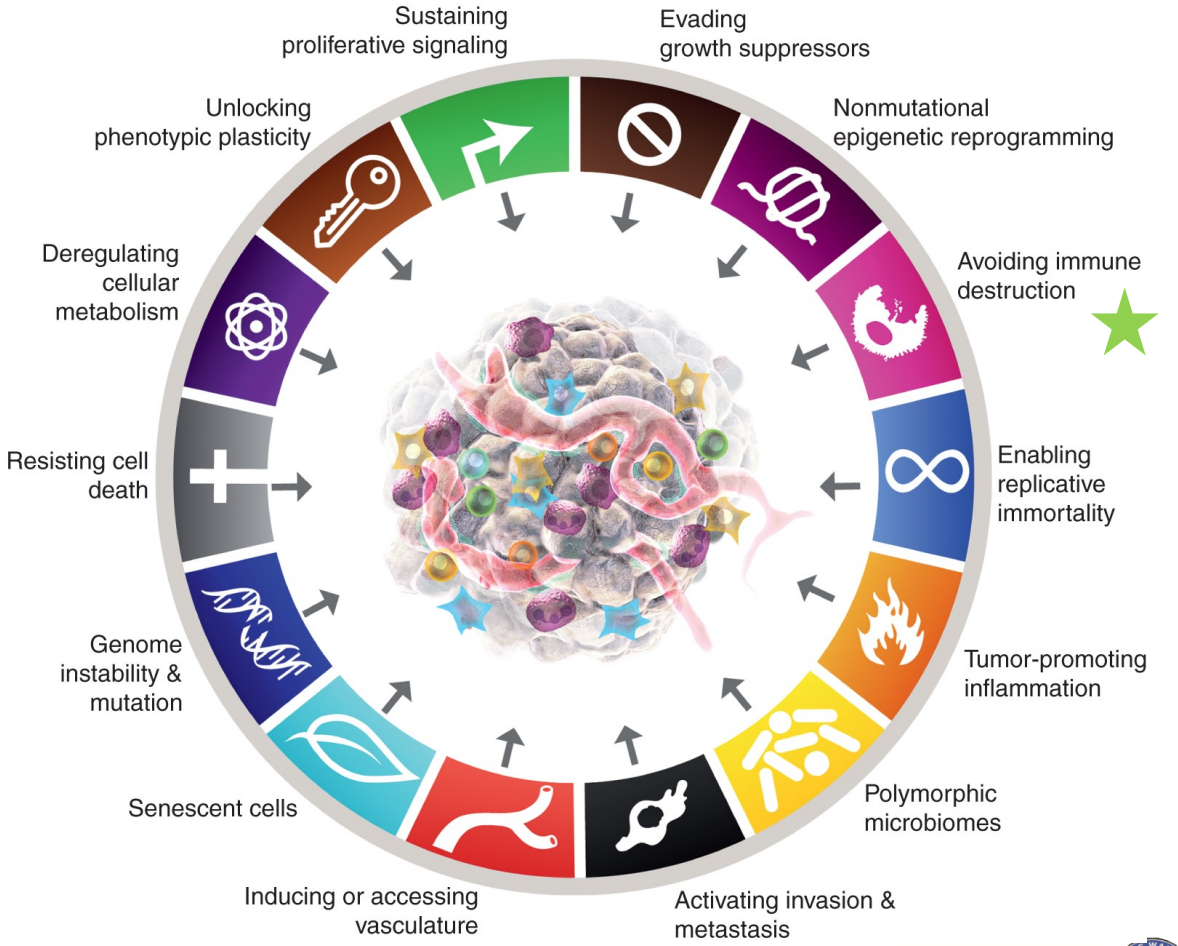
The Prince of Wales Hospital & Community Health Service



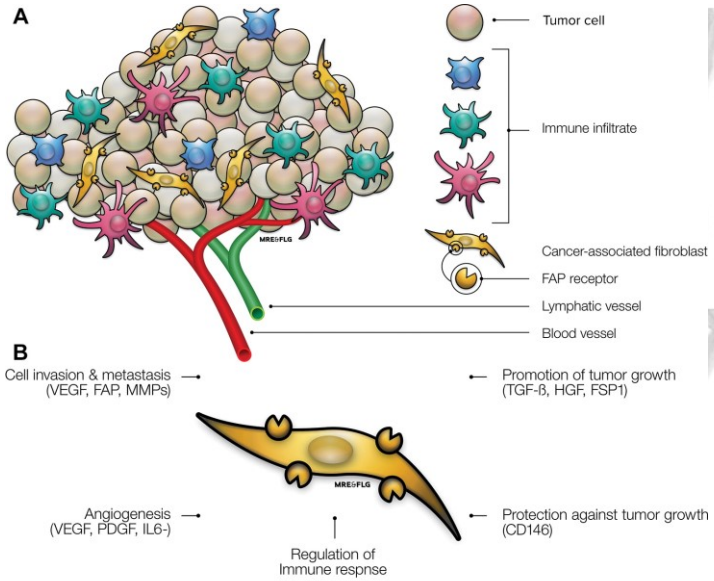


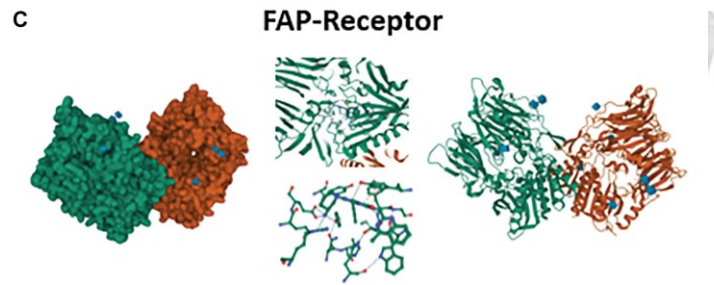
Bading J, Shields S; Journal of Nuclear Medicine.2008, 49 (Suppl 2) 64S-80S;

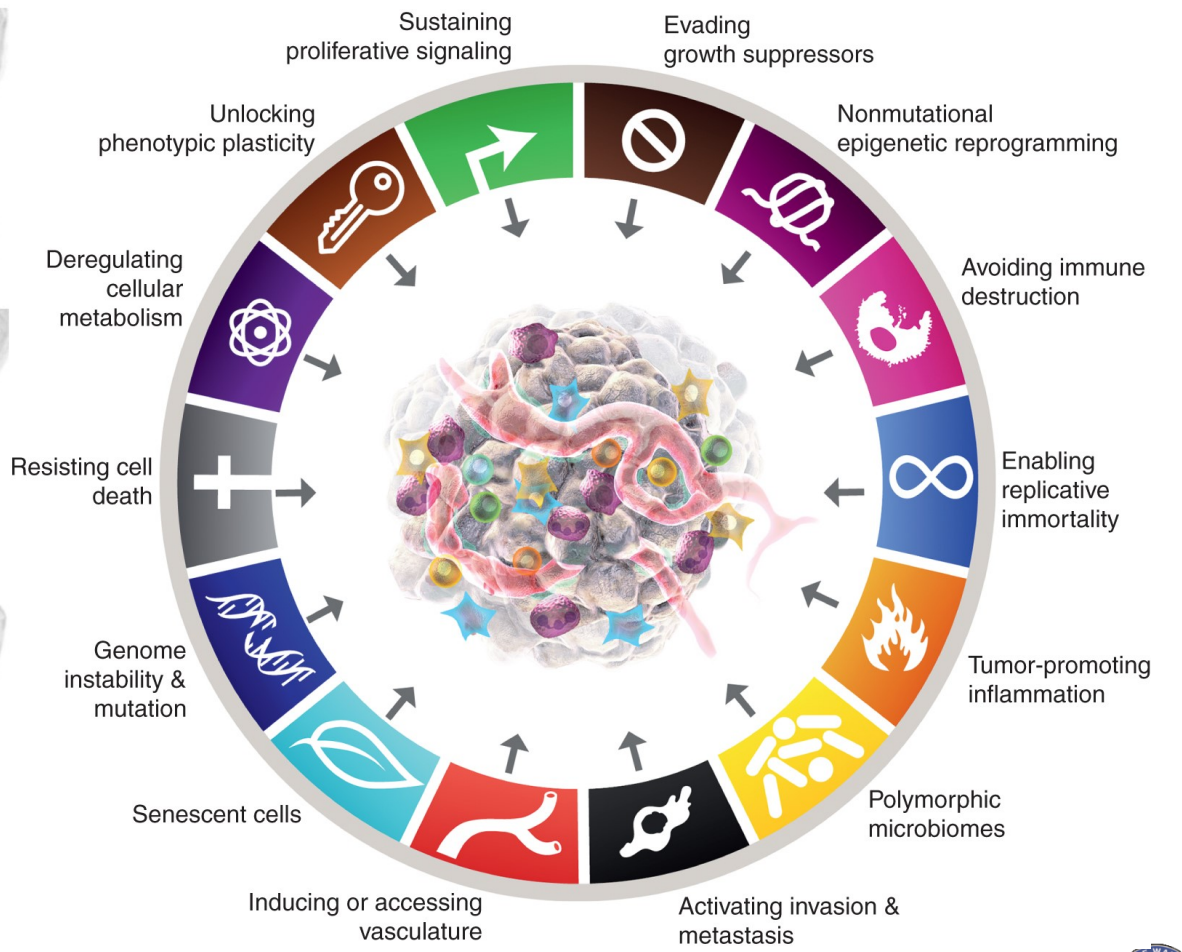




Niemeijer, A.N. et al. Nat Commun 9, 4664 (2018).



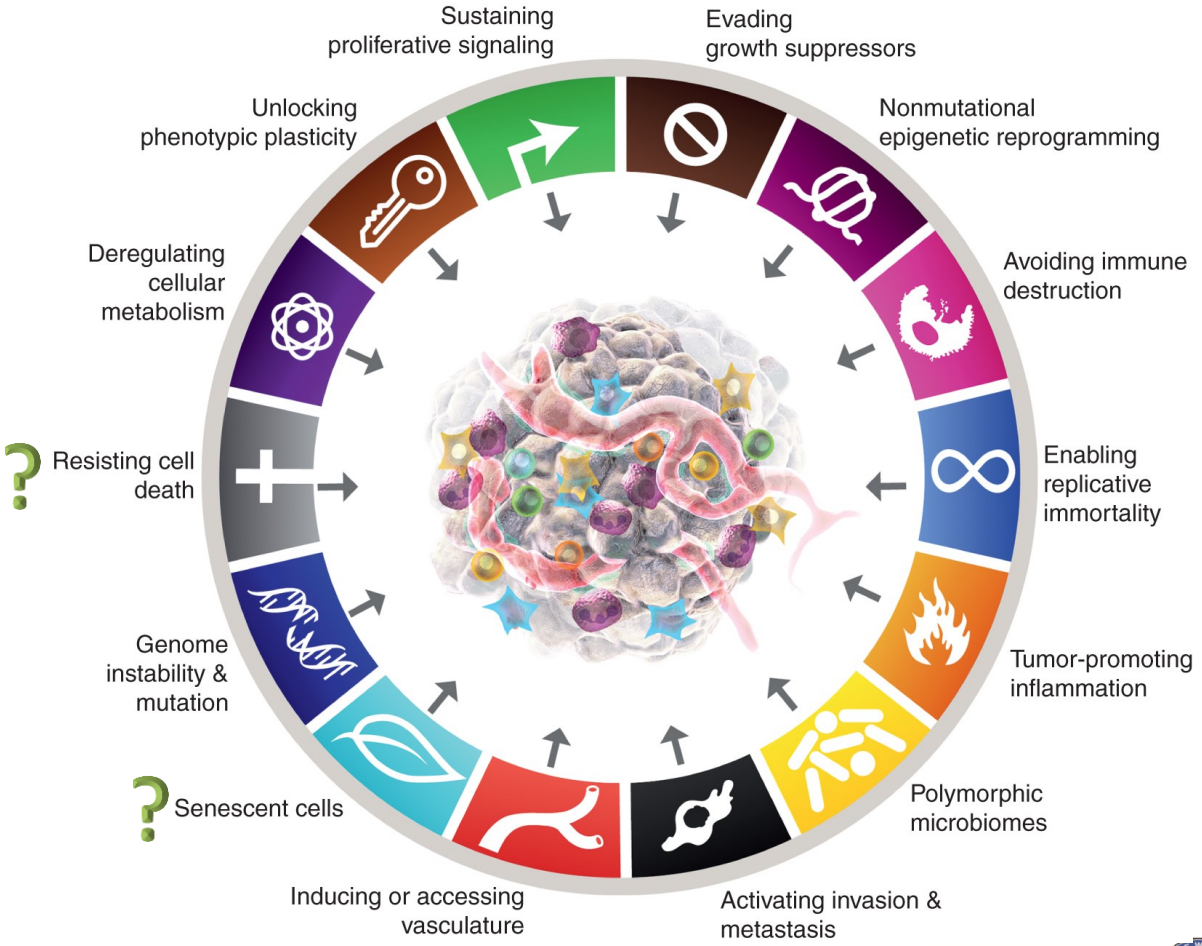




Yuriko M et. al. Radiology 2023 306:2
Kratochwil C et. al. Journal of Nuclear Medicine June 2019, 60 (6) 801-805

UNSW SYDNEY

The Prince of Wales Hospital
& Community Health Service


Sustaining proliferative signaling
Evading growth suppressors
Nonmutational epigenetic reprogramming
Avoiding immune destruction
Enabling replicative immortality
Tumor-promoting inflammation
Polymorphic microbiomes
Activating invasion & metastasis
Inducing or accessing vasculature
Senescent cells
Genome instability & mutation
Resisting cell death
Deregulating cellular metabolism
Unlocking phenotypic plasticity

^{68}Ga PSMA

^{68}Ga dotatate

Why image the hallmarks of cancer?

- Basic science
- Detection
- Prognosis
- Response assessment
- Biomarker of MoA
- Identify theranostic targets

Quantifying

Quantifying Hallmarks of Cancer

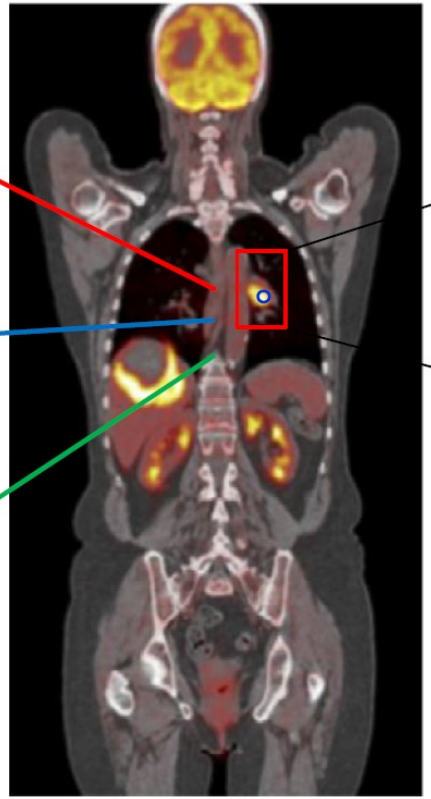
- Standardised uptake value (SUV)
  - If the tracer were distributed *uniformly* SUV = 1 everywhere
  - Areas with higher than average uptake have SUV > 1
  - SUVs potentially allow inter and intra-patient comparisons
    - Confounders
  - For FDG predictive of malignancy, proliferation, tumour grade, prognosis

Quantification in molecular imaging

$$SUV_{max} = \frac{C_{max}\ (Bq/cc)}{A_{inj}\ (Bq) / W\ (g)}$$

$$SUV_{peak} = \frac{C_{1cm^3\ ROI}\ (Bq/cc)}{A_{inj}\ (Bq) / W\ (g)}$$

$$SUV_{mean} = \frac{C_{ROI}\ (Bq/cc)}{A_{inj}\ (Bq) / W\ (g)}$$



SUV_{max}

SUV_{peak}

SUV_{mean} (MATV)

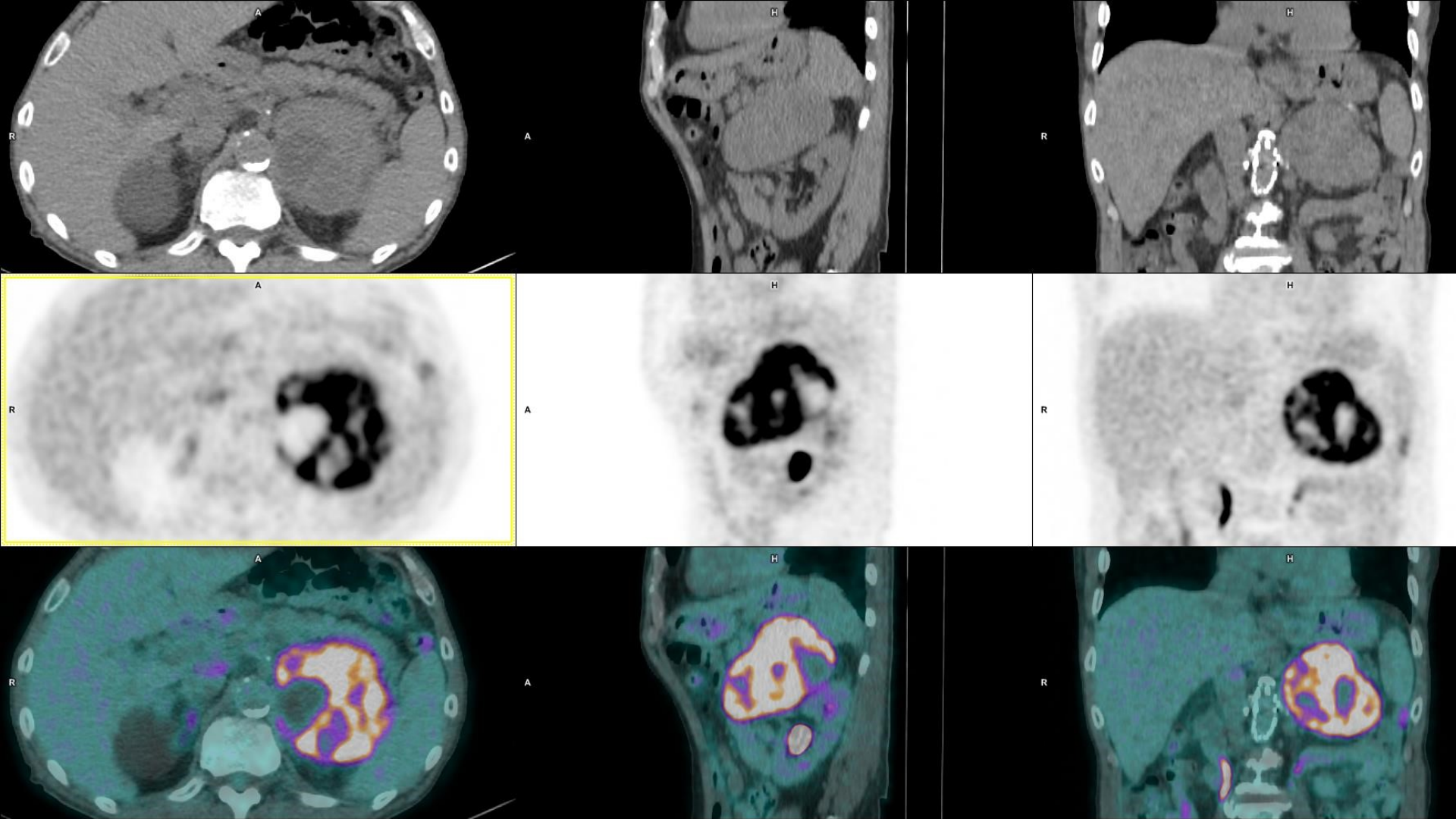
Metabolic Tumour Volume

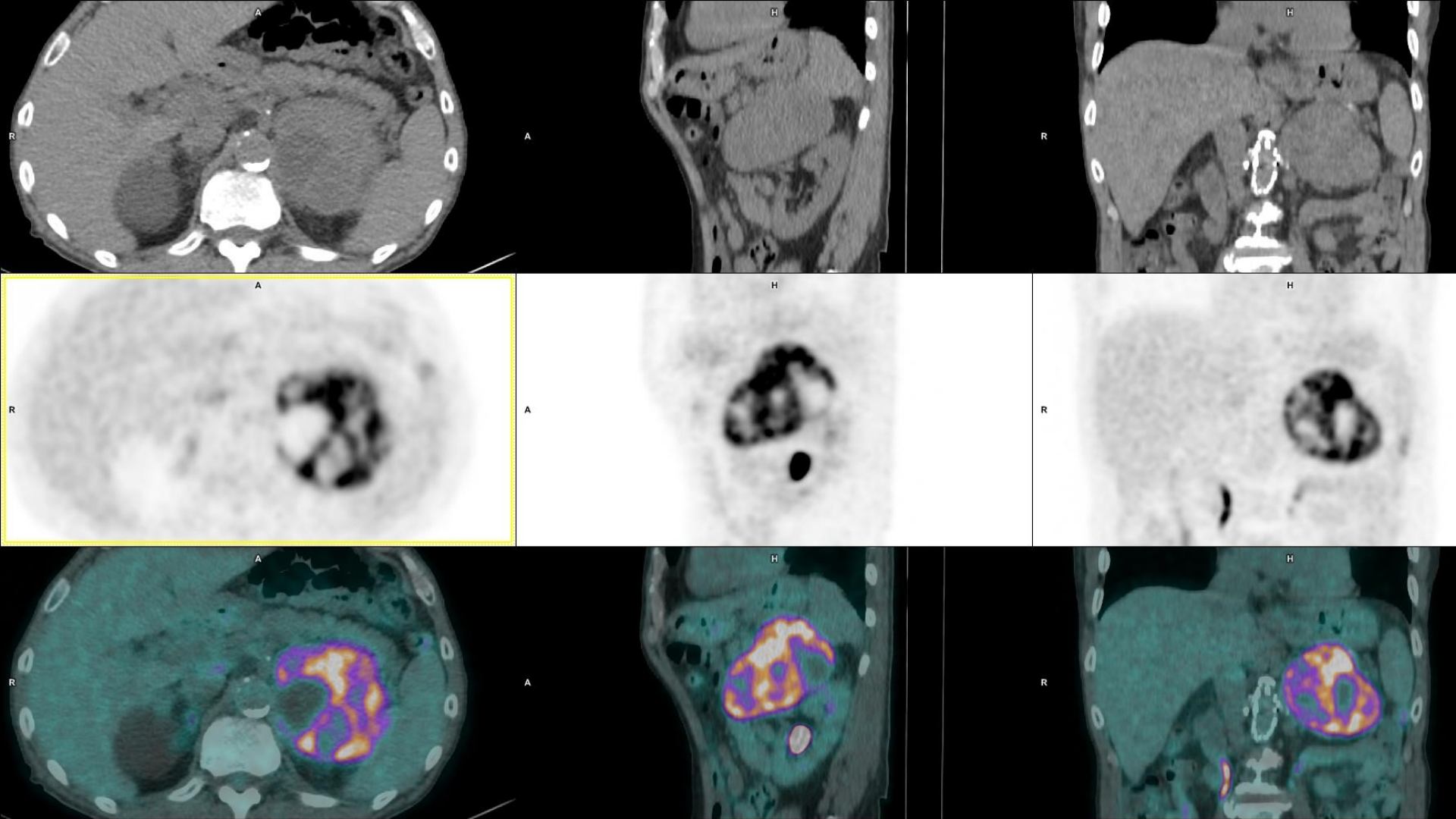
Total Lesion Glycolysis

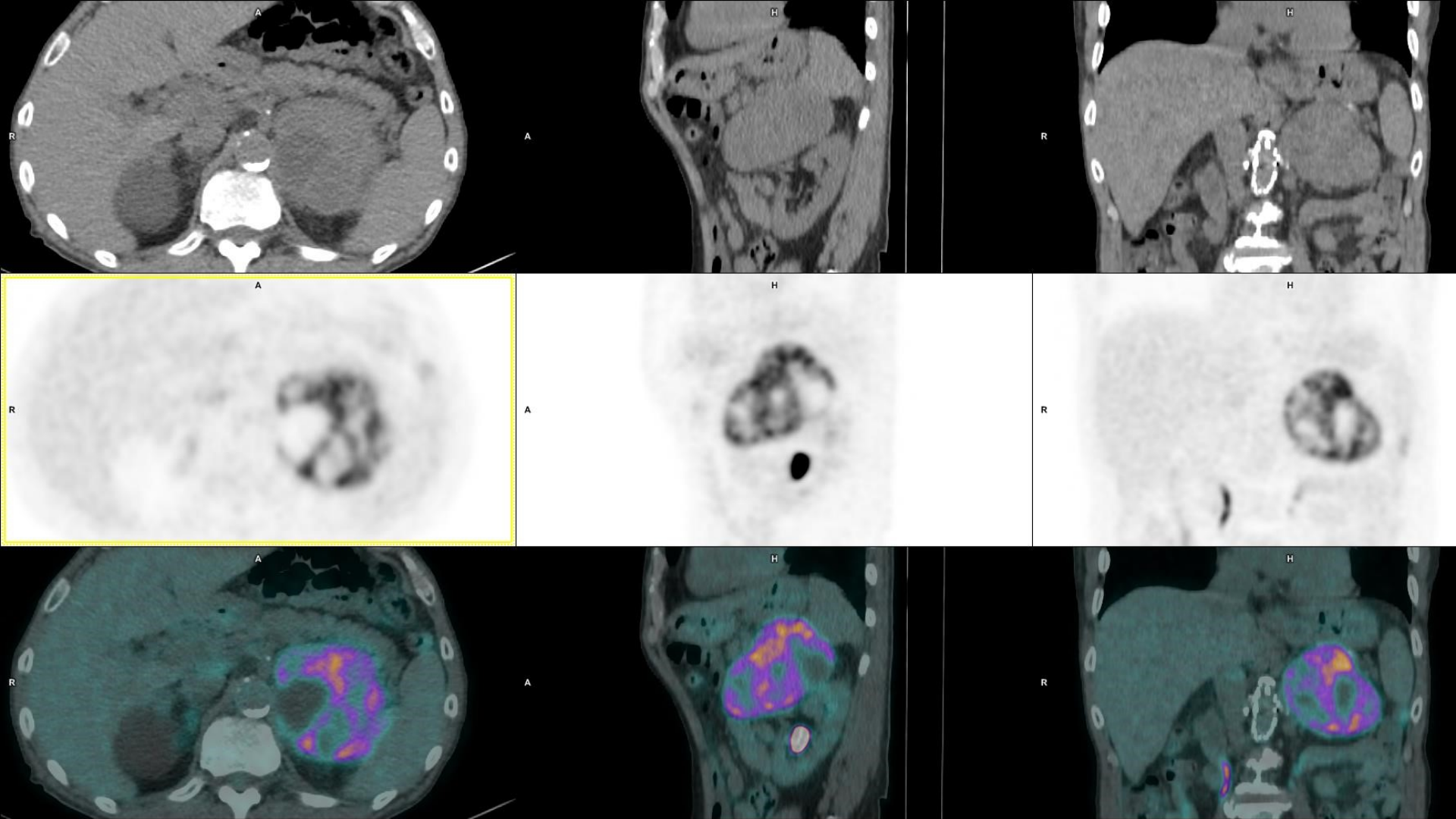
Zaidi et.al. Semin NuclMed. 2018; 48:548-564

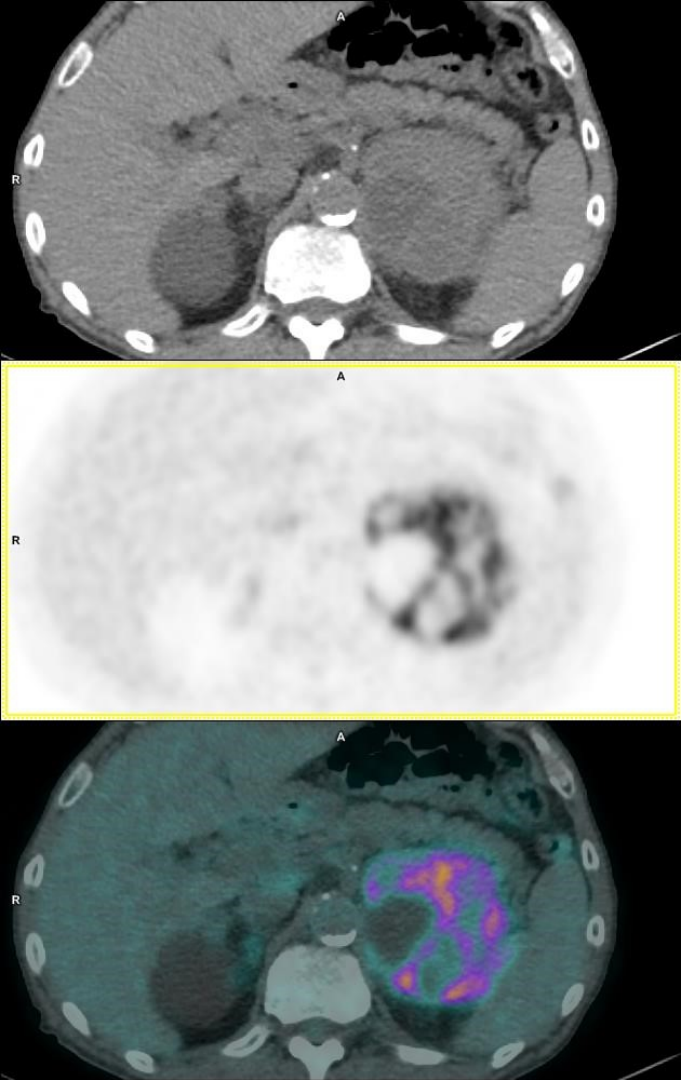
UNSW SYDNEY

The Prince of Wales Hospital & Community Health Service


A
R
A
H
R
H
A
R
A
H
R
H
A
R
A
H
R
H


A
R
H
A
H
R
A
R
H
A
H
R
A
R
H
A
H
R


A
R
A
H
R
H
A
R
A
H
R
H
A
R
A
H
R
H



Biological heterogeneity

- Proliferation / metabolism
- Cellular density
- Necrosis
- Fibrosis
- Perfusion /angiogenesis
- Hypoxia
- Receptor expression

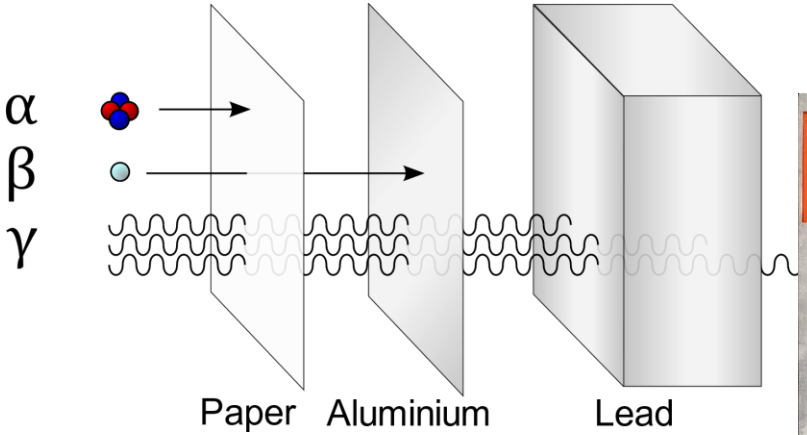
Heterogeneity and Radiomics

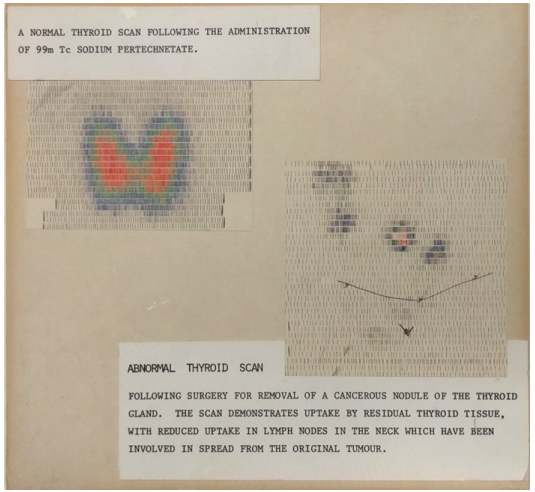
- Clinical reporting
  - "there is *heterogeneous* intense tracer uptake, SUVmax…. in the *irregular* mass…"
- Quantifying heterogeneity
  - "Radiomics focuses on improvements of image analysis, using an automated high-throughput extraction of large amounts (200+) of quantitative features of medical images.."
    - Lambin P et. al. Eur J Cancer. 2012 Mar;48(4):441-6.
- Artificial Intelligence

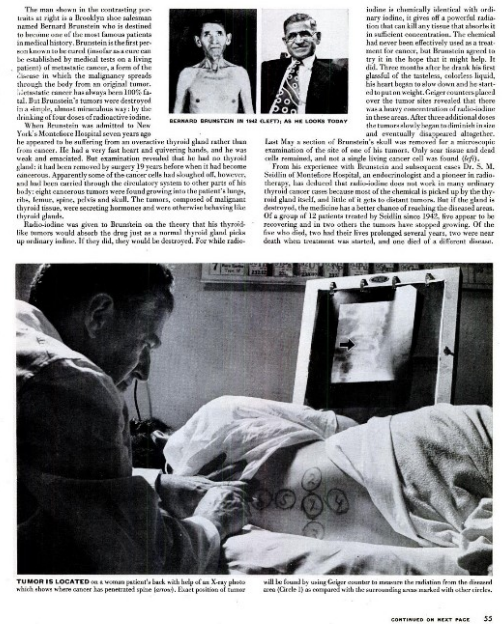
Radiomics

- Advantages
  - Applicable to all imaging modalities
    - Significance modality dependent
  - Use existing data
- Disadvantages
  - Biologic relevance
  - Harmonisation
    - Binning
    - Mathematical
    - Computational
  - Oversampling / overlap

Targeting







RADIO-IODINE HALTS ONE TYPE OF CANCER

Radioactive chemical brings about history-making recovery of patient dying from thyroid tumors

The man shown in the contrasting portraits at right is a Brooklyn shoe salesman named Bernard Brunstein who is destined to become one of the most famous patients in medical history. Brunstein is the first person known to be cured (insofar as a cure can be established by medical tests on a living patient) of metastatic cancer, a form of the disease in which the malignancy spreads through the body from an original tumor. Metastatic cancer has always been 100% fatal. But Brunstein's tumors were destroyed in a simple, almost miraculous way: by the drinking of four doses of radioactive iodine.

When Brunstein was admitted to New York's Montefiore Hospital seven years ago he appeared to be suffering from an overactive thyroid gland rather than from cancer. He had a very fast heart and quivering hands, and he was weak and emaciated. But examination revealed that he had no thyroid gland: it had been removed by surgery 19 years before when it had become cancerous. Apparently some of the cancer cells had sloughed off, however, and had been carried through the circulatory system to other parts of his body: eight cancerous tumors were found growing into the patient's lungs, ribs, femur, spine, pelvis and skull. The tumors, composed of malignant thyroid tissue, were secreting hormones and were otherwise behaving like thyroid glands.

Radio-iodine was given to Brunstein on the theory that his thyroid-like tumors would absorb the drug just as a normal thyroid gland picks up ordinary iodine. If they did, they would be destroyed. For while radio-iodine is chemically identical with ordinary iodine, it gives off a powerful radiation that can kill any tissue that absorbs it in sufficient concentrations. The chemical had never been effectively used as a treatment for cancer, but Brunstein agreed to try it in the hope that it might help. It did. Three months after he drank his first glandful of the tasteless, colorless liquid, his heart began to slow down and he started to put on weight. Geiger counters placed over the tumor sites revealed that there was a heavy concentration of radio-iodine in these areas. After three additional doses the tumors slowly began to diminish in size and eventually disappeared altogether.

BERNARD BRUNSTEIN IN 1942 (LEFT); AS HE LOOKS TODAY

Last May a section of Brunstein's skull was removed for a microscopic examination of the site of one of his tumors. Only scar tissue and dead cells remained, and not a single living cancer cell was found (left).

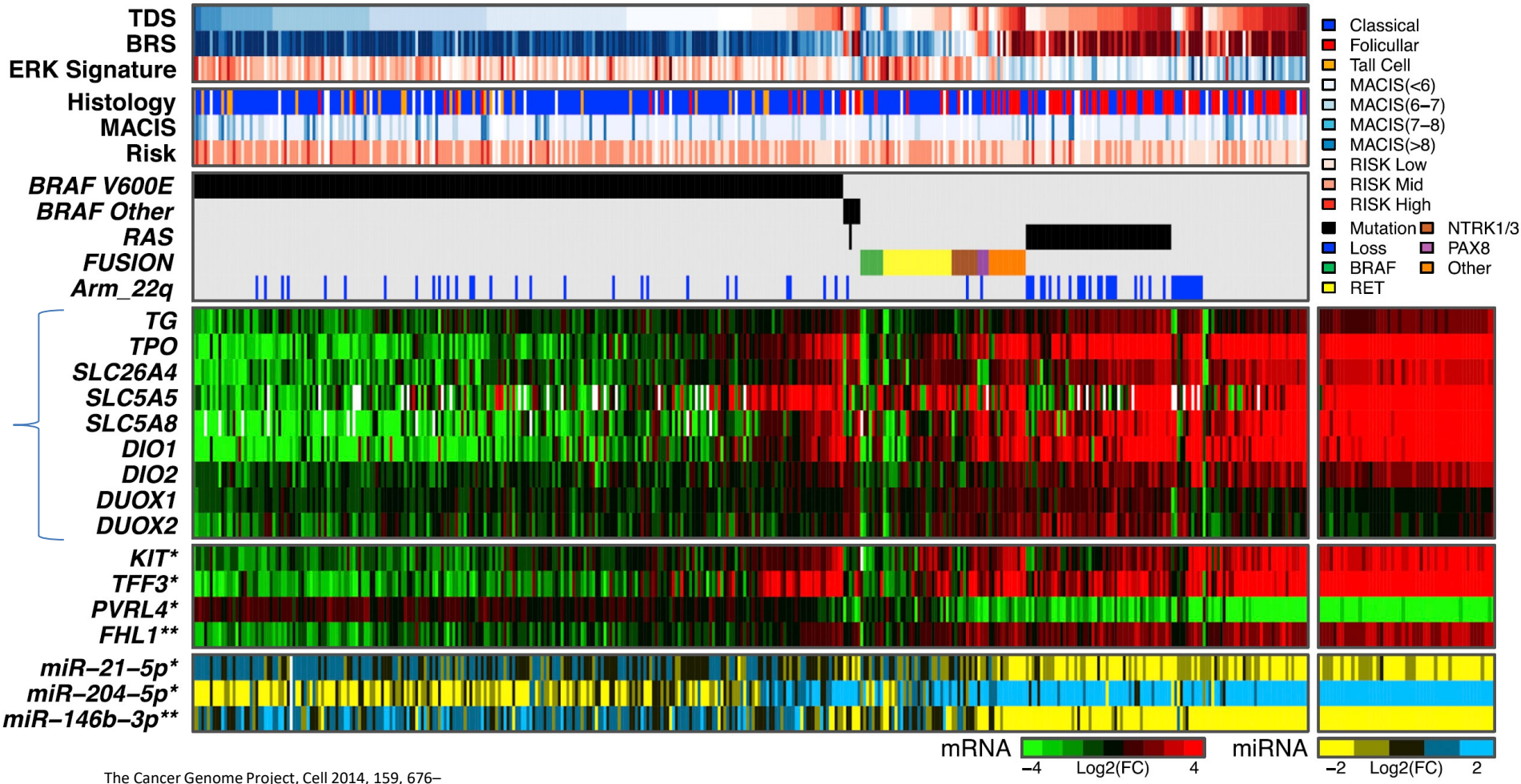
From his experience with Brunstein and subsequent cases Dr. S. M. Seidlin of Montefiore Hospital, an endocrinologist and a pioneer in radiotherapy, has deduced that radio-iodine does not work in many ordinary thyroid cancer cases because most of the chemical is picked up by the thyroid gland itself, and little of it gets to distant tumors. But if the gland is destroyed, the medicine has a better chance of reaching the diseased areas. Of a group of 12 patients treated by Seidlin since 1942, five appear to be recovering and in two others the tumors have stopped growing. Of the five who died, two had their lives prolonged several years, two were near death when treatment was started, and one died of a different disease.

TUMOR IS LOCATED on a woman patient's back with help of an X-ray photo which shows where cancer has penetrated spine (arrow). Exact position of tumor will be found by using Geiger counter to measure the radiation from the diseased area (Circle 2) as compared with the surrounding areas marked with other circles.

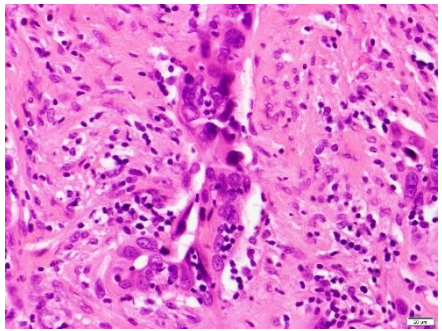
CONTINUED ON NEXT PAGE 55

UNSW SYDNEY

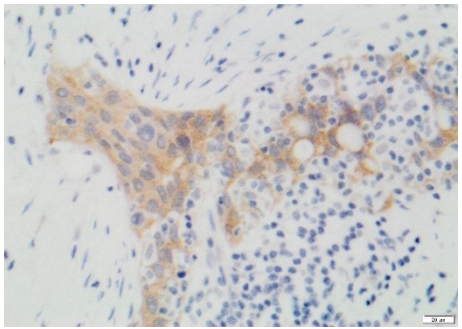
The Prince of Wales Hospital & Community Health Service



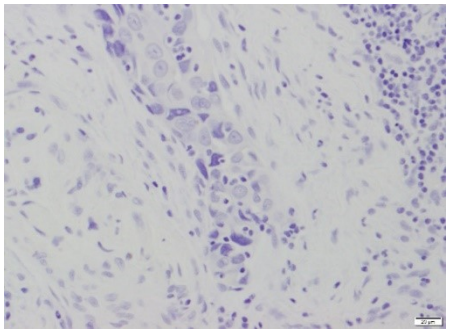
The Cancer Genome Project, Cell 2014, 159, 676–



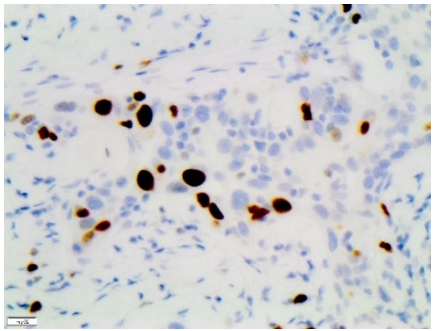
Anaplastic carcinoma



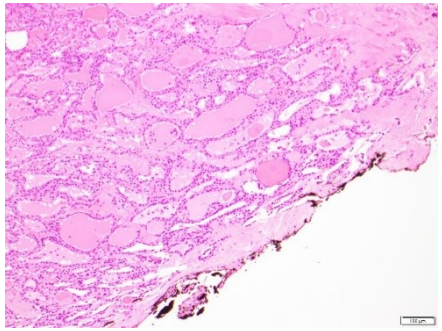
BRAFV600E



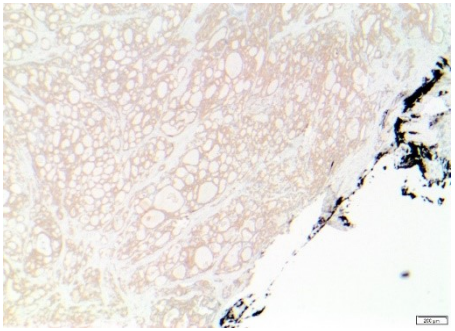
Thyroglobulin



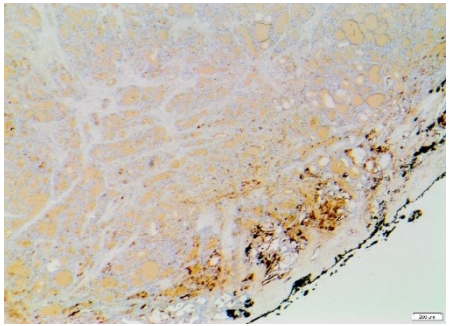
Ki67



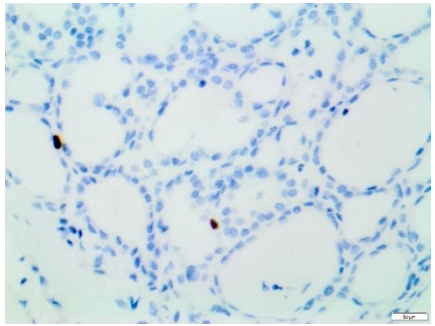
Well differentiated papillary carcinoma



BRAFV600E



Thyroglobulin



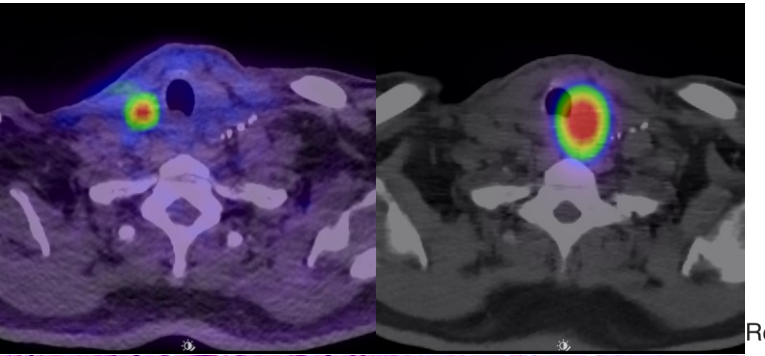
Ki67

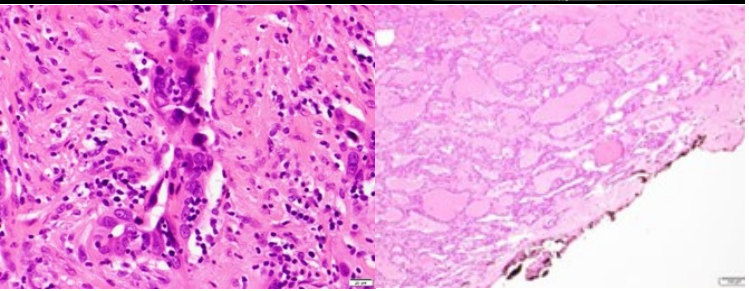
UNSW SYDNEY

The Prince of Wales Hospital & Community Health Service

FDG PET CT

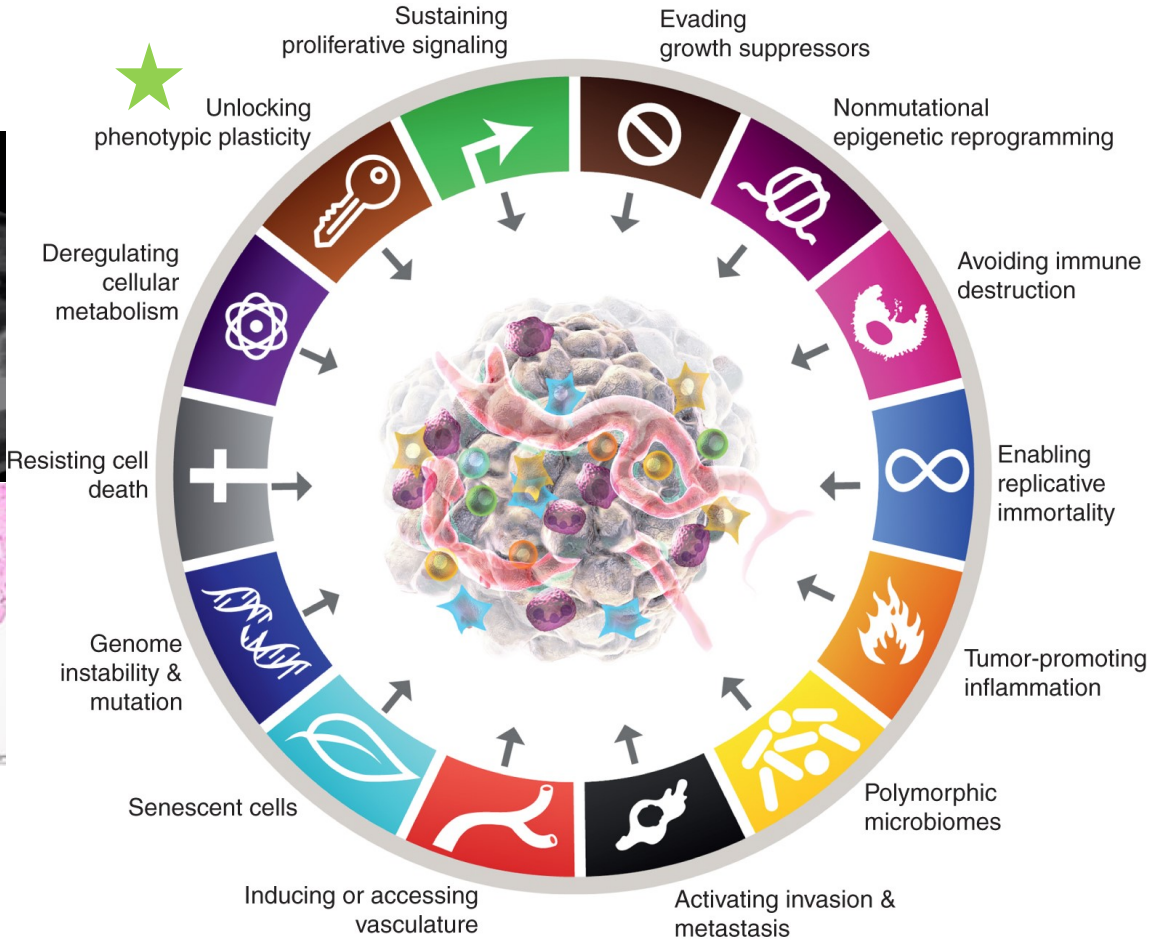
I-131 SPECT CT





Anaplastic

Papillary



UNSW SYDNEY

The Prince of Wales Hospital & Community Health Service

Research Development Workshop

- Imaging, quantifying and targeting hallmarks of cancer
- Translational or novel molecular imaging / theranostics may form the core of a molecularly targeted clinical trial across tumour streams
- Novel and SoC molecular imaging may be additional endpoints to molecularly targeted clinical trial across tumour streams
- Image banking

Research Development Workshop

- Radiation and Research
  - Australian Radiation Protection and Nuclear Safety Agency
  - Code of Practice for the Exposure of Humans to Ionizing Radiation for Research Purposes
    - “This research study involves exposure to a small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this study is about.... mSv. The dose from this study is comparable to that received from many diagnostic medical x-ray and nuclear medicine procedures. At this dose level, no harmful effects of radiation have been demonstrated as any effect is too small to measure.”