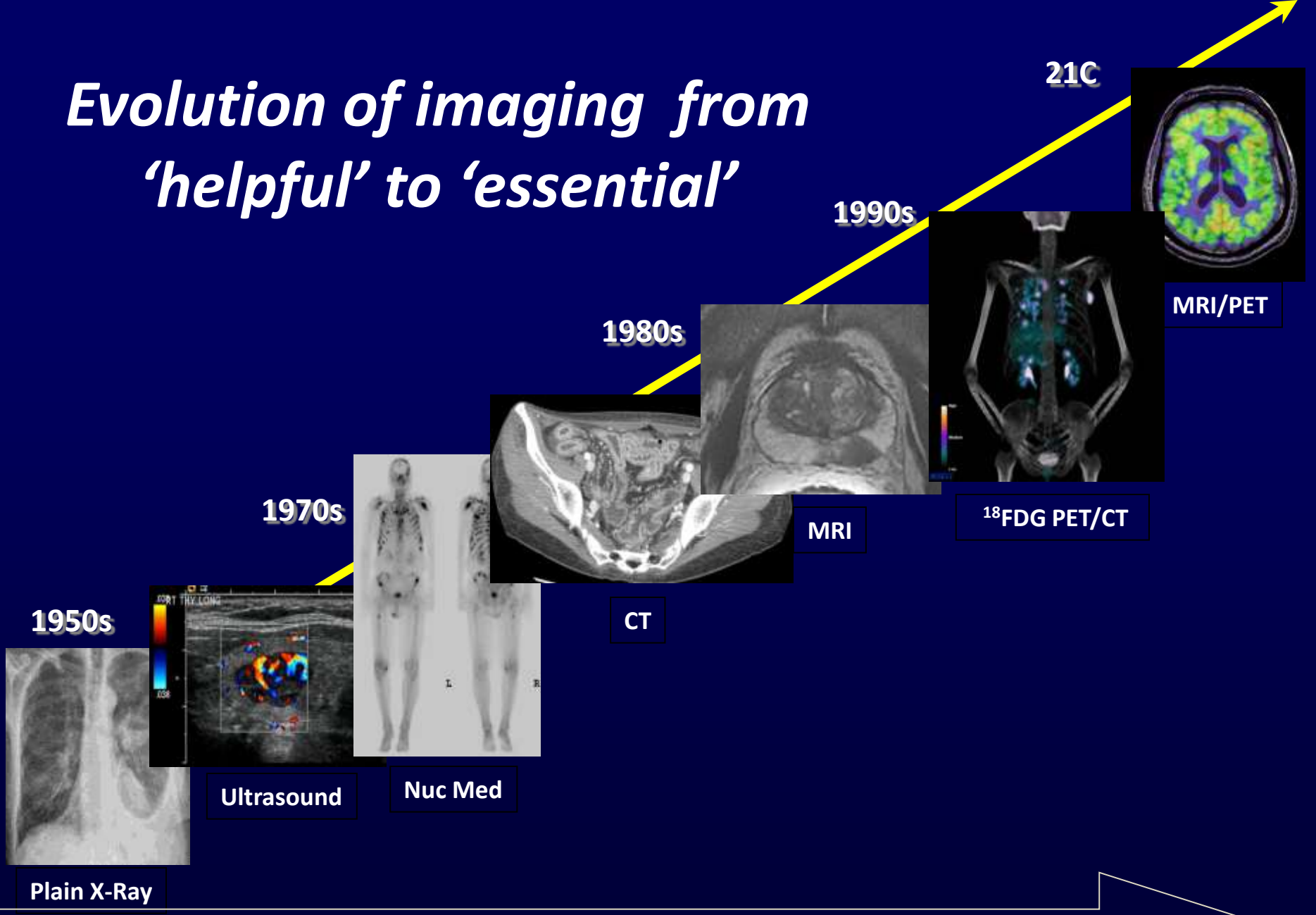
Imaging in the era of Genomics and Precision Medicine

Perspectives of a Clinician Scientist

The history of medicine has been defined by advances born of bioscience. But never before has it been driven to this degree by technology.

Evolution of imaging from 'helpful' to 'essential'

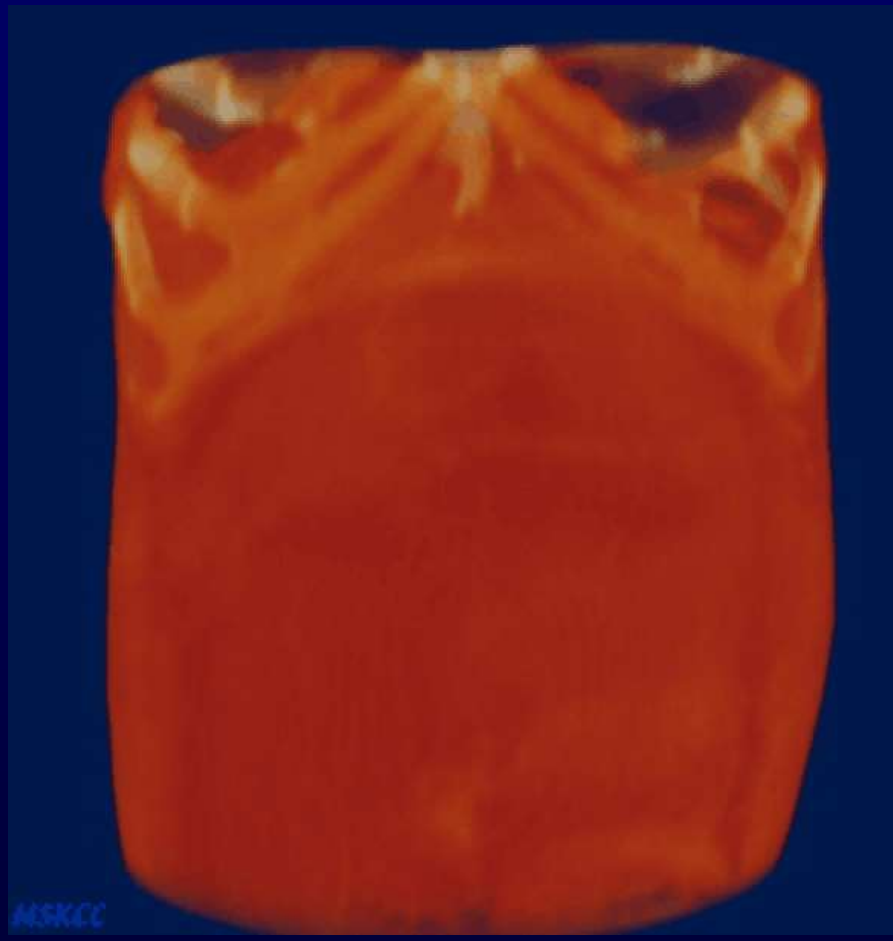


Imaging 2013: Guiding Hand in Precision Medicine

Oncologic Imaging

The last 30 years

- **Cancer Screening**
  (Ca Breast & Lung)
- **Cancer Detection/Localization**
- **Treatment Decision**
  - Evidence-Based Medicine
- **Treatment Planning**
  (Surgery/RTX)
  - Imaging is a Road Map (GPS)
- **Treatment Follow-up**
  - Monitoring Treatment Response
  - Detection of Tumor Recurrence

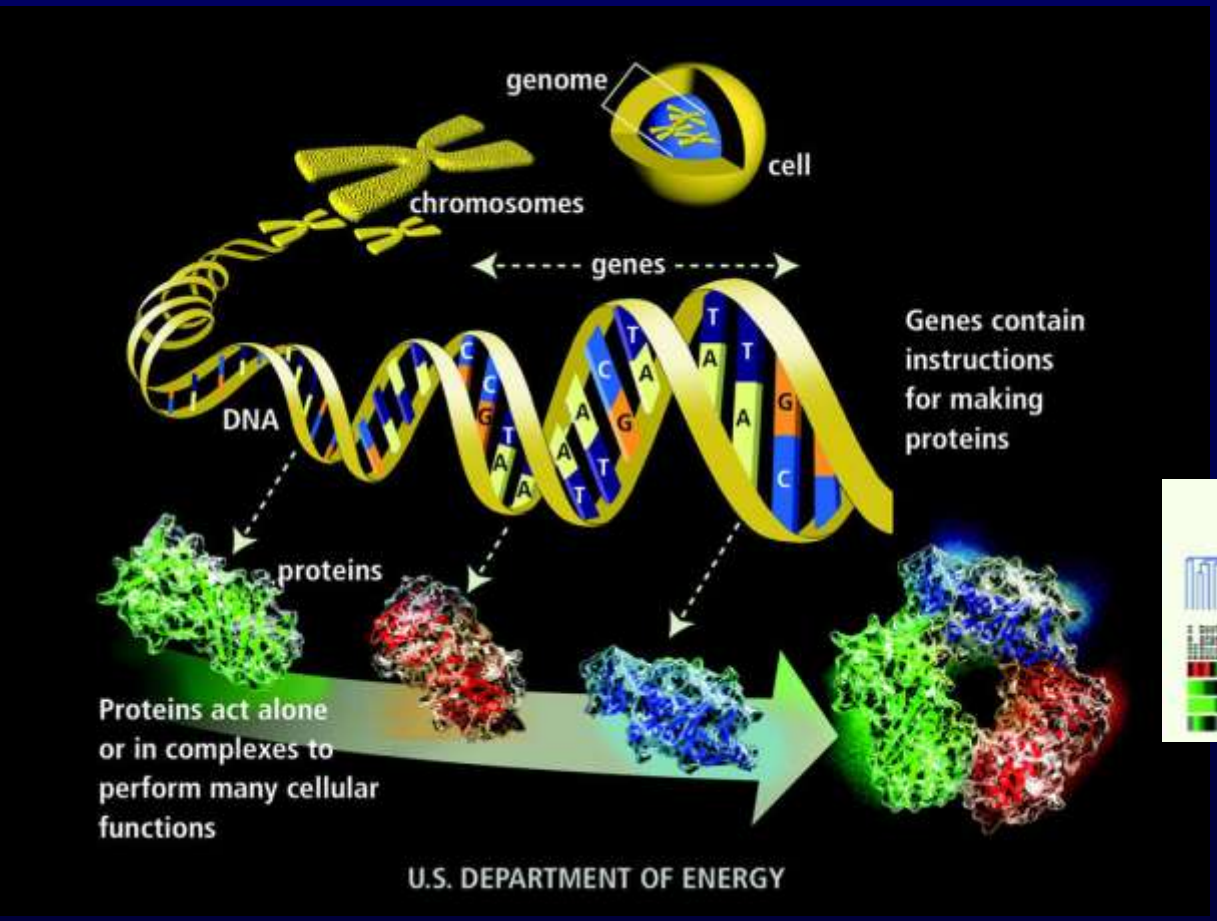


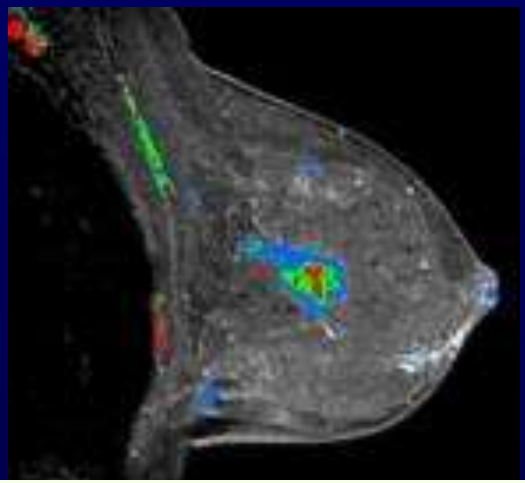
CT Virtual Laparotomy by Imaging

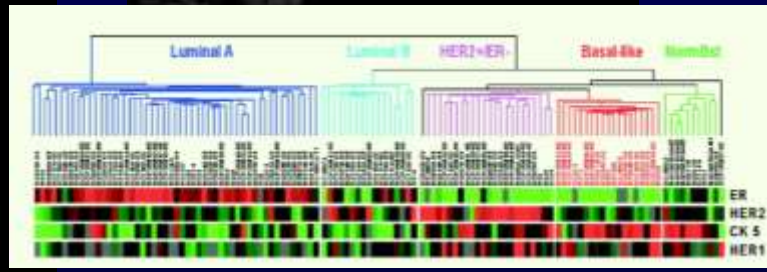
"The Anatomy Lecture of Dr Nicolaes Tulp" – Rembrandt, 1632

Human Genome - Oncology

New Horizons





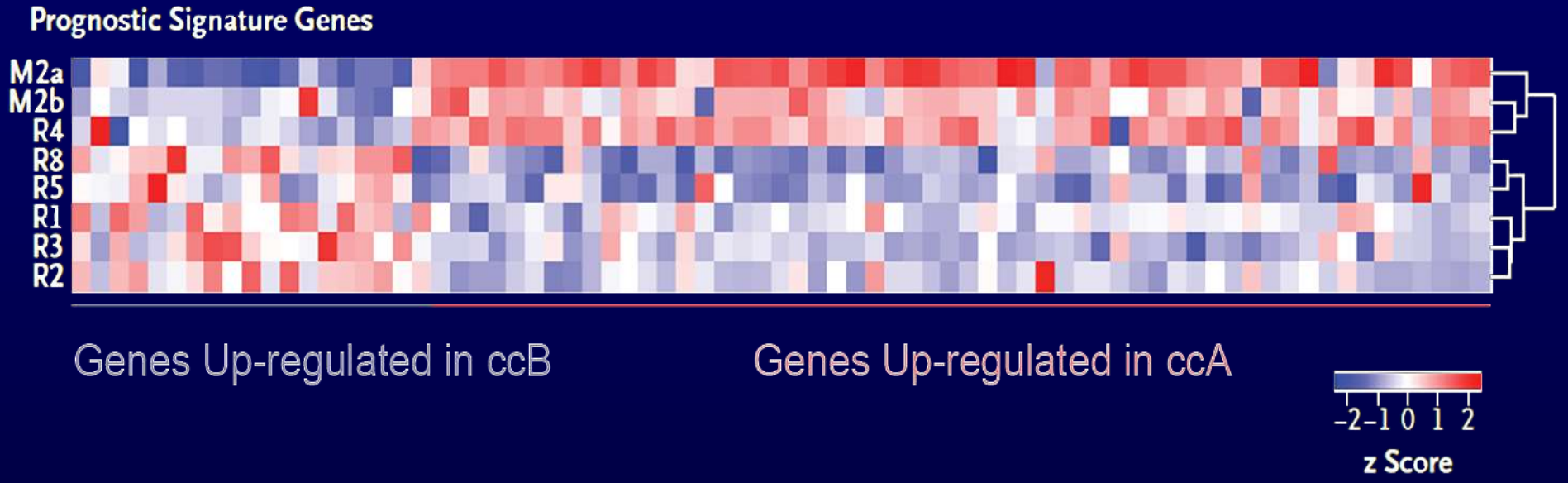


Breast Cancer

Human Genome (name given by Prof. Winkler in 1920) was sequenced in 2003

- "Genetic intratumor heterogeneity contributes to treatment failure and drug resistance" *

*Cancer Genome Atlas Research Network: Nature 2011

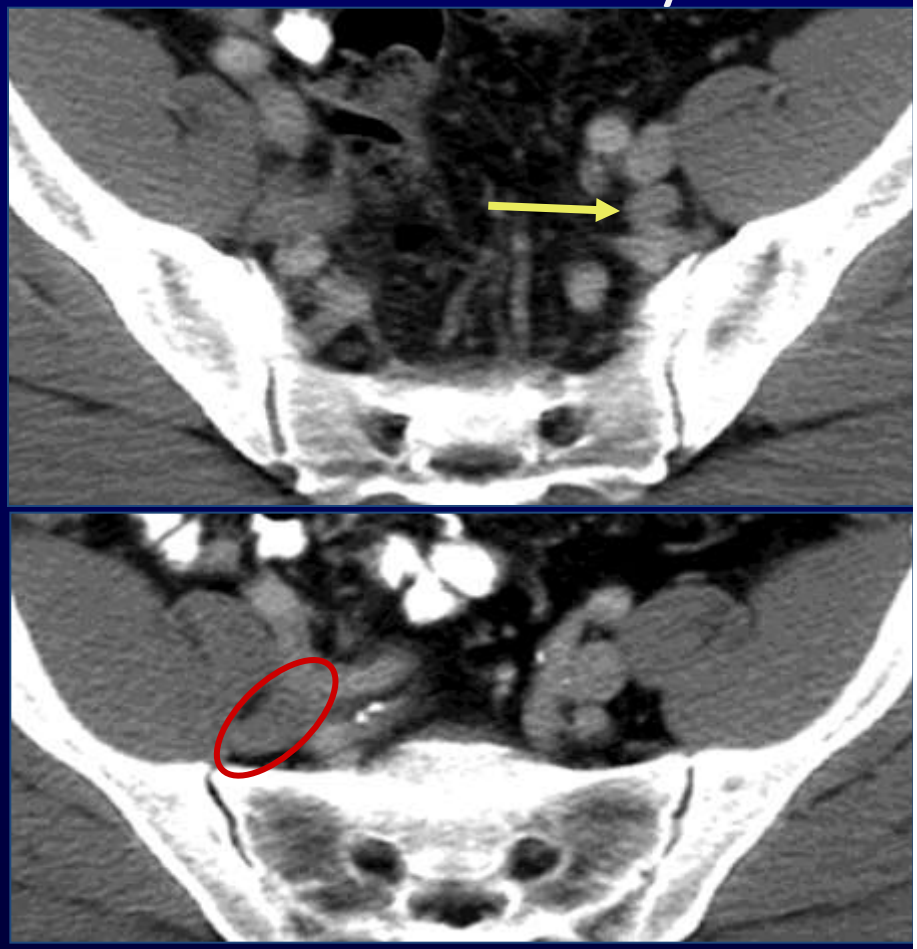


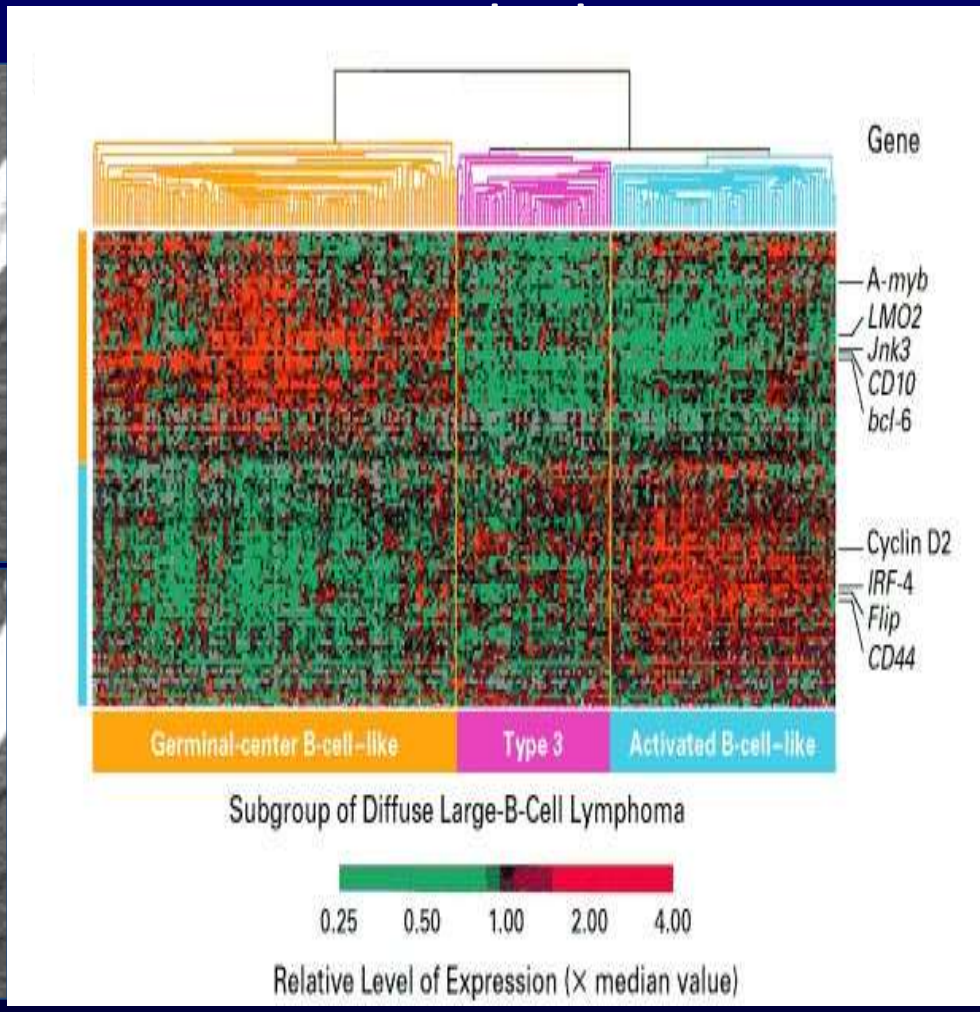
"Intratumor heterogeneity can lead to underestimation of the tumor genomics landscape portrayed from *single tumor-biopsy samples* and may present major challenges to personalized-medicine and biomarker development."

New England Journal of Medicine 366;10 nejm.org march 8, 2012

Lymphoma: *Treatment Follow-up*

Baseline study





Mixed Tumor Response

Breast Cancer Metastasis: *Treatment Follow-up*

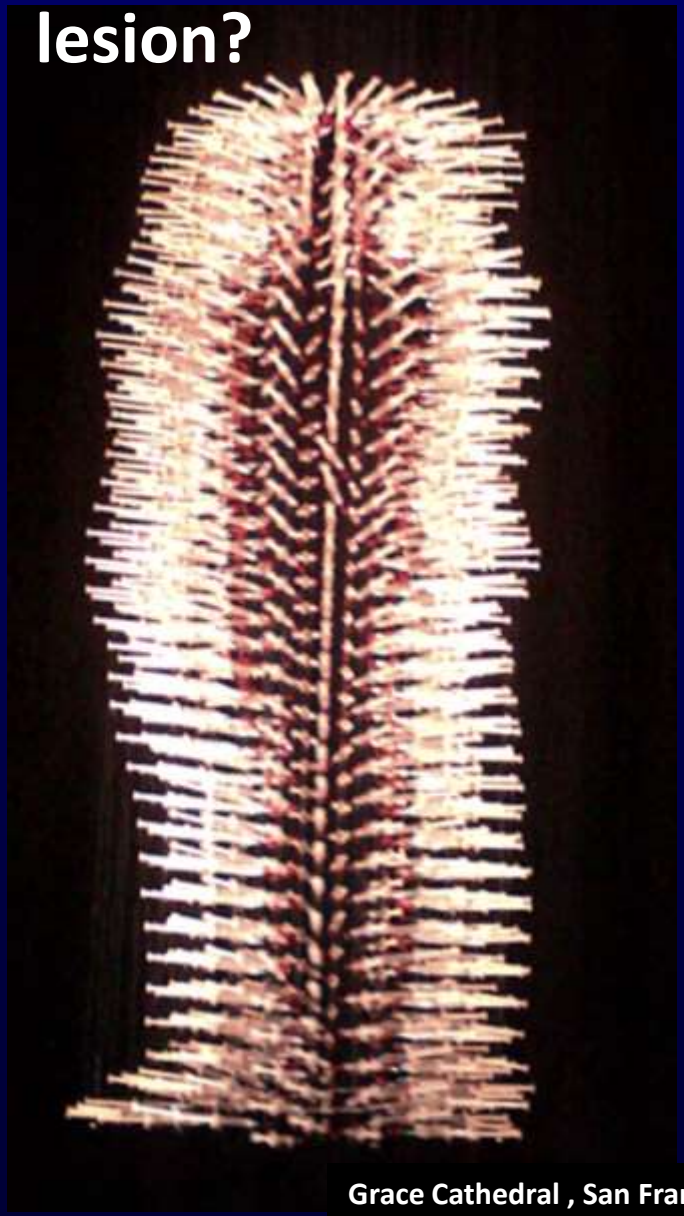
PET/CT April 5, 2013

PET/CT July 18, 2013

Mixed Tumor Response

Inter- and intra-tumoral heterogeneity - A Major Challenge to Precision Medicine: Can we/should we biopsy each and every lesion lesion?

^{18}F-FDHT PET/CT



Grace Cathedral , San Francisco

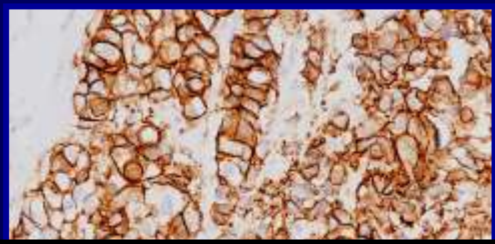
Medicine in the 21st Century

Precision Medicine

Personalized Medicine: a paradigm shift from "one-size fits all" to Predictive, Prognostic & Personalized medicine

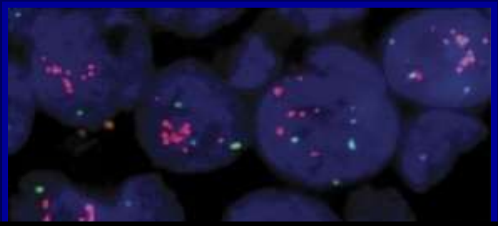
Developing newly-Tailored, Biomarker Driven Evidence-Based Medicine

HER2 Positive Immunophenotype



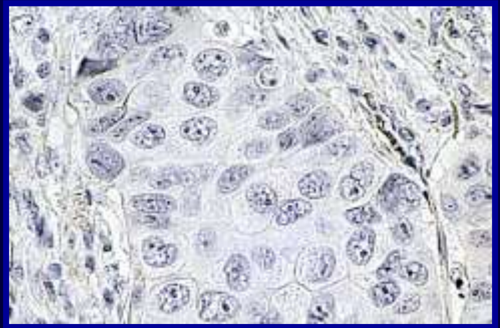
cMRI

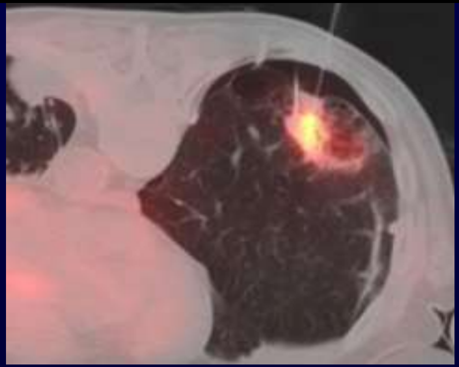
HER2 Amplified Gene Copies

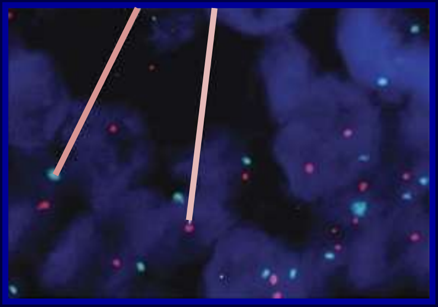


Tumor Metastasis - De-differentiate (Breast Ca ≤30%)

Predictive/Prognostic Biomarkers for Tumor Metastasis







*Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease: NAS/IOM 2012

Oncology in the Age of Molecular Medicine

Predictive, Prognostic & Personalized

Precision Medicine*

Essential to the success of Precision Medicine

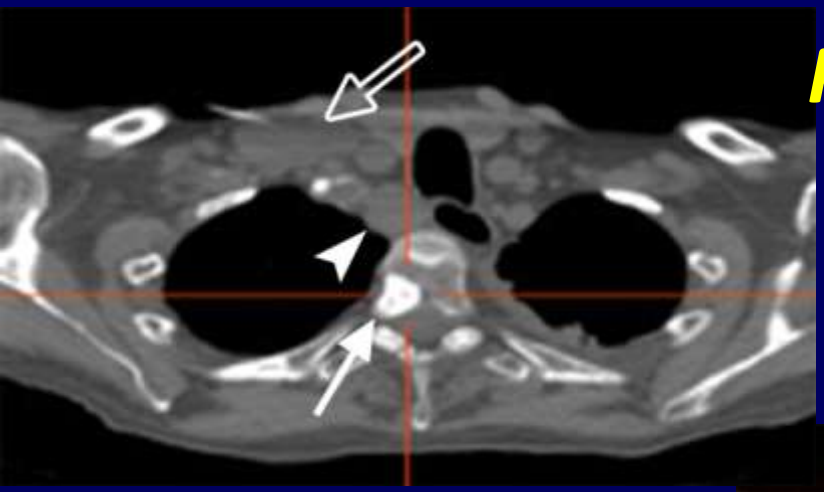
Biomarkers (Serum, Tissue or Imaging)

- **Predictive Biomarkers**
  - For therapy selection: identify relative sensitivity or resistance to specific treatments or agents; identify patients where treatment is not required
- **Early Response Biomarkers**
- **Prognostic Biomarkers**
  - Inform about an outcome independent of specific treatment

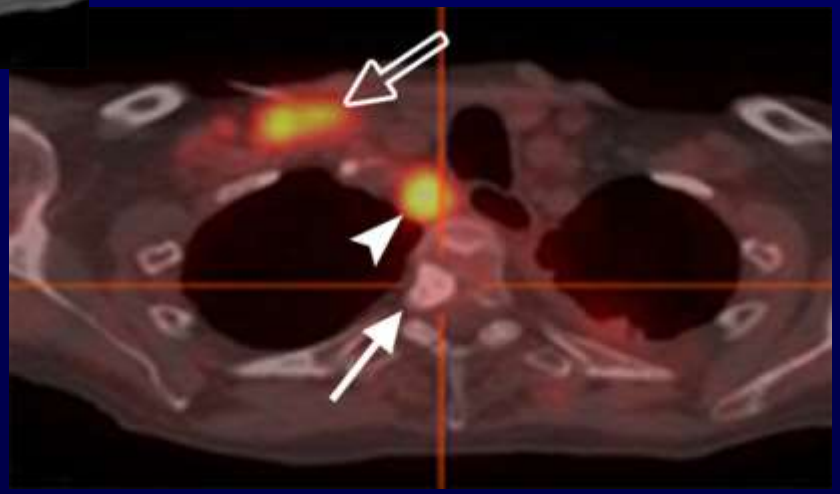
*Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease: NAS/IOM 2012

Precision Medicine – Role of MI

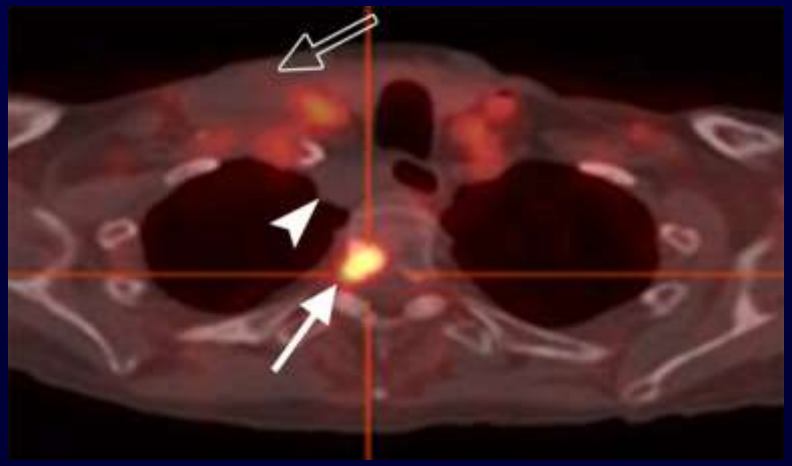
Prostate Cancer
Revealing Heterogeneous Biology of Tumor Metastasis



CT



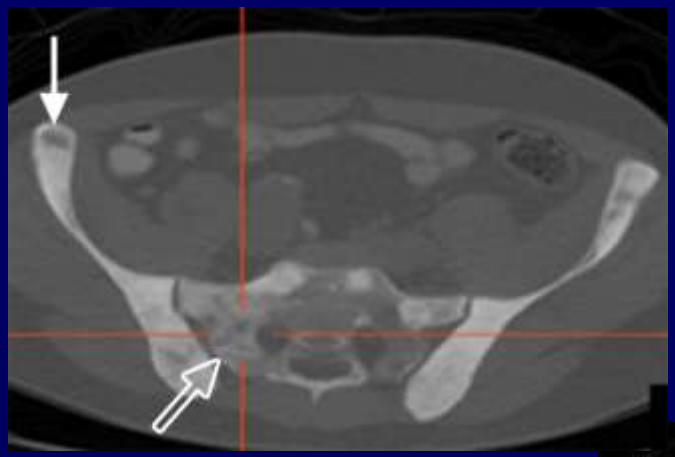
^{18}F-FDG PET/CT
Glycolysis



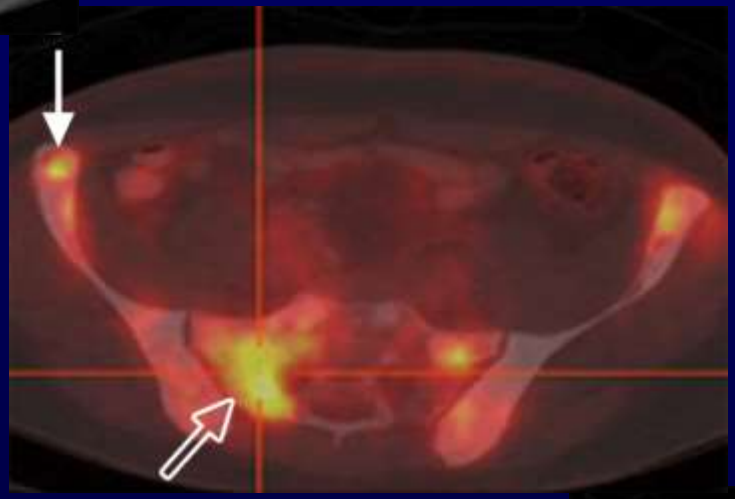
^{18}F-FDHT PET/CT
Androgen Receptor

Precision Medicine – Role of MI

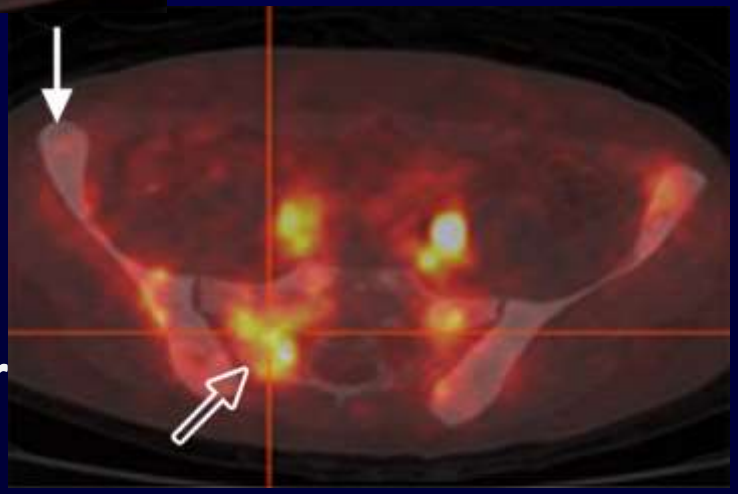
Prostate Cancer
Revealing Heterogeneous Biology of Tumor Metastasis



CT



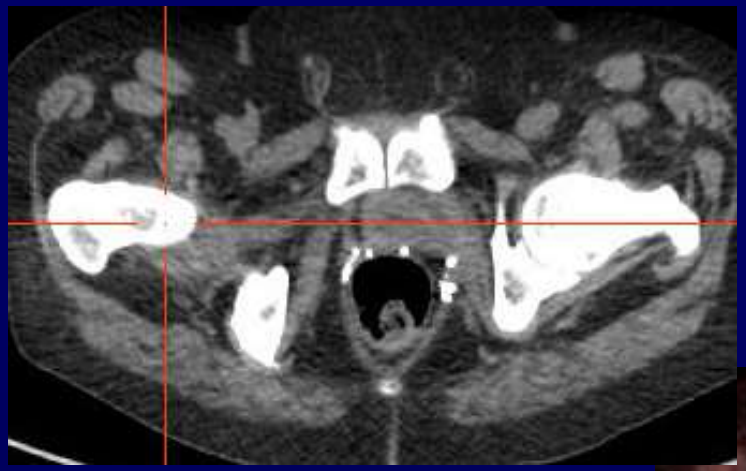
^{18}F-FDG PET/CT
Glycolysis



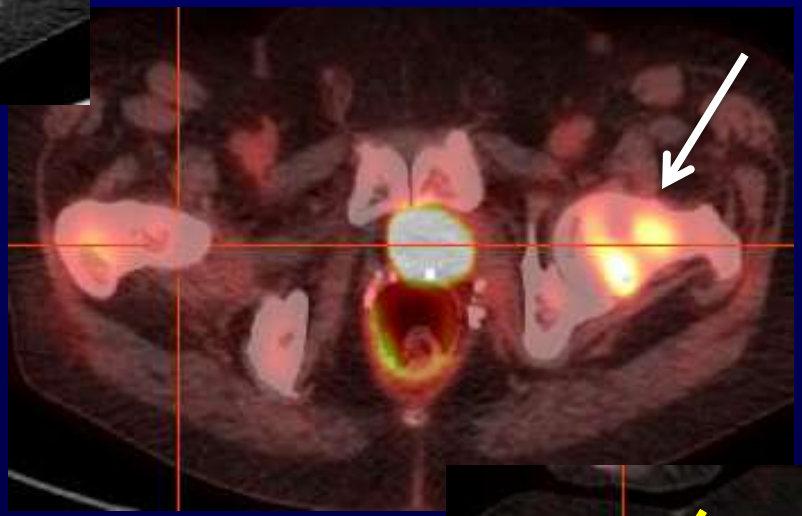
^{18}F-FDHT PET/CT
Androgen Receptor

Precision Medicine – Role of MI

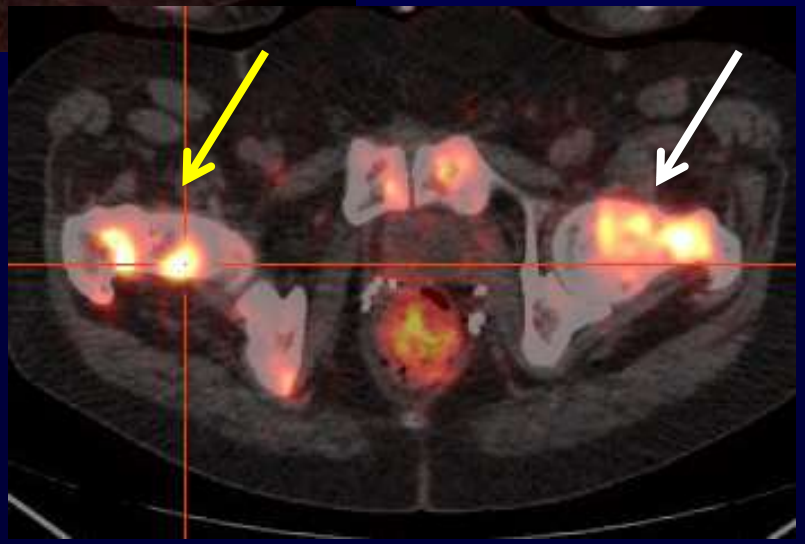
Prostate Cancer Revealing Heterogeneous Biology of Tumor Metastasis



CT



^{18}F-FDG PET/CT
Glycolysis



Zr-89 J591
PSMA mAb

Lewis: JNM 2010

Precision Medicine – MI and image guided Bx

MI & Molecular Pathology - insights into Tumor Biology

Breast Cancer Metastasis

Image-guided robotic biopsy

^{64}Cu Trastuzumab PET/CT

Investigational: MSKCC

Technology and Medicine

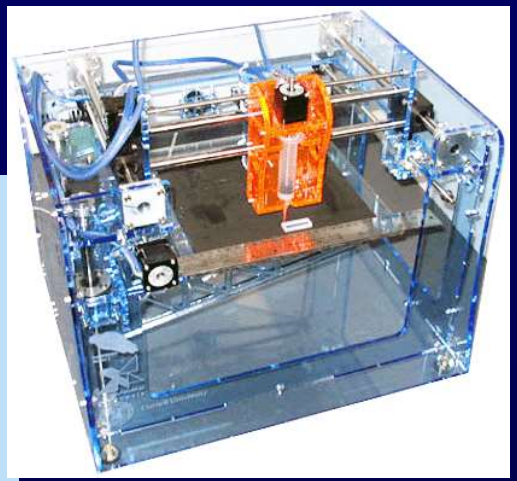
"As much as new ideas are fundamental to the advancement of science, technologic innovations are the engine of scientific progress"

Shirley Tilghman
President, Princeton University

Radiosynthesis of ^{11}C compounds ($T_{½}$ = 20.4 min)

~1975 - "C-glucose was prepared by photosynthesis. It was extracted from mashed up **Swiss-chard leaves** and a "green solution" was injected into the patient; preparation time ~90 min

2013 - "C-glucose is prepared by **a "black box" automated versatile synthesizer** producing drugs ready for human use ; preparation time ~45min



~2023- "C-glucose will be prepared by a widely available synthesizer – **a 3D printer?**

Radiopharmaceuticals Produced In-house for the Clinic @ MSKCC (MSKCC IND=25)

Radiopharmaceutical	Imaging Target	Cancer Site	Human studies
Small Molecules (Imaging)			
[^{18}F]-FLT	tumor cell proliferation	Lymphoma, prostate, H&N, NSCLC	MSKCC IND
[^{18}F]-FES	estrogen receptor status	Breast	RDRC/MSKCC IND pending
[^{18}F]-FDHT	androgen receptor	Prostate	MSKCC IND
[^{18}F]-FMISO	tumor oxygenation	Head & Neck, Rectal	MSKCC IND
[^{18}F]-FACBC	amino acid metabolism	Breast, Prostate, Brain	RDRC/ GEMS IND
[^{18}F]-FIAU	gene expression	Prostate	MSKCC IND
[^{18}F]-ML10	imaging apoptosis	Brain, NSCLC, H&N,	Non-MSKCC IND
[^{18}F]-dasatinib	tyrosine kinases	Prostate, Breast	MSKCC IND
[^{18}F]-glutamine	tumor metabolism	All solid malignancies	MSKCC IND
[^{64}Cu]-ATSM	tumor oxygenation	Uterine Cervix, Rectal	ACRIN
[^{124}I]-IAZGP	tumor oxygenation	Rectal	MSKCC IND
[^{124}I]-FIAU	gene expression	Prostate	MSKCC IND
Na-[^{124}I]	Na Iodide Symporter	Thyroid	MSKCC IND
[^{124}I]-PUH71	HSP-90	All solid malignancies and lymphoma	MSKCC IND
Antibodies and Fragments (Imaging)			
[^{68}Ga]- Her2 F(ab')	HER2	Breast	MSKCC IND
^{64}Cu-DOTA-trastuzumab	HER2	Breast	MSKCC IND
[^{124}I]-A33	A33 antigen	Colon	MSKCC IND
[^{124}I]-3F8	disialoganglioside GD2	Neuroblastoma (pediatrics)	MSKCC IND
[^{124}I]-8H9	8H9 antigen	Multiple tumors e.g. Leptomeninges (pediatrics)	MSKCC IND
[^{124}I]-G250	CA9 antigen	Renal	MSKCC IND
[^{89}Zr]-DFO-huJ591	PSMA	Prostate	MSKCC IND
[^{89}Zr]-Trastuzumab	HER2	Breast	MSKCC IND pending
[^{89}Zr]-DFO-MSTP2109A	PSMA	Prostate	MSKCC IND
^{89}Zr-Df-IAB2M	PSMA	Prostate	ImaginAb/MSKCC IND
^{111}In-DOTA-cG250	CA9 antigen	Renal	LICR IND
Antibodies and Fragments (Therapy)			
^{90}Y-DOTA-cG250	CA9 antigen	Renal	LICR IND
^{131}I-8H9	8H9 antigen	Multiple tumors e.g. Leptomeninges (pediatrics)	MSKCC IND
^{131}I-3F8	disialoganglioside GD2	Neuroblastoma (pediatrics)	MSKCC IND
^{225}Ac-lintuzumab	Anti-CD33	Acute Myeloid Leukemia	MSKCC IND
Nanoparticles (Imaging)			
[^{124}I]-Cdot nanoparticles	αvβ3	Melanoma	MSKCC IND

MR Technology

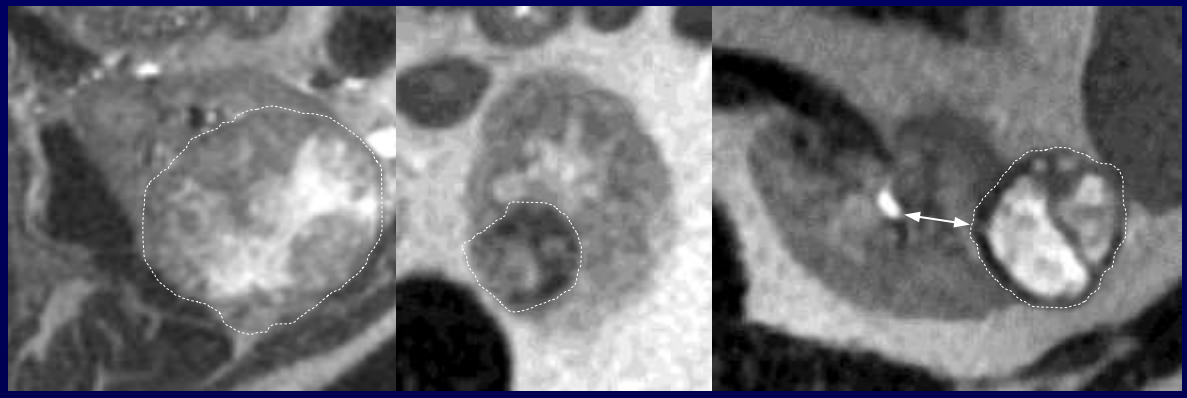
Powerful and Versatile Modality – still not fully explored

MR Imaging

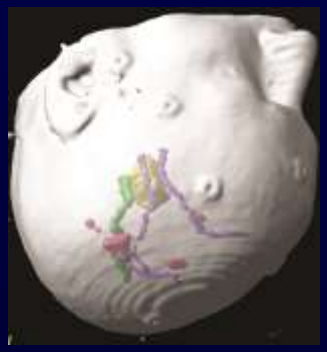
- Spin Echo (T1&T2)
- DWI
- IVIM
- CE-MRI
- $_{f}$MRI

MR Spectroscopic Imaging

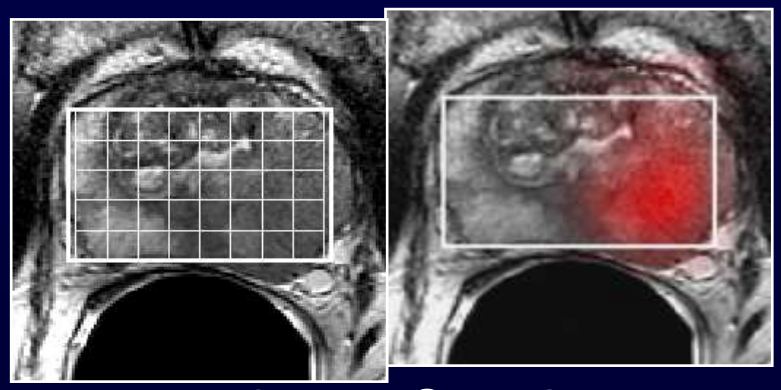
- ^{1}H
  - PRESS- CSI
  - STEAM- CSI
  - Modified/novel sequences
- Multinuclear MRSI (^{31}P etc.)
- DNP-MR (^{13}C, etc.)



C.A. Karlo et al: RCC – MVBI Radiology 2013



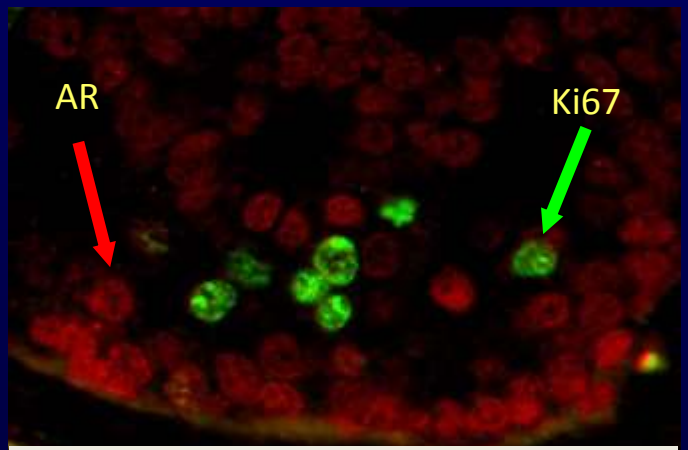
$_{f}$MRI



PCa MRI & MRSI

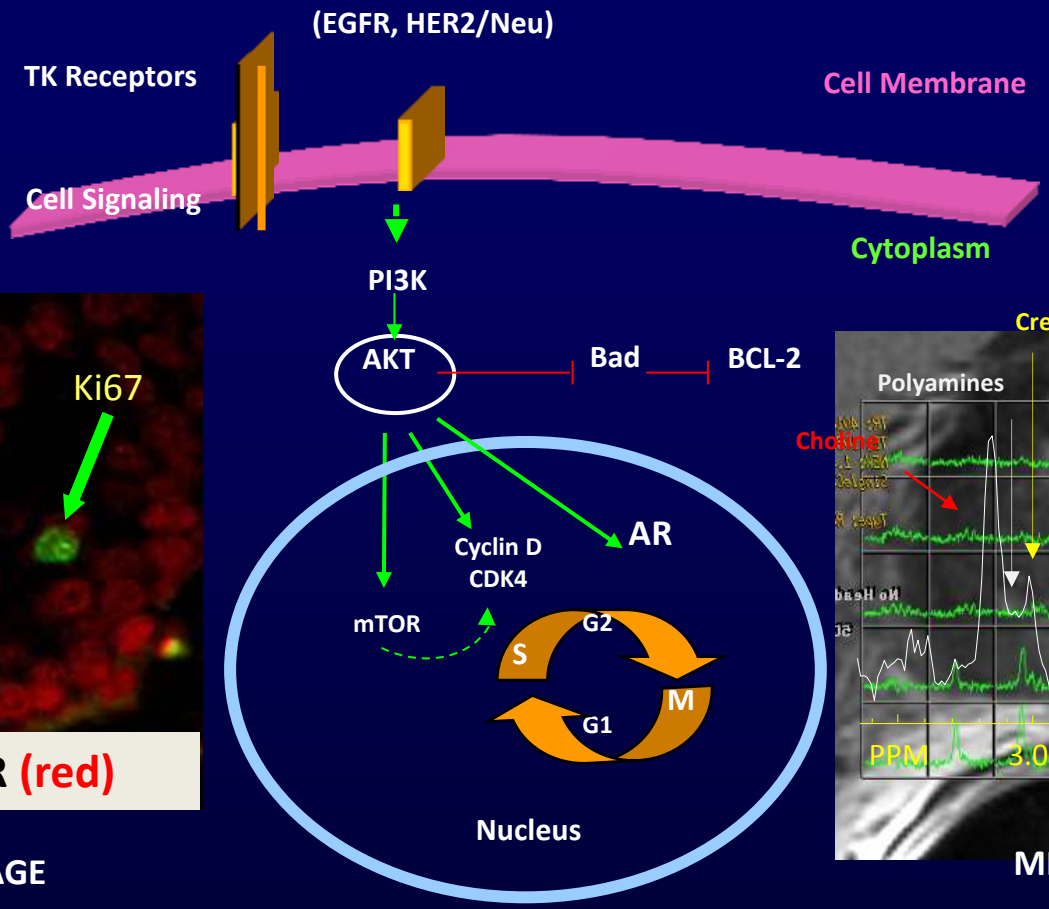
Integrated Diagnostics

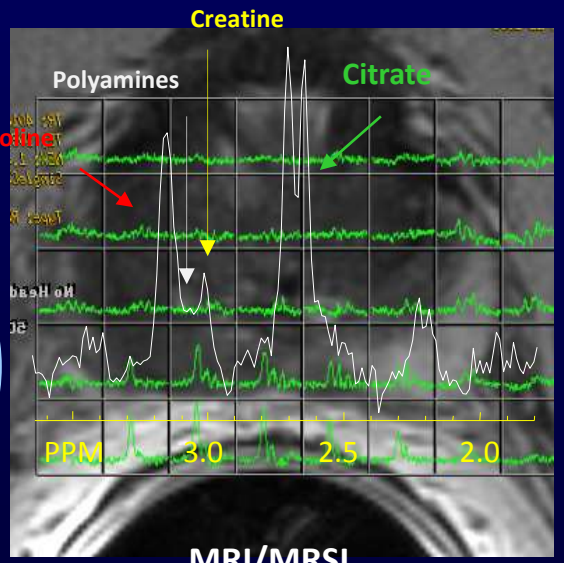
Prostate Cancer: MRI/MRSI and Immunohistochemistry



Ki67 (green) and AR (red)

MULTIPLEXED IMAGE





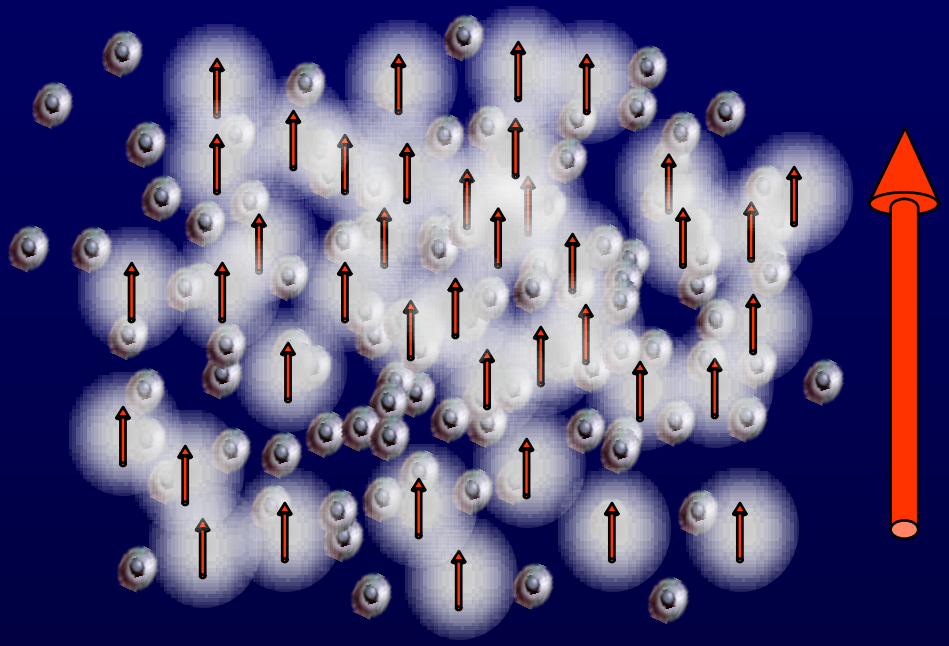
MRI/MRSI

Ki-67 and pAkt (Prognostic Biomarkers of Prostate Cancer aggressiveness) significantly correlate with MRI/MRSI

Shukla-Dave, Hricak , Cordon-Cordo et al, Radiology, 2009

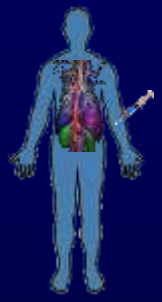
Hyperpolarized ^{13}C MR

Boosting MR sensitivity



HYPERPOLARIZATION OUTSIDE THE SCANNER

INJECTION OF HYPERPOLARIZED AGENT



SCANNING THE PATIENT

^{13}C is a stable (non-radioactive) and magnetically active isotope of carbon

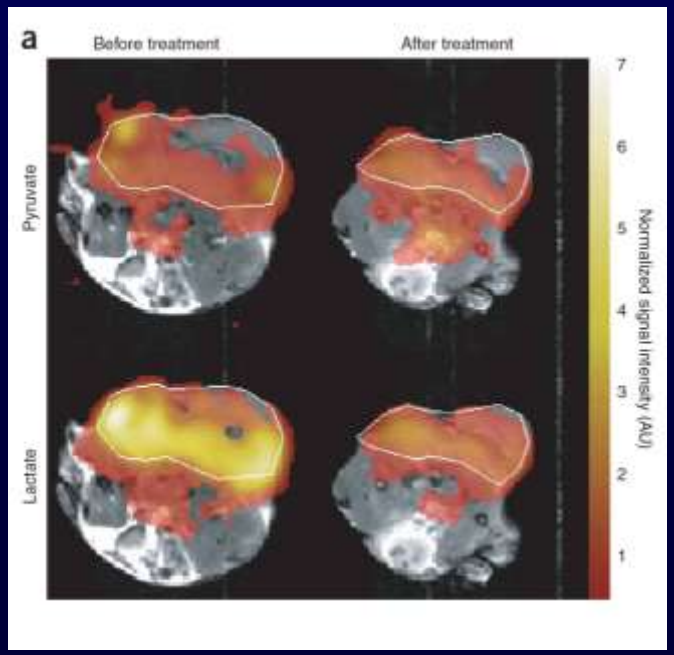
^{13}C has a low natural abundance of 1.1%

^{13}C molecules can be chemically synthesized (^{12}C atom is replaced by a ^{13}C atom)

Hyperpolarized ^{13}C MR

^{13}C labeled substrates and their metabolic products allow for *tumor detection, assessment of tumor aggressiveness and early treatment response.*

Unique way to noninvasively monitor tumor metabolism in patients

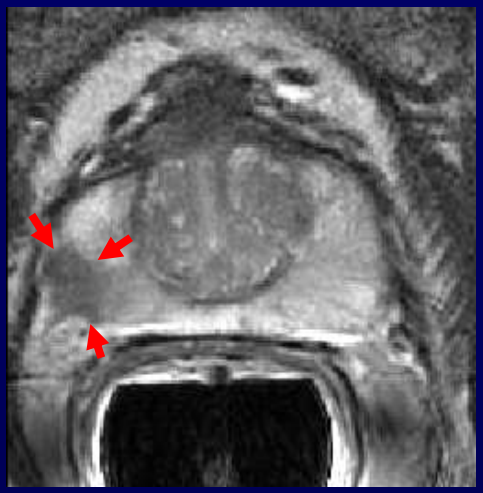


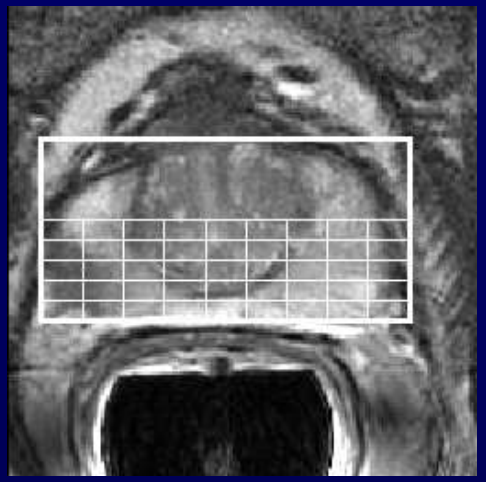
Lymphoma - 20 h Treatment Response to Etoposide

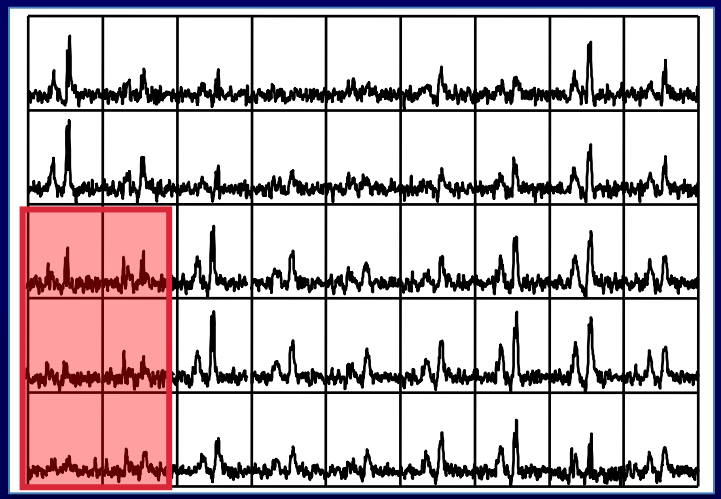
^{13}C-labelled Pyruvate to Lactate Conversion

Day et al. *Nature Medicine* 2007

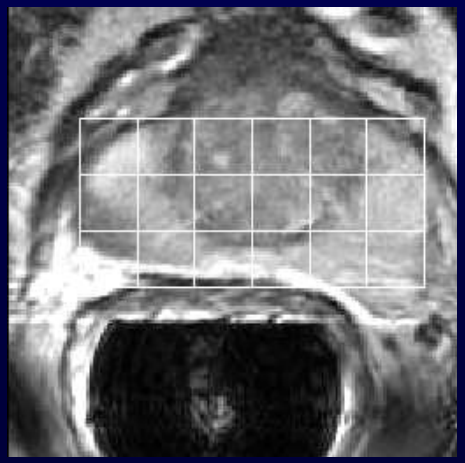
3D Hyperpolarized ^{13}C MRSI – *First in human clinical trial*

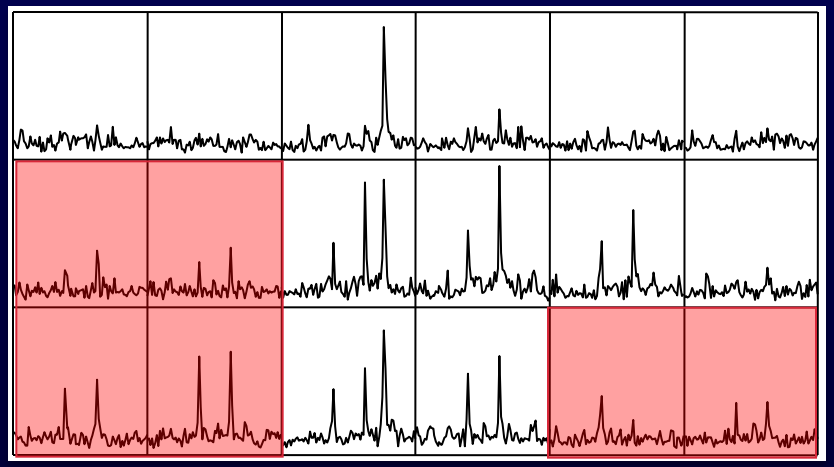


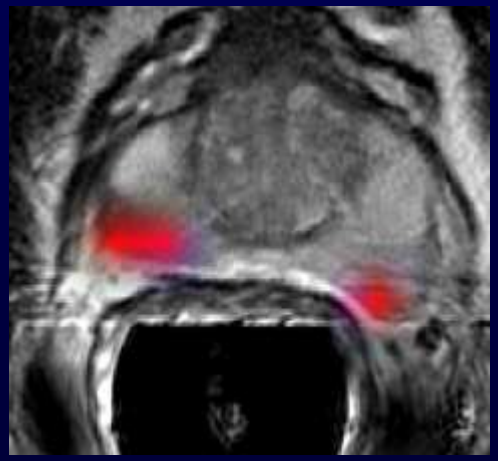




PSA of 4.58 ng/ml, biopsy proven bilateral cancer
(Gleason 3+3, 8/12 cores). MRI & MRSI abnormality in right PZ but no lesion seen on the left.

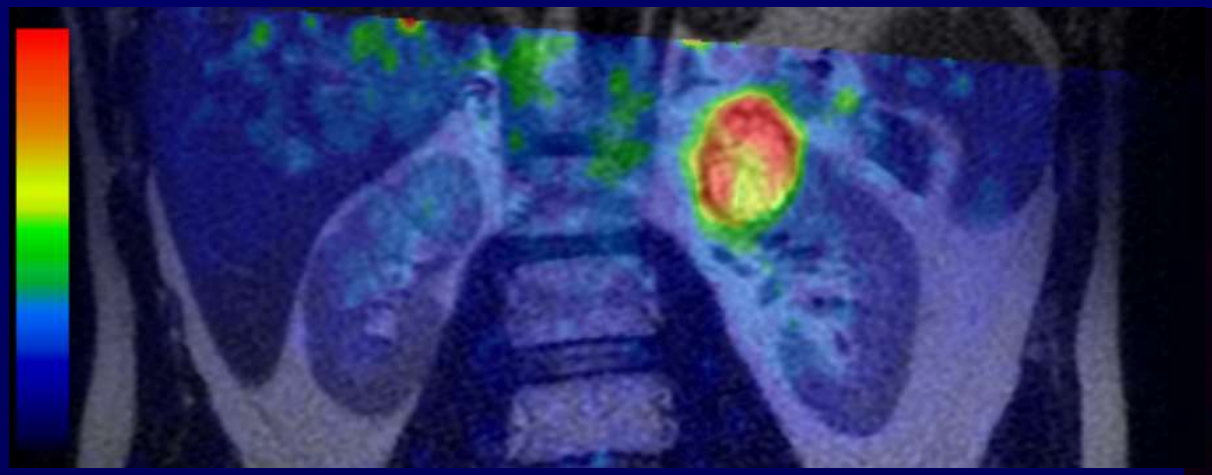




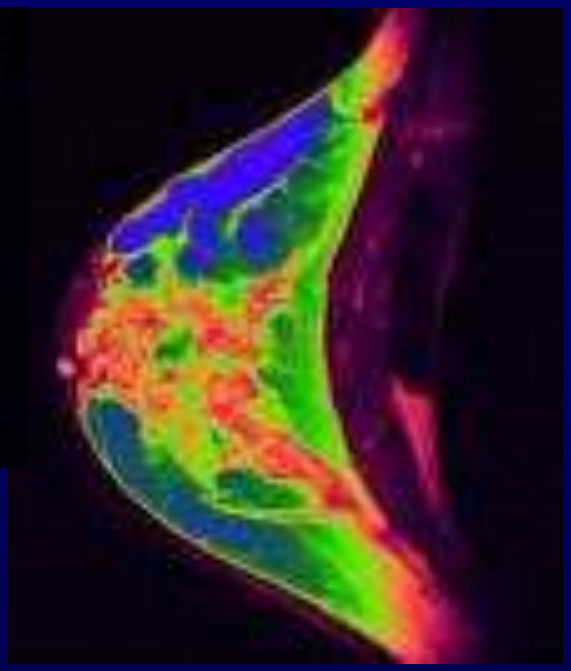


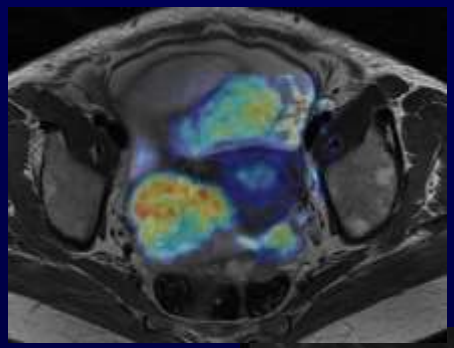
Hyperpolarized ^{13}C Pyruvate MRSI demonstrates both Bx & surgery proven lesions

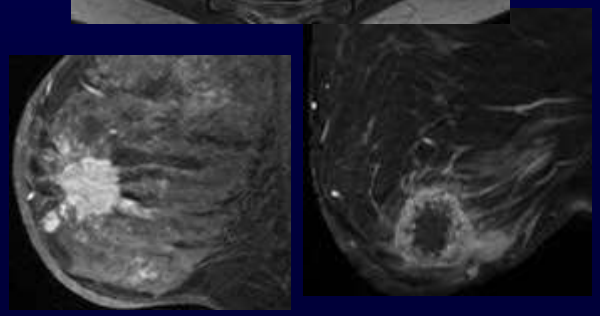
Courtesy: J Kurhanewicz UCSF; Nelson et al. Sci Trans Med 2013



MRI/ ^{124}I-cG250 PET



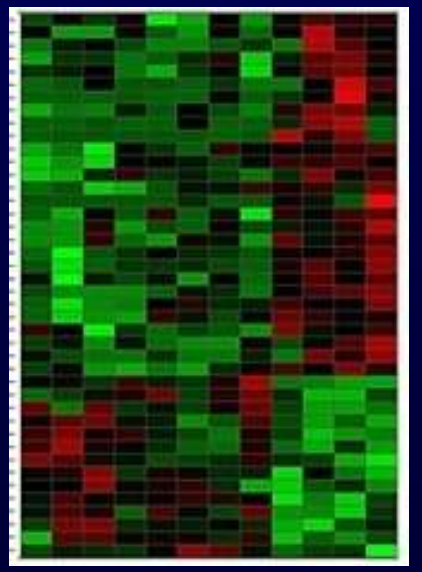




DCE-MRI

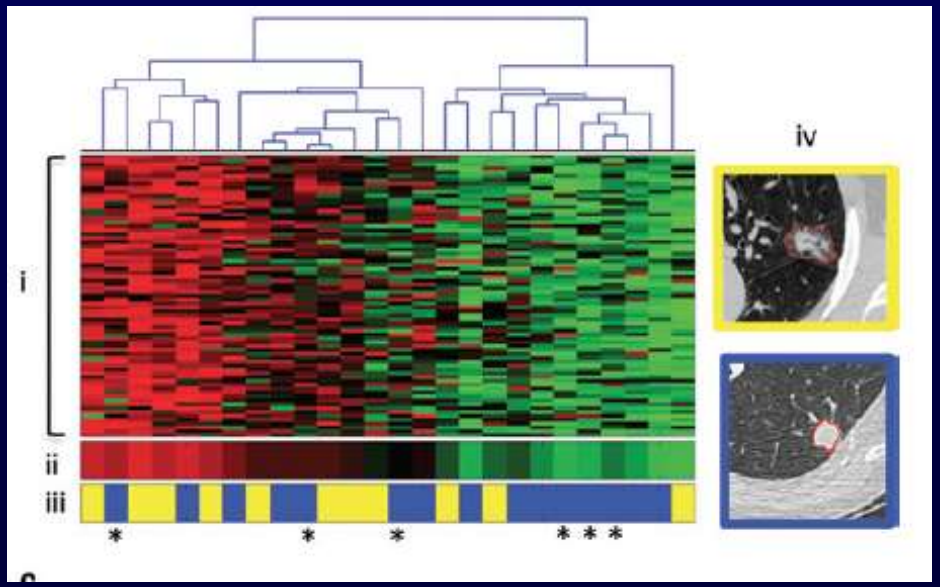
Radiogenomics

From Phenotype to Genotype

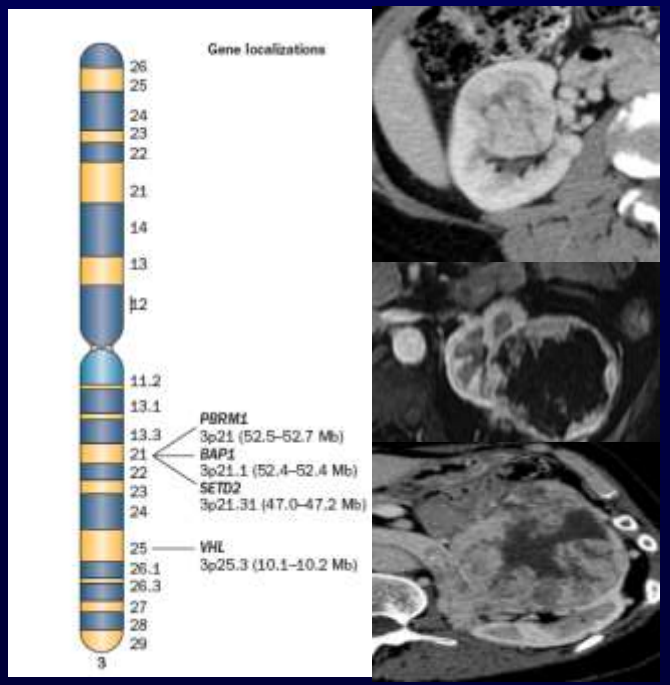


Radiogenomics: *Linking Imaging to Genotype*

- **Evolving research field to establish a bridge between diagnostic imaging and the underlying gene expression patterns**
- **Pilot studies:** GBM, HCC, Breast Ca, Lung Ca & Kidney Ca

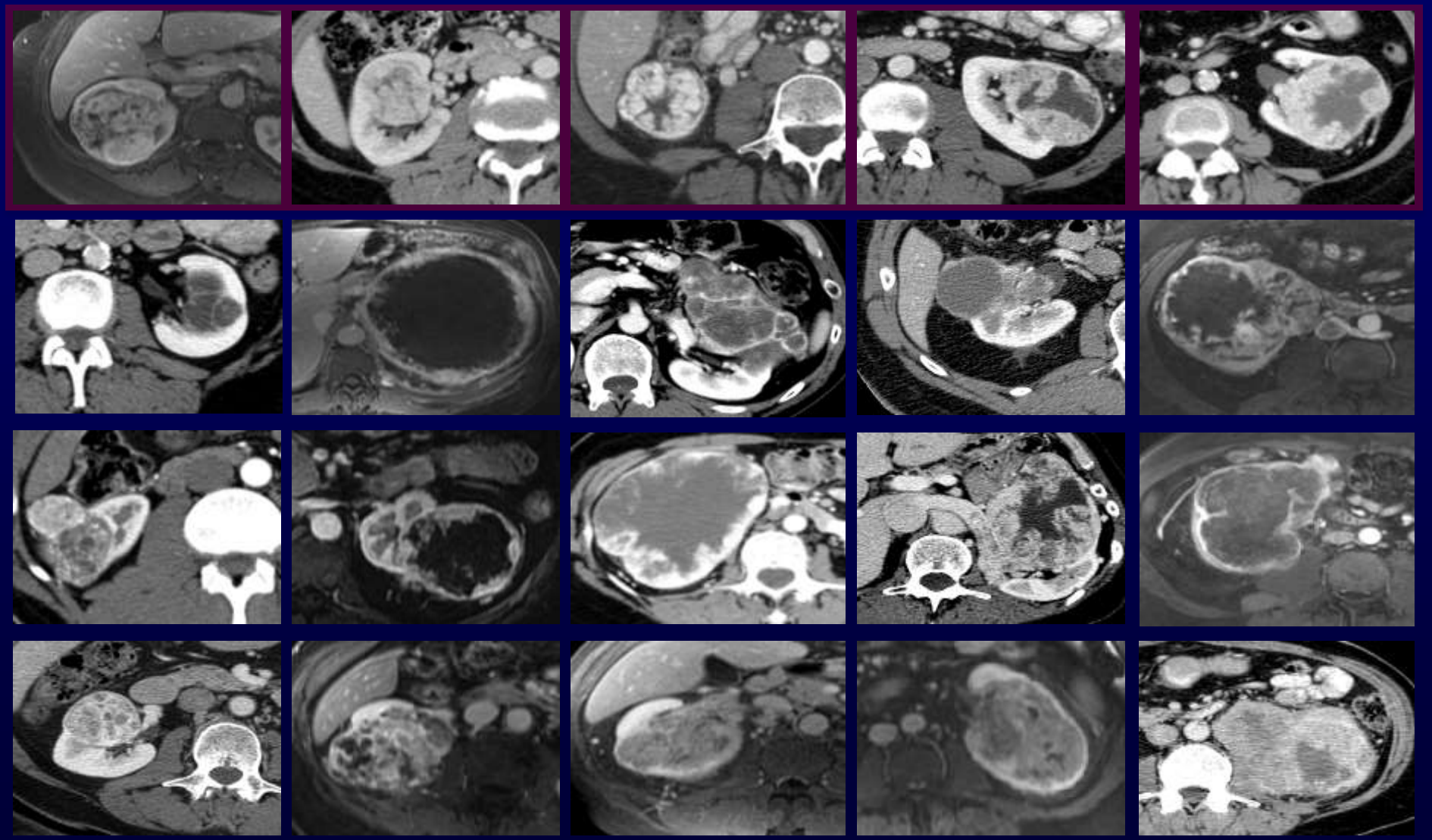


Gevaert O, et al. Radiology 2012



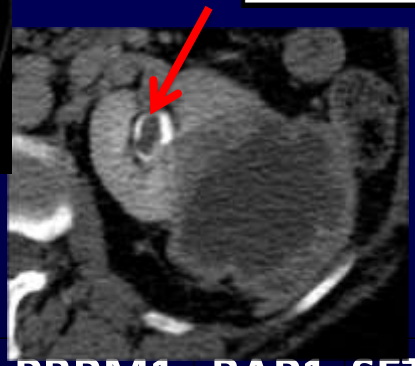
Karlo C ,et all: Radiology 2013

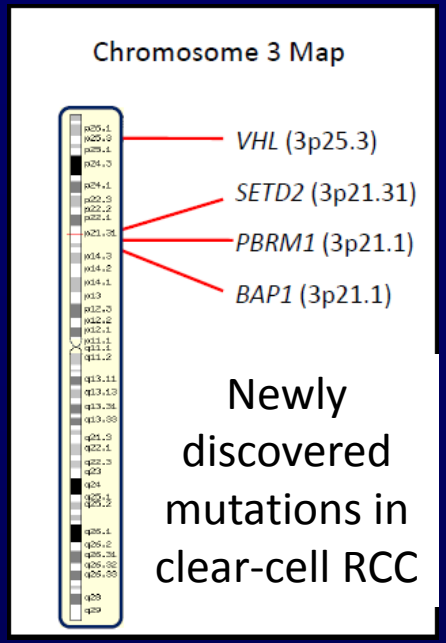
Clear Cell RCC: *Phenotypic Heterogeneity*



Radiogenomics

CT Imaging as a Biomarker – RCC (N=232)





CT Parameter	VHL	PBRM1	BAP1	SETD2	KDM5C
Renal Vein Invasion	0.194	1.000	0.030	0.391	0.030
Lobulated Tumor Enhancement Pattern	0.166	0.010	1.000	0.743	0.747
Low Nephrographic Phase Enhancement	0.737	0.394	0.101	0.023	0.445
Collecting System Invasion	0.031	1.000	0.059	0.168	0.209

C. A. Karlo et al: Radiogenomics of clear-cell renal cell carcinoma: Associations between CT imaging features and mutations; Radiology 2013

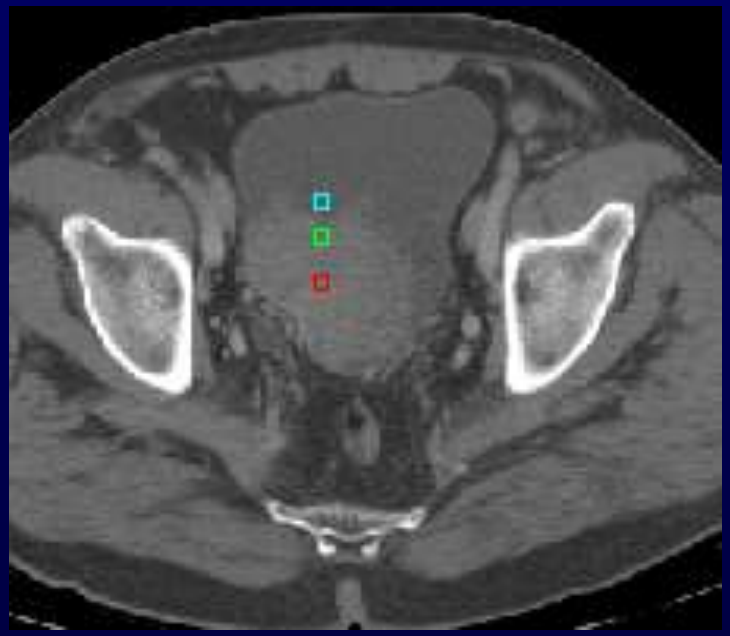
Radiogenomics: ***Discovery Phase***

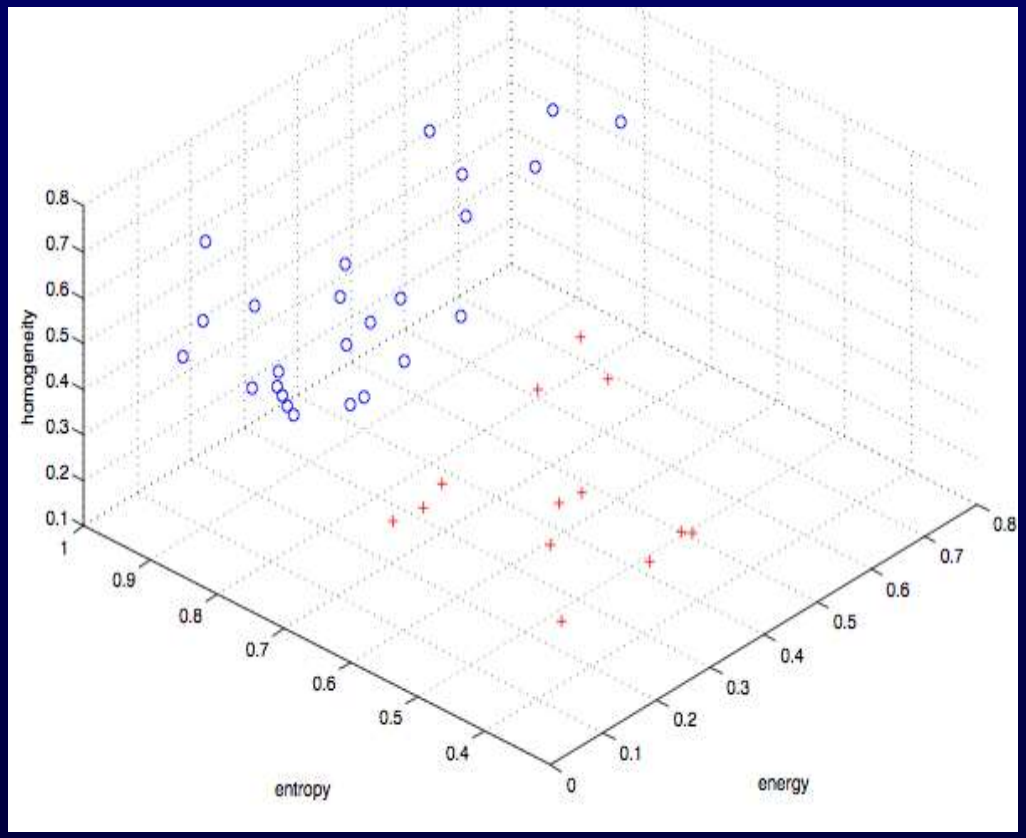
- To identify/validate prognostic imaging biomarkers by leveraging imaging and genomic data.

Pilot Study Methods:

- **Histo pathology** (e.g. tumor size, grade, stage)
- **Clinical outcome** (e.g. time-to-recurrence, survival)
- **Genomic data/Imaging features correlation**
  - **Imaging**
    - CT or MRI qualitative/observational imaging features
    - Quantitative analysis – Texture analysis of CT/MRI
    - Functional parameters – ADC, IVIM etc
    - Clusters of multiparametric data

Bladder Cancer: *Texture Analysis & Radiogenomics*



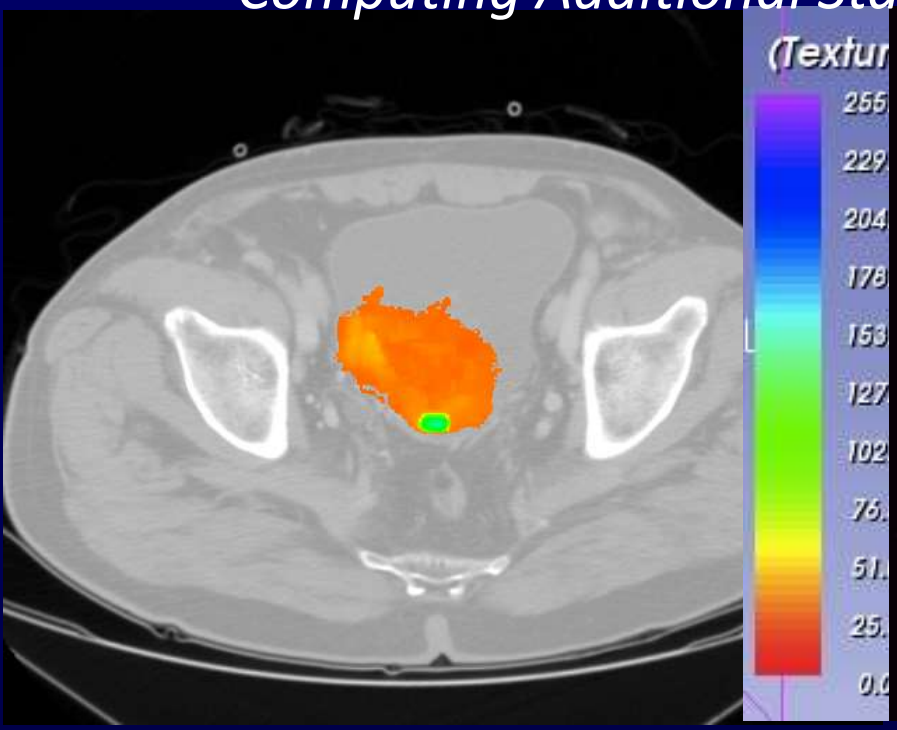


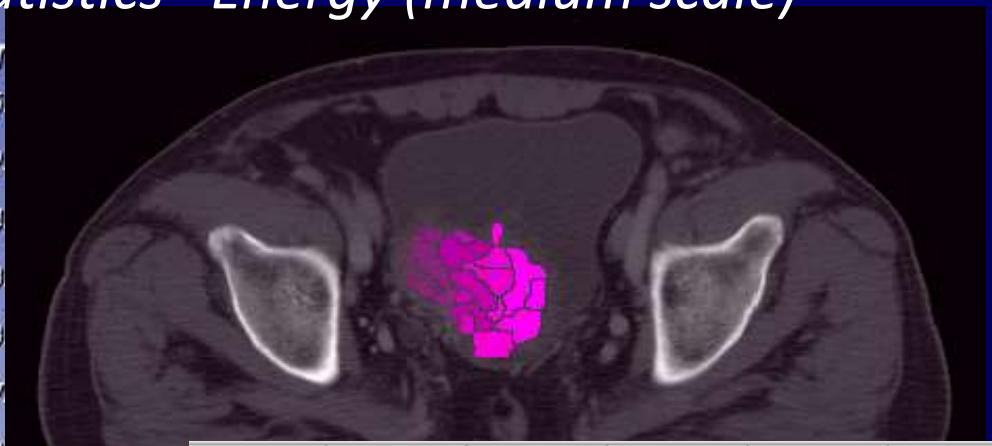
Cluster analysis showing difference in bladder cancer texture that can not be appreciated visually on the CT image

Courtesy: Harini Veeraraghavan, MSKCC

Bladder Cancer:

Computing Additional Statistics –Energy (medium scale)



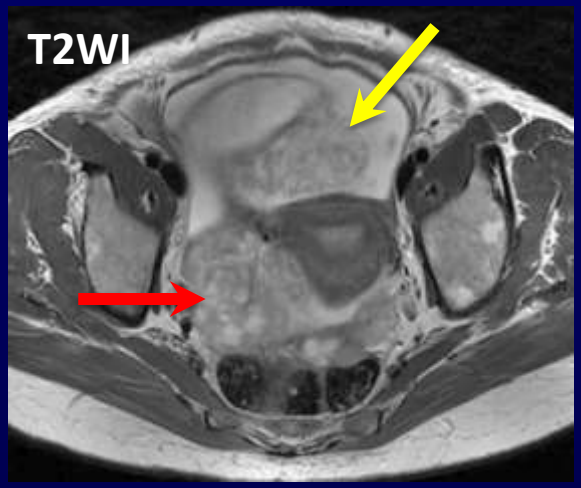


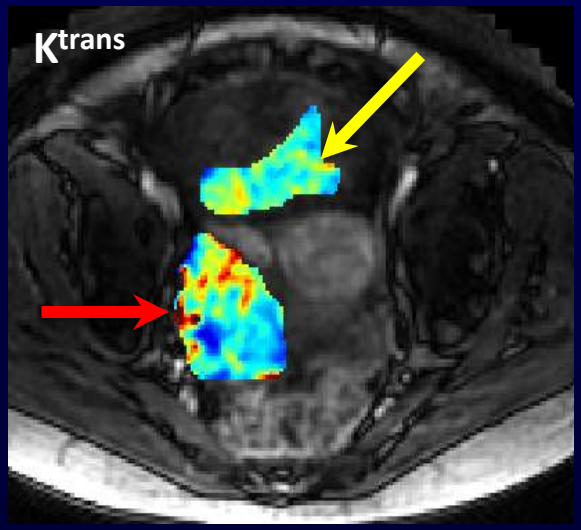
A	B	C	D	E	F
Label	Mean	Median	Kurtosis	Skewness	Volume(pix)
2	27.667	27.5	1.617	0.011	18
3	28.048	29	1.8	-0.222	21
4	32.744	33	1.931	0.085	43
5	35.238	35	1.667	-0.46	21
6	29.553	29	2.163	0.464	374
7	25.18	25	2.076	0.39	61
8	34.429	34.5	2.489	0.433	14
9	11.5	11.5	1	0	2
10	30.8	31	1.847	0.344	5
11	25.278	25	2.106	-0.249	237
12	25.504	25	2.322	0.53	123
13	23.116	23	2.255	-0.066	181
14	23.472	23	2.425	0.728	36
15	22.179	23	24.305	-4.728	28
16	26.839	27	2.183	0.146	56
17	24.133	24	1.851	0.356	173
18	23.683	23	2.842	0.784	104
19	74.458	83	1.511	-0.008	216
20	23.778	24	2.466	0.455	36
21	21	23	10.835	-3.11	39
22	27.435	27	1.843	0.196	216
23	22.851	23	2.756	0.374	282
24	24.474	24	2.257	0.377	95

Statistics calculated for the different energy levels computed as segments

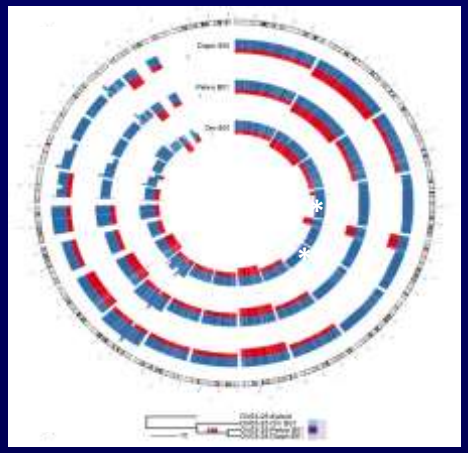
Courtesy: Harini Veeraraghavan, MSKCC

Radiogenomics: *Ovary Cancer*





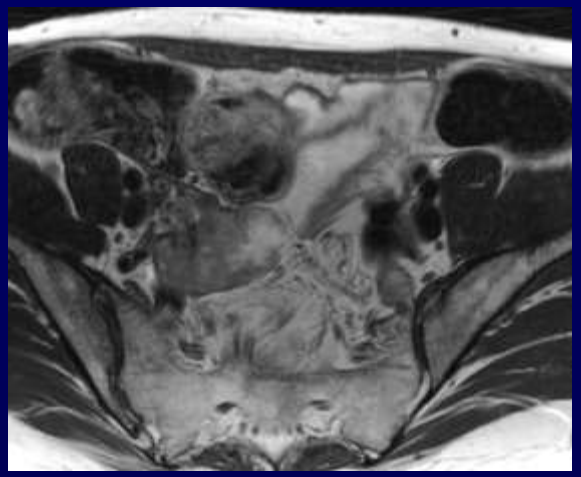
Phenotypic heterogeneity associated with histological and/ or genomic heterogeneity in HGSOC



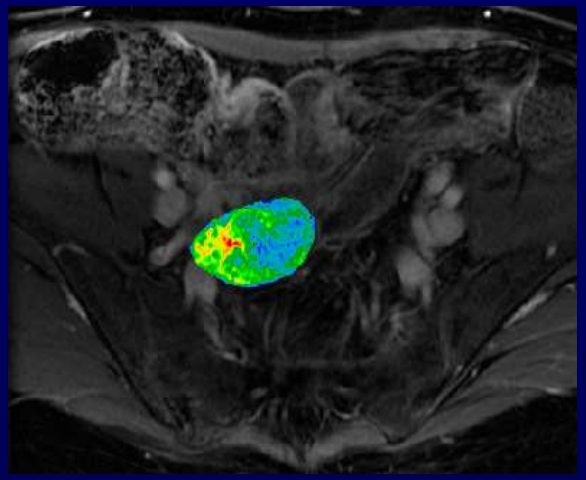
Integrated Diagnostics in Ovarian Cancer

Schwarz R, Ng CKY, Cooke SL, Newman S, Temple J, Piskorz AM, Gale D, Sayal K, Murtaza M, Baldwin P, Rosenfeld N, Earl HM, Sala E, Jimenez-Linan M, Parkinson1 CA, Markowetz F, Brenton JD. Quantification of intra-tumor heterogeneity predicts time to relapse in high-grade serous ovarian cancer. *in review*

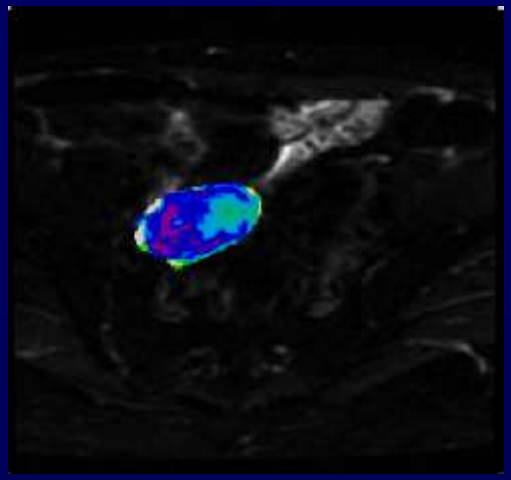
MRI - IVIM: Ovarian Cancer Tumor Heterogeneity



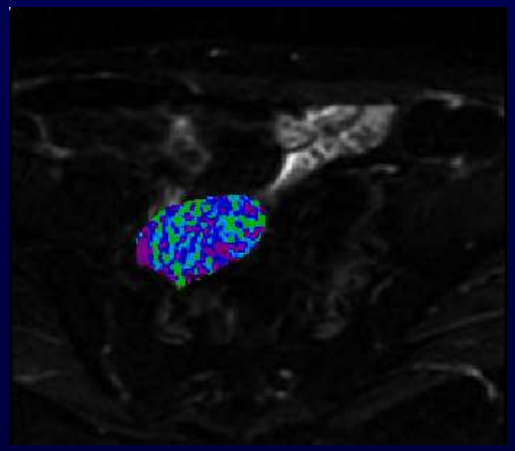
T2WI



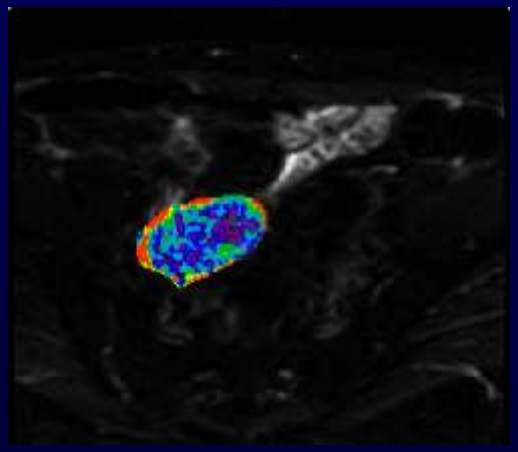
CE map (DCE-MRI)



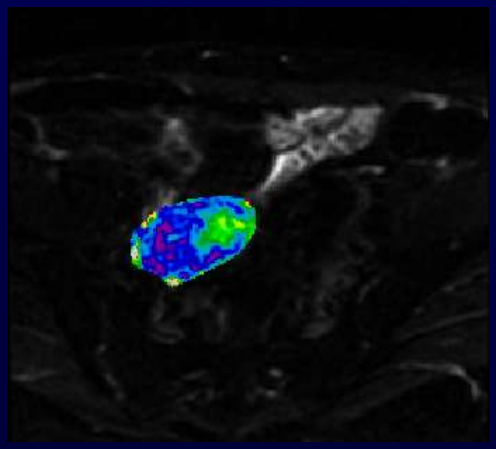
ADC map



D* (pseudo-diffusion)



f (perfusion fraction)

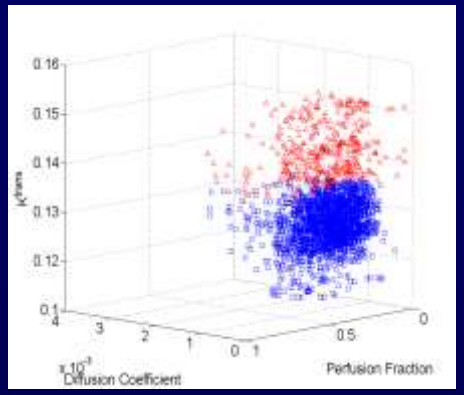


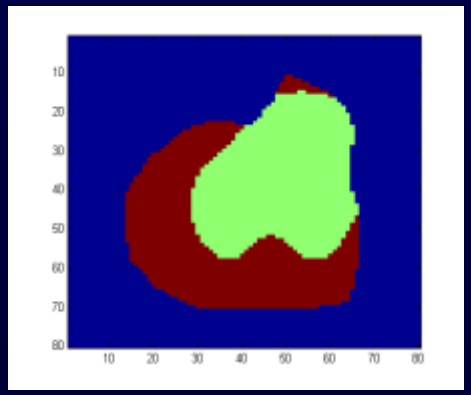
D (diffusion map)

IVIM Parameter map (biexponential diffusion model)

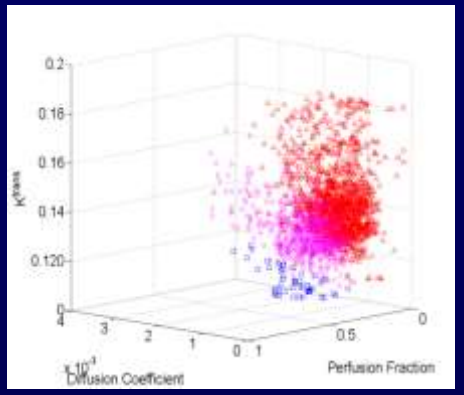
K-means Unsupervised Cluster Analysis

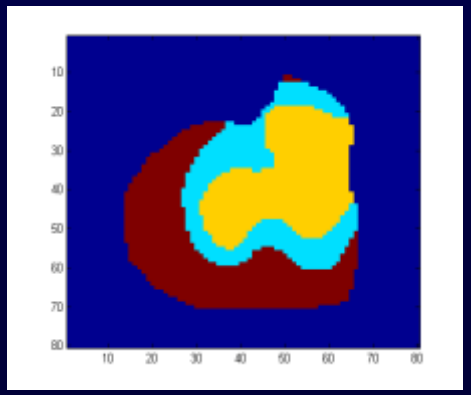
2 clusters





3 clusters

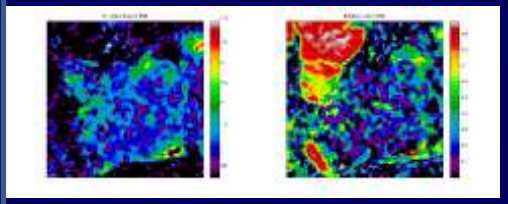




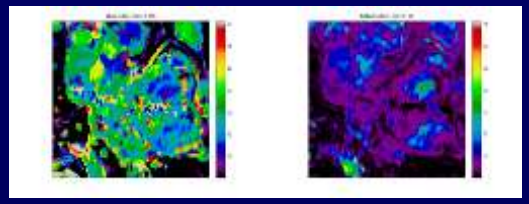
Courtesy: Yousef Mazaheri MSKCC

Multi-parametric MRI/PET Imaging

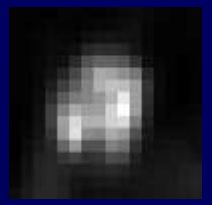
DWI



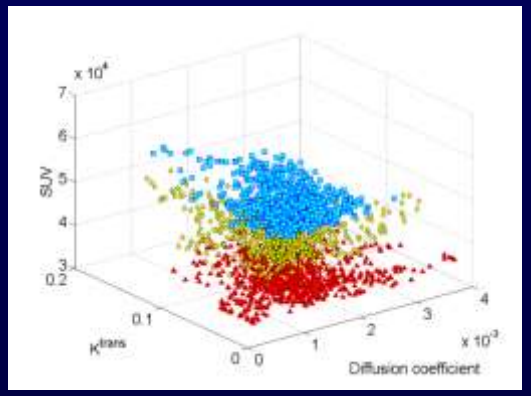
DCE

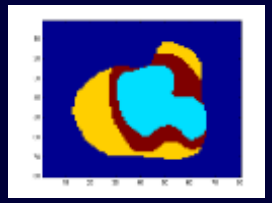


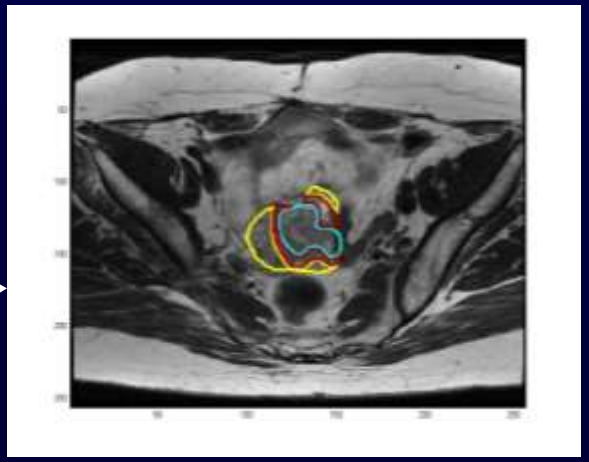
PET



Using multiparametric image clusters (incorporating IVIM-based modelling) to guide tumor sampling for genomic sampling







Courtesy: Yousef Mazaheri, MSKCC

Convergent Evolution

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Why Radiogenomics?

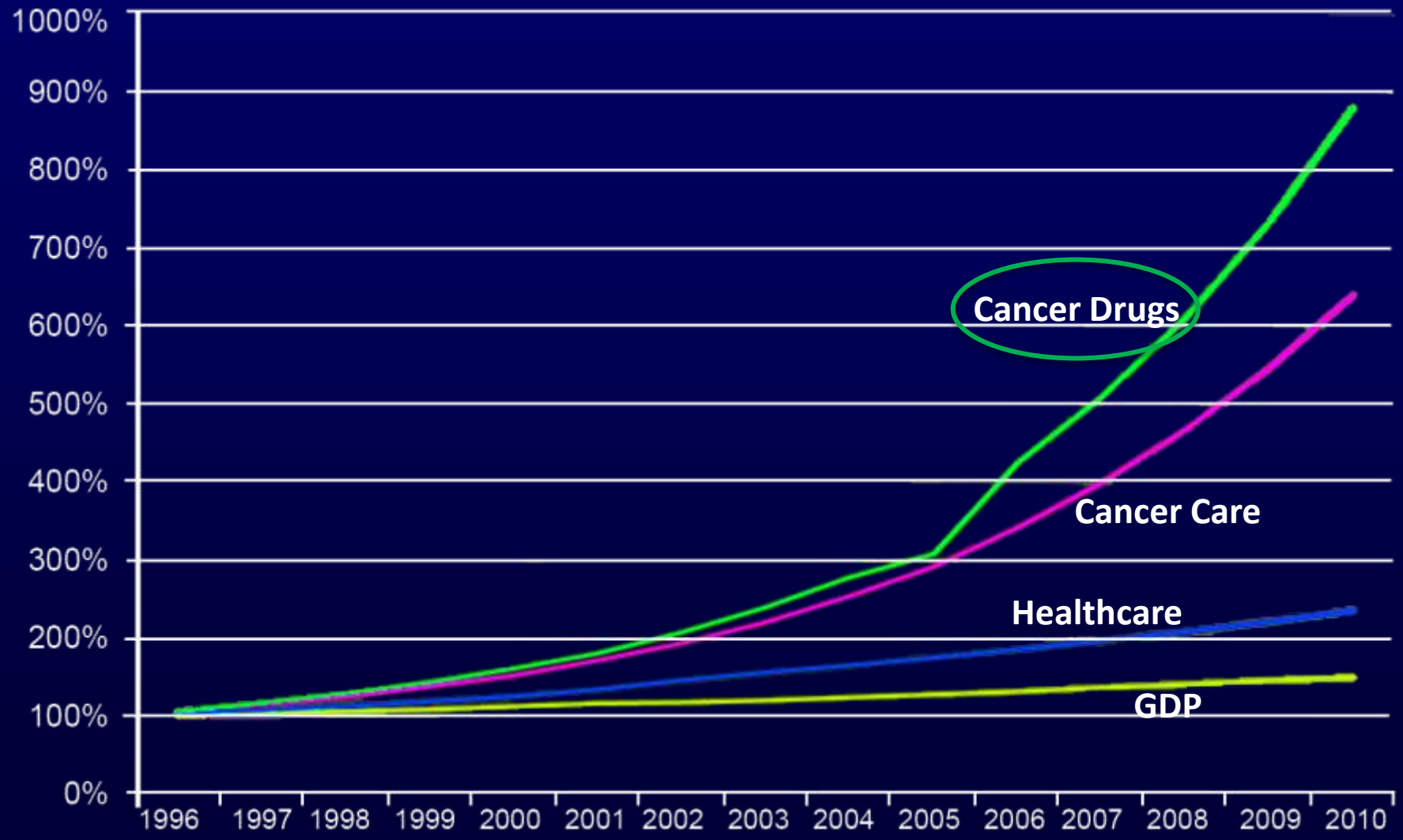
- ***Cancer is the most Genetically Heterogeneous Disease undergoing continuous evolution (Darwinian Dynamics)***
  - Primary Tumors are Spatially and Temporally Heterogeneous
  - Metastasis de-differentiate in up to 50% of cancers and demonstrate different biologic features in different matrices (bone vs. liver vs. lung)
- ***Precision Biopsy***
  - Radiogenomic data from spatial and temporal mapping of tumor regions may replace the need for multiple repeated biopsies
- ***Biomarkers***
  - ***Prognostic and Predictive Biomarker*** - Non-Invasive
  - ***Early Response Biomarker –*** imaging detects heterogeneity in response (versus a serum response biomarker like PSA or CA125)
  - ***Pharmacodynamics –*** imaging demonstrates readout pathway activation –which cannot be answered by labeling the drug

Oncologic Imaging – the Next 10 Years

Unprecedented Convergence of the Life Science, Physical Science and Engineering

- **Imaging Tumor Biology** - *development of probes to interrogate in-vivo tumor biology*
- **Molecular Precision with Image-guided IR**
- **Integrated Diagnostics** - convergence of "omics," molecular pathology, laboratory medicine & imaging as essential driving forces in precision medicine
- **Theranostics & Pharmacodynamics**

Cost of Cancer Care in the U.S.



Toward Precision Medicine: NAS/IOM 2012

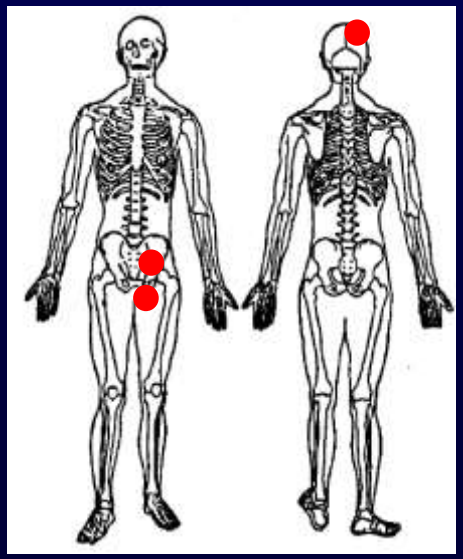
Nuclear Medicine

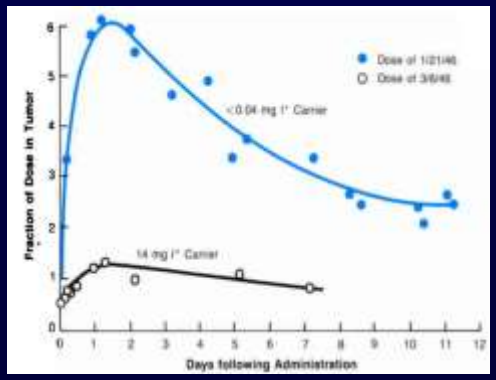
Molecular Imaging and Therapy

The earliest documented use of Nuclear Medicine was **1946** when radioactive iodine, via an *"atomic cocktail,"* was first used to treat thyroid cancer

Radioactive Iodine Therapy: Effect On Functioning Metastases of Adenocarcinoma of the Thyroid

Seidlin, Marinelli, Oshry.
JAMA 1946

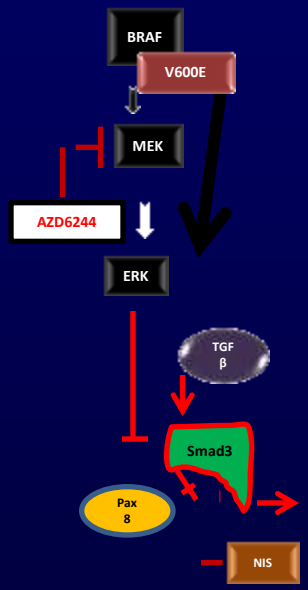




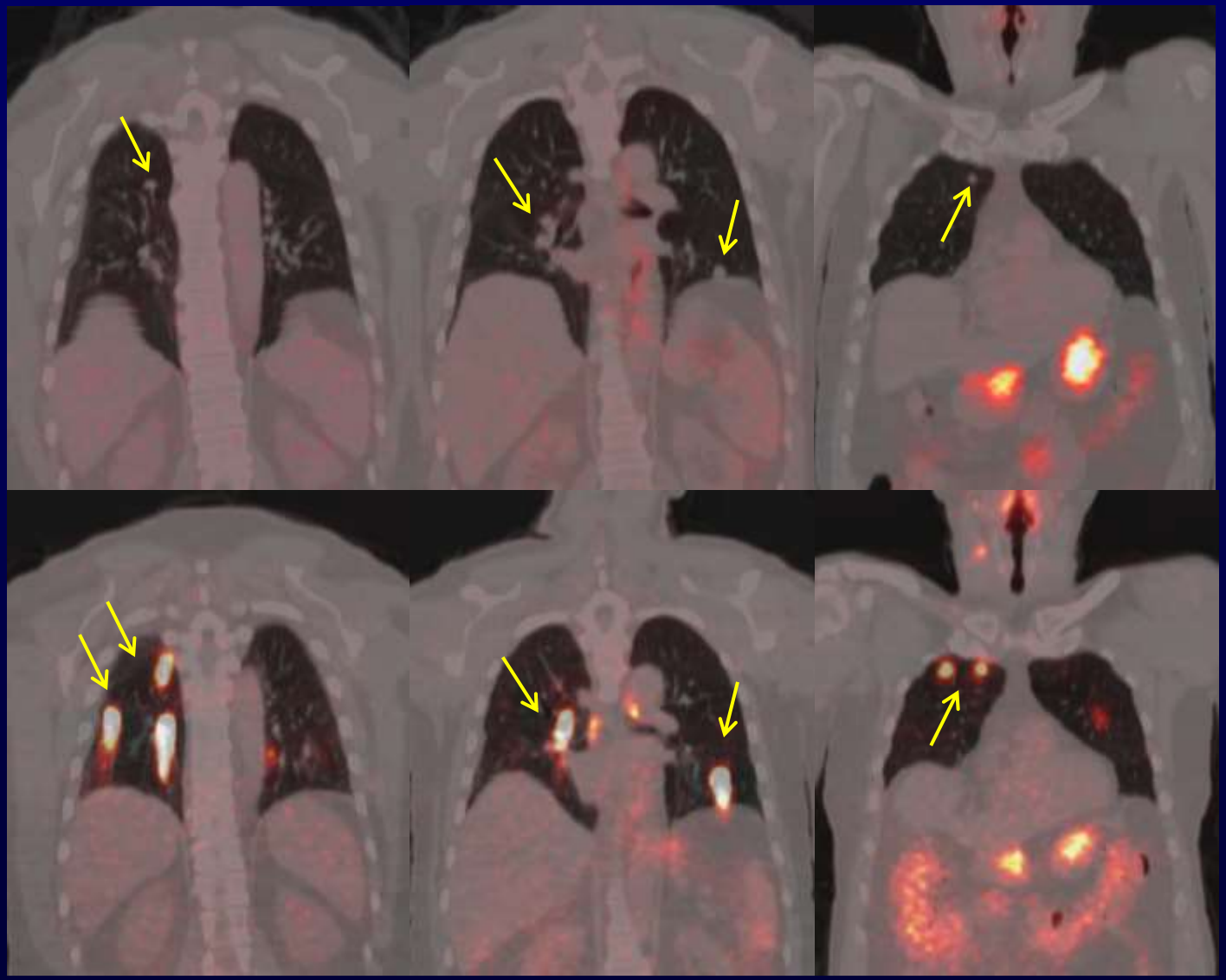
^{131}I Refractory Metastatic Thyroid Cancer: ^{124}I scan as a Predictive Biomarker in selecting patients for ^{131}I therapy following MEK inhibitor (AZD6244)

^{124}I PET/CT
Baseline

Signal transduction ERK-BRAF pathway

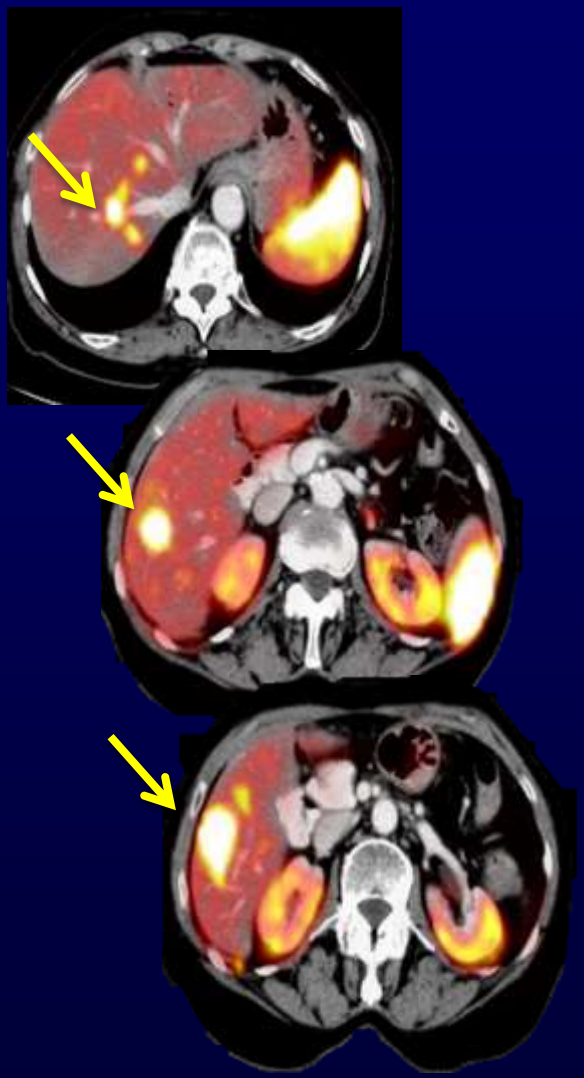


^{124}I PET/CT
5 wks after
MEK Inhibitor

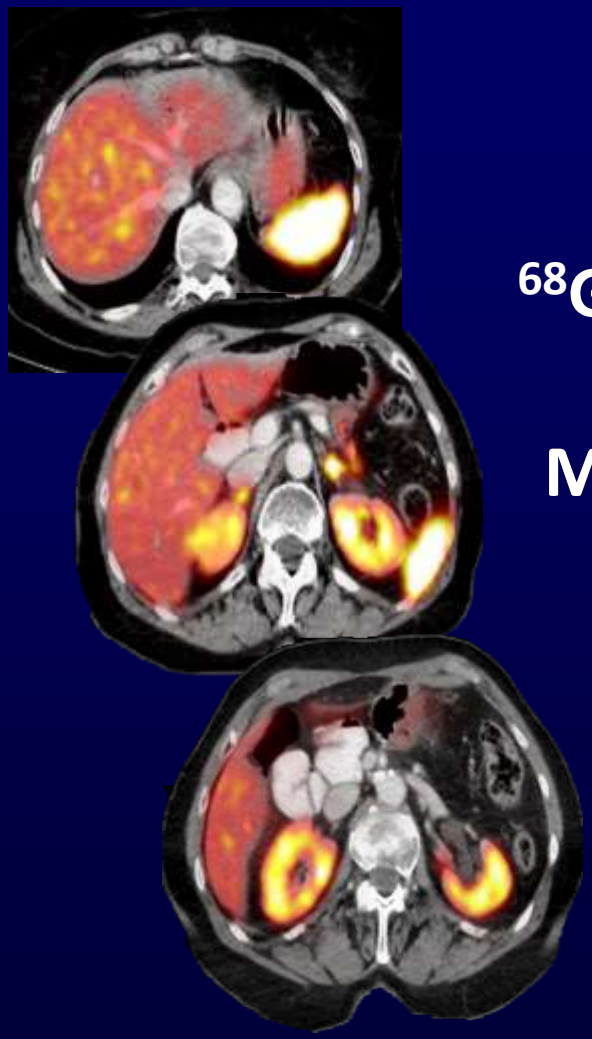


J. Fagin at al: NEJM 2013

Theranostics: *Targeted Imaging & Radio-Immunotherapy*



Before therapy

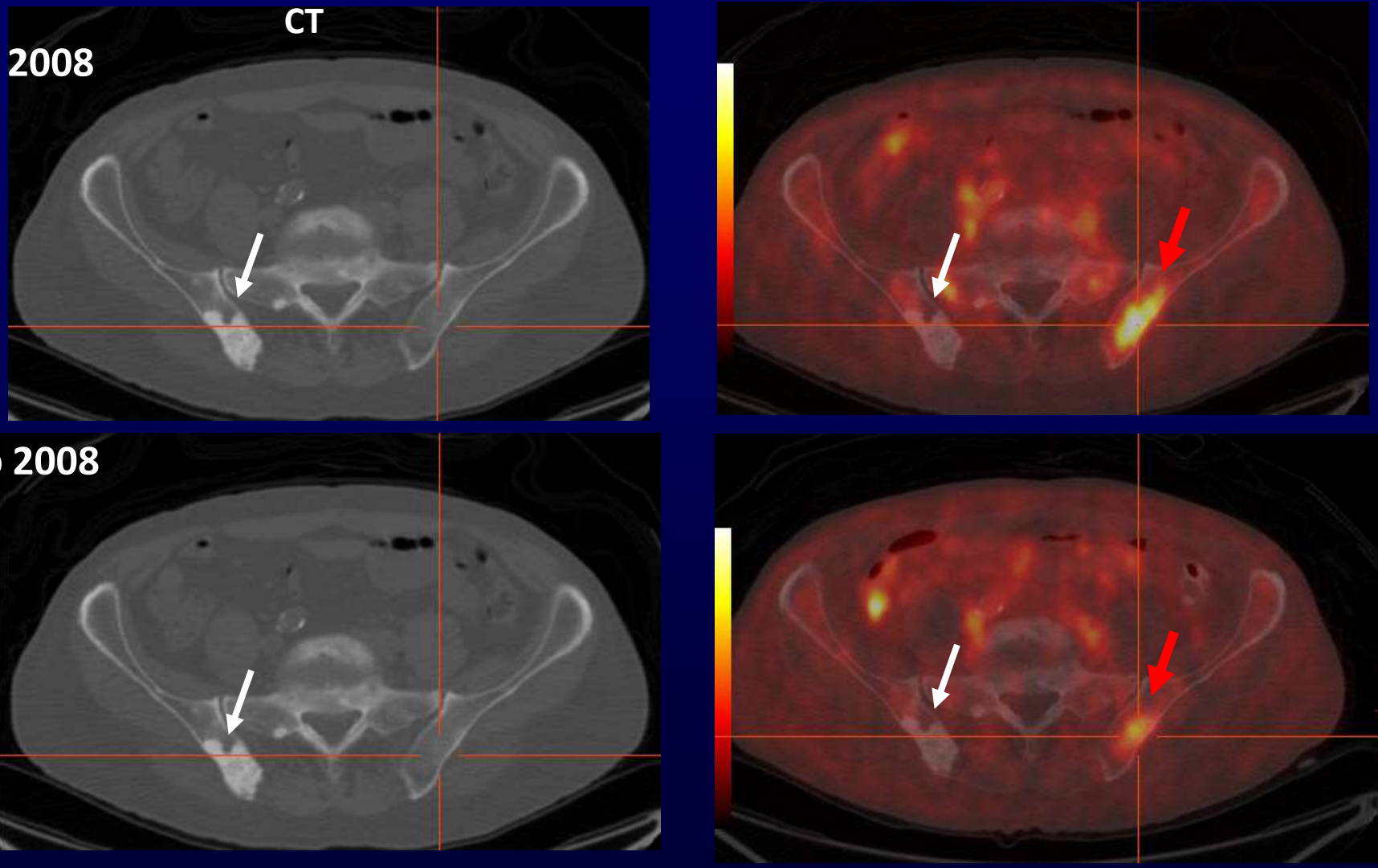


After Lutetium-177
(^{177}Lu) DOTA-TATE

^{68}Ga-DOTATATE – PET/CT Metastatic NET

Courtesy: W. Weber

Theranostics: *Targeted Imaging & Targeted Therapy*



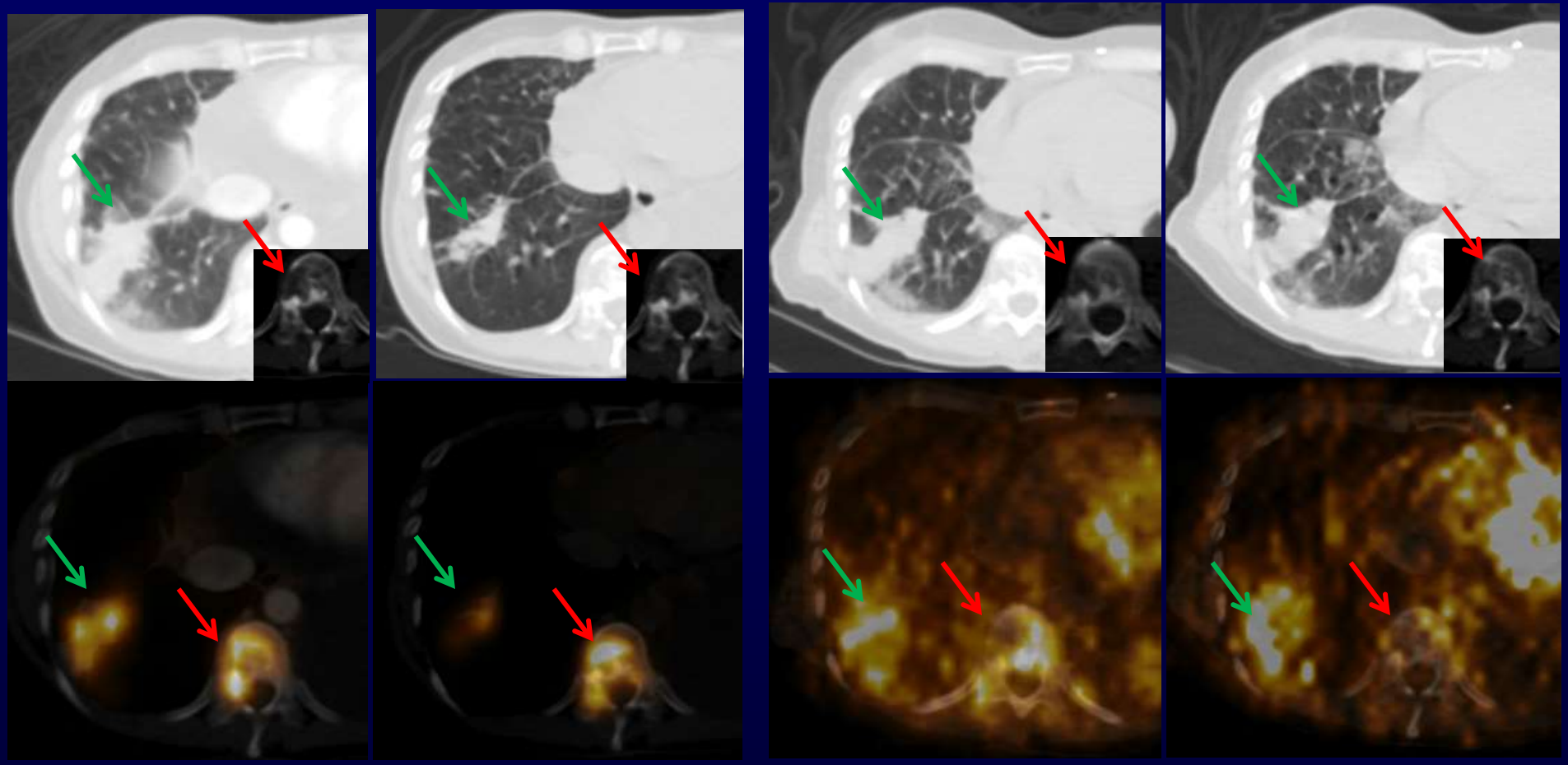
Therapy © Androgen Receptor Inhibitor: good AR treatment response

Theranostics: ^{18}F-FDHT PET/CT: Predictive and Targeted Response Biomarker in patients with metastatic prostate cancer considered for therapy with an androgen receptor antagonist (e.g. MDV3100)

Lancet 2010

Theranostics

^{18}FDG PET/CT Baseline	^{18}FDG PET/CT 19 days after STA-9090 TX	^{124}I-PUh71 PET/CT 20 min post inj.	^{124}I-PUh71 PET/CT 21 hrs. post inj.



48 year old female with breast cancer metastatic to lungs and bones; Hsp90-targeted therapy (STA-9090), induced partial response in lung mass (↑) but progression in spinal lesion (↑); ^{124}I-PUh71 shows uptake and retention in the lung lesion but clearance from spinal bone metastasis.

Investigational MSKCC: M. Dunphy & G. Chiosis

Rene Magritte – “La Clairvoyance” (1936)

Technology and Medicine

"As much as new ideas are fundamental to the advancement of science, technologic innovations are the engine of scientific progress"

Shirley Tilghman
President, Princeton University

We are witnessing unprecedented Convergence of the Life Science, Physical Science and Engineering